

UBIQUITIN SPECIFIC PROCESSING PROTEASE 1 (USP1) COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No.
5 63/594,451, filed, October 31, 2023, the entire content of which is hereby incorporated
herein by reference.

FIELD

This invention relates to compounds which are inhibitors of ubiquitin-specific-
10 processing protease 1 (USP1) useful for treating diseases including, among others, cancer,
autoimmune and inflammatory disorders. The invention further pertains to
pharmaceutical compositions containing at least one compound according to the invention
that are useful for the treatment of conditions related to the inhibition of USP1 in a
mammal.

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BACKGROUND OF THE INVENTION

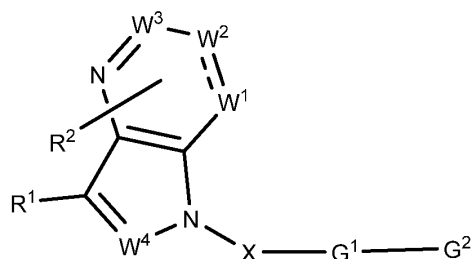
Ubiquitination is important in the regulation of many cellular functions and
cellular homeostasis. The conjugation of ubiquitin to a target protein is a multistep
process involving the sequential action of a ubiquitin activating enzyme (E1), a ubiquitin-
20 conjugating enzyme (E2), and a ubiquitin protein-ligase (E3). The ubiquitin tags can
mediate non-covalent interactions of the ubiquitinated substrate with other proteins
bearing different types of ubiquitin-binding motifs. A family of enzymes, termed
deubiquitinases act on ubiquitinated substrates to catalyze the removal of ubiquitin
moieties. One such enzyme is ubiquitin-specific protease 1 (USP1) which plays an
25 important role in the regulation of DNA repair processes. USP1 is a regulator of several
important steps in the DNA damage response, particularly in the Fanconi anemia
pathway, and in the process of translesion synthesis. USP1 has also been reported to
contribute to the repair of double-strand DNA breaks through homologous recombination.
In addition, USP1 has been reported to deubiquitinate and stabilize members of the family
30 of inhibitors of DNA binding (ID) proteins, ID1, ID2 and ID3. *García-Santisteban, I.,*

Peters, G.J., Giovannetti, E. et al. Mol Cancer 12, 91 (2013); US Patent Nos. 7,754,463, 10,653,676, 9,518,032.

SUMMARY

5 The present disclosure provides compounds that modulate the expression or activity of USP1. The disclosure also provides compositions, including pharmaceutical compositions, kits that include the compounds, and methods of using (or administering) and making the compounds. The compounds provided herein are useful in treating diseases, disorders, or conditions that are mediated by USP1. The disclosure also provides
10 compounds for use in therapy. The disclosure further provides compounds for use in a method of treating a disease, disorder, or condition that is mediated by USP1. Moreover, the disclosure provides uses of the compounds in the manufacture of a medicament for the treatment of a disease, disorder or condition that is mediated by (or mediated, at least in part, by) USP1.

15 In one aspect, provided are compounds of Formula (I):



Formula I

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

- 20 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} ;
- 25 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, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S, and C₃₋₈ cycloalkyl is optionally substituted with one to four R¹⁰⁰;
- X is C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one to four R¹⁰⁰;
- Each W¹ and W² is independently selected from -N(R^a)-, -C(O)- and -C(R^a)-;
- W³ is selected from -N- and -C(R^a)-;
- W⁴ is selected from -N- and -C(R^a)-;
- Wherein at least one of W¹, W² and W³ is -C(R^a)-;
- G¹ is selected from -C₆ aryl-, 5-6 membered heteroaryl, C₃₋₈ cycloalkyl and 5-6 membered heterocyclyl; wherein each C₆ aryl, 5-6 membered heteroaryl, C₃₋₈ cycloalkyl and 5-6 membered heterocyclyl is optionally substituted with one to four R¹⁰⁰;
- G² is a 5 or 6 membered heteroaryl or 5-6 membered heterocyclyl optionally substituted with one to four R¹⁰⁰;
- each R^a and R^b is independently selected from absent, hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S is optionally substituted with one to four R²⁰⁰;
- each R¹⁰⁰ is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^c, -C(O)OR^c, -C(O)NR^cR^d, -N(R^c)C(O)R^d, -S(O)NR^cR^d, -S(O)₂NR^cR^d, -S(O)R^h, -S(O)₂R^h, -NR^cR^d, -OR^c, -SR^c, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ 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 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl is optionally substituted with one to four R²⁰¹;
- each R^c and R^d is independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ 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, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-N(R^e)C(O)R^f$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-S(O)R^i$, $-S(O)_2R^i$, $-NR^eR^f$, $-OR^e$, $-SR^e$, 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
- 5 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;
- 10 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, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^f$, $-N(R^e)C(O)R^f$, $-S(O)NR^eR^f$, $-S(O)_2NR^eR^f$, $-S(O)R^e$, $-S(O)_2R^e$, $-NR^eR^f$, $-OR^e$, $-SR^e$, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6}
- 15 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}
- 20 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
- 25 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.
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In one aspect, provided are processes and intermediates for making the compounds of Formula I.

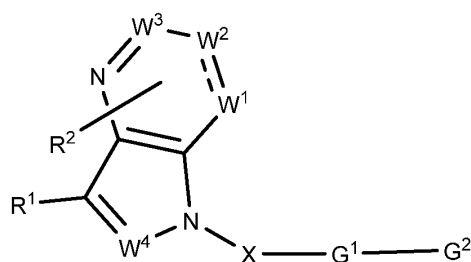
In one aspect, provided are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds disclosed herein.

The present application also provides methods for the inhibition of USP1 comprising administering a therapeutically effective amount of at least one of Formula I.

5 The present application also provides a method for treating proliferative, metabolic, allergic, autoimmune and inflammatory diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds disclosed herein. The compounds of Formula I or a pharmaceutically acceptable salt thereof, may be used to treat cancers that are mediated by, dependent on or
10 associated with USP1 activity. In certain embodiments, the disease is a solid tumor.

DETAILED DESCRIPTION

In a first aspect, provided are compounds of formula (I) that function as inhibitors of USP1:



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

R¹ is selected from C₆ 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, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₃₋₈ cycloalkyl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₃₋₈ cycloalkyl is optionally substituted with one to four R¹⁰⁰;

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R² 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)SO₂NR^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, -

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OC(O)NR^aR^b, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 4-10 membered heterocyclyl containing 1 to 4

heteroatoms selected from N, O, and S, and C₃₋₈ cycloalkyl is optionally substituted with one to four R¹⁰⁰;

X is C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one to four R¹⁰⁰;

Each W¹ and W² is independently selected from -N(R^a)-, -C(O)- and -C(R^a)-;

5 W³ is selected from -N- and -C(R^a)-;

W⁴ is selected from -N- and -C(R^a)-;

Wherein at least one of W¹, W² and W³ is -C(R^a);

G¹ is selected from -C₆ aryl-, 5-6 membered heteroaryl, C₃₋₈ cycloalkyl and 5-6 membered heterocyclyl; wherein each C₆ aryl, 5-6 membered heteroaryl, C₃₋₈ cycloalkyl and 5-6

10 membered heterocyclyl is optionally substituted with one to four R¹⁰⁰;

G² is a 5 or 6 membered heteroaryl or 5-6 membered heterocyclyl optionally substituted with one to four R¹⁰⁰;

each R^a and R^b is independently selected from absent, hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4

15 heteroatoms selected from N, O, and S; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S is optionally substituted with one to four R²⁰⁰;

each R¹⁰⁰ is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^c, -C(O)OR^c, -C(O)NR^cR^d, -N(R^c)C(O)R^d, -S(O)NR^cR^d, -

20 S(O)₂NR^cR^d, -S(O)R^h, -S(O)₂R^h, -NR^cR^d, -OR^c, -SR^c, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ 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 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl is

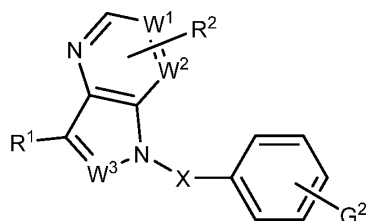
25 optionally substituted with one to four R²⁰¹;

each R^c and R^d is independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ 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;

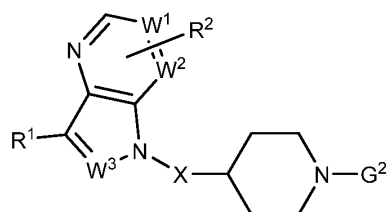
30 each R²⁰⁰ and R²⁰¹ is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -N(R^e)C(O)R^f, -S(O)NR^eR^f, -S(O)₂NR^eR^f, -S(O)Rⁱ, -S(O)₂Rⁱ, -NR^eR^f, -OR^e, -SR^e, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,

- C₃₋₈ cycloalkyl, C₆₋₁₀ 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 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl is optionally substituted with one to four R³⁰⁰;
- each R^g, R^h and Rⁱ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, is optionally substituted with one to four R³⁰⁰;
- wherein each R³⁰⁰ is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -N(R^e)C(O)R^f, -S(O)NR^eR^f, -S(O)₂NR^eR^f, -S(O)R^e, -S(O)₂R^e, -NR^eR^f, -OR^e, -SR^e, C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;
- each R^e and R^f is independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl; C₃₋₈ cycloalkyl, C₆₋₁₀ 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 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl is optionally substituted with one to four R⁴⁰⁰;
- each R⁴⁰⁰ 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, C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;
- each R^k and R^l is independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl; C₃₋₈ cycloalkyl, C₆₋₁₀ 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.

In one embodiment, provided are compounds of formula (IIa or IIb):

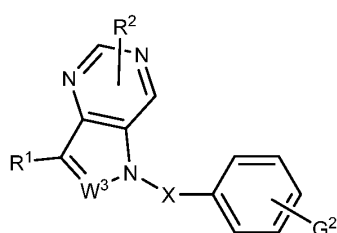


Formula (IIa);

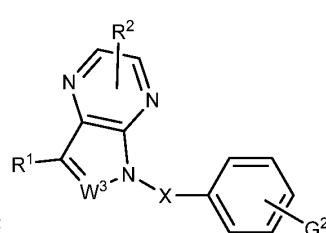


Formula (IIb);

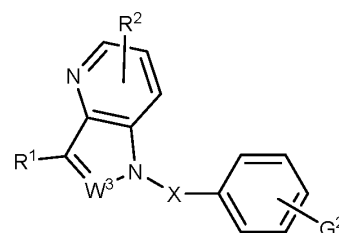
5 In one embodiment, provided are compounds of formula (IIIa, IIIb and IIIc):



Formula (IIIa)



Formula (IIIb)

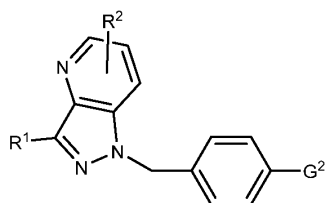


Formula (IIIc)

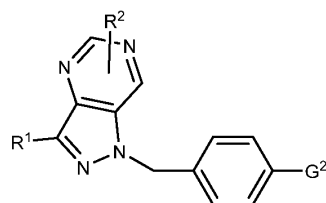
or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

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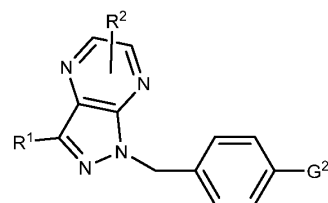
In one embodiment, provided are compounds of Formula (IVa), (IVb) or (IVc):



Formula (IVa)



Formula (IVb)

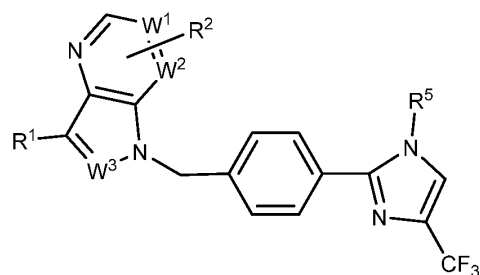


Formula (IVc)

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

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In one embodiment, provided are compounds of Formula (V):

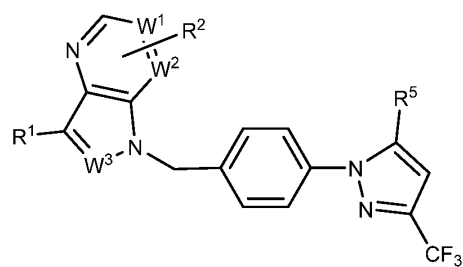


Formula (V)

- 5 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof;
wherein R⁵ is C₁₋₆ alkyl.

In one embodiment, provided are compounds of Formula (VI):

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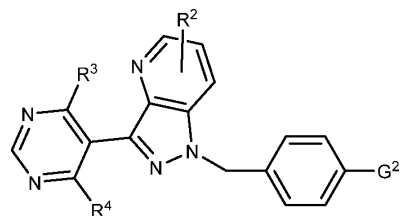


Formula (VI)

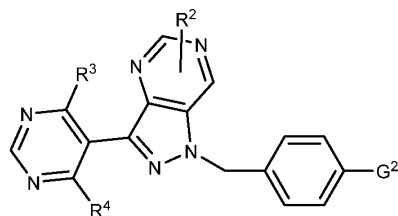
or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof;
wherein R⁵ is C₁₋₆ alkyl.

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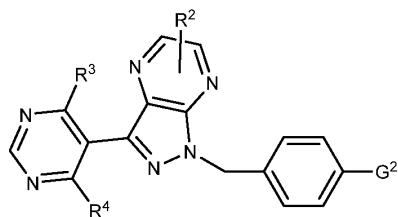
In one embodiment, provided are compounds of Formula (VIIa), (VIIb) or (VIIc):



Formula (VIIa)



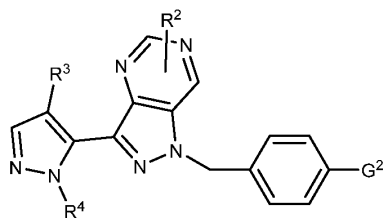
Formula (VIIb)



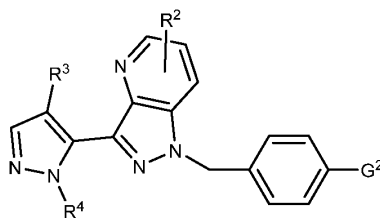
Formula (VIIc)

- Wherein each R³ and R⁴ is independently selected from hydrogen, halo, -OR^a, -SR^b and
 5 C₃₋₈ cycloalkyl;
 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

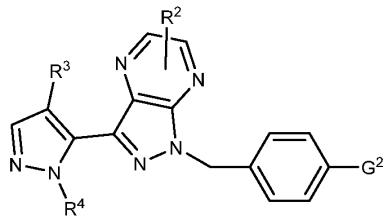
In one embodiment, provided are compounds of Formula (VIIIa) (VIIIb) or (VIIIc):



10 Formula (VIIIa)



Formula (VIIIb)

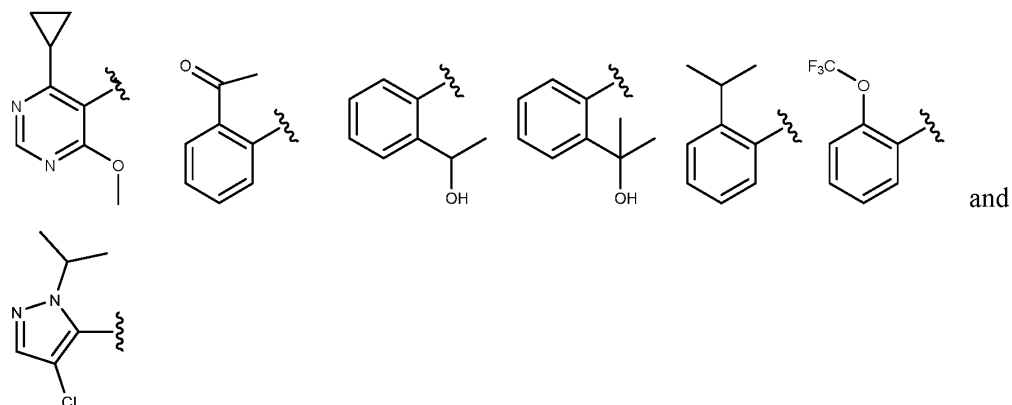


Formula (VIIIc)

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

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In one embodiment, provided are compounds wherein R¹ is selected from:



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

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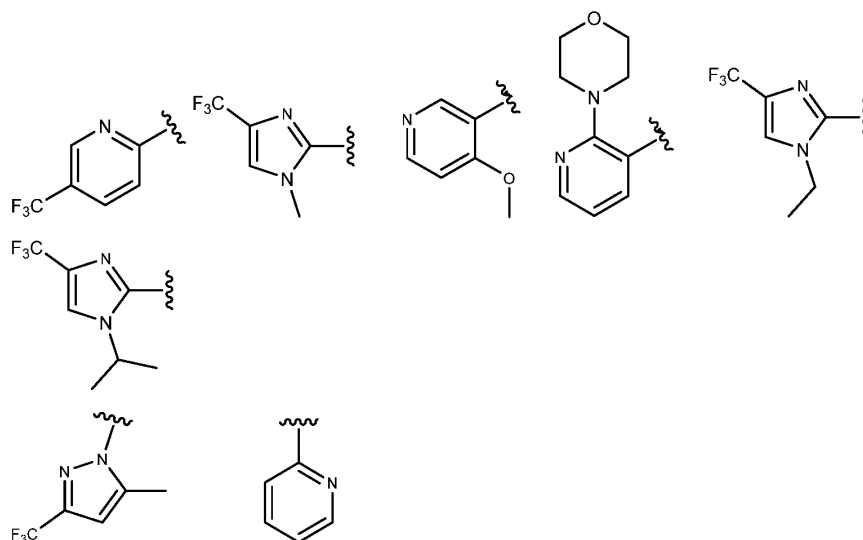
In one embodiment, provided are compounds wherein R² is selected from:

-OCH₃, -H, -SCH₃, -S(O)₂CH₃, -S(O)₂CH₃, -C(O)OCH₃, -C(O)OCH₂CH₃, and -C(O)NH₂.

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

10

In one embodiment, provided are compounds wherein wherein G^2 is selected from:



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

The compounds described herein (e.g., a compound of Formula I, IIa, IIb IIIa, IIIb, IIIc, IVa, IVb, IVc, V, VI, VIIa, VIIb, VIIc, VIIIa, VIIIb, VIIIc or Table A) or a pharmaceutically acceptable salt thereof, may be used to treat cancers that are mediated by, dependent on or associated with USP1 activity. In certain embodiments, the disease is a solid tumor. In particular embodiments, the solid tumor is selected from prostate cancer, pancreatic cancer, bladder cancer, colorectal cancer, breast 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, or soft tissue sarcoma. In some embodiments, the solid tumor is from non-small cell lung cancer or small-cell lung cancer.

The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group, unless otherwise indicated.

As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

Compounds of this invention may have one or more asymmetric centers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms of compounds of the present invention are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. *Cis*- and *trans*-geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

When any variable (*e.g.*, R³) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R³, then said group may optionally be substituted with up to two R³ groups and R³ at each occurrence
5 is selected independently from the definition of R³. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound
10 of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (*e.g.*,
15 MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

In accordance with a convention used in the art,  is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the
20 core or backbone structure.

A dash "-" that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary
25 meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written or named.

The term "optionally substituted" in reference to a particular moiety of the compound of Formula I (*e.g.*, an optionally substituted heteroaryl group) refers to a
30 moiety having 0, 1, 2, or more substituents. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood

by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

As used herein, the term "at least one chemical entity" is interchangeable with the
5 term "a compound".

The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. For example, "C₁₋₆ alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of
10 carbon atoms. For example, "C₁₋₁₀ alkyl" (or alkylene), is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkyl groups. Additionally, for example, "C₁₋₆ alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl groups can be unsubstituted or substituted so that one or more of its hydrogens are replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, *n*-propyl and isopropyl),
15 butyl (*e.g.*, *n*-butyl, isobutyl, *t*-butyl), pentyl (*e.g.*, *n*-pentyl, isopentyl, neopentyl), and the like.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more double carbon-carbon bonds that may occur in any stable point along the chain. For example, "C₂₋₆ alkenyl" (or alkenylene), is
20 intended to include C₂, C₃, C₄, C₅, and C₆ alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight
25 or branched configuration and having one or more triple carbon-carbon bonds that may occur in any stable point along the chain. For example, "C₂₋₆ alkynyl" (or alkynylene), is intended to include C₂, C₃, C₄, C₅, and C₆ alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

One skilled in the field will understand that, when the designation "CO₂" is used
30 herein, this is intended to refer to the group $\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—O—}$.

When the term "alkyl" is used together with another group, such as in "arylalkyl", this conjunction defines with more specificity at least one of the substituents that the

substituted alkyl will contain. For example, "arylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is an aryl, such as benzyl. Thus, the term aryl(C₀₋₄)alkyl includes a substituted lower alkyl having at least one aryl substituent and also includes an aryl directly bonded to another group, *i.e.*, aryl(C₀)alkyl.

- 5 The term "heteroarylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is a heteroaryl.

When reference is made to a substituted alkenyl, alkynyl, alkylene, alkenylene, or alkynylene group, these groups are substituted with one to three substituents as defined above for substituted alkyl groups.

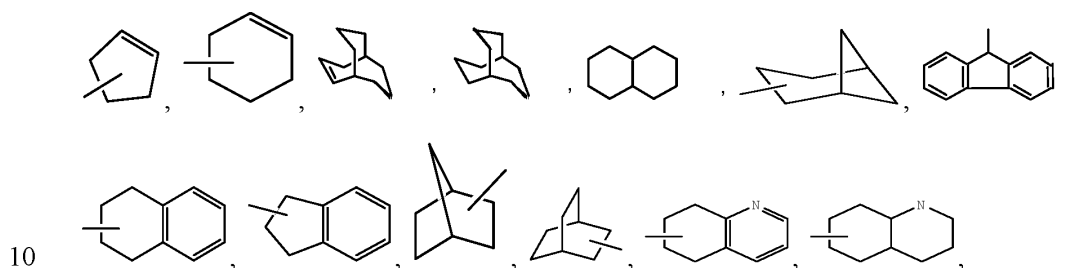
- 10 The term "alkoxy" refers to an oxygen atom substituted by alkyl or substituted alkyl, as defined herein. For example, the term "alkoxy" includes the group -O-C₁₋₆alkyl such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, *tert*-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. "Lower alkoxy" refers to alkoxy groups having one to four
15 carbons.

- The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or polycyclic ring systems. C₃₋₇ cycloalkyl is intended to include C₃, C₄, C₅, C₆, and C₇ cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. As used herein, "carbocycle" or
20 "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane,
25 [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl,
30 cyclobutyl, cyclopentyl, cyclohexyl, and phenyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a

bridge always converts a monocyclic ring into a bicyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, and naphthyl groups, each of which
5 may be substituted.

Accordingly, in compounds of formula I, the term "cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclooctyl, etc., as well as the following ring systems:



and the like, which optionally may be substituted at any available atoms of the ring(s).

The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

15 The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF_3 .

The terms "heterocycle", "heterocycloalkyl", "heterocyclo", "heterocyclic", or "heterocyclyl" may be used interchangeably and refer to substituted and unsubstituted 3- to 7-membered monocyclic groups, 7- to 11-membered bicyclic groups, and 10- to 15-
20 membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N), said heteroatom containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of such a group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further
25 provided that the ring contains at least one carbon atom. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or fully unsaturated. The heterocyclo group

may be attached at any available nitrogen or carbon atom. As used herein the terms "heterocycle", "heterocycloalkyl", "heterocyclo", "heterocyclic", and "heterocyclyl" include "heteroaryl" groups, as defined below.

In addition to the heteroaryl groups described below, exemplary monocyclic heterocyclyl groups include azetidiny, pyrrolidiny, oxetany, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidyl, 2-oxopyrrolodiny, 2-oxoazepinyl, azepinyl, 1-pyridonyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

The term "heteroaryl" refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups, 9- or 10-membered bicyclic groups, and 11- to 14-membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. As valence allows, if said further ring is cycloalkyl or heterocyclo it is additionally optionally substituted with =O (oxo).

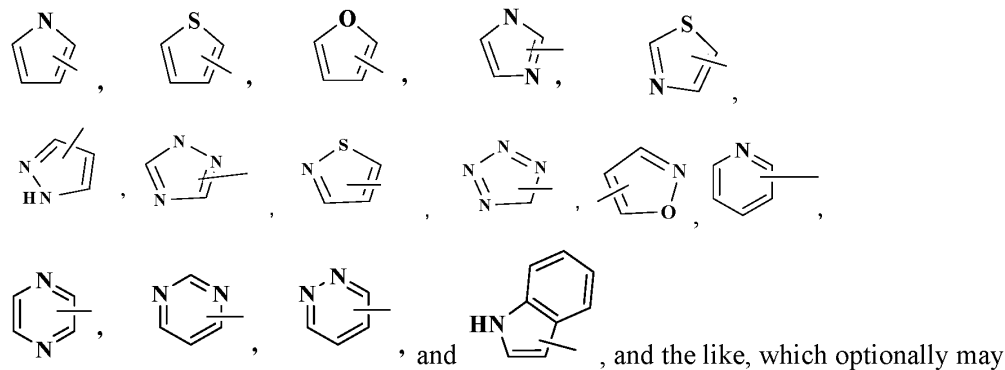
Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl,

coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzindolyl, phenanthroline, acridinyl, phenanthridinyl, xanthenyl and the like.

5 In compounds of formula I, preferred heteroaryl groups include:



10 Unless otherwise indicated, when reference is made to a specifically-named aryl (*e.g.*, phenyl), cycloalkyl (*e.g.*, cyclohexyl), heterocyclo (*e.g.*, pyrrolidinyl, piperidinyl, and morpholinyl) or heteroaryl (*e.g.*, tetrazolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, and furyl) the reference is intended to include rings having 0 to 3, preferably 0 to 2, substituents selected from those recited above for the aryl, cycloalkyl, heterocyclo and/or

15 heteroaryl groups, as appropriate.

The term "carbocyclyl" or "carbocyclic" refers to a saturated or unsaturated monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*,

20 arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of mono- and bicyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl and naphthyl. The carbocyclic ring may be substituted in which case the

25 substituents are selected from those recited above for cycloalkyl and aryl groups.

The term "alkylthio" refers to the group "alkyl-S-".

The term "acyl" refers to a group $-C(O)R$, wherein R is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

5 The term "amido" refers to both a "C-amido" group which refers to the group $-C(O)NR^gR^h$ and an "N-amido" group which refers to the group $-NR^gC(O)R^h$, wherein R^g and R^h are independently selected from hydrogen, alkyl, aryl, haloalkyl, or heteroaryl; each of which may be optionally substituted.

10 The term "amino" refers to the group $-NR^gR^h$ wherein R^g and R^h are independently selected from hydrogen, alkyl, haloalkyl, aryl, or heteroaryl; each of which may be optionally substituted.

The term "azido" refers to $-N_3$.

15 The term "carbamoyl" refers to both an "O-carbamoyl" group which refers to the group $-O-C(O)NR^iR^j$ and an "N-carbamoyl" group which refers to the group $-NR^iC(O)OR^j$, wherein R^i and R^j are independently selected from hydrogen, alkyl, aryl, haloalkyl, or heteroaryl; each of which may be optionally substituted.

The term "carboxyl" refers to $-C(O)OH$.

20 The term "carboxyl ester" refers to both $-OC(O)R$ and $-C(O)OR^g$, wherein R^g is hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

The term "cyano" or "carbonitrile" refers to the group $-CN$.

25 The term "cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e. the cyclic group having at least one double bond). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C.sub.3-20 cycloalkyl), 3 to 12 ring carbon atoms (i.e., C.sub.3-12 cycloalkyl), 3 to 10 ring carbon atoms (i.e., C.sub.3-10 cycloalkyl), 3 to 8 ring carbon atoms (i.e., C.sub.3-8 cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C.sub.3-6 cycloalkyl). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

30 The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds and compounds useful as pharmaceutically-acceptable compounds and/or intermediate compounds useful in making pharmaceutically-acceptable compounds.

5 It should be understood that the selections for all groups, including for example, alkoxy, thioalkyl, and aminoalkyl, will be made by one skilled in the field to provide stable compounds.

 The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is 10 oxo, or keto, (*i.e.*, =O) then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is 15 in the alkyl portion. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

 Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to 20 survive isolation from a reaction mixture to a useful degree of purity, and subsequent formulation into an efficacious therapeutic agent. It is preferred that the presently recited compounds do not contain a N-halo, S(O)₂H, or S(O)H group.

 The compounds described herein may exist in a free form (with no ionization) or can form salts which are also within the scope of this invention. Unless otherwise 25 indicated, reference to an inventive compound is understood to include reference to the free form and to salts thereof. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, the term "salt(s)" may include zwitterions (inner salts), *e.g.*, when a compound of formula I, contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a 30 carboxylic acid. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt.

However, other salts may be useful, *e.g.*, in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of herein may be formed, for example, by reacting a compound described herein with an amount of acid or base, such as an equivalent
5 amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates,
10 citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates
15 (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts; alkaline earth metal salts such as calcium and magnesium salts; barium, zinc, and aluminum salts; salts with organic bases (for example, organic amines) such as trialkylamines such as triethylamine, procaine, dibenzylamine, N-benzyl- β -phenethylamine, 1-phenamine, *N,N'*-dibenzylethylene-diamine, dehydroabietylamine,
25 N-ethylpiperidine, benzylamine, dicyclohexylamine or similar pharmaceutically acceptable amines and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl,
30 lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others. Preferred salts include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate salts.

The compounds described herein can be provided as amorphous solids or crystalline solids. Lyophilization can be employed to provide the compounds as a solid.

It should further be understood that solvates (e.g., hydrates) of the compounds described herein are also within the scope of the present invention. The term "solvate" means a physical association of a compound with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanulates, methanulates, isopropanulates, acetonitrile solvates, and ethyl acetate solvates. Methods of solvation are known in the art.

In addition, compounds described herein subsequent to their preparation, can be isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% of a compound ("substantially pure"), which is then used or formulated as described herein. Such "substantially pure" compounds described herein are also contemplated herein as part of the present invention.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically-acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically-acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic,

benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional
5 chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack
10 Publishing Company, Easton, PA (1990), the disclosure of which is hereby incorporated by reference.

“Stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is
15 intended to embody stable compounds.

“Therapeutically effective amount” is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to act as an inhibitor of USP1, or effective to treat or prevent
20 proliferative disorders, such as cancer.

As used herein, “treating” or “treatment” cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e.,
25 arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. Stereoisomers may include compounds which are optical isomers through possession of one or more chiral atoms, as well as
30 compounds which are optical isomers by virtue of limited rotation about one or more bonds (atropisomers). The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It very particularly embraces the racemic forms

and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C . Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

Prodrugs and solvates of the inventive compounds are also contemplated. The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, and/or a salt and/or solvate thereof. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, the compound for formula I) is a prodrug within the scope and spirit of the invention. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C₁₋₆alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C₁₋₆alkanoyloxy-C₁₋₆alkyl, *e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C₁₋₆alkoxycarbonyloxy-C₁₋₆alkyl, *e.g.*, methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters

used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Various forms of prodrugs are well known in the art and are described in Rautio, J. et al., *Nature Review Drug Discovery*, 17, 559-587 (2018).

5 Compounds described in the application and their salts may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention. Additionally, inventive compounds may have *trans*- and
10 *cis*-isomers.

 The disclosure herein further relates to compounds described herein, the tautomers and stereoisomeric forms thereof, and the pharmaceutically acceptable addition salts, and the solvates thereof, for use as a medicament. Furthermore, the disclosure herein relates to the use of a compound described herein, a tautomer or a stereoisomeric
15 form thereof, or a pharmaceutically acceptable addition salt, or a solvate thereof, or a pharmaceutical composition according to the invention, for the manufacture of a medicament.

 The inventive compositions may contain other therapeutic agents as described above and may be formulated, for example, by employing conventional solid or liquid
20 vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (*e.g.*, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

 Accordingly, the present invention further includes compositions comprising one
25 or more compounds described herein and a pharmaceutically acceptable carrier.

 A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include without limitation
30 the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and, the therapeutic indication being targeted. Pharmaceutically acceptable

carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Remington's Pharmaceutical Sciences*, 17th Edition (1985), which is incorporated herein by reference in its entirety.

The compounds described herein may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin-related diseases, and systematic treatment preferred for cancerous or pre-cancerous conditions, although other modes of delivery are contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques (*e.g.*, as sterile injectable aq. or non-aq. solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be

orally delivered by sublingual and/or buccal administration, *e.g.*, with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (*e.g.*, GANTREZ®); and agents to control release such as polyacrylic copolymer (*e.g.*, CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (*i.e.* Captisol), cosolvent solubilization (*i.e.* propylene glycol) or micellar solubilization (*i.e.* Tween 80).

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In

addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

5 A sterile injectable oil-in-water microemulsion can, for example, be prepared by 1) dissolving at least one compound described herein in an oily phase, such as, for example, a mixture of soybean oil and lecithin; 2) combining the compound-containing oil phase with a water and glycerol mixture; and 3) processing the combination to form a microemulsion.

10 A sterile aqueous or oleaginous suspension can be prepared in accordance with methods already known in the art. For example, a sterile aqueous solution or suspension can be prepared with a non-toxic parenterally-acceptable diluent or solvent, such as, for example, 1,3-butane diol; and a sterile oleaginous suspension can be prepared with a sterile non-toxic acceptable solvent or suspending medium, such as, for example, sterile
15 fixed oils, e.g., synthetic mono- or diglycerides; and fatty acids, such as, for example, oleic acid.

Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other
20 solubilizing or dispersing agents such as those known in the art.

Dispersible powders and granules can, for example, be prepared by admixing at least one compound described herein or a pharmaceutically acceptable salt thereof, with at least one dispersing and/or wetting agent; at least one suspending agent; and/or at least one preservative. Exemplary preservatives include, but are not limited to, for example, anti-oxidants, e.g., ascorbic acid. In addition, dispersible powders and granules can also
25 contain at least one excipient, including, but not limited to, for example, sweetening agents; flavoring agents; and coloring agents.

Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter,
30 synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

The therapeutically-effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to 1000 mg/kg; 1-1000 mg/kg; 1-50 mg/kg; 5-250 mg/kg; 250-1000 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like. Thus, when the term "patient" is used herein, this term is intended to include all subjects, most preferably mammalian species that are affected by modulation of USP1-mediated functions.

The compounds described herein are useful for the treatment of cancer.

In one embodiment, the present application provides a combined preparation of a compound described herein and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof or a tautomer thereof, and additional therapeutic agent(s) for simultaneous, separate or sequential use in the treatment and/or prophylaxis of multiple diseases or disorders associated with USP1.

In another aspect, the application provides a method of treating a patient suffering from or susceptible to a medical condition that is associated with USP1. A number of medical conditions can be treated. The method comprises administering to the patient a therapeutically effective amount of a composition comprising a compound described herein and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof or a tautomer thereof. For example, the compounds described herein may be used to treat or proliferative diseases such as cancer, immunological disorders or inflammatory disorders.

In other embodiments, the compounds described herein may be used to treat cancers that are mediated by, dependent on or associated with USP1 activity. In certain embodiments, the disease is a solid tumor. In particular embodiments, the solid tumor is

selected from prostate cancer, pancreatic cancer, bladder cancer, colorectal cancer, breast 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, or soft tissue sarcoma. In some embodiments, the solid tumor is from non-small cell lung cancer or small-cell lung cancer.

In one embodiment, the compounds herein can be useful in the treatment of haematological malignancies. In one embodiment, hematological malignancy is selected from multiple myeloma, non-Hodgkin's lymphoma, Hodgkin lymphoma, T-cell leukaemia, mucosa-associated lymphoid tissue lymphoma, diffuse large B-cell lymphoma and mantle cell lymphoma. In one embodiment solid tumor is selected from pancreatic cancer, breast cancer, melanoma and non-small cell lung cancer.

In one embodiment, cancer is selected from a carcinoma, preferably a carcinoma of the bladder, breast, colon (including colorectal carcinomas, such as colon adenocarcinoma and colon adenoma), kidney, urothelial, uterus, epidermis, liver, lung (including adenocarcinoma, small cell lung cancer, non-small cell lung carcinomas and squamous lung cancer), oesophagus, head and neck, gall bladder, ovary, pancreas (including exocrine pancreatic carcinoma), stomach, gastrointestinal cancer (including gastrointestinal stromal tumors), cervix, endometrium, thyroid, prostate and skin.

In one embodiment, the cancer is selected from pituitary cancer, a hematopoietic tumor of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell lymphoma (e.g. diffuse large B-cell lymphoma, mantle cell lymphoma), T-cell leukaemia/lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example leukemias, acute and chronic myelogenous leukemias, chronic myelomonocytic leukemia (CMML), myeloproliferative disorder, myeloproliferative syndrome, myelodysplastic syndrome, or promyelocytic leukemia; multiple myeloma; thyroid follicular cancer; hepatocellular cancer, a tumor of mesenchymal origin (e.g. Ewing's sarcoma), for example fibrosarcoma or rhabdomyosarcoma; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma (such as glioblastoma multiforme) or schwannoma;

melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratocanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

In other embodiments, the compounds described herein may be used to treat cancers that are mediated by, dependent on or associated with USP1 activity. In certain
5 embodiments, the disease is a solid tumor. In particular embodiments, the solid tumor is from prostate cancer, pancreatic cancer, bladder cancer, colorectal cancer, breast 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
10 glioblastoma multiforme, and adult anaplastic astrocytoma), bone cancer, or soft tissue sarcoma. In some embodiments, the solid tumor is from non-small cell lung cancer or small-cell lung cancer.

In other embodiments, the disease is a hematologic malignancy. In certain
embodiments, the disease is lymphoma, multiple myeloma, or leukemia. In certain
15 embodiments, the hematologic malignancy is leukemia or lymphoma. In specific
embodiments, the disease 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), juvenile myelomonocytic leukemia (JMML), multiple myeloma (MM),
20 Hodgkin lymphoma, indolent non-Hodgkin's lymphoma (iNHL), refractory iNHL, non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldenström's macroglobulinemia (WM), minimal residual disease (MRD), T-cell lymphoma, B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), T-cell acute lymphoblastic leukemia (T-ALL), B-cell acute lymphoblastic leukemia (B-ALL),
25 lymphoplasmacytic lymphoma, marginal zone lymphoma, or Burkitt lymphoma. In one embodiment, the disease is T-cell acute lymphoblastic leukemia (T-ALL), or B-cell acute lymphoblastic leukemia (B-ALL). In some embodiments, non-Hodgkin lymphoma can be indolent B-cell diseases including follicular lymphoma, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, and marginal zone lymphoma, as well as
30 the aggressive lymphomas that include, for example, Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL).

In some embodiments, the cancer is selected from hematological cancer, a lymphatic cancer. In some embodiments, the cancer comprises cancer cells with DNA damage repair pathway deficiency. In some embodiments, the cancer is a homologous recombination deficient cancer. In some embodiments, the cancer comprises cancer cells
5 with a mutation in a gene encoding p53. In some embodiments, the mutation in a gene encoding p53 is a germline or somatic mutation. In some embodiments, the cancer comprises with cancer cells with loss of function mutation in a gene encoding p53. In some embodiments, the cancer is a BRCA1 and/or BRCA2 deficient cancer. In some
10 embodiments, the cancer is a somatic or germline BRCA1 and/or BRCA2 mutant cancer. In some embodiments, the cancer is a Poly (ADP-ribose) polymerase ("PARP") inhibitor refractory or resistant cancer. In some embodiments, the cancer is a PARP inhibitor resistant or refractory BRCA1 and/or BRCA2 deficient cancer. In some embodiments, the cancer cell has a germline or somatic mutation in a gene encoding ataxia telangiectasia
15 mutated (ATM) protein kinase or ATM deficiency. In some embodiments, the cancer has a mutation in the gene encoding more than two of p53, BRCA1, BRCA2, ATM.

In some embodiments, the disease is an autoimmune or inflammatory disease or disorder. These autoimmune or inflammatory diseases or conditions may be chronic or acute and include, but are not limited to, inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, pericarditis,
20 nephritis including lupus nephritis, osteomyelitis, myositis, eczema, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, primary biliary cirrhosis, cholecystitis, sclerosing cholangitis, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection such as acute graft-versus-host disease, hyperacute rejection of transplanted
25 organs, asthma, chronic obstructive airways disease, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia, vasculitis, glomerulonephritis, giant cell arteritis, Wegener's granulomatosis, Polyarteritis nodosa, dermatomyositis, multiple sclerosis, scleroderma, autoimmune hemolytic and
30 thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, hypophysitis, Parkinson's disease, Alzheimer's disease, Kawasaki disease, Takayasu's Arteritis, depression, retinitis, uveitis, scleritis, Type I diabetes, septic shock, systemic

lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, gout, chronic idiopathic thrombocytopenic purpura, Waldenström macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, bullous skin diseases, autoimmune hypopituitarism,

5 Guillain-Barre syndrome, Behcet's disease, scleracierma, mycosis fungoides, acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease. In some embodiments, the autoimmune and inflammatory diseases and conditions may also include systemic or tissue inflammation, inflammatory responses to hypoxia, cellular activation and proliferation,

10 lipid metabolism, fibrosis, infections with bacteria, infections with viruses (e.g., herpes virus, human papilloma virus, adenovirus, poxvirus and other DNA viruses), fungi, parasites or their toxins, such as sepsis, sepsis syndrome, septic shock, endotoxaemia, systemic inflammatory response syndrome (SIRS), multi-organ dysfunction syndrome, toxic shock syndrome, acute lung injury, ARDS (adult respiratory distress syndrome),

15 acute renal failure, fulminant hepatitis, burns, acute pancreatitis, post-surgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, meningitis, malaria and SIRS associated with viral infections such as influenza, herpes zoster, herpes simplex and coronavirus.

20 Combination Therapies

 In some embodiments, the compounds described herein may be administered in conjunction with standard of care, e.g., surgery, radiation, and/or chemotherapy. In some embodiments, the compounds may be administered in conjunction with a chemotherapeutic agent. In some embodiments, the compounds may be administered in

25 conjunction with one or more of carboplatin, cisplatin, paclitaxel, nab-paclitaxel, gemcitabine or FOLFOX. In some embodiment, the compounds may be administered in conjunction with carboplatin or nab-paclitaxel. In some embodiments, the compounds may be administered in conjunction with carboplatin and paclitaxel. In some

30 embodiments, the compounds may be administered in conjunction with cisplatin and pemetrexed. In some embodiments, the compounds may be administered in conjunction with cisplatin and gemcitabine. In some embodiments, the compounds may be administered in conjunction with FOLFOX. In some embodiments, the compounds may

be administered in conjunction with FOLFIRI. In one embodiment, the compounds may be administered in combination with decarbazine for the treatment of melanoma. In some embodiments, cisplatin is intravenously administered as a 100 mg/ml dose once every four weeks. In some embodiments, the compounds may be administered in conjunction
5 with doxorubicin (adriamycin), cisplatin bleomycin sulfate, carmustine, chlorambucil, dacarbazine and/or cyclophosphamide hydroxyurea. In some embodiments, adriamycin is intravenously administered as a 60 mg/ml to 75 mg/ml dose once every 21 days.

In one embodiment, the compounds of the present application (e.g., a compound described herein or a pharmaceutically acceptable salt, prodrug, or solvate thereof) may
10 be used in combination with one or more additional therapeutic agent that are being used and/or developed to treat cancers or inflammatory disorders. The one or more additional therapeutic agent may be an inhibitor to Janus kinase (JAK) such as JAK1, JAK2 and/or JAK3, Tyroansine kinase (TYK), K-Ras, Mitogen activated protein kinases (MAPK), Bruton's tyrosine kinase (BTK), bromodomain containing protein inhibitor (BRD) such as
15 BRD4, a lysyl oxidase protein (LOX), lysyl oxidase-like protein (LOXL) such as LOXL1-5, matrix metalloprotease (MMP) such as MMP 1-10, adenosine A2B receptor (A2B), isocitrate dehydrogenase (IDH) such as IDH1, apoptosis signal-regulating kinase (ASK) such as ASK1, serine/threonine kinase TPL2, discoidin domain receptor (DDR) such as DDR1 and DDR2, histone deacetylase (HDAC), protein kinase C (PKC), or any
20 combination thereof.

In one embodiment, the compounds of the present application (e.g., a compound described herein or a pharmaceutically acceptable salt, prodrug, or solvate thereof) may be used in combination with additional chemotherapeutic agent, an immunotherapeutic agent, a radiotherapeutic agent, an anti-neoplastic agent, an anti-cancer agent, an anti-
25 fibrotic agent, an anti-angiogenic agent, a therapeutic antibody, or any combination thereof.

Chemotherapeutic agents may be categorized by their mechanism of action into, for example, the following groups: anti-metabolites/anti-cancer agents, such as pyrimidine analogs (floxuridine, capecitabine, and cytarabine); purine analogs, folate
30 antagonists and related inhibitors antiproliferative/antimitotic agents including natural products such as vinca alkaloid (vinblastine, vincristine) and microtubule such as taxane (paclitaxel, docetaxel), vinblastin, nocodazole, epothilones and navelbine,

- epidipodophyllotoxins (etoposide, teniposide); DNA damaging agents (actinomycin, amsacrine, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, Cytosan, dactinomycin, daunorubicin, doxorubicin, epirubicin, iphosphamide, melphalan, merchlorehtamine, mitomycin, mitoxantrone, nitrosourea, procarbazine, taxol, taxotere,
- 5 teniposide, etoposide, triethylenethiophosphoramide); antibiotics such as dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents;
- 10 antiproliferative/antimitotic alkylating agents such as nitrogen mustards (cyclophosphamide and analogs, melphalan, chlorambucil), and (hexamethylmelamine and thiotepa), alkyl nitrosoureas (BCNU) and analogs, streptozocin), trazenes-dacarbazine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate); platinum coordination complexes (cisplatin, oxiloplatinim, carboplatin),
- 15 procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones, hormone analogs (estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (letrozole, anastrozole); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel;
- 20 antimigratory agents; antisecretory agents (breveldin); immunosuppressives tacrolimus sirolimus azathioprine, mycophenolate; compounds (TNP-470, genistein) and growth factor inhibitors (vascular endothelial growth factor inhibitors, fibroblast growth factor inhibitors); angiotensin receptor blocker, nitric oxide donors; anti-sense oligonucleotides; antibodies (trastuzumab, rituximab); cell cycle inhibitors and differentiation inducers
- 25 (tretinoin); inhibitors, topoisomerase inhibitors (doxorubicin (adriamycin), daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin, irinotecan and mitoxantrone, topotecan, irinotecan, camptothecin), corticosteroids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and prednisolone); growth factor signal transduction kinase inhibitors; dysfunction inducers, toxins such as Cholera toxin, ricin,
- 30 Pseudomonas exotoxin, Bordetella pertussis adenylate cyclase toxin, or diphtheria toxin, and caspase activators; and chromatin.

Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; emylerumines and memylamelamines including alfretamine, triemylenemelamine,

5 triethylenephosphoramidate, triethylenethiophosphoramidate and trimemylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189

10 and CBI-TMI); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, foremostine, lomustine, nimustine, ranimustine;

15 antibiotics such as the enediyne antibiotics (e.g., calicheamicin, calicheamicin gammall, dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomorphores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabacin, carrinomyacin, carzinophilin, chromomycins, dactinomycin,

20 daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin,

25 tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as demopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogues such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens

30 such as calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replinisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil;

amsacrine; hestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformthine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; leucovorin; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; fluoropyrimidine; folinic acid; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichloro-2,4,6-triaminotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiopeta; taxoids, e.g., paclitaxel and docetaxel, chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide; ifosfamide; mitroxantrone; vancristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeoloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; FOLFIRI (fluorouracil, leucovorin, and irinotecan) and pharmaceutically acceptable salts, acids or derivatives of any of the above. One or more chemotherapeutic agent is used or included in the present application.

Chemotherapeutic agents may also include, for example, anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, onapristone, and toremifene; inhibitors of the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestane, fadrozole, vorozole, letrozole and anastrozole; and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprohde, and goserelin; and pharmaceutically acceptable salts thereof.

The anti-angiogenic agents include, but are not limited to, retinoid acid and derivatives thereof, 2-methoxyestradiol, suramin, squalamine, tissue inhibitor of metalloproteinase-1, tissue inhibitor of metalloproternase-2, plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, cartilage-derived inhibitor, paclitaxel (nab-paclitaxel), platelet factor 4, protamine sulphate (clupeine), sulphated chitin derivatives

(prepared from queen crab shells), sulphated polysaccharide peptidoglycan complex (sp-pg), staurosporine, modulators of matrix metabolism, including for example, proline analogs ((1-azetidine-2-carboxylic acid (LACA), cishydroxyproline, d,I-3,4-dehydroproline, thiaproline, .alpha.-dipyridyl, beta-aminopropionitrile fumarate, 4-propyl-5-(4-pyridinyl)-2(3h)-oxazolone; methotrexate, mitoxantrone, heparin, interferons, 2 macroglobulin-serum, chimp-3, chymostatin, beta-cyclodextrin tetradecasulfate, eponemycin; fumagillin, gold sodium thiomalate, d-penicillamine (CDPT), beta-1-anticollagenase-serum, alpha-2-antiplasmin, bisantrene, lobenzarit disodium, n-2-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA", thalidomide; angiostatic steroid, cargboxynaminimidazole; metalloproteinase inhibitors such as BB94. Other anti-angiogenesis agents include antibodies, preferably monoclonal antibodies against these angiogenic growth factors: beta-FGF, alpha-FGF, FGF-5, VEGF isoforms, VEGF-C, HGF/SF and Ang-1/Ang-2.

The application also provides a method for treating a subject who is undergoing one or more standard therapies, such as chemotherapy, radiotherapy, immunotherapy, surgery, or combination thereof. Accordingly, one or more therapeutic agent or inhibitors may be administered before, during, or after administration of chemotherapy, radiotherapy, immunotherapy, surgery or combination thereof.

In certain embodiments, the subject may be a human who is (i) substantially refractory to at least one chemotherapy treatment, or (ii) in relapse after treatment with chemotherapy, or both (i) and (ii). In some of embodiments, the subject is refractory to at least two, at least three, or at least four chemotherapy treatments (including standard or experimental chemotherapies).

In certain embodiments, the subject is refractory to at least one, at least two, at least three, or at least four chemotherapy treatment (including standard or experimental chemotherapy) selected from fludarabine, rituximab, obinutuzumab, alkylating agents, alemtuzumab and other chemotherapy treatments such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); R-CHOP (rituximab-CHOP); hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine); R-hyperCVAD (rituximab-hyperCVAD); FCM (fludarabine, cyclophosphamide, mitoxantrone); R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone); bortezomib and rituximab; temsirolimus and rituximab; temsirolimus and

Velcade.RTM.; Iodine-131 tositumomab (Bexxar.RTM.) and CHOP; CVP (cyclophosphamide, vincristine, prednisone); R-CVP (rituximab-CVP); ICE (iphoosphamide, carboplatin, etoposide); R-ICE (rituximab-ICE); FCR (fludarabine, cyclophosphamide, rituximab); FR (fludarabine, rituximab); and D.T. PACE
5 (dexamethasone, thalidomide, cisplatin, Adriamycin.RTM., cyclophosphamide, etoposide).

Examples of immunotherapeutic agents treating lymphoma or leukemia include, but are not limited to, rituximab (such as Rituxan), alemtuzumab (such as Campath, MabCampath), anti-CD19 antibodies, anti-CD20 antibodies, anti-MN-14 antibodies, anti-
10 TRAIL, Anti-TRAIL DR4 and DR5 antibodies, anti-CD74 antibodies, apolizumab, bevacizumab, CHIR-12.12, epratuzumab (hLL2-anti-CD22 humanized antibody), galiximab, ha20, ibritumomab tiuxetan, lumiliximab, milatuzumab, ofatumumab, PRO131921, SGN-40, WT-1 analog peptide vaccine, WT1 126-134 peptide vaccine, tositumomab, autologous human tumor-derived HSPPC-96, and veltezumab. Additional
15 immunotherapy agents includes using cancer vaccines based upon the genetic makeup of an individual patient's tumor, such as lymphoma vaccine GTOP-99.

The therapeutic treatments can be supplemented or combined with any of the abovementioned therapies with stem cell transplantation or treatment. One example of modified approach is radioimmunotherapy, wherein a monoclonal antibody is combined
20 with a radioisotope particle, such as indium In-111, yttrium Y-90, iodine I-131. Examples of combination therapies include, but are not limited to, Iodine-131 tositumomab, Yttrium-90 ibritumomab tiuxetan with CHOP.

The compounds of the application can be used in combination with additional therapeutic procedures. Other therapeutic procedures include peripheral blood stem cell
25 transplantation, autologous hematopoietic stem cell transplantation, autologous bone marrow transplantation, antibody therapy, biological therapy, enzyme inhibitor therapy, total body irradiation, infusion of stem cells, bone marrow ablation with stem cell support, in vitro-treated peripheral blood stem cell transplantation, umbilical cord blood transplantation, immunoenzyme technique, pharmacological study, low-LET cobalt-60
30 gamma ray therapy, bleomycin, conventional surgery, radiation therapy, and nonmyeloablative allogeneic hematopoietic stem cell transplantation.

The compounds of the application can be used in combination with anti-fibrotic agents. The anti-fibrotic agents include, but are not limited to, emylenemamine, hydrazine, phenylhydrazine, and their derivatives, semicarbazide, and urea derivatives, aminonitriles, such as beta-aminopropionitrile (BAPN), or 2-nitroethylamine, unsaturated
 5 or saturated haloamines, such as 2-bromo-ethylamine, 2-chloroethylamine, 2-trifluoroethylamine, 3-bromopropylamine, p-halobenzylamines, selenohomocysteine lactone. Also, the anti-fibrotic agents are copper chelating agents, penetrating or not penetrating the cells. Exemplary compounds include indirect inhibitors such compounds blocking the aldehyde derivatives originating from the oxidative deamination of the lysyl
 10 and hydroxyllysyl residues by the lysyl oxidases, such as the thiolamines, in particular D-penicillamine, or its analogues such as 2-amino-5-mercapto-5-methylhexanoic acid, D-2-amino-3-methyl-3-((2-acetamidoethyl)dithio)butanoic acid, p-2-amino-3-methyl-3-((2-aminoethyl)dithio)butanoic acid, sodium-4-((p-1-dimethyl-2-amino-2-carboxyethyl)dithio)butane sulphurate, 2-acetamidoethyl-2-acetamidoethanethiol
 15 sulphanate, sodium-4-mercaptobutanesulphinate trihydrate.

The compounds of the application can be used in combination with immunotherapeutic and anti-inflammatory treatments. The immunotherapeutic agents include and are not limited to therapeutic antibodies suitable for treating patients; such as
 20 abagovomab, adecatumumab, afutuzumab, alemtuzumab, altumomab, amatuximab, anatumomab, arcitumomab, bavituximab, bectumomab, bevacizumab, bivatuzumab, blinatumomab, brentuximab, cantuzumab, catumaxomab, cetuximab, citatuzumab, cixutumumab, clivatuzumab, conatumumab, daratumumab, drozitumab, duligotumab, dusigitumab, detumomab, dacetuzumab, dalotuzumab, ecromeximab, elotuzumab, ensituximab, ertumaxomab, etaracizumab, farietuzumab, ficlatuzumab, figitumumab,
 25 flantvotumab, futuximab, ganitumab, gentuzumab, girentuximab, glembatumumab, ibritumomab, igovomab, imgatuzumab, indatuximab, inotuzumab, intetumumab, ipilimumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lorvotuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, moxetumomab, narnatumab, naptumomab, necitumumab, nimotuzumab, nofetumomabn,
 30 ocaratuzumab, ofatumumab, olaratumab, onartuzumab, oportuzumab, oregovomab, panitumumab, parsatuzumab, patritumab, pentumomab, pertuzumab, pintumomab, pritumumab, racotumomab, radretumab, rilotumumab, rituximab, robatumumab,

satumomab, sibrotuzumab, siltuximab, simtuzumab, solitomab, tacatuzumab, taplitumomab, tenatumomab, teprotumumab, tigatuzumab, tositumomab, trastuzumab, tucotuzumab, ublituximab, veltuzumab, vorsetuzumab, votumumab, zalutumumab, CC49 and 3F8. The exemplified therapeutic antibodies may be further labeled or combined with
 5 a radioisotope particle, such as indium In-111, yttrium Y-90, iodine I-131.

In one aspect, the immuno-oncology agent is (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses (often referred to as immune checkpoint regulators).

10 Certain of the stimulatory and inhibitory molecules are members of the immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-
 15 stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate TNF receptor family members, which includes CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LT β R,
 20 LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α /TNF β , TNFR2, TNF α , LT β R, Lymphotoxin α 1 β 2, FAS, FASL, RELT, DR6, TROY, NGFR.

In one aspect, T cell responses can be stimulated by a combination of a compound of Formula (I) and one or more of (i) an antagonist of a protein that inhibits T cell
 25 activation (e.g., immune checkpoint inhibitors) such as CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-4, and (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40,
 30 DR3 and CD28H.

Other agents that can be combined with compounds described herein for the treatment of cancer include antagonists of inhibitory receptors on NK cells or agonists of

activating receptors on NK cells. For example, compounds described herein can be combined with antagonists of KIR, such as lirilumab.

Yet other agents for combination therapies include agents that inhibit or deplete macrophages or monocytes, including but not limited to CSF-1R antagonists such as

5 CSF-1R antagonist antibodies including RG7155 (WO11/70024, WO11/107553, WO11/131407, WO13/87699, WO13/119716, WO13/132044) or FPA-008 (WO11/140249; WO13169264; WO14/036357).

In another aspect, compounds of the present application can be used with one or more of agonistic agents that ligate positive costimulatory receptors, blocking agents that

10 attenuate signaling through inhibitory receptors, antagonists, and one or more agents that increase systemically the frequency of anti-tumor T cells, agents that overcome distinct immune suppressive pathways within the tumor microenvironment (e.g., block inhibitory receptor engagement (e.g., PD-L1/PD-1 interactions), deplete or inhibit Tregs (e.g., using an anti-CD25 monoclonal antibody (e.g., daclizumab) or by ex vivo anti-CD25 bead

15 depletion), inhibit metabolic enzymes such as IDO, or reverse/prevent T cell anergy or exhaustion) and agents that trigger innate immune activation and/or inflammation at tumor sites.

In one aspect, the immuno-oncology agent is a CTLA-4 antagonist, such as an antagonistic CTLA-4 antibody. Suitable CTLA-4 antibodies include, for example,

20 YERVOY (ipilimumab) or tremelimumab.

In another aspect, the immuno-oncology agent is a PD-1 antagonist, such as an antagonistic PD-1 antibody. Suitable PD-1 antibodies include, for example, OPDIVO (nivolumab), KEYTRUDA (pembrolizumab), or MEDI-0680 (AMP-514; WO2012/145493). The immuno-oncology agent may also include pidilizumab (CT-011),

25 though its specificity for PD-1 binding has been questioned. Another approach to target the PD-1 receptor is the recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224

In another aspect, the immuno-oncology agent is a PD-L1 antagonist, such as an antagonistic PD-L1 antibody. Suitable PD-L1 antibodies include, for example,

30 MPDL3280A (RG7446; WO2010/077634), durvalumab (MEDI4736), BMS-936559 (WO2007/005874), and MSB0010718C (WO2013/79174).

In another aspect, the immuno-oncology agent is a LAG-3 antagonist, such as an antagonistic LAG-3 antibody. Suitable LAG3 antibodies include, for example, BMS-986016 (WO10/19570, WO14/08218), or IMP-731 or IMP-321 (WO08/132601, WO09/44273).

5 In another aspect, the immuno-oncology agent is a CD137 (4-1BB) agonist, such as an agonistic CD137 antibody. Suitable CD137 antibodies include, for example, urelumab and PF-05082566 (WO12/32433).

In another aspect, the immuno-oncology agent is a GITR agonist, such as an agonistic GITR antibody. Suitable GITR antibodies include, for example, BMS-986153,
10 BMS-986156, TRX-518 (WO06/105021, WO09/009116) and MK-4166 (WO11/028683).

In another aspect, the immuno-oncology agent is an IDO antagonist. Suitable IDO antagonists include, for example, INCB-024360 (WO2006/122150, WO07/75598, WO08/36653, WO08/36642), indoximod, BMS-986205, or NLG-919 (WO09/73620, WO09/1156652, WO11/56652, WO12/142237).

15 In another aspect, the immuno-oncology agent is an OX40 agonist, such as an agonistic OX40 antibody. Suitable OX40 antibodies include, for example, MEDI-6383 or MEDI-6469.

In another aspect, the immuno-oncology agent is an OX40L antagonist, such as an antagonistic OX40 antibody. Suitable OX40L antagonists include, for example, RG-7888
20 (WO06/029879).

In another aspect, the immuno-oncology agent is a CD40 agonist, such as an agonistic CD40 antibody. In yet another embodiment, the immuno-oncology agent is a CD40 antagonist, such as an antagonistic CD40 antibody. Suitable CD40 antibodies include, for example, lucatumumab or dacetuzumab.

25 In another aspect, the immuno-oncology agent is a CD47 antagonist, such as a CD47 antagonist selected from the group MIAP301, MIAP410, TTI-621, CV1, Hu5F9-G4, CC-90002, B6H12 and 2D3.

In another aspect, the immuno-oncology agent is a CD27 agonist, such as an agonistic CD27 antibody. Suitable CD27 antibodies include, for example, varlilumab.

30 In another aspect, the immuno-oncology agent is MGA271 (to B7H3) (WO11/109400).

The combination therapy is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner.

- 5 Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single dosage form having a fixed ratio of each therapeutic agent or in multiple, single dosage forms for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes,
- 10 intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be
- 15 administered orally or all therapeutic agents may be administered by intravenous injection. Combination therapy also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (e.g., surgery or radiation treatment.) Where the combination therapy further comprises a non drug treatment, the non drug treatment may
- 20 be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

- 25 The present invention also provides the compounds of the present invention for use in therapy.

In another embodiment, compounds of Formula I are selected from exemplified compounds or combinations of exemplified compounds or other embodiments herein.

- In another embodiment are compounds having an $IC_{50} < 1000$ nM in at least one of
- 30 the assays described below.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of

preferred aspects and/or embodiments of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is its own
5 independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

METHODS OF PREPARATION

10 The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described
15 below. All references cited herein are hereby incorporated in their entirety by reference. The compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood
20 that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible
25 with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of
30 the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many

alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Third Edition, Wiley and Sons, 1999).

EXAMPLES

Preparation of compounds of Formula I and intermediates used in the preparation of compounds of Formula I can be prepared using procedures shown in the following Examples and related procedures. The methods and conditions used in these examples, and the actual compounds prepared in these Examples, are not meant to be limiting, but are meant to demonstrate how the compounds of Formula I can be prepared. Starting materials and reagents used in these examples, when not prepared by a procedure described herein, are generally either commercially available, or are reported in the chemical literature, or may be prepared by using procedures described in the chemical literature.

15 Examples

The following examples illustrate the particular and preferred embodiments of the present invention and do not limit the scope of the present invention. Chemical abbreviations and symbols as well as scientific abbreviations and symbols have their usual and customary meanings unless otherwise specified. Common intermediates are generally useful for the preparation of more than one Example as shown in the Tables.

Chemical names were determined using ChemBioDraw Ultra, version 14.0.0.126 (CambridgeSoft).

The following abbreviations are used:

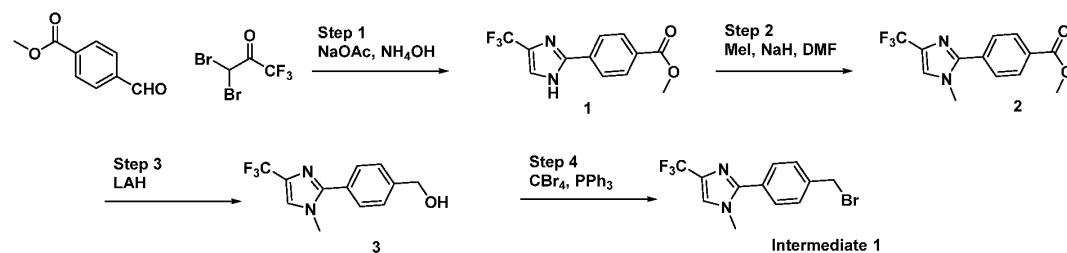
ABBREVIATION	NAME
Boc	<i>tert</i> -butyloxycarbonyl
CDCl ₃	deuterated chloroform
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide

ABBREVIATION	NAME
DMSO- <i>d</i> ₆	deuterated dimethyl sulfoxide
Et ₃ N	triethylamine
EtOAc	ethyl acetate
h	hours
HATU	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
LC	liquid chromatography
LCMS	liquid chromatography – mass spectrometry
MeCN	acetonitrile
MeOH	methanol
MeOH- <i>d</i> ₄	deuterated methanol
mCPBA	meta-chloroperoxybenzoic acid
min	minutes
MsCl	methanesulfonyl chloride
NH ₄ OAc	ammonium acetate
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
rt	room temperature
SFC	super-critical fluid chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UPLC	ultra performance liquid chromatography

Description of analytical LCMS method:

Method A: XBridge C18, 2.1 mm x 50 mm, 1.7 μ m particles; Mobile Phase A: ACN/H₂O (5:95) with 0.05 % TFA; Mobile Phase B: ACN/H₂O (95:5) with 0.05 % TFA;
 5 Temperature: 50 °C; Gradient: 0-100 % B (0-3 min), 100 %B (3-3.5 min); Flow: 1 mL/min; Detection: UV (220 nm) and MS (ESI +/-).

Intermediate 1: 2-(4-(bromomethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole



10 Step 1: Methyl 4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate **1**

A mixture of 3,3-dibromo-1,1,1-trifluoropropan-2-one (49.3 g, 183 mmol) and sodium acetate (20.0 g, 244 mmol) in water (100 mL) was stirred at 95 °C for 30 min. The mixture was cooled to 0 °C and a cold solution of methyl 4-formylbenzoate (20.0 g, 122 mmol) in a mixture of NH₄OH (28% aq, 100 mL) and MeOH (300 mL) was added, and the contents
 15 stirred at RT for 16 h. The reaction mixture was concentrated, and the residue was diluted with ethyl acetate and washed with water. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel, 230-400 mesh, to give methyl 4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate **1** (19 g, 61 mmol, 50%) as a yellow solid. LC-MS, *m/z*: 271.0
 20 [M+H].

Step 2: Methyl 4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate **2**

To a stirred solution of methyl 4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate **1** (2.50 g, 9.25 mmol) in DMF (20 mL) was added sodium hydride (60% dispersion in mineral oil, 0.740 g, 18.5 mmol) followed by iodomethane (0.87 mL, 13.9 mmol) at 0 °C. The mixture
 25 was stirred at RT for 3 h. After reaction completion (monitored by TLC), cold water was added, and the contents extracted with ethyl acetate. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel, 230-400 mesh to give methyl 4-(1-methyl-4-

(trifluoromethyl)-1*H*-imidazol-2-yl)benzoate **2** (1.40 g, 4.87 mmol, 53 %) as a white solid. LC-MS, *m/z*: 285.0 [M+H].

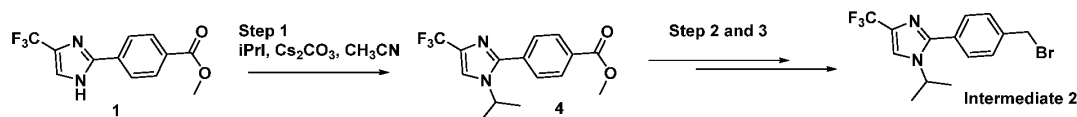
Step 3: 4-(1-Methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol **3**

To a stirred solution of methyl 4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzoate **2** (1.20 g, 4.22 mmol) in THF (25 mL) at 0 °C was added lithium aluminum hydride (2 M in THF, 4.22 mL, 8.44 mmol) and the contents stirred at RT for 3 h. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel, 230-400 mesh, to give 4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol **3** (0.90 g, 3.42 mmol, 81%) as a white solid. LC-MS, *m/z*: 257.0 [M+H].

Step 4: 2-(4-(bromomethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1*H*-imidazole **Intermediate 1**

To a solution of 4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol **3** (100 mg, 0.390 mmol) in tetrahydrofuran (1.5 mL) was added carbon tetrabromide (259 mg, 0.781 mmol) portionwise at 0 °C, followed by the dropwise addition of a solution of triphenylphosphine (205 mg, 0.781 mmol) in tetrahydrofuran (1.0 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and then at RT for 16 h. The reaction mixture was poured into ice water and extracted into ethyl acetate. The organic layer was washed with brine solution, dried over sodium sulphate, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography using gradient of 0-15% ethyl acetate in petroleum ether. The product fractions were concentrated to afford 2-(4-(bromomethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1*H*-imidazole **Intermediate 1** (70 mg, 0.213 mmol, 54.5 % yield) as white solid. LC-MS, *m/z*: 319.1 [M+H]; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.96 (m, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 4.79 (s, 2H), 3.80 (s, 3H).

Intermediate 2: 2-(4-(bromomethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole



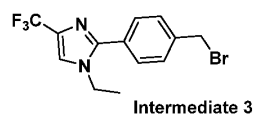
Step 1: Methyl 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzoate **4**

To a stirred solution of methyl 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzoate **1** (2.0 g, 7.4 mmol) in acetonitrile (30 mL) at 0 °C was added Cs₂CO₃ (4.82 g, 14.8 mmol) followed by 2-iodopropane (1.1 mL, 11.1 mmol) over a period of 5 minutes. The reaction mixture was stirred at RT for 16 h and heated at 50 °C for an additional 16 h. After cooling, the reaction was concentrated. The resulting residue was diluted with ethyl acetate and washed with water. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated. This crude material was purified by flash chromatography on silica gel, 230-400 mesh, to give methyl 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzoate **4** (0.80 g, 2.23 mmol, 30%) as a white solid. LC-MS, *m/z*: 313.2 [M+H].

Step 2 and 3: 2-(4-(bromomethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole
Intermediate 2

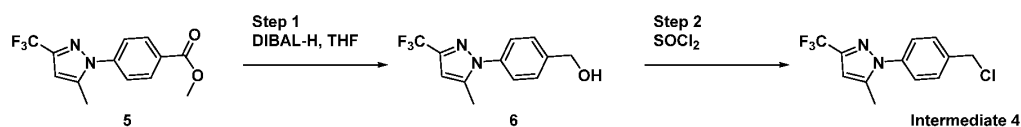
Intermediate 2 was prepared using the same methods as described for **Intermediate 1**, Step 3 and 4. LC-MS, *m/z*: 347.0 [M+H]; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.59 - 7.54 (m, 2H), 7.54 - 7.50 (m, 2H), 7.45 (d, *J* = 1.1 Hz, 1H), 4.66 - 4.57 (m, 1H), 4.56 (s, 2H), 1.49 (d, *J* = 6.6 Hz, 6H).

Intermediate 3: 2-(4-(bromomethyl)phenyl)-1-ethyl-4-(trifluoromethyl)-1*H*-imidazole



Intermediate 3 was prepared using the same methods as described for **Intermediate 1**. LC-MS, *m/z*: 333.1 [M+H]; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.06 (m, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 4.80 (s, 2H), 4.11 (q, *J* = 7.6 Hz, 2H), 1.53 (t, *J* = 7.6 Hz, 3H).

Intermediate 4: 1-(4-(chloromethyl)phenyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazole



Step 1: (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanol **6**

To a stirred solution of methyl 4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzoate **5** [WO2020/132269] (5.0 g, 17.6 mmol) in tetrahydrofuran (20 mL) at 0 °C was added DIBAL-H (1.2 M in toluene, 44.0 mL, 52.8 mmol). This mixture was stirred at RT for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was slowly poured into cold water containing crushed ice and filtered through celite. The filtrate was

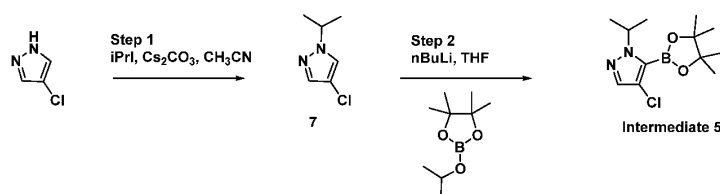
extracted with ethyl acetate and organic layers were dried (Na_2SO_4), filtered and concentrated to give (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanol **6** (3.8 g, 14.2 mmol, 81%) as a pale-yellow liquid. LC-MS, m/z : 257.0 [$\text{M}+\text{H}$].

Step 2: 1-(4-(chloromethyl)phenyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazole

5 Intermediate 4

To a stirred solution of (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanol **6** (0.25 g, 0.98 mmol) in 1,2-dichloroethane (2.5 mL) was added thionyl chloride (0.21 mL, 2.9 mmol). The reaction was allowed to stir at 50 °C for 1 h. The reaction mixture was cooled to RT and concentrated to remove the solvent and excess thionyl chloride. The resulting crude was diluted with DCM, made basic with saturated sodium bicarbonate solution, extracted with dichloromethane, dried on sodium sulphate, and concentrated under reduced pressure. The resulting crude was purified by column chromatography using silica gel (100-200), petroleum ether and ethyl acetate. Fractions containing the desired product was collected to give 1-(4-(chloromethyl)phenyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazole **Intermediate 4** (0.25 g, 93%) as an off white solid. LC-MS, m/z : 274.9 [$\text{M}+\text{H}$]; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.64 (d, $J = 8.03$ Hz, 2H), 7.61 (d, $J = 8.0$ Hz, 2H), 6.78 (s, 1H), 4.87 (s, 2H), 2.37 (s, 3H).

Intermediate 5: 4-chloro-1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole



Step 1: 4-chloro-1-isopropyl-1*H*-pyrazole **7**

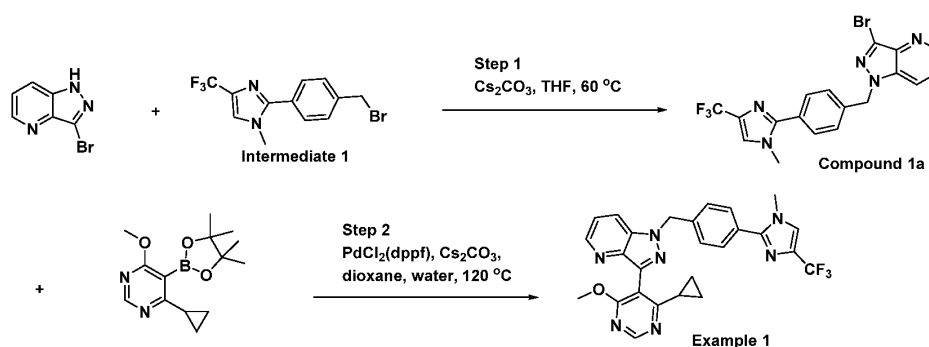
To a stirred solution of 4-chloro-1*H*-pyrazole (5.0 g, 49 mmol) in acetonitrile (60 mL) was added Cs_2CO_3 (32 g, 98 mmol) followed by addition of 2-iodopropane (5.7 mL, 59 mmol). This mixture was heated at 80 °C for 2 h. The reaction mixture was cooled to RT, water was added, and the contents extracted with diethyl ether. The organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated to give crude 4-chloro-1-isopropyl-1*H*-pyrazole **7** (6.0 g, 39 mmol, 81%) as a pale-yellow oil (which was used as such for the next step). LC-MS, m/z : 145.00 [$\text{M}+\text{H}$].

Step 2: 4-chloro-1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

Intermediate 5

To a stirred solution of 4-chloro-1-isopropyl-1H-pyrazole **7** (5.50 g, 38.0 mmol) in tetrahydrofuran (50 mL) at 0 °C was added n-butyllithium (1.6 M in hexanes, 28.5 mL, 45.6 mmol). After the addition was complete, the mixture was warmed to RT and stirred for 1 h. The reaction mixture was cooled to -78 °C before the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.49 g, 45.6 mmol). This was stirred for 2 h at -78 °C. The reaction was warmed to RT, quenched with saturated aqueous NH₄Cl (50 mL) and extracted with ethyl acetate. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated to give crude 4-chloro-1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole **Intermediate 5** (6.0 g, 14 mmol, 38%) as a dark brown oil (which was used as such for the subsequent steps). LC-MS, *m/z*: 271.10 [M+H].

Example 1: 3-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-1-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrazolo[4,3-b]pyridine



Step 1: 3-bromo-1-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrazolo[4,3-b]pyridine **Compound 1a**

To a stirred solution of 3-bromo-1H-pyrazolo[4,3-b]pyridine (46.0 mg, 0.232 mmol) in tetrahydrofuran (2 mL) were added Cs₂CO₃ (151 mg, 0.465 mmol) and **Intermediate 1** (82.1 mg, 0.256 mmol). The reaction mixture was heated at 60 °C for 2 h. The reaction mixture was cooled to RT, filtered, and concentrated. The crude product was added to a silica gel (12 g) column and was eluted with 0-100% EtOAc in hexanes. Fractions containing the desired product were collected to give **Compound 1a** (65 mg, 0.15 mmol, 64 % yield) as a white solid. MS *m/z* = 435.8 (M+H); ¹H NMR (400MHz, CDCl₃) δ 8.64

(dd, $J = 4.4, 1.2$ Hz, 1H), 7.72 - 7.63 (m, 1H), 7.59 (d, $J = 8.3$ Hz, 2H), 7.41 - 7.25 (m, 4H), 5.63 (s, 2H), 3.73 (s, 3H).

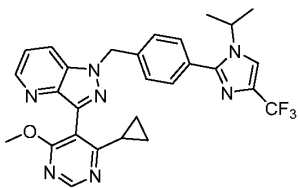
Step 2: 3-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-1-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrazolo[4,3-b]pyridine **Example 1**

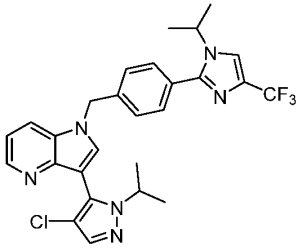
- 5 To 4-cyclopropyl-6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (7.60 mg, 0.0281 mmol) **Compound 1a** (10.1 mg, 0.023 mmol), PdCl₂(dppf) (1.68 mg, 2.29 μmol) and Cs₂CO₃ (14.9 mg, 0.0461 mmol) in a pressure-rated vial were added dioxane (1 mL) and water (0.1 mL). The reaction mixture was evacuated and backfilled with N₂ 3 times and was heated to 120 °C in a microwave for 30 min. The reaction mixture
- 10 was cooled to RT, filtered, concentrated in vacuo, and purified via preparative Reverse Phase chromatography employing the following conditions: Column: XBridge C18, 19 mm x 200 mm, 5 μm particles; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to give 3-(4-cyclopropyl-6-
- 15 methoxypyrimidin-5-yl)-1-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrazolo[4,3-b]pyridine (**Example 1**) (4.2 mg, 36%). MS $m/z = 506.0$ (M+H); HPLC Method A, $R_t = 1.78$ min; purity: 100%; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.72 (s, 1H), 8.54 (dd, $J = 4.3, 1.2$ Hz, 1H), 8.33 (dd, $J = 8.6, 1.2$ Hz, 1H), 7.91 (d, $J = 0.9$ Hz, 1H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.54 - 7.45 (m, 1H), 7.42 (d, $J = 8.3$ Hz, 2H), 5.87 (s, 2H), 3.82 (s, 3H),
- 20 3.75 (s, 3H), 1.82 - 1.69 (m, 1H), 1.13 - 0.96 (m, 2H), 0.86 (br dd, $J = 8.0, 3.2$ Hz, 2H).

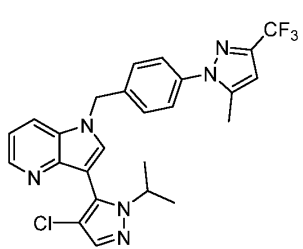
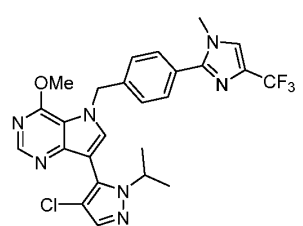
Examples 2 to 6 were prepared using the same methods as described for **Example 1**.

Example Number	Structure	Name	¹ H NMR	LCMS (ESI) m/z : [M+H ⁺]	LC retention time (min), LCMS method, purity
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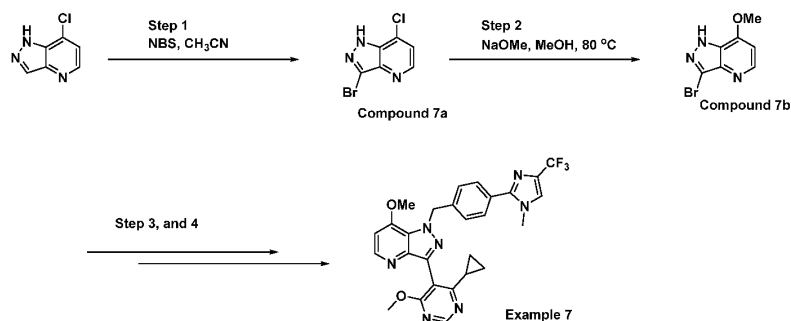
2		3-(4-chloro-1-isopropyl-1H-imidazol-5-yl)-1-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrazolo[3,4-b]pyrazine	¹H NMR (500 MHz, DMSO-d₆) δ 8.89 - 8.73 (m, 2H), 7.91 (s, 1H), 7.82 (s, 1H), 7.72 (br d, <i>J</i> = 8.2 Hz, 2H), 7.49 (br d, <i>J</i> = 8.2 Hz, 2H), 5.93 (s, 2H), 4.71 - 4.52 (m, 1H), 3.76 (s, 2H), 1.38 (d, <i>J</i> = 6.5 Hz, 6H)	500.9	2.11, A, 99%
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3		3-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrazolo[4,3-b]pyridine	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.72 (s, 1H), 8.54 (d, J = 4.2 Hz, 1H), 8.33 (d, J = 7.9 Hz, 1H), 8.15 (s, 1H), 7.60 - 7.52 (m, 2H), 7.48 (dd, J = 8.5, 4.3 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 5.88 (s, 2H), 4.62 - 4.32 (m, 1H), 3.82 (s, 3H), 1.88 - 1.64 (m, 1H), 1.37 (d, J = 6.6 Hz, 6H), 1.05 (br d, J = 3.9 Hz, 2H), 0.85 (br dd, J = 7.6, 3.1 Hz, 2H)	534.0	1.88, A, 100%
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4		3-(4-chloro-1-isopropyl-1H-pyrazol-5-yl)-1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrrolo[3,2-b]pyridine	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.49 - 8.39 (m, 1H), 8.18 (s, 1H), 8.14 (s, 1H), 8.09 - 8.02 (m, 1H), 7.70 (s, 1H), 7.56 (br d, J = 8.1 Hz, 2H), 7.43 (br d, J = 8.1 Hz, 2H), 7.25 (dd, J = 8.3, 4.6 Hz, 1H), 5.67 (s, 2H), 4.65 - 4.50 (m, 1H), 4.43 (dt, J = 13.2, 6.5 Hz, 1H), 1.45 - 1.28 (m, 12H)	527.0	1.74, A, 99.3%
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5		3-(4-chloro-1-isopropyl-1H-pyrazol-5-yl)-1-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-1H-pyrrolo[3,2-b]pyridine	¹H NMR (500 MHz, DMSO-d₆) δ 8.43 (br d, J = 4.5 Hz, 1H), 8.20 (s, 1H), 8.07 (br d, J = 8.3 Hz, 1H), 7.70 (s, 1H), 7.62 - 7.53 (m, 2H), 7.47 (br d, J = 8.2 Hz, 2H), 7.26 (dd, J = 8.2, 4.5 Hz, 1H), 6.74 (s, 1H), 5.68 (s, 2H), 4.58 (quin, J = 6.7 Hz, 1H), 2.32 (s, 3H), 1.36 (br d, J = 6.5 Hz, 6H)	499.1	1.81, A, 100%
6		7-bromo-4-methoxy-5-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-5H-pyrrolo[3,2-d]pyrimidine	¹H NMR (500 MHz, DMSO-d₆) δ 8.49 (s, 1H), 8.25 (s, 1H), 7.92 (s, 1H), 7.77 - 7.69 (m, 3H), 7.39 (br d, J = 8.2 Hz, 2H), 5.73 (s, 2H), 4.60 - 4.44 (m, 1H), 4.08 (s, 3H), 3.77 (s, 3H), 1.36 (br d, J = 6.5 Hz, 6H)	530.0	1.96, A, 100%

Example 7: 3-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methoxy-1-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrazolo[4,3-b]pyridine



Step 1: 3-bromo-7-chloro-1H-pyrazolo[4,3-b]pyridine **Compound 7a**

- 5 To a stirred solution of 7-chloro-1H-pyrazolo[4,3-b]pyridine (110 mg, 0.716 mmol) in acetonitrile (5 mL) was added NBS (147 mg, 0.824 mmol). The reaction was stirred at RT for 4 h and concentrated under reduced pressure. The crude product was added to a silica gel (12 g) column and eluted with 0-100% EtOAc in hexanes, then 0-40% MeOH/DCM. Fractions containing the desired product were collected to give **Compound 7a** (112 mg, 10 0.482 mmol, 67 % yield) as a white solid. MS m/z = 231.7 (M+H); ^1H NMR (400 MHz, METHANOL- d_4) δ 8.48 (d, J = 4.9 Hz, 1H), 7.55 (d, J = 4.9 Hz, 1H).

Step 2: 3-bromo-7-methoxy-1H-pyrazolo[4,3-b]pyridine **Compound 7b**

- To a stirred solution of 3-bromo-7-chloro-1H-pyrazolo[4,3-b]pyridine (50.1 mg, 0.215 mmol) in MeOH (1 mL) was added sodium methoxide (0.199 mL, 1.08 mmol). The 15 reaction was stirred at 80 °C for 24 h, concentrated in vacuo and diluted with EtOAc. The organic layer was washed with saturated aq. NH_4Cl solution, dried over MgSO_4 , filtered and concentrated in vacuo to give **Compound 6b** (50 mg, 0.22 mmol, 102 % yield) as a white solid. MS m/z = 227.8 (M+H); ^1H NMR (500 MHz, METHANOL- d_4) δ 8.40 (d, J = 5.4 Hz, 1H), 6.97 (d, J = 5.3 Hz, 1H), 4.11 (s, 3H).

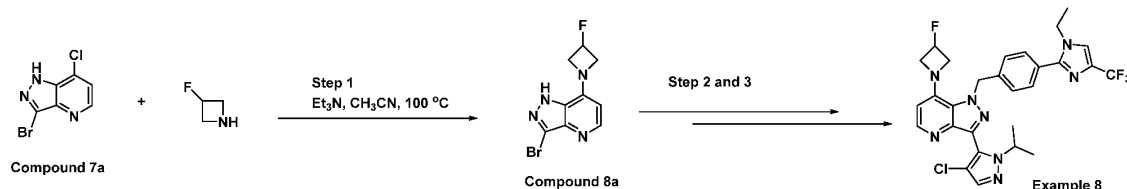
- 20 Step 3 and 4: 3-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methoxy-1-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrazolo[4,3-b]pyridine **Example 7**

Example 7 was prepared using the same methods as described for **Example 1**, Step 1 and 2.

- MS m/z = 536.1 (M+H); HPLC Method A, R_t = 1.66 min; purity: 99%; ^1H NMR (500 25 MHz, DMSO- d_6) δ 8.71 (s, 1H), 8.38 (br d, J = 5.3 Hz, 1H), 7.90 (s, 1H), 7.68 (br d, J =

8.3 Hz, 2H), 7.36 (br d, $J = 8.2$ Hz, 2H), 7.02 (d, $J = 5.3$ Hz, 1H), 5.88 (s, 2H), 4.07 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 1.80 - 1.63 (m, 1H), 1.10 - 0.98 (m, 2H), 0.93 - 0.79 (m, 2H).

Example 8: 3-(4-chloro-1-isopropyl-1H-pyrazol-5-yl)-1-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-(3-fluoroazetidin-1-yl)-1H-pyrazolo[4,3-b]pyridine



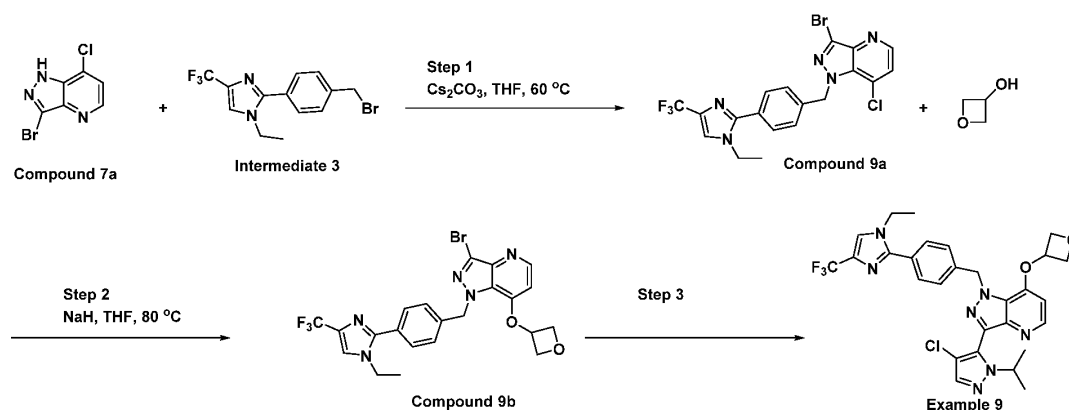
Step 1: 3-bromo-7-(3-fluoroazetidin-1-yl)-1H-pyrazolo[4,3-b]pyridine **Compound 8a**

To a stirred solution of **Compound 7a** (20 mg, 0.086 mmol) in acetonitrile (5 mL) was added 3-fluoroazetidine (19.4 mg, 0.258 mmol) and Et₃N (0.060 mL, 0.430 mmol). The reaction was kept at 100 °C for 2 days, cooled to RT and concentrated in vacuo. The crude product was added to a silica gel (4 g) column and eluted with 0-100% EtOAc in hexanes. Fractions containing the desired product were collected to give **Compound 8a** (10 mg, 0.037 mmol, 43 % yield) as a white solid. MS $m/z = 271.0$ (M+H); ¹H NMR (400 MHz, METHANOL-*d*₄) δ 8.17 (d, $J = 5.2$ Hz, 1H), 6.15 (d, $J = 5.2$ Hz, 1H), 5.68 - 5.35 (m, 1H), 4.70 - 4.50 (m, 2H), 4.45 - 4.28 (m, 2H).

Steps 2 and 3: 3-(4-chloro-1-isopropyl-1H-pyrazol-5-yl)-1-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-(3-fluoroazetidin-1-yl)-1H-pyrazolo[4,3-b]pyridine **Example 8**

Example 8 was prepared using the same methods as described for **Example 1**, Step 1 and 2. MS $m/z = 587.2$ (M+H); HPLC Method A, Rt = 1.80 min; purity: 100%; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.33 (d, $J = 5.3$ Hz, 1H), 8.00 (s, 1H), 7.76 (s, 1H), 7.60 (br d, $J = 8.2$ Hz, 2H), 7.24 (br d, $J = 8.2$ Hz, 2H), 6.67 (d, $J = 5.3$ Hz, 1H), 5.88 (s, 2H), 5.67 - 5.39 (m, 1H), 4.72 - 4.51 (m, 2H), 4.45 - 4.29 (m, 3H), 4.06 (q, $J = 7.2$ Hz, 2H), 1.39 - 1.20 (m, 9H).

Example 9: 3-(4-chloro-1-isopropyl-1H-pyrazol-5-yl)-1-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-(oxetan-3-yloxy)-1H-pyrazolo[4,3-b]pyridine



Step 1: 3-bromo-7-chloro-1-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-1H-pyrazolo[4,3-b]pyridine **Compound 9a**

To a stirred solution of **Compound 7a** (75.0 mg, 0.323 mmol) in tetrahydrofuran (2 mL) were added Cs_2CO_3 (210 mg, 0.645 mmol) and **Intermediate 3** (118 mg, 0.355 mmol). The reaction mixture was heated at 60 °C for 4 h, cooled to RT, filtered and concentrated. The crude product was added to a silica gel (24 g) column and eluted with 0-100% EtOAc in hexanes. Fractions containing the desired product were collected to give **Compound 9a** (100 mg, 0.206 mmol, 64 % yield) as a white solid. MS m/z = 484.0 (M+H); ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.51 (d, J = 4.8 Hz, 1H), 7.65 - 7.48 (m, 2H), 7.38 (d, J = 4.8 Hz, 1H), 7.35 (d, J = 1.1 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 5.94 (s, 2H), 4.03 (q, J = 7.3 Hz, 2H), 1.41 (t, J = 7.3 Hz, 3H).

Step 2: 3-bromo-1-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-(oxetan-3-yloxy)-1H-pyrazolo[4,3-b]pyridine **Compound 9b**

To a stirred solution of oxetan-3-ol (22.9 mg, 0.309 mmol) in THF (1 mL) was added NaH (12.4 mg, 0.309 mmol), and the reaction mixture was stirred at RT for 20 min. **Compound 9a** (30 mg, 0.062 mmol) in THF (0.5 mL) was added and the reaction mixture was heated at 80 °C for 14 h. The reaction mixture was cooled to RT, concentrated in vacuo, and diluted with EtOAc. The organic layer was washed with H_2O , dried over MgSO_4 , filtered and concentrated in vacuo. The crude product was added to a silica gel (4 g) column and eluted with 0-100% EtOAc in hexanes. Fractions containing the desired product were collected to give **Compound 9b** (35 mg, 0.067 mmol, 108 % yield) as a white solid. MS m/z = 521.9 (M+H); ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.43 (d, J = 5.3 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 1.0 Hz, 1H), 7.33 - 7.29 (m, 2H), 6.29 (d, J = 5.1 Hz,

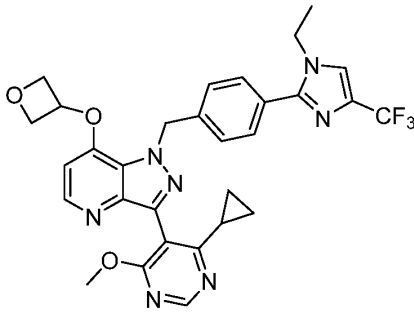
1H), 5.85 (s, 2H), 5.49 - 5.36 (m, 1H), 5.05 (t, $J = 7.1$ Hz, 2H), 4.74 (dd, $J = 8.2, 4.9$ Hz, 2H), 4.04 (q, $J = 7.3$ Hz, 2H), 1.42 (t, $J = 7.3$ Hz, 3H).

Step 3: 3-bromo-7-chloro-1-(4-(1-ethyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-1*H*-pyrazolo[4,3-*b*]pyridine **Compound 9a**

- 5 **Example 9** was prepared using the same methods as described for **Example 1**, Step 2. MS $m/z = 586.0$ (M+H); HPLC Method A, $R_t = 1.98$ min; purity: 100%; ^1H NMR (500 MHz, DMSO- d_6) δ 8.41 (d, $J = 5.0$ Hz, 1H), 8.00 (s, 1H), 7.78 (s, 1H), 7.62 (br d, $J = 8.2$ Hz, 2H), 7.40 (br d, $J = 8.2$ Hz, 2H), 6.72 (d, $J = 5.1$ Hz, 1H), 6.01 (s, 2H), 5.60 (dt, $J = 10.0, 5.2$ Hz, 1H), 5.00 (br t, $J = 6.6$ Hz, 2H), 4.66 (br dd, $J = 7.1, 4.9$ Hz, 2H), 4.59 - 4.44 (m, 10 1H), 4.06 (q, $J = 7.3$ Hz, 2H), 1.36 (br d, $J = 6.5$ Hz, 6H), 1.28 (br t, $J = 7.2$ Hz, 3H).

Example 10 was prepared using the same methods as described for **Example 9**.

Example Number	Structure	Name	^1H NMR	LCMS	LC
				(ESI) m/z : [M+H] ⁺	retention time (min), LCMS method, purity

10		3-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-1-(4-(1-ethyl-4-(trifluoromethyl)-1 <i>H</i> -imidazol-2-yl)benzyl)-7-(oxetan-3-yloxy)-1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridine	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.71 (s, 1H), 8.31 (d, <i>J</i> = 5.1 Hz, 1H), 8.09 - 7.91 (m, 1H), 7.61 (br d, <i>J</i> = 8.1 Hz, 2H), 7.37 (br d, <i>J</i> = 8.1 Hz, 2H), 6.66 (d, <i>J</i> = 5.0 Hz, 1H), 5.97 (s, 2H), 5.69 - 5.50 (m, 1H), 5.00 (br t, <i>J</i> = 6.4 Hz, 2H), 4.64 (br dd, <i>J</i> = 7.1, 4.8 Hz, 2H), 4.05 (q, <i>J</i> = 7.2 Hz, 2H), 3.82 (s, 3H), 1.73 (br dd, <i>J</i> = 8.0, 3.7 Hz, 1H), 1.28 (t, <i>J</i> = 7.2 Hz, 3H), 1.05 (br d, <i>J</i> = 3.4 Hz, 2H), 0.86 (br d, <i>J</i> = 3.1 Hz, 2H)	592.4	1.76, A, 96.4%
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USP1-UAF1 Rhodamine assay

Compounds of the invention were assessed for USP1 activity via the well-known USP1-UAF1 Rhodamine assay described here. USP1/UAF1 ubiquitin-rhodamine 110 hydrolysis assays were performed at room temperature in black, low-volume 384 well plates (Corning 3821). 100X solutions of compounds in DMSO were prepared by three-fold serial dilutions starting from a 10 mM stock. 2X solutions of His6-USP1/His6-UAF1 (200 pM, Internally Produced) and ubiquitin-rhodamine 110 (10 μM, South Bay Bio SBB-PS0001) were prepared in assay buffer (50 mM Tris pH 7.5, 100 mM NaCl, 1 mM EDTA, 1 mM TCEP, 100 ng/μL BSA). Serially diluted compounds in DMSO were transferred to the assay plate by acoustic dispensing (100 nL per well). 5 μL of assay buffer was added to column 1 of the plates, and 5 μL of 2X USP1/UAF1 solution was added to columns 2-24 and incubated with compounds for 3 hrs. Reactions were initiated by addition of 5 μL of 2X ubiquitin-rhodamine 110 solution to each well for final concentrations of 100 pM USP1/UAF1 and 5 μM ubiquitin-rhodamine 110. Fluorescence was read at the minimum kinetic interval for 1 h using a BioTek Synergy HTX plate reader (Agilent Technologies) with excitation at 485 nm and emission at 528 nm. Initial rates were calculated by fitting the linear range of the plot of fluorescence vs time to a linear equation. IC50 values were calculated from dose-response curves.

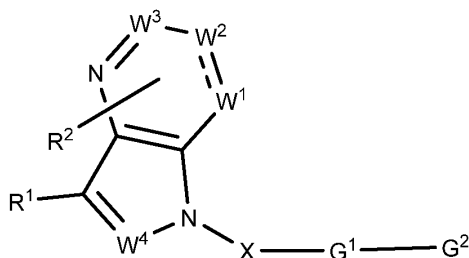
IC50 values for compounds of the invention in the USP1-UAF1 Rhodamine assay are shown below.

Table 1: USP1-UAF1 Rhodamine Assay 3-hour Incubation Results

Compound #	USP1-UAF1 IC ₅₀ μM
1	0.0238
2	0.0173
3	0.0159
4	0.0017
5	0.0117
6	0.0855
7	0.028
8	0.1094
9	0.0229
10	0.0036

WE CLAIM:

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



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

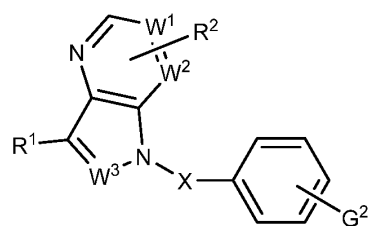
- 5 R¹ is selected from C₆ aryl and 5-6 membered heteroaryls, optionally substituted with one to four halo, hydroxy, amino, -C(O)R^a, -C(O)OR^b, -C(O)NR^aR^b, -N(R^a)C(O)R^b, -S(O)NR^aR^b, -S(O)₂NR^aR^b, -S(O)R^g, -S(O)₂R^g, -NR^aR^b, -OR^a, -SR^b, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₃₋₈ cycloalkyl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and C₃₋₈ cycloalkyl is optionally substituted with one to four R¹⁰⁰;
- 10 R² 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)SO₂NR^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, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S, and C₃₋₈ cycloalkyl is optionally substituted with one to four R¹⁰⁰;
- X is C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one to four R¹⁰⁰;
- Each W¹ and W² is independently selected from -N(R^a)-, -C(O)- and -C(R^a)-;
- 20 W³ is selected from -N- and -C(R^a)-;
- W⁴ is selected from -N- and -C(R^a)-;
- Wherein at least one of W¹, W² and W³ is -C(R^a);
- G¹ is selected from -C₆ aryl-, 5-6 membered heteroaryl, C₃₋₈ cycloalkyl and 5-6 membered heterocyclyl; wherein each C₆ aryl, 5-6 membered heteroaryl, C₃₋₈ cycloalkyl and 5-6 membered heterocyclyl is optionally substituted with one to four R¹⁰⁰;
- 25 G² is a 5 or 6 membered heteroaryl or 5-6 membered heterocyclyl optionally substituted with one to four R¹⁰⁰;

- each R^a and R^b is independently selected from absent, hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms
- 5 selected from N, O, and S is optionally substituted with one to four R²⁰⁰;
- each R¹⁰⁰ is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^c, -C(O)OR^c, -C(O)NR^cR^d, -N(R^c)C(O)R^d, -S(O)NR^cR^d, -S(O)₂NR^cR^d, -S(O)R^h, -S(O)₂R^h, -NR^cR^d, -OR^c, -SR^c, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl containing 1 to 4 heteroatoms
- 10 selected from N, O, and S, and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from N, O, and S; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl is optionally substituted with one to four R²⁰¹;
- each R^c and R^d is independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ 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;
- 15 each R²⁰⁰ and R²⁰¹ is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -N(R^e)C(O)R^f, -S(O)NR^eR^f, -S(O)₂NR^eR^f, -S(O)Rⁱ, -S(O)₂Rⁱ, -NR^eR^f, -OR^e, -SR^e, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ 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 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl is
- 20 optionally substituted with one to four R³⁰⁰;
- each R^g, R^h and Rⁱ is independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, is optionally substituted with one to four R³⁰⁰;
- wherein each R³⁰⁰ is independently selected from hydrogen, halo, cyano, hydroxy, amino, oxo, thioxo, vinyl, -C(O)R^e, -C(O)OR^e, -C(O)NR^eR^f, -N(R^e)C(O)R^f, -S(O)NR^eR^f, -S(O)₂NR^eR^f, -S(O)R^e, -S(O)₂R^e, -NR^eR^f, -OR^e, -SR^e, C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl;
- 30

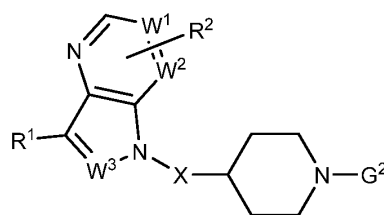
- each R^e and R^f is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl; C_{3-8} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl containing 1 to 4 heteroatoms selected from N, O, and S, and 4-10 membered heterocyclyl containing 1 to 4 heteroatoms selected from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

15

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



Formula (IIa);

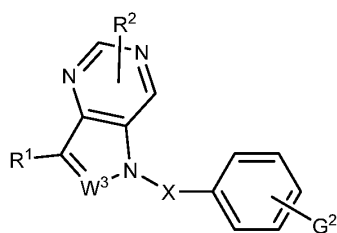


Formula (IIb);

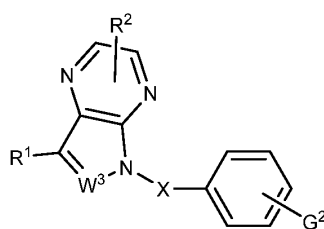
20

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

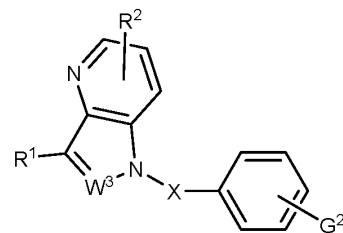
3. A compound of claim 1, having the structure of Formula (IIIa), (IIIb) or (IIIc):



Formula (IIIa)



Formula (IIIb)

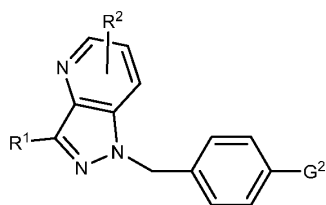


Formula (IIIc)

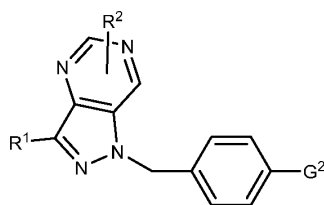
or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

5

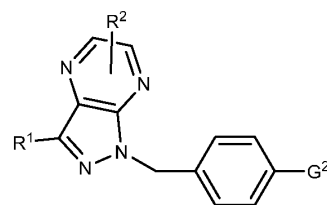
4. A compound of claim 1, having the structure of Formula (IVa), (IVb) or (IVc):



Formula (IVa)



Formula (IVb)

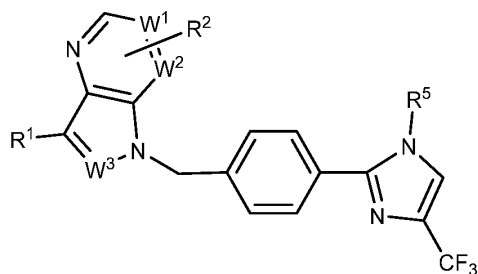


Formula (IVc)

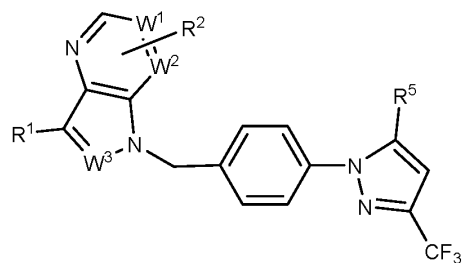
or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

10

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



Formula (V)

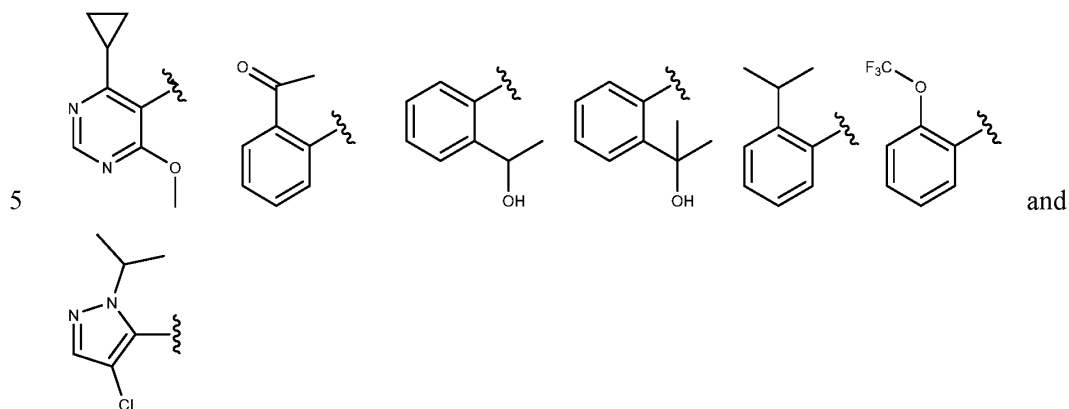


Formula (VI)

15

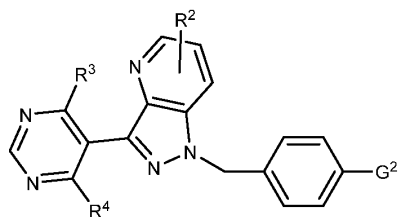
or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof;
wherein R^5 is C_{1-6} alkyl.

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

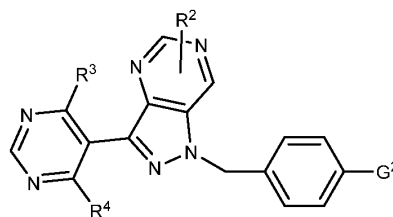


or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers thereof.

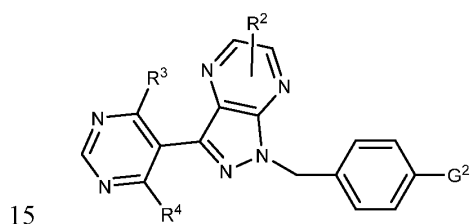
10 7. A compound according to any of claims 1-5 having the structure of formula (VII):



Formula (VIIa)



Formula (VIIb)

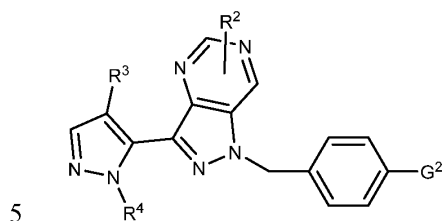


Formula (VIIc)

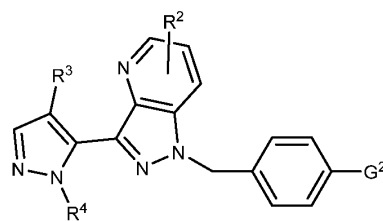
Wherein each R^3 and R^4 is independently selected from hydrogen, halo, $-OR^a$, $-SR^b$ and C_{3-8} cycloalkyl;

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

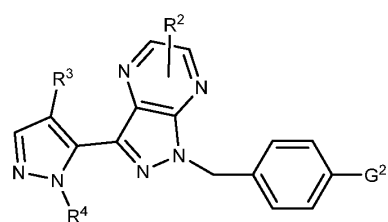
8. A compound according to any of claims 1-5 having the structure of formula (VIIIa) (VIIIb) or (VIIIc):



Formula (VIIIa)



Formula (VIIIb)



Formula (VIIIc)

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

10

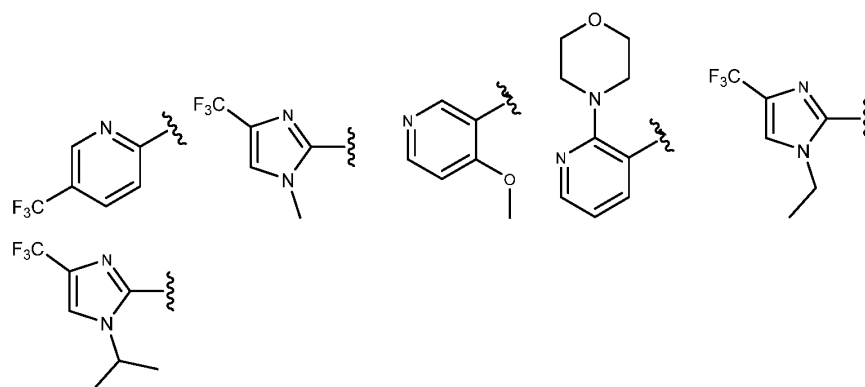
9. A compound according to any of claims 1-8 wherein R² is selected from:

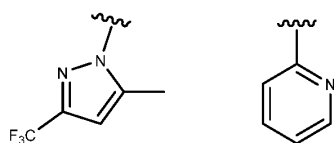
-OCH₃, -H, -SCH₃, -S(O)₂CH₃, -S(O)₂CH₃, -C(O)OCH₃, -C(O)OCH₂CH₃, and -C(O)NH₂.

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

15

10. A compound according to any of claims 1-4, 6-7 and 9 wherein G² is selected from:

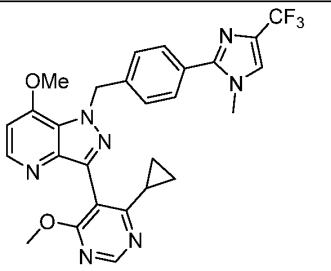
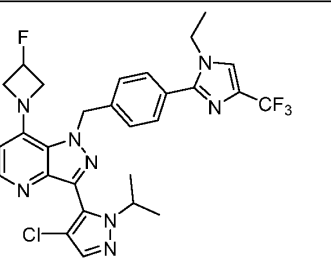
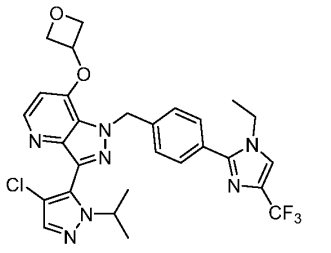
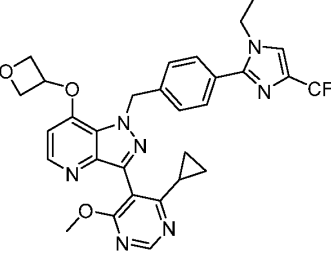




or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or deuterated analog thereof.

- 5 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 above claims and a pharmaceutically acceptable carrier or diluent.
13. A method of treating or preventing a disease or disorder associated with the inhibition of ubiquitin specific protease 1 (USP1) comprising, administering to a patient in need thereof an effective amount of a compound according to any of the above claims.
14. A method for treating cancer comprising administering a therapeutically effective amount of a compound according to claims 1-11 or a pharmaceutically acceptable salt thereof, to a patient in need thereof.
15. The method according to claim 14 wherein said disease or condition 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 method 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 method 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 method according to any of claims 13-17, further comprising administering at least one additional anticancer agent or therapy.