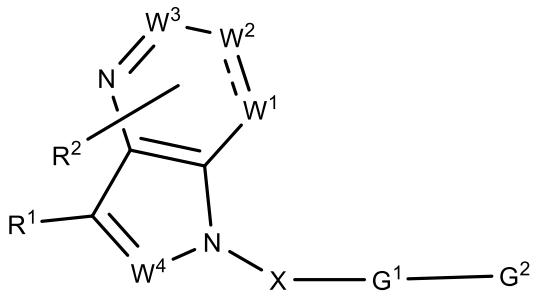
WE CLAIM:

1. A compound having the structure of formula (I):



or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof;

R^1 is selected from C_6 aryl and 5-6 membered heteroaryls, optionally substituted with one to four halo, hydroxy, amino, $-C(O)R^a$, $-C(O)OR^b$, $-C(O)NR^aR^b$, $-N(R^a)C(O)R^b$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-S(O)R^g$, $-S(O)_2R^g$, $-NR^aR^b$, $-OR^a$, $-SR^b$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{3-8} cycloalkyl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{3-8} cycloalkyl is optionally substituted with one to four R^{100};

R^2 is selected from absent, hydrogen, halo, hydroxy, amino, -CN, $-C(O)R^a$, $-C(O)OR^b$, $-C(O)NR^aR^b$, $-N(R^a)C(O)R^b$, $-N(R^a)C(O)NR^aR^b$, $-N(R^a)SO_2NR^aR^b$, $-S(O)NR^aR^b$, $-S(O)_2NR^aR^b$, $-N(R^a)S(O)_2R^b$, $-S(O)R^g$, $-S(O)_2R^g$, $-NR^aR^b$, $-OR^a$, $-SR^b$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S, and C_{3-8} cycloalkyl is optionally substituted with one to four R^{100};

X is C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one to four R^{100};

Each W^1 and W^2 is independently selected from $-N(R^a)-$, -C(O)- and $-C(R^a)-$;

W^3 is selected from -N- and $-C(R^a)-$;

W^4 is selected from -N- and $-C(R^a)-$;

Wherein at least one of W^1, W^2 and W^3 is $-C(R^a)$;

G^1 is selected from $-C_6$ aryl-, 5-6 membered heteroaryl, C_{3-8} cycloalkyl and 5-6 membered heterocyclyl; wherein each C_6 aryl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl and 5-6 membered heterocyclyl is optionally substituted with one to four R^{100};

G^2 is a 5 or 6 membered heteroaryl or 5-6 membered heterocyclyl optionally substituted with one to four R^{100};

each R^a and R^b is independently selected from absent, hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,C_{3-6} cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S is optionally substituted with one to four R^{200};

each R^{100} is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^c, -C(O)OR^c, -C(O)N$R^c R^d$, -N(R^e)C(O)R^d, -S(O)N$R^c R^d$, -$S(O)_2$N$R^c R^d$, -S(O)R^h, -$S(O)_2R^h$, -N$R^c R^d$, -OR^c, -SR^c, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl containing 1 to 4 heteroatoms selected from N, O, and S, and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl is optionally substituted with one to four R^{201};

each R^c and R^d is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl containing 1 to 4 heteroatoms selected from N, O, and S, and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S;

each R^{200} and R^{201} is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^e, -C(O)OR^e, -C(O)N$R^e R^f$, -N(R^e)C(O)R^f, -S(O)N$R^e R^f$, -$S(O)_2$N$R^e R^f$, -S(O)R^i, -$S(O)_2R^i$, -N$R^e R^f$, -OR^e, -SR^e, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl containing 1 to 4 heteroatoms selected from N, O, and S, and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl is optionally substituted with one to four R^{300};

each R^g, R^h and R^i is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, is optionally substituted with one to four R^{300};

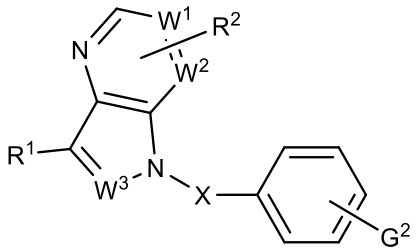
wherein each R^{300} is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^e, -C(O)OR^e, -C(O)N$R^e R^f$, -N(R^e)C(O)R^f, -S(O)N$R^e R^f$, -$S(O)_2$N$R^e R^f$, -S(O)R^e, -$S(O)_2R^e$, -N$R^e R^f$, -OR^e, -SR^e, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

each R^e and R^f is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl; C_{3-8} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl containing 1 to 4 heteroatoms selected from N, O, and S, and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl is optionally substituted with one to four R^{400};

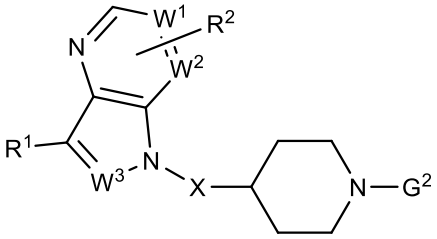
each R^{400} is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, $-C(O)R^k$, $-C(O)OR^k$, $-C(O)NR^kR^l$, $-N(R^k)C(O)R^l$, $-S(O)NR^kR^l$, $-S(O)_2NR^kR^l$, $-NR^kR^l$, $S(O)R^k$, $-S(O)_2R^k$, $-NR^kR^l$, $-OR^k$, $-SR^k$, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

each R^k and R^l is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl; C_{3-8} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl containing 1 to 4 heteroatoms selected from N, O, and S, and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S.

2. A compound of claim 1, having the structure of Formula (IIa) or (IIb):



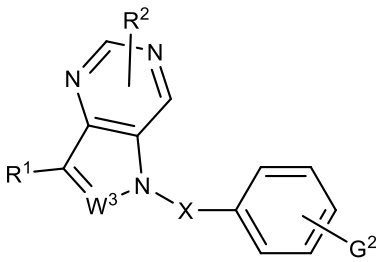
Formula (IIa);



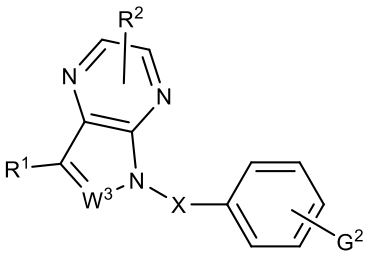
Formula (IIb);

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

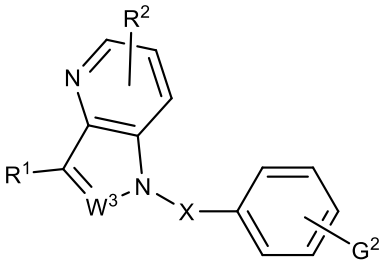
3. A compound of claim 1, having the structure of Formula (IIIa), (IIIb) or (IIIc):



Formula (IIIa)



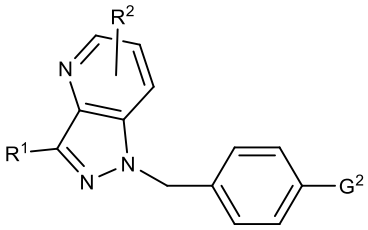
Formula (IIIb)



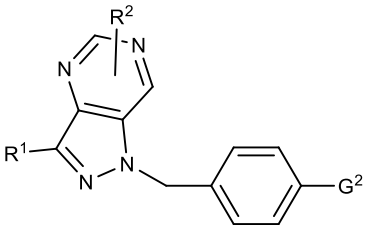
Formula (IIIc)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

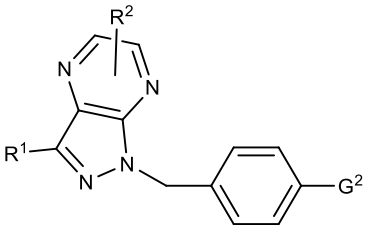
4. A compound of claim 1, having the structure of Formula (IVa), (IVb) or (IVc):



Formula (IVa)



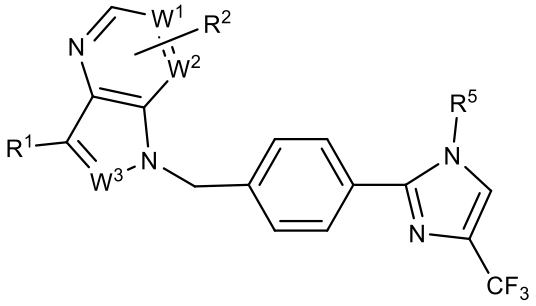
Formula (IVb)



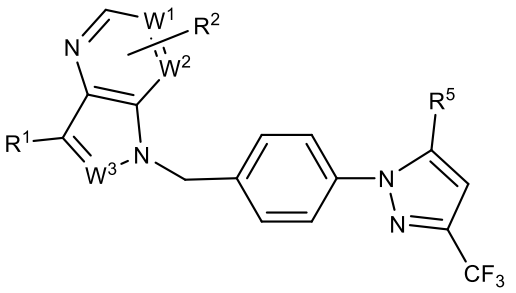
Formula (IVc)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

5. A compound of claim 1, having the structure of Formula (V) or (VI):



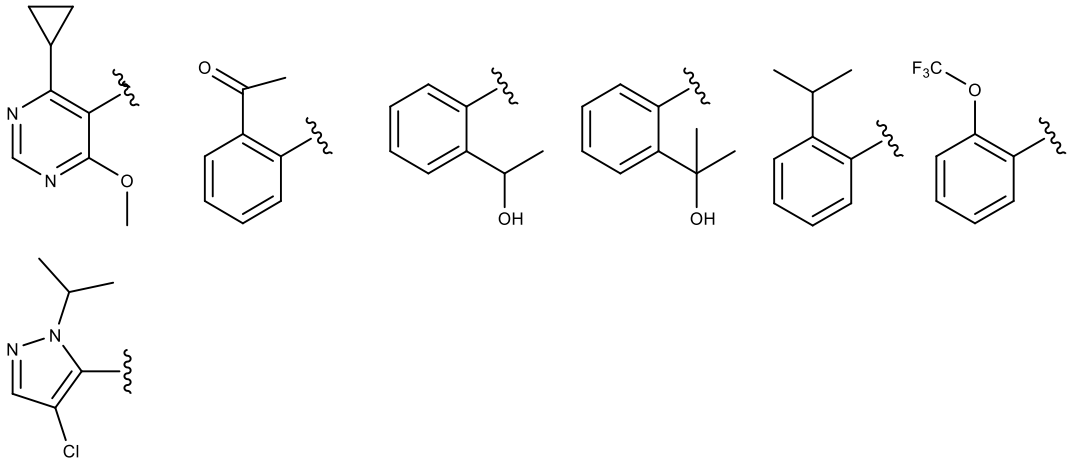
Formula (V)



Formula (VI)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof; wherein R^5 is $C_{1\text{-}6}$ alkyl.

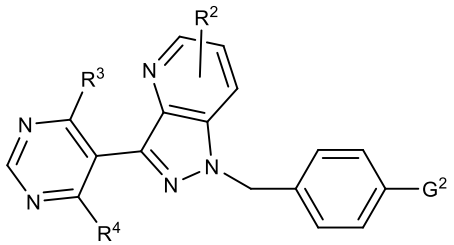
6. A compound according to any of claims 1-5 wherein R^1 is selected from:



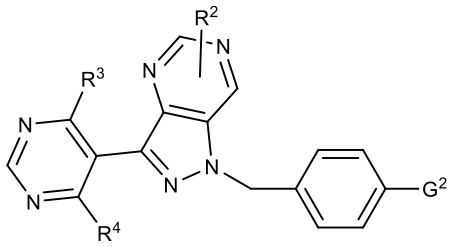
and

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

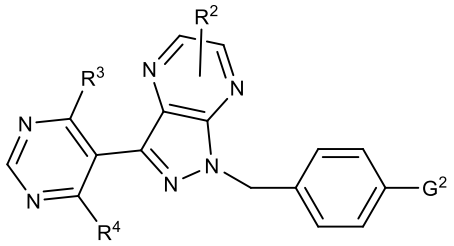
7. A compound according to any of claims 1-5 having the structure of formula (VII):



Formula (VIIa)



Formula (VIIb)

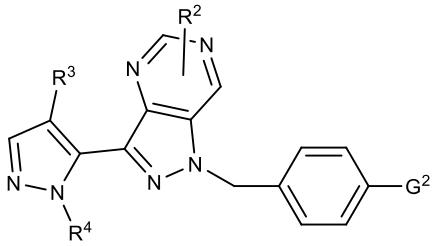


Formula (VIIc)

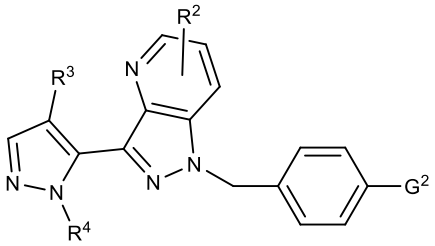
Wherein each R^3 and R^4 is independently selected from hydrogen, halo, $-OR^a$, $-SR^b$ and C_{3-8} cycloalkyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

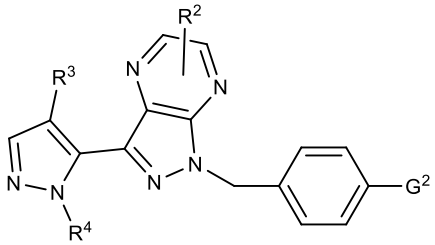
8. A compound according to any of claims 1-5 having the structure of formula (VIIIa) (VIIIb) or (VIIIc):



Formula (VIIIa)



Formula (VIIIb)

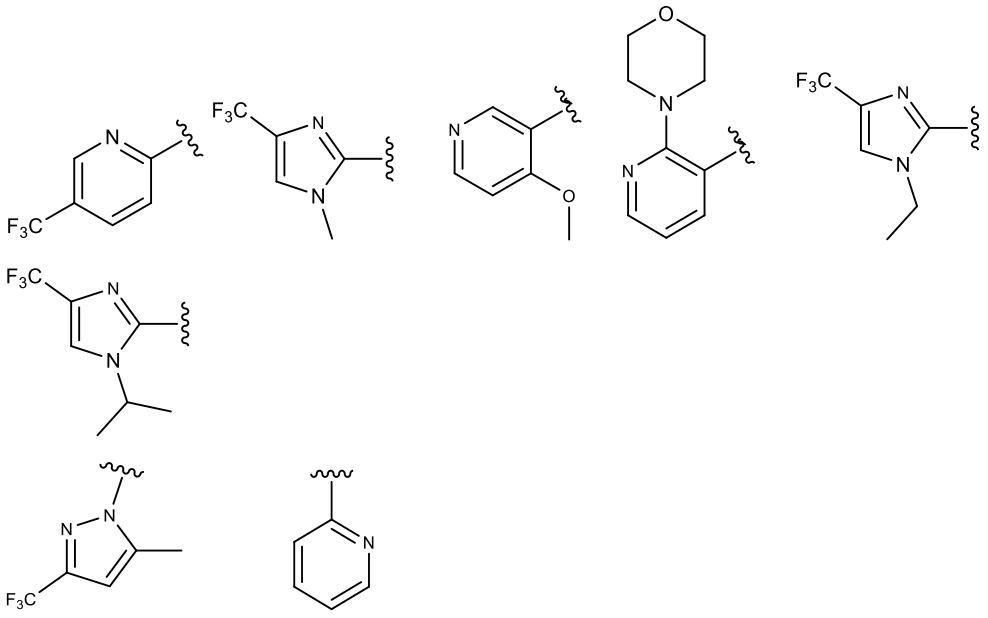


Formula (VIIIc)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

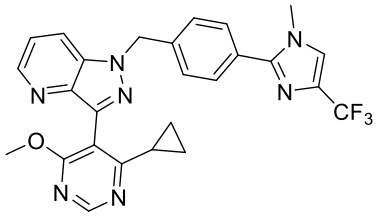
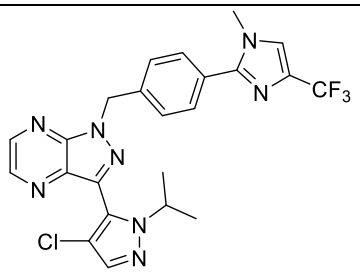
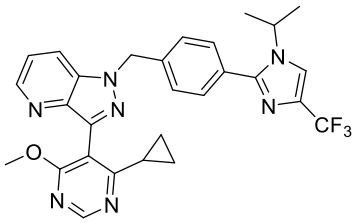
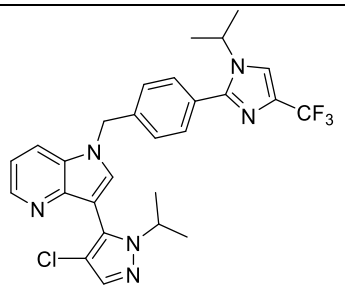
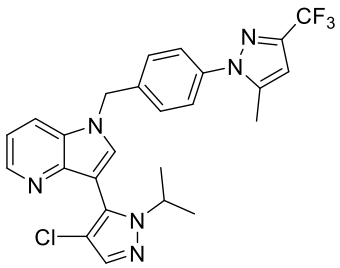
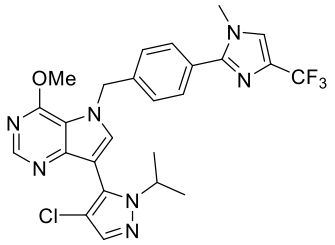
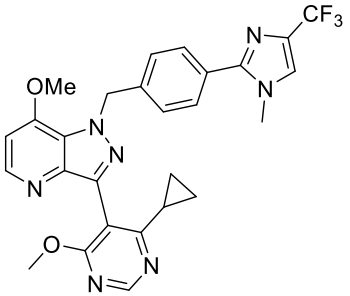
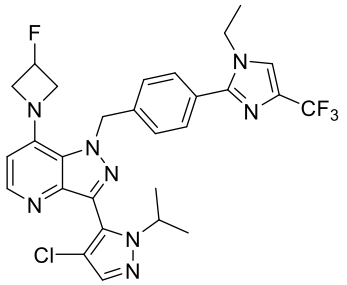
9. A compound according to any of claims 1-8 wherein R^2 is selected from: $-OCH_3$, -H, $-SCH_3$, $-S(O)_2CH_3$, $-S(O)_2CH_3$, $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, and $-C(O)NH_2$. or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or deuterated analog thereof.

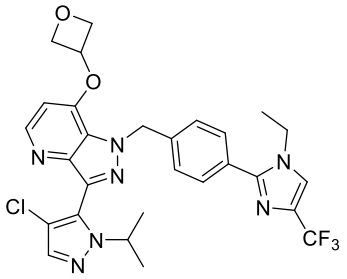
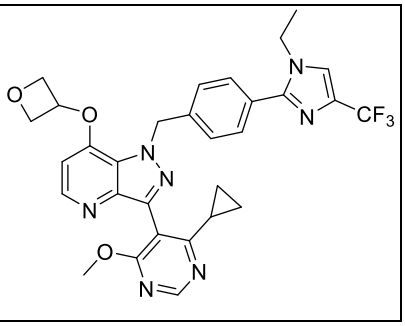
10. A compound according to any of claims 1-4, 6-7 and 9 wherein G^2 is selected from:



or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or deuterated analog thereof.

11. A compound of claim 1, selected from the Table A or a pharmaceutically acceptable salt thereof;

Example		Example	
1		2	
3		4	
5		6	
7		8	

9		10	

12. A pharmaceutical composition comprising one or more compounds according to any of the claims 1-11 and a pharmaceutically acceptable carrier or diluent.

13. The compound according to any one of claims 1-11 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 12, for use in a method of treating or preventing a disease or disorder associated with the inhibition of ubiquitin specific protease 1 (USP1).

14. Use of compound according to claims 1-11 or a pharmaceutically acceptable salt thereof, or pharmaceutical composition according to claim 12, in the manufacture of a medicament for treating cancer.

15. The use according to claim 14 wherein said cancer is a solid tumor selected from pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancers, CNS cancers, brain tumors (e.g., glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma), bone cancer, and soft tissue sarcoma.

16. The use according to claim 14, wherein the cancer is pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer or colon cancer.

17. The use according to claim 14, wherein the cancer is acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldenström's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma or diffuse large B-cell lymphoma (DLBCL).

18. The use according to any of claims 14-17, wherein the medicament is to be administered in combination with at least one additional anticancer agent or therapy.