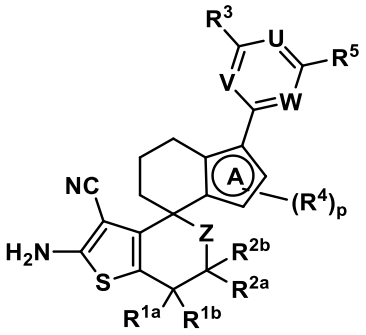
Summary

In one aspect, the present disclosure provides a compound of the formula **(I)**



(I)

, wherein

R^{1a} and **R^{1b}** are both independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

R^{2a} and **R^{2b}** are both independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

and/or, optionally, one of **R^{1a}** or **R^{1b}** and one of **R^{2a}** or **R^{2b}** together with the carbon atoms they are attached form a cyclopropane ring;

Z is $-(CR^{6a}R^{6b})_n-$;

each **R^{6a}** and **R^{6b}** is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

or **R^{6a}** and **R^{6b}** together with the carbon atom they are attached to form a cyclopropane ring;

n is selected from the group consisting of 0, 1 and 2;

R^3 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, $-N_3$, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally and independently substituted with one or more, identical or different **R^7** and/or **R^8**;

each **R^7** is independently selected from the group consisting of -OR^8, -NR^{8}R^8, halogen, -CN, -C(=O)R^8, -C(=O)OR^8, -C(=O)NR^{8}R^8, -NHC(=O)OR^8 and the bivalent substituent =O;

each **R^8** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^9** and/or **R^{10}**;

each **R^9** is independently selected from the group consisting of -OR^{10}, -NR^{10}R^{10} and -C(O)NR^{10}R^{10};

each **R^{10}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with a substituent selected from the group consisting of C_{1-6}alkoxy, C_{3-10}cycloalkyl and 3-11 membered heterocyclyl optionally substituted with C_{1-6}alkyl;

W is nitrogen (-N=) or -CH=;

V is nitrogen (-N=) or -CH=;

U is nitrogen (-N=) or -C(**R^{11}**)=;

R^{11} is selected from hydrogen, halogen and C_{1-4}alkoxy;

ring **A** is a ring selected from the group consisting of pyrrole, furan, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole and triazole;

each **R^4**, if present, is independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, cyano-C_{1-6}alkyl, halogen, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -CN, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

p is selected from the group consisting of 0, 1, 2 and 3;

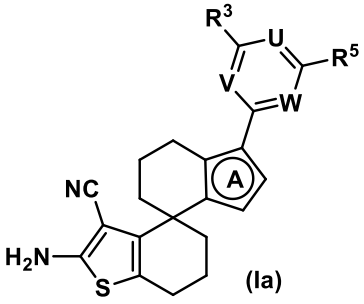
R^5 is a 3-11 membered heterocyclyl optionally substituted with one or more identical or different C_{1-6}alkyl, C_{1-6}alkoxy or a 5-6 membered heterocyclyl, wherein the C_{1-6}alkyl is optionally substituted with cyclopropyl;

or **R5** is -O-C_{1-6}alkyl substituted with a 3-11 membered heterocyclyl, wherein the 3-11 membered heterocyclyl is optionally substituted with one or more, identical or different **R12**,

each **R12** is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen and 3-11 membered heterocyclyl;

or a salt thereof.

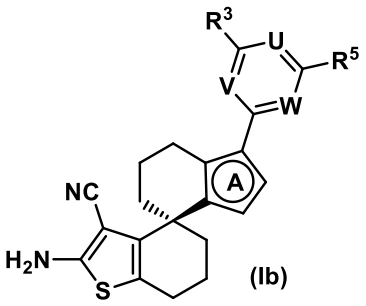
In another aspect, the present disclosure provides a compound of the formula **(Ia)** or its salt



(Ia) , wherein

A, **V**, **U**, **W**, **R3** and **R5** are as described herein.

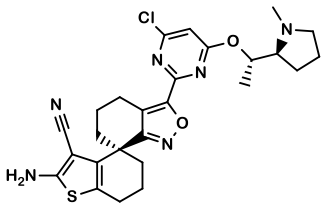
In another aspect, the present disclosure provides a compound of the formula **(Ib)** or its salt



(Ib) , wherein

A, **V**, **U**, **W**, **R3** and **R5** are as described herein.

In another aspect, the present disclosure provides a compound selected from the compounds in the following table, or a salt thereof:

I-1 
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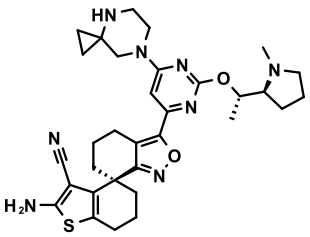
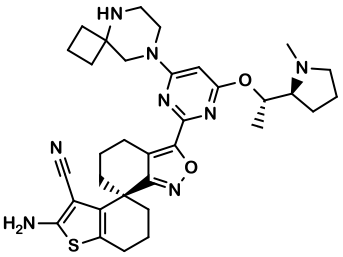
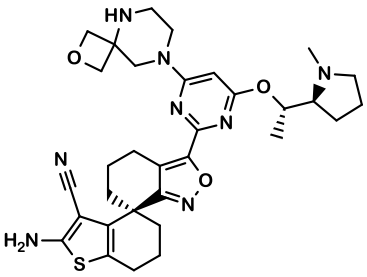
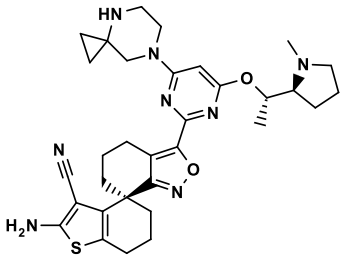
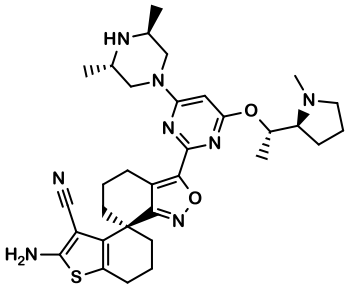
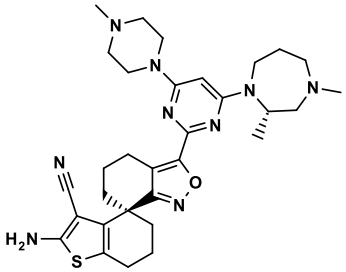
I-2  ,

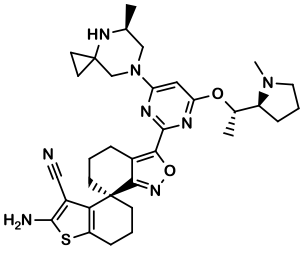
I-3  ,

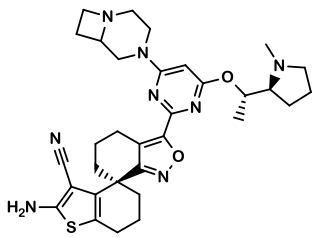
I-4  ,

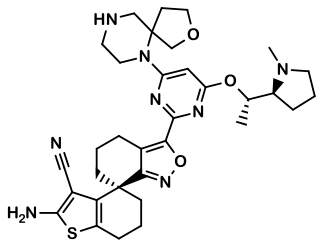
I-5  ,

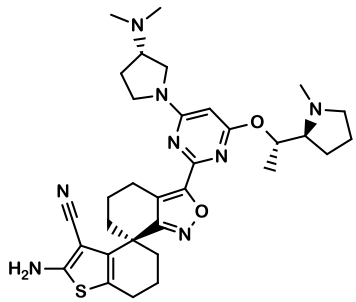
I-6  ,

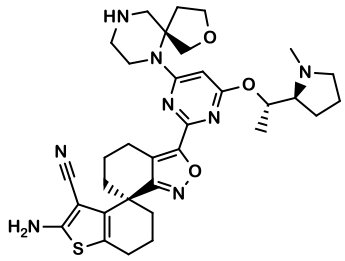
I-7  ,

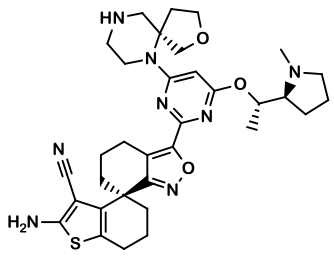
I-8  ,

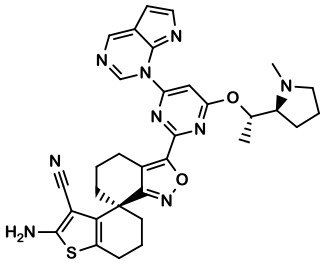
I-9  ,

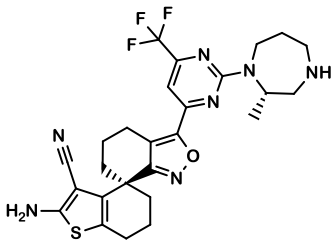
I-10  ,

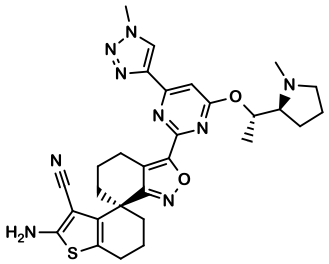
I-11  ,

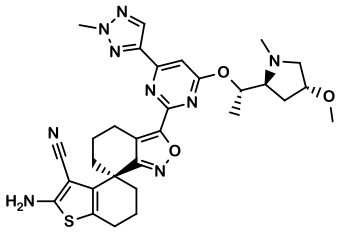
I-12  ,

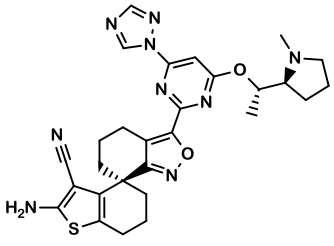
I-13  ,

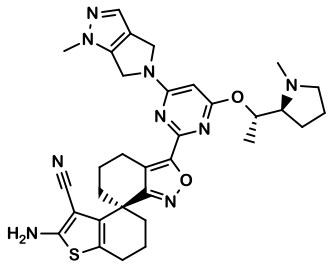
I-14  ,

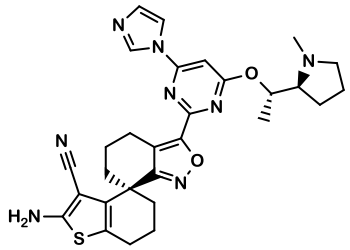
I-15  ,

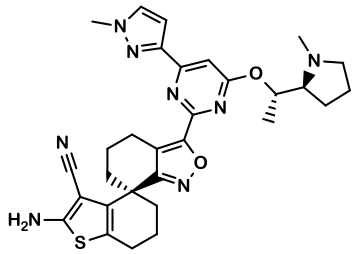
I-16  ,

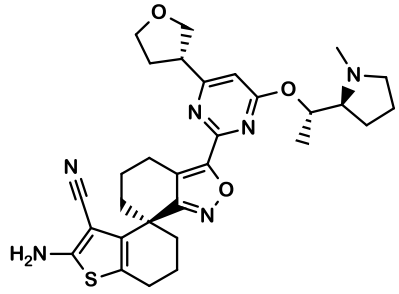
I-17  ,

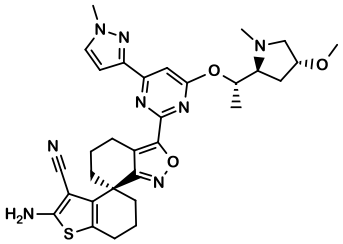
I-18  ,

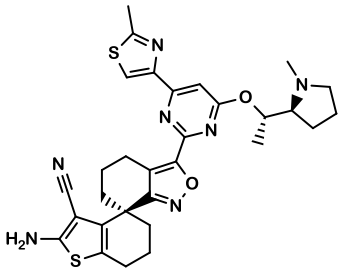
I-19  ,

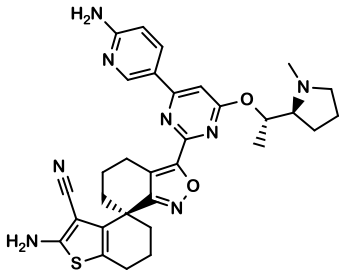
I-20  ,

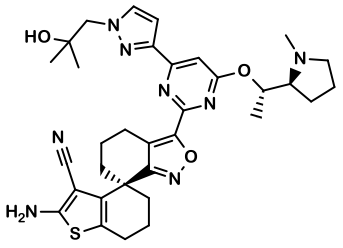
I-21  ,

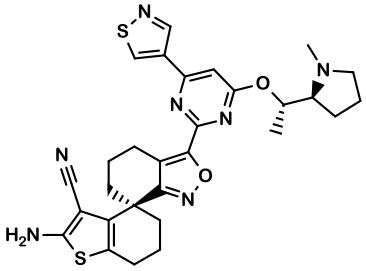
I-22  ,

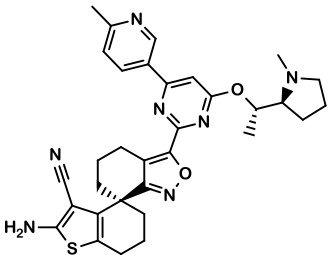
I-23  ,

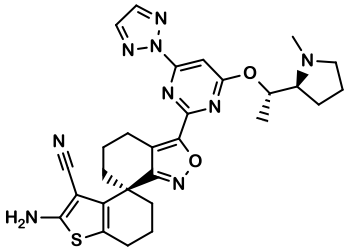
I-24  ,

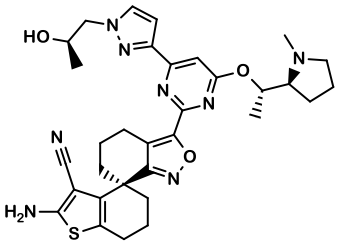
I-25  ,

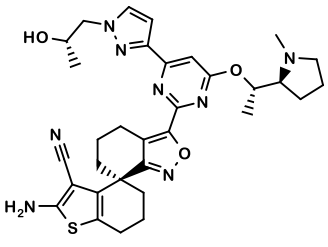
I-26  ,

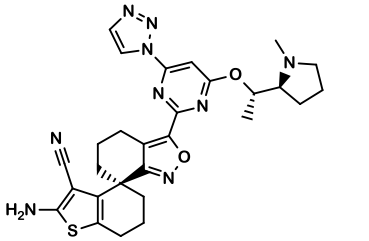
I-27  ,

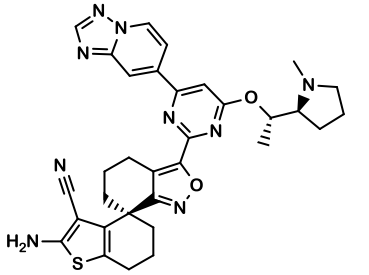
I-28  ,

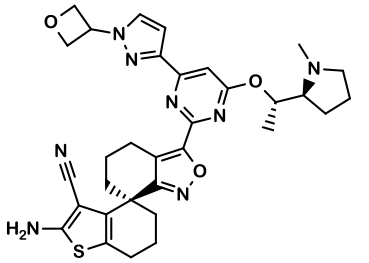
I-29  ,

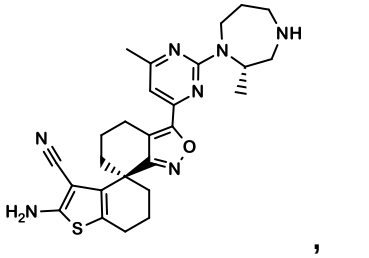
I-30  ,

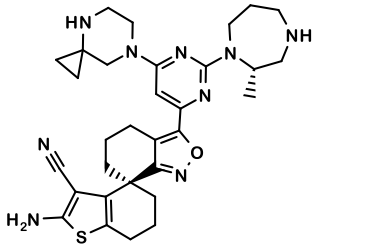
I-31  ,

I-32  ,

I-33  ,

I-34  ,

I-35  ,

I-36  ,

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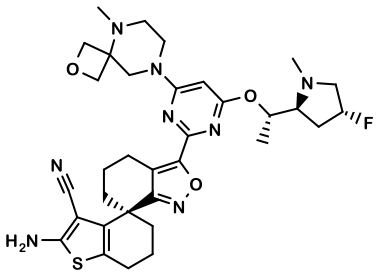

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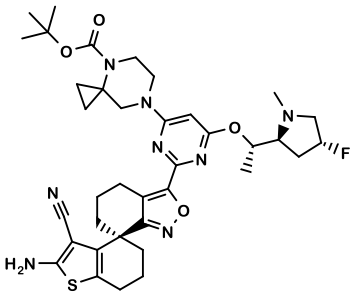

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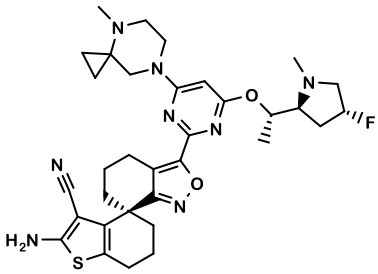

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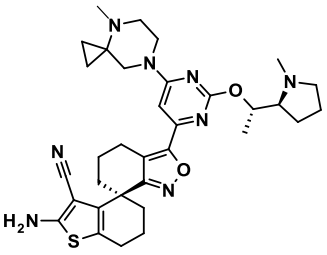

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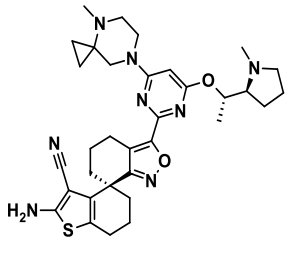

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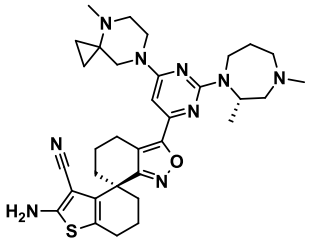

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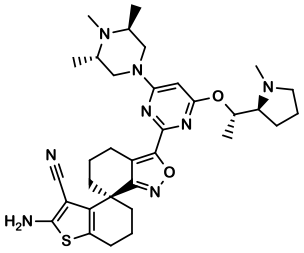

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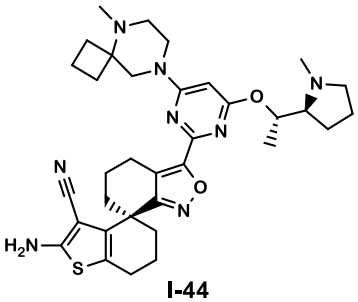

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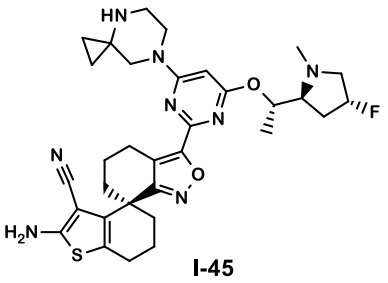
I-45 

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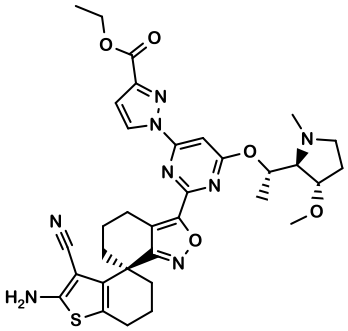
I-46 

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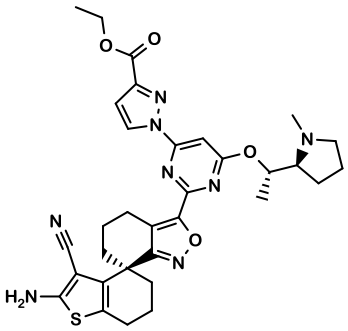
I-47 

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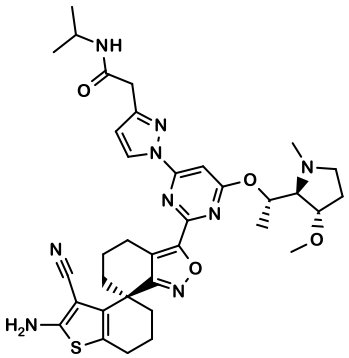
I-48 

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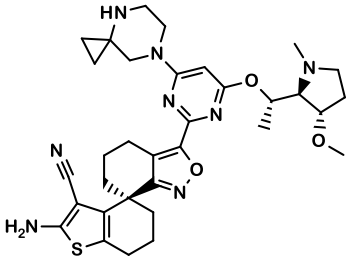
I-49 

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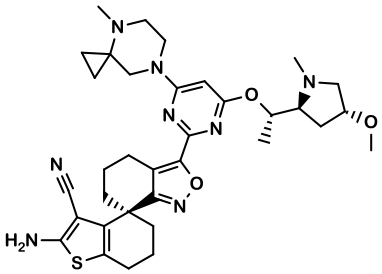
I-50 

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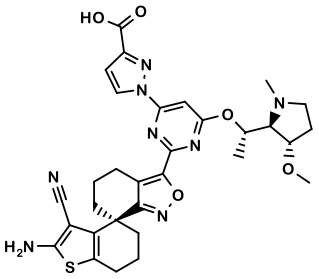
I-51 

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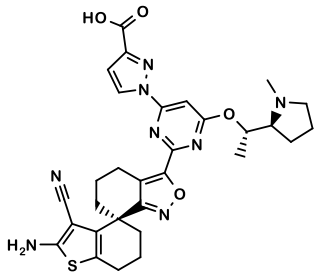
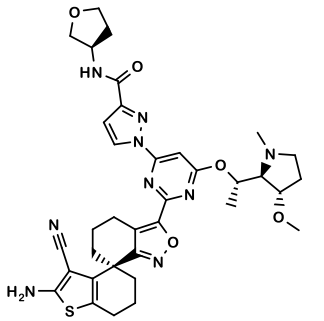
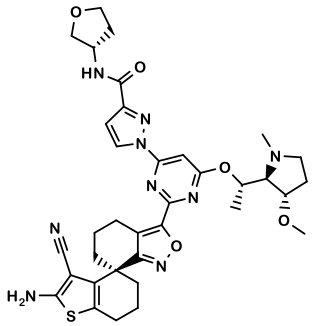
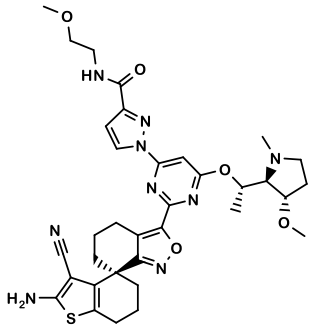
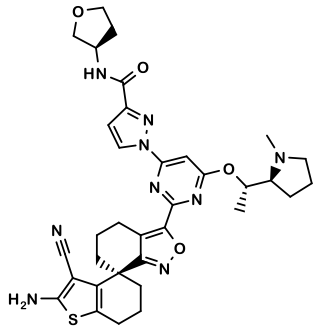
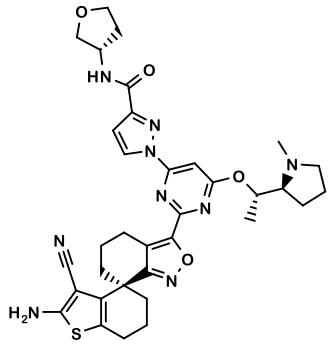
I-52  ,

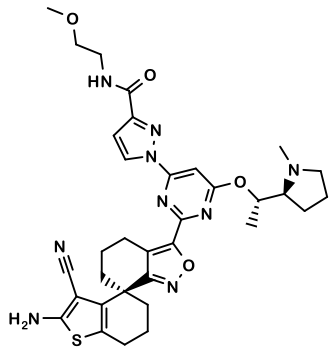
I-53  ,

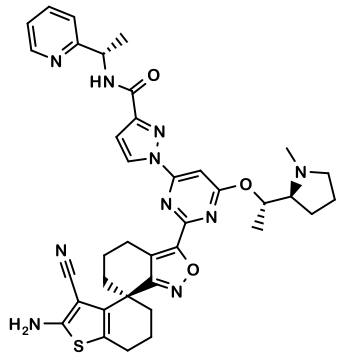
I-54  ,

I-55  ,

I-56  ,

I-57  ,

I-58  ,

I-59  ,

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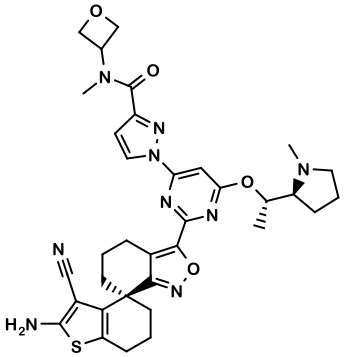

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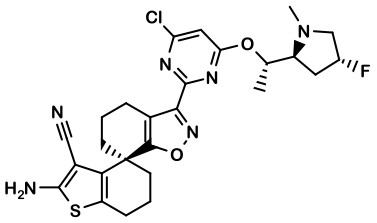

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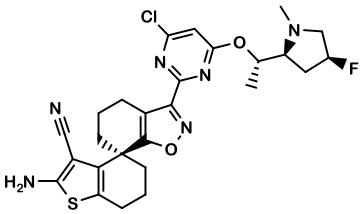

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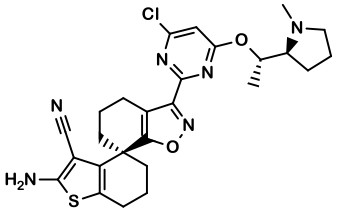

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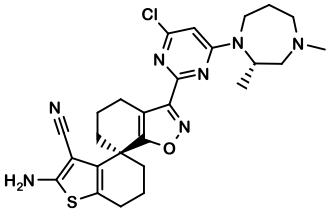

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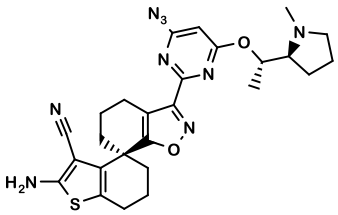

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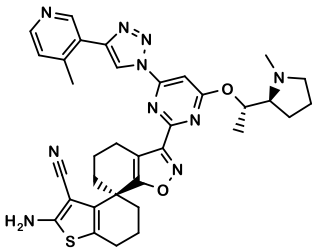

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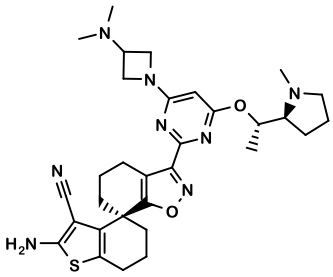

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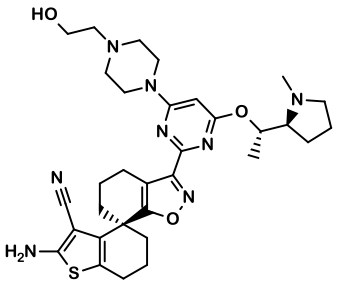

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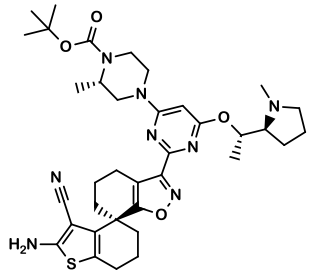
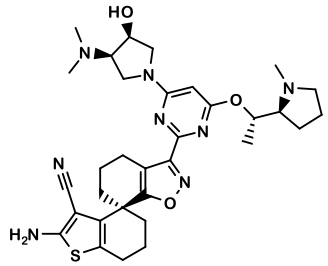
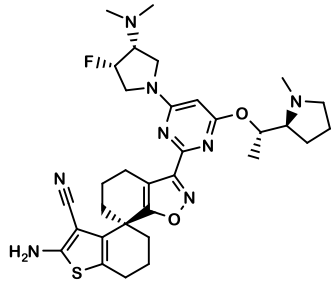
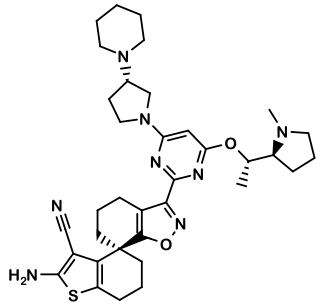
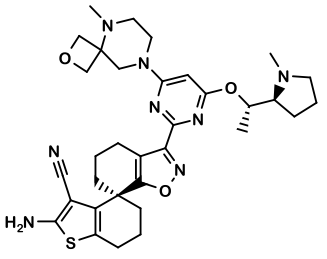
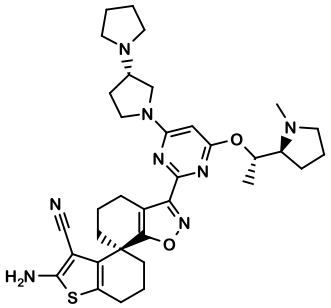
II-9  ,

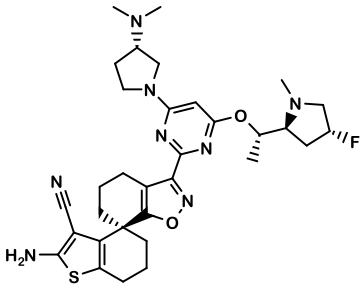
II-10  ,

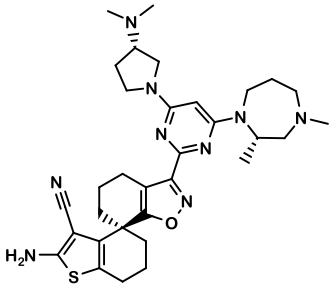
II-11  ,

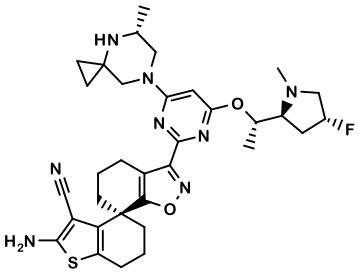
II-12  ,

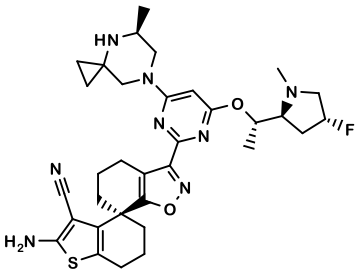
II-13  ,

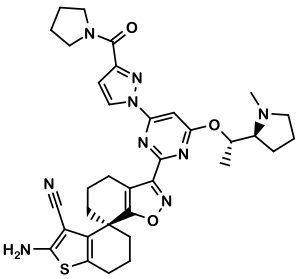
II-14  ,

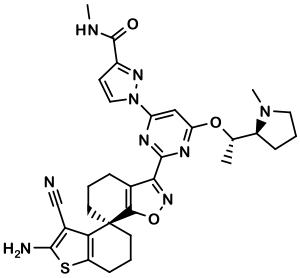
II-15  ,

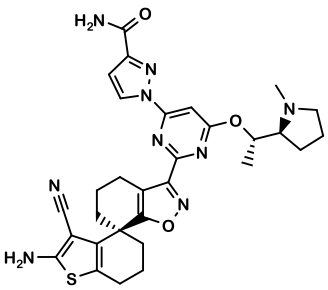
II-16  ,

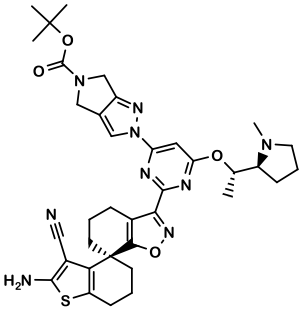
II-17  ,

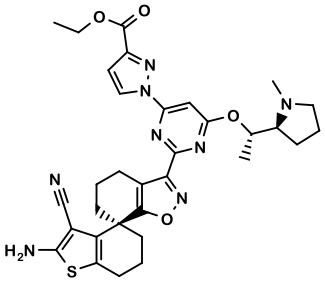
II-18  ,

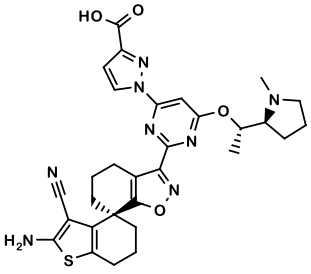
II-19  ,

II-20  ,

II-21  ,

II-22  ,

II-23  ,

II-24  ,

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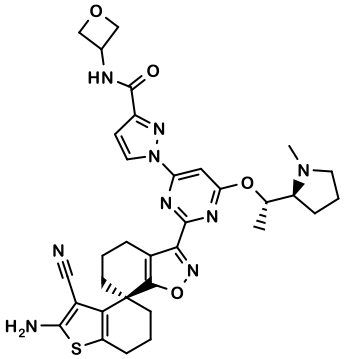

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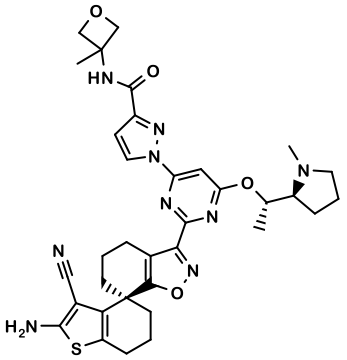

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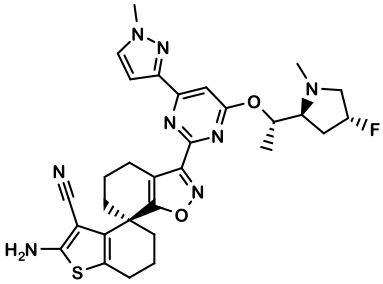

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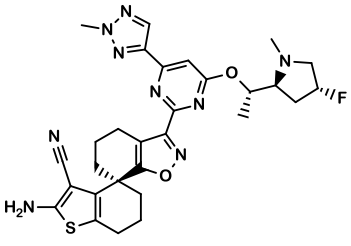

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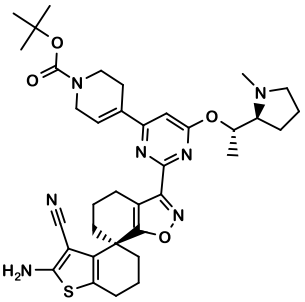

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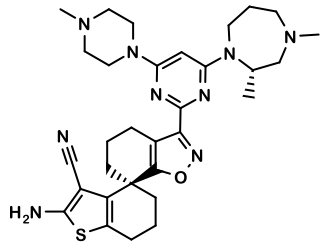

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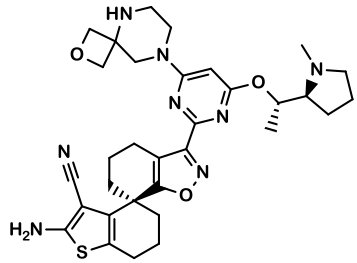

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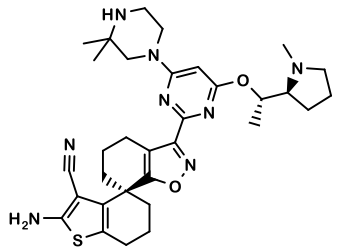

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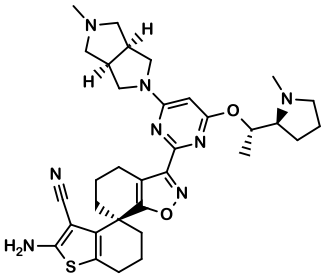
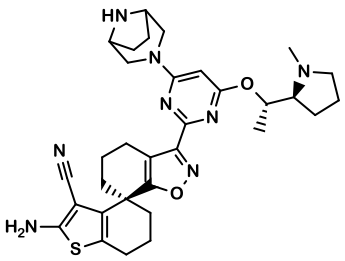
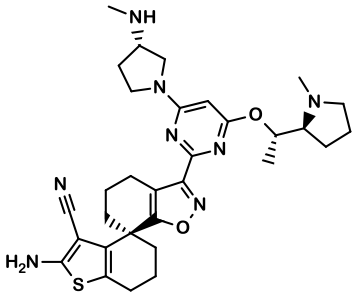
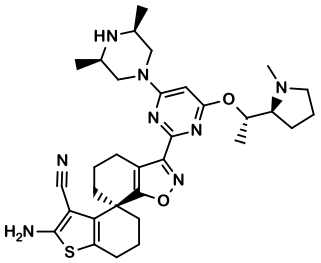
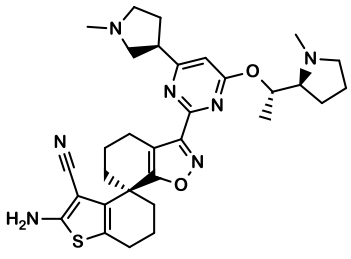
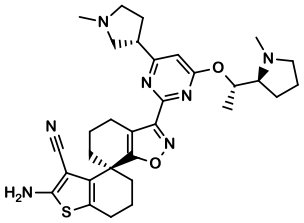
II-33  ,

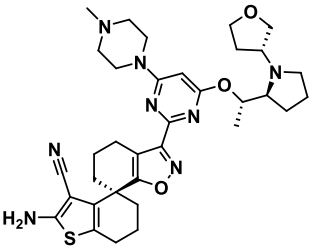
II-34  ,

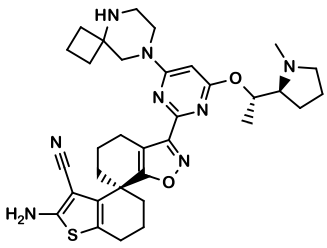
II-35  ,

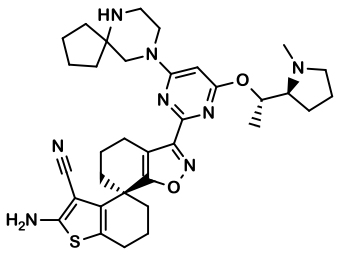
II-36  ,

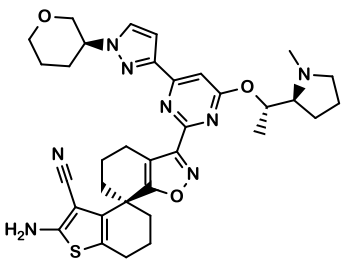
II-37  ,

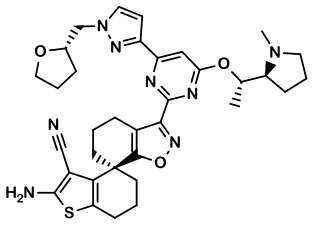
II-38  ,

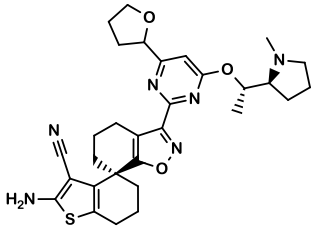
II-39  ,

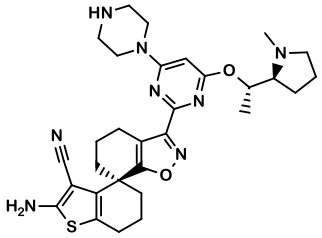
II-40  ,

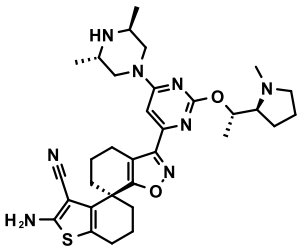
II-41  ,

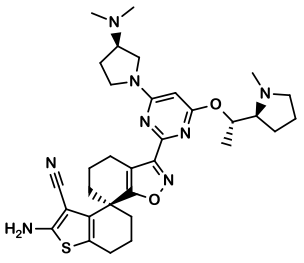
II-42  ,

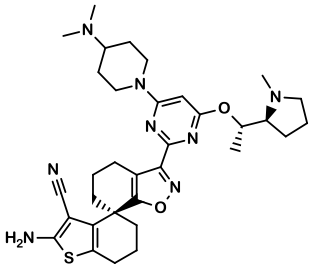
II-43  ,

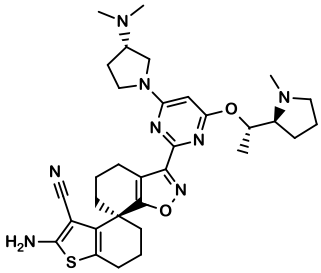
II-44  ,

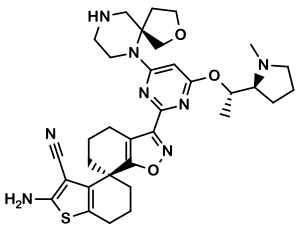
II-45  ,

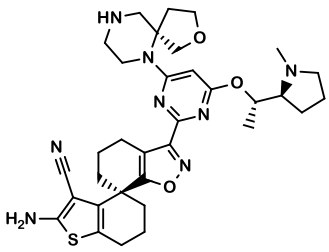
II-46  ,

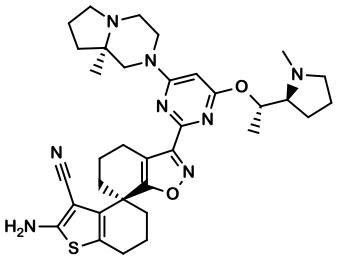
II-47  ,

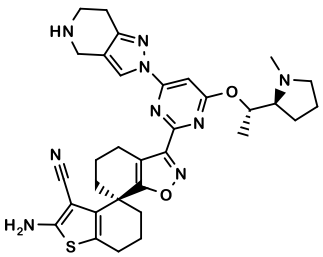
II-48  ,

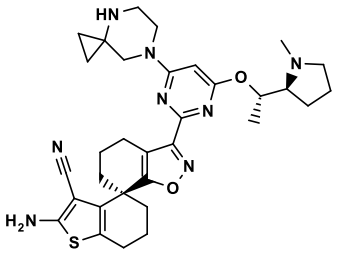
II-49  ,

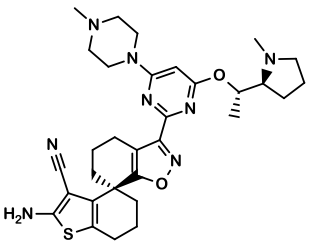
II-50  ,

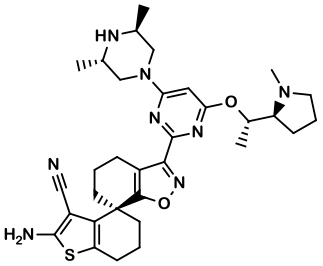
II-51  ,

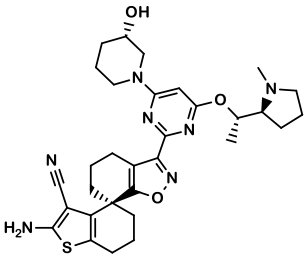
II-52  ,

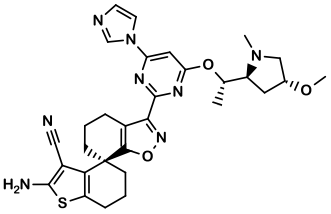
II-53  ,

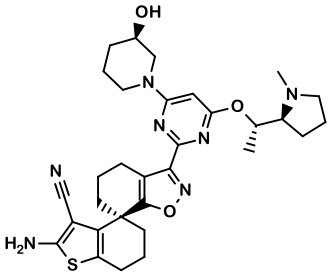
II-54  ,

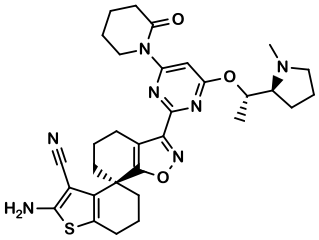
II-55  ,

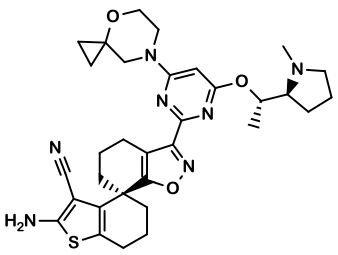
II-56  ,

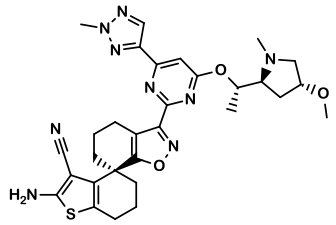
II-57  ,

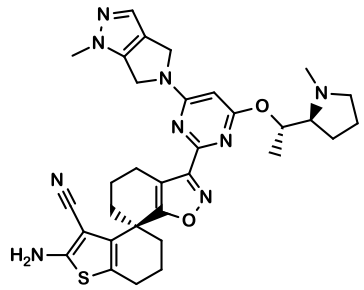
II-58  ,

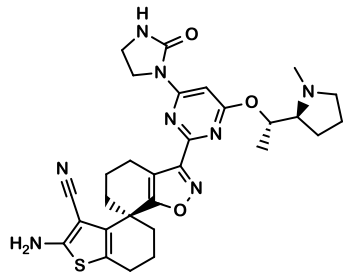
II-59  ,

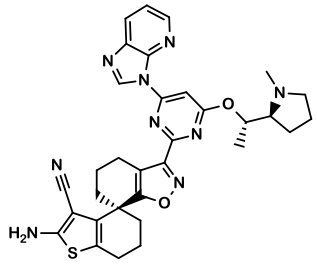
II-60  ,

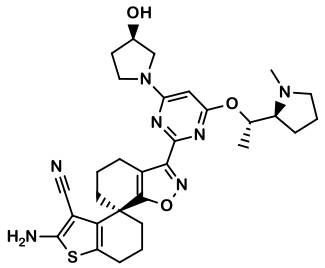
II-61  ,

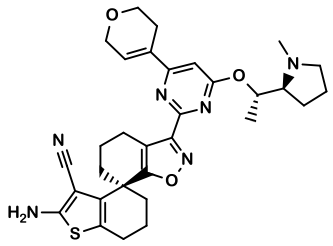
II-62  ,

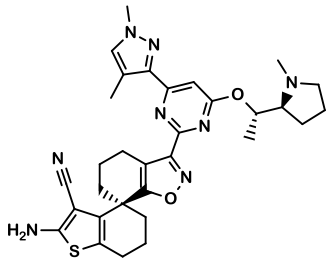
II-63  ,

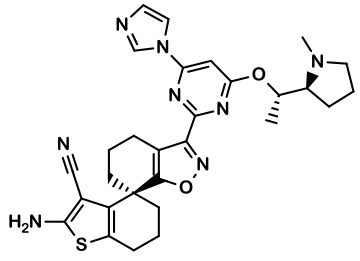
II-64  ,

II-65  ,

II-66  ,

II-67  ,

II-68  ,

II-69  ,

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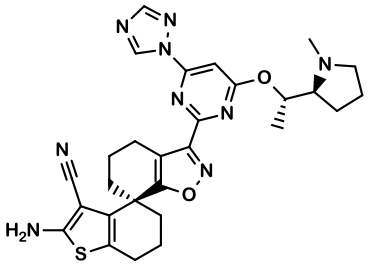

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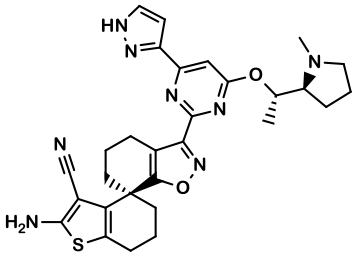

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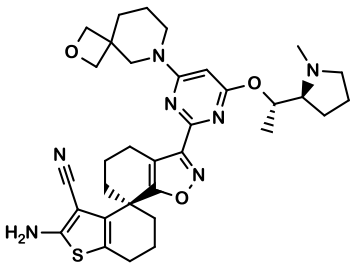

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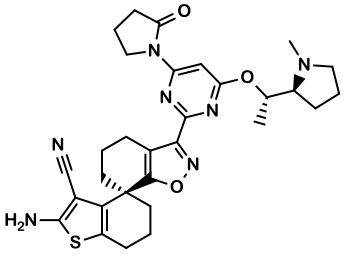

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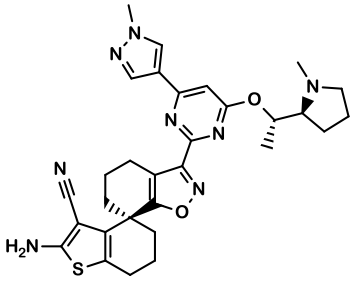

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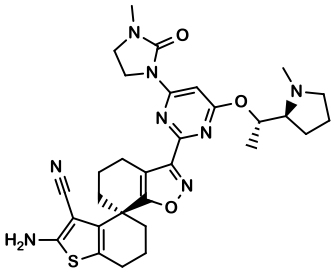

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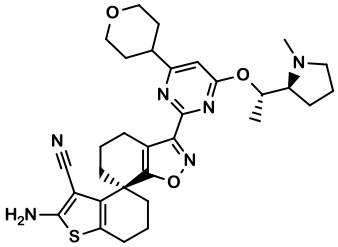

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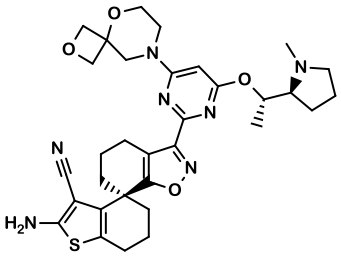

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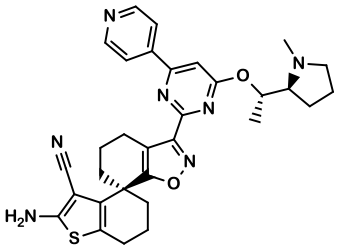

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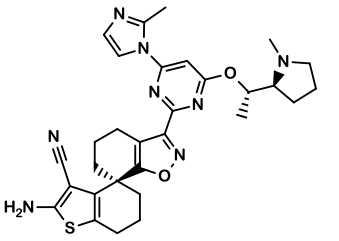

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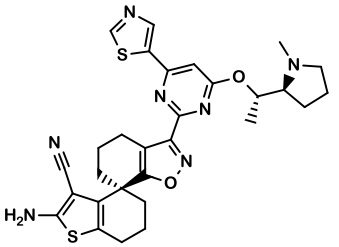

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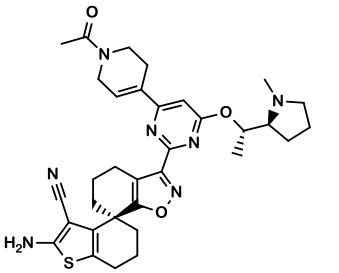

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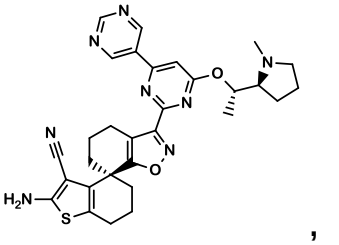

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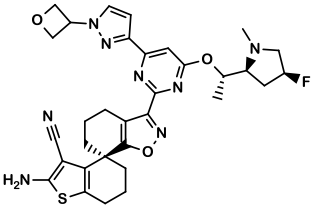

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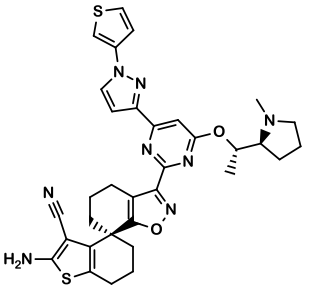

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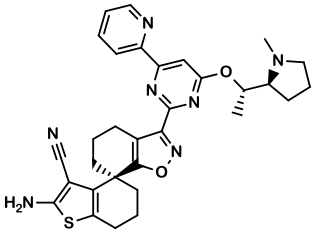

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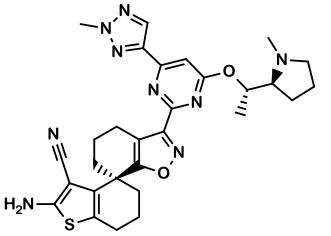

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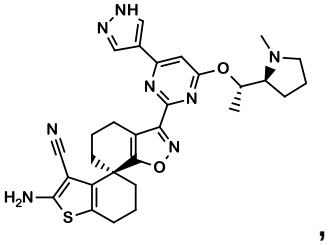

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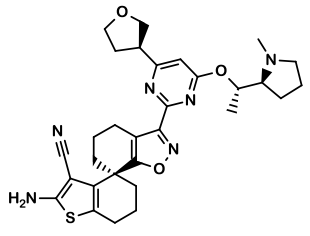
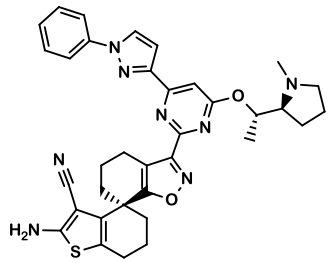
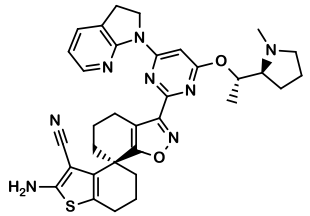
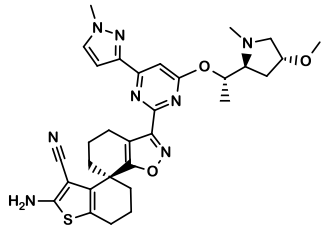
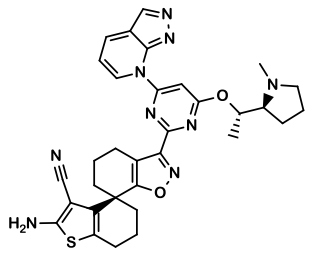
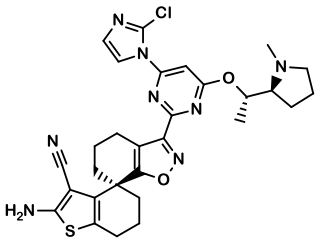
II-88  ,

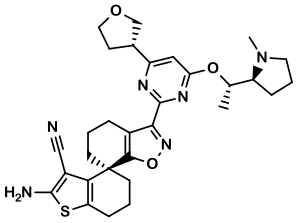
II-89  ,

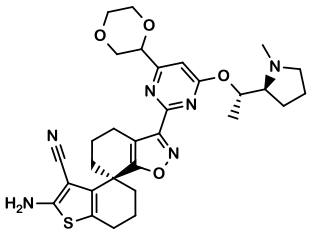
II-90  ,

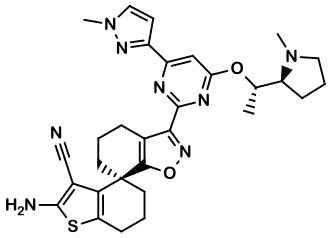
II-91  ,

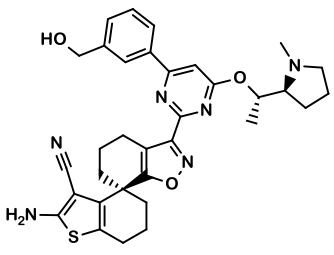
II-92  ,

II-93  ,

II-94  ,

II-95  ,

II-96  ,

II-97  ,

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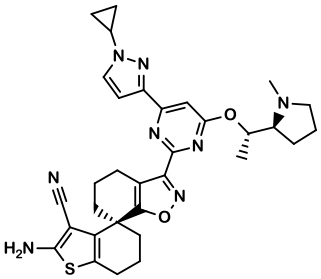

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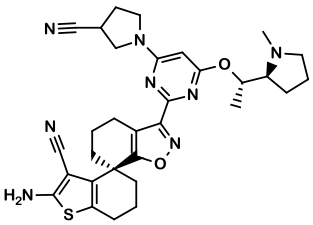

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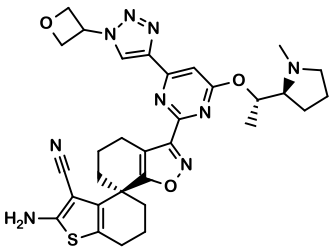

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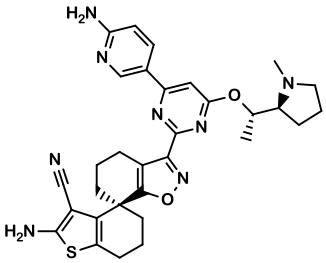

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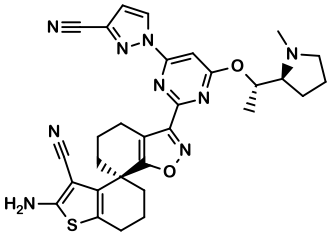

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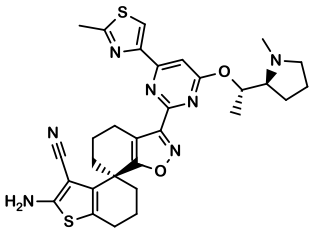

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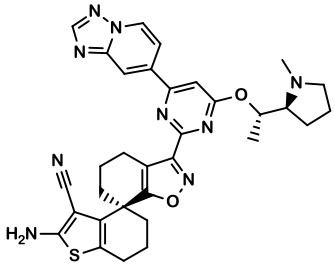

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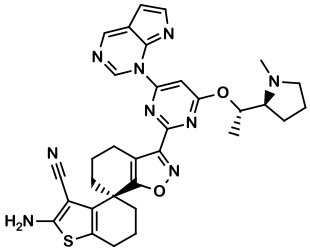

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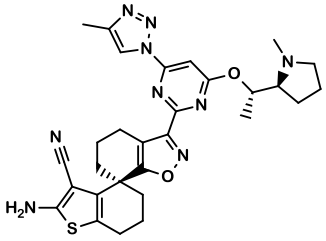

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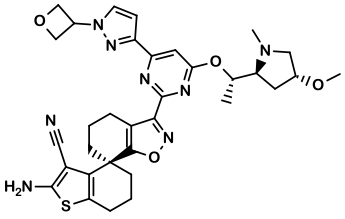

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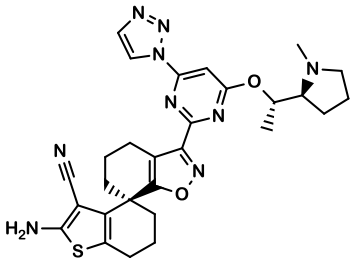

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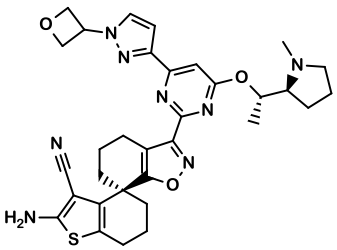

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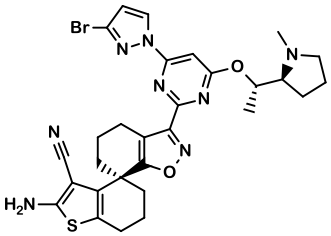

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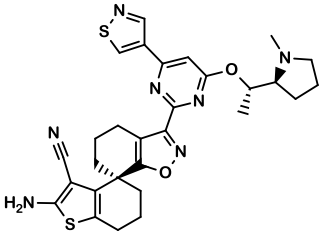

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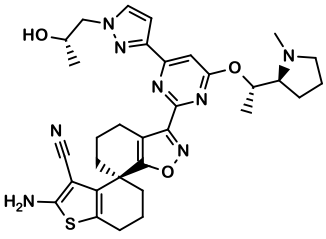

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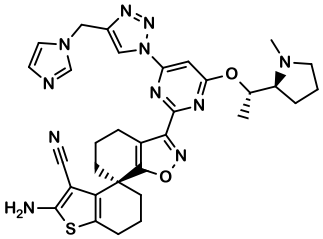

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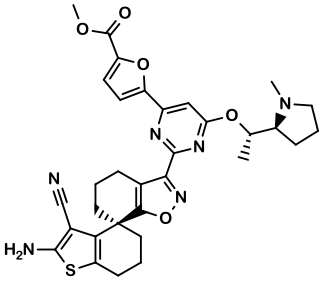

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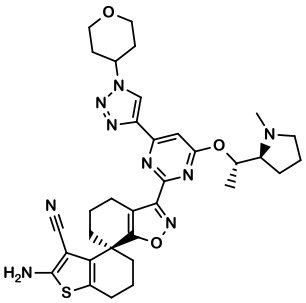

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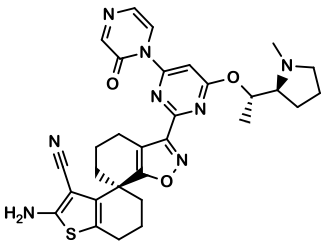

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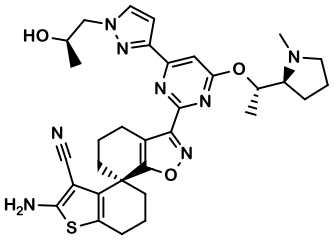

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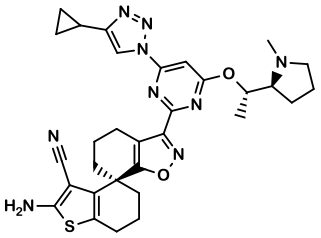

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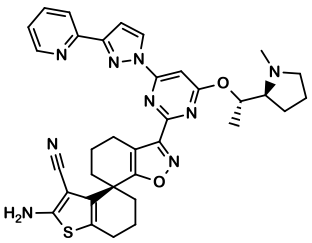

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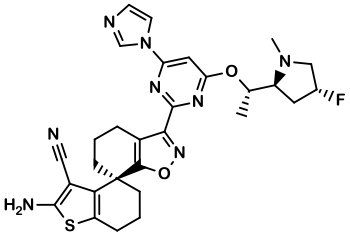

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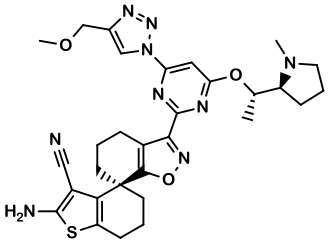

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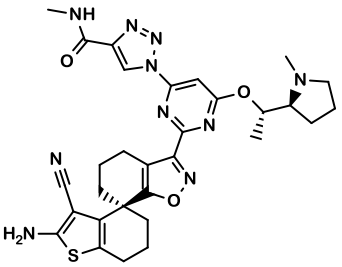

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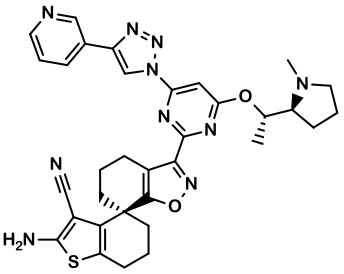

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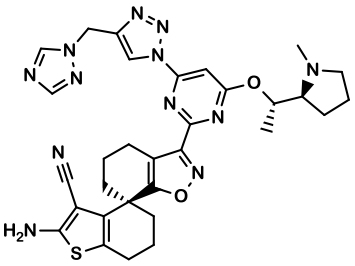

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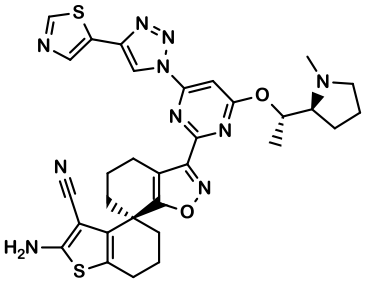

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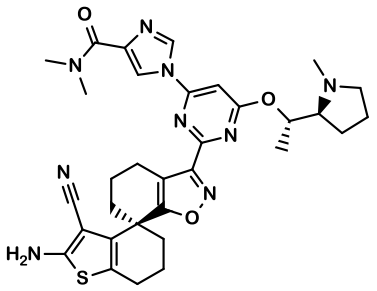

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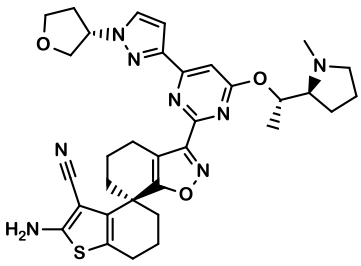

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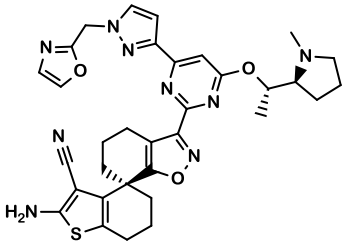

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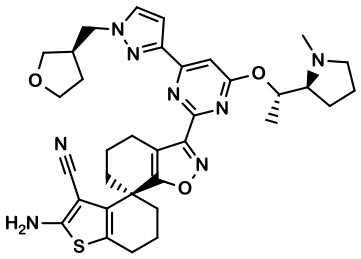

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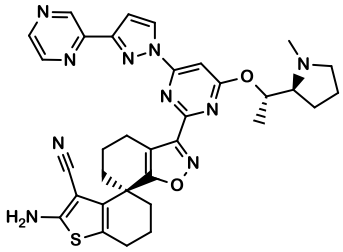

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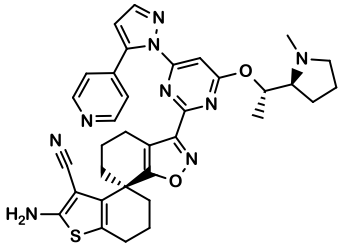

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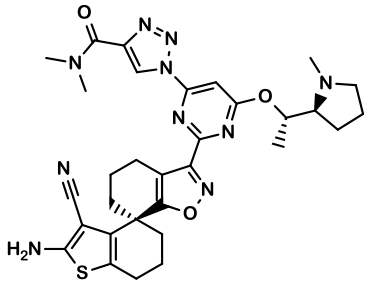

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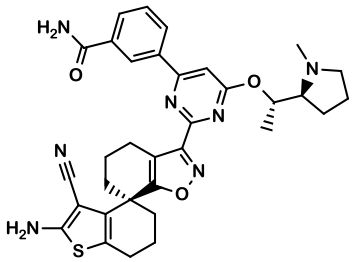

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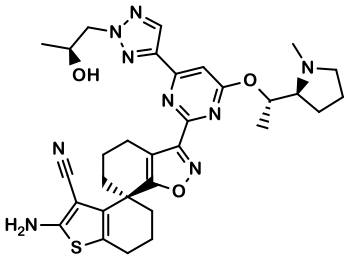

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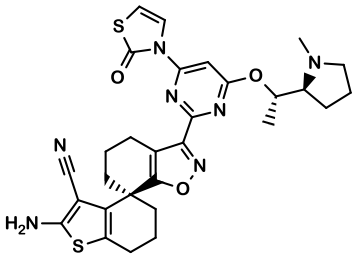

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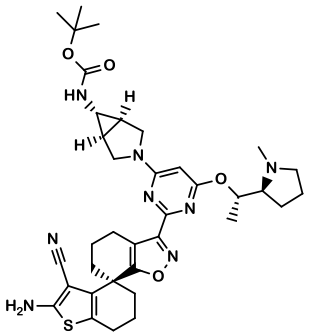

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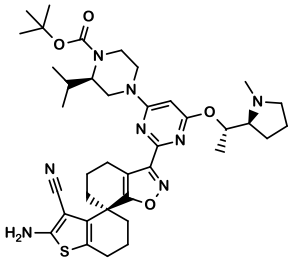

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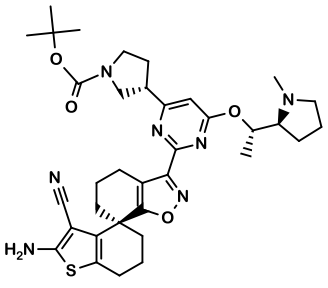

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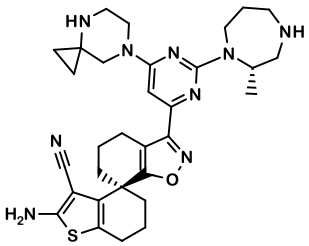

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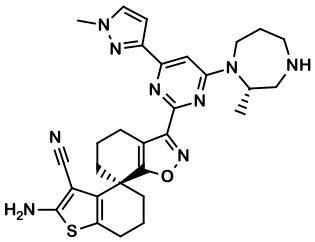

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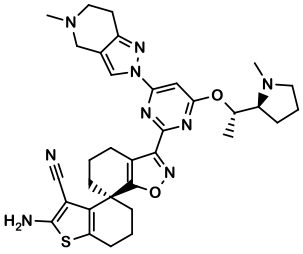

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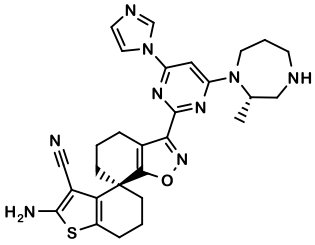

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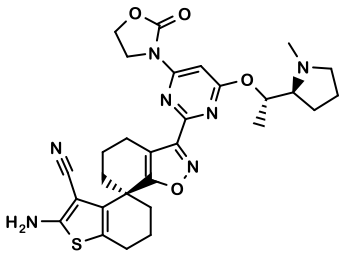

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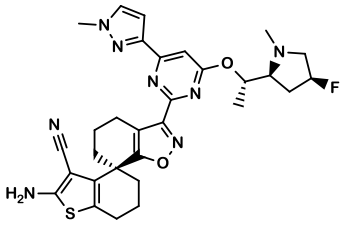

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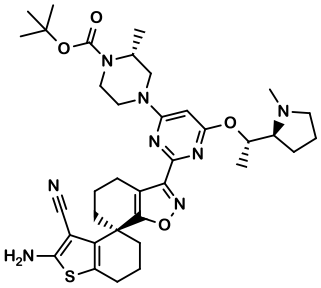

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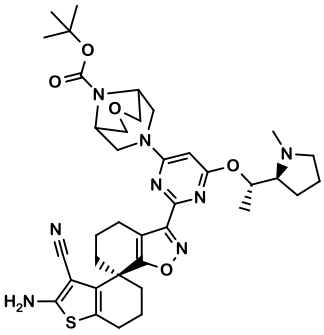

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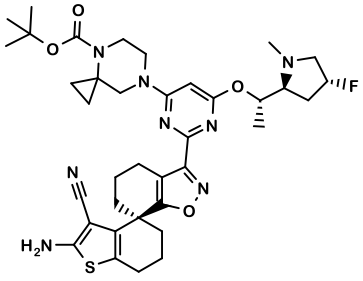

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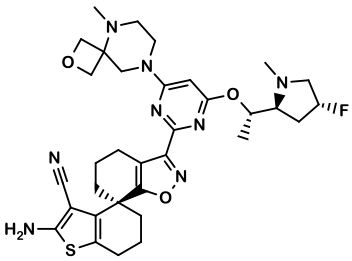

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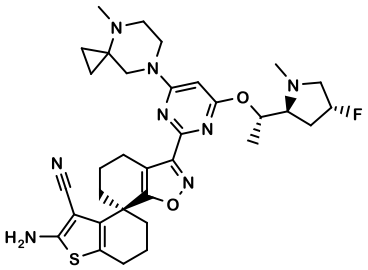

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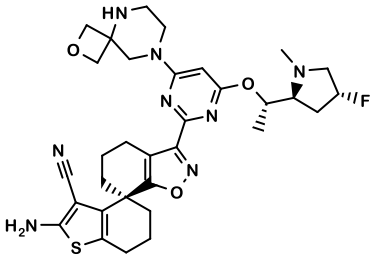

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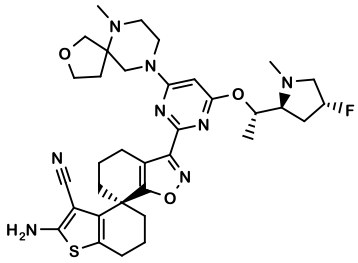
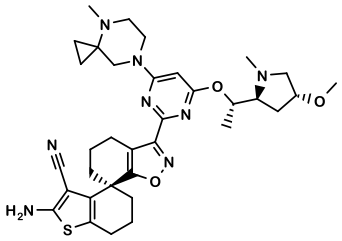
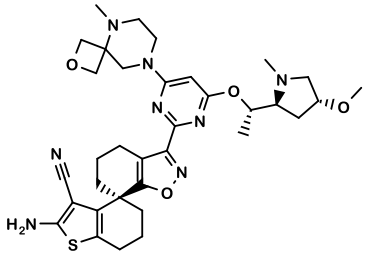
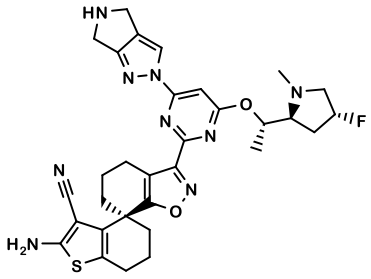
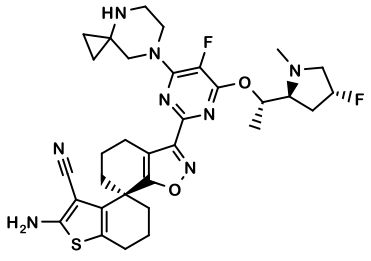
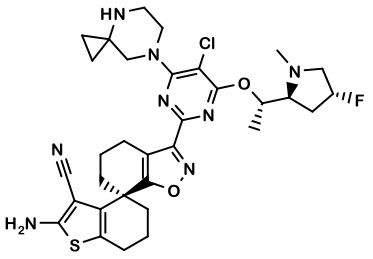
II-151  ,

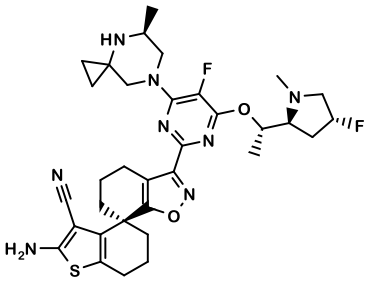
II-152  ,

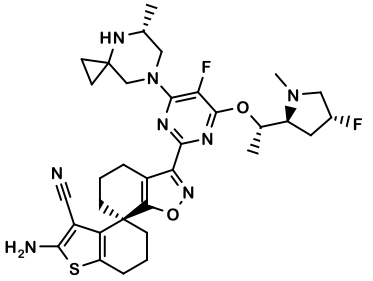
II-153  ,

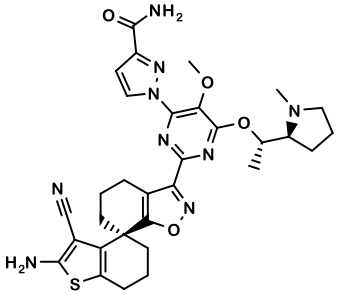
II-154  ,

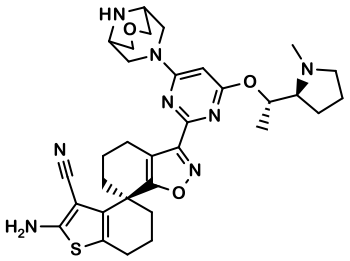
II-155  ,

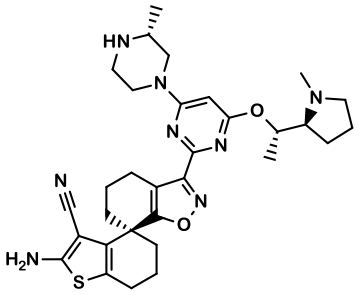
II-156  ,

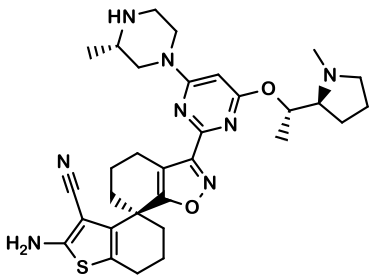
II-157  ,

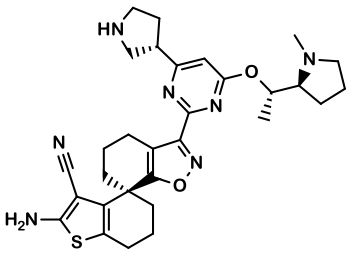
II-158  ,

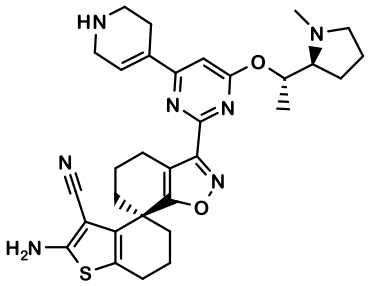
II-159  ,

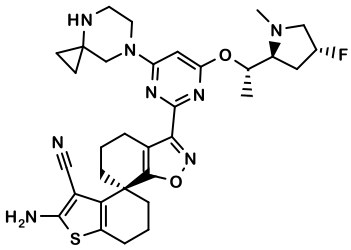
II-160  ,

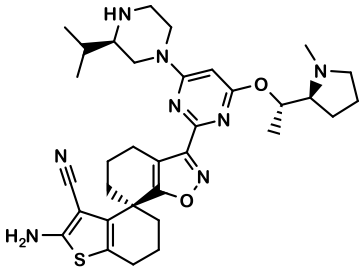
II-161  ,

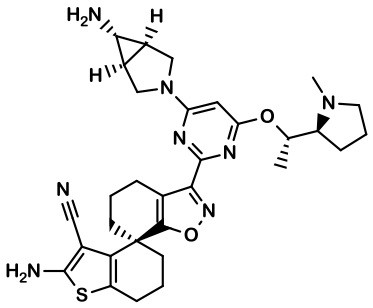
II-162  ,

II-163  ,

II-164  ,

II-165  ,

II-166  ,

II-167  ,

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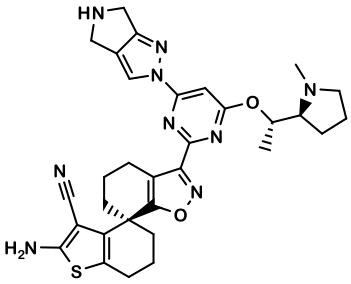

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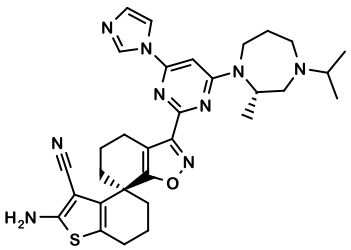

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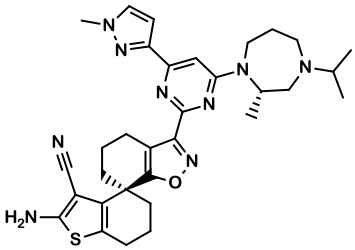

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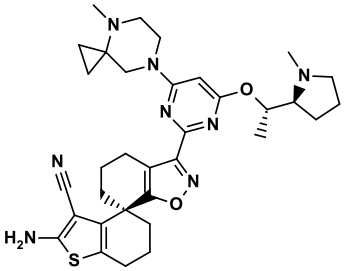

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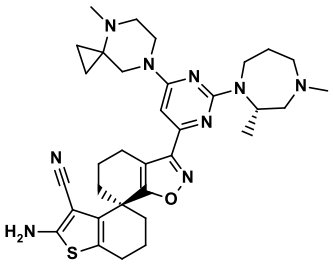

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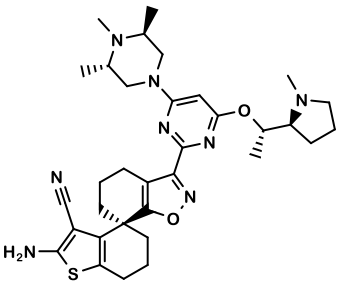

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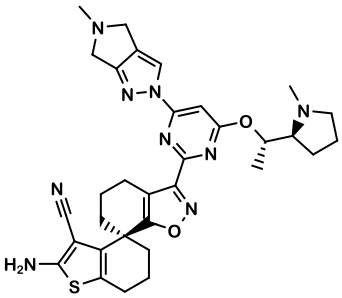

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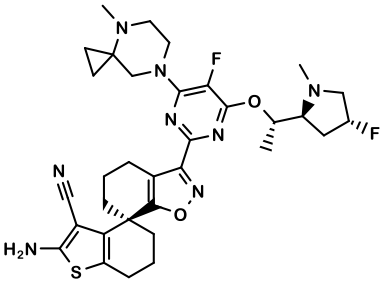

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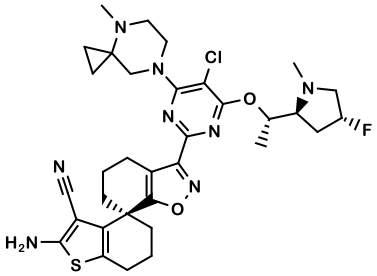
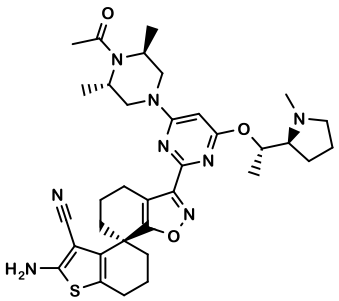
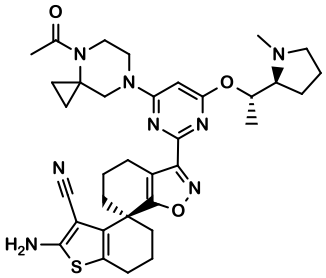
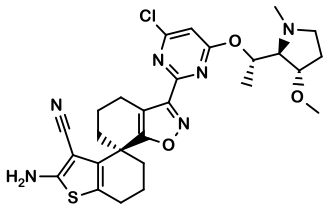
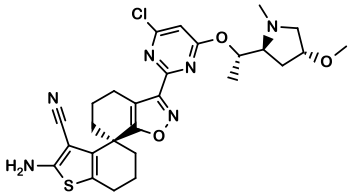
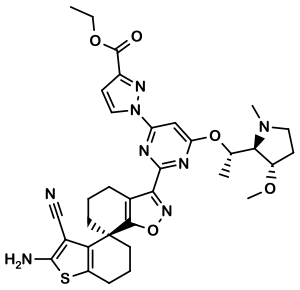
II-176  ,

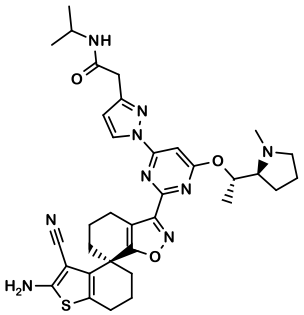
II-177  ,

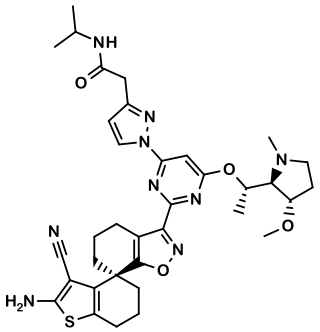
II-178  ,

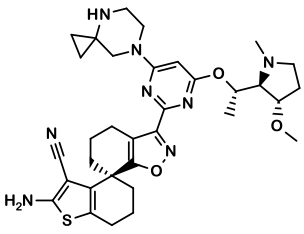
II-179  ,

II-180  ,

II-181  ,

II-182  ,

II-183  ,

II-184  ,

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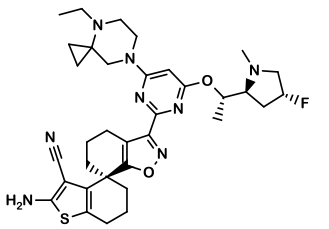

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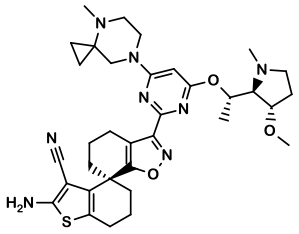

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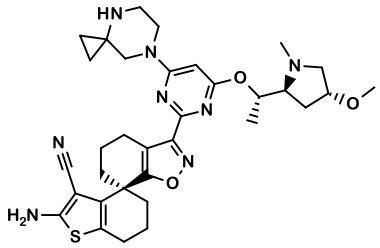

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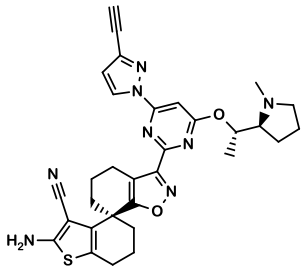

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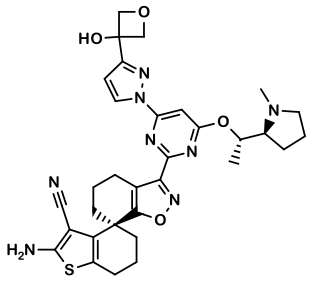

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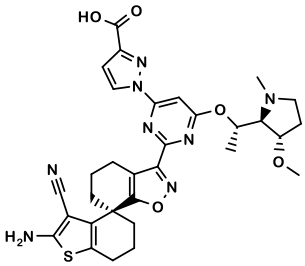

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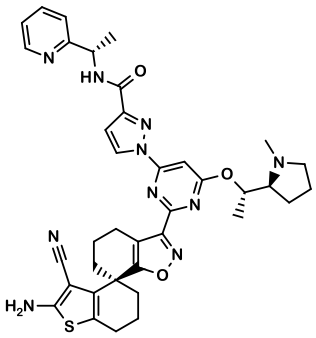

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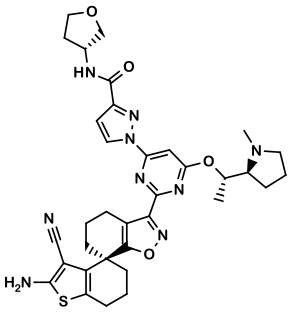

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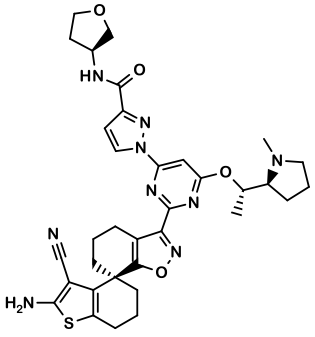

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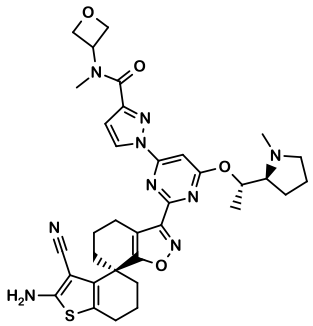

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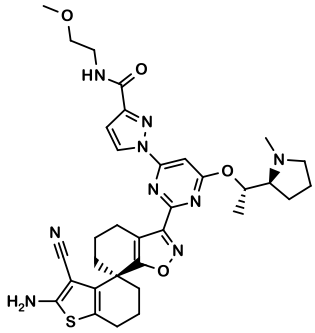

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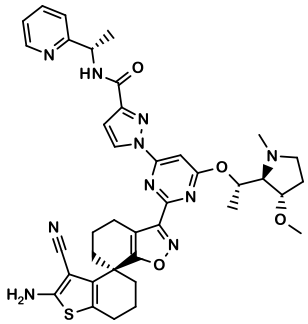

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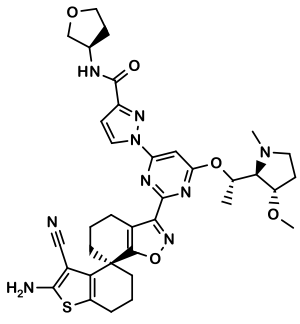

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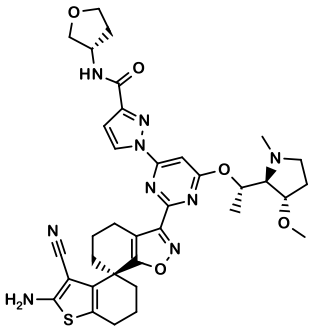

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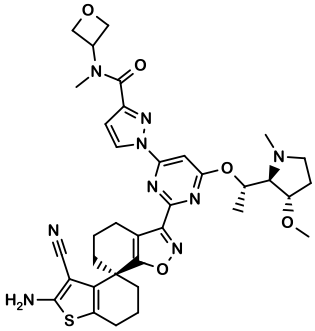

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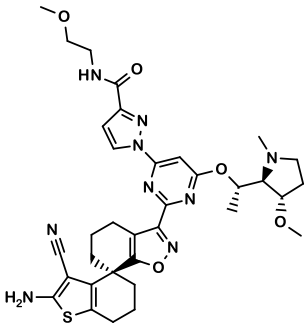

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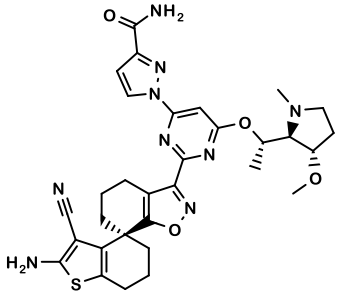

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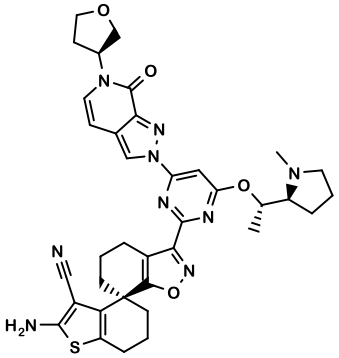
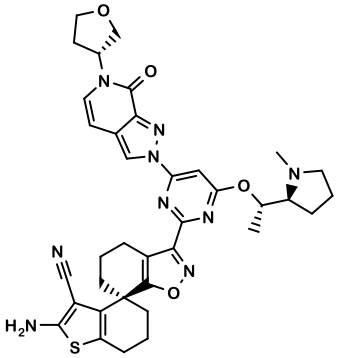
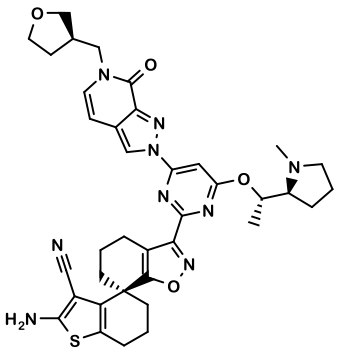
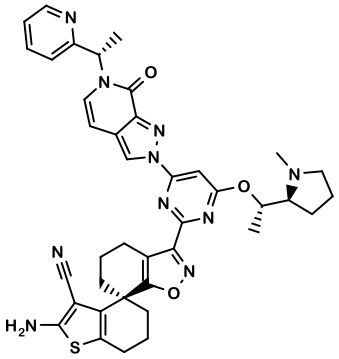
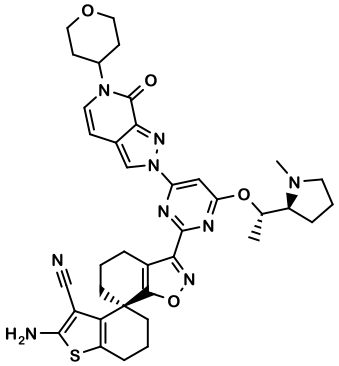
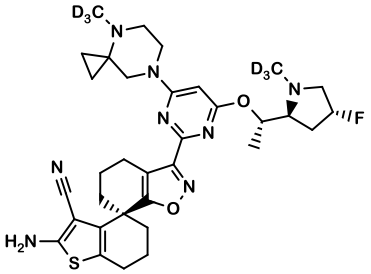
II-202  ,

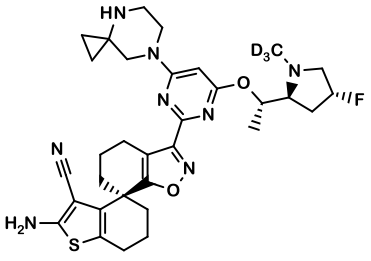
II-203  ,

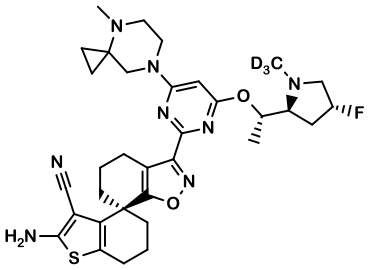
II-204  ,

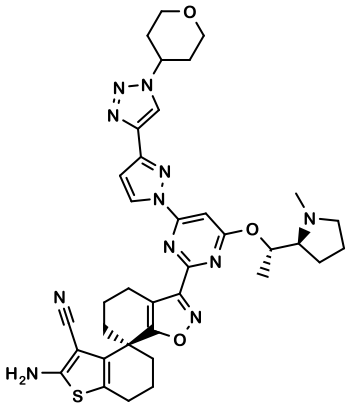
II-205  ,

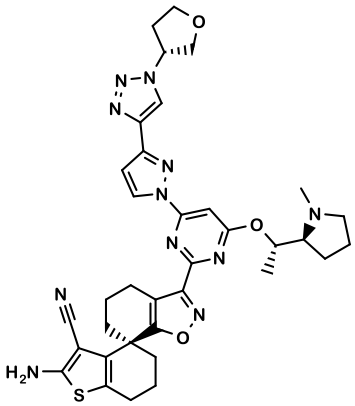
II-206  ,

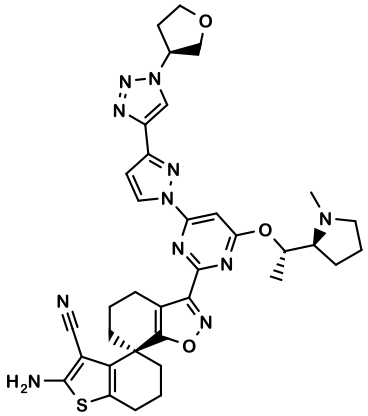
II-207  ,

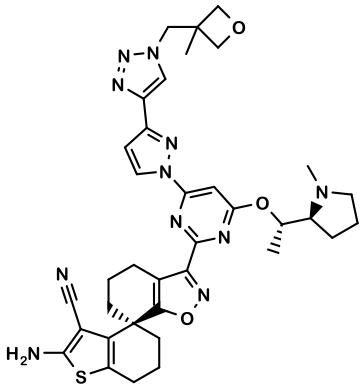
II-208  ,

II-209  ,

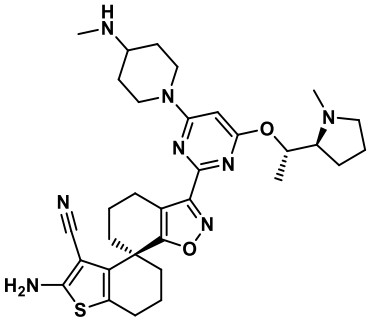
II-210  ,

II-211  ,

II-212  ,

II-213 

and

II-214  .

In another aspect, the present disclosure provides the compound as described herein – or a pharmaceutically acceptable salt thereof – for use as a medicament.

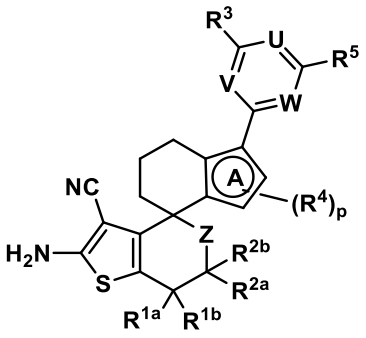
In another aspect, the present disclosure provides the compound as described herein – or a pharmaceutically acceptable salt thereof – for use in the treatment and/or prevention of cancer.

In another aspect, the present disclosure provides use of the compound as described herein – or a pharmaceutically acceptable salt thereof – in the manufacture of a medicament for the treatment and/or prevention of cancer.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein – or a pharmaceutically acceptable salt thereof – and one or more other pharmaceutically acceptable excipient(s).

Claims

1. A compound of the formula **(I)**



(I) , wherein

R^{1a} and **R^{1b}** are both independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

R^{2a} and **R^{2b}** are both independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

and/or, optionally, one of **R^{1a}** or **R^{1b}** and one of **R^{2a}** or **R^{2b}** together with the carbon atoms they are attached form a cyclopropane ring;

Z is $-(CR^{6a}R^{6b})_n-$;

each **R^{6a}** and **R^{6b}** is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

or **R^{6a}** and **R^{6b}** together with the carbon atom they are attached to form a cyclopropane ring;

n is selected from the group consisting of 0, 1 and 2;

R^3 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, $-N_3$, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally and independently substituted with one or more, identical or different **R^7** and/or **R^8**;

each **R^7** is independently selected from the group consisting of -OR^8, -NR^{8}R^8, halogen, -CN, -C(=O)R^8, -C(=O)OR^8, -C(=O)NR^{8}R^8, -NHC(=O)OR^8 and the bivalent substituent =O;

each **R^8** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^9** and/or **R^{10}**;

each **R^9** is independently selected from the group consisting of -OR^{10}, -NR^{10}R^{10} and -C(O)NR^{10}R^{10};

each **R^{10}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with a substituent selected from the group consisting of C_{1-6}alkoxy, C_{3-10}cycloalkyl and 3-11 membered heterocyclyl optionally substituted with C_{1-6}alkyl;

W is nitrogen (-N=) or -CH=;

V is nitrogen (-N=) or -CH=;

U is nitrogen (-N=) or -C(**R^{11}**)=;

R^{11} is selected from hydrogen, halogen and C_{1-4}alkoxy;

ring **A** is a ring selected from the group consisting of pyrrole, furan, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole and triazole;

each **R^4**, if present, is independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, cyano-C_{1-6}alkyl, halogen, -OH, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -CN, C_{3-5}cycloalkyl and 3-5 membered heterocyclyl;

p is selected from the group consisting of 0, 1, 2 and 3;

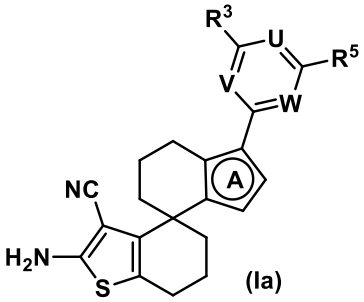
R^5 is a 3-11 membered heterocyclyl optionally substituted with one or more identical or different C_{1-6}alkyl, C_{1-6}alkoxy or a 5-6 membered heterocyclyl, wherein the C_{1-6}alkyl is optionally substituted with cyclopropyl;

or **R^5** is -O-C_{1-6}alkyl substituted with a 3-11 membered heterocyclyl, wherein the 3-11 membered heterocyclyl is optionally substituted with one or more, identical or different **R^{12}**,

each **R^{12}** is selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen and 3-11 membered heterocyclyl;

or a salt thereof.

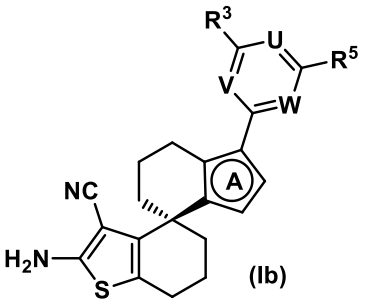
2. A compound of the formula **(Ia)** or its salt



(Ia) , wherein

A, **V**, **U**, **W**, **R^3** and **R^5** are defined as in claim 1.

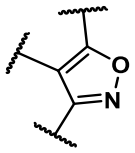
3. A compound of the formula **(Ib)** or its salt

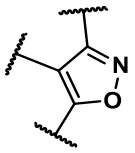


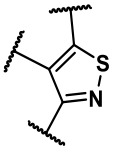
(Ib) , wherein

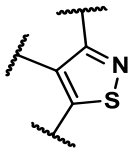
A, **V**, **U**, **W**, **R^3** and **R^5** are defined as in claim 1.

4. The compound or its salt according to anyone of claims 1 to 3, wherein ring **A** is selected from



, 

, 

and 

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5. A compound or its salt according to anyone of claims 1 to 4, wherein

R^3 is selected from the group consisting of 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally and independently substituted with one or more, identical or different **R^7** and/or **R^8**;

each **R^7** is independently selected from the group consisting of -OH, C_{1-6}alkoxy, $-NR^8R^8$, halogen, -CN, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^8$, $-NHC(=O)OR^8$ and the bivalent substituent =O;

each **R^8** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^9** and/or **R^{10}**;

each **R^9** is independently selected from the group consisting of $-OR^{10}$, $-NR^{10}R^{10}$ and $-C(O)NR^{10}R^{10}$;

each **R^{10}** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with a substituent selected from the group consisting of C_{1-6}alkoxy, C_{3-10}cycloalkyl and 3-11 membered heterocyclyl optionally substituted with C_{1-6}alkyl.

6. The compound or its salt according to anyone of claims 1 to 5, wherein

R^3 is selected from the group consisting of 3-11 membered heterocyclyl and 5-10 membered heteroaryl, wherein the 3-11 membered heterocyclyland 5-10 membered heteroaryl are all optionally and independently substituted with one or more, identical or different **R^7** and/or **R^8**;

each **R^7** is independently selected from the group consisting of $-OR^8$, $-NR^8R^8$, halogen, -CN, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^8$, $-NHC(=O)OR^8$ and the bivalent substituent =O;

each **R^8** is independently selected from the group consisting of hydrogen, C_{1-6}alkyl,

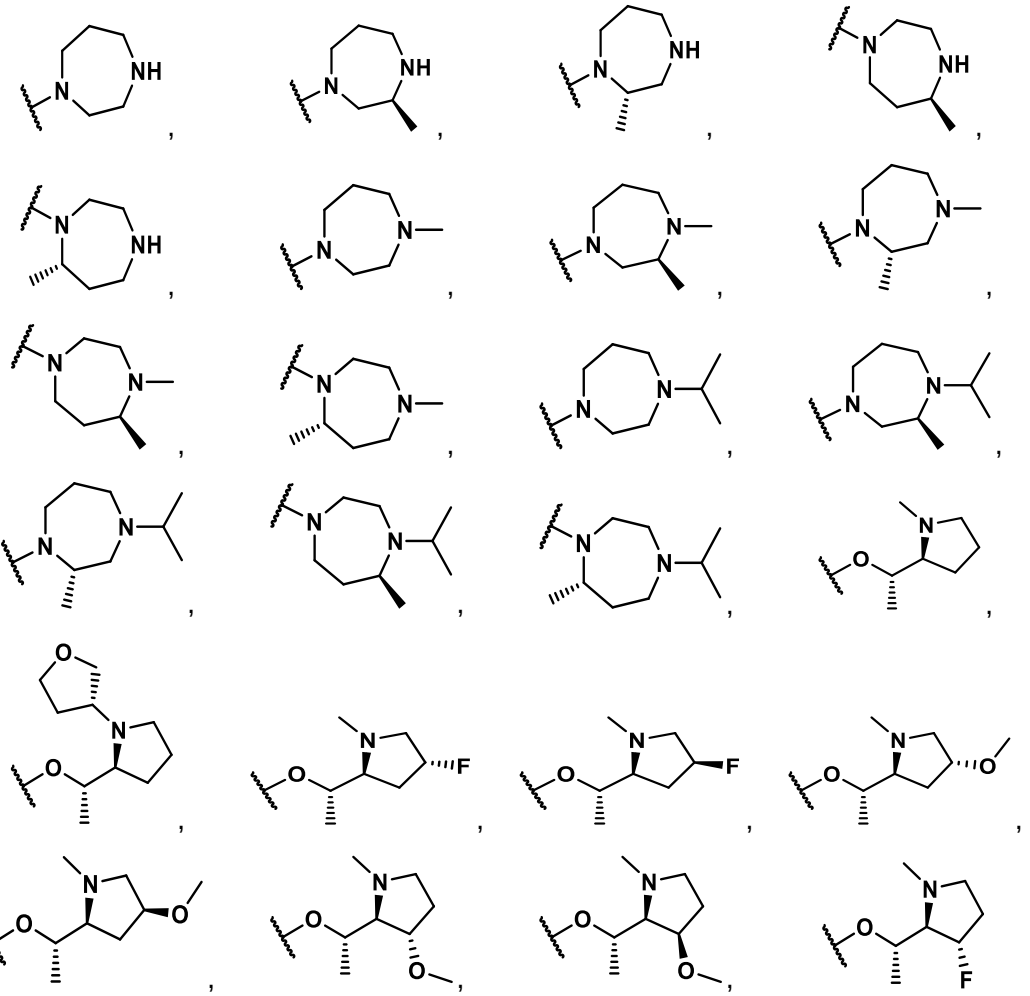
C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R^{9}** and/or **R^{10}**;

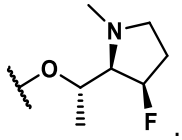
each **R^{9}** is -OH or C_{1-6}alkoxy;

each **R^{10}** is independently selected from the group consisting of C_{1-6}alkyl, 3-11 membered heterocyclyl and 5-10 membered heteroaryl.

7. The compound or its salt according to anyone of claims 1 to 6, wherein

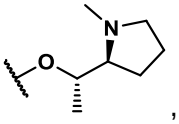
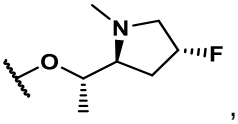
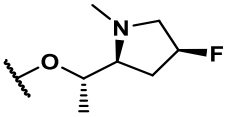
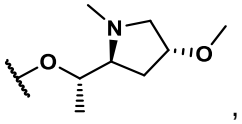
R^{5} is selected from the group consisting of

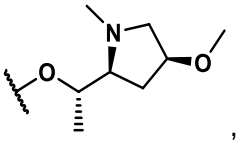
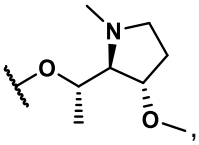
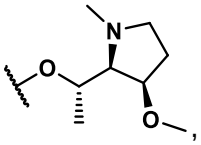
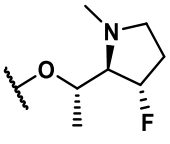


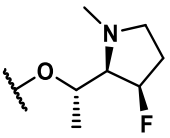
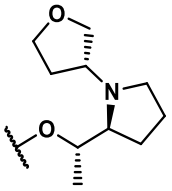
and  .

8. The compound or its salt according to claim 7, wherein

R^5 is selected from the group consisting of

 ,  ,  ,  ,

 ,  ,  ,  ,

 and  .

9. The compound or its salt according to anyone of claims 1 to 8, wherein

W is nitrogen (-N=);

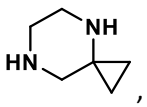
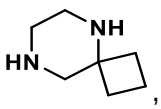
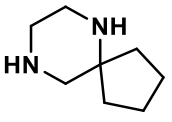
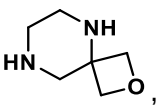
V is nitrogen (-N=)

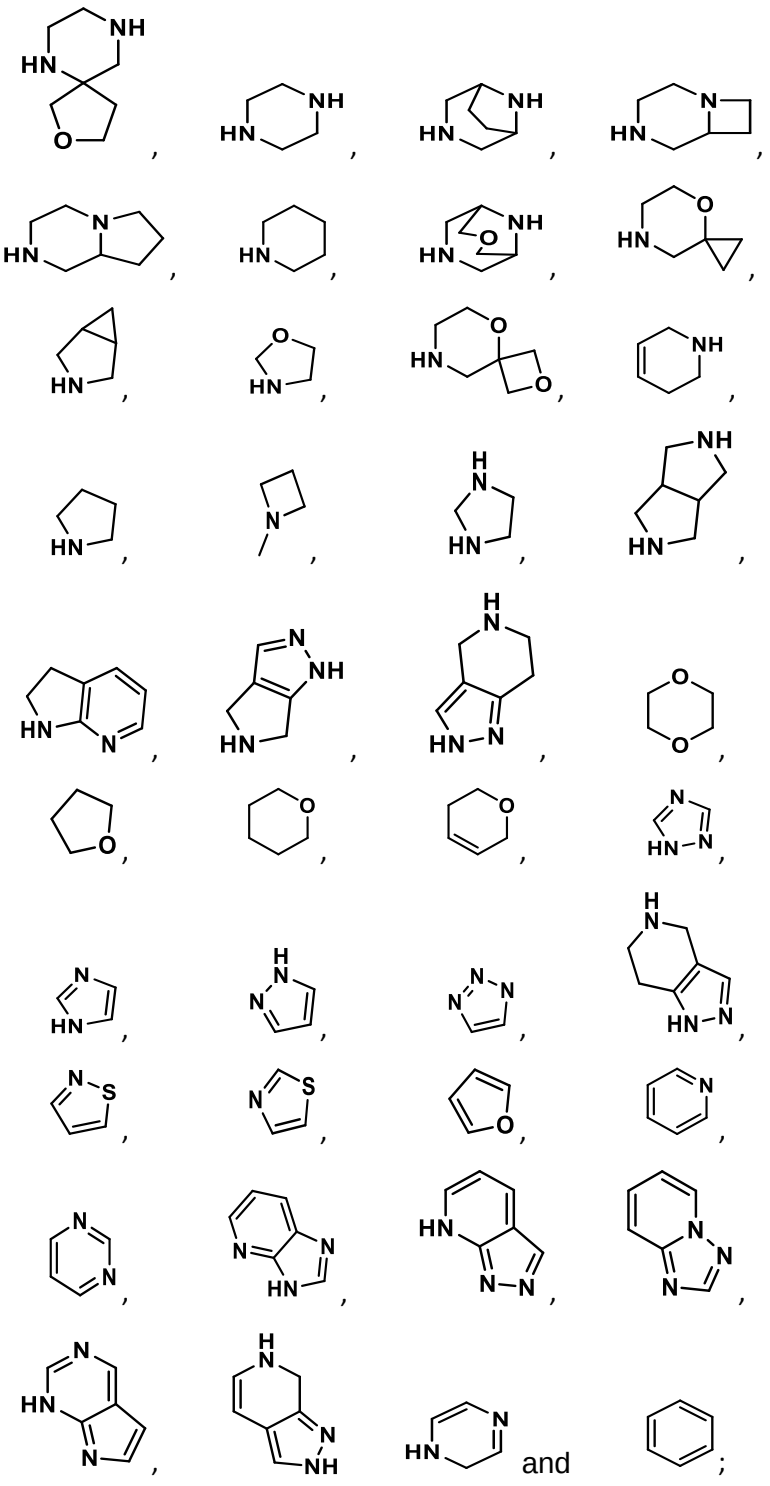
U is =C(**R^{11}**)-;

R^{11} is selected from hydrogen, halogen and C_{1-4}alkoxy.

10. The compound or its salt according to anyone of claims 1 to 9, wherein

R^3 is selected from the group consisting of

 ,  ,  ,  ,



each of which groups is bound to formula **(I)** at any ring position by removal of a hydrogen atom and is optionally and independently substituted with one or more, identical or different

R^{7} and/or **R**^{8}, wherein

each **R**^{7} is independently selected from the group consisting of -OR^{8}, -NR^{8}R^{8}, halogen, -CN, -C(=O)R^{8}, -C(=O)OR^{8}, -C(=O)NR^{8}R^{8}, -NHC(=O)OR^{8} and the bivalent substituent =O;

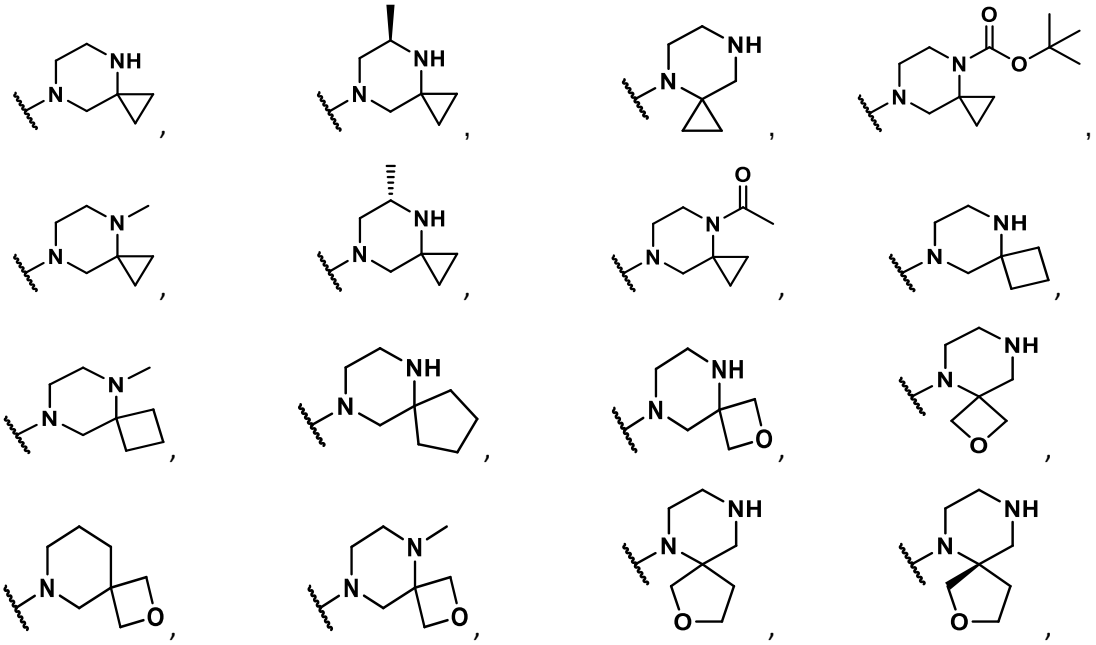
each **R**^{8} is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-11 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted with one or more, identical or different **R**^{9} and/or **R**^{10};

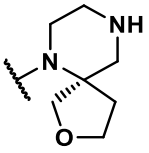
each **R**^{9} is -OH or C_{1-6}alkoxy;

each **R**^{10} is independently selected from the group consisting of C_{1-6}alkyl, 3-11 membered heterocyclyl and 5-10 membered heteroaryl.

11. The compound or its salt according to anyone of claims 1 to 10, wherein

R^{3} is selected from the group consisting of

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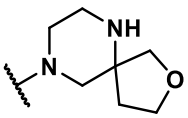
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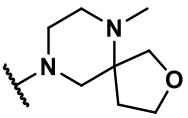
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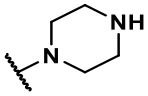
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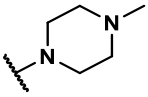
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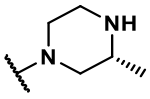
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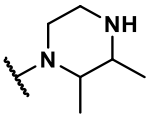
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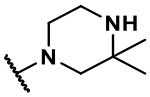
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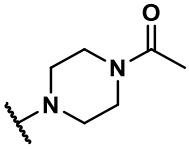
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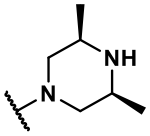
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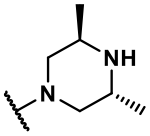
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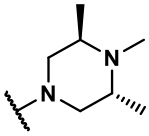
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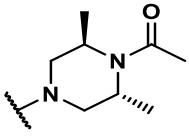
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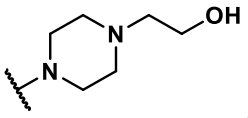
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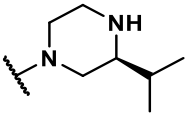
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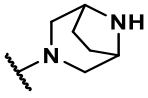
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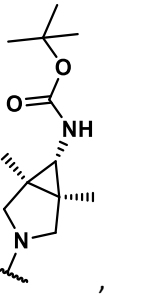
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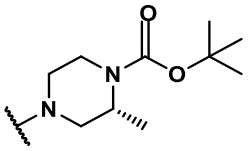
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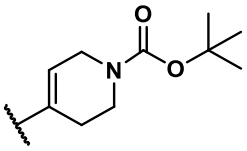
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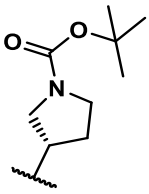
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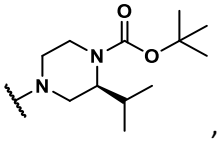
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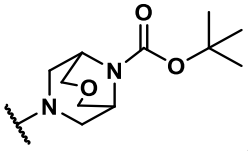
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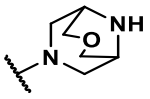
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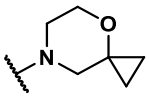
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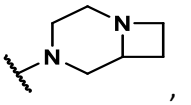
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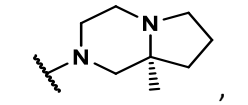
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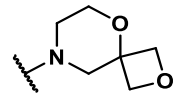
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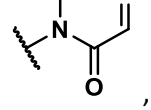
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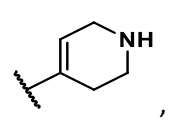
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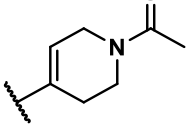
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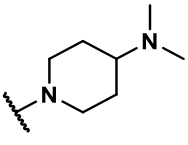
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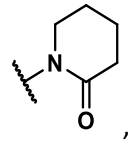
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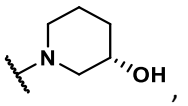
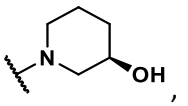
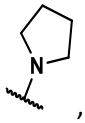
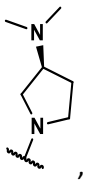
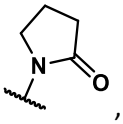
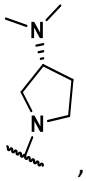
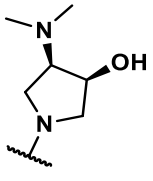
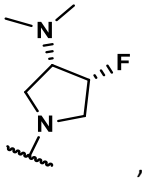
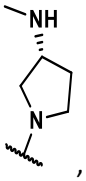
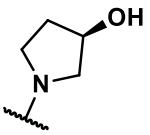

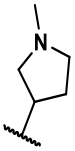
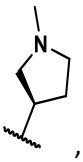
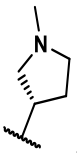
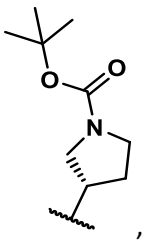
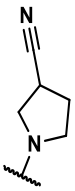
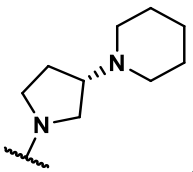
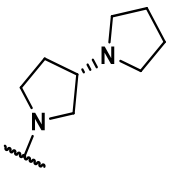
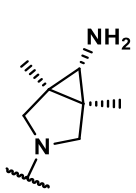
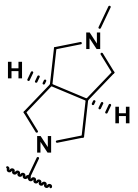
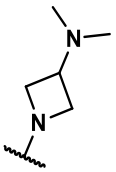
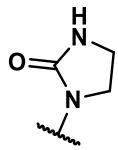
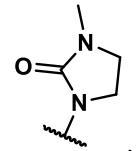
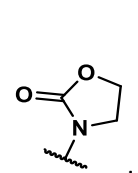
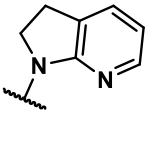
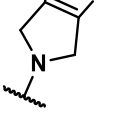
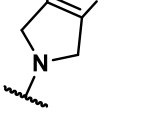
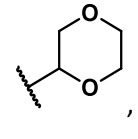
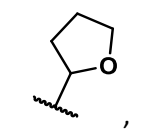
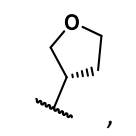
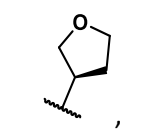
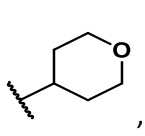

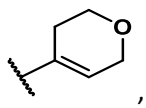
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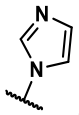
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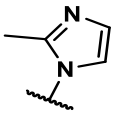
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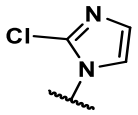
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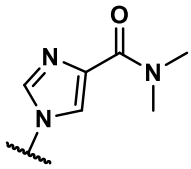
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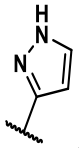
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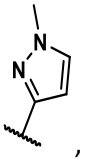
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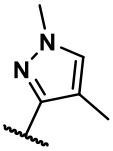
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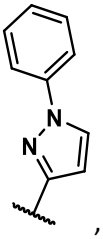
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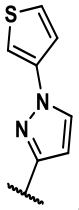
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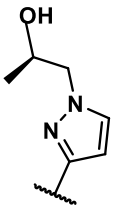
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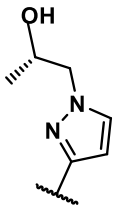
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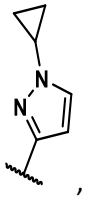
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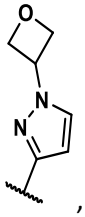
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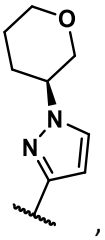
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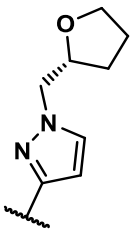
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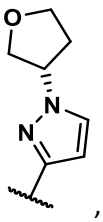
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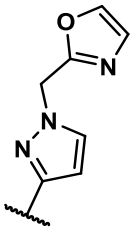
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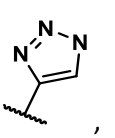
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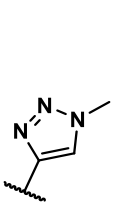
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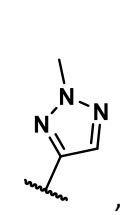
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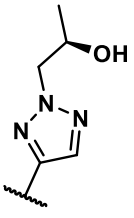
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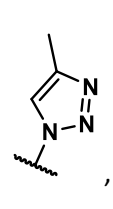
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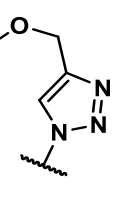
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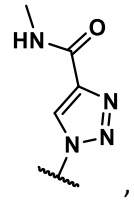
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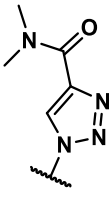
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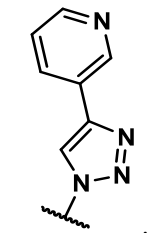
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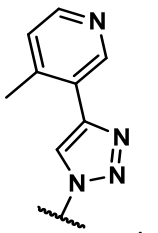
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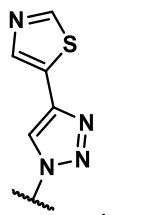
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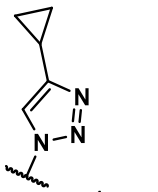
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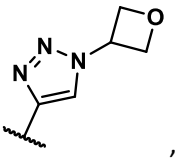
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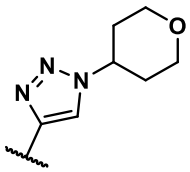
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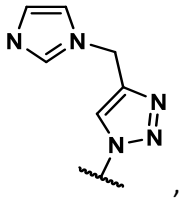
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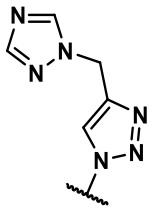
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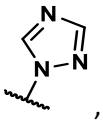
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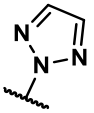
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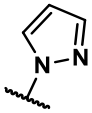
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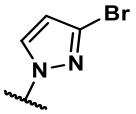
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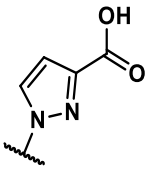
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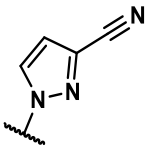
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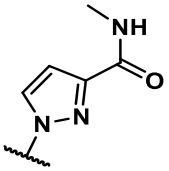
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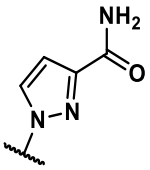
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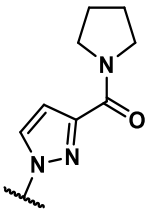
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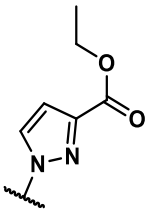
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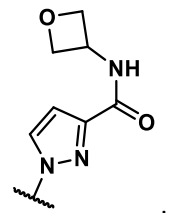
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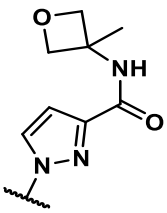
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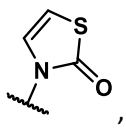
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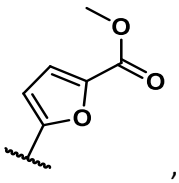
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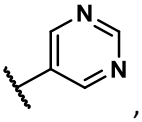
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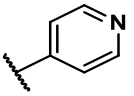
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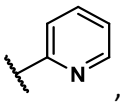
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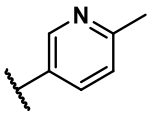
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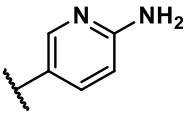
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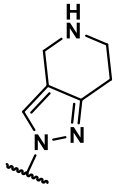
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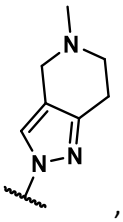
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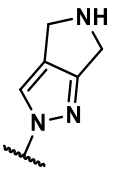
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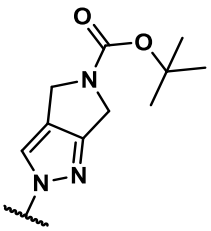
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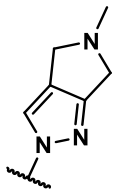
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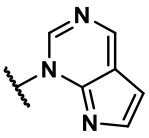
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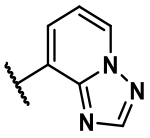
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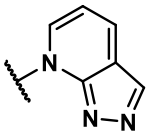
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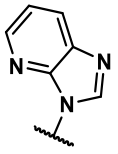
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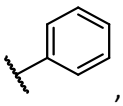
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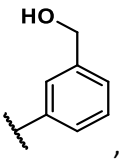
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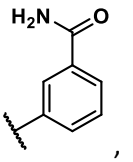
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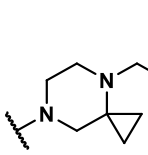
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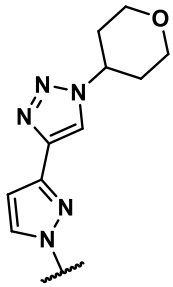
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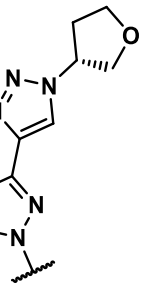
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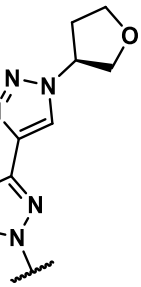
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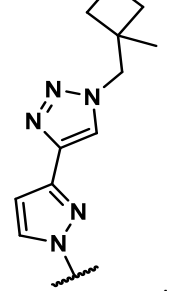
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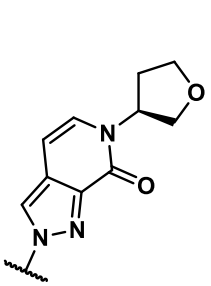
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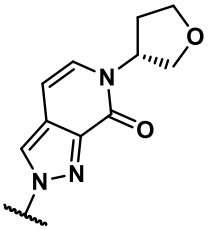
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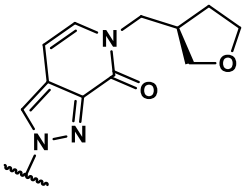
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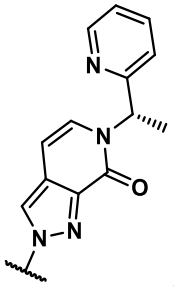
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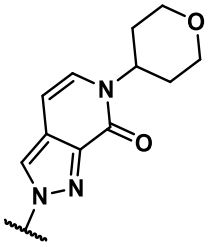
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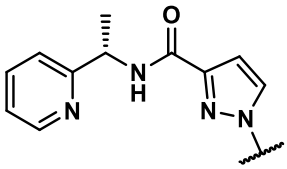
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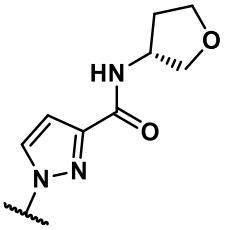
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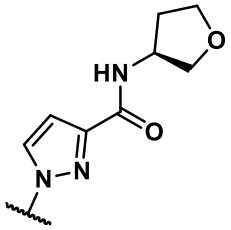
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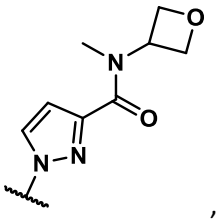
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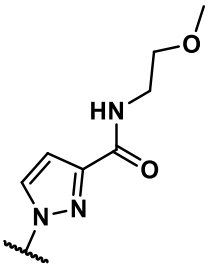
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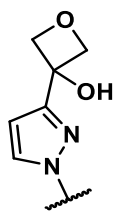
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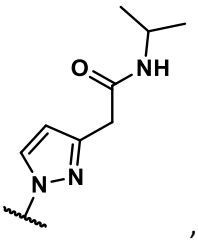
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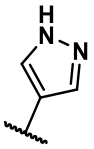
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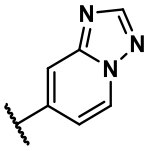
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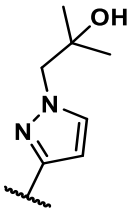
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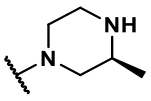
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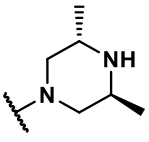
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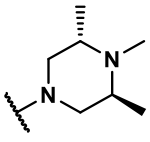
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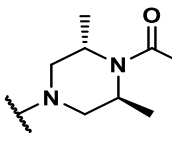
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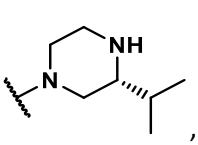
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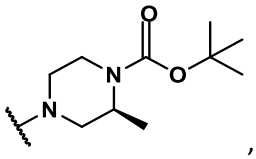
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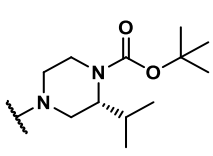
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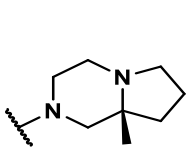
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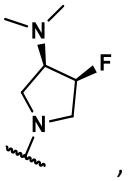
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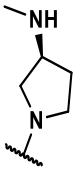

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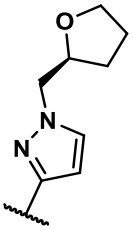

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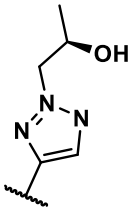

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12. A compound selected from the compounds in the following table, or a salt thereof:

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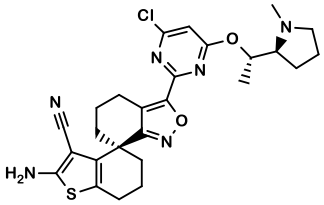

I-1

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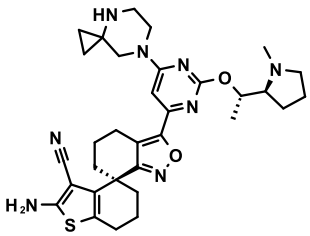
I-2



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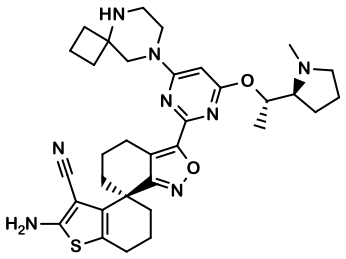

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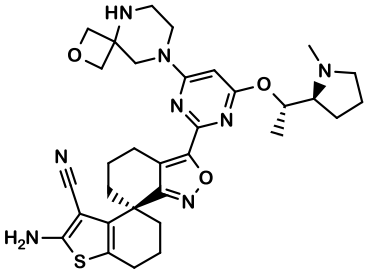

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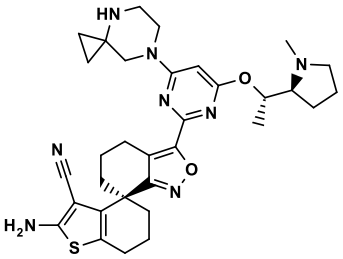

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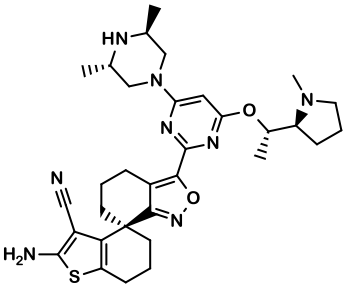

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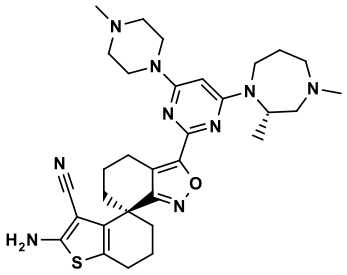
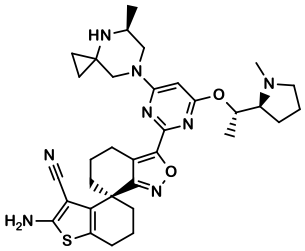
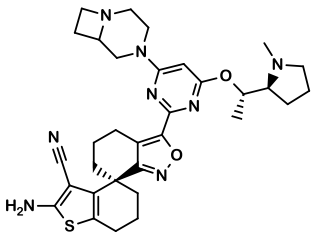
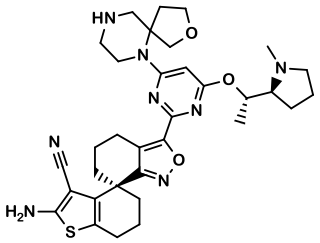
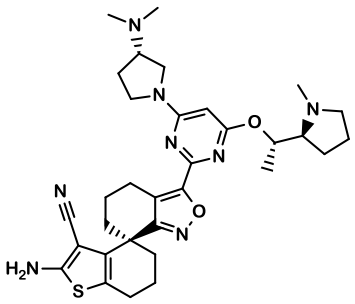
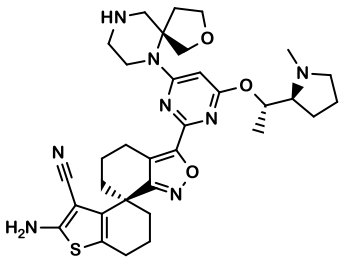
I-7  ,

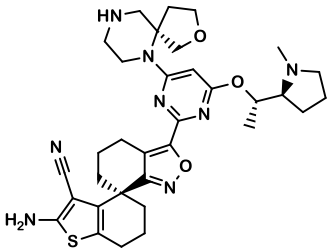
I-8  ,

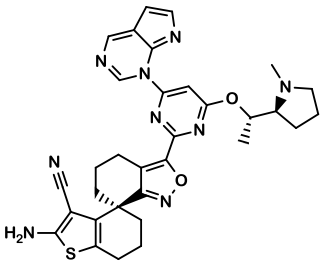
I-9  ,

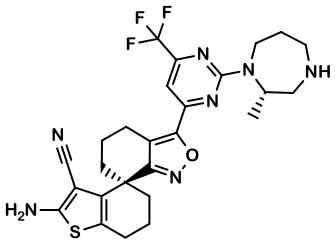
I-10  ,

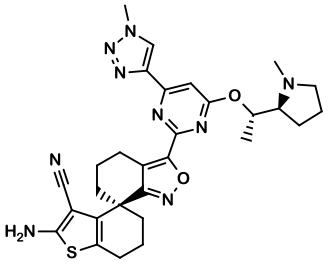
I-11  ,

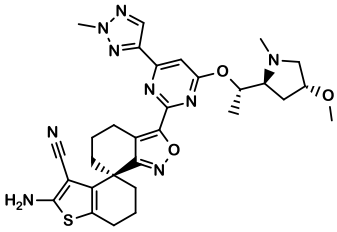
I-12  ,

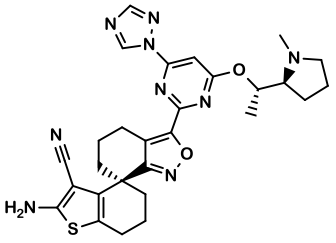
I-13  ,

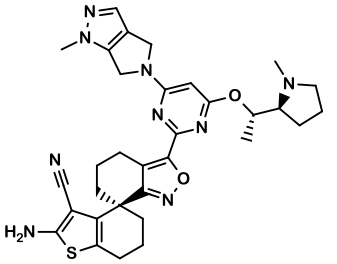
I-14  ,

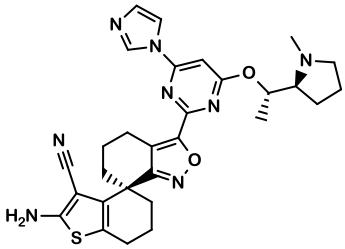
I-15  ,

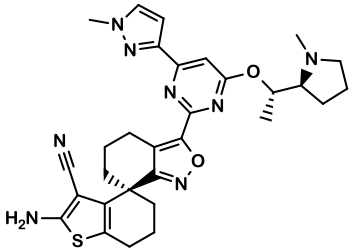
I-16  ,

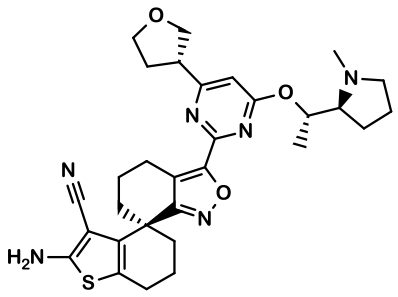
I-17  ,

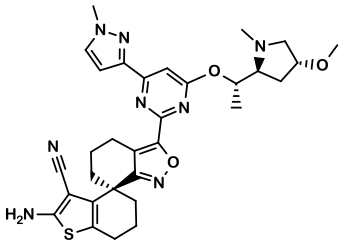
I-18  ,

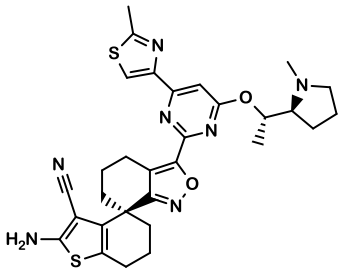
I-19  ,

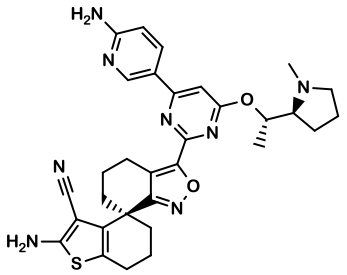
I-20  ,

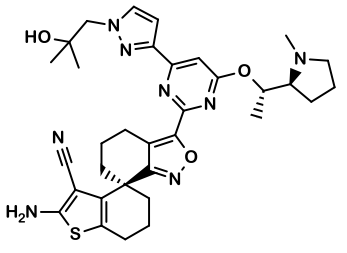
I-21  ,

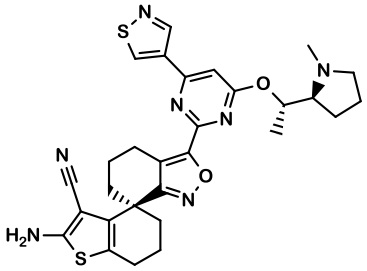
I-22  ,

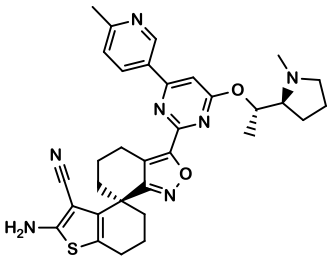
I-23  ,

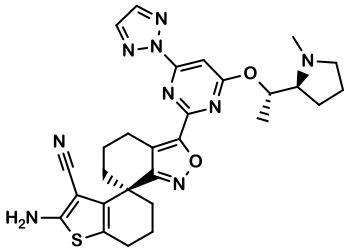
I-24  ,

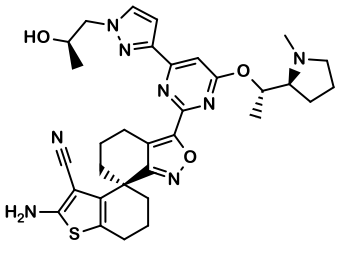
I-25  ,

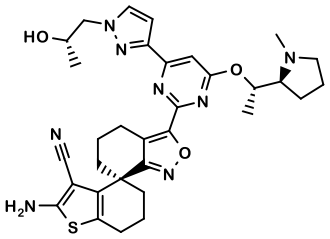
I-26  ,

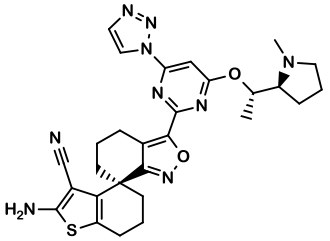
I-27  ,

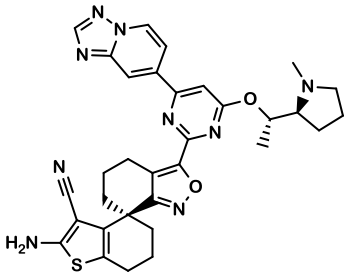
I-28  ,

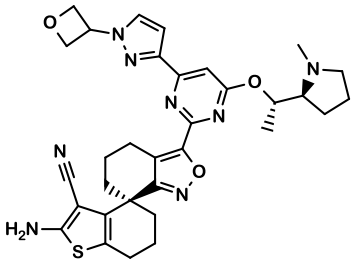
I-29  ,

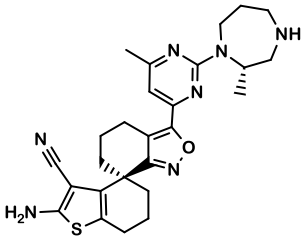
I-30  ,

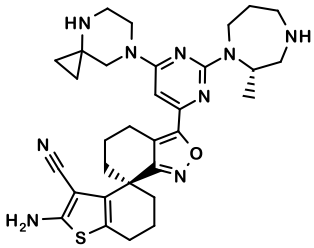
I-31  ,

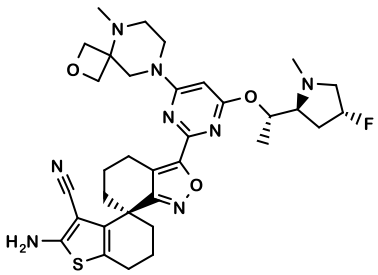
I-32  ,

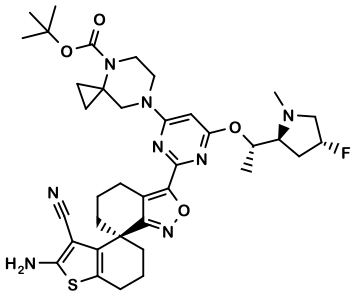
I-33  ,

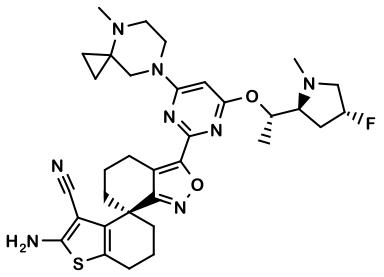
I-34  ,

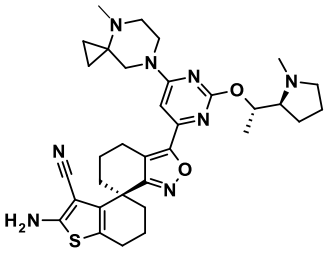
I-35  ,

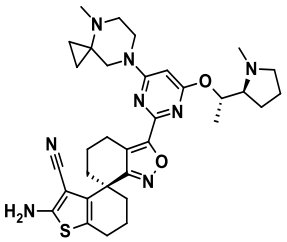
I-36  ,

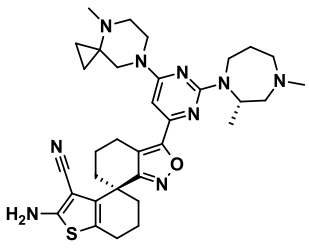
I-37  ,

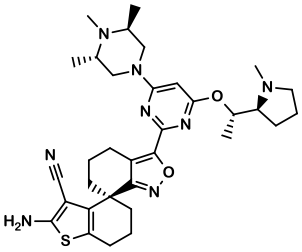
I-38  ,

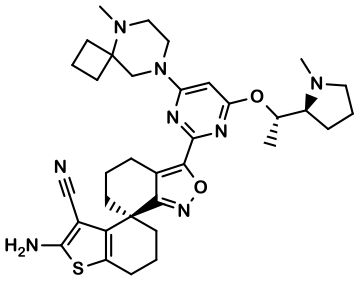
I-39  ,

I-40  ,

I-41  ,

I-42  ,

I-43  ,

I-44 

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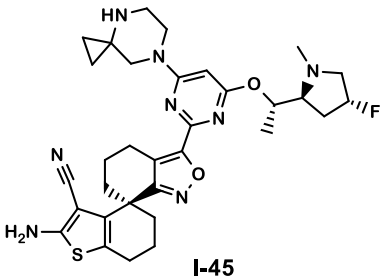
I-45 

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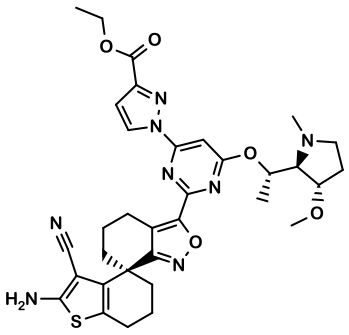

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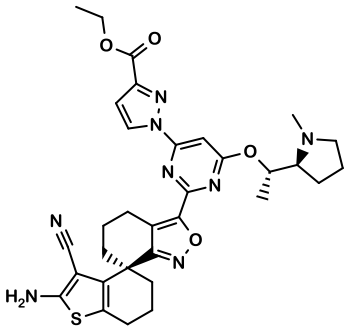

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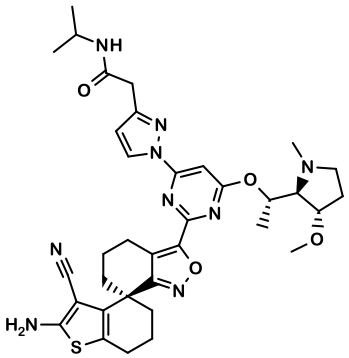

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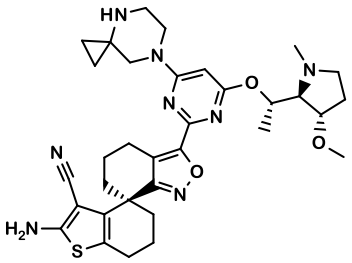

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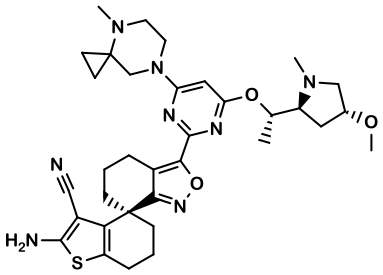

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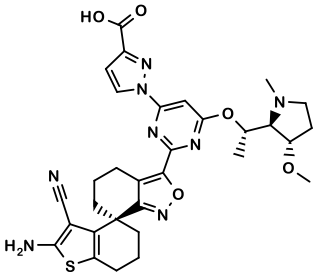

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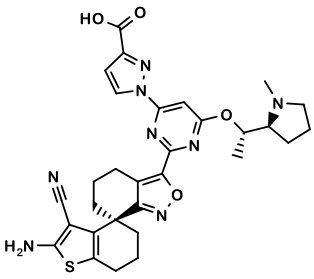

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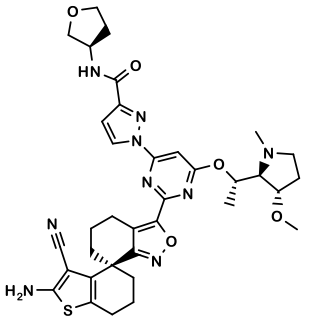
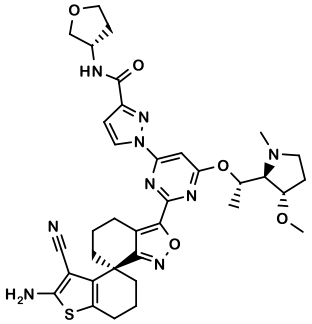
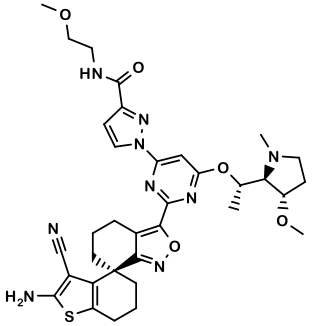
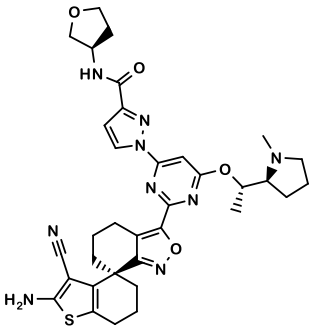
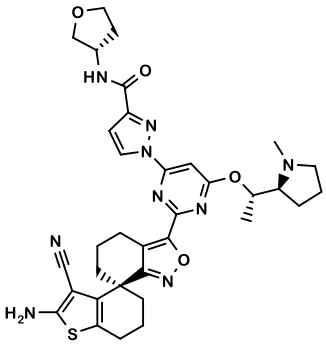
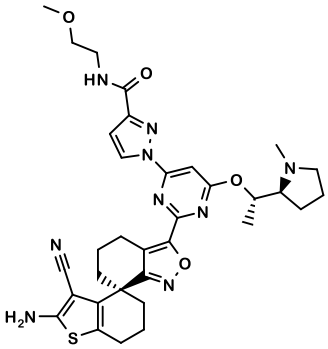
I-53  ,

I-54  ,

I-55  ,

I-56  ,

I-57  ,

I-58  ,

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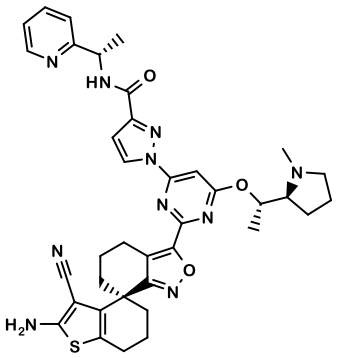

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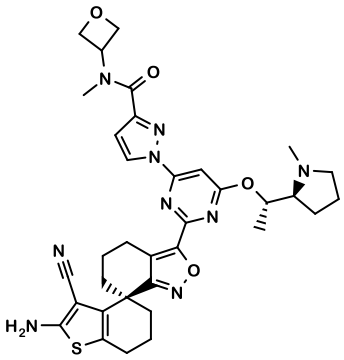

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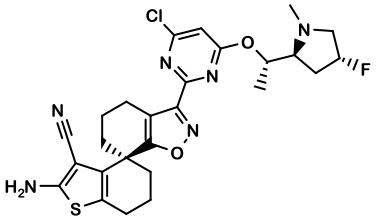

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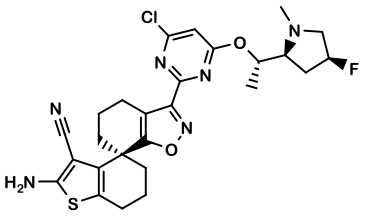

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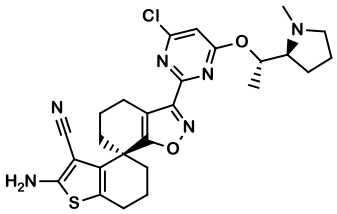

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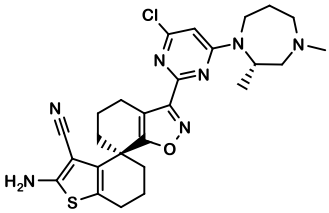

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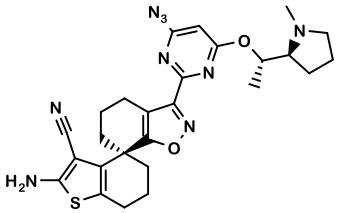

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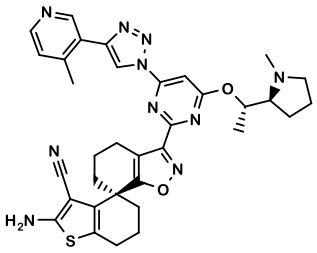

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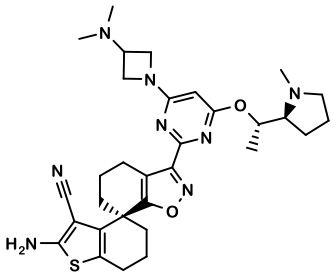
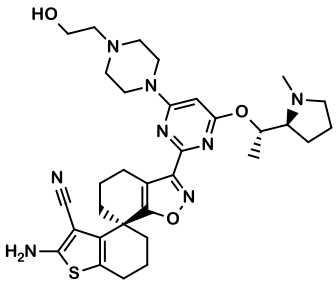
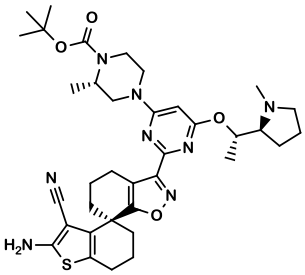
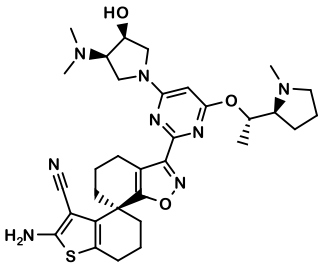
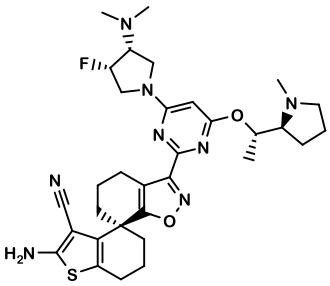
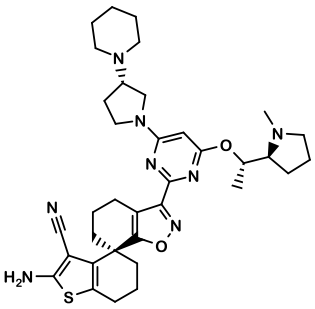
II-7  ,

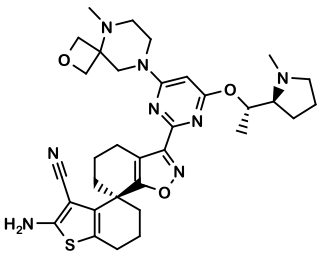
II-8  ,

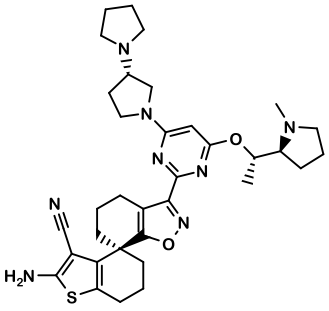
II-9  ,

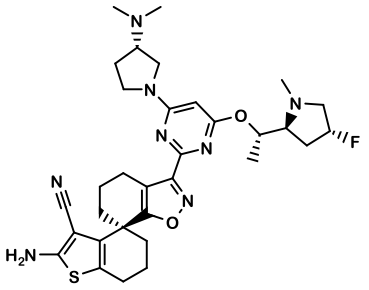
II-10  ,

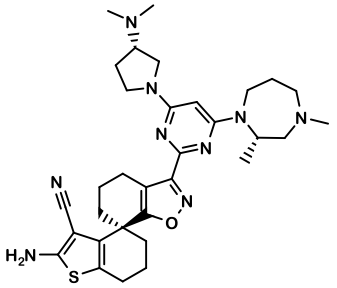
II-11  ,

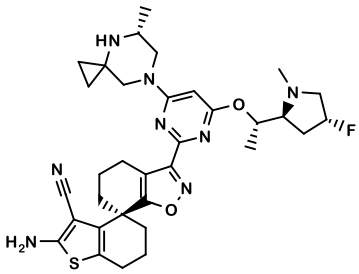
II-12  ,

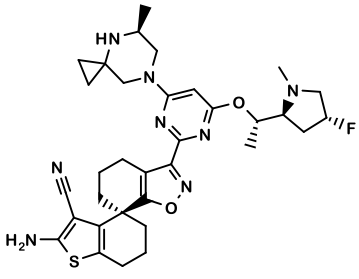
II-13  ,

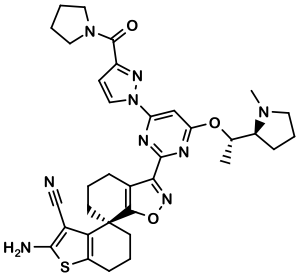
II-14  ,

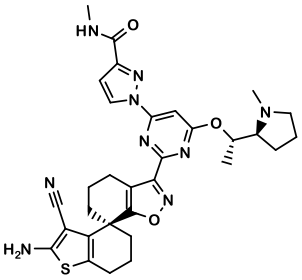
II-15  ,

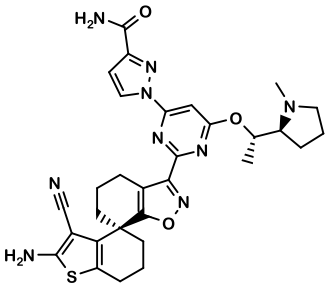
II-16  ,

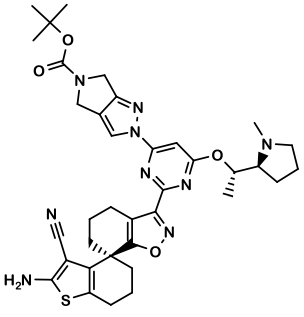
II-17  ,

II-18  ,

II-19  ,

II-20  ,

II-21  ,

II-22  ,

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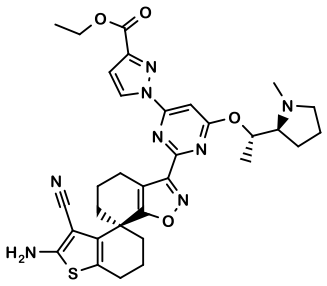

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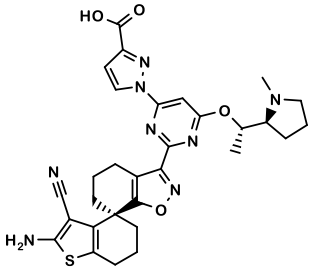

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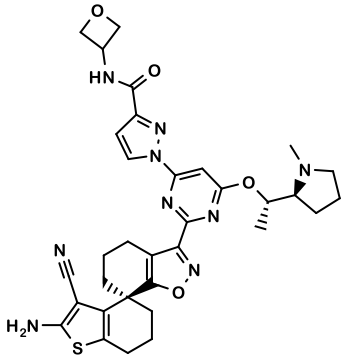

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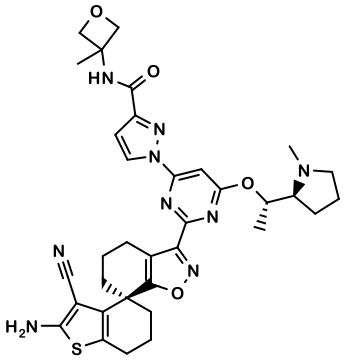

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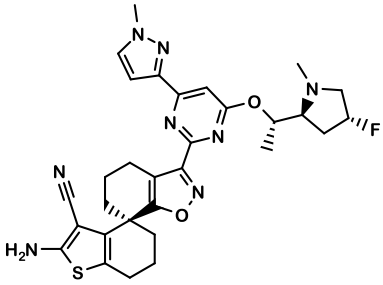

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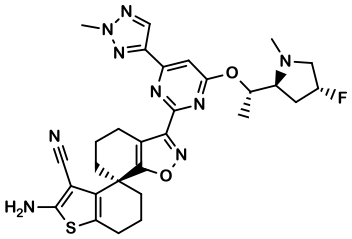

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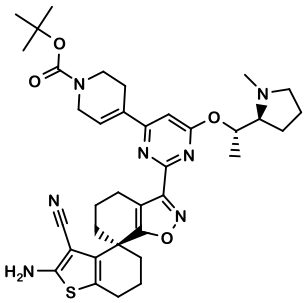

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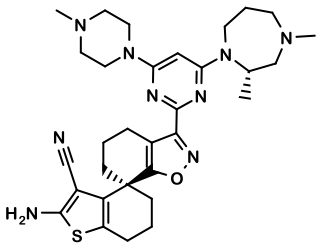

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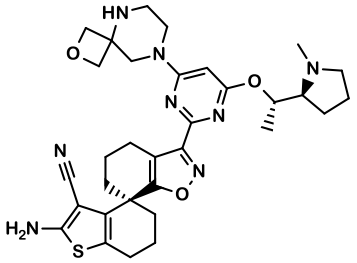

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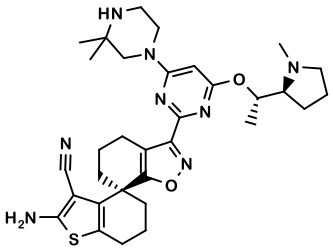

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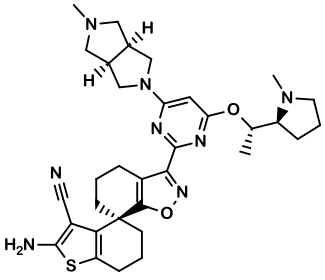

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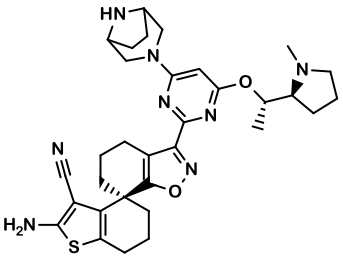

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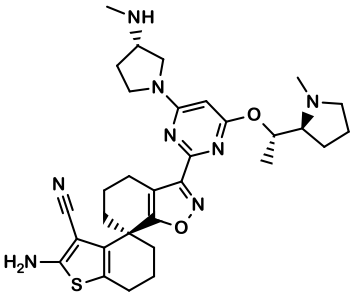

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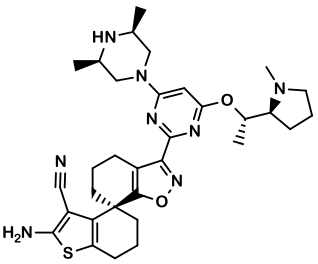

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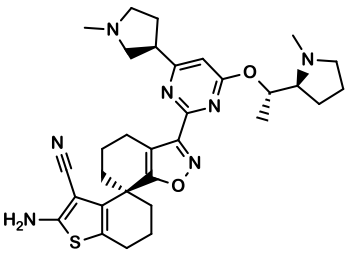

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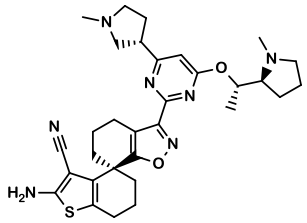
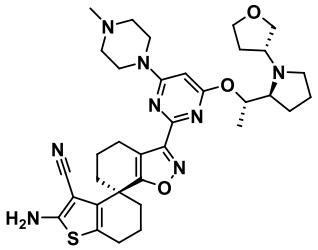
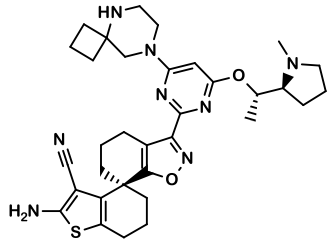
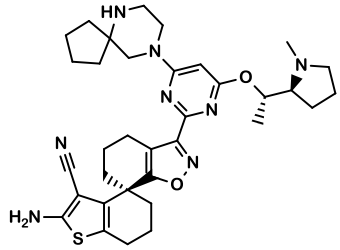
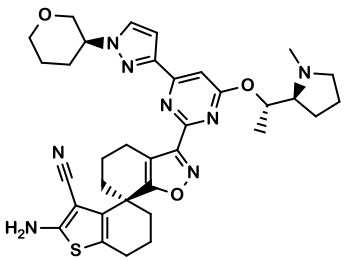
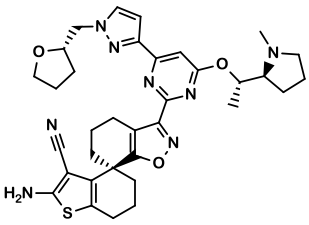
II-38  ,

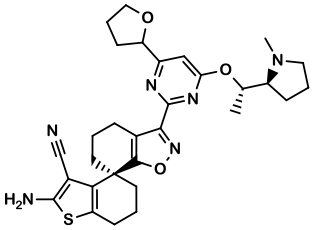
II-39  ,

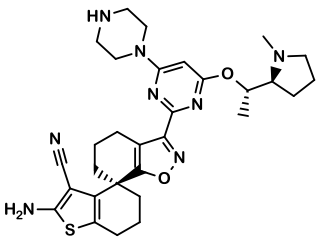
II-40  ,

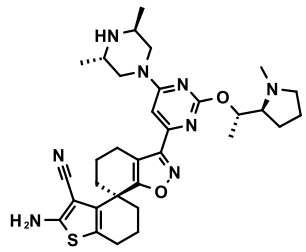
II-41  ,

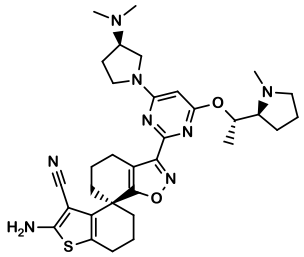
II-42  ,

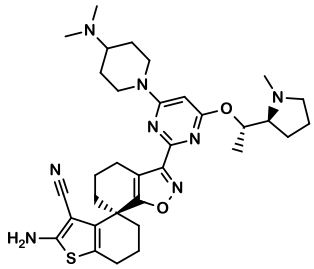
II-43  ,

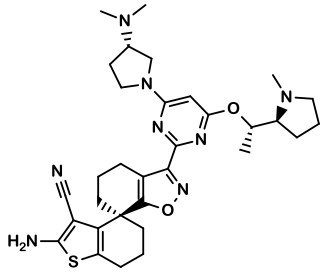
II-44  ,

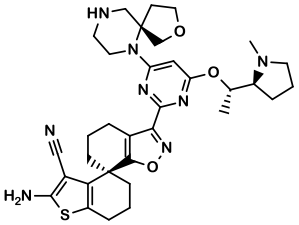
II-45  ,

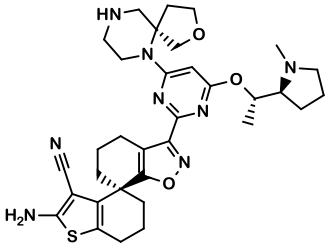
II-46  ,

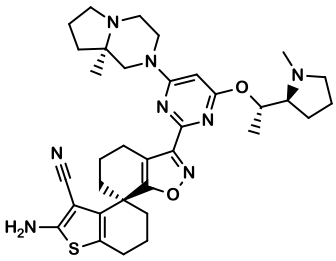
II-47  ,

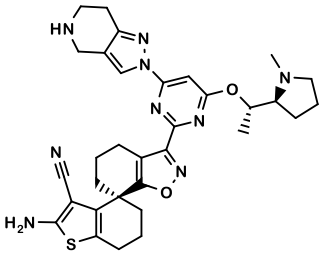
II-48  ,

II-49  ,

II-50  ,

II-51  ,

II-52  ,

II-53  ,

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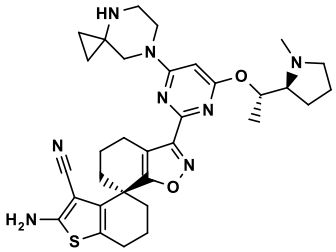

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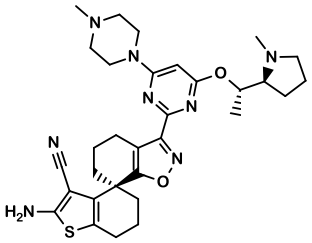

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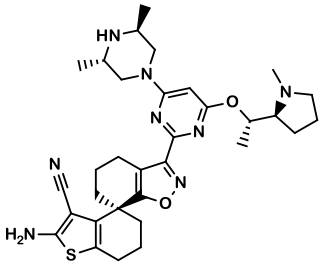

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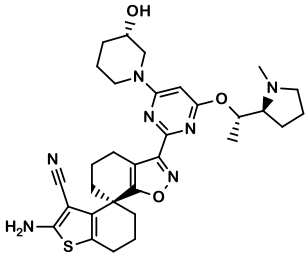

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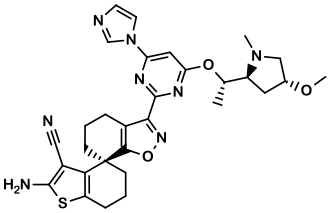

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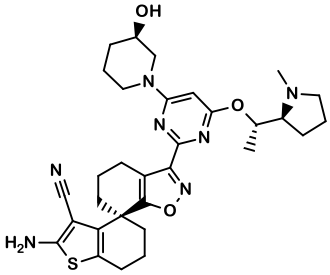

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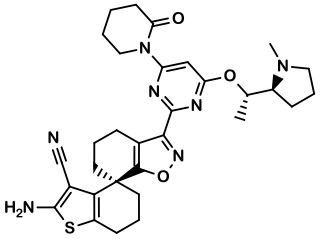

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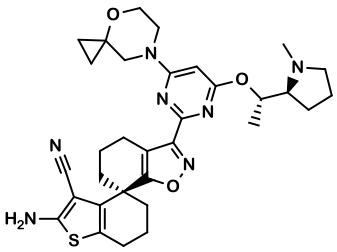

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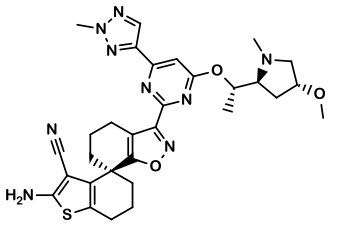

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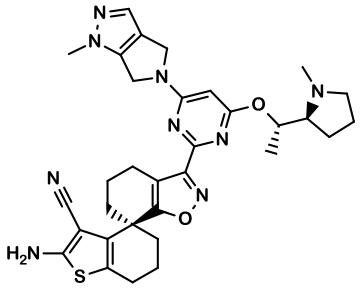

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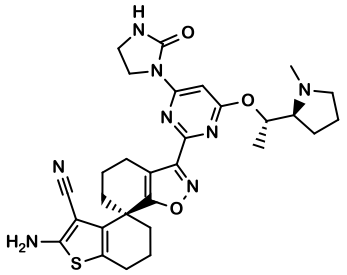

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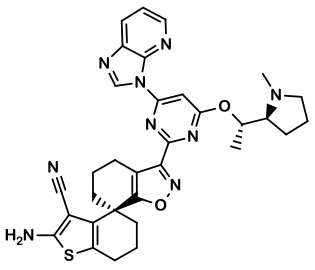

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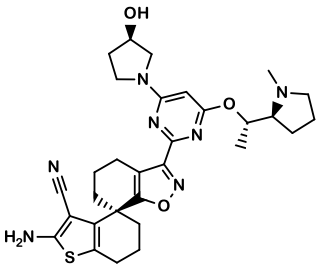

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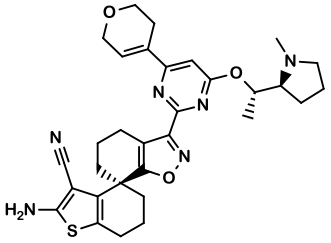

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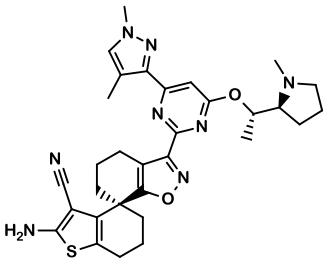

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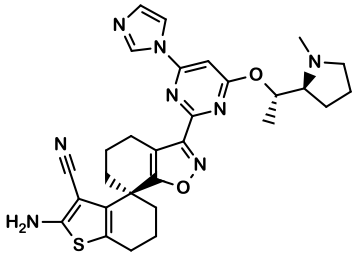

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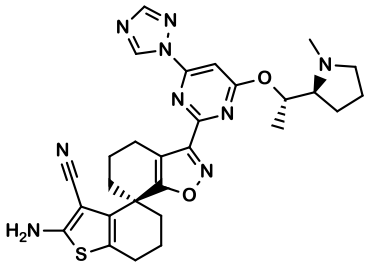
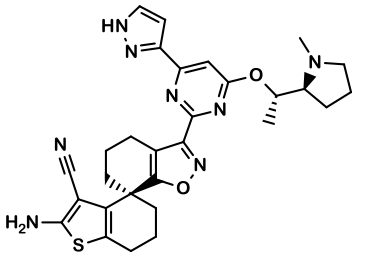
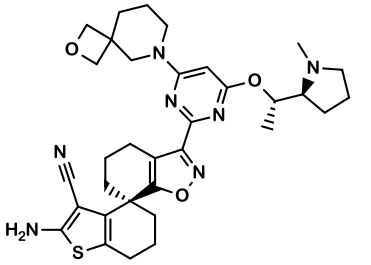
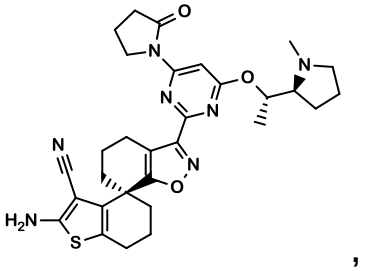
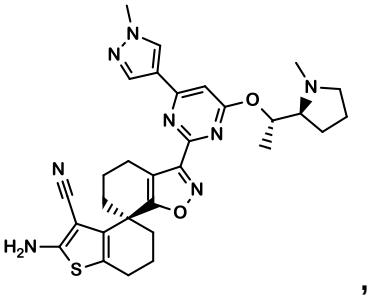
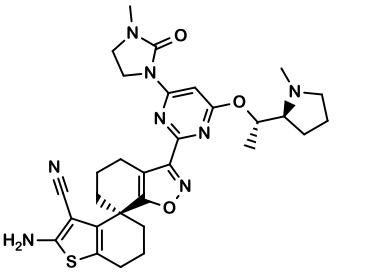
II-70  ,

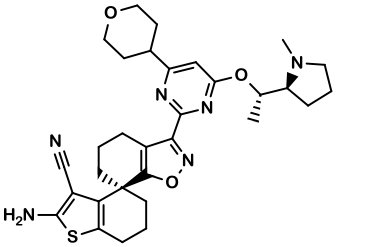
II-71  ,

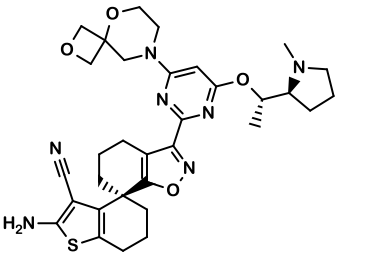
II-72  ,

II-73  ,

II-74  ,

II-75  ,

II-76  ,

II-77  ,

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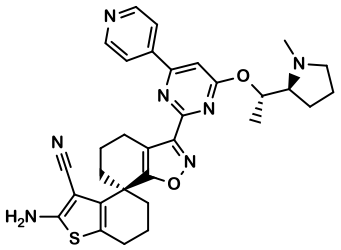

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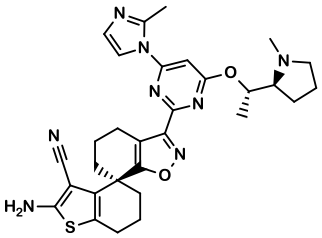

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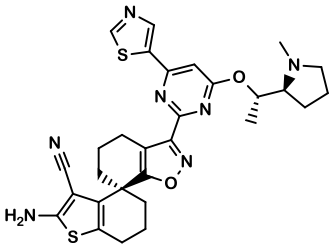

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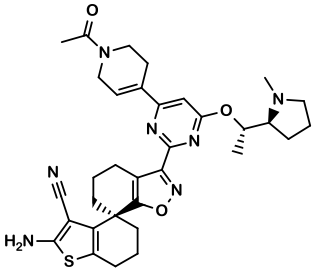

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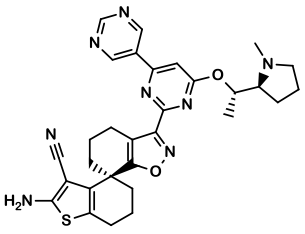

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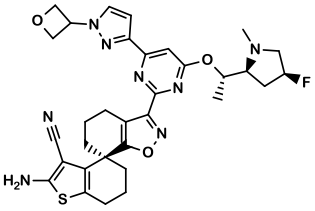

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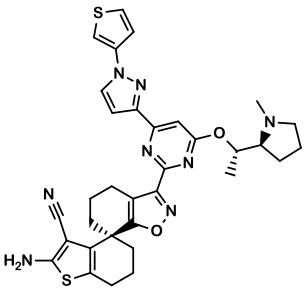

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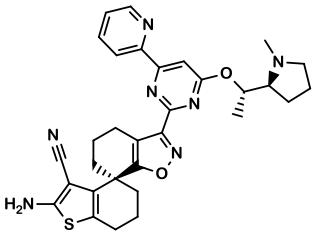

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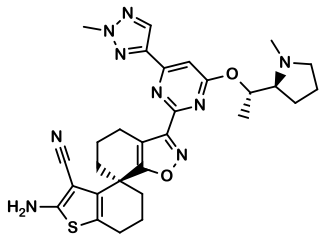
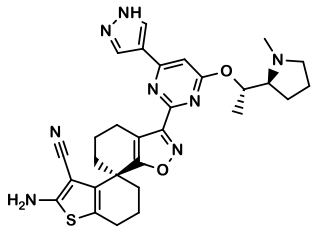
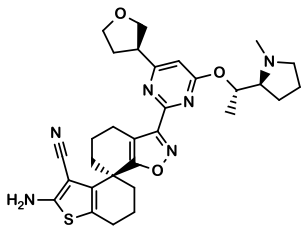
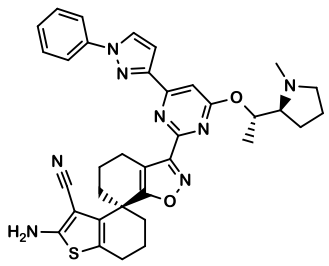
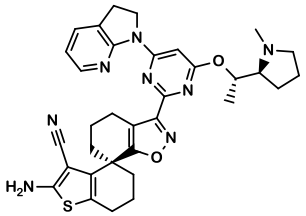
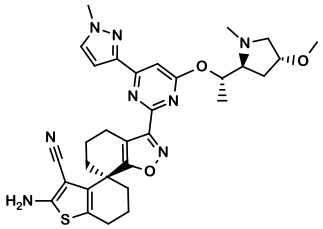
II-86  ,

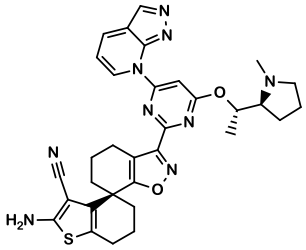
II-87  ,

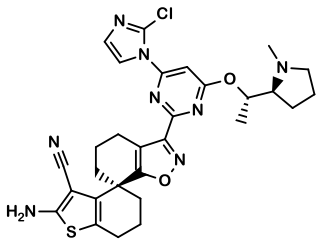
II-88  ,

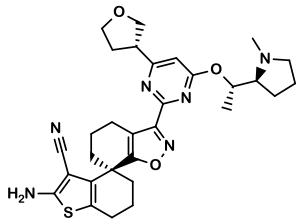
II-89  ,

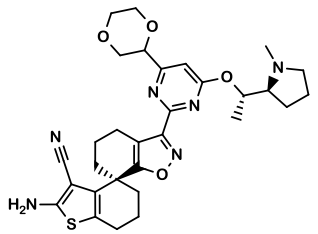
II-90  ,

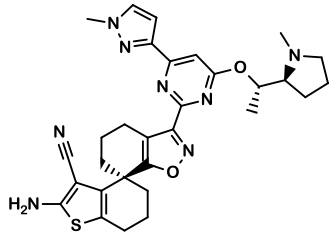
II-91  ,

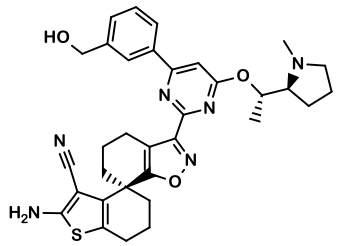
II-92  ,

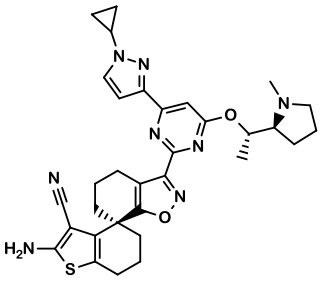
II-93  ,

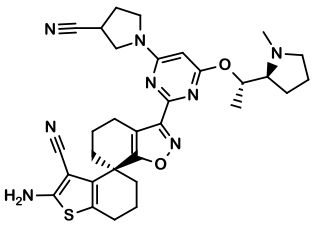
II-94  ,

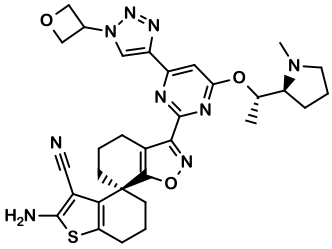
II-95  ,

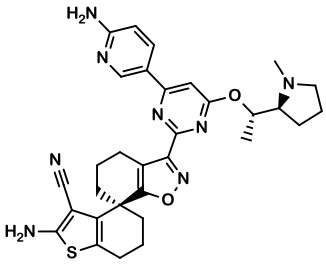
II-96  ,

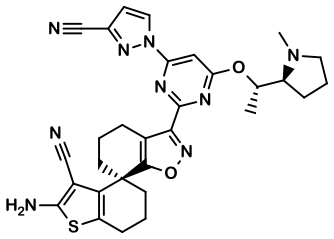
II-97  ,

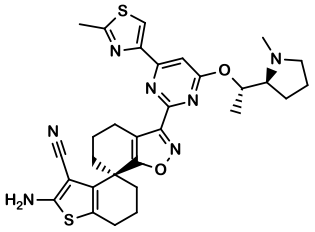
II-98  ,

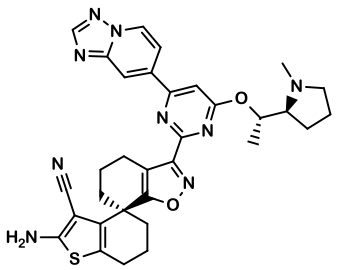
II-99  ,

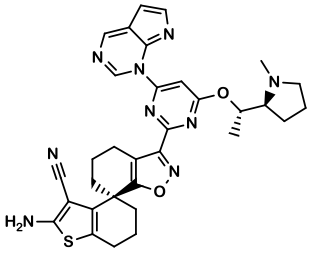
II-100  ,

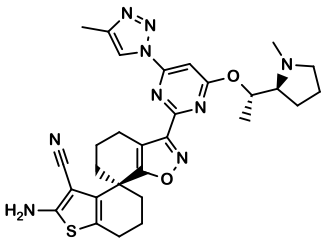
II-101  ,

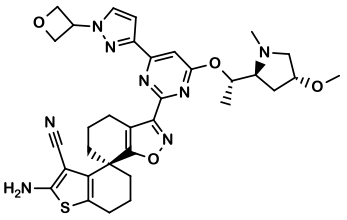
II-102  ,

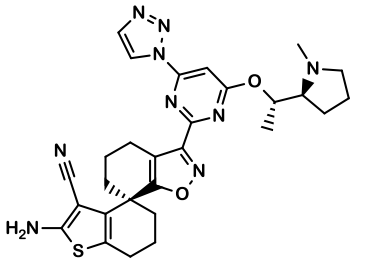
II-103  ,

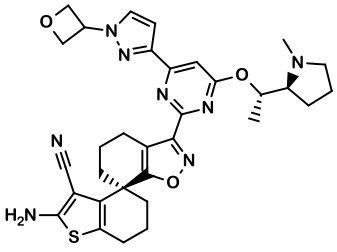
II-104  ,

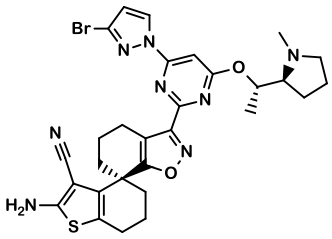
II-105  ,

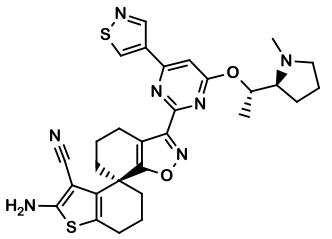
II-106  ,

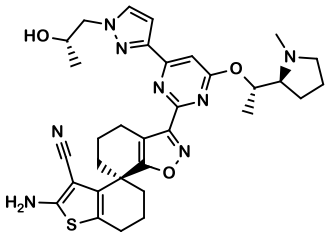
II-107  ,

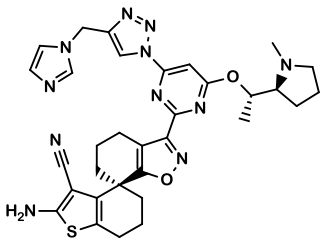
II-108  ,

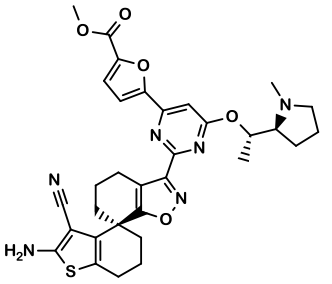
II-109  ,

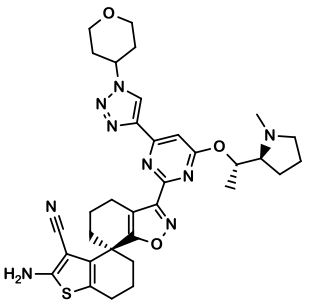
II-110  ,

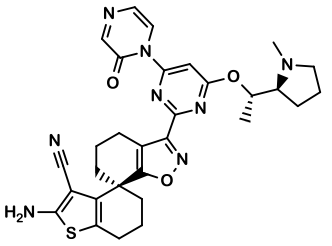
II-111  ,

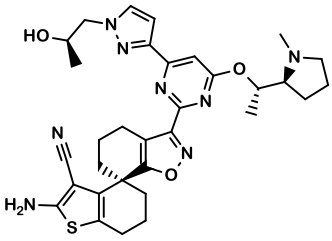
II-112  ,

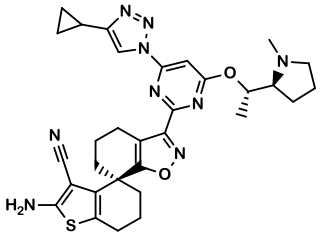
II-113  ,

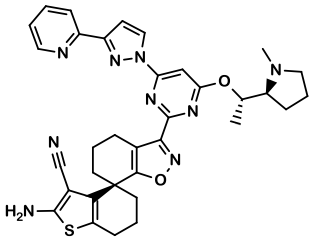
II-114  ,

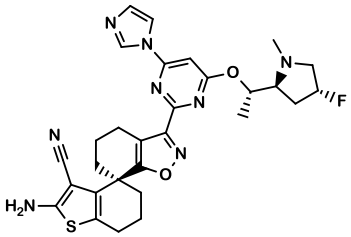
II-115  ,

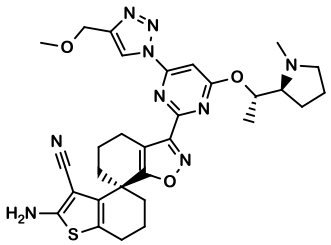
II-116  ,

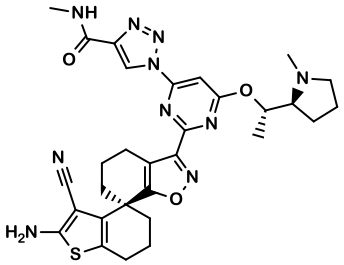
II-117  ,

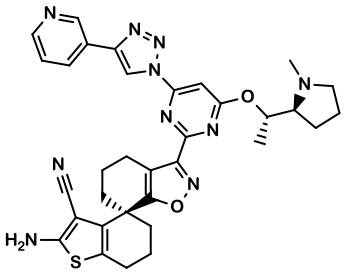
II-118  ,

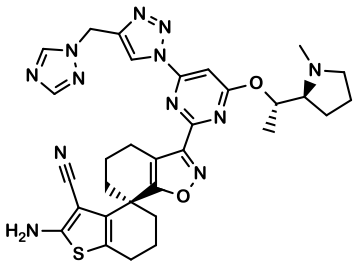
II-119  ,

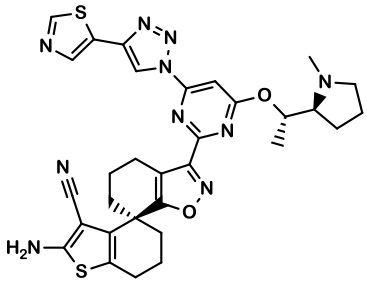
II-120  ,

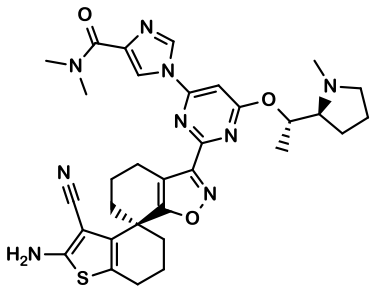
II-121  ,

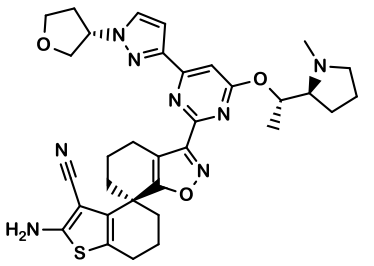
II-122  ,

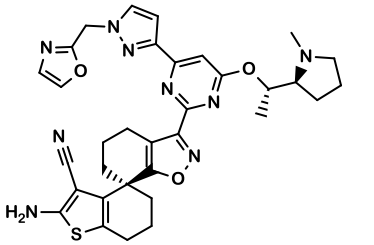
II-123  ,

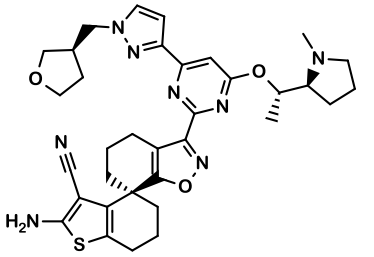
II-124  ,

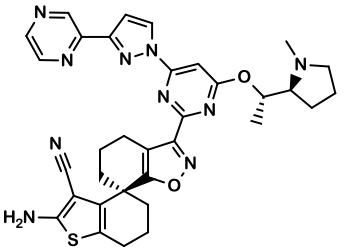
II-125  ,

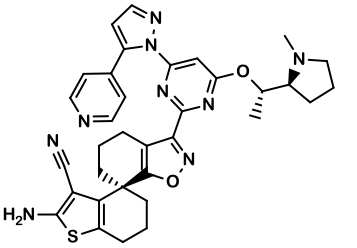
II-126  ,

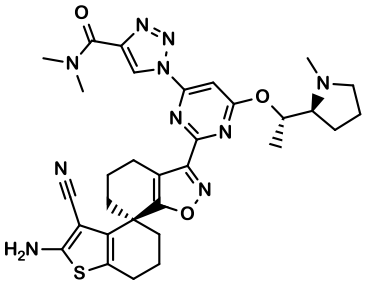
II-127  ,

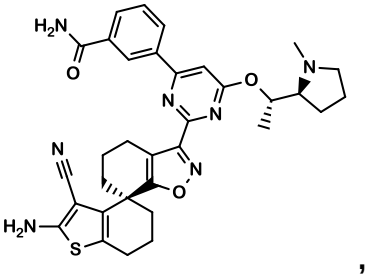
II-128  ,

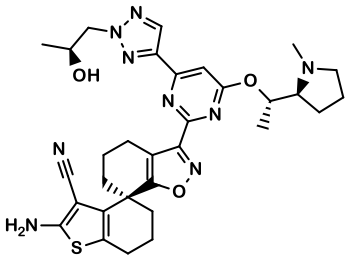
II-129  ,

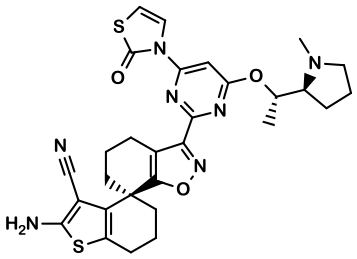
II-130  ,

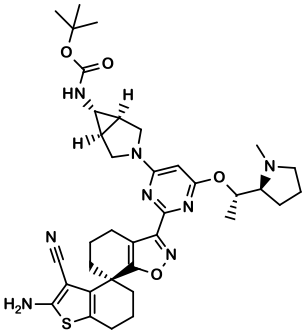
II-131  ,

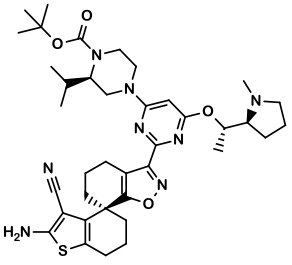
II-132  ,

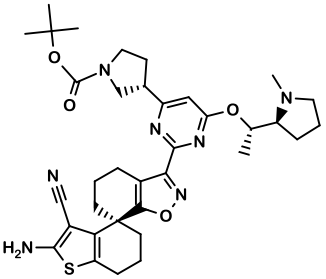
II-133  ,

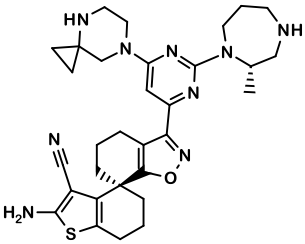
II-134  ,

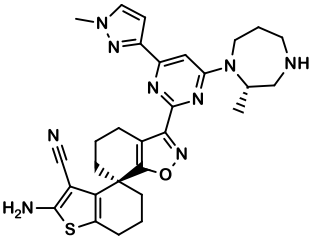
II-135  ,

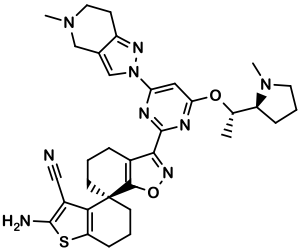
II-136  ,

II-137  ,

II-138  ,

II-139  ,

II-140  ,

II-141  ,

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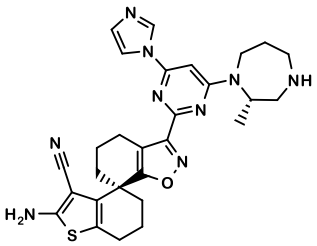

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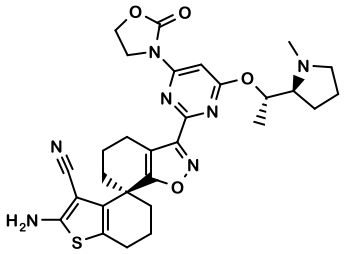

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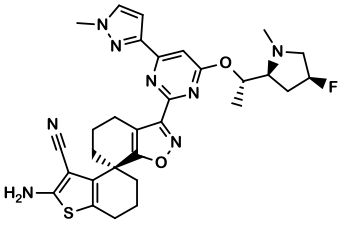

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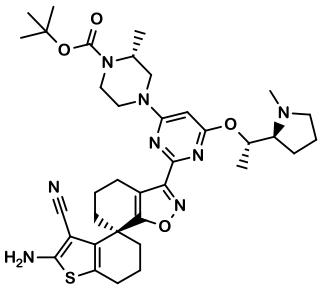

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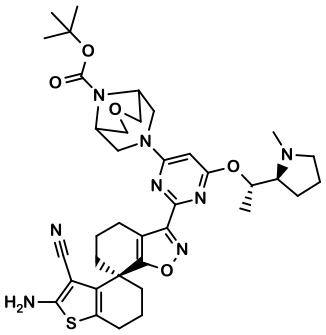

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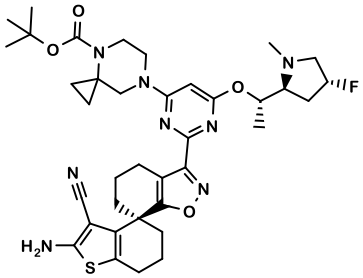

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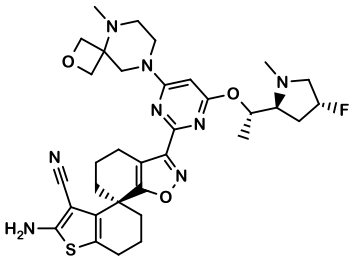

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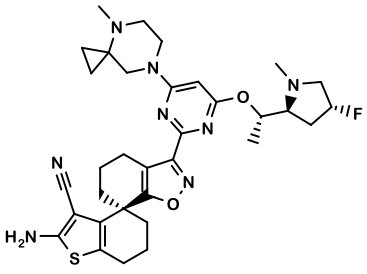

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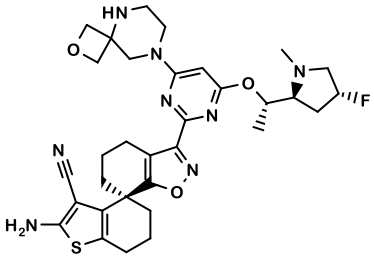
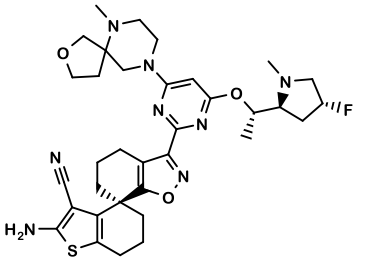
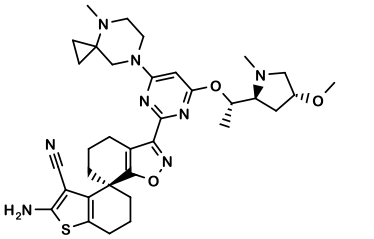
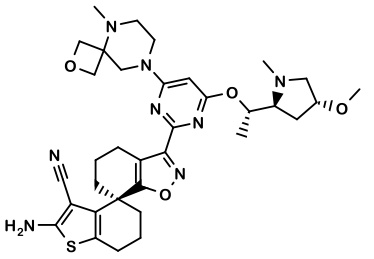
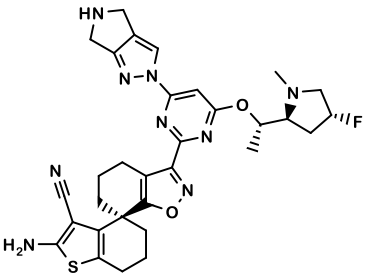
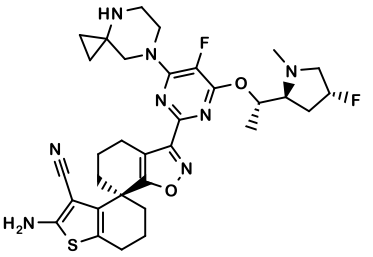
II-150  ,

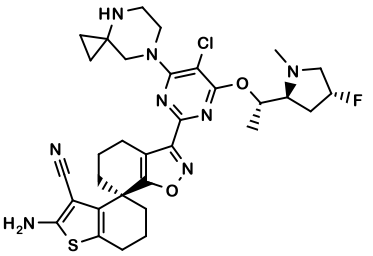
II-151  ,

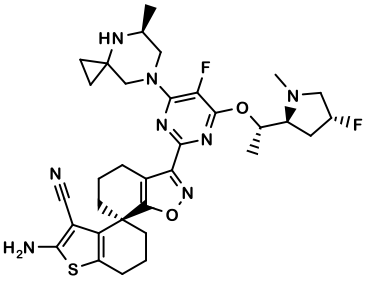
II-152  ,

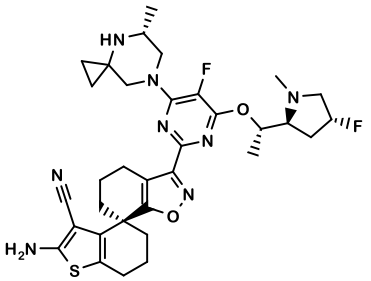
II-153  ,

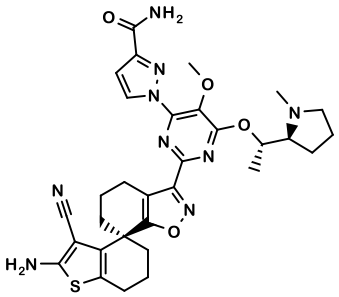
II-154  ,

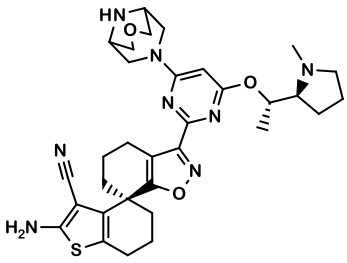
II-155  ,

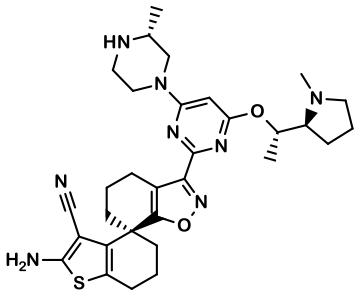
II-156  ,

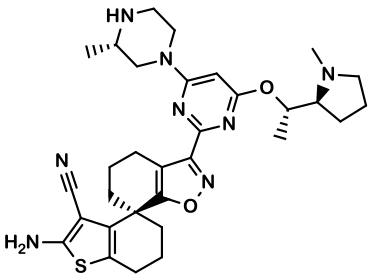
II-157  ,

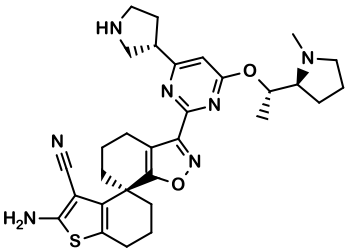
II-158  ,

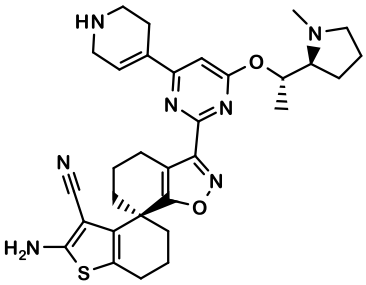
II-159  ,

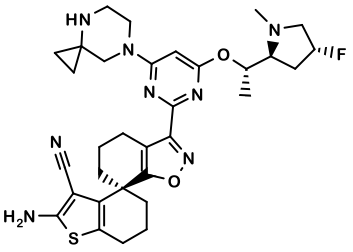
II-160  ,

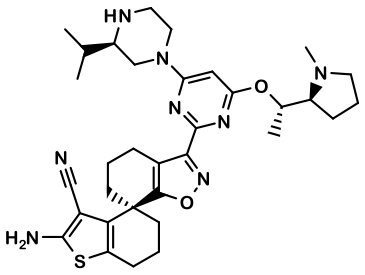
II-161  ,

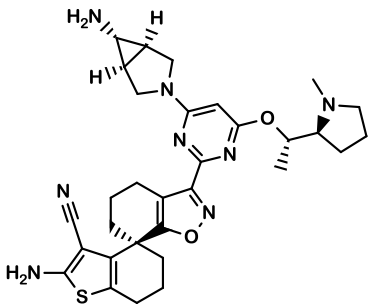
II-162  ,

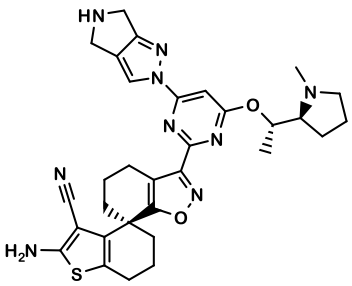
II-163  ,

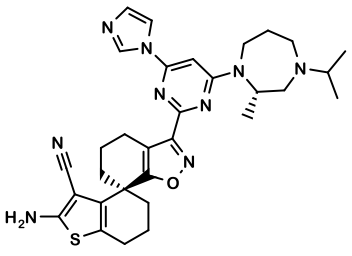
II-164  ,

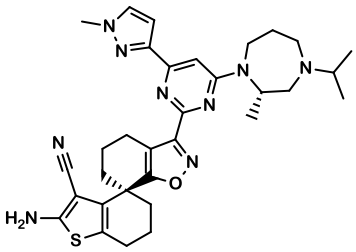
II-165  ,

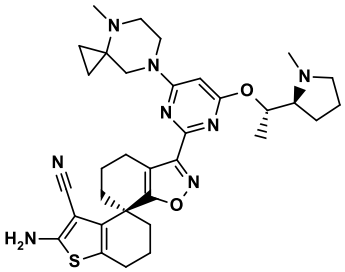
II-166  ,

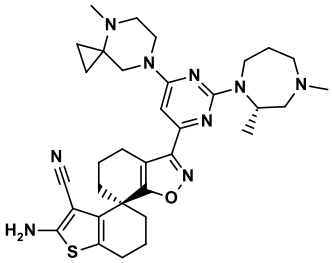
II-167  ,

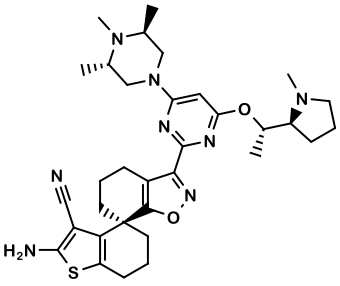
II-168  ,

II-169  ,

II-170  ,

II-171  ,

II-172  ,

II-173  ,

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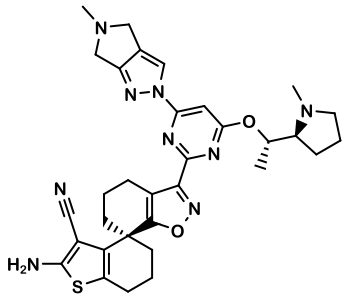

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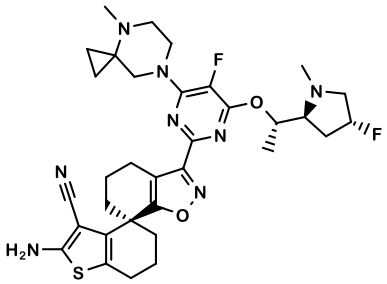

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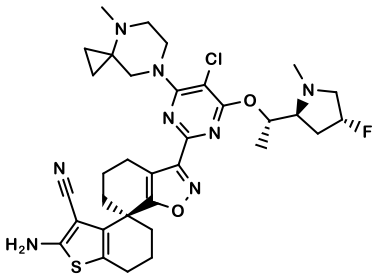

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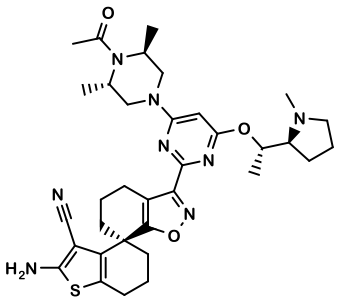

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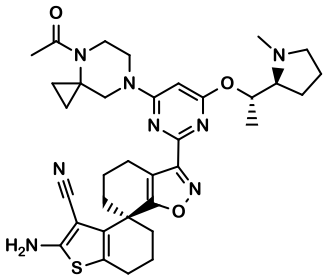

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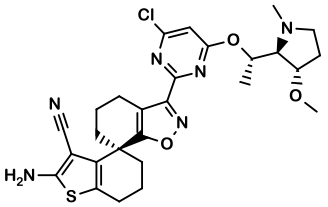

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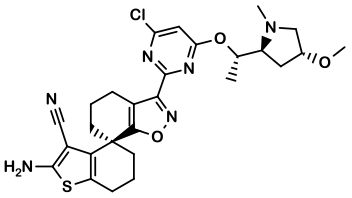

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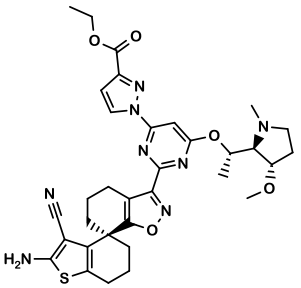

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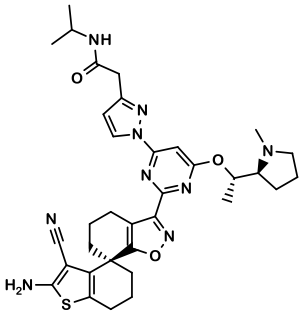

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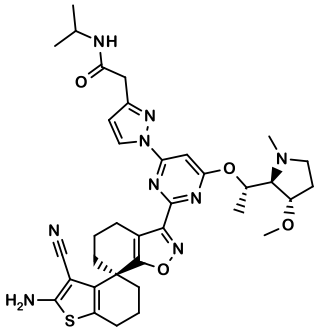

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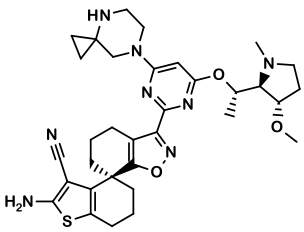

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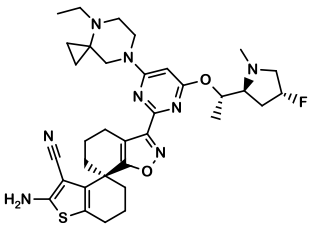

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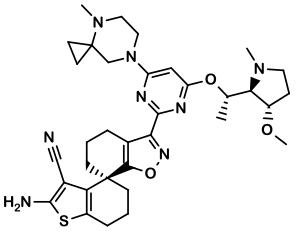

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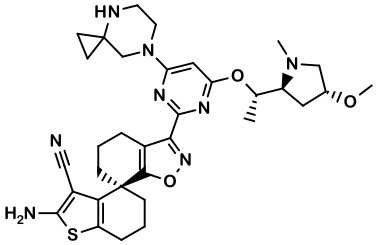

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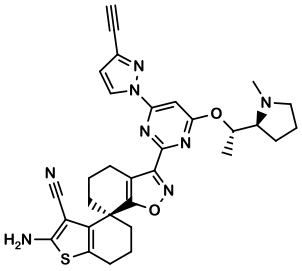

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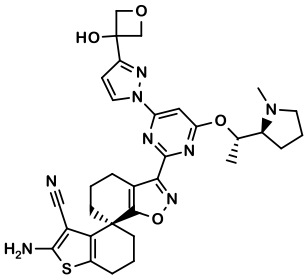

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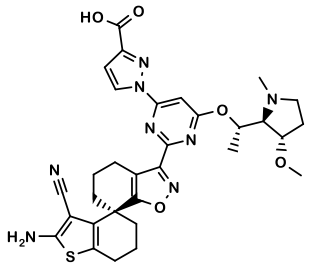

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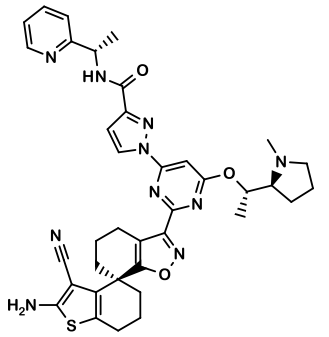

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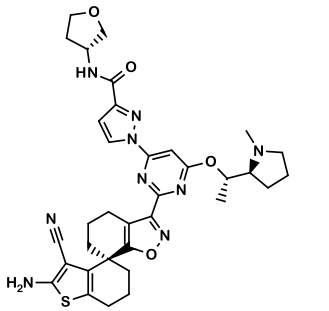

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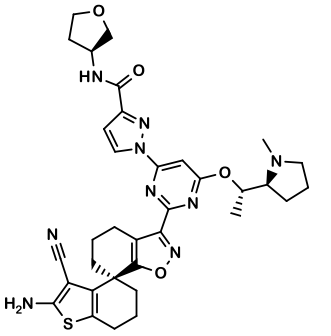

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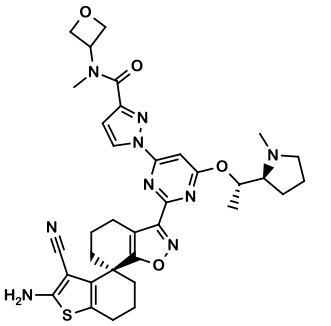

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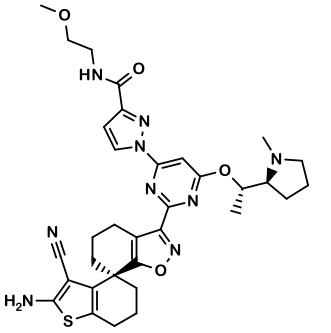

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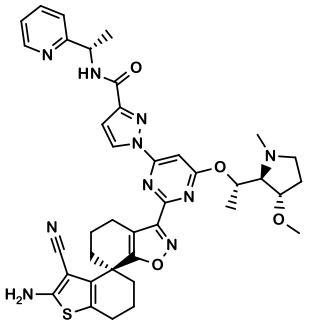

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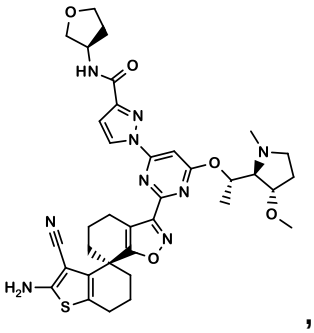

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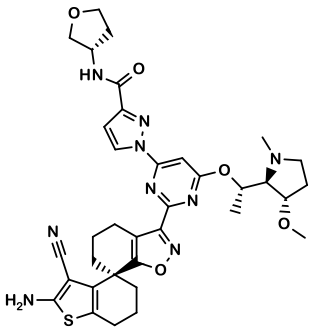

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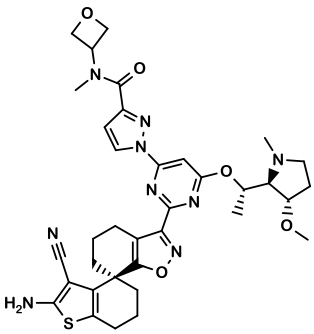

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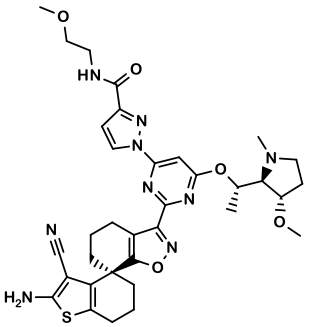

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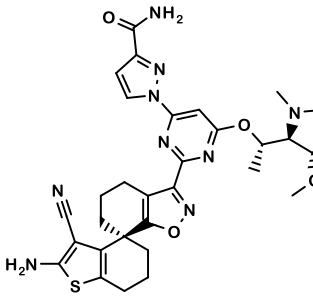

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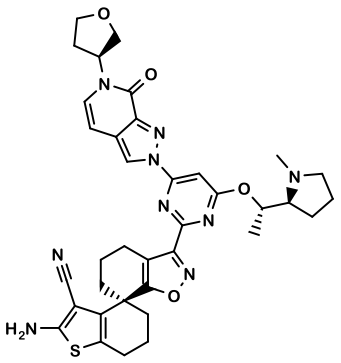
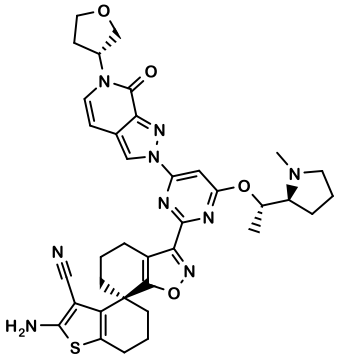
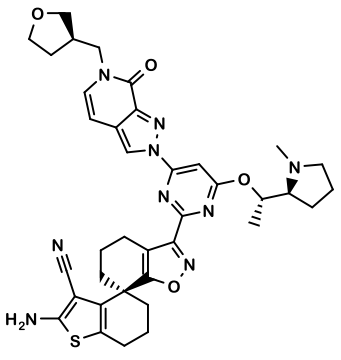
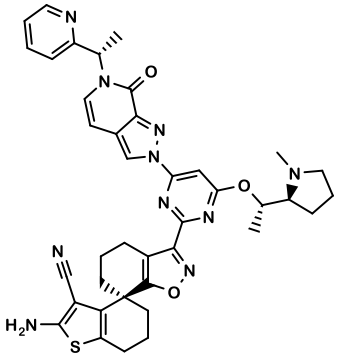
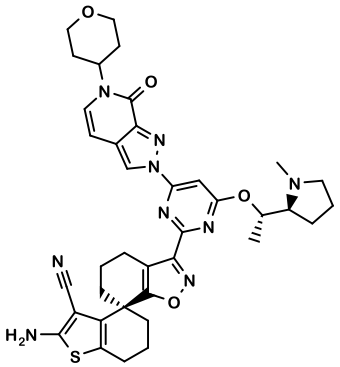
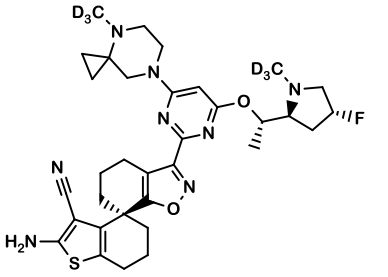
II-202  ,

II-203  ,

II-204  ,

II-205  ,

II-206  ,

II-207  ,

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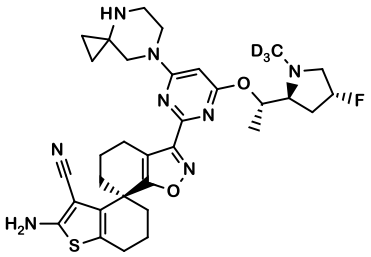

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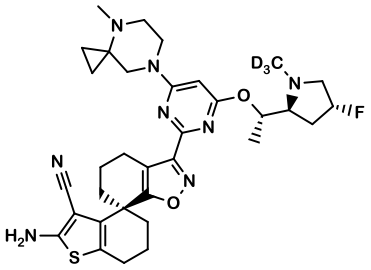

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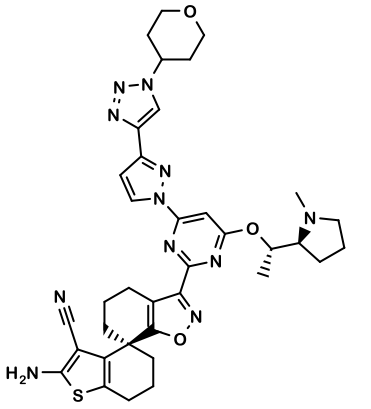

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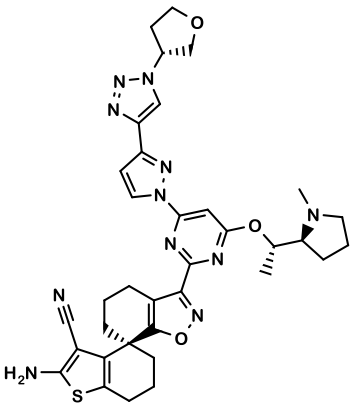

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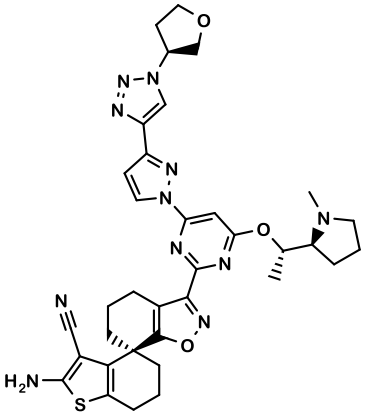

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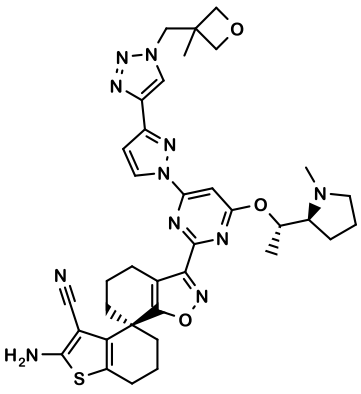
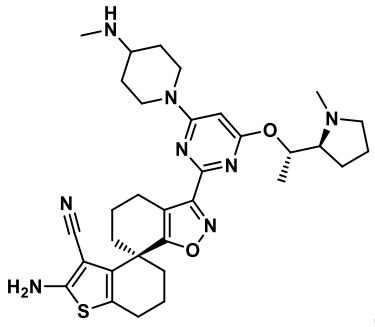
II-213



and

II-214



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13. The compound according to any one of claim 1 to 12 – or a pharmaceutically acceptable salt thereof – for use as a medicament.

14. The compound according to any one of claim 1 to 12 – or a pharmaceutically acceptable salt thereof – for use in the treatment and/or prevention of cancer.

15. Use of the compound according to any one of claim 1 to 12 – or a pharmaceutically acceptable salt thereof – in the manufacture of a medicament for the treatment and/or prevention of cancer.

16. The compound – or a pharmaceutically acceptable salt thereof – for use according to claim 14, or the use according to claim 15, wherein said compound or salt is to be administered in combination with one or more other pharmacologically active substance(s).

17. The compound – or the pharmaceutically acceptable salt thereof – for use according to claim 14 or 16, or the use according to claim 15 or 16, wherein the cancer is selected from the group consisting of pancreatic cancer, lung cancer, colorectal cancer, cholangiocarcinoma, appendiceal cancer, multiple myeloma, melanoma, uterine cancer, endometrial cancer, thyroid cancer, acute myeloid leukaemia, bladder cancer, urothelial cancer, gastric cancer, cervical cancer, head and neck squamous cell carcinoma, diffuse large B cell lymphoma, oesophageal cancer, gastroesophageal cancer, chronic lymphocytic leukaemia, hepatocellular cancer, breast cancer, ovarian cancer, prostate cancer,

glioblastoma, renal cancer and sarcoma.

18. The compound – or the pharmaceutically acceptable salt thereof – for use according to any one of claims 14, 16 and 17, or the use according to any one of claims 15 to 17, wherein the cancer comprises tumor cells harbouring a KRAS mutation or an amplification of KRAS wildtype.

19. The compound – or the pharmaceutically acceptable salt thereof – for use or the use according to claim 18, wherein the KRAS mutation is selected from the group consisting of: KRAS G12C, KRAS G12D, KRAS G12V and KRAS G13D.

20. A pharmaceutical composition comprising a compound according to any one of claim 1 to 12 – or a pharmaceutically acceptable salt thereof – and one or more other pharmaceutically acceptable excipient(s).