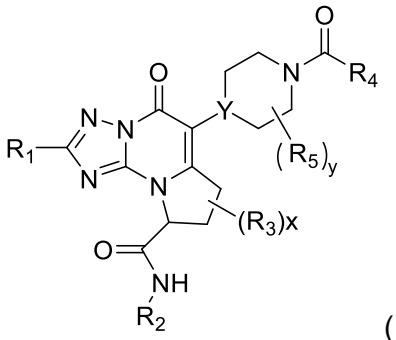
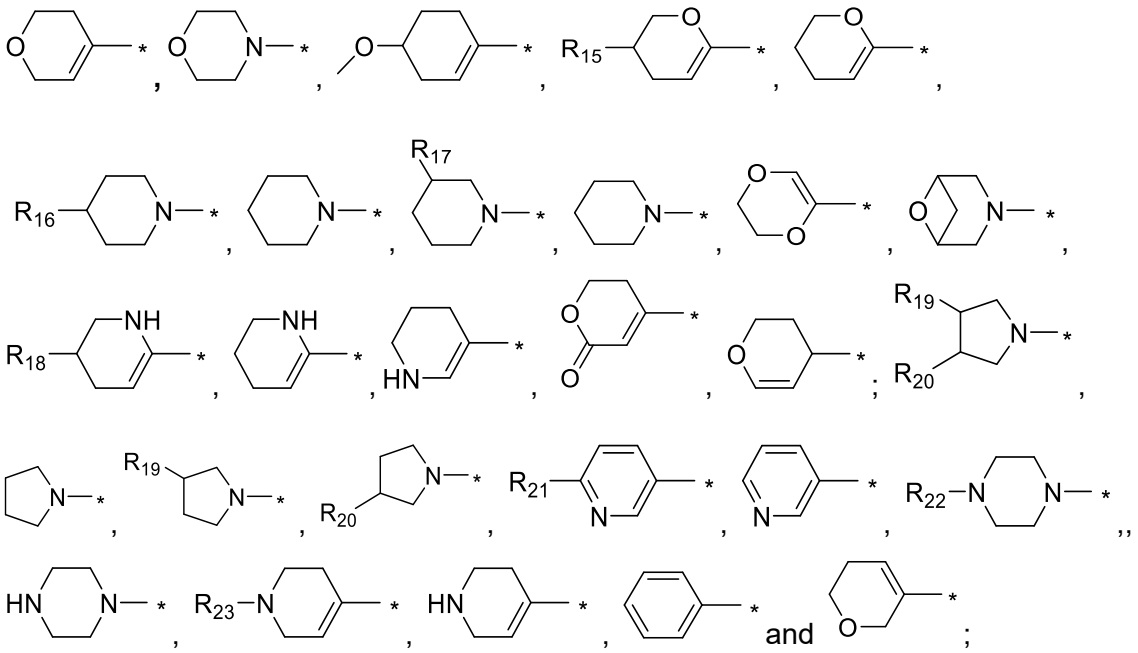
CLAIMS

1. A compound of formula (1g) or a pharmaceutically acceptable salt thereof,



(1g)

and wherein R_1 is selected from:



R_{15} is F;

R_{16} is $R_{25}(R_{24})N$-;

R_{17} is F;

R_{18} is F;

R_{19} is F;

R_{20} is F;

R_{21} is CH_3;

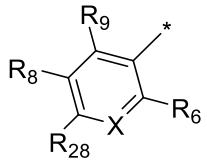
R_{22} is CF_3, CHF_2CH_2, $HOC(O)\text{-}CH_2\text{-}$, $H_3C\text{-}C(O)\text{-}$, $(H_3C)_3C\text{-}O\text{-}C(O)\text{-}$;

R_{23} is CF_3, $CHF_2CH_2\text{-}$, $(H_3C)_3C\text{-}O\text{-}C(O)\text{-}$;

R_{24} is CH_3; and

R_{25} is $CHF_2CH_2\text{-}$;

R_2 is the moiety:



wherein

R_6 is selected from H, halo, $(C_1\text{-}C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo;

R_8 is selected from H, halo, $(C_1\text{-}C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo;

R_9 is selected from H, $O\text{-}CH_3$, OH, CN, CH_3 and halo;

R_{28} is selected from SF_5, halo, $(C_1\text{-}C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 halo and -C(O)H;

X is selected from $C\text{-}R_7$ and N; and

R_7 is selected from H and halo;

R_3 is $(C_1\text{-}C_4)$alkyl unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halo and OH;

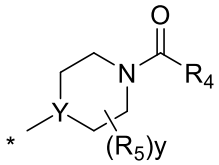
x is 0 or 1;

Y is N;

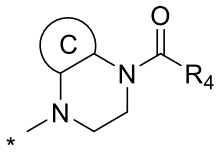
y is 0, 1 or 2;

R_5 is selected from CH_3;

or wherein in the moiety:



two R_5 substituents on adjacent carbon atoms join to form ring C:

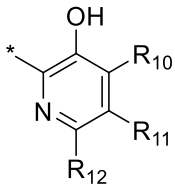


-wherein ring C is a fused (C_3-C_6)cycloalkyl ring, and said fused (C_3-C_6)cycloalkyl ring is unsubstituted or substituted with 1 or 2 R_{40} groups, wherein said R_{40} is selected from:

- (C_1-C_2)alkyl, wherein each (C_1-C_2)alkyl is independently unsubstituted or substituted by OH or 1, 2 or 3 halo,
- halo, in particular F,
- or wherein two R_{40} substituents on the same ring carbon atom may join, together with the carbon atom to which they are attached, to form a (C_3-C_4)cycloalkyl spiro ring or a 3 or 4-membered heterocyclyl spiro ring, wherein said heterocyclyl spiro ring contains ring carbon ring atoms and one ring heteroatom selected from O, N and S;
- or wherein two R_{40} substituents on adjacent carbon atoms join together with the carbon atoms to which they are attached, to form a fused cyclopropyl ring;

R_4 is selected from:

CH_3,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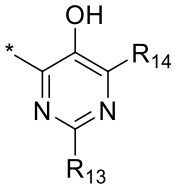
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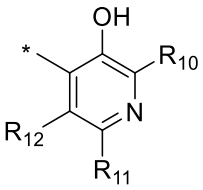
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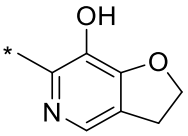
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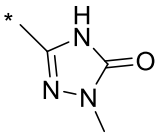
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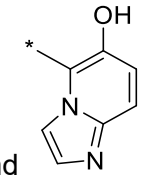
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wherein

R_{10} is selected from H, halo, $(C_1\text{-}C_2)$alkyl unsubstituted or substituted by 1, 2 or 3 halo substituents, -O-$(C_1\text{-}C_2)$alkyl unsubstituted or substituted by 1, 2 or 3 halo substituents;

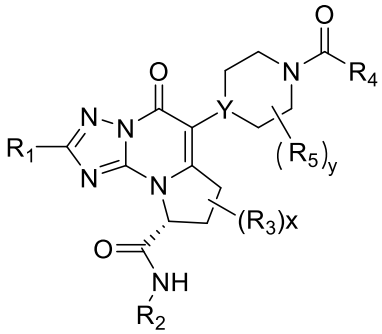
R_{11} is selected from H, halo, $(C_1\text{-}C_2)$alkyl unsubstituted or substituted by 1, 2 or 3 halo substituents;

R_{12} is selected from H, halo, $(C_1\text{-}C_2)$alkyl unsubstituted or substituted by 1, 2 or 3 halo substituents;

R_{13} is selected from H, -S-CH_3, halo, $(C_1\text{-}C_2)$alkyl unsubstituted or substituted by 1, 2 or 3 halo substituents; and

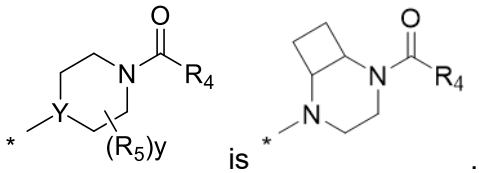
R_{14} is selected from H, halo, $(C_1\text{-}C_2)$alkyl unsubstituted or substituted by 1, 2 or 3 halo substituents, O-$(C_1\text{-}C_2)$alkyl unsubstituted or substituted by 1, 2 or 3 halo substituents, and cyclopropyl.

2. A compound of formula (1g) or a pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound of formula (1g) is formula (1g') or a pharmaceutically acceptable salt thereof:



(1g').

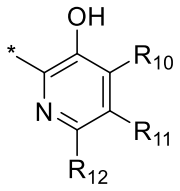
3. A compound of formula (1g) or a pharmaceutically acceptable salt thereof according to claim 1, or a compound of formula (1g') or a pharmaceutically acceptable salt thereof according to claim 2, wherein the moiety:



is

.

4. A compound of formula (1g) or a pharmaceutically acceptable salt thereof according to any of claims 1 to 3, or a compound of formula (1g') or a pharmaceutically acceptable salt thereof according to any of claims 1 to 3, wherein R_4 is selected from:



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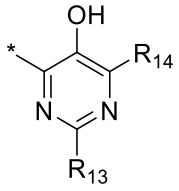
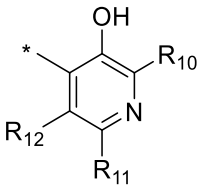


and



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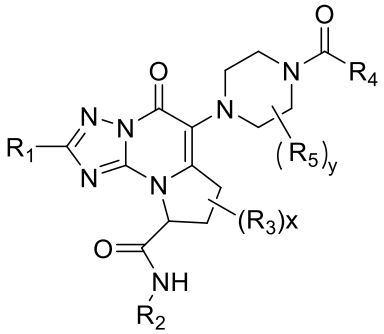
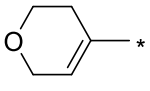
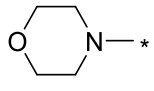
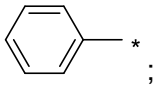
5. A compound of formula (1g) or (1g'), or a pharmaceutically acceptable salt thereof, according to any of claims 1 to 4, wherein the compound is formula (1h)



(1h),

wherein:

R_1 is selected from:


, 
and 
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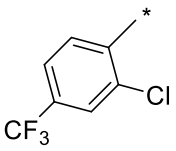
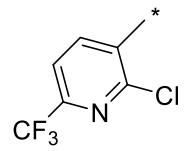
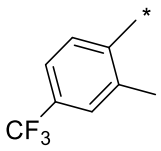
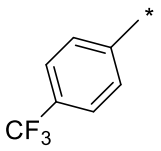
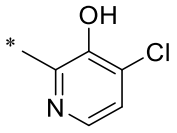
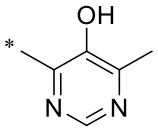
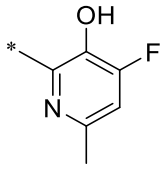
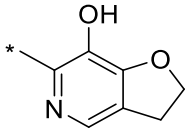
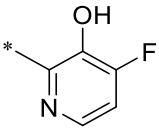
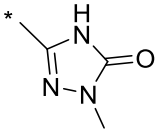
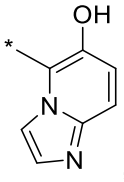
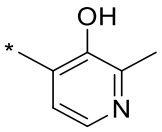
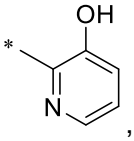
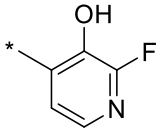
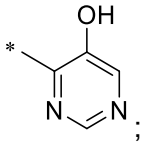
R_2 is selected from:


, 
, 
and 
;

R_3 is CH_3;

x is 0 or 1;

R_4 is selected from:

-CH_3, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
and 
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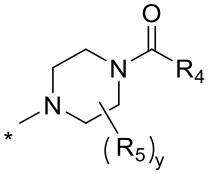
y is 0 or 1;

R_5 is selected from CH_3;

or wherein the moiety:



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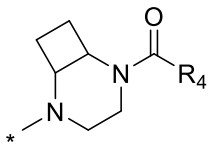

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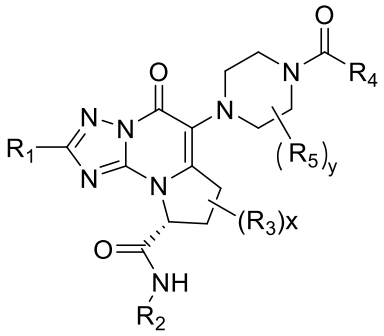
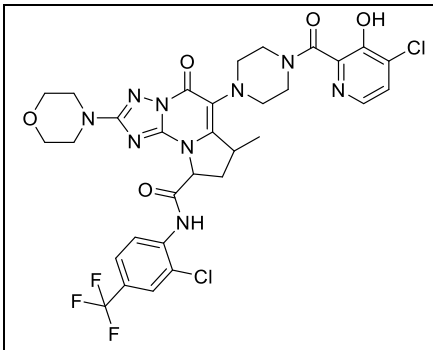
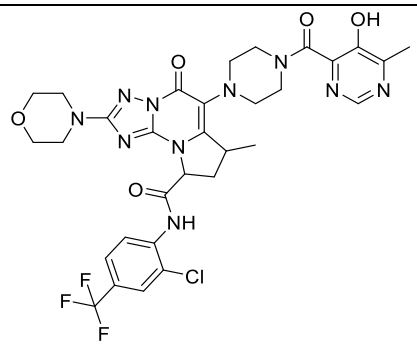
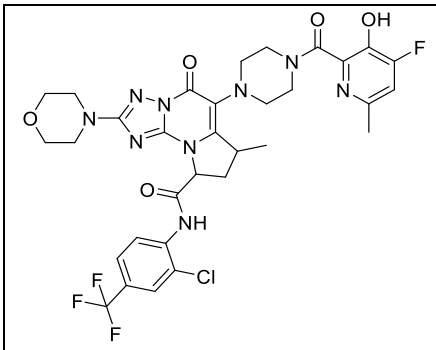
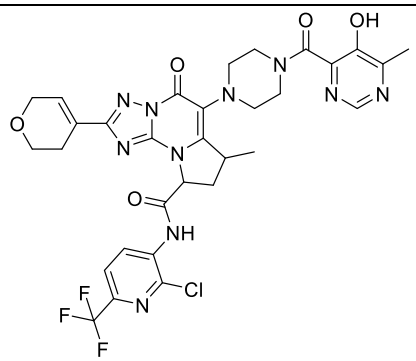
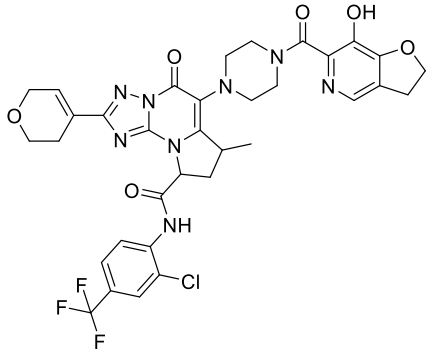
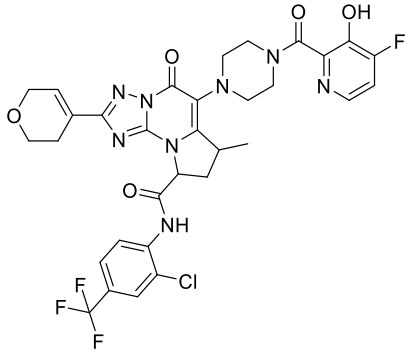
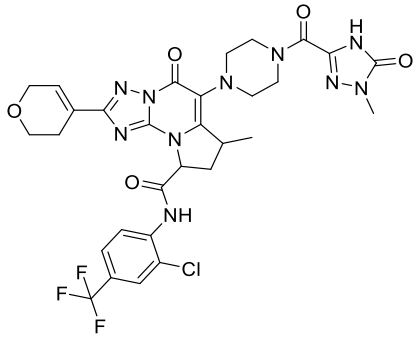
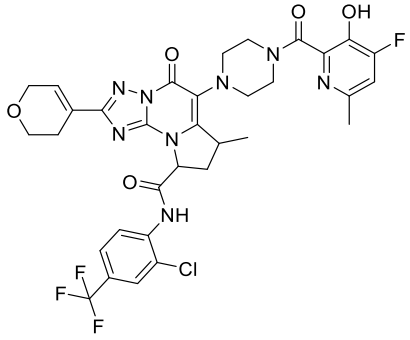
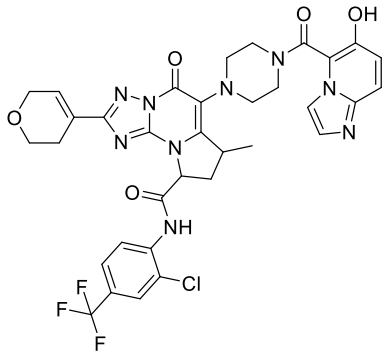
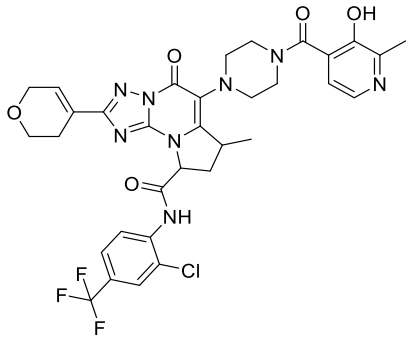
6. A compound of formula (1h), or a pharmaceutically acceptable salt thereof, according to claim 5, wherein the compound is formula (1h')

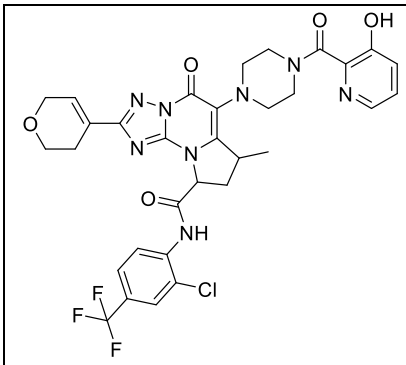
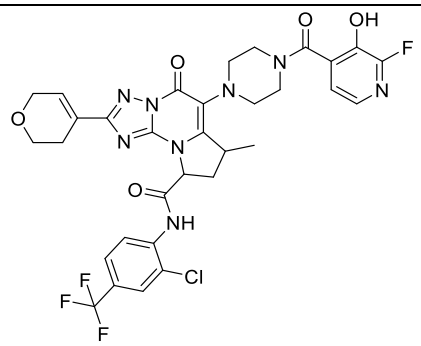
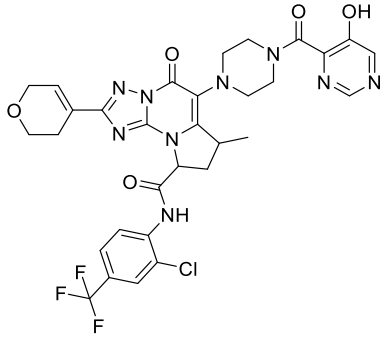
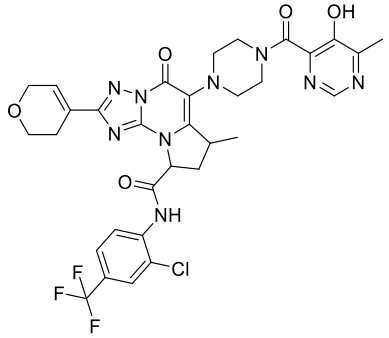
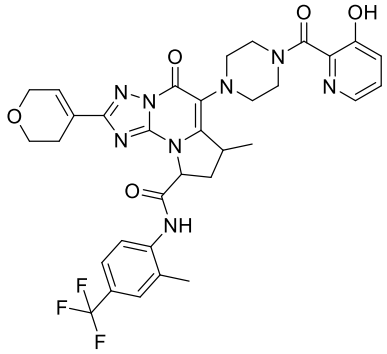
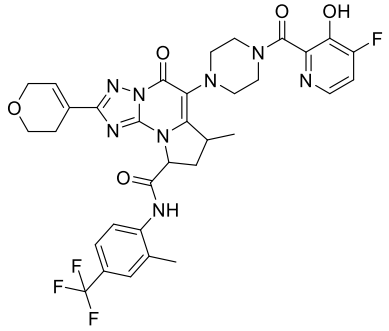
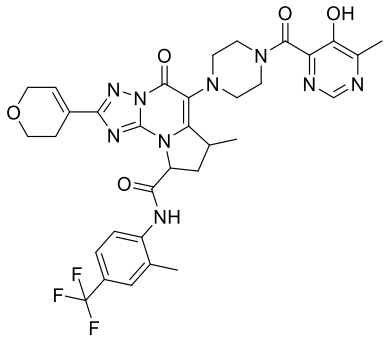
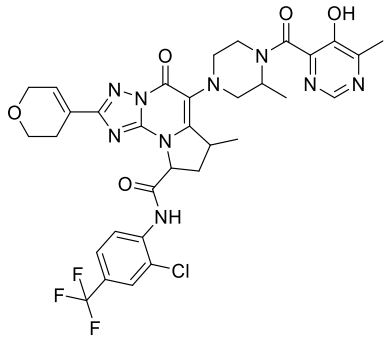


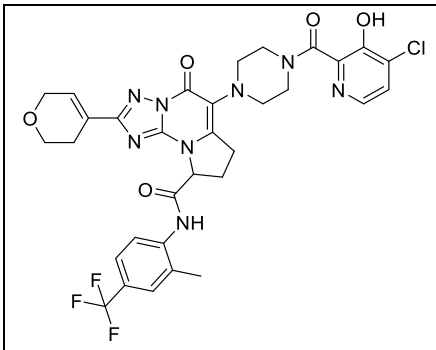
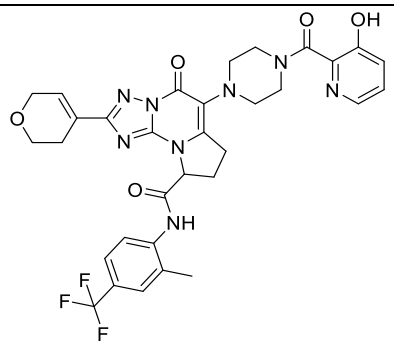
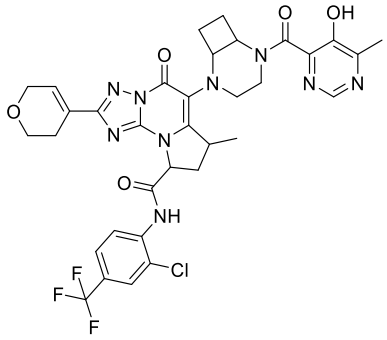
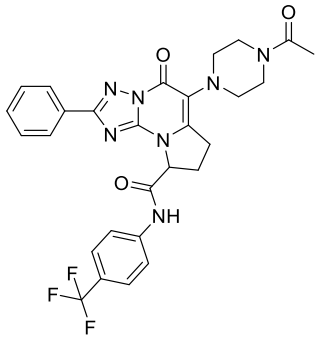
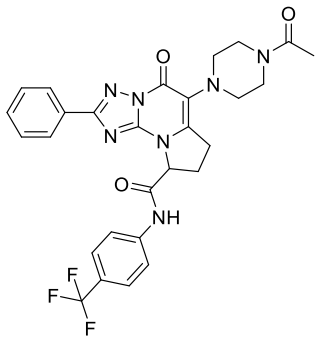
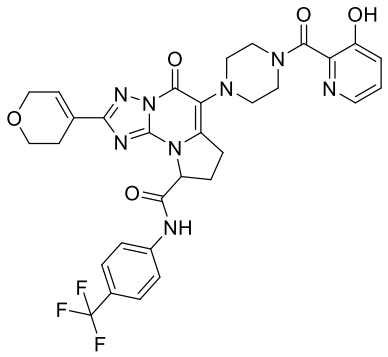
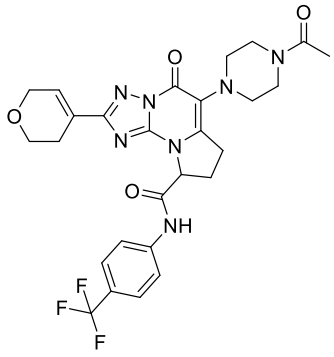
(1h')

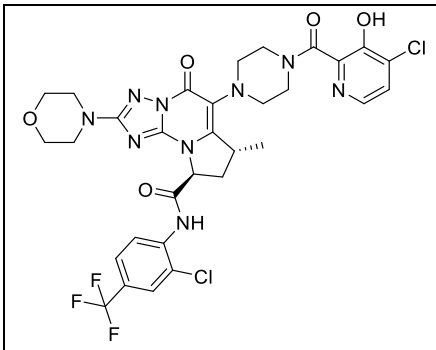
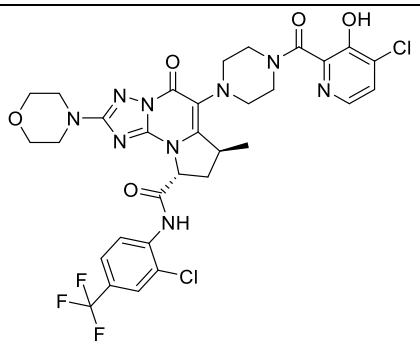
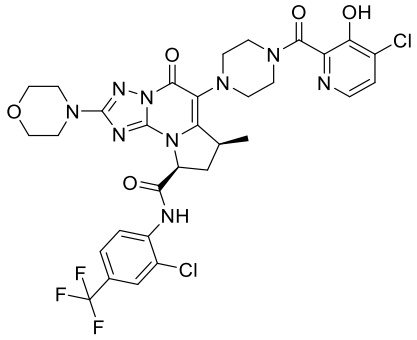
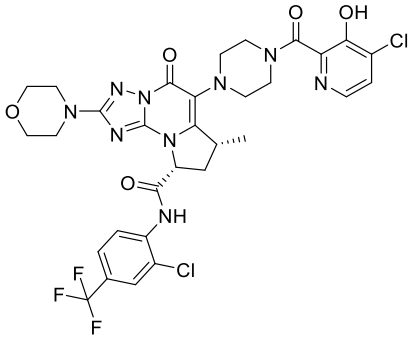
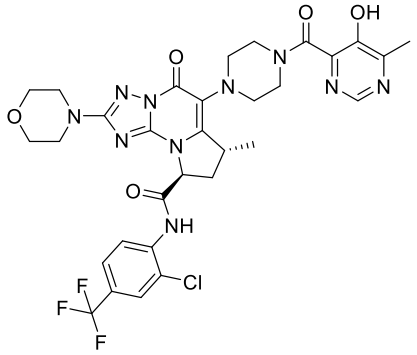
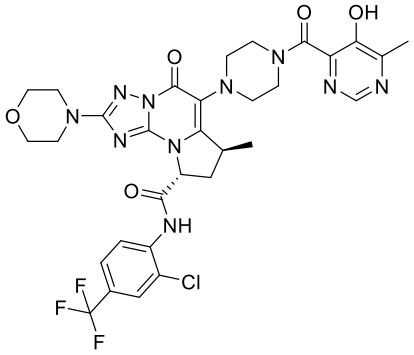
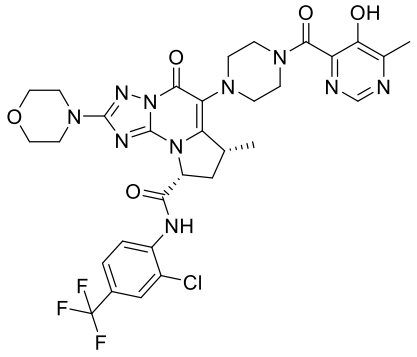
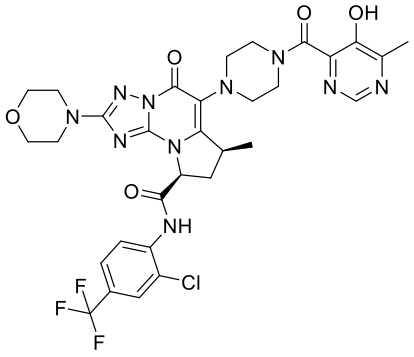
7. A compound of formula (1g) or a pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is selected from:

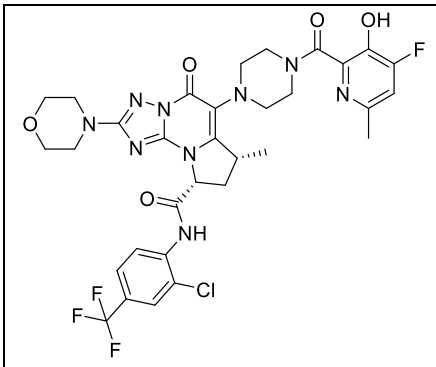
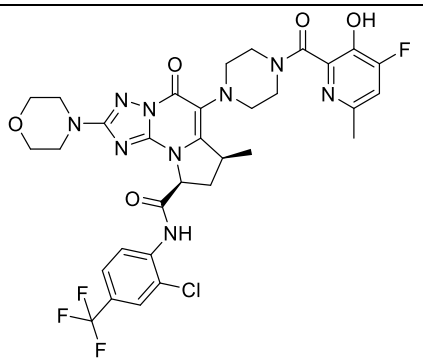
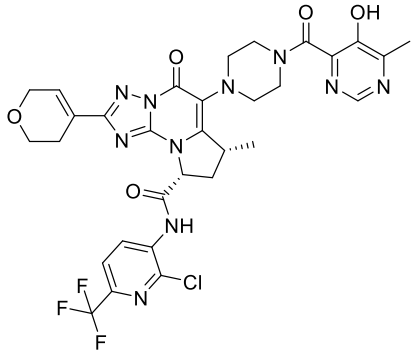
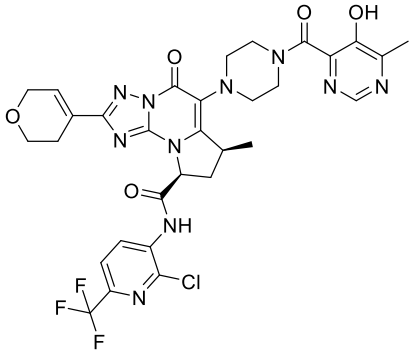
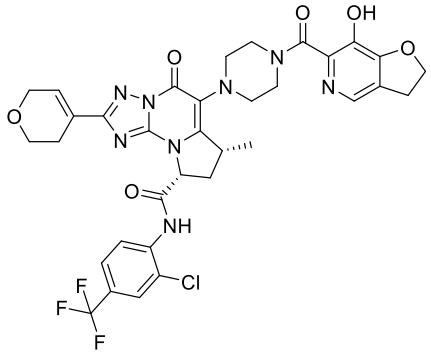
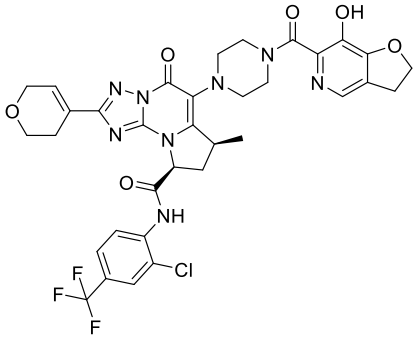
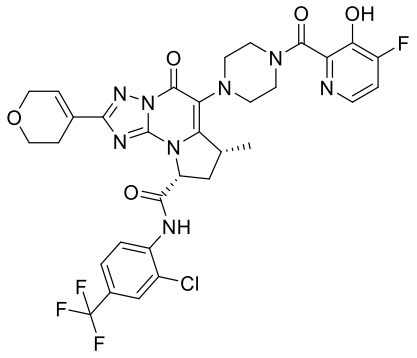
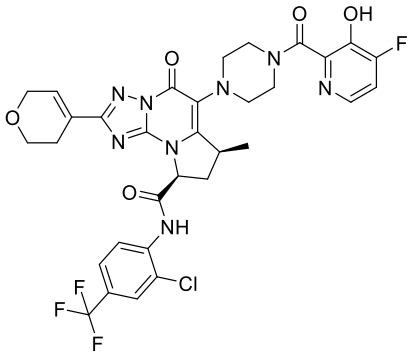
	

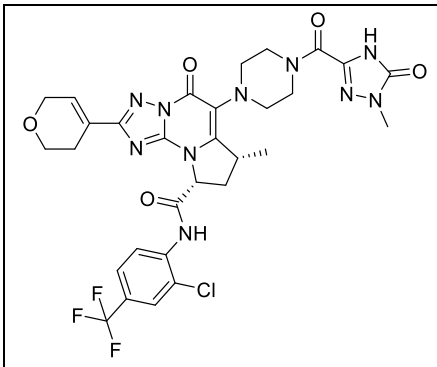
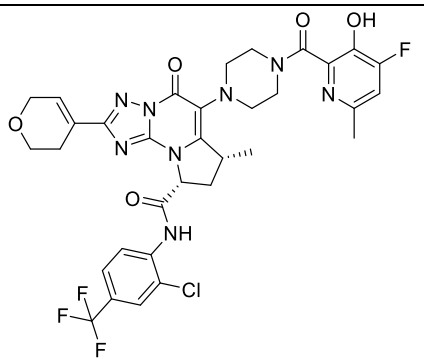
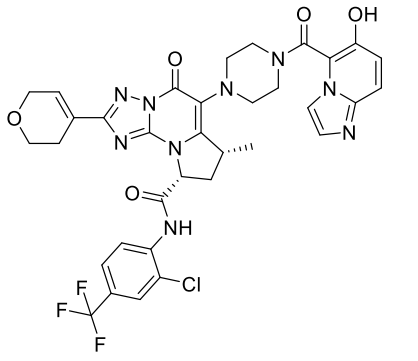
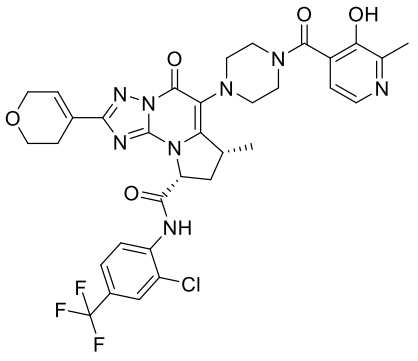
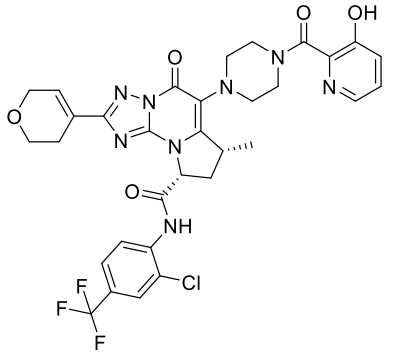
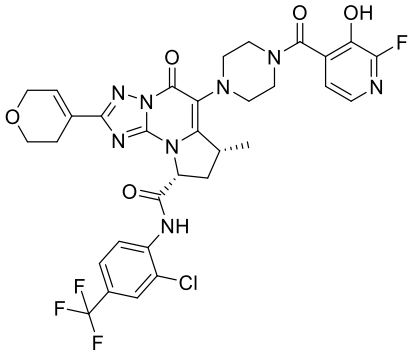
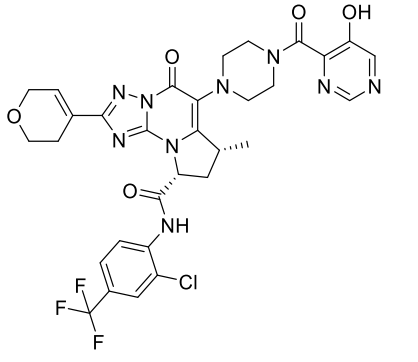
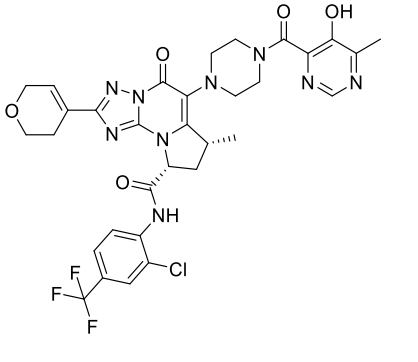
	
	
	
	

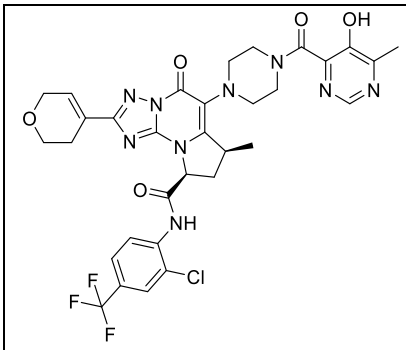
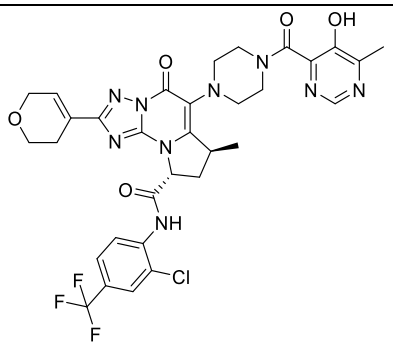
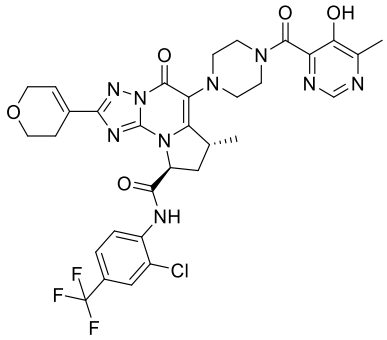
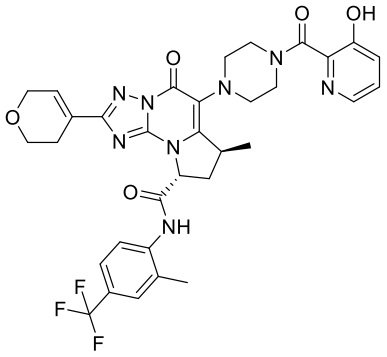
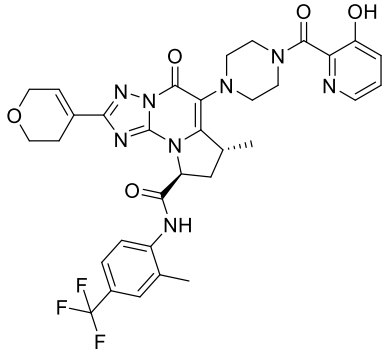
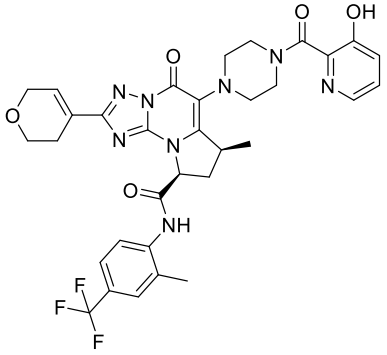
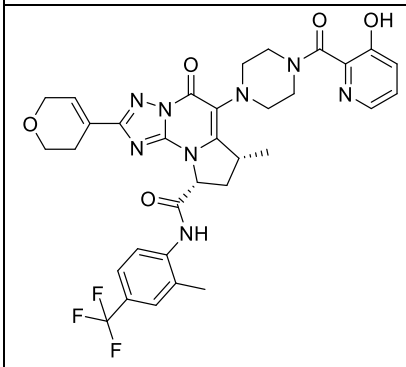
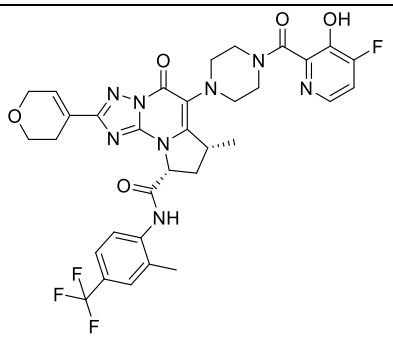
	
	
	
	

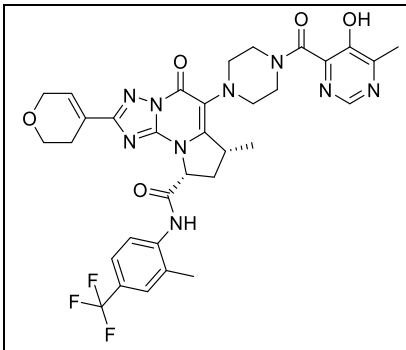
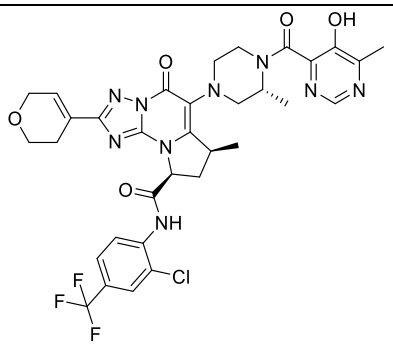
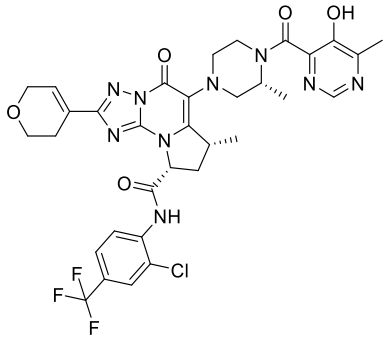
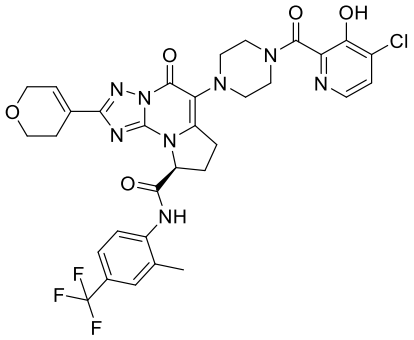
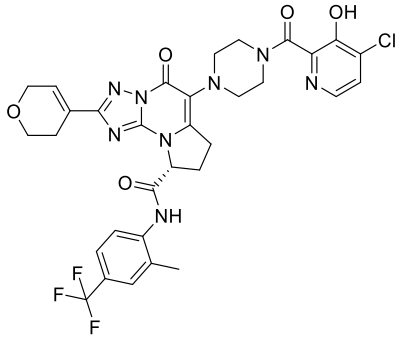
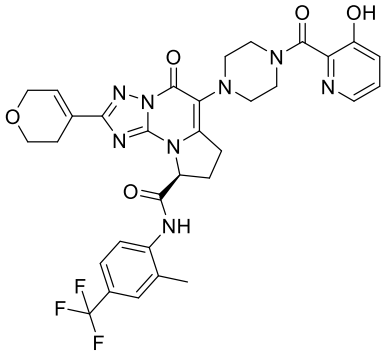
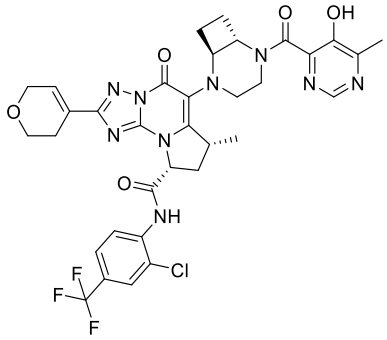
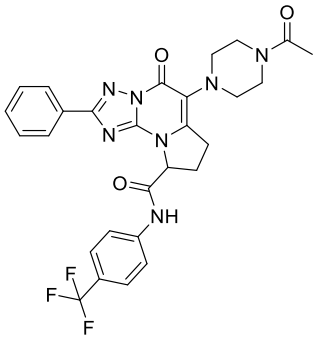
	
	
	
	

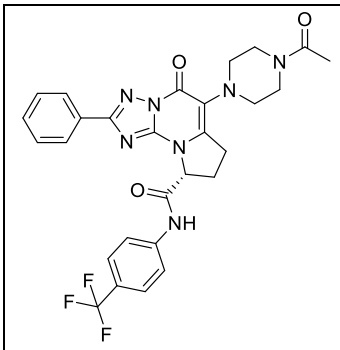
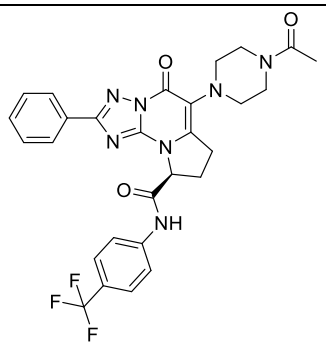
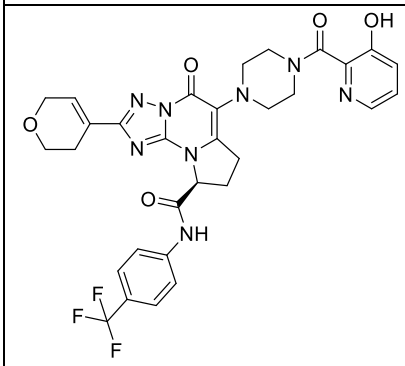
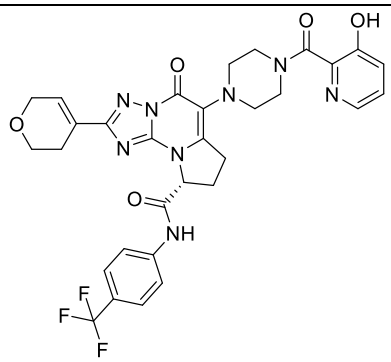
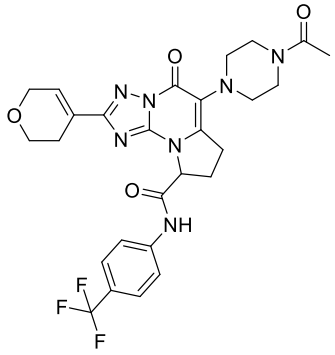
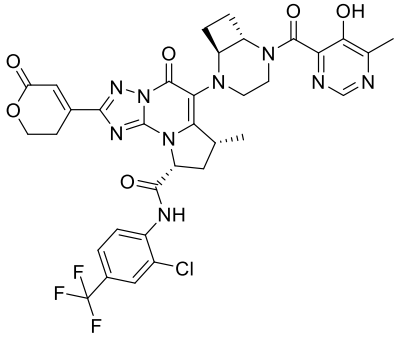
	
	
	
	

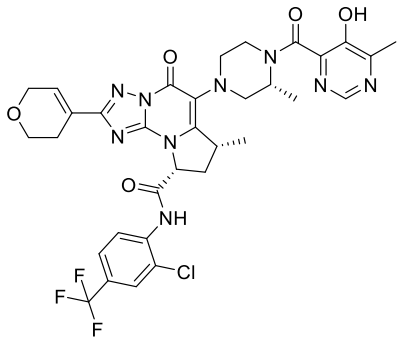
	
	
	
	

8. A compound of formula (1g), according to claim 1, wherein the compound is (7R,9R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-dihydro-2H-pyran-4-yl)-6-((R)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-methylpiperazin-1-yl)-7-methyl-5-oxo-5,7,8,9-tetrahydropyrrolo[1,2-c][1,2,4]triazolo[1,5-a]pyrimidine-9-carboxamide, or a pharmaceutically acceptable salt thereof



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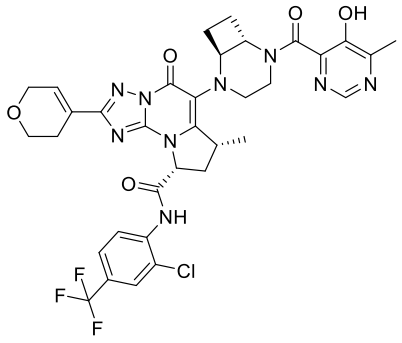
9. A compound of formula (1g), according to claim 1, wherein the compound is (7R,9R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-dihydro-2H-pyran-4-yl)-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-methyl-5-oxo-5,7,8,9-tetrahydropyrrolo[1,2-c][1,2,4]triazolo[1,5-a]pyrimidine-9-carboxamide, or a pharmaceutically acceptable salt thereof



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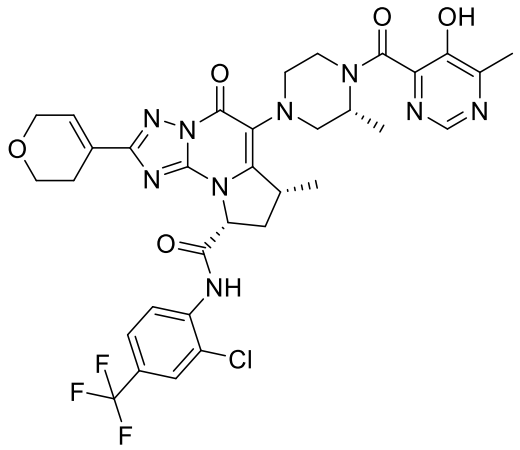
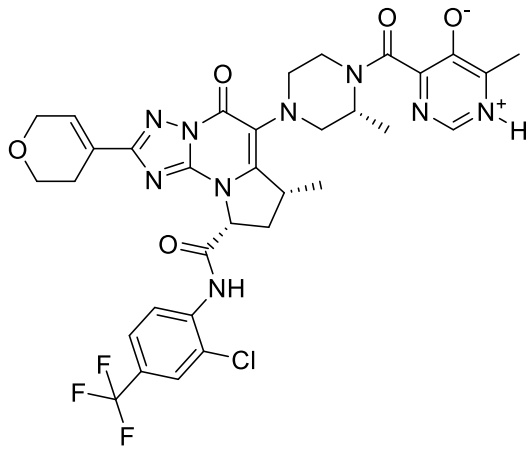
10. A compound of formula (1g), according to claim 1, wherein the compound is (7R,9R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-dihydro-2H-pyran-4-yl)-6-((R)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-methylpiperazin-1-yl)-7-methyl-5-oxo-5,7,8,9-tetrahydropyrrolo[1,2-c][1,2,4]triazolo[1,5-a]pyrimidine-9-carboxamide:

in non-zwitterionic form:



or zwitterionic form:



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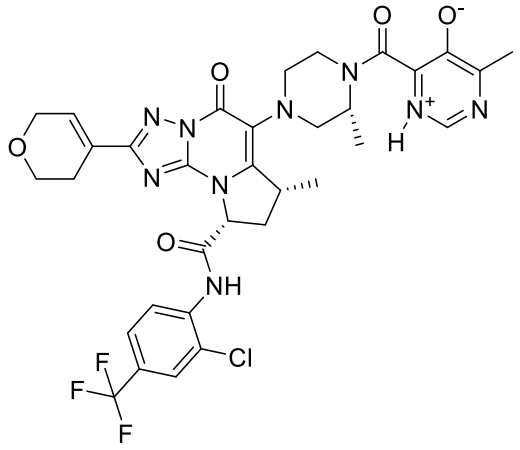
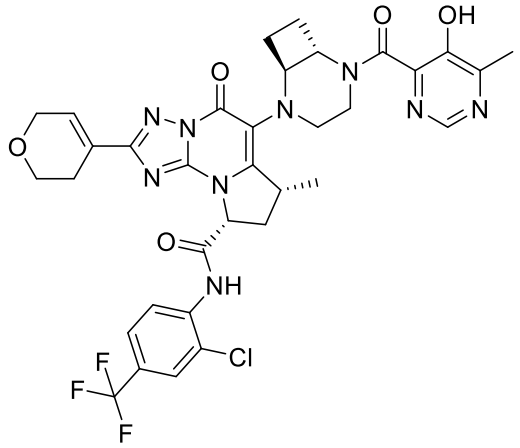


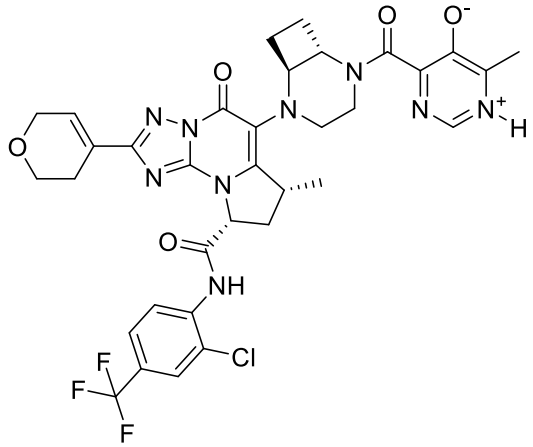
or a mixture of any two or three of said forms.

11.. A compound of formula (1g), according to claim 1, wherein the compound is (7R,9R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-dihydro-2H-pyran-4-yl)-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-methyl-5-oxo-5,7,8,9-tetrahydropyrrolo[1,2-c][1,2,4]triazolo[1,5-a]pyrimidine-9-carboxamide:

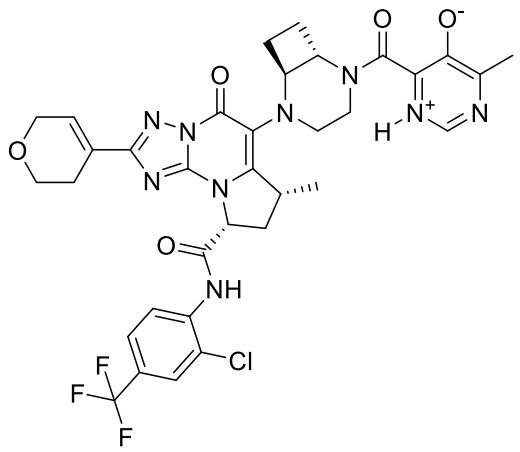
in non-zwitterionic form



or in zwitterionic form:



or in zwitterionic form:

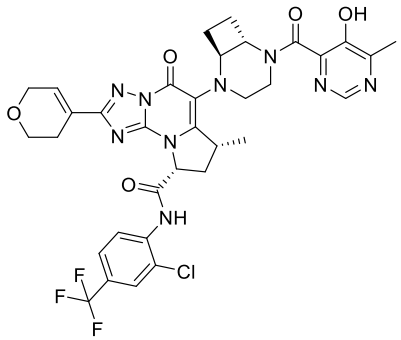


or a mixture of any two or three of said forms.

12. A compound of formula (1g), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is (7R,9R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-dihydro-2H-pyran-4-yl)-6-((R)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-methylpiperazin-1-yl)-7-methyl-5-oxo-5,7,8,9-tetrahydropyrrolo[1,2-c][1,2,4]triazolo[1,5-a]pyrimidine-9-carboxamide, in crystalline form.

13. A compound of formula (1g), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is (7R,9R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-dihydro-2H-pyran-4-yl)-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-methyl-5-oxo-5,7,8,9-tetrahydropyrrolo[1,2-c][1,2,4]triazolo[1,5-a]pyrimidine-9-carboxamide, in crystalline form.

14. The compound of formula (1g), according to claim 1, wherein the compound is (7R,9R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-dihydro-2H-pyran-4-yl)-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-methyl-5-oxo-5,7,8,9-tetrahydropyrrolo[1,2-c][1,2,4]triazolo[1,5-a]pyrimidine-9-carboxamide,

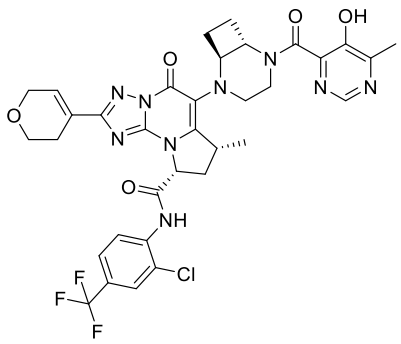


characterized by a X-ray powder diffraction pattern comprising 4 or more 2θ values selected from the group consisting of 5.77±0.2, 6.67±0.2, 10.54±0.2, 12.36±0.2, 12.90±0.2, 13.02±0.2, 14.83±0.2, 15.27±0.2, 15.65±0.2, 15.99±0.2, 17.34±0.2, 18.52±0.2, 19.18±0.2, 20.04±0.2, 21.17±0.2, 21.47±0.2, 21.86±0.2, 22.96±0.2, 23.18±0.2 and 23.9±0.2 at a temperature of about 22°C, when measured with CuKα radiation having a wavelength of 0.15418nm.

15. A compound of formula (1g), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is in amorphous form.

16. A compound of formula (1g), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is a sodium salt.

17. A compound of formula (1g), according to claim 16, wherein the compound is (7R,9R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-dihydro-2H-pyran-4-yl)-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-methyl-5-oxo-5,7,8,9-tetrahydropyrrolo[1,2-c][1,2,4]triazolo[1,5-a]pyrimidine-9-carboxamide,



sodium salt.

18. A combination comprising a compound of formula (1g), or a pharmaceutically acceptable salt thereof, according to any of claims 1 to 17, and one or more additional therapeutically active agents.

19. A combination according to claim 18, wherein an additional therapeutically active agent is an anti-cancer agent.

20. A combination according to claim 18, wherein an additional therapeutically active anti-cancer agent is a chemotherapy.

21. A combination according to claim 20, wherein an additional therapeutically active agent is a chemotherapy selected from anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone

(Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®), in particular irinotecan.

22. A combination according to claim 18, wherein an additional therapeutically active agent is a PD-1 inhibitor.

23. A combination according to claim 18, wherein an additional therapeutically active agent is an anti-PD-1 antibody molecule.

24. A combination according to claim 22, wherein an additional therapeutically active agent is a PD-1 inhibitor selected from PDR001 (Novartis), Nivolumab (Bristol-Myers Squibb), Pembrolizumab (Merck & Co), Pidilizumab (CureTech), MEDI0680 (Medimmune), Cemiplimab (REGN2810, Regeneron), Dostarlimab (TSR-042, Tesaro), PF-06801591 (Pfizer), Tislelizumab (BGB-A317, Beigene), BGB-108 (Beigene), INCSHR1210 (Incyte), Balstilimab (AGEN2035, Agenus), Sintilimab (InnoVent), Toripalimab (Shanghai Junshi Bioscience), Camrelizumab (Jiangsu Hengrui Medicine Co.), and AMP-224 (Amplimmune), in particular PDR001 or Tislelizumab.

25. A pharmaceutical composition comprising a compound of formula (1g) or a pharmaceutically acceptable salt thereof, according to any of claims 1 to 17, and one or more pharmaceutically acceptable carriers.

26. A compound of formula (1g), or a pharmaceutically acceptable salt thereof, according to any of claims 1 to 17, for use as a medicament.

27. Use of a compound of formula (1g), or a pharmaceutically acceptable salt thereof, according to any of claims 1 to 17, in the manufacture of a medicament for the treatment of a disease that is treated by WRN inhibition.

28. The use according to claim 27, wherein the disease is cancer.

29. The use according to claim 28, wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

30. The use according to claim 29, wherein the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, and endometrial, adrenocortical, uterine, cervical, esophageal, breast, kidney, prostate and ovarian cancer.

31. The use according to claim 30, wherein the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, prostate and endometrial cancer.

32. The use according to claim 29, wherein the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from prostate cancer, uterine corpus endometrial carcinoma, colon adenocarcinoma, stomach adenocarcinoma, rectal adenocarcinoma, adrenocortical carcinoma, uterine carcinosarcoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, esophageal carcinoma, breast carcinoma, kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma.

33. A compound of formula (1g), or a salt thereof, according to any of claims 1 to 17, as a research chemical, for example a tool compound or chemical probe.

34. Use of a compound of formula (1g), or a salt thereof, according to any of claims 1 to 17, as a research chemical, for example a tool compound or chemical probe.