MONOCYCLIC AGONISTS OF STIMULATOR OF INTERFERON GENES STING

[0001] This application claims the benefit of priority to U.S. Patent Application No. 62/889,669 filed on August 21, 2019.

BACKGROUND

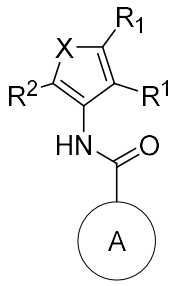
[0002] The cGAS-STING signaling pathway plays a critical role in the innate immune response that mammalian host cells mount to eliminate diverse DNA and RNA viruses. STING (Stimulator of Interferon Genes) is an endoplasmic reticulum (ER) resident signaling protein, partially localized to mitochondria-associated membranes, which is broadly expressed in both immune and non-immune cell types. In response to cyclic dinucleotides (CDNs), including 2'-3' cGAMP produced in response to cytosolic DNA by cyclic GMP-AMP synthase (cGAS), STING translocates to the perinuclear region where it rapidly induces type I interferon (IFN) and pro-inflammatory cytokine production in a TBK1-/IRF3-dependent fashion. STING has also been found to directly bind cytosolic DNA, although the physiological relevance of direct DNA sensing activity remains to be fully characterized.

[0003] Recent work has demonstrated that STING plays essential roles in immune responses to tumor cells. Efficient tumor-initiated T cell priming within the tumor microenvironment requires interferon-beta (IFN-b) production by resident dendritic cells and the expression of IFN-b has been demonstrated to be dependent upon activation of the STING pathway (1). Indeed, intratumoral delivery of nucleotide-based STING agonists have been demonstrated to induce the profound regression of established tumors in syngeneic mouse models (1). In addition, activation of the STING pathway has also been demonstrated to significantly contribute to the anti-tumor effect of radiation, via IFN-b mediated immune response within the irradiated tumor microenvironment.

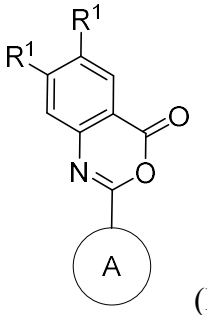
SUMMARY

[0004] In various examples, the present disclosure provides an agonist of the Stimulator of Interferon Genes (STING), which can be used in the treatment of tumors.

[0005] The present disclosure provides, in various examples a compound of formula (IA) or formula (II), or a pharmaceutically acceptable salt thereof,



(IA)



(II),

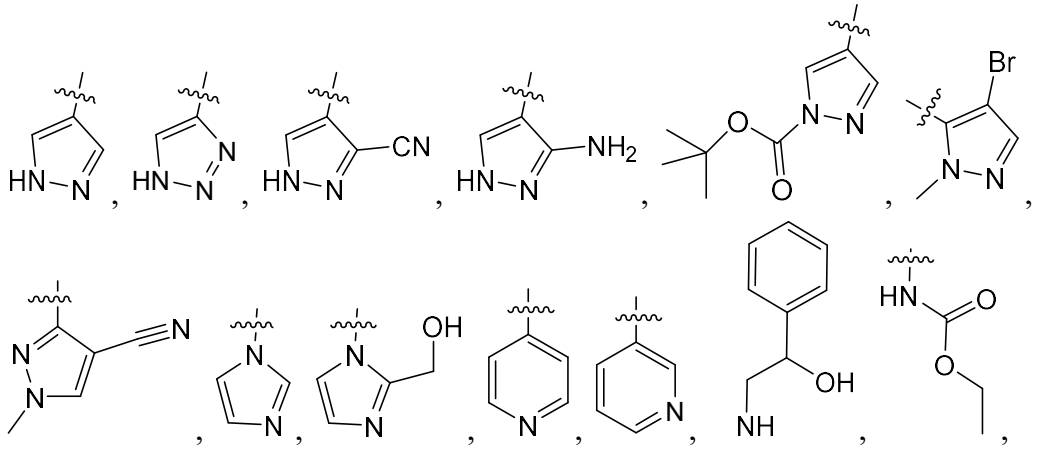
wherein X = S, -N=C(R^1)-, or -C(R^1)=C(R^1).

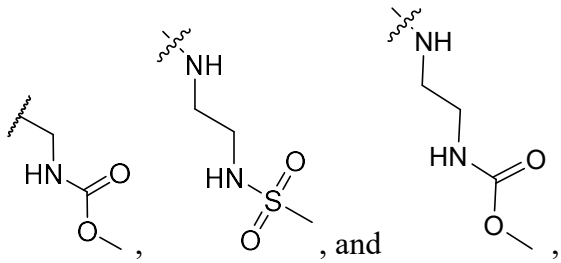
[0006] Each R^1 is independently H, F, Cl, C_1-C_6-alkyl, ethenyl or ethynyl (either of which can be substituted), cyano, alkoxyl, or haloalkyl.

[0007] R^2 is selected from the group consisting of -C(O)OR, -C(O)NH(C_1-C_6-alkyl) (wherein the alkyl is optionally substituted), optionally substituted C_3-C_6-cycloalkenyl, and a 3- to 10-membered heterocyclyl.

[0008] R is selected from the group consisting of H, alkyl optionally substituted with –((C_1-C_6-alkyl)OC(O)OC_1-C_6-alkyl) or a 3- to 10-membered heterocyclyl, and benzyl, wherein the benzyl can be unsubstituted or substituted with methoxyl or with an acid or ester isostere.

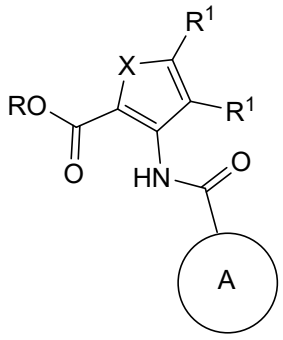
[0009] Ring A is a 5- or 6-membered heteroaryl comprising 1, 2, or 3 N atoms, unsubstituted or substituted with 1, 2, or 3 groups independently selected from the set consisting of NH_2, NH-benzyl unsubstituted or substituted with methoxyl, cyano, alkylnitrile, haloalkyl, hydroxymethyl, aminomethyl, aminopropyl, carboxamido, alkoxy,





, and , wherein a wavy line indicates a position of bonding.

[0010] In various examples, the compound of formula (IA) is of formula (I):



(I),

wherein X is S, -N=C(R^1)-, or -C(R^1)=C(R^1)-; R^1= each independently H, F, Cl, ethenyl or ethynyl (either of which can be substituted), cyano, alkoxyl, or haloalkyl; and R is H, alkyl, or benzyl, wherein the benzyl can be unsubstituted or substituted with methoxyl or with an acid or ester isostere such as 1,2,3,4 tetrazole.

[0011] In some examples, optionally in combination with any other example described herein, ring A comprises any one of pyridazinyl, triazolyl, pyrimidinyl, or pyridinyl, any of which can be unsubstituted or substituted.

[0012] More specifically, per illustrative examples, a compound of the present disclosure includes any of the specific compounds shown in Table 1 below.

[0013] Further, per an example, the present disclosure provides a method of stimulating expression of interferon genes, comprising administering to a patient an effective dose of an agonist of the Stimulator of Interferon Genes (STING), comprising a compound described herein, and a method of treating a tumor in a patient, comprising administering to the patient an effective dose of an agonist of the Stimulator of Interferon Genes (STING), comprising a compound described herein.

[0014] Additionally, a method of the present disclosure can be carried out using an effective dose of any one of the specific compounds disclosed in the application; see, for example, Table 1.

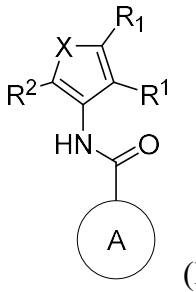
[0015] In various examples, the method of treatment of a tumor can further comprise administering an effective dose of a compound as disclosed herein via oral or intratumoral administration, or both.

[0016] In various examples, the method of treatment of a tumor can further comprise administering an effective dose of a compound as disclosed herein, wherein administering comprises administering the compound to the patient as an antibody-drug conjugate, or in a liposomal formulation.

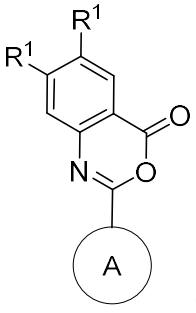
[0017] In various examples, the method of treatment of a tumor can further comprise administering an effective dose of a compound as disclosed herein, further comprising administration of an effective dose of an immune-checkpoint targeting drug. For example, the immune-checkpoint targeting drug can be an anti-PD-L1 antibody, anti-PD-1 antibody, anti-CTLA-4 antibody, or an anti-4-1BB antibody.

[0018] In various examples, the method of treatment of a tumor can further comprise administering an effective dose of a compound as disclosed herein, further comprising administration of ionizing radiation or anticancer drugs.

[0018a] In one aspect, the present disclosure relates to a compound of formula (IA) or formula (II):



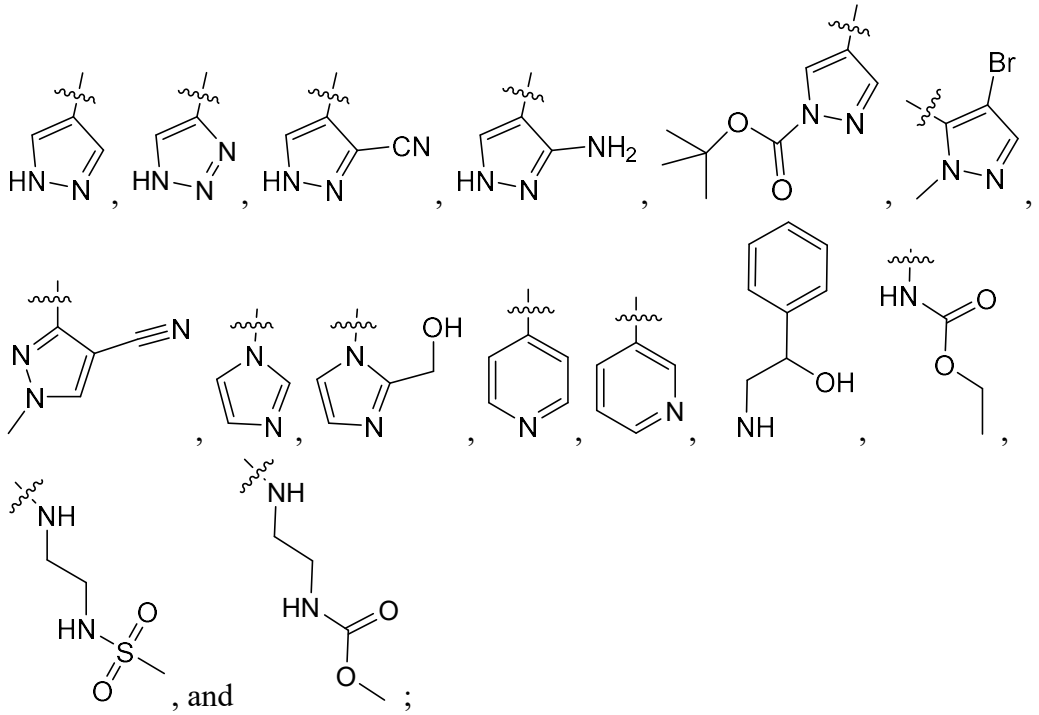
(IA)



(II),

Wherein X is S, -N=C(R^1)-, or -C(R^1)=C(R^1)-; each R^1 is independently H, F, Cl, ethenyl which can be substituted, ethynyl which can be substituted, cyano, alkoxyl, or haloalkyl; R^2 is -C(O)OR; R is selected from the group consisting of H, alkyl, and benzyl, wherein the benzyl can be unsubstituted or substituted with

methoxyl or with1,2,3,4 triazole; Ring A is a 5- or 6-membered heteroaryl comprising 1, 2, or 3 N as the only heteroatoms, substituted with 1, 2, or 3 groups independently selected from the group consisting of NH_2, NH-benzyl (wherein the benzyl is unsubstituted or is substituted with methoxyl), cyano, alkylnitrile, haloalkyl, hydroxymethyl, aminomethyl, aminopropyl, carboxamido, alkoxy,



wherein a wavy line indicates a position of bonding; or a pharmaceutically acceptable salt thereof; wherein the compound of formula (IA) does not include:

methyl 2-(5-amino-1H-pyrazole-4-carboxamido)benzoate;
methyl 2-(2,4-diaminopyrimidine-5-carboxamido)benzoate;
methyl 5-cyano-2-(pyrazine-2-carboxamido)benzoate;
methyl 2-(picolinamido)benzoate;
methyl 2-(nicotinamido)benzoate;
methyl 2-(isonicotinamido)benzoate;
methyl 2-(pyrazine-2-carboxamido)benzoate;
2-(1H-pyrrole-2-carboxamido)benzoic acid;
methyl 2-(1H-pyrrole-2-carboxamido)benzoate;
4-fluoro-2-(picolinamido)benzoic acid;
4,5-difluoro-2-(picolinamido)benzoic acid;
methyl 2-(4-(benzylamino)nicotinamido)benzoate;
methyl 2-(4-(1H-imidazol-1-yl)nicotinamido)benzoate;
RN 1919708-07-8 2-(3-aminopicolinamido)-5-fluorobenzoic acid;

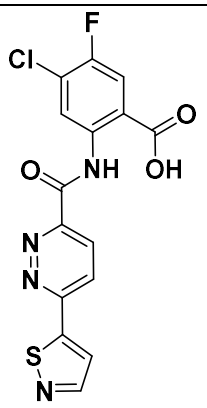
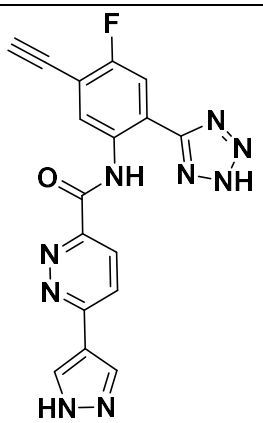
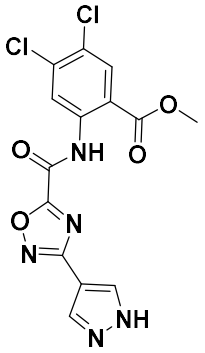
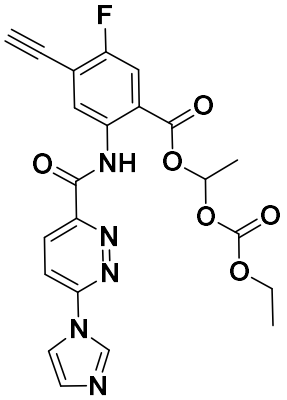
RN 1909907-55-6 methyl 2-(6-((4-methoxybenzyl)amino)pyridazine-3 carboxamido)benzoate; or
RN 1480334-45-9 2-(5-amino-4H-1,2,4-triazole-3-carboxamido)-4,5-difluorobenzoic acid.

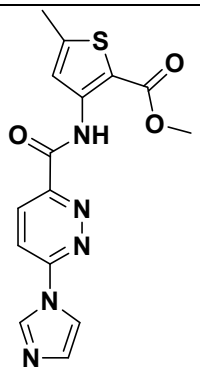
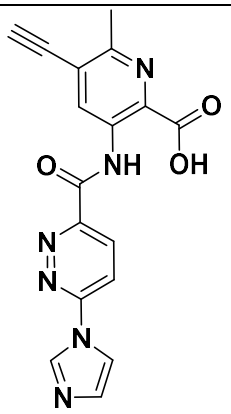
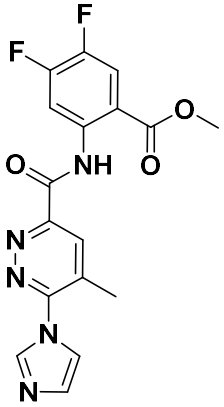
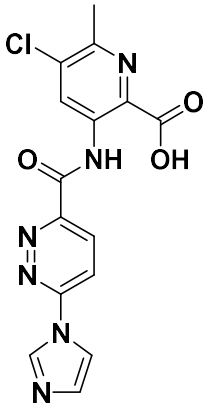
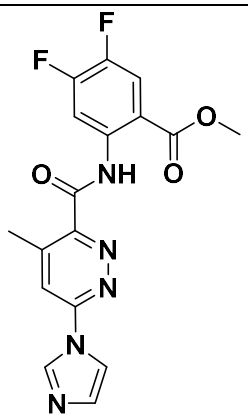
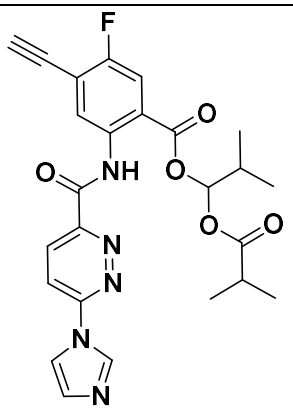
[0018b] In another aspect, the present disclosure relates to use of a compound or pharmaceutically acceptable salt thereof as disclosed herein in the manufacture of a medicament for treating a tumor in a human patient.

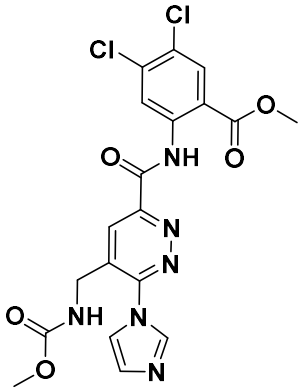
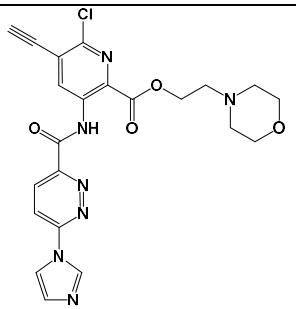
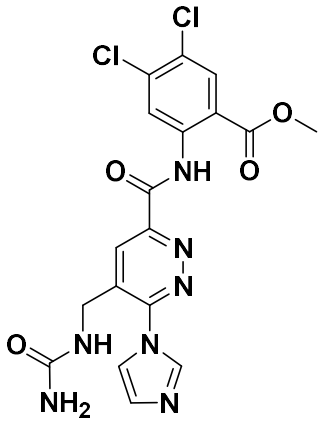
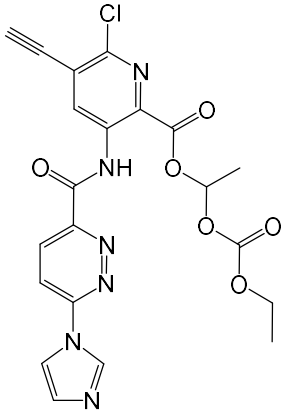
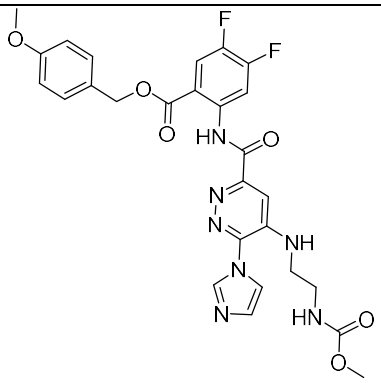
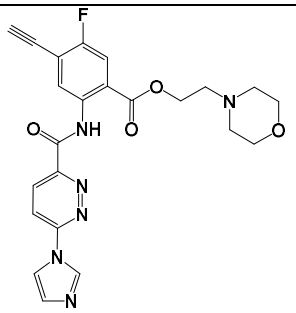
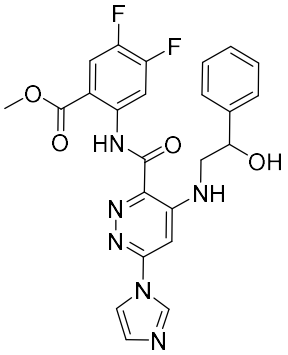
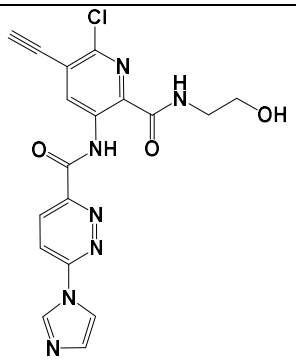
[0018c] In another aspect, the present disclosure relates to a compound or pharmaceutically acceptable salt thereof as disclosed herein for use in therapy.

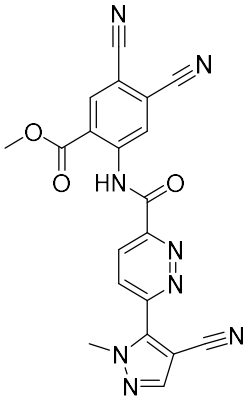
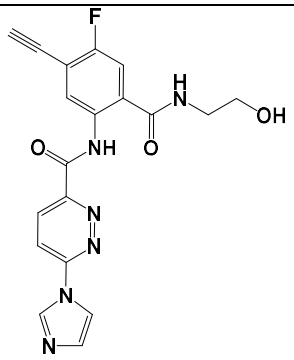
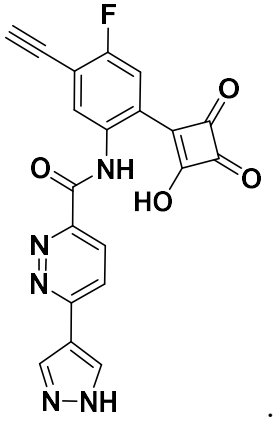
[0018d] In another aspect, the present disclosure relates to a compound selection from the following table:

A compound selected from the following table:

31		84	
37		86	

39		90	
42		91	
43		94	

47		98	
48		102	
61		103	
62		105	

71		106	
83			

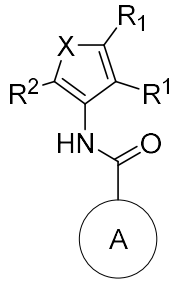
DETAILED DESCRIPTION

[0019] There is significant interest in the development of STING pathway agonists for diverse immuno-oncology applications. Most notably, STING pathway agonists have significant potential application as part of combination therapies involving immune-checkpoint targeting drugs, in patients that fail to respond to checkpoint blockade alone.

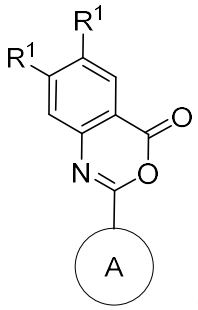
[0020] We have established a robust platform for identifying non-nucleotide small molecule STING agonists. This has been established using a primary assay involving a human THP-1 cell line carrying an IRF-inducible reporter with 5 copies of the IFN signaling response element. Counter screens, involving alternative reporter constructs, rodent cell-based assays, as well as cGAS and STING knock-out cell lines, are used to eliminate luciferase artifacts and ensure human-rodent cross species reactivity, as well as pathway selectivity.

WE CLAIM:

1. A compound of formula (IA) or formula (II):



(IA)



(II),

wherein

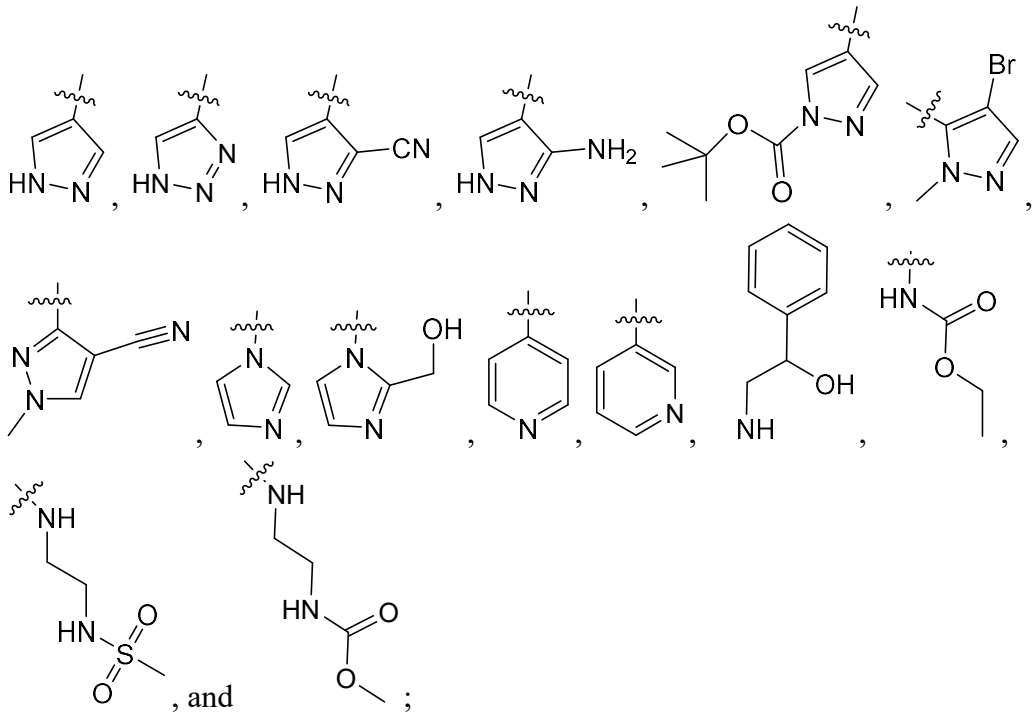
X is S, -N=C(R^1)-, or -C(R^1)=C(R^1)-;

each R^1 is independently H, F, Cl, ethenyl which can be substituted, ethynyl which can be substituted, cyano, alkoxyl, or haloalkyl;

R^2 is -C(O)OR;

R is selected from the group consisting of H, alkyl, and benzyl, wherein the benzyl can be unsubstituted or substituted with methoxyl or with1,2,3,4 tetrazole;

Ring A is a 5- or 6-membered heteroaryl comprising 1, 2, or 3 N as the only heteroatoms, substituted with 1, 2, or 3 groups independently selected from the group consisting of NH_2, NH-benzyl (wherein the benzyl is unsubstituted or is substituted with methoxyl), cyano, alkylnitrile, haloalkyl, hydroxymethyl, aminomethyl, aminopropyl, carboxamido, alkoxy,



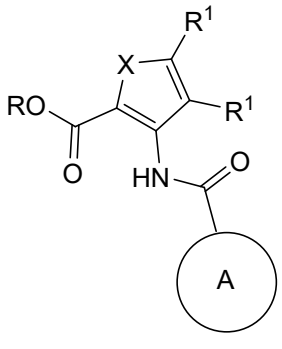
wherein a wavy line indicates a position of bonding;

or a pharmaceutically acceptable salt thereof;

wherein the compound of formula (IA) does not include:

methyl 2-(5-amino-1H-pyrazole-4-carboxamido)benzoate;
methyl 2-(2,4-diaminopyrimidine-5-carboxamido)benzoate;
methyl 5-cyano-2-(pyrazine-2-carboxamido)benzoate;
methyl 2-(picolinamido)benzoate;
methyl 2-(nicotinamido)benzoate;
methyl 2-(isonicotinamido)benzoate;
methyl 2-(pyrazine-2-carboxamido)benzoate;
2-(1H-pyrrole-2-carboxamido)benzoic acid;
methyl 2-(1H-pyrrole-2-carboxamido)benzoate;
4-fluoro-2-(picolinamido)benzoic acid;
4,5-difluoro-2-(picolinamido)benzoic acid;
methyl 2-(4-(benzylamino)nicotinamido)benzoate;
methyl 2-(4-(1H-imidazol-1-yl)nicotinamido)benzoate;
RN 1919708-07-8 2-(3-aminopicolinamido)-5-fluorobenzoic acid;
RN 1909907-55-6 methyl 2-(6-((4-methoxybenzyl)amino)pyridazine-3 carboxamido)benzoate; or
RN 1480334-45-9 2-(5-amino-4H-1,2,4-triazole-3-carboxamido)-4,5-difluorobenzoic acid.

2. The compound according to claim 1, wherein the compound of formula (IA) is of formula (I):



(I),

wherein

X is S, -N=C(R^1)-, or -C(R^1)=C(R^1)-;

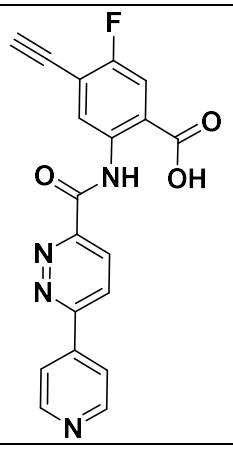
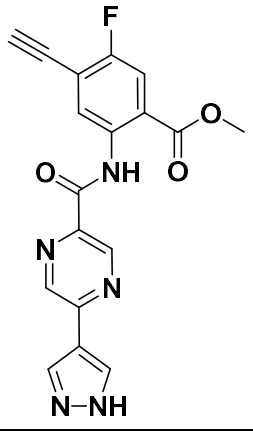
each R^1 is independently H, F, Cl, ethenyl which can be substituted, ethynyl which can be substituted, cyano, alkoxyl, or haloalkyl; and

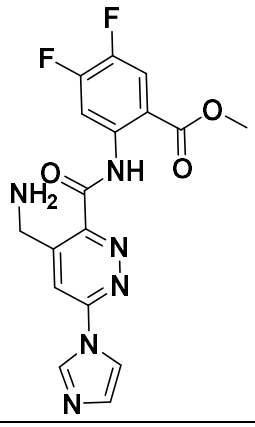
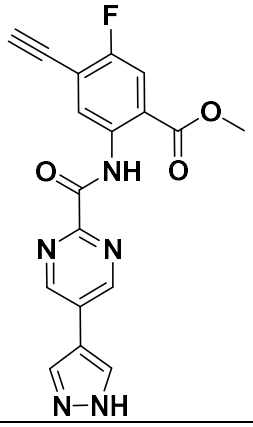
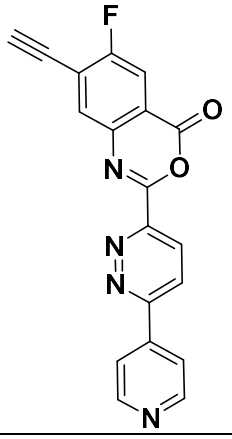
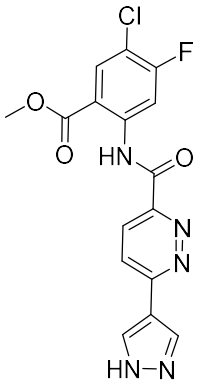
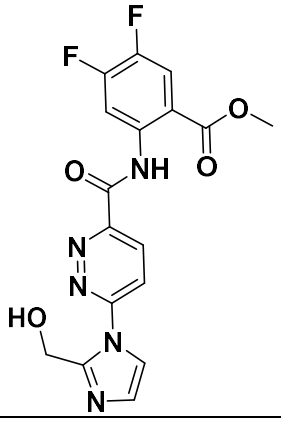
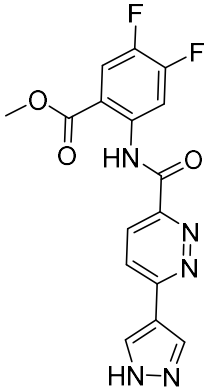
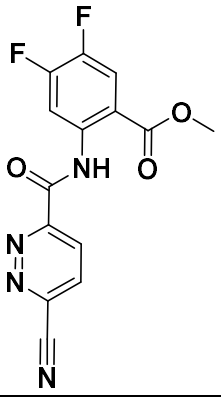
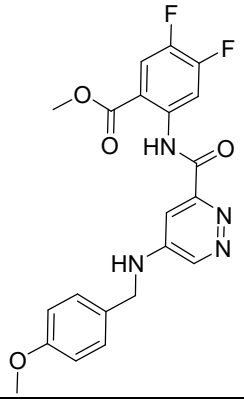
R is H, alkyl, or benzyl, wherein the benzyl can be unsubstituted or substituted with methoxyl or with 1,2,3,4 tetrazole.

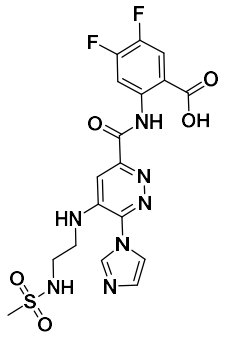
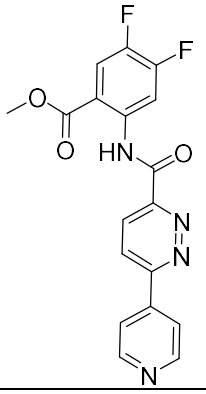
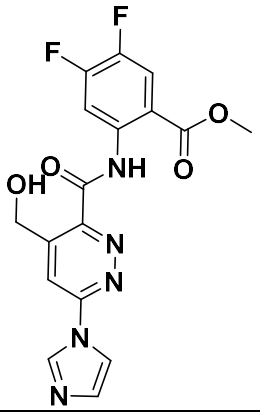
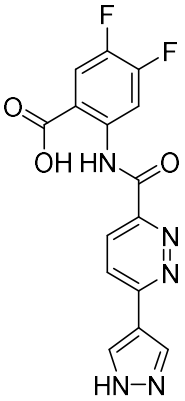
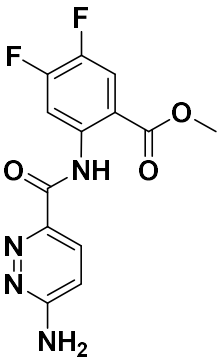
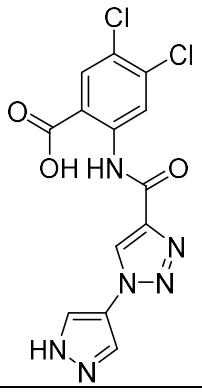
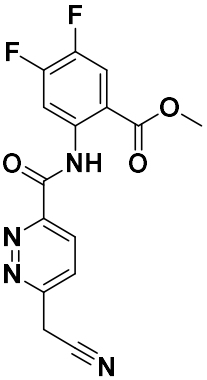
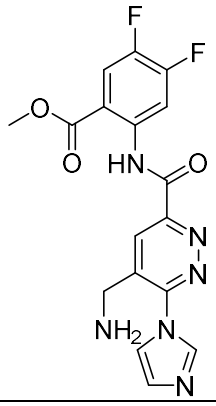
3. The compound according to claim 1, wherein the compound is of formula (II).

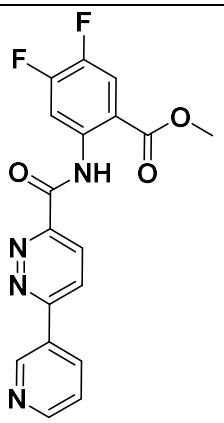
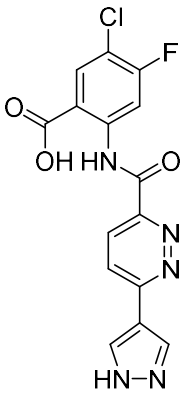
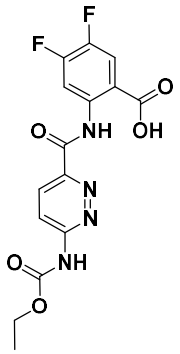
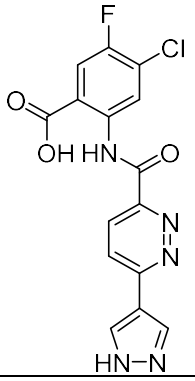
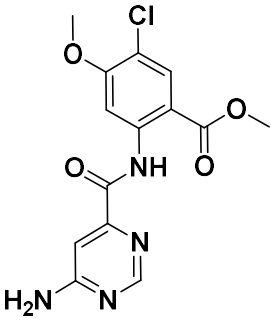
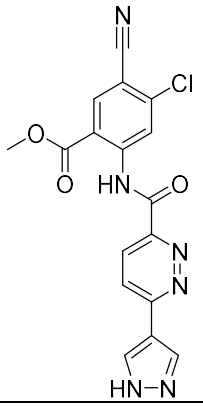
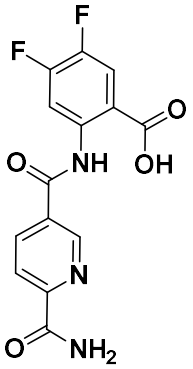
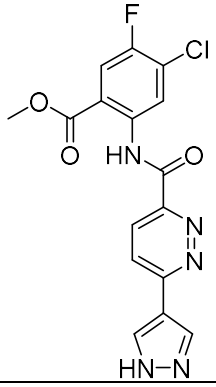
4. The compound according to any one of claims 1 to 3, wherein ring A comprises any one of pyridazinyl, triazolyl, pyrimidinyl, and pyridinyl, any of which can be unsubstituted or substituted.

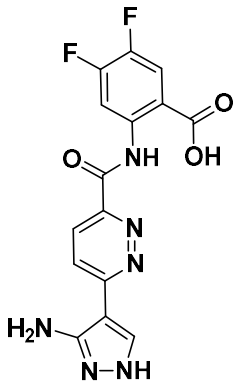
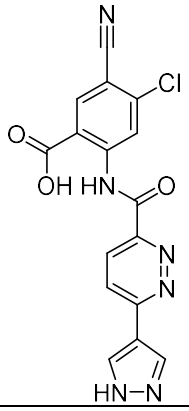
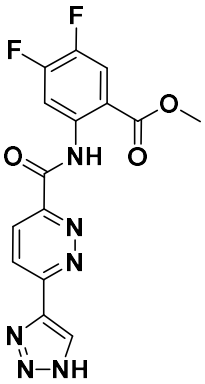
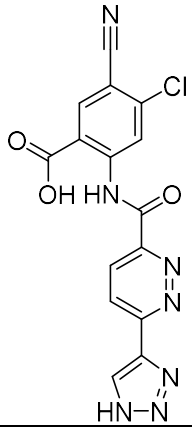
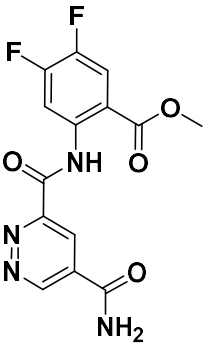
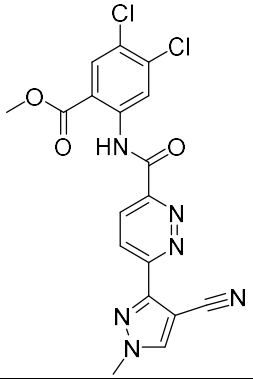
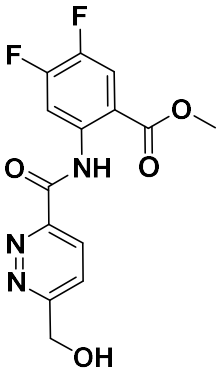
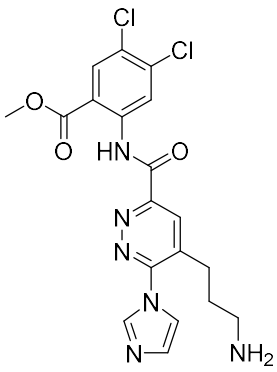
5. The compound according to claim 1, wherein the compound is one selected from the following table:

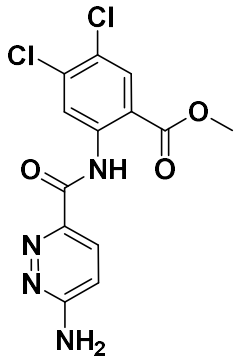
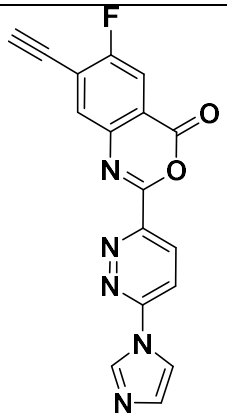
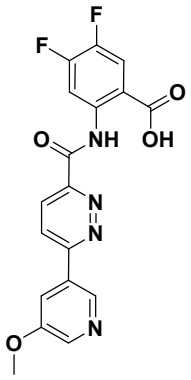
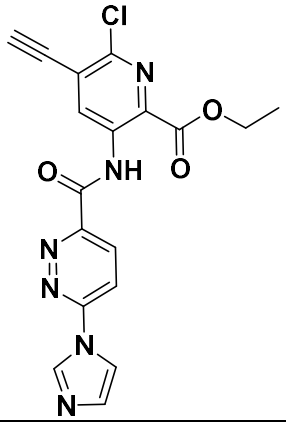
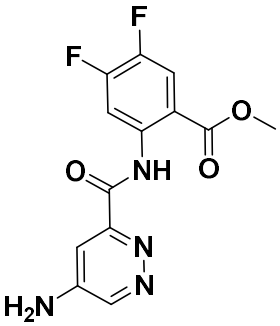
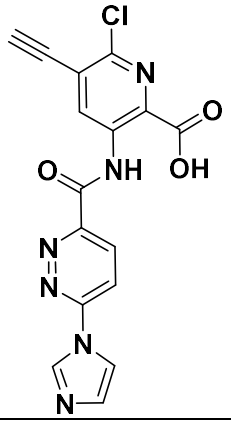
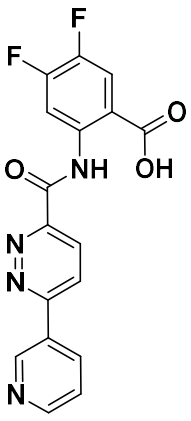
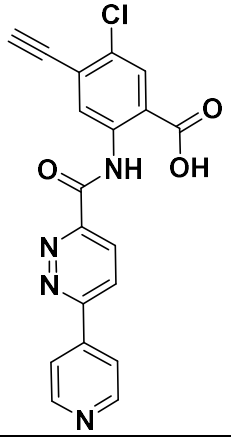
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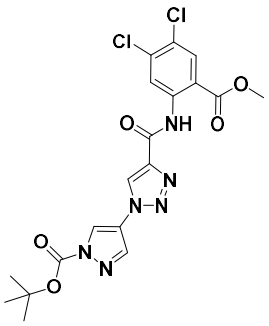
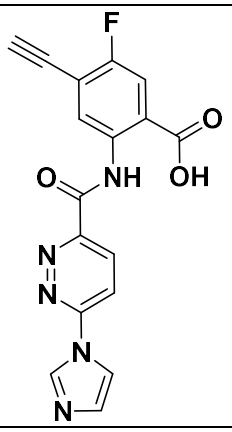
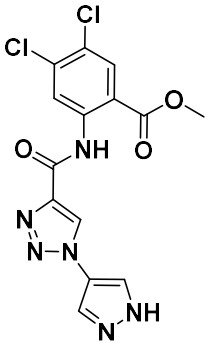
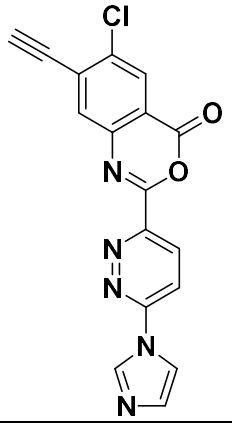
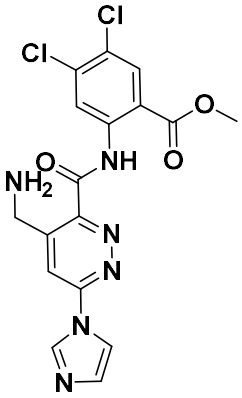
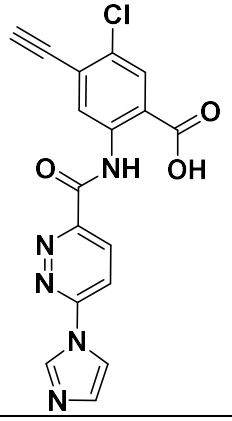
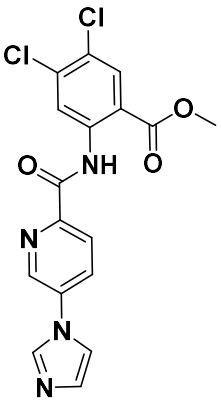
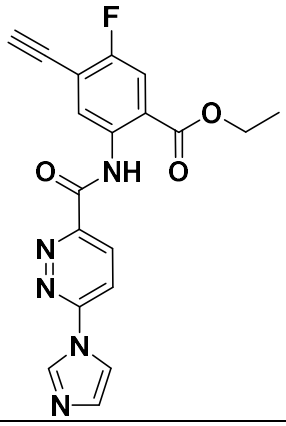
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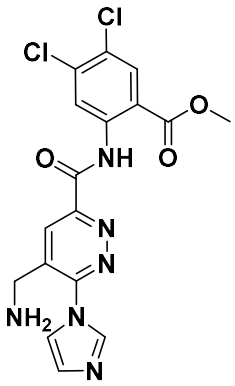
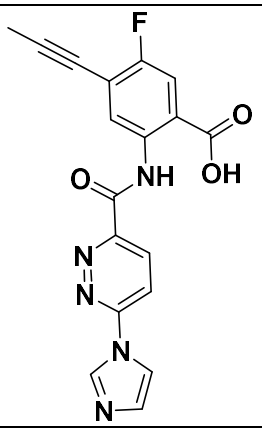
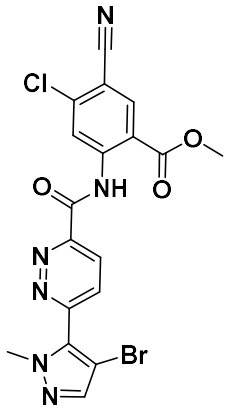
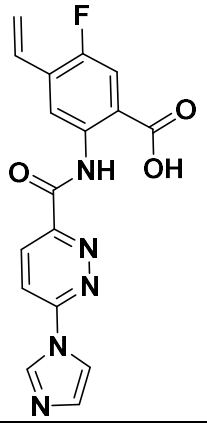
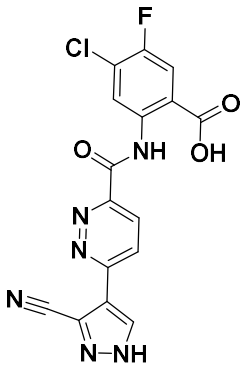
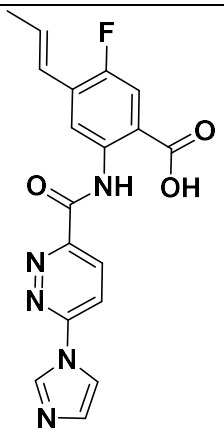
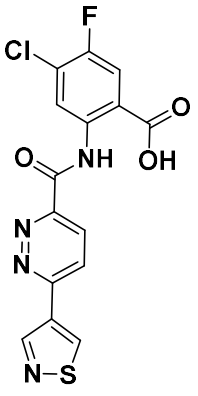
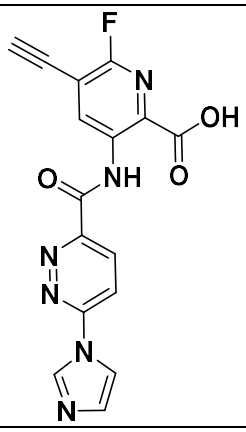
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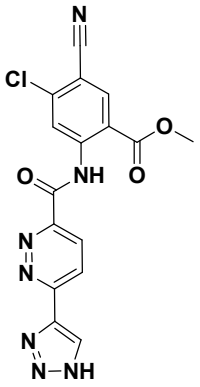
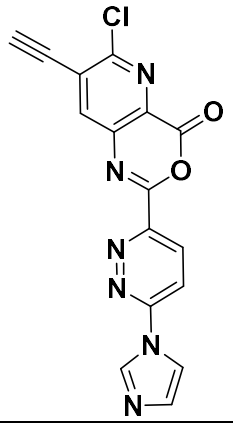
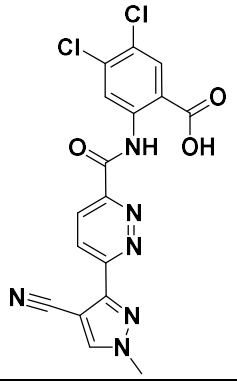
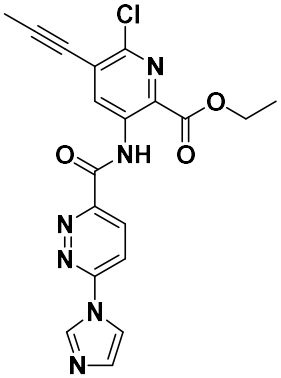
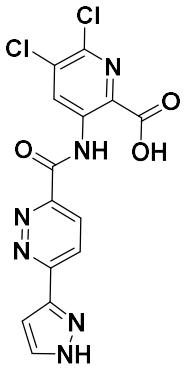
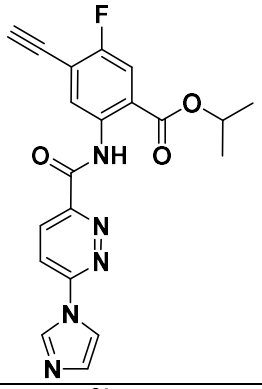
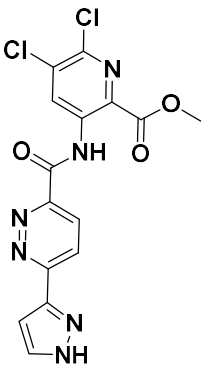
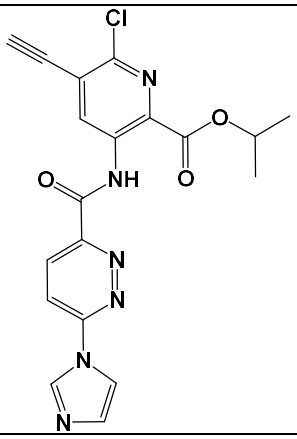
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13		**69**	

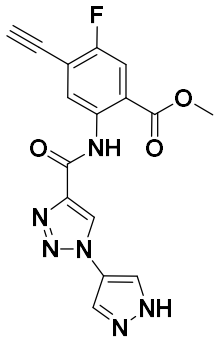
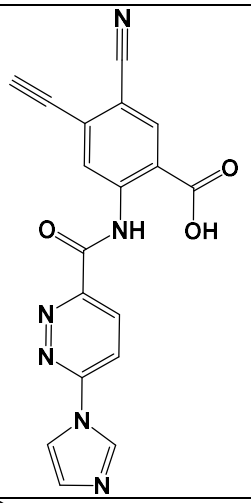
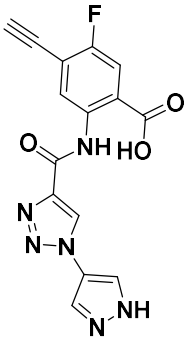
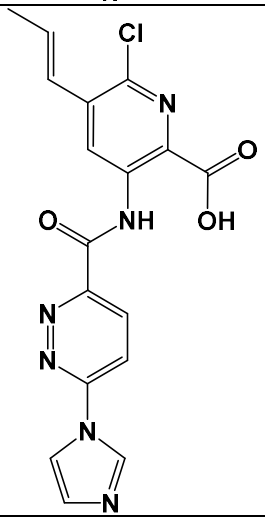
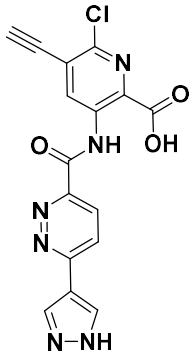
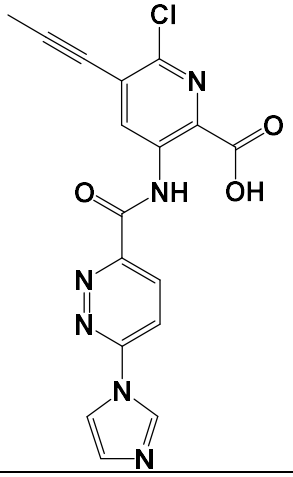
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15		**72**	
16		**73**	
17		**74**	

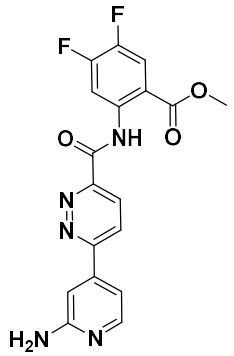
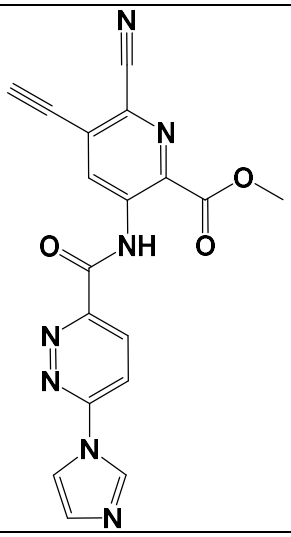
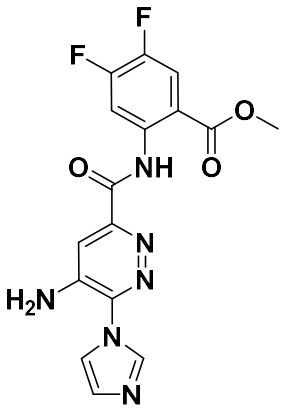
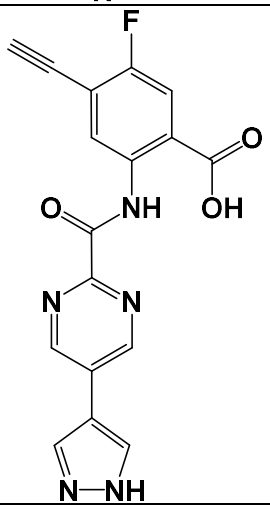
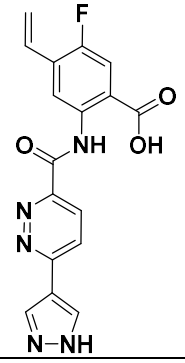
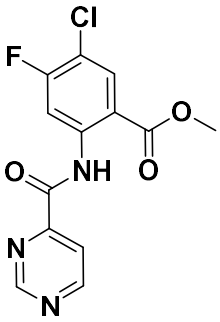
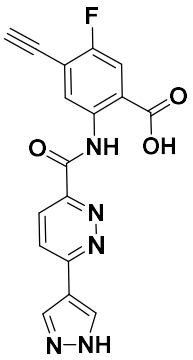
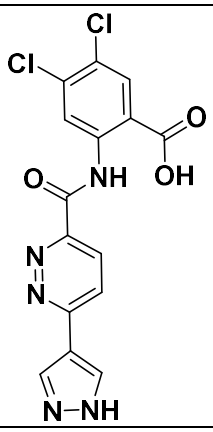
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19		**76**	
20		**77**	
21		**78**	

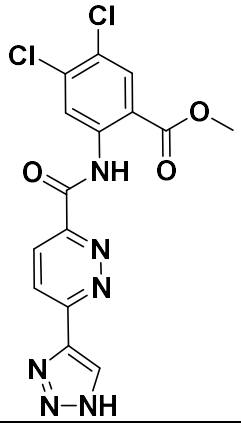
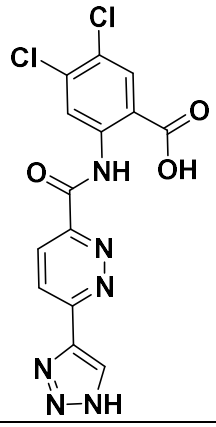
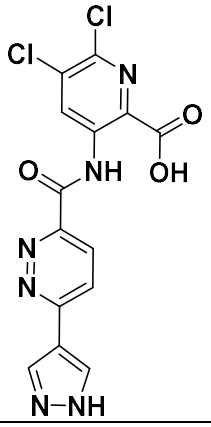
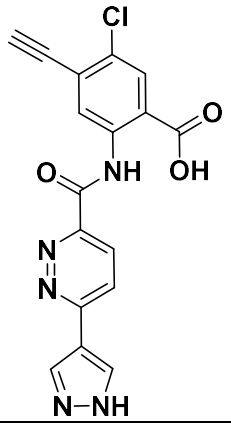
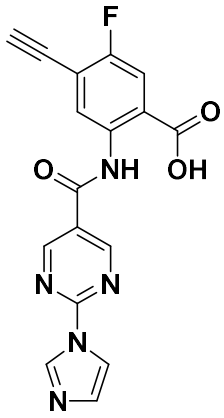
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23		**80**	
24		**81**	
25		**85**	

26		**87**	
27		**88**	
28		**89**	
29		**92**	

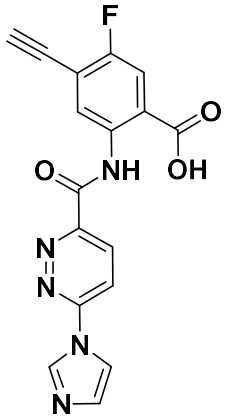
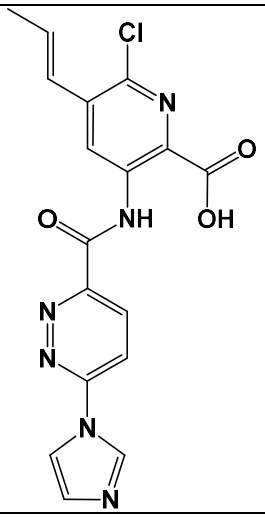
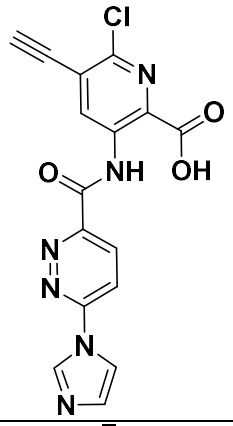
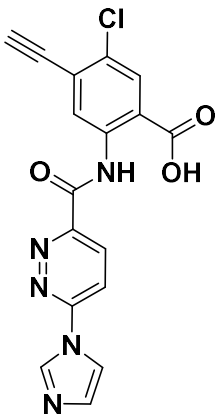
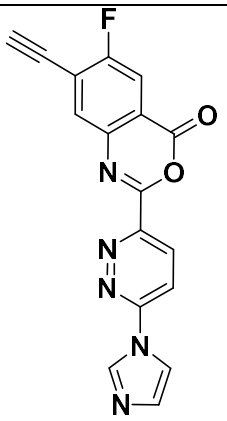
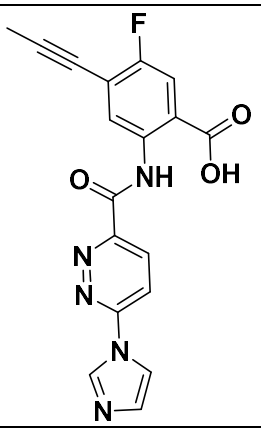
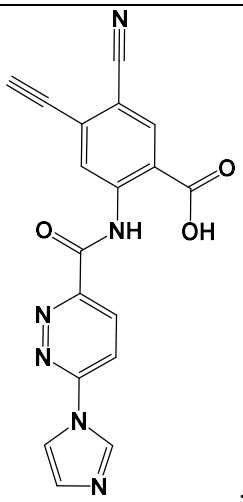
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32		**95**	
33		**96**	
34		**97**	

35		**100**	
36		**101**	
38		**104**	

40		**107**	
41		**108**	
44		**45**	
46		**49**	

50		**51**	
52		**53**	
54			

6. The compound according to claim 1, wherein the compound is one selected from the following table:

79		**101**	
77		**81**	
75		**87**	
100			

7. Use of a compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 6 in the manufacture of a medicament for treating a tumor in a human patient.

8. The use according to claim 7, wherein the compound stimulates expression of interferon genes in the patient.

9. The use according to claim 7 or 8, wherein the medicament is to be administered by oral or intratumoral administration, or both.

10. The use according to claim 7 or 8, wherein the medicament is to be administered to the patient as an antibody-drug conjugate or in a liposomal formulation.

11. The use according to claim 7 or 8, wherein the medicament is to be administered in combination therapy with an immune-checkpoint targeting drug.

12. The use according to claim 11, wherein the immune-checkpoint targeting drug comprises an anti-PD-L1 antibody, anti-PD-1 antibody, anti-CTLA-4 antibody, or an anti-4-1BB antibody.

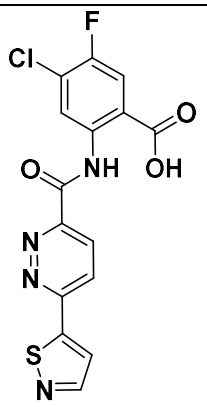
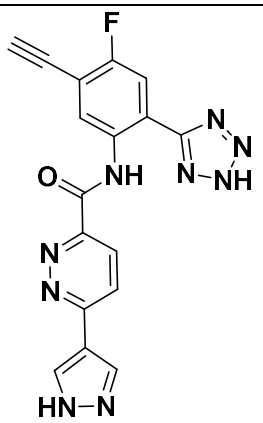
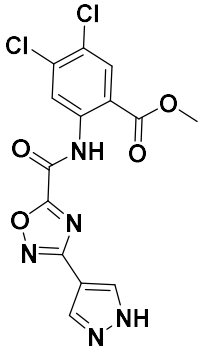
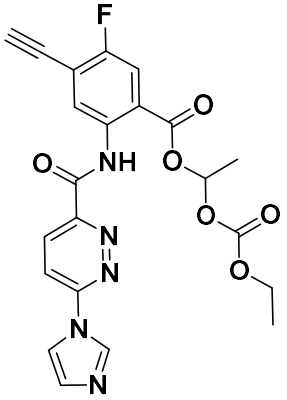
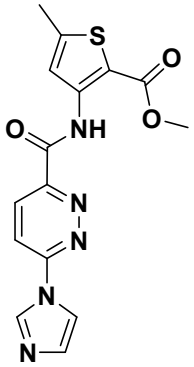
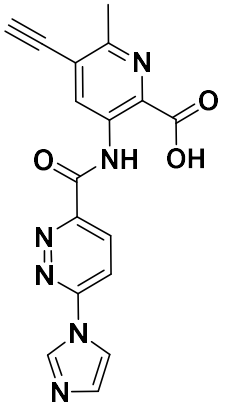
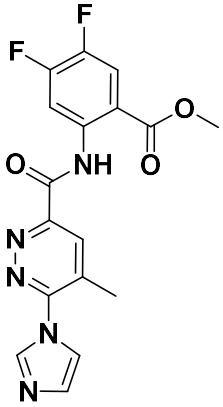
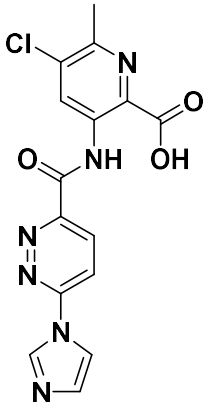
13. The use according to claim 7 or 8, wherein the medicament is to be administered in combination therapy with ionizing radiation or anticancer drugs.

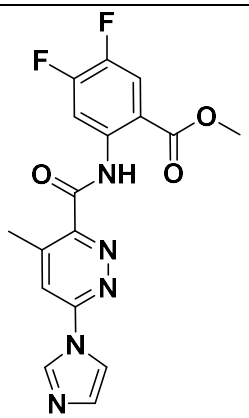
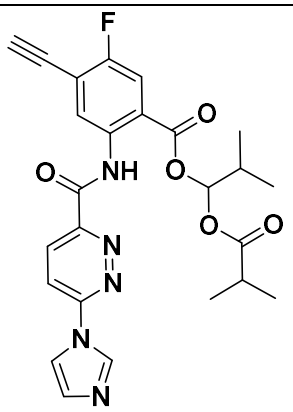
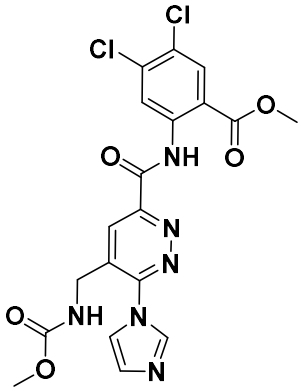
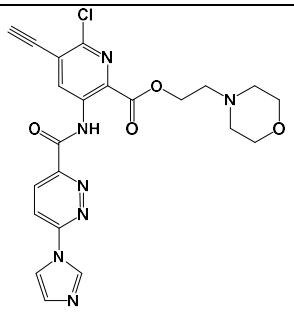
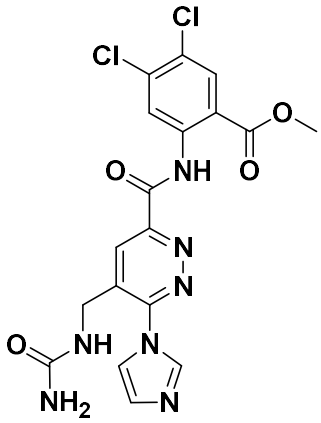
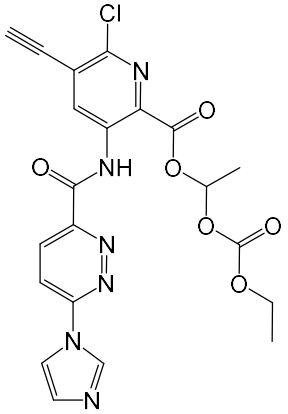
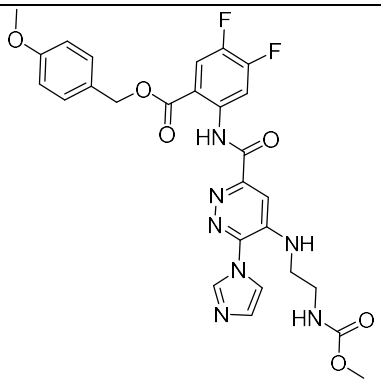
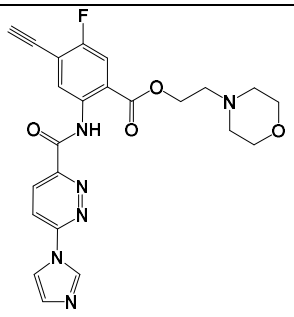
14. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 6 for use in therapy.

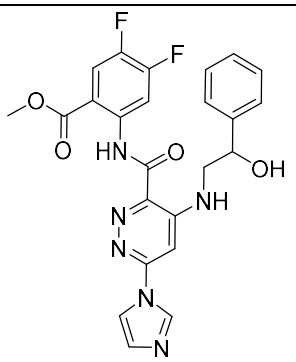
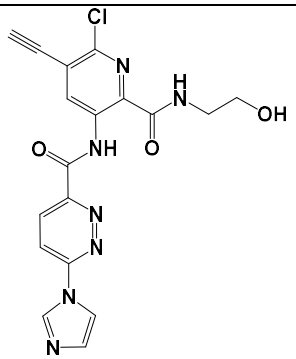
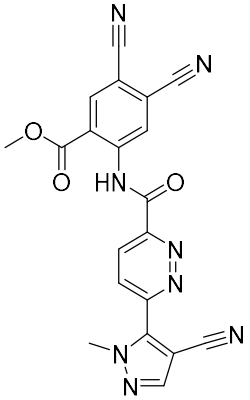
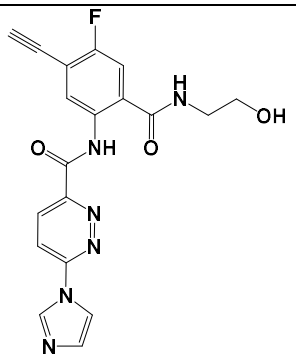
15. The compound for use according to claim 14, wherein the compound stimulates expression of interferon genes in a human patient.

16. The compound for use according to claim 14 or 15, wherein the compound is to be administered to the patient by oral or intratumoral administration, or both.

17. A compound selected from the following table:

31		84	
37		86	
39		90	
42		91	

43		94	
47		98	
48		102	
61		103	

62		105	
71		106	
83	