PHARMACEUTICAL COMPOSITIONS COMPRISING WRN HELICASE INHIBITORS

FIELD OF DISCLOSURE

[0001] This invention relates to compounds that are inhibitors of Werner syndrome helicase (WRN helicase), pharmaceutical compositions comprising said inhibitors and methods of treatment using said inhibitors.

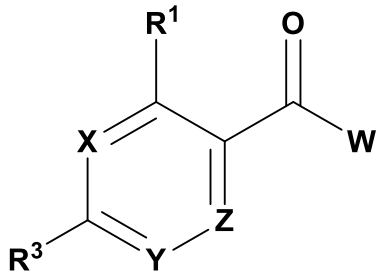
BACKGROUND OF THE DISCLOSURE

[0002] RECQ helicases are 3' to 5' DNA unwinding DNA-dependent ATPases. Three RECQ helicases, BLM, Werner (WRN) and RECQL4, cause human syndromes that overlap, but are also distinct symptomatically, when their expression is altered or lost (de Renty C, Ellis N A. Ageing Res Rev 2017; 33:36-51). WRN was identified as a potential synthetic lethal target for cancer that expresses high levels of microsatellite instability (MSI-H cancer) in 2019 by multiple groups independently (Chan, E.M. et al., Nature 2019, 568, 551-556; Behan, F.M. et al., Nature 2019, 568, 511–516; Lieb et al. eLife 2019, 8, e43333). There are a few reports describing identification of small molecules that inhibit WRN helicase activity with unknown mechanism (Aggarwal et al., Cancer Res. 2013, 73, 5497; Aggarwal et al., PNAS 2011, 108, 4, 1525-1530; Sommers et al., PLoS ONE 2019, 14(1), e0210525).

[0003] There is therefore a need to provide novel inhibitors of WRN helicase for the treatment of MSI-H cancer.

SUMMARY

[0004] The present disclosure relates to a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is CR^2 or N;

Y is CR^4 or N;

Z is CR^5 or N;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heterocyclyl;

with the proviso that X, Y, and Z are not simultaneously N;

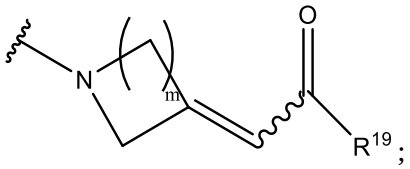
 indicates the point of attachment;

R^{17} is H;

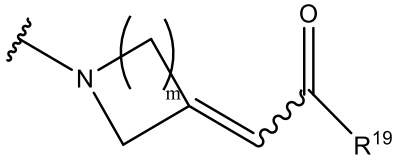
R^{18} is H or optionally substituted C_1-C_6 alkyl; and

each R^a independently is optionally substituted C_1-C_6 alkyl;

W^5 is:



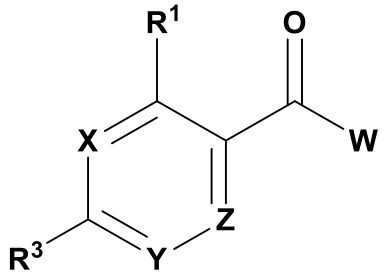
wherein:

the bond represented by indicates that  can exist as either a (Z)- or (E)- geometric isomer, and wherein  indicates the point of attachment;

m is 1, 2, or 3; and

R^{19} is selected from the group consisting of C_1-C_6 alkyl and -O-(C_1-C_6 alkyl).

[0004a] In one aspect, the present disclosure relates to a compound of Formula (I):

 (I),

or a pharmaceutically acceptable salt thereof, wherein:

X is CR^2 or N;

Y is CR^4 or N;

Z is CR^5 or N;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heterocyclyl;

with the proviso that X, Y, and Z are not simultaneously N;

R^1 is H, -O-(optionally substituted C_3-C_8 cycloalkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_6-C_{10} aryl), -O-(optionally substituted five- to six-membered heteroaryl), -O-(optionally substituted five- to six-membered heterocyclyl), or optionally substituted C_3-C_8 cycloalkyl;

or R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl;

R^2 is H, optionally substituted C_1-C_6 alkyl, or halo;

R^3 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_8 cycloalkenyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkenyl, -NR_2, -N(R)(optionally substituted C_3-C_8 cycloalkyl), -S-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_3-C_8 cycloalkyl), optionally substituted four- to six-membered heterocyclyl or heterocyclenyl, optionally substituted five- to six-membered heteroaryl, or -O-(optionally substituted C_3-C_8 cycloalkyl);

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^4 is H, C_1-C_6 alkyl, cyano, or halo;

or R^4 together with the carbon atom to which it is shown attached and Z form an optionally substituted five- to six-membered heteroaryl;

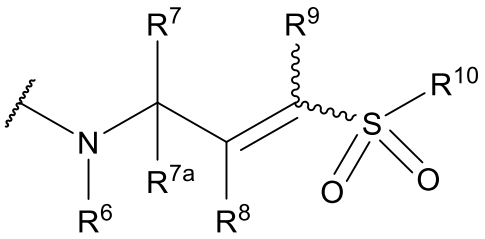
or R^3 and R^4 taken together with the carbon atoms to which they are shown attached form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_4-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^5 is H, C_1-C_6 alkyl, -NR_2, or -N(R)-C(=O)-(C_1-C_6 alkyl);

each R independently is H, or optionally substituted C_1-C_6 alkyl;

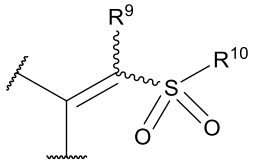
W is W^1, W^2, W^3, W^4, or W^5;

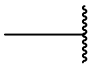
W^1 is:



;

wherein:

the bonds represented by indicate that 

can exist as either a (Z)- or (E)- geometric isomer wherein  indicates the point of attachment;

R^6 is H;

R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted five- to six-membered heterocyclyl;

R^{7a} is H or deuterium;

R^8 is H;

R^9 is H; and

R^{10} is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted five- to six-membered heterocyclyl ;

or R^6 together with the nitrogen atom to which it is shown attached and R^7 and R^{7a} together with the carbon atom to which they are shown attached form an azetidinyl ring;

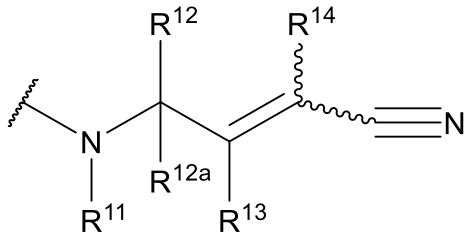
or R^6 together with the nitrogen atom to which it is shown attached and R^7, R^{7a}, and R^8 together with the carbon atoms to which they are shown attached form an azetidinyl or pyrrolodinyl ring;

or R^6 together with the nitrogen atom to which it is shown attached and R^7, R^{7a}, R^8, and R^9 together with the carbon atoms to which they are shown attached form a dihydropyrrolyl ring; or

or R^7, R^{7a}, R^8, R^9, and R^{10} together with the carbon atoms to which they are shown attached form a 2,3-dihydrothiophene 1,1-dioxide;

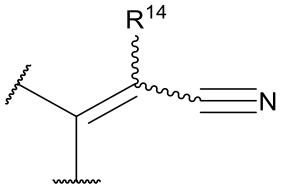
or R^8, R^9, and R^{10} together with the carbon atoms to which they are shown attached form a 1,1-dioxido-2H-thietyl ring;

W^2 is:



;

wherein:

the bonds represented by indicate that 

can exist as either a (Z)- or (E)- geometric isomer, wherein  indicates the point of attachment;

R^{11} is H;

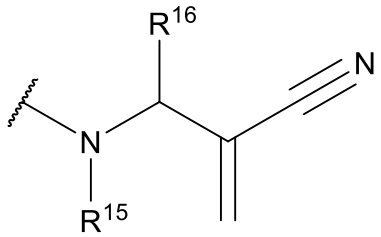
R^{12} is H or optionally substituted C_1-C_6 alkyl;

R^{12a} is H; and

R^{13} and R^{14} are each H;

or R^{11} together with the nitrogen atom to which it is shown attached and R^{12}, R^{12a}, and R^{13} together with the carbon atoms to which they are shown attached form an optionally substituted azetidinyl ring;

W^3 is:



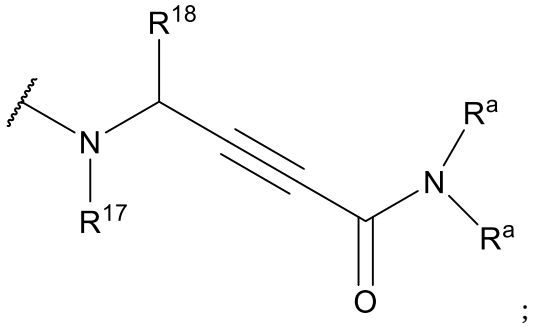
wherein:

 indicates the point of attachment;

R^{15} is H;

R^{16} is H or optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_8 cycloalkyl;

W^4 is:



;

wherein:

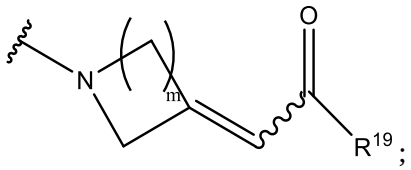
 indicates the point of attachment;

R^{17} is H;

R^{18} is H or optionally substituted C_1-C_6 alkyl; and

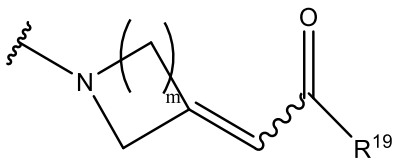
each R^a independently is optionally substituted C_1-C_6 alkyl; and

W^5 is:



;

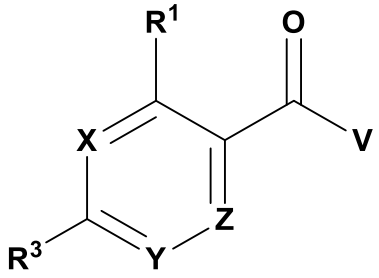
wherein:

the bond represented by ~~~ indicates that  can exist as either a (Z)- or (E)- geometric isomer, and wherein ——≈ indicates the point of attachment;

m is 1, 2, or 3; and

R^{19} is selected from the group consisting of C_1-C_6 alkyl and -O-(C_1-C_6 alkyl).

[0005] The present disclosure relates to a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is CR^2 or N;

Y is CR^4 or N;

Z is CR^5 or N;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heterocyclyl;

with the proviso that X, Y, and Z are not simultaneously N;

R^1 is H, -O-(optionally substituted C_3-C_8 cycloalkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_6-C_{10} aryl), -O-(optionally substituted five- to six-membered heteroaryl), -O-(optionally substituted five- to six-membered heterocyclyl), or optionally substituted C_3-C_8 cycloalkyl;

or R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl;

R^2 is H, optionally substituted C_1-C_6 alkyl, or halo;

R^3 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_8 cycloalkenyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkenyl, -NR_2, -N(R)(optionally substituted C_3-C_8 cycloalkyl), -S-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_3-C_8 cycloalkyl), optionally substituted four- to six-membered heterocyclyl or heterocyclenyl, optionally substituted five- to six-membered heteroaryl, or -O-(optionally substituted C_3-C_8 cycloalkyl);

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^4 is H, C_1-C_6 alkyl, cyano, or halo;

or R^4 together with the carbon atom to which it is shown attached and Z form an optionally substituted five- to six-membered heteroaryl;

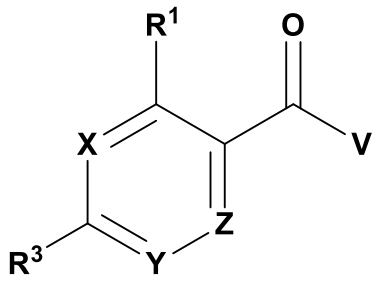
or R^3 and R^4 taken together with the carbon atoms to which they are shown attached and R^3 taken form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_4-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^5 is H, C_1-C_6 alkyl, -NR_2, or -N(R)-C(=O)-(C_1-C_6 alkyl);

each R independently is H, or optionally substituted C_1-C_6 alkyl; and

V comprises an electrophile that reacts and forms a covalent bond with the sulfur atom at cysteine 727 as set forth in SEQ ID NO: 1 or a variant thereof.

[0005a] In another aspect, the present disclosure provides a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X is CR^2 or N;

Y is CR^4 or N;

Z is CR^5 or N;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heterocyclyl;

with the proviso that X, Y, and Z are not simultaneously N;

R^1 is H, -O-(optionally substituted C_3-C_8 cycloalkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_6-C_{10} aryl), -O-(optionally substituted five- to six-membered heteroaryl), -O-(optionally substituted five- to six-membered heterocyclyl), or optionally substituted C_3-C_8 cycloalkyl;

or R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl;

R^2 is H, optionally substituted C_1-C_6 alkyl, or halo;

R^3 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_8 cycloalkenyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkenyl, $-NR_2$, -N(R)(optionally substituted C_3-C_8 cycloalkyl), -S-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_3-C_8 cycloalkyl), optionally substituted four- to six-membered heterocyclyl or heterocyclenyl, optionally substituted five- to six-membered heteroaryl, or -O-(optionally substituted C_3-C_8 cycloalkyl);

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^4 is H, C_1-C_6 alkyl, cyano, or halo;

or R^4 together with the carbon atom to which it is shown attached and Z form an optionally substituted five- to six-membered heteroaryl;

or R^3 and R^4 taken together with the carbon atoms to which they are shown attached and R^3 taken from an optionally substituted C_6-C_{10} aryl, an optionally substituted C_4-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^5 is H, C_1-C_6 alkyl, -NR_2, or -N(R)-C(=O)-(C_1-C_6 alkyl);

each R independently is H, or optionally substituted C_1-C_6 alkyl; and

V comprises an electrophile that reacts and forms a covalent bond with the sulfur atom at cysteine 727 as set forth in SEQ ID NO:1 or variants thereof.

[0006] examplesThe present disclosure also provides a pharmaceutical composition comprising a compound of Formula (I) or Formula (II) (or any of the examples thereof described herein), or a pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable excipient.

[0007] The present disclosure also provides a method of treating a disease (such as a proliferative disease, e.g., cancer) in a patient which method comprises administering to the patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or Formula (II) (or any of the examples thereof described herein), and/or a pharmaceutically acceptable salt thereof.

[0007a] In another aspect, the present disclosure also provides a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a proliferative disease.

[0007b] In another aspect, the present disclosure also provides use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a proliferative disease.

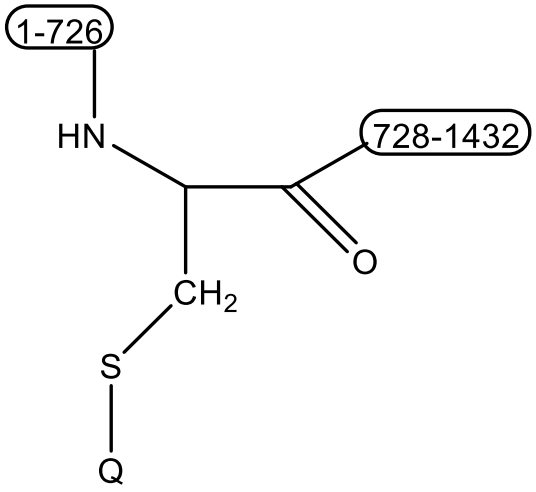
[0008] The present disclosure also provides a method of inhibiting WRN helicase (Werner syndrome ATP-dependent helicase) in a subject in need of such inhibition, comprising administering to the subject a therapeutically effective amount of at least one compound of Formula (I) or Formula (II) (or any of the examples thereof described herein), or a pharmaceutically acceptable salt or solvate thereof.

[0008a] In another aspect, the present disclosure also provides a compound as described herein, or a pharmaceutically acceptable salt thereof for use in inhibiting WRN helicase (Werner syndrome ATP-dependent helicase) in a subject in need of such inhibition.

[0009] The present disclosure also provides a method of inhibiting WRN helicase (Werner syndrome ATP-dependent helicase) comprising effecting a non-naturally occurring covalent modification at cysteine 727 as set forth in SEQ ID NO: 1 or the variant thereof, the modification resulting from a bond forming reaction between an electrophile and the cysteine 727 as set forth in SEQ ID NO:1 or a variant thereof, wherein a sulfur atom at the cysteine residue undergoes a reaction with the electrophile.

[0009a] In another aspect, the present disclosure also provides an electrophile for use in inhibiting WRN helicase (Werner syndrome ATP-dependent helicase) comprising effecting a non-naturally occurring covalent modification at cysteine 727 as set forth in SEQ ID NO: 1 or a variant thereof, the modification resulting from a bond forming reaction between the electrophile and the cysteine 727 as set forth in SEQ ID NO: 1 or the variant thereof, wherein a sulfur atom at the cysteine residue undergoes a reaction with the electrophile.

[0010] In another aspect, the present disclosure also provides a modified WRN helicase protein comprising a non-naturally occurring small molecule fragment having a covalent bond to cysteine 727 of the WRN helicase protein, wherein the modified WRN helicase protein comprises SEQ ID NO: 1 or a variant thereof; and has the structure of Formula (III):



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Formula (III)

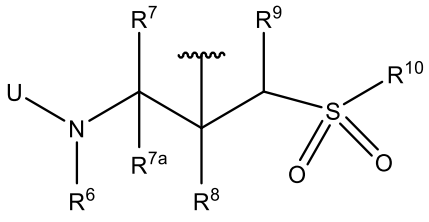
wherein:

S is the sulfur atom of Cysteine 727 in SEQ ID NO: 1 or a variant thereof;

1-726 and 728-1432 represent amino acid positions 1-726 and 7288-1432 respectively of SEQ ID NO: 1 or the variant thereof; and

Q is Q^1, Q^2, Q^3, Q^4, or Q^5; wherein:

Q^1 is:



;

R^4 is H, C_1-C_6 alkyl, cyano, or halo,

or R^4 together with the carbon atom to which it is shown attached and Z form an optionally substituted five- to six-membered heteroaryl;

or R^3 and R^4 taken together with the carbon atoms to which they are shown attached form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_4-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^5 is H, C_1-C_6 alkyl, -NR_2, or -N(R)-C(=O)-(C_1-C_6 alkyl); and

each R independently is H, or optionally substituted C_1-C_6 alkyl.

[0011] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative examples of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different examples, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0012] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

DETAILED DESCRIPTION OF THE DISCLOSURE

Definitions

[0013] Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning. All undefined technical and scientific terms used in this Application have the meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0014] As used herein, “a” or “an” entity refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound unless stated otherwise. As such, the terms “a” (or “an”), “one or more”, and “at least one” can be used interchangeably herein.

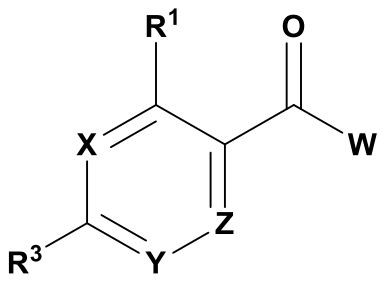
[0015] “Patient” includes both human and animals. “Patient” and “subject” are used interchangeably herein.

[0016] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example, “$C_{1–6}$ alkyl” (or “C_1-C_6 alkyl”) is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, $C_{1–6}$, $C_{1–5}$, $C_{1–4}$, $C_{1–3}$, $C_{1–2}$, $C_{2–6}$, $C_{2–5}$, $C_{2–4}$, $C_{2–3}$, $C_{3–6}$, $C_{3–5}$, $C_{3–4}$, $C_{4–6}$, $C_{4–5}$, and $C_{5–6}$ alkyl.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

X is CR^2 or N;

Y is CR^4 or N;

Z is CR^5 or N;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heterocyclyl;

with the proviso that X, Y, and Z are not simultaneously N;

R^1 is H, -O-(optionally substituted C_3-C_8 cycloalkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_6-C_{10} aryl), -O-(optionally substituted five- to six-membered heteroaryl), -O-(optionally substituted five- to six-membered heterocyclyl), or optionally substituted C_3-C_8 cycloalkyl;

or R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl;

R^2 is H, optionally substituted C_1-C_6 alkyl, or halo;

R^3 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_8 cycloalkenyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkenyl, -NR_2, -N(R)(optionally substituted C_3-C_8 cycloalkyl), -S-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_3-C_8 cycloalkyl), optionally substituted four- to six-membered heterocyclyl or heterocyclenyl, optionally substituted five- to six-membered heteroaryl, or -O-(optionally substituted C_3-C_8 cycloalkyl);

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^4 is H, C_1-C_6 alkyl, cyano, or halo;

or R^4 together with the carbon atom to which it is shown attached and Z form an optionally substituted five- to six-membered heteroaryl;

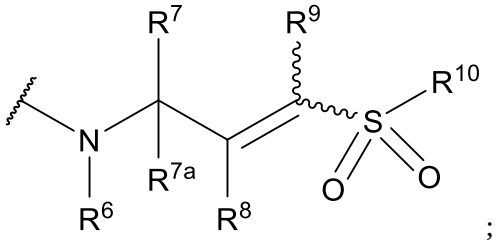
or R^3 and R^4 taken together with the carbon atoms to which they are shown attached form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_4-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^5 is H, C_1-C_6 alkyl, -NR_2, or -N(R)-C(=O)-(C_1-C_6 alkyl);

each R independently is H, or optionally substituted C_1-C_6 alkyl;

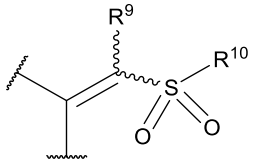
W is W^1, W^2, W^3, W^4, or W^5;

W^1 is:



;

wherein:

the bonds represented by indicate that 

can exist as either a (Z)- or (E)- geometric isomer wherein  indicates the point of attachment;

R^6 is H;

R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted five- to six-membered heterocyclyl;

R^{7a} is H or deuterium;

R^8 is H;

R^9 is H; and

R^{10} is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted five- to six-membered heterocyclyl ;

or R^6 together with the nitrogen atom to which it is shown attached and R^7 and R^{7a} together with the carbon atom to which they are shown attached form an azetidinyl ring;

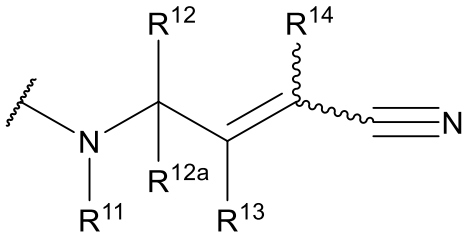
or R^6 together with the nitrogen atom to which it is shown attached and R^7, R^{7a}, and R^8 together with the carbon atoms to which they are shown attached form an azetidinyl or pyrrolodinyl ring;

or R^6 together with the nitrogen atom to which it is shown attached and R^7, R^{7a}, R^8, and R^9 together with the carbon atoms to which they are shown attached form a dihydropyrrolyl ring; or

or R^7, R^{7a}, R^8, R^9, and R^{10} together with the carbon atoms to which they are shown attached form a 2,3-dihydrothiophene 1,1-dioxide;

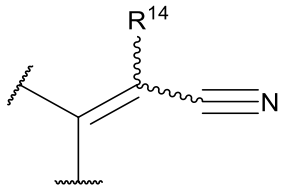
or R^8, R^9, and R^{10} together with the carbon atoms to which they are shown attached form a 1,1-dioxido-2H-thietyl ring;

W^2 is:



;

wherein:

the bonds represented by indicate that 

can exist as either a (Z)- or (E)- geometric isomer, wherein  indicates the point of attachment;

R^{11} is H;

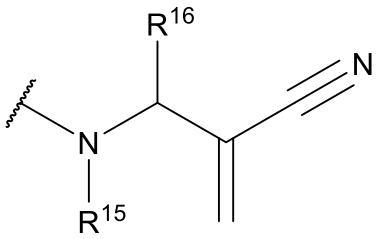
R^{12} is H or optionally substituted C_1-C_6 alkyl;

R^{12a} is H; and

R^{13} and R^{14} are each H;

or R^{11} together with the nitrogen atom to which it is shown attached and R^{12}, R^{12a}, and R^{13} together with the carbon atoms to which they are shown attached form an optionally substituted azetidinyl ring;

W^3 is:



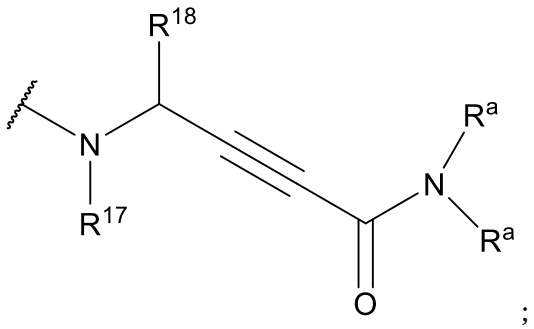
wherein:

 indicates the point of attachment;

R^{15} is H;

R^{16} is H or optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_8 cycloalkyl;

W^4 is:



;

wherein:

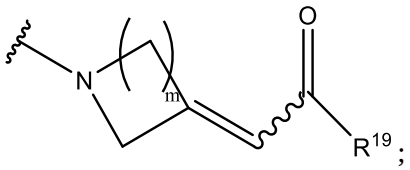
 indicates the point of attachment;

R^{17} is H;

R^{18} is H or optionally substituted C_1-C_6 alkyl; and

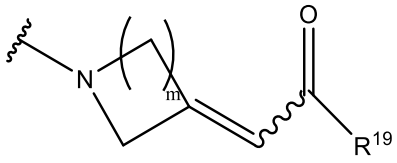
each R^a independently is optionally substituted C_1-C_6 alkyl; and

W^5 is:



;

wherein:

the bond represented by indicates that 

can exist as either a (Z)- or (E)- geometric isomer, and wherein  indicates the point of attachment;

m is 1, 2, or 3; and

R^{19} is selected from the group consisting of C_1-C_6 alkyl and -O-(C_1-C_6 alkyl).

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

Y is N; and

Z is CR^5;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heterocyclyl.

3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is CR^2;

Y is CR^4; and

Z is CR^5;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heteroaryl;

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl.

4. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is CR^2;

Y is N; and

Z is CR^5;

or R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl.

5. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

X is N;

Y is CR^4; and

Z is CR^5;

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

Y is CR^4; and

Z is N.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is CR^2;

Y is CR^4; and

Z is N.

8. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

Y is N;

Z is CR^5;

R^1 is H, -O-(optionally substituted C_3-C_8 cycloalkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_6-C_{10} aryl), -O-(optionally substituted five- to six-membered heteroaryl), -O-(optionally substituted five- to six-membered heterocyclyl), or optionally substituted C_3-C_8 cycloalkyl;

R^3 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_8 cycloalkenyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkenyl, -NR_2, -N(R)(optionally substituted C_3-C_8 cycloalkyl), -S-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_3-C_8 cycloalkyl), optionally substituted four- to six-

membered heterocyclyl or heterocyclenyl, optionally substituted five- to six-membered heteroaryl, or -O-(optionally substituted C_3-C_8 cycloalkyl);R^5 is H, C_1-C_6 alkyl, -NR_2, or -N(R)-C(=O)-(C_1-C_6 alkyl);

each R independently is H, or optionally substituted C_1-C_6 alkyl;

W is W^1;

R^6 is H;

R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted five- to six-membered heterocyclyl;

R^{7a} is H or deuterium;

R^8 is H;

R^9 is H; and

R^{10} is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted five- to six-membered heterocyclyl.

9. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is -O-(C_6-C_{10} aryl);

R^3 is fluoro substituted C_1-C_6 alkyl;

R^5 is H;

R^6 is H;

R^7 is C_3-C_8 cycloalkyl;

R^{7a} is H or deuterium;

R^8 is H;

R^9 is H; and

R^{10} is C_1-C_6 alkyl.

10. The compound according to any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein:

in R^1:

the optional substituents of the -O-(optionally substituted C_3-C_8 cycloalkyl) are 1-3 substituents selected from the group consisting of halo, cyano, and hydroxy; or when there are two substituents on the same ring carbon atom of the C_3-C_8 cycloalkyl, the substituents together with the ring carbon atom to which they are attached form a C_3-C_6 cycloalkyl; or when there are two substituents on adjacent ring carbon atoms of the C_3-C_8 cycloalkyl, the substituents taken together with the ring carbon atoms to which they are attached form a C_3-C_6 cycloalkyl;

the optional substituents of the -O-(optionally substituted C_6-C_{10} aryl) are 1-3 substituents selected from the group consisting of halo, C_1-C_6 alkyl, cyano, hydroxy, and -NH_2, or 1-5 deuterium atoms;

or when R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl, two substituents on the same ring carbon atom of the five- to

six-membered heterocyclyl together with the ring carbon atom to which they are attached form a five- to six-membered cycloalkyl;

in R^3:

the optional substituents of the optionally substituted C_3-C_8 cycloalkyl are 1-3 substituents selected from hydroxy, halo, C_1-C_6 alkyl, and C_6-C_{10} aryl; or when there are two substituents on the same carbon atom of the C_3-C_8 cycloalkyl, the substituents together with the ring carbon atom to which they are attached form a C_3-C_6 cycloalkyl; or when there are two substituents on adjacent ring carbon atoms of the C_3-C_8 cycloalkyl, the substituents taken together with the ring carbon atoms to which they are attached form C_6-C_{10} aryl;

or when R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, the optional substituents are 1-3 substituents selected from the group consisting of halo, and C_1-C_6 alkyl; or two geminal hydrogens on a ring carbon atom of the C_3-C_8 cycloalkyl or cycloalkenyl can be replaced with the group =O;

or when R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl, the optional substituents are 1-3 substituents selected from the group consisting of halo and C_1-C_6 alkyl;

the optional substituents of the optionally substituted C_6-C_{10} aryl are 1-3 substituents selected from the group consisting of halo;

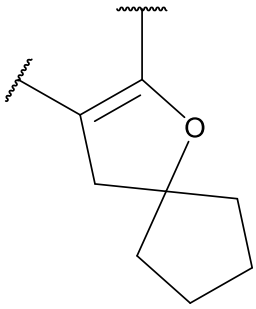
the optional substituents of the optionally substituted C_1-C_6 alkyl or C_6 alkenyl are 1-5 substituents selected from the group consisting of halo, hydroxy, -O-(C_1-C_6 alkyl), and optionally substituted C_3-C_6 cycloalkyl, wherein the optional substituents of the C_3-C_6 cycloalkyl are 1-3 substituents selected from the group consisting of C_1-C_6 alkyl;

the optional substituents of the C_1-C_6 alkyl of R of -NR_2 are 1-3 substituents selected from the group consisting of halo; and

the optional substituents of the optionally substituted four- to six-membered heterocyclyl are 1-3 substituents selected from the group consisting of -O-(C_1-C_6 alkyl), C_1-C_6 alkyl, halo; or when there are two substituents on the same carbon atom of the optionally substituted four- to six-membered heterocyclyl, the substituents together with the ring carbon atom to which they are attached form a C_3-C_6 cycloalkyl.

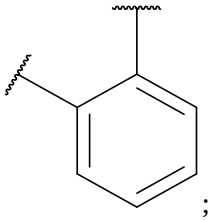
11. The compound according to any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein:

the optionally substituted five- to six-membered heterocyclyl formed by R^1 together with the carbon atoms to which it is shown attached is

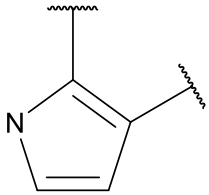


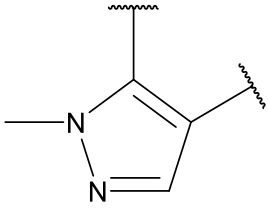
wherein the double bond shown is between the carbon bearing the R^1 group and X ;

the optionally substituted C_6-C_{10} aryl formed by R^3 taken together with the carbon atom to which it is shown attached and Y is


;

the optionally substituted five- to six-membered heterocyclenyl formed by R^3 taken together with the carbon atom to which it is shown attached and Y is

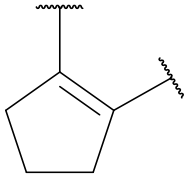
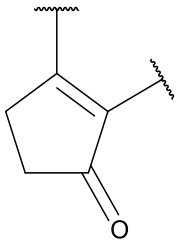


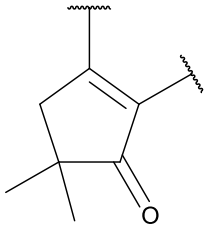
or


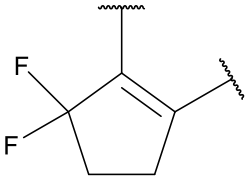
, wherein the carbon-carbon double bond shown between the two carbons bearing the

groups is between the carbon bearing the R^3 group and Y;

when R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, the optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl is

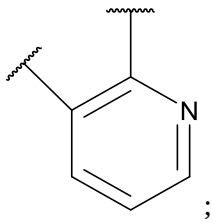

,


,


, or


, wherein the carbon-carbon double bond shown is between the carbon bearing the R^3 group and Y; and

wherein the optionally substituted five- to six-membered heteroaryl formed by R^4 together with the carbon atom to which it is shown attached and Z is



; wherein in each structure  indicates the point of attachment.

12. The compound according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein:

in R^1:

the -O-(optionally substituted C_3-C_8 cycloalkyl) is -O-cyclobutyl, -O-cyclopropyl, -O-cyclohexyl, -O-cyclopentyl, -O-(4,4-difluorocyclohexyl), -O-(spiro[2.3]hexan-5-yl), -O-(spiro[3.3]heptan-2-yl), -O-(3-chrlorocyclobutyl), -O-(bicyclo[3.1.0]hexan-3-yl), -O-(bicyclo[2.2.1]heptan-1-yl), -O-(1-cyanocyclopentanyl), -O-(3,3-difluorocyclobutyl), -O-(2-hydroxycyclohexyl), -O-cycloheptyl, -O-(2-fluorocyclohexyl), -O-(3,3-difluorocyclopentyl), -O-(2-fluorocyclohexyl), or -O-(2,2-difluorocyclopentyl),

the -O-(optionally substituted C_1-C_6 alkyl) is ethoxy, isopropoxy, or cyclopropylmethyloxy;

the -O-(optionally substituted C_6-C_{10} aryl) is phenoxy, 4-chlorophenoxy, 3-fluorophenoxy, 2-chlorophenoxy, 3-chlorophenoxy, 2-fluorophenoxy, *p*-tolyloxy, 3,5-difluorophenoxy, 4-fluoro-3-methylphenoxy, 3,5-dichlorophenoxy, 4-cyanophenoxy, 3,4-dimethylphenoxy, *m*-tolyloxy, 4-ethylphenoxy, 3-ethylphenoxy, *o*-tolyloxy, 2-hydroxyphenoxy, 3-hydroxyphenoxy, 4-hydroxyphenoxy, 3-chlro-5-fluorophenoxy, 3-aminophenoxy, naphthalen-1-oxy, or phenoxy-d5;

the -O-(optionally substituted five- to six-membered heteroaryl) is pyridine-2-yloxy, or pyridine-3-yloxy;

the -O-(optionally substituted five- to six-membered heterocyclyl) is tetrahydro-2H-pyran-4-yl, or tetrahydro-2H-pyran-3-yl; and

the optionally substituted C_3-C_8 cycloalkyl is cyclohexyl;

in R^2:

the optionally substituted C_1-C_6 alkyl is methyl; and

in R^3:

the optionally substituted C_3-C_8 cycloalkyl is cyclopentyl, cyclobutyl, cyclohexyl, cyclopropyl, hydroxycyclopentyl, fluorocyclopentyl, methylcyclobutyl, methylcyclopropyl, phenylcyclopropyl, methylcyclopentyl, difluorocyclobutyl, fluorocyclopentyl, bicyclo[4.2.0]octa-1,3,5-trien-7-yl, or (trifluoromethyl)cyclopropyl, or spiro[2.3]hexan-5-yl;

the optionally substituted C_3-C_8 cycloalkenyl is cyclopentenyl;

the optionally substituted C_6-C_{10} aryl is phenyl;

the optionally substituted C_1-C_6 alkyl is methyl, ethyl, isopropyl, *tert*-butyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, trifluoromethyl, trifluoroethyl, hydroxypropanyl,

fluropropanyl, methoxypropanyl, difluoroethyl, difluoropropyl, (methylcyclopropyl)methyl, perfluoroethyl, or cyclopropyldifluoromethyl;

the optionally substituted C_1-C_6 alkenyl is 2-methylprop-1-en-1-yl;

the NR_2 is -N(H)(cyclopentyl), -N(H)(methyl), -N(methyl)(ethyl), -N(methyl)(isopropyl), -N(ethyl)$_2$, or -N(methyl)(trifluoroethyl);

the -N(R)(optionally substituted C_3-C_8 cycloalkyl) is N(methyl)(cyclopropyl);

the -S-(optionally substituted C_1-C_6 alkyl) is methylthiol;

the -O-(optionally substituted C_1-C_6 alkyl) is trifluoroethoxy, or methoxy;

the -O-(optionally substituted C_3-C_8 cycloalkyl) is cyclopentyloxy, or cyclopropyloxy; and

the optionally substituted four- to six-membered heterocyclyl or hetrocyclenyl is tetrahydrofuranyl, 7-azabicyclo[2.2.1]heptan-7-yl, bicyclo[1.1.1]pentan-1-yl, methoxyazetadin-1-yl, 2-azaspiro[3.3]heptan-2-yl, tetrahydropyranyl, tetrahydro-2H-pyran-3-yl, tetrahydro-2H-pyran-4-yl, dihydropyranyl, 5,6-dihydro-2H-pyran-3-yl, dimethylpyrrolidinyl, 2,2-dimethylpyrrolidin-1-yl, difluoropyrrolidinyl, methylcyclobutyl, pyrrolidinyl, pyrrolidine-1-yl, methylpyrrolidinyl, 2-methylpyrrolidin-1-yl, azetidinyl, azetidine-1-yl, fluoroazetidinyl, 3-fluoroazetidin-1-yl, difluoroazetidinyl, or 3,3-difluoro-azetidin-1-yl;

in R^5:

the C_1-C_6 alkyl is methyl;

the -NR_2 is -NH_2; and

the -N(R)-C(=O)-(C_1-C_6 alkyl) is -N(H)-C(=O)-CH_3.

13. The compound according to any one of claims 1-7 and 10-12, or a pharmaceutically acceptable salt thereof, wherein W is W^1.

14. The compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein:

the optionally substituted C_1-C_6 alkyl of R^7 is methyl, ethyl, isopropyl, methoxymethyl, cyclopropylmethyl, cyclopropyloxymethyl, tolyl, -CH(CH_3)-OCH_3, difluoroethyl, phenoxymethyl, -CH_2-C(=O)-N(CH_3)$_2$, or *tert*-butoxymethyl, difluoromethoxymethyl;

the optionally substituted C_3-C_8 cycloalkyl of R^7 is cyclopropyl, cyclobutyl, difluorocyclobutyl, -CH_2-S-CH_3, difluorocyclohexyl;

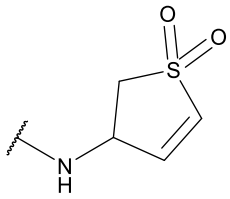
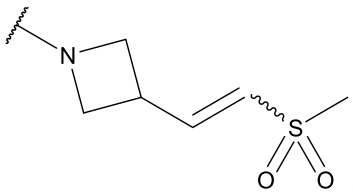
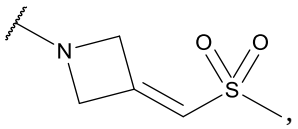
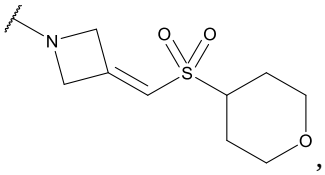
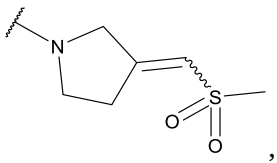
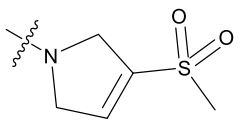
the optionally substituted five- to six-membered heterocyclyl of R^7 is tetrahydropyranyl, or tetrahydro-2H-pyran-4-yl;

the optionally substituted C_1-C_6 alkyl of R^{10} is methyl;

the optionally substituted C_3-C_8 cycloalkyl of R^{10} is cyclopropyl;

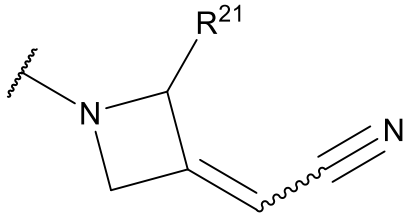
the optionally five- to six-membered heterocyclyl of R^{10} is tetrahydropyranyl or tetrahydro-2H-pyran-4-yl;

or wherein W^1 is:







; wherein in each structure above,  indicates the point of attachment.

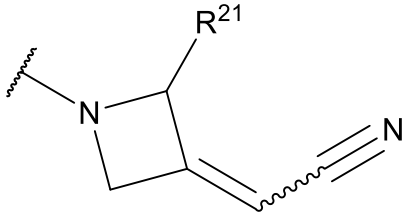
15. The compound according to any one of claims 1-7 and 10-12, or a pharmaceutically acceptable salt thereof, wherein W is W^2.

16. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein W^2 is:


;

wherein:

R^{21} is H or C_1-C_6 alkyl;

the bond represented by indicates that  can exist as either a (Z)- or (E)- geometric isomer, and wherein  indicates the point of attachment.

17. The compound according to any one of claims 1-8 and 10-12, or a pharmaceutically acceptable salt thereof, wherein W is W^3.

18. The compound according to claim 17, or a pharmaceutically acceptable salt thereof, wherein:

the optionally substituted C_1-C_6 alkyl of R^{16} is methyl; and

the optionally substituted C_3-C_8 cycloalkyl of R^{16} is cyclopropyl.

19. The compound according to any one of claims 1-8 and 10-12, or a pharmaceutically acceptable salt thereof, wherein W is W^4.

20. The compound according to claim 19, or a pharmaceutically acceptable salt thereof, wherein:

the optionally substituted C_1-C_6 alkyl of R^{18} is methyl; and

the optionally substituted C_1-C_6 alkyl is methyl.

21. The compound according to any one of claims 1-8 and 10-12, or a pharmaceutically acceptable salt thereof, wherein W is W^5.

22. The compound according to claim 21, or a pharmaceutically acceptable salt thereof, wherein:

the C_1-C_6 alkyl of R^{19} is methyl; and

the -O-(C_1-C_6 alkyl) of R^{19} is methoxy.

23. The compound according to any one of claims 2 and 8-14, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(E)-N-(3-(methylsulfonyl)allyl)-4-phenoxy-2-(pyrrolidin-1-yl)pyrimidine-5-carboxamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-phenylpyrimidine-5-carboxamide;

(S,E)-2-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-ethyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(E)-2-cyclopentyl-N-(3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(E)-2-isopropyl-N-(3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-2-cyclobutyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclobutyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclohexyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(E)-2-ethyl-N-(3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-isopropyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(cyclopentylamino)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(E)-2-cyclopropyl-N-(3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(E)-2-(tert-butyl)-N-(3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(R,Z)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,Z)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(E)-2-cyclobutyl-N-(3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(E)-4-(4-chlorophenoxy)-2-cyclopentyl-N-(3-(methylsulfonyl)allyl)pyrimidine-5-carboxamide;

(S,E)-4-(4-chlorophenoxy)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(E)-2-cyclopentyl-4-(3-fluorophenoxy)-N-(3-(methylsulfonyl)allyl)pyrimidine-5-carboxamide;

(E)-2-cyclohexyl-N-(3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(E)-N-(3-(methylsulfonyl)allyl)-2-(methylthio)-4-phenoxypyrimidine-5-carboxamide;

2-cyclopropyl-N-((1,1-dioxido-2H-thiet-3-yl)methyl)-4-phenoxypyrimidine-5-carboxamide;

2-cyclopropyl-N-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-phenoxypyrimidine-5-carboxamide;

(E)-2-cyclopentyl-4-(4-fluorophenoxy)-N-(3-(methylsulfonyl)allyl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(4-fluorophenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-4-(2-chlorophenoxy)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-4-(3-chlorophenoxy)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(3-fluorophenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(2-fluorophenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-4-(cyclohexyloxy)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(E)-2-cyclopentyl-N-methyl-N-(3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(E)-2-cyclopentyl-N-(3-(methylsulfonyl)allyl)-4-(p-tolyloxy)pyrimidine-5-carboxamide;

(E)-N-(3-(methylsulfonyl)allyl)-4-phenoxy-2-(1H-pyrazol-5-yl)pyrimidine-5-carboxamide;

(E)-4-(3-chlorophenoxy)-2-cyclopentyl-N-(3-(methylsulfonyl)allyl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(3,5-difluorophenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(4-fluoro-3-methylphenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(3,5-dichlorophenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-(cyclopentyloxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(2-cyclopropyl-4-phenoxypyrimidin-5-yl)(3-((methylsulfonyl)methylene)azetidin-1-yl)methanone;

(S,E)-2-cyclopentyl-4-(cyclopentyloxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-4-(4-cyanophenoxy)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(tetrahydro-2H-pyran-4-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(3,4-dimethylphenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-(m-tolyloxy)pyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(4-ethylphenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(3-ethylphenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-(o-tolyloxy)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidine-5-carboxamide;

(S,E)-2-(cyclopropylmethyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-4-cyclobutoxy-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-(1-hydroxycyclopentyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(1-(methylsulfonyl)pent-1-en-3-yl)-4-phenoxypyrimidine-5-carboxamide;

N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(tetrahydrofuran-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-(pyridin-2-yloxy)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-(pyridin-3-yloxy)pyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-(spiro[3.3]heptan-2-yloxy)pyrimidine-5-carboxamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(trifluoromethyl)pyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-4-(cyclohexyloxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-4-((4,4-difluorocyclohexyl)oxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

2-cyclopentyl-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-(((S)-tetrahydro-2H-pyran-3-yl)oxy)pyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-(spiro[2.3]hexan-5-yloxy)pyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-4-(cyclopropylmethoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

4-((1R,3S)-3-chlorocyclobutoxy)-2-cyclopropyl-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-4-cyclohexyl-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

4-[[(1S,5R)-3-bicyclo[3.1.0]hexanyl]oxy]-2-tert-butyl-N-[(E,1S)-1-methyl-3-methylsulfonyl-allyl]pyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-4-((1-cyanocyclopentyl)oxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-4-(3,3-difluorocyclobutoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-6-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(1-fluorocyclopentyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(3-hydroxyphenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(4-hydroxyphenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(2-(tert-butyl)-4-phenoxypyrimidin-5-yl)(3-((methylsulfonyl)methylene)azetidin-1-yl)methanone;

(S,E)-2-(tert-butyl)-4-(cyclopentyloxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-(cyclopentylmethyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

S,E)-2-(7-azabicyclo[2.2.1]heptan-7-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide;

(S,E)-4-(3-chloro-5-fluorophenoxy)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-(cyclohexylmethyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-4-(3-aminophenoxy)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-(cyclobutylmethyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-N-(4-(cyclopropylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(Z)-(2-cyclopropyl-4-phenoxypyrimidin-5-yl)(3-(2-(methylsulfonyl)vinyl)azetidin-1-yl)methanone;

(E)-(2-cyclopropyl-4-phenoxypyrimidin-5-yl)(3-(2-(methylsulfonyl)vinyl)azetidin-1-yl)methanone;

(S,E)-4-(cyclopentyloxy)-2-cyclopropyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

2-cyclopentyl-4-(((1R,2R)-2-hydroxycyclohexyl)oxy)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-4-amino-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-6-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-(naphthalen-1-yloxy)pyrimidine-5-carboxamide;

(R,E)-2-(2-fluorophenyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-4-(2-hydroxyphenoxy)-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-4-(cycloheptyloxy)-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

2-cyclopentyl-4-(((1S,2R)-2-hydroxycyclohexyl)oxy)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

2-cyclopentyl-4-(((1R,2S)-2-hydroxycyclohexyl)oxy)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-(bicyclo[1.1.1]pentan-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

2-((1S,3R)-3-methylcyclobutyl)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

2-((1R,3S)-3-methylcyclobutyl)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(3-methoxyazetidin-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

2-cyclopropyl-4-((3,3-difluorocyclopentyl)oxy)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

2-cyclopropyl-4-(((S)-2,2-difluorocyclopentyl)oxy)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

2-cyclopropyl-4-(((R)-2,2-difluorocyclopentyl)oxy)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(2-azaspiro[3.3]heptan-2-yl)pyrimidine-5-carboxamide;

2-(bicyclo[4.2.0]octa-1,3,5-trien-7-yl)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(tetrahydro-2H-pyran-3-yl)pyrimidine-5-carboxamide;

(S,E)-2-(5,6-dihydro-2H-pyran-3-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(4-methyl-1-(methylsulfonyl)pent-1-en-3-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(2-hydroxypropan-2-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-isobutyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(2-methylprop-1-en-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

2-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

2-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-4-(bicyclo[2.2.1]heptan-1-yloxy)-2-cyclopropyl-N-(4-(methylsulfonyl)but-3-en-2-yl)pyrimidine-5-carboxamide;

(S,E)-2-(3,3-difluoropyrrolidin-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(2-methoxypropan-2-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(1,1-difluoroethyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopentyl-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(1-methylcyclopropyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(2-(1-methylcyclopropyl)-4-phenoxypyrimidin-5-yl)(3-((methylsulfonyl)methylene)azetidin-1-yl)methanone;

(2-(tert-butyl)-4-phenoxypyrimidin-5-yl)(3-(((tetrahydro-2H-pyran-4-yl)sulfonyl)methylene)azetidin-1-yl)methanone;

(2-((1S,3S)-3-methylcyclobutyl)-4-phenoxypyrimidin-5-yl)(3-((methylsulfonyl)methylene)azetidin-1-yl)methanone;

(2-((1r,3r)-3-methylcyclobutyl)-4-phenoxypyrimidin-5-yl)(3-((methylsulfonyl)methylene)azetidin-1-yl)methanone;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(pyrrolidin-1-yl)pyrimidine-5-carboxamide;

(S,E)-2-(2,2-dimethylpyrrolidin-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

2-((S)-2-methylpyrrolidin-1-yl)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

2-((R)-2-methylpyrrolidin-1-yl)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

1-(1-(2-(tert-butyl)-4-phenoxypyrimidine-5-carbonyl)azetidin-3-ylidene)propan-2-one;

(S,E)-2-((1-methylcyclopropyl)methyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(2-((1-methylcyclopropyl)methyl)-4-phenoxypyrimidin-5-yl)(3-((methylsulfonyl)methylene)azetidin-1-yl)methanone;

(E)-(2-cyclopropyl-4-phenoxypyrimidin-5-yl)(3-((methylsulfonyl)methylene)pyrrolidin-1-yl)methanone;

(S,E)-2-(tert-butyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-(phenoxy-d5)pyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-(phenoxy-d5)pyrimidine-5-carboxamide;

(R,E)-2-(tert-butyl)-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(1-phenylcyclopropyl)pyrimidine-5-carboxamide;

2-((1R,3S)-3-methylcyclopentyl)-N-((S,E)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(1-cyclopropyl-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-N-(1-cyclopropyl-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(3,3-difluorocyclobutyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-2-(1,1-difluoroethyl)-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(1-cyclobutyl-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclobutyl-3-(methylsulfonyl)allyl)-2-cyclopropyl-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(1-(3,3-difluorocyclobutyl)-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-N-(1-(3,3-difluorocyclobutyl)-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(1-fluorocyclopropyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(E)-2-(tert-butyl)-N-(1-(2-(methylsulfonyl)vinyl)cyclopropyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-4-acetamido-2-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-6-phenoxypyrimidine-5-carboxamide;

(R,E)-2-(tert-butyl)-N-(4-(methylsulfonyl)-1-(methylthio)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-2-cyclopropyl-N-(4-(methylsulfonyl)-1-(methylthio)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-(perfluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-isopropyl-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(2-fluoropropan-2-yl)-4-phenoxypyrimidine-5-carboxamide;

N-((S,E)-1-cyclopropyl-3-(methylsulfonyl)allyl)-2-((1S,3S)-3-methylcyclobutyl)-4-phenoxypyrimidine-5-carboxamide;

N-((S,E)-1-cyclopropyl-3-(methylsulfonyl)allyl)-2-((1R,3R)-3-methylcyclobutyl)-4-phenoxypyrimidine-5-carboxamide;

(2-cyclopropyl-4-phenoxypyrimidin-5-yl)(3-(methylsulfonyl)-2,5-dihydro-1H-pyrrol-1-yl)methanone;

(S,E)-2-cyclopropyl-N-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,Z)-2-cyclopropyl-N-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

2-(tert-butyl)-N-((3R,4R,E)-4-methoxy-1-(methylsulfonyl)pent-1-en-3-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(3-(methylsulfonyl)-1-(tetrahydro-2H-pyran-4-yl)allyl)-4-phenoxypyrimidine-5-carboxamide;

2-cyclopropyl-N-((3R,4R,E)-4-methoxy-1-(methylsulfonyl)pent-1-en-3-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopropyl-N-(3-(methylsulfonyl)-1-(tetrahydro-2H-pyran-4-yl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(cyclopropylmethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,Z)-2-(tert-butyl)-N-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-2-cyclopentyl-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclobutyl-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(cyclopropyldifluoromethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(cyclopropyldifluoromethyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-2-(cyclopropyldifluoromethyl)-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(1,1-difluoroethyl)-4-phenoxy-N-(5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-yl)pyrimidine-5-carboxamide;

(S,E)-N-(1-cyclobutyl-3-(methylsulfonyl)allyl)-2-cyclopentyl-4-phenoxypyrimidine-5-carboxamide;

(E)-2-(tert-butyl)-N-(4-(methylsulfonyl)-1-phenoxybut-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclobutyl-3-(methylsulfonyl)allyl)-2-(cyclopropyldifluoromethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclobutyl-3-(methylsulfonyl)allyl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(5-(dimethylamino)-1-(methylsulfonyl)-5-oxopent-1-en-3-yl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-2-(1,1-difluoroethyl)-4-phenoxy-N-(5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-yl)pyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(perfluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)-2-(perfluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxy-2-(trifluoromethyl)pyrimidine-5-carboxamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(1-(trifluoromethyl)cyclopropyl)pyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxy-2-(1-(trifluoromethyl)cyclopropyl)pyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxy-2-(2,2,2-trifluoroethyl)pyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(1-fluorocyclopropyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(1-(4,4-difluorocyclohexyl)-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(5,5-difluoro-1-(methylsulfonyl)pent-1-en-3-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(5,5-difluoro-1-(methylsulfonyl)pent-1-en-3-yl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-(4,4-difluorocyclohexyl)-3-(methylsulfonyl)allyl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(2,2,2-trifluoroethyl)pyrimidine-5-carboxamide;

4-(((1R,3S,5S)-bicyclo[3.1.0]hexan-3-yl)oxy)-2-(tert-butyl)-N-((E)-3-(methylsulfonyl)allyl)pyrimidine-5-carboxamide;

4-(((1R,3S,5S)-bicyclo[3.1.0]hexan-3-yl)oxy)-2-cyclopropyl-N-((E)-3-(methylsulfonyl)allyl)pyrimidine-5-carboxamide;

(R,E)-N-(1-(tert-butoxy)-4-(methylsulfonyl)but-3-en-2-yl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-2-(tert-butyl)-N-(4-(methylsulfonyl)-1-phenoxybut-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(tert-butyl)-N-(4-(methylsulfonyl)-1-phenoxybut-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxy-2-(spiro[2.3]hexan-5-yl)pyrimidine-5-carboxamide;

(R,E)-2-(1,1-difluoroethyl)-N-(1-(difluoromethoxy)-4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(1,1-difluoroethyl)-N-(5-(dimethylamino)-1-(methylsulfonyl)-5-oxopent-1-en-3-yl)-4-phenoxypyrimidine-5-carboxamide;

N-((S,E)-1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(cyclopropylfluoromethyl)-4-phenoxypyrimidine-5-carboxamide;

4-(((1R,3S,5S)-bicyclo[3.1.0]hexan-3-yl)oxy)-2-(tert-butyl)-N-((S,E)-1-cyclopropyl-3-(methylsulfonyl)allyl)pyrimidine-5-carboxamide;

(S,E)-N-(1-(3,3-difluorocyclobutyl)-3-(methylsulfonyl)allyl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-N-(1-(3,3-difluorocyclobutyl)-3-(methylsulfonyl)allyl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(cyclopropyldifluoromethyl)-N-(1-(3,3-difluorocyclobutyl)-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(R,E)-2-(cyclopropyldifluoromethyl)-N-(1-(3,3-difluorocyclobutyl)-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

2-(1,1-difluoroethyl)-N-((3R,4S,E)-4-methoxy-1-(methylsulfonyl)pent-1-en-3-yl)-4-phenoxypyrimidine-5-carboxamide;

4-(((1R,3R,5S)-bicyclo[3.1.0]hexan-3-yl)oxy)-N-((S,E)-1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(1,1-difluoroethyl)pyrimidine-5-carboxamide;

(R,E)-N-(1-cyclopropoxy-4-(methylsulfonyl)but-3-en-2-yl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(dimethylamino)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(methylamino)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-cyclopropoxy-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxy-2-(2,2,2-trifluoroethoxy)pyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(diethylamino)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(cyclopropyl(methyl)amino)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-methoxy-4-phenoxypyrimidine-5-carboxamide;

(S,E)-2-(azetidin-1-yl)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(methyl(2,2,2-trifluoroethyl)amino)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(3-fluoroazetidin-1-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(ethyl(methyl)amino)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-1-methyl-6-phenoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(3,3-difluoroazetidin-1-yl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(1,1-difluoropropyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl-1-d)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(S)-N-(3-cyanobut-3-en-2-yl)-2-(cyclopropyldifluoromethyl)-4-phenoxypyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(cyclopropyldifluoromethyl)-4-(phenoxy-d5)pyrimidine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl-1-d)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide; and

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(cyclopropyldifluoromethyl)-4-(phenoxy-d5)pyrimidine-5-carboxamide.

24. The compound according to claim 23, or a pharmaceutically acceptable salt thereof, wherein when the R or S stereochemical configuration at one or more chiral carbons is specified, the compound includes a mixture of R or S configurations at that carbon;

or a mixture of E or Z geometric isomers of the aforementioned compounds.

25. The compound according to any one of claims 2 and 8-14, or a pharmaceutically acceptable salt thereof, wherein the compound is:

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide.

26. The compound according to any one of claims 3 and 10-14, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(E)-2-cyclobutoxy-4-cyclopentyl-N-(3-(methylsulfonyl)allyl)benzamide;

(E)-4-cyclopentyl-2-ethoxy-N-(3-(methylsulfonyl)allyl)benzamide;

(E)-4-cyclopentyl-2-isopropoxy-N-(3-(methylsulfonyl)allyl)benzamide;

(E)-4-cyclopentyl-N-(3-(methylsulfonyl)allyl)-2-phenoxybenzamide;

(E)-4-cyclopentyl-2-cyclopropoxy-N-(3-(methylsulfonyl)allyl)benzamide;

4-cyclopentyl-2-cyclopropoxy-N-((1,1-dioxido-2H-thiet-3-yl)methyl)benzamide;

(E)-2-cyclobutoxy-4-cyclopentyl-N-(3-(methylsulfonyl)allyl)benzamide;

(E)-4-cyclopentyl-2-ethoxy-N-(3-(methylsulfonyl)allyl)benzamide;

(E)-4-cyclopentyl-2-isopropoxy-N-(3-(methylsulfonyl)allyl)benzamide;

(E)-4-cyclopentyl-N-(3-(methylsulfonyl)allyl)-2-phenoxybenzamide;

(E)-4-cyclopentyl-2-cyclopropoxy-N-(3-(methylsulfonyl)allyl)benzamide;

4-cyclopentyl-2-cyclopropoxy-N-((1,1-dioxido-2H-thiet-3-yl)methyl)benzamide;

(S,E)-5-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)quinoline-8-carboxamide;

(S,E)-6-(cyclopent-1-en-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxynicotinamide;

(E)-4-cyclopentyl-2-(cyclopentyloxy)-N-(3-(methylsulfonyl)allyl)benzamide;

rac-(R,E)-4-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxybenzamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-3-oxo-6-phenoxy-2,3-dihydro-1H-indene-5-carboxamide;

(S,E)-2,2-dimethyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-3-oxo-6-phenoxy-2,3-dihydro-1H-indene-5-carboxamide; and

2,2-dimethyl-6-(3-((methylsulfonyl)methylene)azetidine-1-carbonyl)-5-phenoxy-2,3-dihydro-1H-inden-1-one.

27. The compound according to claim 26, or a pharmaceutically acceptable salt thereof, wherein when the (R) or (S) stereochemical configuration at one or more chiral carbon atoms is specified, the compound includes a mixture of (R) or (S) configurations at those carbon atoms;

or a mixture of (E) or (Z) geometric isomers of the aforementioned compounds.

28. The compound according to any one of claims 4 and 10-14, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(S,E)-6-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxynicotinamide;

(S,E)-6-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxynicotinamide;

(S,E)-6-(cyclopent-1-en-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxynicotinamide;

(S,E)-6-(cyclopent-1-en-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxynicotinamide;

(S,E)-6-cyclopropyl-5-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxynicotinamide;

(S,E)-6-(tert-butyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxynicotinamide; and

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-6-(1,1-difluoroethyl)-4-phenoxynicotinamide.

29. The compound according to claim 28, or a pharmaceutically acceptable salt thereof, wherein when the (R) or (S) stereochemical configuration at one or more chiral carbon atoms is specified, the compound includes a mixture of (R) or (S) configurations at those carbon atoms;

or a mixture of (E) and (Z) geometric isomers of the aforementioned compounds.

30. The compound according to any one of claims 5 and 10-14, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(S,E)-6-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxynicotinamide;

(S,E)-6-(cyclopent-1-en-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxynicotinamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxyquinoline-3-carboxamide;

(S,E)-5-cyano-6-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxynicotinamide;

(S,E)-6-(cyclopent-1-en-1-yl)-5-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxynicotinamide;

(S,E)-6-cyclopropyl-5-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)-4-phenoxynicotinamide;

(S,E)-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxy-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide;

(S,E)-6-cyclopentyl-5-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxynicotinamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-6-(1,1-difluoroethyl)-2-phenoxynicotinamide;

S,E)-6-(1,1-difluoroethyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-2-phenoxynicotinamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-1-methyl-6-phenoxy-1H-pyrrolo[2,3-b]pyridine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-1-methyl-6-phenoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-6-(1,1-difluoroethyl)-5-fluoro-2-phenoxynicotinamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-7,7-difluoro-2-phenoxy-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxamide;

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-3-methyl-5-phenoxy-3H-imidazo[4,5-b]pyridine-6-carboxamide; and

(S,E)-N-(1-cyclopropyl-3-(methylsulfonyl)allyl)-6-(cyclopropyldifluoromethyl)-5-fluoro-2-phenoxynicotinamide.

31. The compound according to claim 30, or a pharmaceutically acceptable salt thereof, wherein when the (R) or (S) stereochemical configuration at one or more chiral carbon atoms is specified, the compound includes a mixture of R or S configurations at that carbon;

or a mixture of (E) or (Z) geometric isomers of the aforementioned compounds.

32. The compound according to any one of claims 6 and -10-14, or a pharmaceutically acceptable salt thereof, wherein the compound is:

(S,E)-5-(cyclopent-1-en-1-yl)-N-(4-(methylsulfonyl)but-3-en-2-yl)-3-phenoxypyrazine-2-carboxamide.

33. The compound according to claim 32, or a pharmaceutically acceptable salt thereof, wherein when the (R) or (S) stereochemical configuration at one or more chiral carbon atoms is specified, the compound includes a mixture of (R) or (S) configurations at those carbon atoms;

or a mixture of E or Z geometric isomers of the aforementioned compounds.

34. The compound according to any one of claims 7 and -10-14, or a pharmaceutically acceptable salt thereof, wherein the compound is:

(S,E)-5-cyclopentyl-N-(4-(methylsulfonyl)but-3-en-2-yl)-3-phenoxypicolinamide.

35. The compound according to claim 34, or a pharmaceutically acceptable salt thereof, wherein when the (R) or (S) stereochemical configuration at one or more chiral carbon atoms is specified, the compound includes a mixture of (R) or (S) configurations at those carbon atoms;

or a mixture of E or Z geometric isomers of the aforementioned compounds.

36. The compound according to any one of claims 2, 10-12 and 15-17, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

2-(1-(2-cyclopropyl-4-phenoxypyrimidine-5-carbonyl)azetidin-3-ylidene)acetonitrile;

2-(1-(2-cyclopropyl-4-phenoxypyrimidine-5-carbonyl)-2-methylazetidin-3-ylidene)acetonitrile;

(E)-N-(3-cyanoallyl)-2-cyclopropyl-4-phenoxypyrimidine-5-carboxamide; and

(Z)-N-(3-cyanoallyl)-2-cyclopropyl-4-phenoxypyrimidine-5-carboxamide.

37. The compound according to claim 36, or a pharmaceutically acceptable salt thereof, wherein an (E) or (Z) geometric isomer of a compound has been specified, a mixture of (E) or (Z) geometric isomers of said compounds.

38. The compound according to any one of claims 2, 10-12 and 17-18, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

N-(2-cyanoallyl)-2-cyclopropyl-4-phenoxypyrimidine-5-carboxamide;

2-(tert-butyl)-N-(2-cyanoallyl)-4-phenoxypyrimidine-5-carboxamide;

N-(2-cyanoallyl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

N-(2-cyanoallyl)-2-cyclopentyl-4-phenoxypyrimidine-5-carboxamide;

N-(2-cyanoallyl)-2-(cyclopropyldifluoromethyl)-4-phenoxypyrimidine-5-carboxamide;

(R)-N-(3-cyanobut-3-en-2-yl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(S)-N-(3-cyanobut-3-en-2-yl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide;

(S)-N-(3-cyanobut-3-en-2-yl)-2-(cyclopropyldifluoromethyl)-4-phenoxypyrimidine-5-carboxamide; and

(S)-N-(2-cyano-1-cyclopropylallyl)-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide.

39. The compound according to claim 38, or a pharmaceutically acceptable salt thereof, wherein when the (R) or (S) stereochemical configuration at one or more chiral carbon atoms is specified, the compound includes a mixture of (R) or (S) configurations at those carbon atoms.

40. The compound according to any one of claims 2, 10-12 and 19-20, or a pharmaceutically acceptable salt thereof, wherein the compound is:

(S)-2-(1,1-difluoroethyl)-N-(5-(dimethylamino)-5-oxopent-3-yn-2-yl)-4-phenoxypyrimidine-5-carboxamide.

41. The compound according to claim 40, or a pharmaceutically acceptable salt thereof, wherein when the (R) or (S) stereochemical configuration at one or more chiral carbon atoms is specified, the compound includes a mixture of (R) or (S) configurations at those carbon.

42. The compound according to any one of claims 2, 10-12 and 21-22, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

1-(1-(2-(tert-butyl)-4-phenoxypyrimidine-5-carbonyl)azetidin-3-ylidene)propan-2-one; and

methyl 2-(1-(2-(tert-butyl)-4-phenoxypyrimidine-5-carbonyl)azetidin-3-ylidene)acetate.

43. A compound according to any one of claims 1-42, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

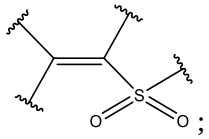
44. A compound according to any of claims 1-42, or a pharmaceutically acceptable salt thereof for use in inhibiting WRN helicase (Werner syndrome ATP-dependent helicase) in a subject in need of such inhibition.

45. An electrophile for use in inhibiting WRN helicase (Werner syndrome ATP-dependent helicase) comprising effecting a non-naturally occurring covalent modification at cysteine 727 as set forth in SEQ ID NO: 1 or a variant thereof, the modification resulting from a bond forming reaction between the electrophile and the cysteine 727 as set forth in SEQ ID NO: 1 or the variant thereof, wherein a sulfur atom at the cysteine residue undergoes a reaction with the electrophile.

46. The electrophile for use according to claim 45, wherein the electrophile comprises at least one chemical moiety selected from the group consisting of: a vinyl sulfone, an alkynyl sulfone, a vinyl sulfonamide, a vinyl sulfoxide, an alkynyl sulfoxide, a vinyl sulfoximine, an alkynyl sulfoximine, an acrylamide, an acrylonitrile, an alkynenitrile, an enone, a ynone, an enoate, and a ynoate.

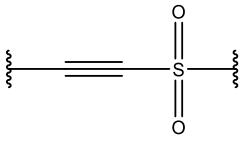
47. The electrophile for use according to claim 46, wherein:

the vinyl sulfone is represented by the structure



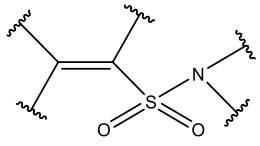
;

the alkynyl sulfone is represented by the structure



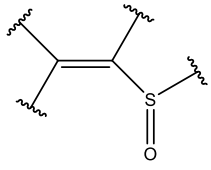
;

the vinyl sulfonamide is represented by the structure



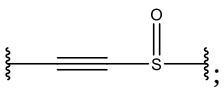
;

the vinyl sulfoxide is represented by the structure



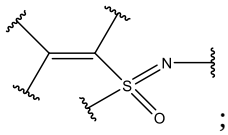
;

the alkynyl sulfoxide is represented by the structure



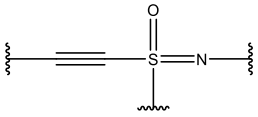
;

the vinyl sulfoximine is represented by the structure



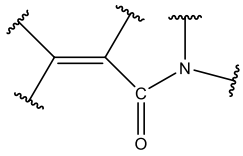
;

the alkynyl sulfoximine is represented by the structure



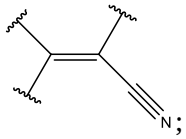
;

the acrylamide is represented by the formula



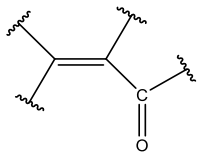
;

the acrylonitrile is represented by the structure



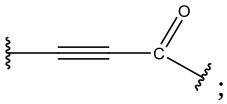
;

the enone is represented by the structure



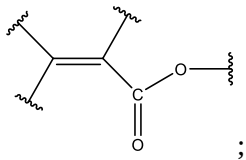
;

the ynone is represented by the structure



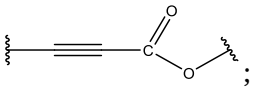
;

the enoate is represented by the structure



; and

the ynoate is represented by the structure

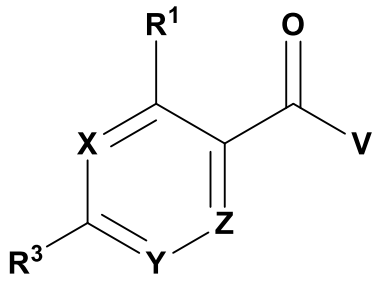


;

wherein:


represents a possible point of attachment of the chemical moiety to the remainder of the electrophile.

48. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X is CR^2 or N;

Y is CR^4 or N;

Z is CR^5 or N;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heterocyclyl;

with the proviso that X, Y, and Z are not simultaneously N;

R^1 is H, -O-(optionally substituted C_3-C_8 cycloalkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_6-C_{10} aryl), -O-(optionally substituted five- to six-membered heteroaryl), -O-(optionally substituted five- to six-membered heterocyclyl), or optionally substituted C_3-C_8 cycloalkyl;

or R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl;

R^2 is H, optionally substituted C_1-C_6 alkyl, or halo;

R^3 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_8 cycloalkenyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkenyl, -NR_2, -N(R)(optionally substituted C_3-C_8 cycloalkyl), -S-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_3-C_8 cycloalkyl), optionally substituted four- to six-membered heterocyclyl or heterocyclenyl, optionally substituted five- to six-membered heteroaryl, or -O-(optionally substituted C_3-C_8 cycloalkyl);

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^4 is H, C_1-C_6 alkyl, cyano, or halo;

or R^4 together with the carbon atom to which it is shown attached and Z form an optionally substituted five- to six-membered heteroaryl;

or R^3 and R^4 taken together with the carbon atoms to which they are shown attached and R^3 taken from an optionally substituted C_6-C_{10} aryl, an optionally substituted C_4-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^5 is H, C_1-C_6 alkyl, -NR_2, or -N(R)-C(=O)-(C_1-C_6 alkyl);

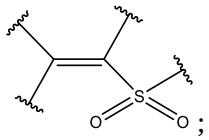
each R independently is H, or optionally substituted C_1-C_6 alkyl; and

V comprises an electrophile that reacts and forms a covalent bond with the sulfur atom at cysteine 727 as set forth in SEQ ID NO:1 or variants thereof.

49. The compound according to claim 48, or a pharmaceutically acceptable salt thereof, wherein the electrophile comprises at least one chemical moiety selected from the group consisting of: a vinylsulfone, an alkynylsulfone, a vinylsulfonamide, a vinylsulfoxide, an alkynylsulfoxide, a vinylsulfoximine, an alkynylsulfoximine, an acrylamide, an acrylonitrile, an alkynenitrile, an enone, a ynone, an enoate, and a ynoate.

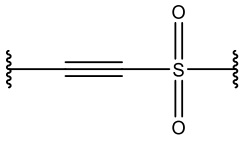
50. The compound according to claim 49, or a pharmaceutically acceptable salt thereof, wherein:

the vinyl sulfone is represented by the structure



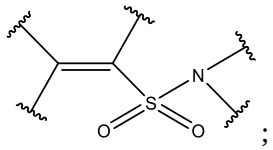
;

the alkynyl sulfone is represented by the structure



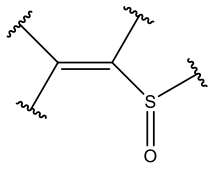
;

the vinyl sulfonamide is represented by the structure



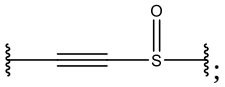
;

the vinyl sulfoxide is represented by the structure



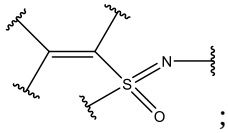
;

the alkynyl sulfoxide is represented by the structure



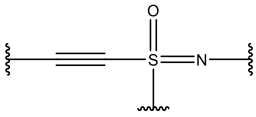
;

the vinyl sulfoximine is represented by the structure



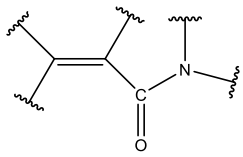
;

the alkynyl sulfoximine is represented by the structure



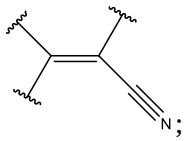
;

the acrylamide is represented by the formula



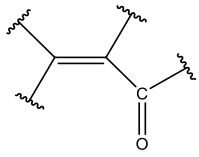
;

the acrylonitrile is represented by the structure



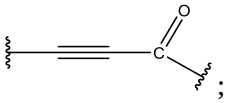
;

the enone is represented by the structure



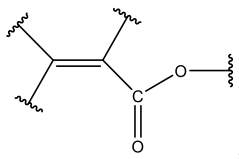
;

the ynone is represented by the structure



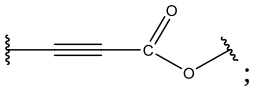
;

the enoate is represented by the structure



; and

the ynoate is represented by the structure



;

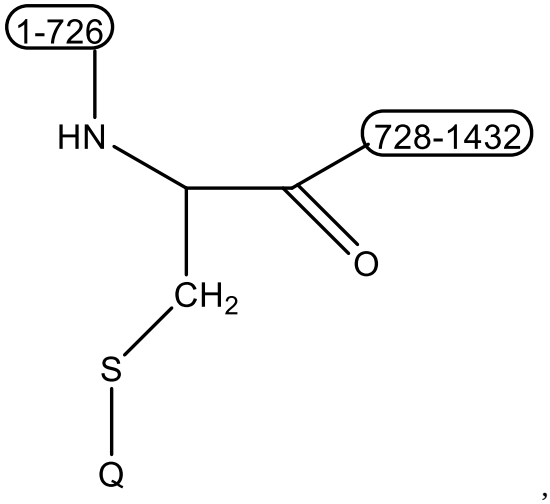
wherein:

 represents a possible point of attachment of the chemical moiety to the remainder of the electrophile.

51. A compound according to any one of claims 48-50, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

52. A modified WRN helicase protein comprising a non-naturally occurring small molecule fragment having a covalent bond to cysteine 727 of the WRN helicase protein, wherein the

modified WRN helicase protein comprises SEQ ID NO: 1 or a variant thereof; and has the structure of Formula (III):



,

Formula (III)

wherein:

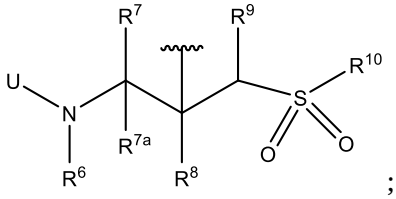
S is the sulfur atom of Cysteine 727 in SEQ ID NO: 1 or a variant thereof;

1-726 and 728-1432 represent amino acids at positions 1-726 and 728-1432 respectively of SEQ ID NO: 1 or the variant thereof; and

Q is Q^1, Q^2, Q^3, Q^4, or Q^5;

wherein:

Q^1 is:



;

wherein:

 indicates the point of attachment;

R^6 is H;

R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted five- to six-membered heterocyclyl;

R^{7a} is H or deuterium;

R^8 is H;

R^9 is H; and

R^{10} is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted five- to six-membered heterocyclyl ;

or R^6 together with the nitrogen atom to which it is shown attached and R^7 and R^{7a} with the carbon atom to which they are shown attached form an azetidinyl ring;

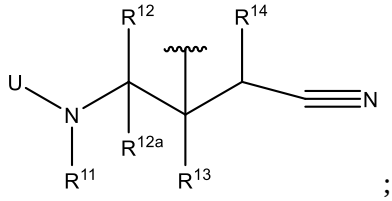
or R^6 together with the nitrogen atom to which it is shown attached and R^7, R^{7a}, and R^8 together with the carbon atoms to which they are shown attached form an azetidinyl or pyrrolodinyl ring;

or R^6 together with the nitrogen atom to which it is shown attached and R^7, R^{7a}, R^8, and R^9 together with the carbon atoms to which they are shown attached form a dihydropyrrolyl ring;

or R^7, R^{7a}, R^8, R^9, and R^{10} together with the carbon atoms to which they are shown attached form a 1,1-dioxido-2,3-dihydrothiophenyl ring;

or R^8, R^9, and R^{10} together with the carbon atoms to which they are shown attached form a 1,1-dioxido-2H-thietyl ring;

Q^2 is:



;

wherein:

 indicates the point of attachment;

R^{11} is H;

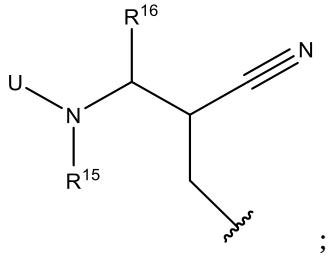
R^{12} is H or optionally substituted C_1-C_6 alkyl;

R^{12a} is H; and

R^{13} and R^{14} are each H;

or R^{11} together with the nitrogen atom to which it is shown attached and R^{12}, R^{12a}, and R^{13} together with the carbon atoms to which they are shown attached form an optionally substituted azetidinyl ring;

Q^3 is:



;

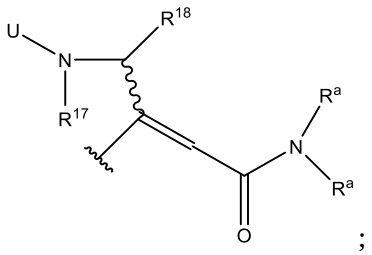
wherein:

 indicates the point of attachment;

R^{15} is H; and

R^{16} is H or optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_8 cycloalkyl;

Q^4 is:



;

wherein:

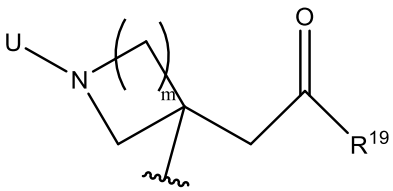
 indicates the point of attachment;

R^{17} is H;

R^{18} is H or optionally substituted C_1-C_6 alkyl; and

each R^a independently is optionally substituted C_1-C_6 alkyl;

Q^5 is:



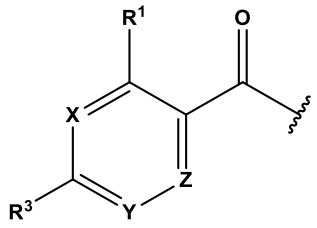
wherein:

 indicates the point of attachment;

m is 1, 2, or 3; and

R^{19} is selected from the group consisting of C_1-C_6 alkyl and -O-(C_1-C_6 alkyl); and

U is:



;

wherein:

 indicates the point of attachment;

X is CR^2 or N;

Y is CR^4 or N;

Z is CR^5 or N;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heterocyclyl;

with the proviso that X, Y, and Z are not simultaneously N;

R^1 is H, -O-(optionally substituted C_3-C_8 cycloalkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_6-C_{10} aryl), -O-(optionally substituted five- to six-membered heteroaryl), -O-(optionally substituted five- to six-membered heterocyclyl), or optionally substituted C_3-C_8 cycloalkyl;

or R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl;

R^2 is H, optionally substituted C_1-C_6 alkyl, or halo;

R^3 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_8 cycloalkenyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkenyl, -NR_2, -N(R)(optionally substituted C_3-C_8 cycloalkyl), -S-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_1-C_6 alkyl), -O-(optionally substituted C_3-C_8 cycloalkyl), optionally substituted four- to six-membered heterocyclyl or heterocyclenyl, optionally substituted five- to six-membered heteroaryl, or -O-(optionally substituted C_3-C_8 cycloalkyl);

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^4 is H, C_1-C_6 alkyl, cyano, halo,

or R^4 together with the carbon atom to which it is shown attached and Z form an optionally substituted five- to six-membered heteroaryl;

or R^3 and R^4 taken together with the carbon atoms to which they are shown attached form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_4-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl;

R^5 is H, C_1-C_6 alkyl, -NR_2, or -N(R)-C(=O)-(C_1-C_6 alkyl); and

each R independently is H, or optionally substituted C_1-C_6 alkyl.

53. The modified WRN helicase protein according to claim 52, wherein:

X is N;

Y is N; and

Z is CR^5;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heterocyclyl.

54. The modified WRN helicase protein according to claim 52, wherein:

X is CR^2;

Y is CR^4; and

Z is CR^5;

or Y and Z taken together form an optionally substituted five- to six-membered heteroaryl, or an optionally substituted five- to six-membered heteroaryl;

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl.

55. The modified WRN helicase protein according to claim 52, wherein:

X is CR^2;

Y is N; and

Z is CR^5;

or R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl.

56. The modified WRN helicase protein according to claim 52, wherein:

X is N;

Y is CR^4; and

Z is CR^5;

or R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_6-C_{10} aryl, an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, or an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl.

57. The modified WRN helicase protein according to claim 52, wherein:

X is N;

Y is CR^4; and

Z is N.

58. The modified WRN helicase protein according to claim 52, wherein:

X is CR^2;

Y is CR^4; and

Z is N.

59. The modified WRN helicase protein according to any one of claims 52-58, wherein:

in R^1:

the optional substituents of the -O-(optionally substituted C_3-C_8 cycloalkyl) are 1-3 substituents selected from the group consisting of halo, cyano, and hydroxy; or when there are two substituents on the same ring carbon atom of the C_3-C_8 cycloalkyl, the substituents together with the ring carbon atom to which they are attached form a C_3-C_6 cycloalkyl; or when there are two substituents on adjacent ring carbon atoms of the C_3-C_8 cycloalkyl, the substituents taken together with the ring carbon atoms to which they are attached form a C_3-C_6 cycloalkyl;

the optional substituents of the -O-(optionally substituted C_6-C_{10} aryl are 1-3 substituents selected from the group consisting of halo, C_1-C_6 alkyl, cyano, hydroxy, and $-NH_2$, or 1-5 deuterium atoms;

or when R^1 together with the carbon atoms to which it is shown attached and X form an optionally substituted five- to six-membered heterocyclyl, two substituents on the same ring carbon atom of the five- to six-membered heterocyclyl together with the ring carbon atom to which they are attached form a five- to six-membered cycloalkyl;

in R^3:

the optional substituents of the optionally substituted C_3-C_8 cycloalkyl are 1-3 substituents selected from hydroxy, halo, C_1-C_6 alkyl, and C_6-C_{10} aryl; or when there are two substituents on the same carbon atom of the C_3-C_8 cycloalkyl, the substituents together with the ring carbon atom to which they are attached form a C_3-C_6 cycloalkyl; or when there are two substituents on adjacent ring carbon atoms of the C_3-C_8 cycloalkyl, the substituents taken together with the ring carbon atoms to which they are attached form C_6-C_{10} aryl;

or when R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, the optional substituents are 1-3 substituents selected from the group consisting of halo, and C_1-C_6 alkyl; or two geminal hydrogens on a ring carbon atom of the C_3-C_8 cycloalkyl or cycloalkenyl can be replaced with the group =O;

or when R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted five- to six-membered heterocyclyl or heterocyclenyl, the optional substituents are 1-3 substituents selected from the group consisting of halo and C_1-C_6 alkyl;

the optional substituents of the optionally substituted C_6-C_{10} aryl are 1-3 substituents selected from the group consisting of halo;

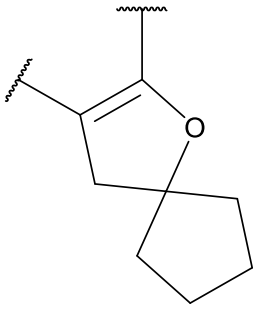
the optional substituents of the optionally substituted C_1-C_6 alkyl or C_6 alkenyl are 1-5 substituents selected from the group consisting of halo, hydroxy, -O-(C_1-C_6 alkyl), and optionally substituted C_3-C_6 cycloalkyl, wherein the optional substituents of the C_3-C_6 cycloalkyl are 1-3 substituents selected from the group consisting of C_1-C_6 alkyl;

the optional substituents of the C_1-C_6 alkyl of R of -NR_2 are 1-3 substituents selected from the group consisting of halo; and

the optional substituents of the optionally substituted four- to six-membered heterocyclyl are 1-3 substituents selected from the group consisting of -O-(C_1-C_6 alkyl), C_1-C_6 alkyl, halo; or when there are two substituents on the same carbon atom of the optionally substituted four- to six-membered heterocyclyl, the substituents together with the ring carbon atom to which they are attached form a C_3-C_6 cycloalkyl.

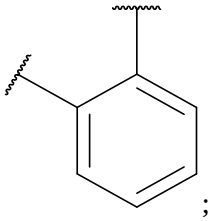
60. The modified WRN helicase protein according to any one of claims 52-59, wherein:

the optionally substituted five- to six-membered heterocyclyl formed by R^1 together with the carbon atoms to which it is shown attached is

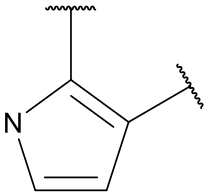


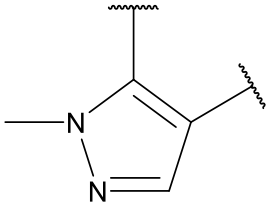
wherein the double bond shown is between the carbon bearing the R^1 group and X ;

the optionally substituted C_6-C_{10} aryl formed by R^3 taken together with the carbon atom to which it is shown attached and Y is


;

the optionally substituted five- to six-membered heterocyclenyl formed by R^3 taken together with the carbon atom to which it is shown attached and Y is

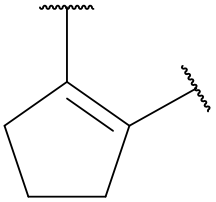
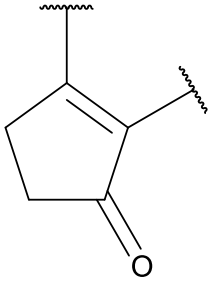


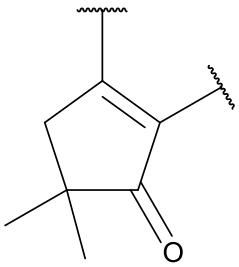
or


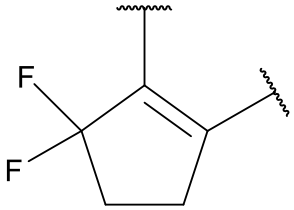
, wherein the carbon-carbon double bond shown between the two carbons bearing the

groups is between the carbon bearing the R^3 group and Y;

when R^3 taken together with the carbon atom to which it is shown attached and Y form an optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl, the optionally substituted C_3-C_8 cycloalkyl or cycloalkenyl is

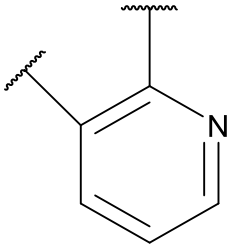

,


,


, or


, wherein the carbon-carbon double bond shown is between the carbon bearing the R^3 group and Y; and

wherein the optionally substituted five- to six-membered heteroaryl formed by R^4 together with the carbon atom to which it is shown attached and Z is



; wherein in each structure  indicates the point of attachment.

61. The modified WRN helicase protein according to any one of claims 52-60, wherein:

in R^1:

the -O-(optionally substituted C_3-C_8 cycloalkyl) is -O-cyclobutyl, -O-cyclopropyl, -O-cyclohexyl, -O-cyclopentyl, -O-(4,4-difluorocyclohexyl), -O-(spiro[2.3]hexan-5-yl), -O-(spiro[3.3]heptan-2-yl), -O-(3-chrlorocyclobutyl), -O-(bicyclo[3.1.0]hexan-3-yl), -O-(bicyclo[2.2.1]heptan-1-yl), -O-(1-cyanocyclopentanyl), -O-(3,3-difluorocyclobutyl), -O-(2-hydroxycyclohexyl), -O-cycloheptyl, -O-(2-fluorocyclohexyl), -O-(3,3-difluorocyclopentyl), -O-(2-fluorocyclohexyl), or -O-(2,2-difluorocyclopentyl),

the -O-(optionally substituted C_1-C_6 alkyl) is ethoxy, isopropoxy, or cyclopropylmethyloxy;

the -O-(optionally substituted C_6-C_{10} aryl) is phenoxy, 4-chlorophenoxy, 3-fluorophenoxy, 2-chlorophenoxy, 3-chlorophenoxy, 2-fluorophenoxy, *p*-tolyloxy, 3,5-difluorophenoxy, 4-fluoro-3-methylphenoxy, 3,5-dichlorophenoxy, 4-cyanophenoxy, 3,4-dimethylphenoxy, *m*-tolyloxy, 4-ethylphenoxy, 3-ethylphenoxy, *o*-tolyloxy, 2-hydroxyphenoxy, 3-hydroxyphenoxy, 4-hydroxyphenoxy, 3-chlro-5-fluorophenoxy, 3-aminophenoxy, naphthalen-1-oxy, or phenoxy-d5;

the -O-(optionally substituted five- to six-membered heteroaryl) is pyridine-2-yloxy, or pyridine-3-yloxy;

the -O-(optionally substituted five- to six-membered heterocyclyl) is -O-tetrahydro-2H-pyran-4-yl, or -O-tetrahydro-2H-pyran-3-yl; and

the optionally substituted C_3-C_8 cycloalkyl is cyclohexyl;

in R^2:

the optionally substituted C_1-C_6 alkyl is methyl; and

in R^3:

the optionally substituted C_3-C_8 cycloalkyl is cyclopentyl, cyclobutyl, cyclohexyl, cyclopropyl, hydroxycyclopentyl, fluorocyclopentyl, methylcyclobutyl, methylcyclopropyl, phenylcyclopropyl, methylcyclopentyl, difluorocyclobutyl, fluorocyclopentyl, bicyclo[4.2.0]octa-1,3,5-trien-7-yl, or (trifluoromethyl)cyclopropyl, or spiro[2.3]hexan-5-yl;

the optionally substituted C_3-C_8 cycloalkenyl is cyclopentenyl;

the optionally substituted C_6-C_{10} aryl is phenyl;

the optionally substituted C_1-C_6 alkyl is methyl, ethyl, isopropyl, *tert*-butyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, trifluoromethyl, trifluoroethyl, hydroxypropanyl,

fluropropanyl, methoxypropanyl, difluoroethyl, difluoropropyl, (methylcyclopropyl)methyl, perfluoroethyl, or cyclopropyldifluoromethyl;

the optionally substituted C_1-C_6 alkenyl is 2-methylprop-1-en-1-yl;

the NR_2 is -N(H)(cyclopentyl), -N(H)(methyl), -N(methyl)(ethyl), -N(methyl)(isopropyl), -N(ethyl)$_2$, or -N(methyl)(trifluoroethyl);

the -N(R)(optionally substituted C_3-C_8 cycloalkyl) is N(methyl)(cyclopropyl);

the -S-(optionally substituted C_1-C_6 alkyl) is methylthiol;

the -O-(optionally substituted C_1-C_6 alkyl) is trifluoroethoxy, or methoxy;

the -O-(optionally substituted C_3-C_8 cycloalkyl) is cyclopentyloxy, or cyclopropyloxy; and

the optionally substituted four- to six-membered heterocyclyl or hetrocyclenyl is tetrahydrofuranyl, 7-azabicyclo[2.2.1]heptan-7-yl, bicyclo[1.1.1]pentan-1-yl, methoxyazetadin-1-yl, 2-azaspiro[3.3]heptan-2-yl, tetrahydropyranyl, tetrahydro-2H-pyran-3-yl, tetrahydro-2H-pyran-4-yl, dihydropyranyl, 5,6-dihydro-2H-pyran-3-yl, dimethylpyrrolidinyl, 2,2-dimethylpyrrolidin-1-yl, difluoropyrrolidinyl, methylcyclobutyl, pyrrolidinyl, pyrrolidine-1-yl, methylpyrrolidinyl, 2-methylpyrrolidin-1-yl, azetidinyl, azetidine-1-yl, fluoroazetidinyl, 3-fluoroazetidin-1-yl, difluoroazetidinyl, or 3,3-difluoro-azetidin-1-yl;

in R^5:

the C_1-C_6 alkyl is methyl;

the -NR_2 is -NH_2; and

the -N(R)-C(=O)-(C_1-C_6 alkyl) is -N(H)-C(=O)-CH_3.

62. The modified WRN helicase protein according to any one of claims 52-61, wherein Q is Q^1.

63. The modified WRN helicase protein according to claim 52, wherein:

the optionally substituted C_1-C_6 alkyl of R^7 is methyl, ethyl, isopropyl, methoxymethyl, cyclopropylmethyl, cyclopropyloxymethyl, tolyl, -CH(CH_3)-OCH_3, difluoroethyl, phenoxymethyl, -CH_2-C(=O)-N(CH_3)$_2$, or *tert*-butoxymethyl, difluoromethoxymethyl;

the optionally substituted C_3-C_8 cycloalkyl of R^7 is cyclopropyl, cyclobutyl, difluorocyclobutyl, -CH_2-S-CH_3, difluorocyclohexyl;

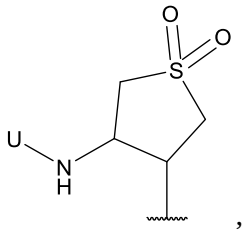
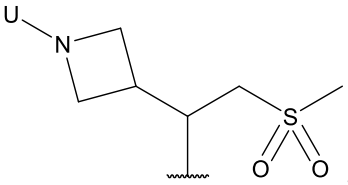
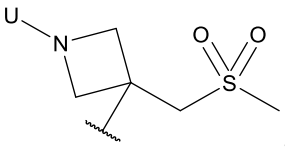
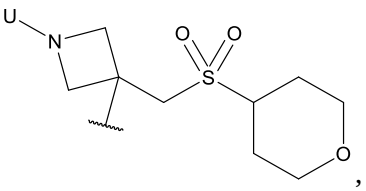
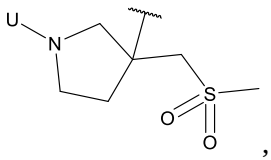
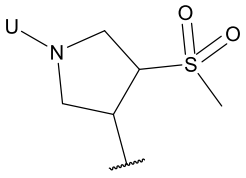
the optionally substituted five- to six-membered heterocyclyl of R^7 is tetrahydropyranyl, or tetrahydro-2H-pyran-4-yl;

the optionally substituted C_1-C_6 alkyl of R^{10} is methyl;

the optionally substituted C_3-C_8 cycloalkyl of R^{10} is cyclopropyl;

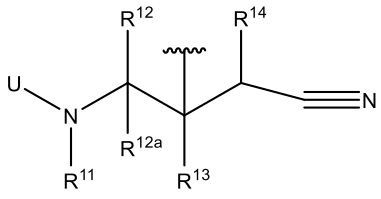
the optionally five- to six-membered heterocyclyl of R^{10} is tetrahydropyranyl or tetrahydro-2H-pyran-4-yl;

or wherein Q^1 is:


, 
, 
, 
, 
, or 
; wherein in each structure  indicates the point of attachment.

64. The modified WRN helicase protein according to any one of claims 52-61, wherein Q is Q^2.

65. The modified WRN helicase protein according to claim 64, wherein Q^2 is


;

wherein R^{21} is H or C_1-C_6 alkyl; wherein  indicates the point of attachment.

66. The modified WRN helicase protein according to any one of claims 52-61, wherein Q is Q^3.

67. The modified WRN helicase protein according to claim 66, wherein:

the optionally substituted C_1-C_6 alkyl of R^{16} is methyl; and

the optionally substituted C_3-C_8 cycloalkyl of R^{16} is cyclopropyl.

68. The modified WRN helicase protein according to any one of claims 52-61, wherein Q is Q^4.

69. The modified WRN helicase protein according to claim 68, wherein:

the optionally substituted C_1-C_6 alkyl of R^{18} is methyl; and

the optionally substituted C_1-C_6 alkyl is methyl.

70. The modified WRN helicase protein according to any one of claims 52-61, wherein Q is Q^5.

71. The modified WRN helicase protein according to claim 70, wherein:

the C_1-C_6 alkyl of R^{19} is methyl; and

the -O-(C_1-C_6 alkyl) of R^{19} is methoxy.

72. A compound according to any one of claims 1-42 and 48-50, or a pharmaceutically acceptable salt thereof, for use in the treatment of a proliferative disease.

73. The compound or the pharmaceutically acceptable salt thereof for use according to claim 72, wherein the proliferative disease is cancer.

74. The compound or the pharmaceutically acceptable salt thereof for use according to claim 73, wherein the cancer is selected from the group consisting of colon cancer, colorectal cancer, gastric cancer,

endometrium cancer, ovarian cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, skin cancer, and MSI-H cancer.

75. Use of a compound according to any one of claims 1-42 and 48-50, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a proliferative disease.

76. The use according to claim 75, wherein the proliferative disease is cancer.

77. The use according to claim 76, wherein the cancer is selected from the group consisting of colon cancer, colorectal cancer, gastric cancer, endometrium cancer, ovarian cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, skin cancer, and MSI-H cancer.