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(71) Applicant (for all designated States except US): **MILLENNIUM PHARMACEUTICALS, INC.** [US/US]; 40 Landsdowne Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BOYLE, Robert George** [GB/GB]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **IMOGAI, Hassan Julien** [FR/GB]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **CHERRY, Michael** [GB/GB]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **HUMPHRIES, Alfred John** [GB/GB]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **NAVARRO, Eva Figueroa** [ES/GB]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **OWEN, David Rodney** [GB/GB]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **DALES, Natalie, A.** [US/US]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **LAMARCHE, Matthew, J.** [US/US]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA

02139 (US). **CULLIS, Courtney** [US/US]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **GOULD, Alexandra, E.** [US/US]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US). **GREENSPAN, Paul, D.** [US/US]; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (US).

(74) Agents: **DAVIS, Steven, G.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).

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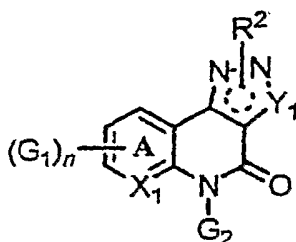
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(54) Title: 2, 5-DIHYDRO-PYRAZOLO⁴, 3-C!QUINOLIN-4-ONES AS CHK-1 INHIBITORS

(57) Abstract: Disclosed are novel inhibitors of Chk-1 and methods of using the same for therapy.



(I)



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2,5-DIHYDRO-PYRAZOLO[4,3-C]QUINOLIN-4-ONES AS CHK-1 INHIBITORS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Nos. 60/575,159, filed on May 28, 2004, 60/634,359, filed on December 8, 2004, and
5 60/634,360, filed on December 8, 2004. The entire teachings of the above applications are incorporated herein by reference.

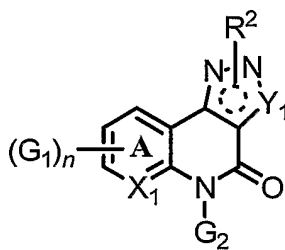
BACKGROUND OF THE INVENTION

Cell cycle checkpoints are regulatory pathways that control the order and
10 timing of cell cycle transitions. They ensure that critical events such as DNA replication and chromosome segregation are completed in high fidelity. The regulation of these cell cycle checkpoints is a critical determinant of the manner in which tumor cells respond to many chemotherapies and radiation. Many effective cancer therapies work by causing DNA damage; however, resistance to these agents
15 remains a significant limitation in the treatment of cancer. There are several mechanisms of drug resistance: an important one is attributed to the prevention of cell cycle progression through the control of critical activation of a checkpoint pathway that arrests the cell cycle to provide time for repair and induces the transcription of genes to facilitate repair, thereby avoiding immediate cell death. By
20 abrogating checkpoint arrests at, for example, the G2 checkpoint, it may be possible to synergistically augment tumor cell death induced by DNA damage and circumvent resistance. (Shyjan et al., U.S. Patent 6,723,498 (2004)). Human Chk-1 plays a role in regulating cell cycle arrest by phosphorylating the phosphatase cdc25 on Serine 216, which may be involved in preventing activation of cdc2/cyclin B and
25 initiating mitosis. (Sanchez et al., Science, 277:1497 (1997)). Therefore, inhibition of Chk-1 should enhance DNA damaging agents by initiating mitosis before DNA repair is complete and thereby causing tumor cell death.

SUMMARY OF THE INVENTION

It has now been found that certain 2,5-dihydro-pyrazolo[4,3-c]quinolin-4-ones are effective inhibitors of Chk-1. For example, compounds as described in Example 57 have IC₅₀ values less than 1 μM when tested in an *in vitro* assay that assesses the inhibitory activity of test compounds. Based on these discoveries, novel Chk-1 inhibitors, methods of inhibiting Chk-1 in a subject and methods of treating cancer are disclosed herein.

In one embodiment the present invention is a Chk-1 inhibitor represented by Structural Formula (I):



(I)

Ring A is optionally substituted at any one or more substitutable ring carbon atoms.

Y₁ is N or CR³.

G₂ is -H, or a C1-C8 aliphatic group optionally substituted with one or more fluoro, -OR¹², -CONR¹¹R¹², -COOR¹², cycloalkyl or phenyl, wherein the cycloalkyl and phenyl are optionally substituted with halo or alkyl.

R² is -H or a group that is cleavable *in vivo*.

R³ is -H, halogen, alkyl, haloalkyl or -V₁-R⁷, wherein V₁ is a covalent bond or a C1-C4 alkylidene optionally substituted with one or more -OR¹⁴, -NR¹⁵R¹⁶, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, or with a spiro cycloalkyl group; R⁷ is -OR¹⁴, -SR¹⁴, -CONR¹⁵R¹⁶, -NR¹⁵R¹⁶, -NHC(O)NR¹⁵R¹⁶, -CN, -COOR¹⁴, -NHC(O)H, -NHC(O)R¹⁴, -OC(O)R¹⁴, -OC(O)NR¹⁵R¹⁶, -NHC(O)-OR¹⁴, -S(O)₂NR¹⁵R¹⁶, -S(O)₂(R¹⁴), boronate, alkyl boronate, -C(=NR¹⁴)-NR¹⁵R¹⁶, -NH-C(=NR¹⁴)-NR¹⁵R¹⁶, -NH-C(=NR¹⁴)R¹⁴, an optionally substituted cycloaliphatic or non-aromatic heterocyclic group, or an optionally substituted aromatic group; R¹⁴

is -H, alkyl or an optionally substituted aromatic or aralkyl group; and R^{15} and R^{16} are independently -H, alkyl or an optionally substituted aromatic or aralkyl group; or $-NR^{15}R^{16}$ is an optionally substituted nitrogen-containing non-aromatic heterocyclic group.

5 X_1 is N, or CR^4 .

R^4 is -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, $-NO_2$, C1-C3 alkoxy, C1-C3 haloalkoxy, -CN, $-NH_2$, C1-C3 alkylamino, C1-C3 dialkylamino, $-C(O)NH_2$, $-C(O)NH(C1-C3 \text{ alkyl})$, $-C(O)N(C1-C3 \text{ alkyl})_2$, $-NHC(O)O-(C1-C3 \text{ alkyl})$, $-C(O)O-(C1-C3 \text{ alkyl})$, $-NHC(O)NH_2$, $-NHC(O)NH(C1-C3 \text{ alkyl})$, $-NHC(O)N(C1-C3 \text{ alkyl})_2$, or $-NHC(O)O-(C1-C3 \text{ alkyl})$.

Each G_1 is independently $-R^{13b}$, $-V_3-R^{13}$, $-V_3-R^{13a}$, $-T_0-T_1-V_3-R^{13}$, $-T_0-T_1-V_3-R^{13a}$, $-T_0-T_1-R^{13a}$, $-T_0-Cy-V_4-R^{13}$, $-T_0-Cy-V_4-R^{13a}$, $-T_0-Cy-T_1-V_4-R^{13}$, $-T_0-Cy-T_1-V_4-R^{13a}$, T_0-Cy-R^{13} , or $-T_0-Cy-R^{13a}$; or n is 2, one G_1 is $(-T_2-R^{200})_x$ and the other G_1 is $(-T_3-V_5-R^{50})_y$, x is 1 or 2, y is 0 or 1 and $x + y$ is 1 or 2.

15 T_0 is absent, $-CH_2-$, $-CH_2-CH_2-$, or $-CH_2-CH_2-CH_2-$.

T_1 is -O-, -S-, $-N(R^6)-$, $-S(O)-$, $-SO_2-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-N(R^6)C(O)-$, $-C(O)N(R^6)-$, $-SO_2N(R^6)-$, or $-N(R^6)SO_2-$.

T_2 is a covalent bond, -O-, -S-, $-N(R^6)-$, $-S(O)-$, $-SO_2-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-N(R^6)C(O)-$, $-C(O)N(R^6)-$, $-SO_2N(R^6)-$, or $-N(R^6)SO_2-$.

20 T_3 is a covalent bond, -O-, -NH-, $-C(O)O-$, $-C(O)-$ or $-C(O)NH-$.

Cy is an optionally substituted arylene group or an optionally substituted non-aromatic heterocyclene or non-aromatic carbocyclene group.

V_3 is an optionally substituted C1-C8 alkylidene, provided that V_3 is a C2-C8 alkylidene when T_1 is -O-, $-N(R^6)-$, $-C(O)O-$, or $-C(O)N(R^6)-$ and R^{13} is -CN, $-OR^{12}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-OC(O)R^{12}$, $-NR^{11}C(O)NR^{11}R^{12}$, $-OC(O)NR^{11}R^{12}$ or $-NR^{11}C(O)OR^{12}$, and wherein V_3 is optionally substituted with alkyl, halo, haloalkyl, alkoxy, hydroxy, $NR^{11}R^{12}$ or oxo.

V_4 is an optionally substituted bivalent C1-C8 aliphatic group provided that V_4 is a C2-C8 aliphatic group when T_1 is -O-, $-N(R^6)-$, $-C(O)O-$, or $-C(O)N(R^6)-$ and R^{13} is -CN, $-OR^{12}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-OC(O)R^{12}$, $-NR^{11}C(O)NR^{11}R^{12}$,

30

-OC(O)NR¹¹R¹² or -NR¹¹C(O)OR¹², and wherein V₄ is optionally substituted with alkyl, halo, haloalkyl, alkoxy, hydroxy, NR¹¹R¹² or oxo.

V₅ is a covalent bond or a C1-C4 alkylidene, provided that V₅ is C2-C4 alkylidene when T₃ is -O-, -NH-, -C(O)O-, or -C(O)NH- and R⁵⁰ is -CN, -OH, -NR⁵¹R⁵², -NHC(O)R⁵¹, -NHC(O)NR⁵¹R⁵², -NHC(O)OR⁵¹ or a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group wherein a C1-C4 alkylidene group represented by V₅ is optionally substituted with a spirocyclopropyl group or one or two methyl groups and wherein a C1-C4 alkylidene group represented by V₅ is optionally fused to a cyclopropyl group.

Each R⁶ is independently -H or C1-C3 alkyl.

Each R¹¹ is independently -H or a C1-C3 alkyl group.

Each R¹² is independently -H or an optionally substituted alkyl, aromatic, aralkyl, non-aromatic heterocyclic or non-aromatic heterocyclalkyl group; or -NR¹¹R¹² is an optionally substituted aromatic or non-aromatic nitrogen-containing heterocyclic group.

R¹³ is -OR¹², -CN, -COOR¹², -NR¹¹R¹², -NR¹¹CONR¹¹R¹², -NR¹¹COR¹², -NH-C(=NR¹¹)NR¹¹R¹², -N=C(NR¹¹R¹²)₂, -SO₂NR¹¹R¹², -NR¹¹SO₂R¹², -OC(O)R¹², -NR¹¹C(O)OR¹², -O-C(O)-OR¹², -OC(O)-NR¹¹R¹², -NR¹¹CO-CH(OR¹⁸)-R¹², -NR¹¹CO-CH(NR¹⁸R¹⁸)-R¹², -NR¹¹CO-(CH₂)_mCH(NR¹⁸R¹⁸)-R¹², -OC(O)-CH(OR¹⁸)-R¹², -OC(O)-CH(NR¹⁸R¹⁸)-R¹², -NR¹¹CO-C(R¹⁹R¹⁹)-OR¹², -NR¹¹CO-C(R¹⁹R¹⁹)-NR¹¹R¹², -OC(O)-C(R¹⁹R¹⁹)-OR¹², -OC(O)-C(R¹⁹R¹⁹)-NR¹¹R¹², -NR¹¹-C(R¹²)-C(O)OR¹², -NR¹¹-C(R¹²)-C(O)NR¹¹R¹², -NR¹¹-C(R¹²)CH₂OR¹², -C(O)NR¹¹R¹², -NHC(O)NR¹¹R¹², or -C(=NR¹¹)-NR¹¹R¹².

R^{13a} is an optionally substituted nitrogen-containing heteroaromatic group or a nitrogen-containing non-aromatic heterocyclic group.

R^{13b} is an optionally substituted nitrogen-containing heteroaromatic group or a nitrogen-containing non-aromatic heterocyclic group.

Each R¹⁸ is independently -H, a C1-C3 alkyl group, -C(O)H, -C(O)-(C1-C3 alkyl), -C(O)NH₂, -C(O)NH-(C1-C3 alkyl), -C(O)N-(C1-C3 alkyl)₂, -C(O)O-(C1-C3 alkyl), -S(O)₂(C1-C3 alkyl) or -NR¹⁸R¹⁸ taken together is a substituted or unsubstituted non-aromatic nitrogen-containing heterocyclic group.

Each R¹⁹ is independently -H, a C1-C3 alkyl group or -C(R¹⁹R¹⁹)- taken together is a C3-C8 cycloalkyl group.

R⁵⁰ is -CN, -OR⁵¹, -NR⁵¹R⁵², -C(O)NR⁵¹R⁵², -NHC(O)R⁵¹, -NHC(O)NR⁵¹R⁵², -NHC(O)OR⁵¹, -C(O)OR⁵¹ or an optionally substituted aromatic group or non-
5 aromatic heterocyclic group.

Each R⁵¹ and each R⁵² are independently -H or C1-C3 alkyl or -NR⁵¹R⁵² is an optionally substituted non-aromatic heterocyclic group.

R²⁰⁰ is an optionally substituted C2-C4 alkenyl or C2-C4 alkynyl group.

m is 1 or 2.

10 n is 1 or 2.

Another embodiment of the present invention is a method of treating cancer in a subject. The method comprises administering to the subject an effective amount of a Chk-1 inhibitor disclosed herein.

Yet another embodiment of the present invention is a method of inhibiting
15 Chk-1 in a subject in need of such treatment. The method comprises administering to the subject an effective amount of a Chk-1 inhibitor disclosed herein.

Yet another embodiment of the present invention is a method of treating a proliferative disorder in a subject comprising administering an effective amount of a Chk-1 inhibitor disclosed herein.

20 Yet another embodiment of the present invention is a method of inhibiting Chk-1 in a cell in a subject in need of such treatment by contacting the cell with an effective amount of a Chk-1 inhibitor disclosed herein.

Yet another embodiment of the present invention is a method of inhibiting Chk-1 in a cell *in vitro* by contacting the cell with an effective amount of a Chk-1
25 inhibitor disclosed herein.

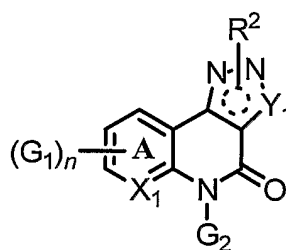
Yet another embodiment of the present invention is a pharmaceutical composition comprising a Chk-1 inhibitor disclosed herein and a pharmaceutically effective excipient, carrier or diluent. The pharmaceutical compositions can be used in therapy, e.g., to inhibit Chk-1 activity in a subject in need of such inhibition or to
30 treat a subject with cancer.

Yet another embodiment of the present invention is the use of a Chk-1 inhibitor disclosed herein for the manufacture of a medicament for inhibiting Chk-1 in a subject in need of such inhibition or for treating a subject with cancer.

The compounds disclosed herein are effective inhibitors of Chk-1. They are therefore expected to be effective in treating subjects with cancer and enhancing the effectiveness of many current anti-cancer therapies, including radiation therapy and anti-cancer agents that exert their cytotoxic activity by damaging the genetic material of cancer cells and inhibiting cellular replication. In addition, the disclosed Chk-1 inhibitors, when used in combination with current anti-cancer therapies are expected to be effective against multidrug resistant cancers.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to Chk-1 inhibitors represented by Structural Formula (I) and to novel methods of therapy utilizing the Chk-1 inhibitors represented by Structural Formula (I):



(I)

The values and preferred values for the values for the variables in Structural Formula (I) are as described below.

Ring A is substituted with one or two G_1 . Additionally, Ring A is optionally substituted at any one or more substitutable ring carbon atoms. Suitable Ring A substituents include those described below in the section describing suitable aryl group substituents generally. Preferred substituents are represented by R^5 and are independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, $-\text{NO}_2$, C1-C3 alkoxy, C1-C3 haloalkoxy, $-\text{CN}$, $-\text{NH}_2$, C1-C3 alkylamino, C1-C3 dialkylamino, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C1-C3 alkyl})_2$, $-\text{NHC}(\text{O})\text{O}-(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{O}-$

(C1-C3 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-C3 alkyl), -NHC(O)N(C1-C3 alkyl)₂, or -NHC(O)O-(C1-C3 alkyl). Preferably, each R⁵ is independently -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy. More preferably, each R⁵ is independently -H, halogen, -CH₃, halomethyl, -OCH₃, or haloalkoxy;

5 Y₁ is N or CR³. Preferably, Y₁ is CR³.

X₁ is N, or CR⁴. Preferably, X₁ is CR⁴.

R² is -H or a group that is cleavable *in vivo*. Preferably R² is -H.

R³ is -H, halogen, alkyl, haloalkyl or -V₁-R⁷, wherein V₁ is a covalent bond or a C1-C4 alkylidene optionally substituted with one or more -OR¹⁴, -NR¹⁵R¹⁶, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, or with a spiro cycloalkyl group; R⁷ is -OR¹⁴,
 10 -SR¹⁴, -CONR¹⁵R¹⁶, -NR¹⁵R¹⁶, -NHC(O)NR¹⁵R¹⁶, -CN, -COOR¹⁴, -NHC(O)H, -NHC(O)R¹⁴, -OC(O)R¹⁴, -OC(O)NR¹⁵R¹⁶, -NHC(O)-OR¹⁴, -S(O)₂NR¹⁵R¹⁶, -S(O)₂(R¹⁴), boronate, alkyl boronate, -C(=NR¹⁴)-NR¹⁵R¹⁶, -NH-C(=NR¹⁴)NR¹⁵R¹⁶, -NH-C(=NR¹⁴)R¹⁴, an optionally substituted cycloaliphatic or non-aromatic
 15 heterocyclic group, or an optionally substituted aromatic group (or carbocyclic or heteroaromatic group). Preferably, R³ is -H, methyl, ethyl, n-propyl, iso-propyl, C1-C3 haloalkyl, or V₁-R⁷, wherein V₁ is a covalent bond or a C1-C2 alkylidene optionally substituted with one or two methyl groups or with a spiro cyclopropyl group; R⁷ is -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -CONH₂, -CONHCH₃,
 20 -CON(CH₃)₂, -CN, -COOH, -COOCH₃, -NHC(O)H, -NHC(O)CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)NH₂, -OC(O)NHCH₃, C3-C6 cycloalkyl, furyl, tetrahydrofuryl, N-piperazinyl, N'-alkyl-N-piperazinyl, N'-acyl-N-piperazinyl, N-pyrrolidyl, N-piperidinyl or N-morpholinyl; additional values for R³ include -OC(O)N(CH₃)₂, -NHC(O)NH₂, -NHC(O)NH(CH₃), -NHC(O)N(CH₃)₂, -NHC(O)OCH₃. More
 25 preferably, R³ is methyl or ethyl; or R³ is V₁-R⁷, wherein V₁ is a C1-C2 alkylidene and R⁷ is -OH or -OCH₃; or V₁ is a covalent bond and R⁷ is cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl.

R⁴ is -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, -NO₂, C1-C3 alkoxy, C1-C3 haloalkoxy, -CN, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂,
 30 -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂, -NHC(O)O-(C1-C3 alkyl), -C(O)O-(C1-C3 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-C3 alkyl), -NHC(O)N(C1-C3 alkyl)₂, or -NHC(O)O-(C1-C3 alkyl). Preferably, R⁴ is -H, C1-C3 alkyl, C1-C3 haloalkyl,

- halogen, hydroxy, C1-C3 alkoxy, C1-C3 haloalkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -NHC(O)H, -NHC(O)(C1-C3 alkyl), -C(O)NH₂, -C(O)NH(C1-C3 alkyl) or -C(O)N(C1-C3 alkyl)₂. More preferably, R⁴ is -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy. Alternatively, R⁴ is -H, halogen, -CH₃, halomethyl, -OCH₃, or haloalkoxy.

Each G₁ is independently -R^{13b}, -V₃-R¹³, -V₃-R^{13a}, -T₀-T₁-V₃-R¹³, -T₀-T₁-V₃-R^{13a}, -T₀-T₁-R^{13a}, -T₀-Cy-V₄-R¹³, -T₀-Cy-V₄-R^{13a}, -T₀-Cy-T₁-V₄-R¹³, -T₀-Cy-T₁-V₄-R^{13a}, T₀-Cy-R¹³, or -T₀-Cy-R^{13a}. Additional values for G₁ include (-T₂-R²⁰⁰)_x and (-T₃-V₅-R⁵⁰)_y, where x is 1 or 2, y is 0 or 1 and x + y is 1 or 2.

- In one preferred embodiment, G₁ is -R^{13b}. Alternatively, G₁ is -V₃-R¹³, -V₃-R^{13a}, -T₀-T₁-V₃-R¹³, -T₀-T₁-V₃-R^{13a}, or -T₀-T₁-R^{13a}. In another alternative, G₁ is -T₀-Cy-V₄-R¹³, -T₀-Cy-V₄-R^{13a}, -T₀-Cy-T₁-V₄-R¹³, -T₀-Cy-T₁-V₄-R^{13a}, T₀-Cy-R¹³, or -T₀-Cy-R^{13a}.

- G₂ is -H, or a C1-C8 aliphatic group optionally substituted with one or more fluoro, -OR¹², -CONR¹¹R¹², -COOR¹², cycloalkyl or phenyl, wherein the cycloalkyl and phenyl are optionally substituted with halo or alkyl. Preferably, G₂ is -H, or a C1-C6 aliphatic group optionally substituted with one or more, fluoro, -OR¹², -CONR¹¹R¹², -COOR¹², cycloalkyl or phenyl, wherein the cycloalkyl and phenyl are optionally substituted with halo or alkyl. Preferably, the cycloalkyl and phenyl substituents on G₂ are unsubstituted. More preferably, G₂ is C1-C4 alkyl, wherein the alkyl is optionally substituted with fluoro or G₂ is a C3-C8 cycloalkyl wherein the cycloalkyl is optionally substituted with halo or alkyl.

In an alternative embodiment, G₂ is -W₁-R¹.

- R¹ is -H, -CONR¹¹R¹², -COOR¹², fluoro, or a cycloalkyl wherein the cycloalkyl is optionally substituted with halo or alkyl and W₁ is a linear C1-C6 alkylidene chain; or R¹ is -OR¹² and W₁ is a linear C2-C6 alkylidene group, wherein the alkylidene group represented by W₁ is optionally substituted with one or more -CH₃ or fluoro groups; or -W₁-R¹ is -H. More preferably, W₁ is a linear C1-C4 alkylidene chain optionally substituted with one or more -CH₃ or fluoro groups and R¹ is -H, fluoro or a cycloalkyl wherein the cycloalkyl is optionally substituted with halo or alkyl.

T₀ is absent, -CH₂-, -CH₂-CH₂-, or -CH₂-CH₂-CH₂-. Preferably T₀ is absent.

T₁ is -O-, -S-, -N(R⁶)-, -S(O)-, -SO₂-, -C(O)-, -OC(O)-, -C(O)O-, -N(R⁶)C(O)-, -C(O)N(R⁶)-, -SO₂N(R⁶)-, or -N(R⁶)SO₂. Preferably T₁ is -O- or -N(R⁶);

5 T₂ is a covalent bond, -O-, -S-, -N(R⁶)-, -S(O)-, -SO₂-, -C(O)-, -OC(O)-, -C(O)O-, -N(R⁶)C(O)-, -C(O)N(R⁶)-, -SO₂N(R⁶)-, or -N(R⁶)SO₂-. Preferably T₂ is a covalent bond, -S(O)-, -SO₂-, -C(O)-, -OC(O)-, -N(R⁶)C(O)-, or -N(R⁶)SO₂-. More preferably, T₂ is a covalent bond.

T₃ is a covalent bond, -O-, -NH-, -C(O)O-, -C(O)- or -C(O)NH-. Preferably, T₃ is a covalent bond -O- or -N(R⁶). More preferably, T₃ is a covalent bond.

10 T₁₁ is -S(O)-, -S(O)₂-, -C(O)-, -C(O)O-, -C(O)N(R⁶)-, or -SO₂N(R⁶)-. Preferably, T₁₁ is -C(O)-, -C(O)N(R⁶)-, or -SO₂N(R⁶)-.

Cy is an optionally substituted arylene group or an optionally substituted non-aromatic heterocyclene or non-aromatic carbocyclene group. Preferably, Cy is an optionally substituted phenylene, pyrrolylene, thienylene, furanylene, imidazolylene, triazolylene, tetrazolylene, oxazolylene, isoxazolylene, oxadiazolylene, pyrazolylene, 15 pyridinylene, pyrimidinylene, pyrazinylene, thiazolylene, cyclopropylene, cyclopentylene, cyclohexylene, cycloheptylene, piperidinylene, piperazinylene, pyrrolidinylene, pyrazolidinylene, imidazolidinylene, tetrahydrofuranylene, tetrahydrothienylene, isooxazolidinylene, oxazolidinylene, isothiazolidinylene, thiazolidinylene, oxathiolanylene, dioxolanylene, or dithiolanylene. More preferably, Cy is [2,5]thienylene or [2,5]furanylene. Suitable substituents for an arylene Cy group include those described below in the section describing aromatic group substituents generally; and suitable substituents for non-aromatic heterocyclene and carbocyclene Cy groups include those described below in the sections describing 20 suitable substituents for a non-aromatic heterocyclic group and aliphatic groups generally. Preferred substituents for a substitutable aromatic ring carbon in a group represented by Cy and a substitutable ring carbon or ring nitrogen atom in a non-aromatic ring represented by Cy are as described below for R^{13a} and R^{13b}.

V₃ is an optionally substituted C1-C8 alkylidene, provided that V₃ is a C2-C8 alkylidene when T₁ is -O-, -N(R⁶)-, -C(O)O-, or -C(O)N(R⁶)- and R¹³ is -CN, -OR¹², -NR¹¹R¹², -NR¹¹C(O)R¹², -OC(O)R¹², -NR¹¹C(O)NR¹¹R¹², -OC(O)NR¹¹R¹² or -NR¹¹C(O)OR¹², and wherein V₃ is optionally substituted with alkyl, halo, haloalkyl, 30

alkoxy, hydroxy, $\text{NR}^{11}\text{R}^{12}$ or oxo. Preferably, V_3 is C1-C4 alkylidene. More preferably, V_3 is C1-C2 alkylidene.

V_4 is an optionally substituted bivalent C1-C8 aliphatic group provided that V_4 is a C2-C8 aliphatic group when T_1 is -O-, $-\text{N}(\text{R}^6)-$, $-\text{C}(\text{O})\text{O}-$, or $-\text{C}(\text{O})\text{N}(\text{R}^6)-$ and R^{13} is -CN, $-\text{OR}^{12}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{OC}(\text{O})\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{OC}(\text{O})\text{NR}^{11}\text{R}^{12}$ or $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{12}$, and wherein V_4 is optionally substituted with alkyl, halo, haloalkyl, alkoxy, hydroxy, $\text{NR}^{11}\text{R}^{12}$ or oxo. Preferably, V_4 is C1-C4 alkylidene, alkenylidene or alkynylidene group optionally substituted with C1-C3 alkyl. More preferably, V_4 is C1-C4 alkylidene. Even more preferably, V_4 is C1-C2 alkylidene.

V_5 is a covalent bond or a C1-C4 alkylidene, provided that V_5 is C2-C4 alkylidene when T_3 is -O-, -NH-, $-\text{C}(\text{O})\text{O}-$, or $-\text{C}(\text{O})\text{NH}-$ and R^{50} is -CN, -OH, $-\text{NR}^{51}\text{R}^{52}$, $-\text{NHC}(\text{O})\text{R}^{51}$, $-\text{OC}(\text{O})\text{R}^{51}$, $-\text{NHC}(\text{O})\text{NR}^{51}\text{R}^{52}$, $-\text{OC}(\text{O})\text{NR}^{51}\text{R}^{52}$, -NHC(O)OR⁵¹ or a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group. The C1-C4 alkylidene group represented by V_5 is optionally substituted with a spirocyclopropyl group or one or two methyl groups and the C1-C4 alkylidene group represented by V_5 is optionally fused to a cyclopropyl group.

V_6 is a C1-C4 alkylidene, wherein V_6 is optionally substituted with alkyl, halo, haloalkyl, alkoxy, hydroxy, $\text{NR}^{11}\text{R}^{12}$ or oxo. Preferably, V_6 is a C1-C4 alkylidene group optionally substituted with C1-C3 alkyl. More preferably, V_6 is C1-C4 alkylidene. Even more preferably, V_6 is C1-C2 alkylidene.

Each R^6 is independently -H or C1-C3 alkyl.

Each R^{11} is independently -H or a C1-C3 alkyl group.

Each R^{12} is independently -H, or an optionally substituted alkyl, aryl, aralkyl, non-aromatic heterocyclic or non-aromatic heterocyclalkyl group. Alternatively, R^{12} is -H, an optionally substituted alkyl, or an optionally substituted non-aromatic heterocyclic group. Preferably, R^{12} is H, an optionally substituted alkyl, imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrazinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, pyranziny, thiomorpholinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl. More

preferably R^{12} is $-H$, an optionally substituted alkyl or an optionally substituted piperidinyl ring;

$NR^{11}R^{12}$ is an optionally substituted aromatic or non-aromatic nitrogen-containing heterocyclic group. Preferably, $-NR^{11}R^{12}$ is imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrazinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, pyranzyl, thiomorpholinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl. More preferably $-NR^{11}R^{12}$ is pyrrolidinyl, piperidinyl, piperazinyl, tetrahydroisoquinolinyl, morpholinyl or pyrazolyl.

R^{13} is $-OR^{12}$, $-CN$, $-COOR^{12}$, $-NR^{11}R^{12}$, $-NR^{11}CONR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NH-C(=NR^{11})NR^{11}R^{12}$, $-N=C(NR^{11}R^{12})_2$, $-SO_2NR^{11}R^{12}$, $-NR^{11}SO_2R^{12}$, $-OC(O)R^{12}$, $-NR^{11}C(O)OR^{12}$, $-O-C(O)-OR^{12}$, $-OC(O)-NR^{11}R^{12}$, $-NR^{11}CO-CH(OR^{18})-R^{12}$, $-NR^{11}CO-CH(NR^{18}R^{18})-R^{12}$, $-NR^{11}CO-(CH_2)_mCH(NR^{18}R^{18})-R^{12}$, $-OC(O)-CH(OR^{18})-R^{12}$, $-OC(O)-CH(NR^{18}R^{18})-R^{12}$, $-NR^{11}CO-C(R^{19}R^{19})-OR^{12}$, $-NR^{11}CO-C(R^{19}R^{19})-NR^{11}R^{12}$, $-OC(O)-C(R^{19}R^{19})-OR^{12}$, $-OC(O)-C(R^{19}R^{19})-NR^{11}R^{12}$, $-NR^{11}-C(R^{12})-C(O)OR^{12}$, $-NR^{11}-C(R^{12})-C(O)NR^{11}R^{12}$, $-NR^{11}-C(R^{12})CH_2OR^{12}$, $-C(O)NR^{11}R^{12}$, $-NHC(O)NR^{11}R^{12}$, or $-C(=NR^{11})-NR^{11}R^{12}$.

In one preferred embodiment, R^{13} is $-CN$, $-OR^{12}$, $-NR^{11}R^{12}$, $-NHC(O)R^{12}$, $-NHC(O)OR^{12}$, $-NHC(O)NR^{11}R^{12}$, $-NHC(O)OR^{12}$, or $-OC(O)R^{12}$. Preferably, R^{13} is $-NR^{11}R^{12}$.

In another preferred embodiment, R^{13} is $-OH$, $-CN$, C1-C3 alkoxy, NH_2 , C1-C3 alkylamino, C1-C3 dialkylamino, C1-C3 hydroxyalkyl, or C1-C3 haloalkylamino. Preferably, R^{13} is NH_2 , C1-C3 alkylamino, or C1-C3 dialkylamino.

In yet another preferred embodiment, R^{13} is $-OH$, $-CN$, C1-C3 alkoxy, or $NR^{11}R^{12}$, where R^{11} is $-H$ or a C1-C3 alkyl group and R^{12} is $-H$, an optionally substituted alkyl, or an optionally substituted non-aromatic heterocyclic group, or $NR^{11}R^{12}$ is an optionally substituted aromatic or non-aromatic nitrogen containing heterocyclic group. Preferably, R^{13} is NH_2 , C1-C3 alkylamino, or C1-C3 dialkylamino. More preferably, R^{13} is $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NH(CH_2CH_3)$, or $-N(CH_2CH_3)_2$.

- R^{13a} and R^{13b} are independently an optionally substituted nitrogen-containing heteroaromatic group or a nitrogen-containing non-aromatic heterocyclic group. Suitable substituents for a nitrogen-containing heteroaromatic group or nitrogen-containing non-aromatic heterocyclic group represented by R^{13a} or R^{13b} include those
- 5 described below for nitrogen-containing heteroaromatic groups generally and nitrogen-containing non-aromatic heterocyclic groups generally. Preferably, each substitutable ring nitrogen atom of the group represented by R^{13a} or R^{13b} is optionally substituted with a C1-C3 alkyl, C1-C3 acyl, C1-C3 alkylsulfonyl, -OC(O)N(R')₂, -NR'C(O)OR', or -NR'C(O)N(R')₂ group; each substitutable ring carbon atom of a
- 10 non-aromatic ring in the group represented by R^{13a} or R^{13b} is optionally substituted with a C1-C3 alkyl group, hydroxy, fluoro, oxo, -C(O)OH, -C(O)O(C1-C3 alkyl), C1-C3 alkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, amido, C1-C3 alkylamido, C1-C3 fluoroalkylamido, amino (C1-C3) alkyl, (C1-C3)alkylamino(C1-C3)alkyl, (C1-C3)dialkylamino(C1-C3)alkyl, hydroxy(C1-C3)alkyl, (C1-C3)alkoxy(C1-
- 15 C3)alkyl; each substitutable ring carbon atom of an aromatic ring in the group represented by R^{13a} or R^{13b} is optionally substituted with halo, hydroxy, cyano, C1-C3 alkyl, C1-C3 fluoroalkyl, C1-C3 alkoxy, C1-C3 fluoroalkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), C(O)N(C1-C3 alkyl)₂, -NR'CO(C1-C3 alkyl), -NR'CO(C1-C3 haloalkyl), -NR'C(O)O(C1-C3 alkyl),
- 20 -C(O)O(C1-C3 alkyl), -NR'C(O)NH₂, -NR'C(O)NH(C1-C3 alkyl), -NR'C(O)N(C1-C3 alkyl)₂, -NR'C(O)O-(C1-C3 alkyl) -SH, -S(C1-C3 alkyl), -NO₂, -S(O)₂H, -S(O)₂(C1-C3 alkyl), -SO₂N(R')₂, -S(O)H, -S(O)(C1-C3 alkyl), -NR'S(O)₂NH₂, -NR'S(O)₂NH(C1-C3 alkyl), -NR'S(O)₂N(C1-C3 alkyl)₂, -NR'S(O)₂H or -NR'S(O)₂(C1-C3 alkyl); and each R' is hydrogen or a C1-C3 alkyl group.
- 25 In preferred embodiment, R^{13a} and R^{13b} are independently an optionally substituted non-aromatic heterocyclic group selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azetidiny, tetrahydrofuranyl, oxazolidinyl, thiomorpholinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and azabicyclopentyl, azabicyclohexyl, azabicycloheptyl, azabicyclooctyl,
- 30 azabicyclononyl, azabicyclodecyl, diazabicyclohexyl, diazabicycloheptyl, diazabicyclooctyl, diazabicyclononyl, or diazabicyclodecyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl,

triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. More preferably, R^{13a} and R^{13b} are independently an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, 5 *N*-thiomorpholinyl, *N*-azetidiny, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl and 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl or an optionally substituted 10 heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl.

In one embodiment, R^{13a} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, 15 *N*-piperazinyl, *N*-azetidiny, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl. In certain preferred 20 embodiments, R^{13a} is *N*-pyrrolidinyl, 2,5-dimethyl-*N*-pyrrolidinyl, *N*-piperidinyl, *N*-methyl-*N*-piperazinyl, *N*-tetrahydroisoquinolinyl, *N*-morpholinyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl.

In one embodiment, R^{13b} is an optionally substituted nitrogen-containing heteroaromatic group. More preferably, R^{13b} is an optionally substituted imidazolyl, 25 pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl or thiadiazolyl. More preferably R^{13b} is pyrazolyl or *N*-methyl-pyrazolyl.

R^{14} is -H, alkyl or an optionally substituted aromatic or aralkyl group; and R^{15} and R^{16} are independently -H, alkyl or an optionally substituted aromatic or 30 aralkyl group; or - $NR^{15}R^{16}$ is an optionally substituted nitrogen-containing non-aromatic heterocyclic group. Preferably R^{14} is -H or alkyl. Preferably, - $NR^{15}R^{16}$ is pyrrolidinyl, piperidinyl, morpholinyl, pyrazinyl, thiomorpholinyl, pyrazinyl,

thiomorpholinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl.

Each R^{18} is independently -H, a C1-C3 alkyl group, -C(O)H, -C(O)-(C1-C3 alkyl), -C(O)NH₂, -C(O)NH-(C1-C3 alkyl), -C(O)N-(C1-C3 alkyl)₂, -C(O)O-(C1-C3 alkyl), -S(O)₂(C1-C3 alkyl) or -NR¹⁸R¹⁸ taken together is a substituted or
 5 unsubstituted non-aromatic nitrogen-containing heterocyclic group. Preferably, each R^{18} is independently -H, a C1-C3 alkyl group, and -NR¹⁸R¹⁸ is pyrrolidinyl, piperidinyl, morpholinyl, pyrazinyl, thiomorpholinyl, pyrazinyl, thiomorpholinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl.

Each R^{19} is independently -H, a C1-C3 alkyl group or -C(R¹⁹R¹⁹)- taken
 10 together is a C3-C8 cycloalkyl group.

Each R^{20} is independently -H or C1-C3 alkyl.

R^{50} is -CN, -OR⁵¹, -NR⁵¹R⁵², -C(O)NR⁵¹R⁵², -NHC(O)R⁵¹, -NHC(O)NR⁵¹R⁵²,
 -NHC(O)OR⁵¹, -C(O)OR⁵¹ or an optionally substituted aromatic group or non-
 aromatic heterocyclic group. Preferably, R^{50} is -CN, -OR⁵¹, -NR⁵¹R⁵², -C(O)NR⁵¹R⁵²,
 15 -NHC(O)R⁵¹, -NHC(O)NR⁵¹R⁵², -NHC(O)OR⁵¹, -C(O)OR⁵¹ or an optionally
 substituted aromatic group or non-aromatic heterocyclic group. More preferably, R^{50}
 is -OH, -OCH₃, -CN, -NH₂, -NHCH₃, -N(CH₃)₂, -NHCH₂CH₃,
 -NH(CH₃)CH₂CH₃, -N(CH₂CH₃)₂, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂,
 -NHC(O)H, -NHC(O)CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)NH₂, -OC(O)NHCH₃,
 20 -OC(O)N(CH₃)₂, -NHC(O)NH₂, -NHC(O)NHCH₃, -NHC(O)N(CH₃)₂,
 -NHC(O)OCH₃, piperazinyl, N-piperazinyl, N'-alkyl-N-piperazinyl, N'-acyl-N-
 piperazinyl, N-alkyl-piperazinyl, N-acyl-piperazinyl, pyrrolidinyl, N-pyrrolidyl, N-
 alkyl-pyrrolidyl, N-acyl-pyrrolidyl, piperidinyl, N-piperidinyl, N-alkyl-piperidinyl,
 N-acyl-piperidinyl or N-morpholinyl, imidazolyl, N-imidazolyl, pyrrolyl, N-pyrrolyl,
 25 pyridyl or phenyl optionally substituted with alkyl, -OH, -NH₂, -NHCH₃, -N(CH₃)₂,
 -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, -NHC(O)H, -NHC(O)CH₃, -OC(O)H,
 -OC(O)CH₃, -OC(O)NH₂, -OC(O)NHCH₃, -OC(O)N(CH₃)₂, -NHC(O)NH₂,
 -NHC(O)NH(CH₃), -NHC(O)N(CH₃)₂, -NHC(O)OCH₃, alkoxy, haloalkyl,
 haloalkoxy, -CN, NO₂ or halogen. Even more preferably, R^{50} is -OH, -CN, C1-C3
 30 alkoxy, NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, C1-C3 hydroxyalkyl, or C1-C3
 haloalkylamino. Preferably, R^{50} is NH₂, C1-C3 alkylamino, or C1-C3 dialkylamino.
 Suitable substituents for the nitrogen-containing heteroaromatic group or nitrogen-

containing non-aromatic heterocyclic group represented by R^{50} are as described below for nitrogen-containing heteroaromatic groups generally and nitrogen-containing non-aromatic heterocyclic groups generally.

Each R^{51} and each R^{52} are independently -H or C1-C3 alkyl or $-NR^{51}R^{52}$ is an optionally substituted non-aromatic heterocyclic group. Preferably, each R^{51} or R^{52} is independently -H, a C1-C3 alkyl group, and, $-NR^{51}R^{52}$ is pyrrolidinyl, piperidinyl, morpholinyl, pyrazinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, pyranziny, thiomorpholinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl.

R^{60} is $-OR^{12}$, $-CN$, $-COOR^{12}$, $-NR^{11}R^{12}$, $-NR^{11}CONR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NH-C(=NR^{11})NR^{11}R^{12}$, $-N=C(NR^{11}R^{12})_2$, $-SO_2NR^{11}R^{12}$, $-NR^{11}SO_2R^{12}$, $-OC(O)R^{12}$, $-NR^{11}C(O)OR^{12}$, $-O-C(O)-OR^{12}$, $-OC(O)-NR^{11}R^{12}$, $-NR^{11}CO-CH(OR^{62})-R^{12}$, $-NR^{11}CO-CH(NR^{62}R^{62})-R^{12}$, $-NR^{11}CO-(CH_2)_zCH(NR^{62}R^{62})-R^{12}$, $-OC(O)-CH(OR^{62})-R^{12}$, $-OC(O)-CH(NR^{62}R^{62})-R^{12}$, $-NR^{11}CO-C(R^{62}R^{63})-OR^{12}$, $-NR^{11}CO-C(R^{63}R^{63})-NR^{11}R^{12}$, $-OC(O)-C(R^{63}R^{63})-OR^{12}$, $-OC(O)-C(R^{63}R^{63})-NR^{11}R^{12}$, $-NR^{11}-C(R^{12})-C(O)OR^{12}$, $-NR^{11}-C(R^{12})-C(O)NR^{11}R^{12}$, $-NR^{11}-C(R^{12})CH_2OR^{12}$, $-C(O)NR^{11}R^{12}$, $-NHC(O)NR^{11}R^{12}$, or $-C(=NR^{11})-NR^{11}R^{12}$.

In one preferred embodiment, R^{60} is $-CN$, $-OR^{12}$, $-NR^{11}R^{12}$, $-NHC(O)R^{12}$, $-NHC(O)OR^{12}$, $-NHC(O)NR^{11}R^{12}$, $-NHC(O)OR^{12}$, or $-OC(O)R^{12}$.

In another preferred embodiment, R^{60} is $-OH$, $-CN$, C1-C3 alkoxy, NH_2 , C1-C3 alkylamino, C1-C3 dialkylamino, C1-C3 hydroxyalkyl, or C1-C3 haloalkylamino. Preferably, R^{60} is NH_2 , C1-C3 alkylamino, or C1-C3 dialkylamino.

In yet another preferred embodiment, R^{60} is $-OH$, $-CN$, C1-C3 alkoxy, or $NR^{11}R^{12}$, where R^{11} is -H or a C1-C3 alkyl group and R^{12} is -H, an optionally substituted alkyl, or an optionally substituted non-aromatic heterocyclic group, or $NR^{11}R^{12}$ is an optionally substituted aromatic or non-aromatic nitrogen containing heterocyclic group. Preferably, R^{60} is NH_2 , C1-C3 alkylamino, or C1-C3 dialkylamino. More preferably, R^{60} is $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NH(CH_2CH_3)$, or $-N(CH_2CH_3)_2$.

R^{61} is an optionally substituted nitrogen-containing heteroaromatic group or a nitrogen-containing non-aromatic heterocyclic group. Suitable substituents for a nitrogen-containing non-aromatic heteroaromatic group or nitrogen-containing non-aromatic heterocyclic group represented by R^{60} are as described below for nitrogen

- containing heteroaromatic groups generally and nitrogen-containing non-aromatic heterocyclic groups generally. Preferably, each substitutable ring nitrogen atom of the group represented by R^{61} is optionally substituted with a C1-C3 alkyl, C1-C3 acyl, C1-C3 alkylsulfonyl, $-OC(O)N(R')_2$, $-NR'C(O)OR'$, or $-NR'C(O)N(R')_2$
- 5 group; each substitutable ring carbon atom of a non-aromatic ring in the group represented by R^{61} is optionally substituted with a C1-C3 alkyl group, hydroxy, fluoro, oxo, $-C(O)OH$, $-C(O)O(C1-C3 \text{ alkyl})$, C1-C3 alkoxy, $-NH_2$, C1-C3 alkylamino, C1-C3 dialkylamino, amido, C1-C3 alkylamido, C1-C3 fluoroalkylamido, amino (C1-C3) alkyl, (C1-C3)alkylamino(C1-C3)alkyl,
- 10 (C1-C3)dialkylamino(C1-C3)alkyl, hydroxy(C1-C3)alkyl, (C1-C3)alkoxy(C1-C3)alkyl; each substitutable ring carbon atom of an aromatic ring in the group represented by R^{61} is optionally substituted with halo, hydroxy, cyano, C1-C3 alkyl, C1-C3 fluoroalkyl, C1-C3 alkoxy, C1-C3 fluoroalkoxy, $-NH_2$, C1-C3 alkylamino, C1-C3 dialkylamino, $-C(O)NH_2$, $-C(O)NH(C1-C3 \text{ alkyl})$, $C(O)N(C1-C3 \text{ alkyl})_2$,
- 15 $-NR'CO(C1-C3 \text{ alkyl})$, $-NR'CO(C1-C3 \text{ haloalkyl})$, $-NR'C(O)O(C1-C3 \text{ alkyl})$, $-C(O)O(C1-C3 \text{ alkyl})$, $-NR'C(O)NH_2$, $-NR'C(O)NH(C1-C3 \text{ alkyl})$, $-NR'C(O)N(C1-C3 \text{ alkyl})_2$, $-NR'C(O)O-(C1-C3 \text{ alkyl})-SH$, $-S(C1-C3 \text{ alkyl})$, $-NO_2$, $-S(O)_2H$, $-S(O)_2(C1-C3 \text{ alkyl})$, $-SO_2N(R')_2$, $-S(O)H$, $-S(O)(C1-C3 \text{ alkyl})$, $-NR'S(O)_2NH_2$, $-NR'S(O)_2NH(C1-C3 \text{ alkyl})$, $-NR'S(O)_2N(C1-C3 \text{ alkyl})_2$, $-NR'S(O)_2H$ or -
- 20 $NR'S(O)_2(C1-C3 \text{ alkyl})$; and each R' is hydrogen or a C1-C3 alkyl group.

- In a preferred embodiment, R^{61} is an optionally substituted non-aromatic heterocyclic group selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azetidiny, tetrahydrofuranyl, oxazolidinyl, thiomorpholinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl and azabicyclopentanyl, azabicyclohexanyl,
- 25 azabicycloheptanyl, azabicyclononanyl, azabicyclodecanyl, diazabicyclohexanyl, diazabicycloheptanyl, diazabicyclooctanyl, diazabicyclononanyl, or diazabicyclodecanyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl
- 30 and thiadiazolyl.

In a preferred embodiment, R^{61} is an optionally substituted non-aromatic heterocyclic group selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl,

azetidiny, tetrahydrofuranyl, oxazolidiny, thiomorpholinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl, or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, 5 isothiazolyl, thiadiazolyl, azabicyclopentanyl, azabicyclohexanyl, azabicycloheptanyl, azabicyclononanyl, azabicyclodecanyl, diazabicyclohexanyl, diazabicycloheptanyl, diazabicyclooctanyl, diazabicyclononanyl, or diazabicyclodecanyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, 10 pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl. More preferably, R⁶¹ is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-thiomorpholinyl, *N*-azetidiny, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, 15 tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl and *N*-tetrahydroisoquinolinyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl or an optionally substituted 20 heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl.

In one preferred embodiment, R⁶¹ is an optionally substituted non-aromatic 25 heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-azetidiny, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl, 3-oxo-*N*- 30 8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl. In a certain preferred embodiment, R⁶¹ is *N*-pyrrolidinyl, 2,5-dimethyl-*N*-pyrrolidinyl, *N*-piperidinyl,

*N*⁷-methyl-*N*-piperazinyl, *N*-tetrahydroisoquinolyl, *N*-morpholynyl 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl.

Each R⁶² is independently -H, a C1-C3 alkyl group, -C(O)H, -C(O)-(C1-C3 alkyl), -C(O)NH₂, -C(O)NH-(C1-C3 alkyl), -C(O)N-(C1-C3 alkyl)₂, -C(O)O-(C1-C3 alkyl), -S(O)₂(C1-C3 alkyl) or -NR⁶²R⁶² taken together is a substituted or unsubstituted non-aromatic nitrogen-containing heterocyclic group. Preferably, each R⁶² is independently -H, a C1-C3 alkyl group, and, -NR⁶²R⁶² is pyrrolidinyl, piperidinyl, morpholynyl, pyrazinyl, thiomorpholynyl, pyrrolidinyl, piperidinyl, pyranziny, thiomorpholynyl, tetrahydroquinolyl or tetrahydroisoquinolyl.

Each R⁶³ is independently -H, a C1-C3 alkyl group or -C(R⁶³R⁶³)- taken together is a C3-C8 cycloalkyl group.

R²⁰⁰ is an optionally substituted C2-C4 alkenyl or C2-C4 alkynyl group. In one embodiment, R²⁰⁰ is -C≡CR²⁰¹, -CH=CHR²⁰¹, -C≡C-(C(R²⁰R²⁰))_pR²⁰², or -CH=CH-(C(R²⁰R²⁰))_pR²⁰². Preferably R²⁰⁰ is -C≡C-(C(R²⁰R²⁰))_pR²⁰² or -C=C-(C(R²⁰R²⁰))_pR²⁰². More preferably R²⁰⁰ is -C≡C-(C(R²⁰R²⁰))_pR²⁰². In another embodiment, R²⁰⁰ is -C≡C-R²⁰³ or -C=CHR²⁰³.

R²⁰¹ is -H, alkyl, haloalkyl, hydroxyalkyl, CO₂R⁵¹, or an optionally substituted aromatic group or non-aromatic heterocyclic group. Preferably, R²⁰¹ is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholynyl, *N*-piperazinyl, *N*-azetidynyl, *N*-thiomorpholynyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholynyl, 2-azetidynyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholynyl, 3-thiomorpholynyl, 3-azetidynyl, 4-piperidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, *N*-tetrahydroquinolyl, *N*-tetrahydroisoquinolyl 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl.

R²⁰² is -H, -CN, -OR⁵¹, -OC(O)NR⁵¹R⁵², -OC(O)R⁵¹, -NR⁵¹R⁵², -C(O)NR⁵¹R⁵², -NR⁵¹C(O)R⁵¹, -NR⁵¹C(O)NR⁵¹R⁵², -NR⁵¹C(O)OR⁵¹, -NR⁵¹S(O)₂R^x, -S(O)₂NR⁵¹, -CO₂R⁵¹ or an optionally substituted aromatic group or non-aromatic heterocyclic group. Preferably, R²⁰² is -CN, -OH, C1-C3 alkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholynyl, *N*-piperazinyl, *N*-thiomorpholynyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholynyl,

- 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl. More preferably, R²⁰² is NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, an optionally substituted non-aromatic heterocyclic group selected from
- 5 *N*-pyrrolidinyl, *N*-piperidinyl, *N*-piperazinyl, *N*-morpholinyl, *N*-azetidiny, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-azetidiny, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 3-azetidiny, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl,
- 10 *N*-tetrahydroquinolinyl and *N*-tetrahydroisoquinolinyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl..

- Suitable substituents for the nitrogen-containing heteroaromatic group or nitrogen-containing non-aromatic heterocyclic group represented by R²⁰¹ and R²⁰² are as described below for nitrogen-containing heteroaromatic groups generally and
- 15 nitrogen-containing non-aromatic heterocyclic groups generally. Preferably, each substitutable ring nitrogen atom in an aromatic or non-aromatic heterocyclic group represented by R²⁰¹ or R²⁰² is optionally substituted with a C1-C3 alkyl, C1-C3 acyl, C1-C3 alkylsulfonyl, -OC(O)N(R')₂, -NR'C(O)OR', or -NR'C(O)N(R')₂ group; each substitutable ring carbon atom of a non-aromatic heterocyclic group represented by
- 20 R²⁰¹ or R²⁰² is optionally substituted with a C1-C3 alkyl group, hydroxy, halo, oxo, -C(O)OH, -C(O)O(C1-C3 alkyl), C1-C3 alkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, amido, C1-C3 alkylamido, C1-C3 haloalkylamido, (C1-C3)aminoalkyl, (C1-C3)alkoxyalkyl, (C1-C3)hydroxyalkyl; and each substitutable ring carbon atom of an aromatic group represented by R²⁰¹ or R²⁰² is optionally substituted with halo,
- 25 hydroxy, cyano, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), C(O)N(C1-C3 alkyl)₂, -NR'CO(C1-C3 alkyl), -NR'CO(C1-C3 haloalkyl), -NR'C(O)O(C1-C3 alkyl), -C(O)O(C1-C3 alkyl), -NR'C(O)NH₂, -NR'C(O)NH(C1-C3 alkyl), -NR'C(O)N(C1-C3 alkyl)₂, or -NR'C(O)O-(C1-C3 alkyl). -SH, -S(C1-C3
- 30 alkyl), -NO₂, -S(O)₂H, -S(O)₂(C1-C3 alkyl), -SO₂N(R')₂, -S(O)H, -S(O)(C1-C3 alkyl), -NR'S(O)₂NH₂, -NR'S(O)₂NH(C1-C3 alkyl), -NR'S(O)₂N(C1-C3 alkyl)₂, -NR'S(O)₂H or -NR'S(O)₂(C1-C3 alkyl).

R^{203} has the formula $-V_6-R^{60}$, $-V_6-R^{61}$, $-T_{11}-V_6-R^{60}$, or $-T_{11}-V_6-R^{61}$.

R^x is alkyl or an optionally substituted aromatic group or non-aromatic heterocyclic group.

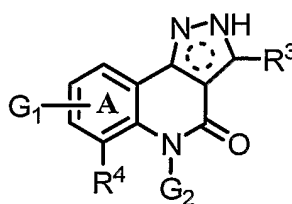
p is 1 or 2.

5 m is 1 or 2.

n is 1 or 2. Preferably n is 1.

z is an integer from 1 to 4.

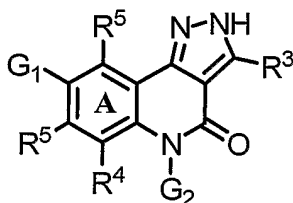
In a preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (II):



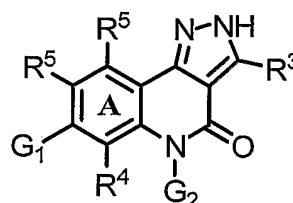
(II)

Values and preferred values for the variables in Structural Formula (II) are as described above for Structural Formula (I).

15 In another preferred embodiment the Chk-1 inhibitor of the present invention is represented by a Structural Formula selected from (III) and (IV):



(III)

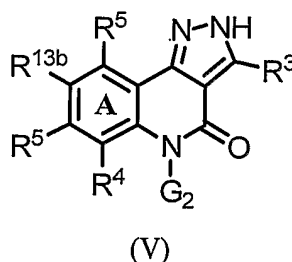


(IV)

Each R^5 is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, $-\text{NO}_2$, C1-C3 alkoxy, C1-C3 haloalkoxy, $-\text{CN}$, $-\text{NH}_2$, C1-C3 alkylamino, C1-C3 dialkylamino, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C1-C3 alkyl})_2$, $-\text{NHC}(\text{O})\text{O}-(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{O}-(\text{C1-C3 alkyl})$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}(\text{C1-C3 alkyl})$, $-\text{NHC}(\text{O})\text{N}(\text{C1-C3 alkyl})_2$, or $-\text{NHC}(\text{O})\text{O}-(\text{C1-C3 alkyl})$. The values and preferred values for the remaining variables in Structural Formulas (III) and (IV) are as described above for Structural Formula (I).

25 In another preferred embodiment the Chk-1 inhibitor of the present invention

is represented by Structural Formula (V):



R^5 is as defined above for Structural Formula (III) and (IV). The values and preferred values for each remaining variable in Structural Formula (V) are as described above for Structural Formula (I).

In a first more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (II), (III), (IV) or (V);

G_2 is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl; and

the values for all other variables and their preferred values are as described above for Structural Formula (I).

In a second more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (III), (IV) or (V);

G_2 is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl;

each R^5 is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, $-NO_2$, C1-C3 alkoxy, C1-C3 haloalkoxy, $-CN$, $-NH_2$, C1-C3 alkylamino, C1-C3 dialkylamino, $-C(O)NH_2$, $-C(O)NH(C1-C3 \text{ alkyl})$, $-C(O)N(C1-C3 \text{ alkyl})_2$, $-NHC(O)O-(C1-C3 \text{ alkyl})$, $-C(O)O-(C1-C3 \text{ alkyl})$, $-NHC(O)NH_2$, $-NHC(O)NH(C1-C3 \text{ alkyl})$, $-NHC(O)N(C1-C3 \text{ alkyl})_2$, or $-NHC(O)O-(C1-C3 \text{ alkyl})$;

the values for all other variables and their preferred values are as described above for Structural Formula (I).

In a third more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (III), (IV) or (V);

G_2 is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl;

R^3 is -H, methyl, ethyl, n-propyl, iso-propyl, C1-C3 haloalkyl, or V_1-R^7 , wherein V_1 is a covalent bond or a C1-C2 alkylidene optionally substituted with one or two methyl groups or with a spiro cyclopropyl group; and R^7 is -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -CONH₂, -CONHCH₃, -CON(CH₃)₂, -CN, -COOH, -COOCH₃, -NHC(O)H, -NHC(O)CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)NH₂, -OC(O)NHCH₃, C3-C6 cycloalkyl, furyl, tetrahydrofuryl, N-piperazinyl, N'-alkyl-N-piperazinyl, N'-acyl-N-piperazinyl, N-pyrrolidyl, N-piperidinyl or N-morpholinyl;

each R^5 is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, -NO₂, C1-C3 alkoxy, C1-C3 haloalkoxy, -CN, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂, -NHC(O)O-(C1-C3 alkyl), -C(O)O-(C1-C3 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-C3 alkyl), -NHC(O)N(C1-C3 alkyl)₂, or -NHC(O)O-(C1-C3 alkyl); and

the values for all other variables and their preferred values are as described above for Structural Formula (I).

In a fourth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (III), (IV) or (V);

G_2 is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl;

R^3 is methyl, or ethyl; or R^3 is V_1-R^7 , wherein V_1 is a C1-C2 alkylidene and R^7 is -OH, -OCH₃; or V_1 is a covalent bond and R^7 is cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl;

each R^5 is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, -NO₂, C1-C3 alkoxy, C1-C3 haloalkoxy, -CN, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂, -NHC(O)O-(C1-C3 alkyl), -C(O)O-(C1-C3 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-C3 alkyl), -NHC(O)N(C1-C3 alkyl)₂, or -NHC(O)O-(C1-C3 alkyl); and

the values for all other variables and their preferred values are as described above for Structural Formula (I).

In a fifth more preferred embodiment, the Chk-1 inhibitor of the present

invention is represented by Structural Formula (III), (IV) or (V);

G₂ is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl;

R³ is methyl, or ethyl; or R³ is V₁-R⁷, wherein V₁ is a C1-C2 alkylidene and
 5 R⁷ is -OH, -OCH₃; or V₁ is a covalent bond and R⁷ is cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl;

R⁴ and each R⁵ are independently -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy; and

the values for all other variables and their preferred values are as described
 10 above for Structural Formula (I).

In a sixth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (I), (II), (III) or (IV);

G₂ is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl;

15 R¹³ is -CN, -OR¹², -NR¹¹R¹², -NHC(O)R¹², -NHC(O)OR¹², -NHC(O)NR¹¹R¹², -NHC(O)OR¹², or -OC(O)R¹²;

G₁ is -V₃-R¹³, -V₃-R^{13a}, -T₀-T₁-V₃-R¹³, -T₀-T₁-V₃-R^{13a}, or -T₀-T₁-R^{13a};

V₃ is C1-C4 alkylidene; and

the values for the remainder of the variables and their preferred values are as
 20 described for Structural Formula (I).

Preferably, V₃ is C1-C4 alkylidene and T₀ is absent. More preferably, V₃ is C1-C4 alkylidene, T₀ is absent, and T₁ is -O- or -N(R⁶)-.

In a seventh more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (I), (II), (III) or (IV);

25 G₂ is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl;

R¹³ is -CN, -OR¹², -NR¹¹R¹², -NHC(O)R¹², -NHC(O)OR¹², -NHC(O)NR¹¹R¹², -NHC(O)OR¹², or -OC(O)R¹²;

- R^{13a} is an optionally substituted non-aromatic heterocyclic group selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azetidiny, tetrahydrofuranyl, oxazolidinyl, thiomorpholinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and azabicyclopentyl, azabicyclohexyl, azabicycloheptyl, azabicyclooctyl, azabicyclononyl, azabicyclodecyl, diazabicyclohexyl, diazabicycloheptyl, diazabicyclooctyl, diazabicyclononyl, or diazabicyclodecyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl;
- T_0 is absent;
- T_1 is $-O-$ or $-N(R^6)-$;
- G_1 is $-V_3-R^{13}$, $-V_3-R^{13a}$, $-T_0-T_1-V_3-R^{13}$, $-T_0-T_1-V_3-R^{13a}$, or $-T_0-T_1-R^{13a}$;
- V_3 is C1-C4 alkylidene; and
- the values for the remainder of the variables and their preferred values are as described for Structural Formula (I) above.

In an eighth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (I), (II), (III) or (IV);

G_2 is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl;

- R^{13a} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-thiomorpholinyl, *N*-azetidiny, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl and 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl;
- T_0 is absent;
- T_1 is $-O-$ or $-N(R^6)-$;

G_1 is $-V_3-R^{13}$, $-V_3-R^{13a}$, $-T_0-T_1-V_3-R^{13}$, $-T_0-T_1-V_3-R^{13a}$, or $-T_0-T_1-R^{13a}$; V_3 is C1-C4 alkylene;

R^{13} is $-OH$, $-CN$, C1-C3 alkoxy, NH_2 , C1-C3 alkylamino, C1-C3 dialkylamino, C1-C3 hydroxyalkyl, or C1-C3 haloalkylamino; and

5 the values for the remainder of the variables and their preferred values are as described for Structural Formula (I) above.

Preferably, R^{13} is NH_2 , C1-C3 alkylamino, or C1-C3 dialkylamino; and R^{13a} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-azetidiny, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl.

15 In a ninth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (I), (II), (III) or (IV);

G_2 is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl;

R^{13} is $-CN$, $-OR^{12}$, $-NR^{11}R^{12}$, $-NHC(O)R^{12}$, $-NHC(O)OR^{12}$, $-NHC(O)NR^{11}R^{12}$, $-NHC(O)OR^{12}$, or $-OC(O)R^{12}$;

G_1 is $-T_0-Cy-V_4-R^{13}$, $-T_0-Cy-V_4-R^{13a}$, $-T_0-Cy-T_1-V_4-R^{13}$, $-T_0-Cy-T_1-V_4-R^{13a}$, T_0-Cy-R^{13} , or $-T_0-Cy-R^{13a}$;

T_0 is absent;

V_4 is a C1-C4 alkylidene, alkenylidene or alkynylidene group optionally substituted with C1-C3 alkyl; and

the values for the remainder of the variables and their preferred values are as described for Structural Formula (I).

Preferably, V_4 is C1-C4 alkylidene. More preferably V_4 is C1-C4 alkylidene and T_0 is absent. Even more preferably, V_4 is C1-C4 alkylidene, T_0 is absent, and T_1 is $-O-$ or $-N(R^6)-$.

In a tenth more preferred embodiment, the Chk-1 inhibitor of the present

invention is represented by Structural Formula (I), (II), (III) or (IV);

G₂ is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl, wherein the cycloalkyl group is optionally substituted with halo or alkyl;

R¹³ is -CN, -OR¹², -NR¹¹R¹², -NHC(O)R¹², -NHC(O)OR¹²,
 5 -NHC(O)NR¹¹R¹², -NHC(O)OR¹², or -OC(O)R¹²;

R^{13a} is an optionally substituted non-aromatic heterocyclic group selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azetidiny, tetrahydrofuranyl, oxazolidinyl, thiomorpholinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and azabicyclopentyl, azabicyclohexyl, azabicycloheptyl, azabicyclooctyl,
 10 azabicyclononyl, azabicyclodecyl, diazabicyclohexyl, diazabicycloheptyl, diazabicyclooctyl, diazabicyclononyl, or diazabicyclodecyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl;

15 T₀ is absent;

T₁ is -O- or -N(R⁶)-;

G₁ is -T₀-Cy-V₄-R¹³, -T₀-Cy-V₄-R^{13a}, -T₀-Cy-T₁-V₄-R¹³, -T₀-Cy-T₁-V₄-R^{13a},
 T₀-Cy-R¹³, or -T₀-Cy-R^{13a};

V₄ is C1-C4 alkylidene;

20 Cy is an optionally substituted arylene group or an optionally substituted non-aromatic heterocyclene or non-aromatic carbocyclene group; and

the values for the remainder of the variables and their preferred values are as described for Structural Formula (I) above.

Preferably Cy is an optionally substituted phenylene, pyrrolylene, thienylene, furanylene, imidazolylene, triazolylene, tetrazolylene, oxazolylene, isoxazolylene, oxadiazolylene, pyrazolylene, pyridinylene, pyrimidylene, pyrazinylene, thiazolylene, cyclopropylene, cyclopentylene, cyclohexylene, cycloheptylene, piperidinylene, piperazinylene, pyrrolidinylene, pyrazolidinylene, imidazolidinylene, tetrahydrofuranylene, tetrahydrothienylene, isooxazolidinylene, oxazolidinylene,
 25 isothiazolidinylene, thiazolidinylene, oxathiolanylene, dioxolanylene, or dithiolanylene.
 30

More preferably, Cy is [2,5]thienylene or [2,5]furanylene.

In an eleventh more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (I), (II), (III) or (IV);

G₂ is C1-C4 alkyl optionally substituted with fluoro or C3-C8 cycloalkyl,
5 wherein the cycloalkyl group is optionally substituted with halo or alkyl;

R^{13a} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-thiomorpholinyl, *N*-azetidiny, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl,
10 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl and 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl,
15 oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl;

T₀ is absent;

T₁ is -O- or -N(R⁶)-;

G₁ is -T₀-Cy-V₄-R¹³, -T₀-Cy-V₄-R^{13a}, -T₀-Cy-T₁-V₄-R¹³, -T₀-Cy-T₁-V₄-R^{13a},
T₀-Cy-R¹³, or -T₀-Cy-R^{13a};

20 V₄ is a C1-C4 alkylidene;

Cy is an optionally substituted phenylene, pyrrolylene, thienylene, furanylene, imidazolylene, triazolylene, tetrazolylene, oxazolylene, isoxazolylene, oxadiazolylene, pyrazolylene, pyridinylene, pyrimidylene, pyrazinylene, thiazolylene, cyclopropylene, cyclopentylene, cyclohexylene, cycloheptylene, piperidinylene, piperazinylene,
25 pyrrolidinylene, pyrazolidinylene, imidazolidinylene, tetrahydrofuranylene, tetrahydrothienylene, isooxazolidinylene, oxazolidinylene, isothiazolidinylene, thiazolidinylene, oxathiolanylene, dioxolanylene, or dithiolanylene;

R¹³ is -OH, -CN, C1-C3 alkoxy, or -NR¹¹R¹², where R¹¹ is -H or a C1-C3 alkyl group and R¹² is -H, an optionally substituted alkyl, or an optionally substituted
30 non-aromatic heterocyclic group or NR¹¹R¹² is an optionally substituted aromatic or non-aromatic nitrogen containing heterocyclic group; and

the values for the remainder of the variables and their preferred values are as described for Structural Formula (I) above.

Preferably, Cy is [2,5]thienylene or [2,5]furanylene; R¹³ is NH₂, C1-C3 alkylamino, or C1-C3 dialkylamino; and R^{13a} is an optionally substituted non-
 5 aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-azetidiny, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl,
 10 *N*-tetrahydroisoquinolinyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl.

More preferably, R¹³ is -NH₂, -NHCH₃, -N(CH₃)₂, -NH(CH₂CH₃), or -N(CH₂CH₃)₂; and R^{13a} is *N*-pyrrolidinyl, 2,5-dimethyl-*N*-pyrrolidinyl, *N*-piperidinyl, *N*'-methyl-*N*-piperazinyl, *N*-tetrahydroisoquinolinyl, *N*-morpholinyl,
 15 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl.

For the first more preferred embodiment through the eleventh more preferred embodiment, the variables are as described above. Preferably, however:

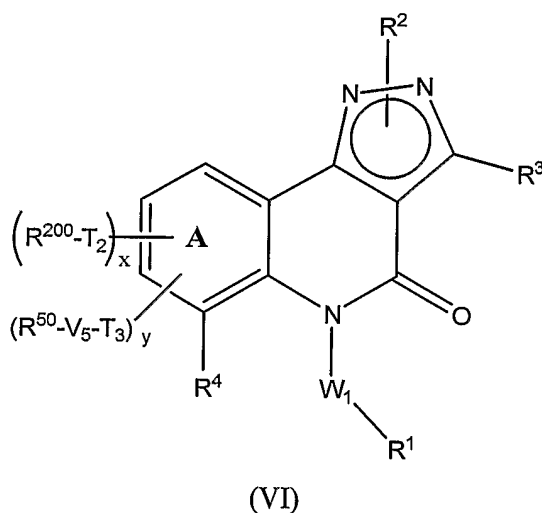
R³ is -H, methyl, ethyl, *n*-propyl, iso-propyl, C1-C3 haloalkyl, or V₁-R⁷, wherein V₁ is a covalent bond or a C1-C2 alkylidene optionally substituted with one
 20 or two methyl groups or with a spiro cyclopropyl group; and R⁷ is -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -CONH₂, -CONHCH₃, -CON(CH₃)₂, -CN, -COOH, -COOCH₃, -NHC(O)H, -NHC(O)CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)NH₂, -OC(O)NHCH₃, C3-C6 cycloalkyl, furyl, tetrahydrofuryl, *N*-piperazinyl, *N*'-alkyl-*N*-piperazinyl, *N*'-acyl-*N*-piperazinyl, *N*-pyrrolidyl, *N*-piperidinyl or *N*-
 25 morpholinyl. More preferably, R³ is methyl, or ethyl; or R³ is V₁-R⁷, wherein V₁ is a C1-C2 alkylidene and R⁷ is -OH, -OCH₃; or V₁ is a covalent bond and R⁷ is cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl; and/or

each R⁵ is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, -NO₂, C1-C3 alkoxy, C1-C3 haloalkoxy, -CN, -NH₂, C1-C3 alkylamino, C1-C3
 30 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂, -NHC(O)O-(C1-C3 alkyl), -C(O)O-(C1-C3 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-

C3 alkyl), -NHC(O)N(C1-C3 alkyl)₂, or -NHC(O)O-(C1-C3 alkyl). More preferably, each R⁵ are independently -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy.

Even more preferably R³ is methyl, or ethyl; or R³ is V₁-R⁷, wherein V₁ is a C1-C2 alkylidene and R⁷ is -OH, -OCH₃; or V₁ is a covalent bond and R⁷ is cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl, and/or R⁴ and each R⁵ are independently -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy.

In another preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (VI):



Values and preferred values for the variables in Structural Formula (VI) are as described above for Structural Formula (I).

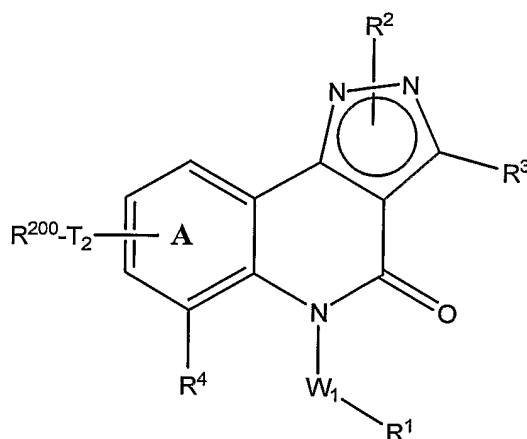
In a preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (VI):

Ring A is optionally substituted at any one or more substitutable ring carbon atoms;

R¹ is -H, -CONR¹¹R¹², -COOR¹², fluoro, or a cycloalkyl wherein the cycloalkyl is optionally substituted with halo or alkyl and W₁ is a linear C1-C6 alkylidene chain; or R¹ is -OR¹² and W₁ is a linear C2-C6 alkylidene group, wherein the alkylidene group represented by W₁ is optionally substituted with one or more -CH₃ or fluoro groups; or -W₁-R¹ is -H; and

the values for all other variables and their preferred values are as described above for Structural Formula (I).

In another preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof. Values and preferred values for the variables in Structural Formula (VII) are as described above for Structural Formula (I).

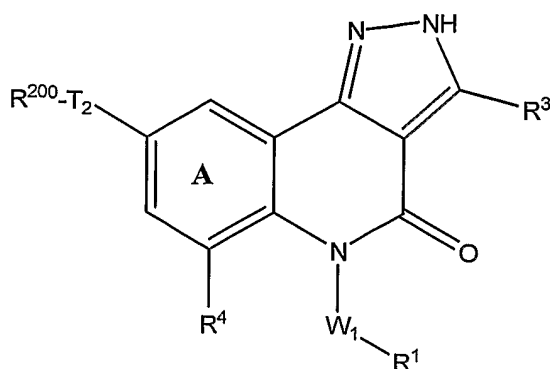
10 In a preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (VII):

R^1 is -H, $-\text{CONR}^{11}\text{R}^{12}$, $-\text{COOR}^{12}$, fluoro, or a cycloalkyl wherein the cycloalkyl is optionally substituted with halo or alkyl and W_1 is a linear C1-C6 alkylidene chain; or R^1 is $-\text{OR}^{12}$ and W_1 is a linear C2-C6 alkylidene group, wherein the alkylidene group represented by W_1 is optionally substituted with one or more $-\text{CH}_3$ or fluoro groups; or $-\text{W}_1-\text{R}^1$ is -H;

15 R^4 is -H, C1-C3 alkyl, C1-C3 haloalkyl, halogen, hydroxy, C1-C3 alkoxy, C1-C3 haloalkoxy, $-\text{NH}_2$, C1-C3 alkylamino, C1-C3 dialkylamino, $-\text{NHC(O)H}$, $-\text{NHC(O)(C1-C3 alkyl)}$, $-\text{C(O)NH}_2$, $-\text{C(O)NH(C1-C3 alkyl)}$ or $-\text{C(O)N(C1-C3 alkyl)}_2$; and

the values for all other variables and their preferred values are as described above for Structural Formula (I).

In another preferred embodiment the Chk-1 inhibitor of the present invention is represented by Structural Formula (VIII):



(VIII)

The values and preferred values for the variables in Structural Formula (VIII) are as described above for Structural Formula (I).

5 In a preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (VII) or (VIII);

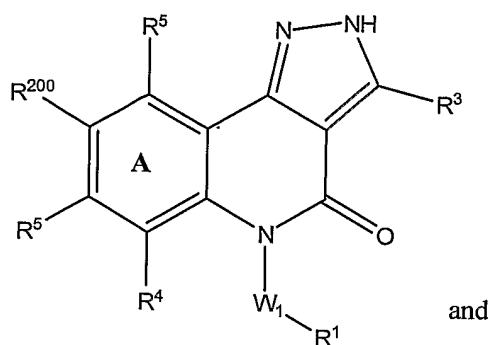
R^1 is -H, -CONR¹¹R¹², -COOR¹², fluoro, or a cycloalkyl wherein the cycloalkyl is optionally substituted with halo or alkyl and W_1 is a linear C1-C6 alkylidene chain; or R^1 is -OR¹² and W_1 is a linear C2-C6 alkylidene group, wherein the alkylidene group represented by W_1 is optionally substituted with one or more -CH₃ or fluoro groups; or - W_1 - R^1 is -H. Preferably, W_1 is a linear C1-C4 alkylidene chain optionally substituted with one or more -CH₃ or fluoro groups and R^1 is -H, fluoro or a cycloalkyl wherein the cycloalkyl is optionally substituted with halo or alkyl;

15 T_2 is a covalent bond, -S(O)-, -SO₂-, -C(O)-, -OC(O)-, -N(R⁶)C(O)-, or -N(R⁶)SO₂. Preferably, T_2 is a covalent bond; and

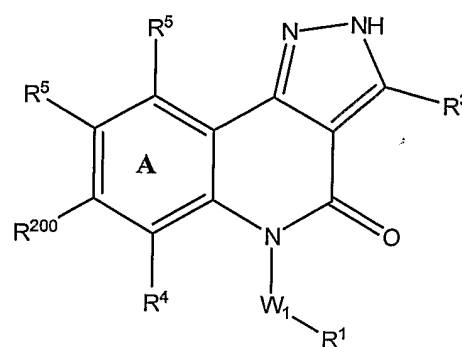
the values for all other variables and their preferred values are as described above for Structural Formula (I).

In another preferred embodiment the Chk-1 inhibitor of the present invention is represented a Structural Formula selected from (IX) and (X):

20



(IX)



(X)

- 5 Each R^5 is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, $-\text{NO}_2$, C1-C3 alkoxy, C1-C3 haloalkoxy, $-\text{CN}$, $-\text{NH}_2$, C1-C3 alkylamino, C1-C3 dialkylamino, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C1-C3 alkyl})_2$, $-\text{NHC}(\text{O})\text{O}-(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{O}-(\text{C1-C3 alkyl})$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}(\text{C1-C3 alkyl})$, $-\text{NHC}(\text{O})\text{N}(\text{C1-C3 alkyl})_2$, or $-\text{NHC}(\text{O})\text{O}-(\text{C1-C3 alkyl})$. The values and preferred values for the remaining variables in Structural Formulas (IX) and (X) are as described above for Structural Formula (I).

In a twelfth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (VI), (VII), (VIII), (IX) or (X);

- 15 R^1 is $-\text{H}$, $-\text{CONR}^{11}\text{R}^{12}$, $-\text{COOR}^{12}$, fluoro, or a cycloalkyl wherein the cycloalkyl is optionally substituted with halo or alkyl and W_1 is a linear C1-C6 alkylidene chain; or R^1 is $-\text{OR}^{12}$ and W_1 is a linear C2-C6 alkylidene group, wherein the alkylidene group represented by W_1 is optionally substituted with one or more $-\text{CH}_3$ or fluoro groups; or $-\text{W}_1-\text{R}^1$ is $-\text{H}$. Preferably, W_1 is a linear C1-C4 alkylidene chain optionally substituted with one or more $-\text{CH}_3$ or fluoro groups and R^1 is $-\text{H}$, fluoro or a cycloalkyl wherein the cycloalkyl is optionally substituted with halo or alkyl;

- 20 each R^5 , when present, is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, $-\text{NO}_2$, C1-C3 alkoxy, C1-C3 haloalkoxy, $-\text{CN}$, $-\text{NH}_2$, C1-C3 alkylamino, C1-C3 dialkylamino, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C1-C3 alkyl})_2$, $-\text{NHC}(\text{O})\text{O}-(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{O}-(\text{C1-C3 alkyl})$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}(\text{C1-C3 alkyl})$, $-\text{NHC}(\text{O})\text{N}(\text{C1-C3 alkyl})_2$, or $-\text{NHC}(\text{O})\text{O}-(\text{C1-C3 alkyl})$; and

the values for all other variables and their preferred values are as described above for Structural Formula (I).

In a thirteenth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (VI), (VII), (VIII), (IX) or (X);

5 R^{200} is $-C\equiv CR^{201}$, $-CH=CHR^{201}$, $-C\equiv C-(C(R^{20}R^{20}))_pR^{202}$, or $-CH=CH-(C(R^{20}R^{20}))_pR^{202}$;

R^{201} is -H, alkyl, haloalkyl, hydroxyalkyl, CO_2R^{51} , or an optionally substituted aromatic group or non-aromatic heterocyclic group;

10 R^{202} is -H, -CN, $-OR^{51}$, $-OC(O)NR^{51}R^{52}$, $-OC(O)R^{51}$, $-NR^{51}R^{52}$, $-C(O)NR^{51}R^{52}$, $-NR^{51}C(O)R^{51}$, $-NR^{51}C(O)NR^{51}R^{52}$, $-NR^{51}C(O)OR^{51}$, $-NR^{51}S(O)_2R^x$, $-S(O)_2NR^{51}$, $-CO_2R^{51}$ or an optionally substituted aromatic group or non-aromatic heterocyclic group;

each R^{20} is independently -H or C1-C3 alkyl;

15 R^x is alkyl or an optionally substituted aromatic group or non-aromatic heterocyclic group;

p is 1 or 2; and

the values for all other variables and their preferred values are as described above for the twelfth more preferred embodiment.

20 In a fourteenth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula ((VI), (VII), (VIII), (IX) or (X);

R^3 is -H, methyl, ethyl, n-propyl, iso-propyl, C1-C3 haloalkyl, or V_1-R^7 , wherein V_1 is a covalent bond or a C1-C2 alkylidene optionally substituted with one or two methyl groups or with a spiro cyclopropyl group; R^7 is -OH, -OCH₃, -NH₂,
25 -NHCH₃, -N(CH₃)₂, -CONH₂, -CONHCH₃, -CON(CH₃)₂, -CN, -COOH, -COOCH₃, -NHC(O)H, -NHC(O)CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)NH₂, -OC(O)NHCH₃, -OC(O)N(CH₃)₂, -NHC(O)NH₂, -NHC(O)NH(CH₃), -NHC(O)N(CH₃)₂, -NHC(O)OCH₃, C3-C6 cycloalkyl, furyl, tetrahydrofuryl, N-piperazinyl, N'-alkyl-N-piperazinyl, N'-acyl-N-piperazinyl, N-pyrrolidyl, N-piperidinyl or N-morpholinyl;
30 and

the values for all other variables and their preferred values are as described above for the thirteenth more preferred embodiment.

In a fifteenth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (VI), (VII), (VIII), (IX) or (X);

R^{201} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-azetidiny, 5 *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-azetidiny 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 3-azetidiny, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl;

10 R^{202} is -CN, -OH, C1-C3 alkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, 15 tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl. Preferably, R^{202} is NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-piperazinyl, *N*-morpholinyl, *N*-azetidiny, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2- 20 piperazinyl, 2-morpholinyl, 2-azetidiny, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 3-azetidiny, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl and *N*-tetrahydroisoquinolinyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl; and

the values for all other variables and their preferred values are as 25 described above for the fourteenth more preferred embodiment.

In a sixteenth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formulas (VI), (VII), (VIII), (IX) or (X);

R^{200} is -C≡C- R^{203} or -C=CHR²⁰³;

R^{203} has the formula -V₆-R⁶⁰, -V₆-R⁶¹, -T₁₁-V₆-R⁶⁰, or -T₁₁-V₆-R⁶¹;

30 V₆ is a C1-C4 alkylidene, wherein V₆ is optionally substituted with alkyl, halo, haloalkyl, alkoxy, hydroxy, NR¹¹R¹² or oxo;

T₁₁ is -S(O)-, -S(O)₂-, -C(O)-, -C(O)O-, -C(O)N(R⁶)-, or -SO₂N(R⁶)-;

R^{60} is $-OR^{12}$, $-CN$, $-COOR^{12}$, $-NR^{11}R^{12}$, $-NR^{11}CONR^{11}R^{12}$, $-NR^{11}COR^{12}$,
 $-NH-C(=NR^{11})NR^{11}R^{12}$, $-N=C(NR^{11}R^{12})_2$, $-SO_2NR^{11}R^{12}$, $-NR^{11}SO_2R^{12}$, $-OC(O)R^{12}$,
 $-NR^{11}C(O)OR^{12}$, $-O-C(O)-OR^{12}$, $-OC(O)-NR^{11}R^{12}$, $-NR^{11}CO-CH(OR^{62})-R^{12}$,
 $-NR^{11}CO-CH(NR^{62}R^{62})-R^{12}$, $-NR^{11}CO-(CH_2)_2CH(NR^{62}R^{62})-R^{12}$,
5 $-OC(O)-CH(OR^{62})-R^{12}$, $-OC(O)-CH(NR^{62}R^{62})-R^{12}$, $-NR^{11}CO-C(R^{63}R^{63})-OR^{12}$,
 $-NR^{11}CO-C(R^{63}R^{63})-NR^{11}R^{12}$, $-OC(O)-C(R^{63}R^{63})-OR^{12}$,
 $-OC(O)-C(R^{63}R^{63})-NR^{11}R^{12}$, $-NR^{11}-C(R^{12})-C(O)OR^{12}$, $-NR^{11}-C(R^{12})-C(O)NR^{11}R^{12}$,
 $-NR^{11}-C(R^{12})CH_2OR^{12}$, $-C(O)NR^{11}R^{12}$, $-NHC(O)NR^{11}R^{12}$, or $-C(=NR^{11})-NR^{11}R^{12}$;

R^{61} is an optionally substituted nitrogen-containing heteroaromatic group or
10 a nitrogen-containing non-aromatic heterocyclic group; and

the values for all other variables and their preferred values are as described
above for the twelfth more preferred embodiment.

In a seventeenth more preferred embodiment, the Chk-1 inhibitor of the
present invention is represented by Structural Formula (IX) or (X);

15 R^{60} is $-CN$, $-OR^{12}$, $-NR^{11}R^{12}$, $-NHC(O)R^{12}$, $-NHC(O)OR^{12}$,
 $-NHC(O)NR^{11}R^{12}$, $-NHC(O)OR^{12}$, or $-OC(O)R^{12}$;

R^{61} is an optionally substituted non-aromatic heterocyclic group selected
from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azetidiny,
tetrahydrofuranyl, oxazolidinyl, thiomorpholinyl, tetrahydroquinoliny,
20 tetrahydroisoquinoliny and azabicyclopentany, azabicyclohexany,
azabicycloheptany, azabicyclononany, azabicyclodecany, diazabicyclohexany,
diazabicycloheptany, diazabicyclooctany, diazabicyclononany, or
diazabicyclodecany or an optionally substituted heteroaromatic group selected from
imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridiny, pyraziny,
25 pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl
and thiadiazolyl; and

the values for all other variables and their preferred values are as described
above for the sixteenth more preferred embodiment.

In an eighteenth more preferred embodiment, the Chk-1 inhibitor of the
30 present invention is represented by Structural Formula (IX) or (X);

R^{60} is $-OH$, $-CN$, C1-C3 alkoxy, or $NR^{11}R^{12}$, where R^{11} is $-H$ or a C1-C3
alkyl group and R^{12} is $-H$, an optionally substituted alkyl, or an optionally

substituted non-aromatic heterocyclic group, or $\text{NR}^{11}\text{R}^{12}$ is an optionally substituted aromatic or non-aromatic nitrogen containing heterocyclic group. Preferably, R^{60} is NH_2 , C1-C3 alkylamino, or C1-C3 dialkylamino. More preferably, R^{60} is $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NH}(\text{CH}_2\text{CH}_3)$, or $-\text{N}(\text{CH}_2\text{CH}_3)_2$;

- 5 R^{61} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-thiomorpholinyl, *N*-azetidiny, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, 10 *N*-tetrahydroquinolinyl, *N*-tetrahydroisoquinolinyl and 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl. Preferably, R^{61} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, 15 *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-azetidiny, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl 20 *N*-tetrahydroisoquinolinyl 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl. More preferably, R^{61} is *N*-pyrrolidinyl, 2,5-dimethyl-*N*-pyrrolidinyl, *N*-piperidinyl, *N*'-methyl-*N*-piperazinyl, *N*-tetrahydroisoquinolinyl, *N*-morpholinyl, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl; and
- 25 the values for all other variables and their preferred values are as described above for the seventeenth more preferred embodiment.

In an nineteenth more preferred embodiment, the Chk-1 inhibitor of the present invention is represented by Structural Formula (IX) or (X)

- R^3 is methyl, or ethyl; or R^3 is $\text{V}_1\text{-R}^7$, wherein V_1 is a C1-C2 alkylidene and R^7 30 is $-\text{OH}$, $-\text{OCH}_3$; or wherein V_1 is a covalent bond and R^7 is - cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl;

-OC(O)N(CH₃)₂, -NHC(O)NH₂, -NHC(O)NH(CH₃), -NHC(O)N(CH₃)₂,
 -NHC(O)OCH₃, C3-C6 cycloalkyl, furyl, tetrahydrofuryl, N-piperazinyl, N'-alkyl-N-
 -piperazinyl, N'-acyl-N- piperazinyl, N-pyrrolidyl, N-piperidinyl or N-morpholinyl;

each R⁵ is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, -NO₂,

5 C1-C3 alkoxy, C1-C3 haloalkoxy, -CN, -NH₂, C1-C3 alkylamino, C1-C3
 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂,
 -NHC(O)O-(C1-C3 alkyl), -C(O)O-(C1-C3 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-
 C3 alkyl), -NHC(O)N(C1-C3 alkyl)₂, or -NHC(O)O-(C1-C3 alkyl); and

the values for all other variables and their preferred values are as

10 described above for Structural Formula (I).

In a twenty second more preferred embodiment, the Chk-1 inhibitor of the
 present invention is represented by Structural Formula (XI) or (XII);

W₁ is a linear C1-C4 alkylidene chain optionally substituted with one
 or more -CH₃ or fluoro groups and R¹ is -H, fluoro or a cycloalkyl

15 optionally substituted with halo or alkyl;

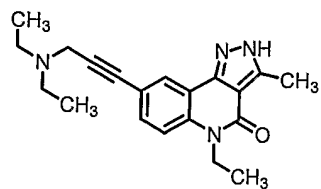
R³ is methyl, or ethyl; or R³ is V₁-R⁷, wherein V₁ is a C1-C2 alkylidene and R⁷
 is -OH, -OCH₃; or wherein V₁ is a covalent bond and R⁷ is - cyclopropyl, cyclopentyl,
 furyl or tetrahydrofuryl;

R⁴ and each R⁵ is independently -H, halogen, -CH₃, halomethyl, -OCH₃, or
 20 haloalkoxy;

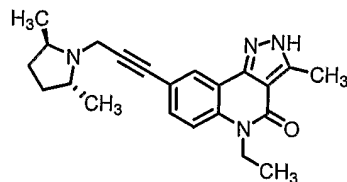
the values for all other variables and their preferred values are as
 described above for Structural Formula (I).

Specific examples of Chk-1 inhibitors of the present invention are provided
 below in Table 1.

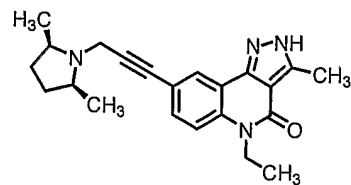
Table 1.



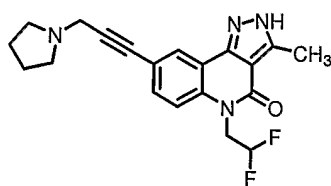
I-1



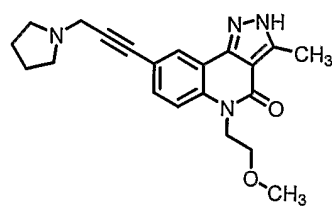
I-2



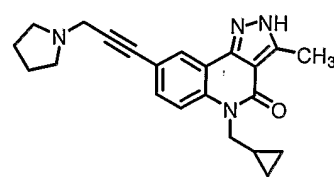
I-3



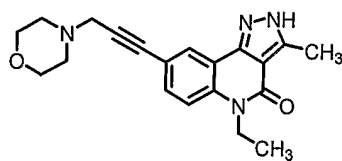
I-4



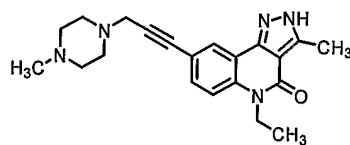
I-5



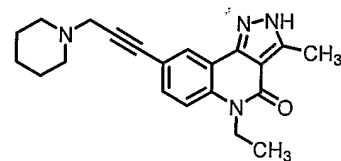
I-6



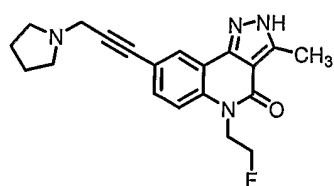
I-7



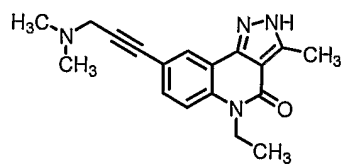
I-8



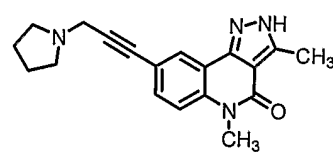
I-9



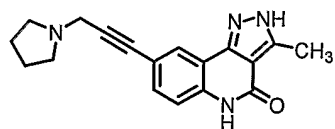
I-10



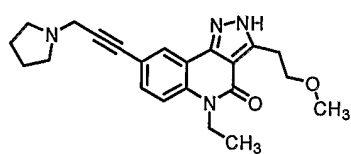
I-11



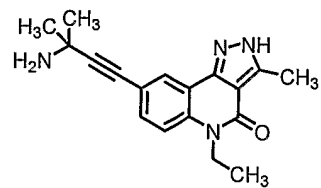
I-12



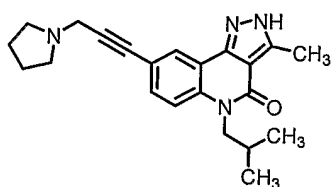
I-13



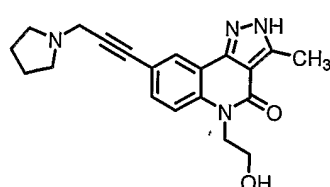
I-14



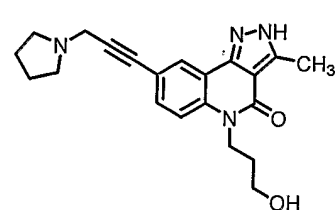
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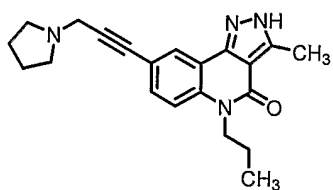
I-16



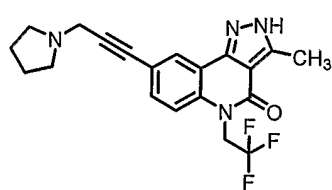
I-17



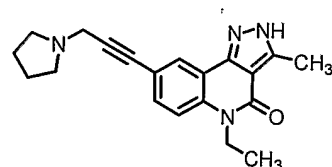
I-18



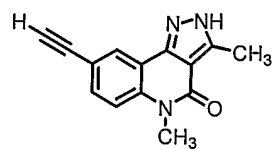
I-19



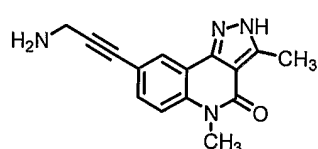
I-20



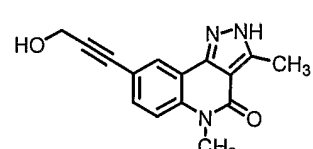
I-21



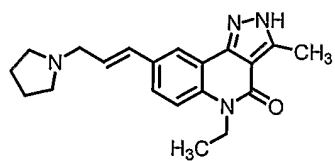
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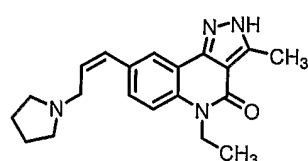
I-23



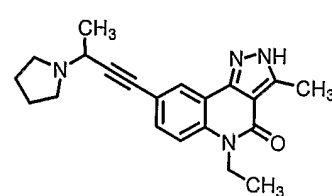
I-24



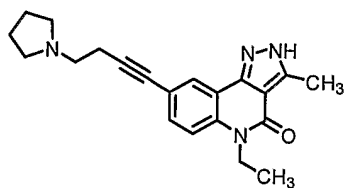
I-25



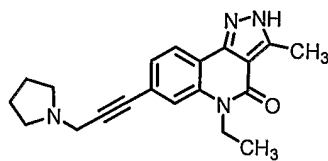
I-26



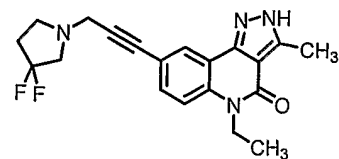
I-27



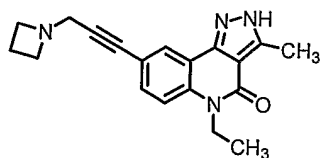
I-28



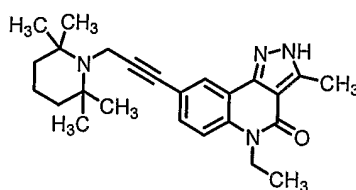
I-29



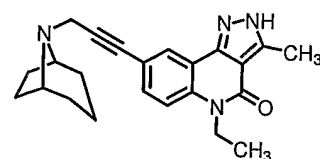
I-30



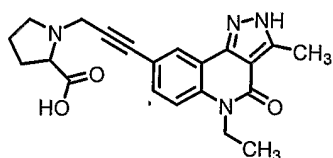
I-31



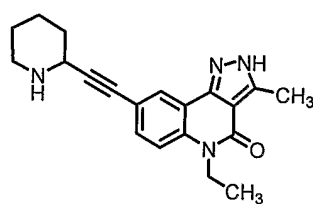
I-32



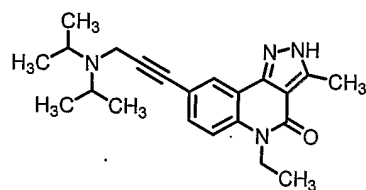
I-33



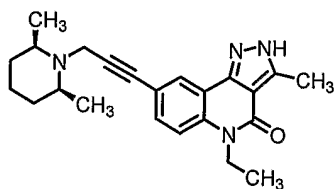
I-34



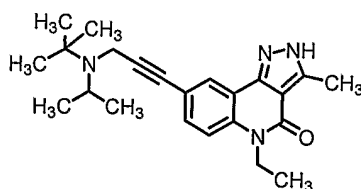
I-35



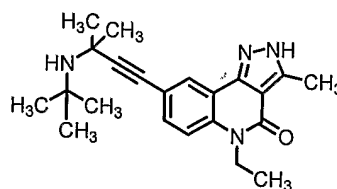
I-36



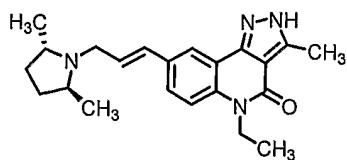
I-37



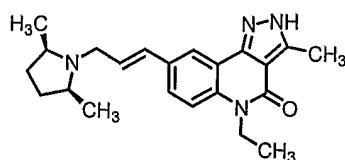
I-38



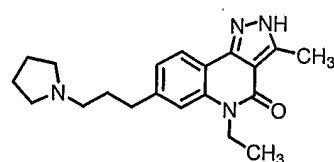
I-39



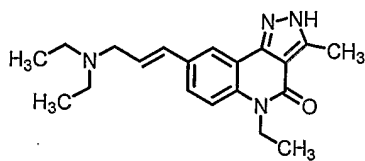
I-40



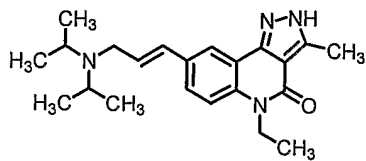
I-41



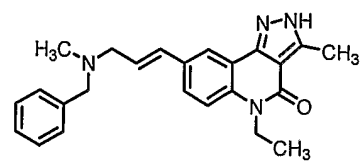
I-42



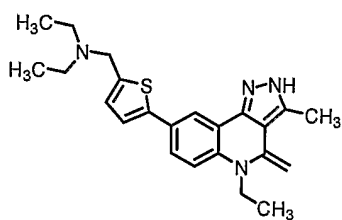
I-43



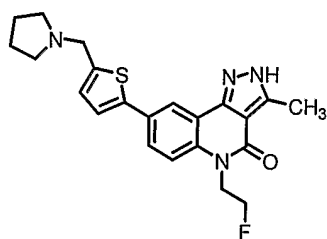
I-44



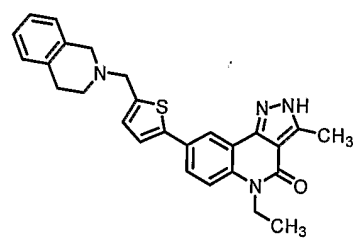
I-45



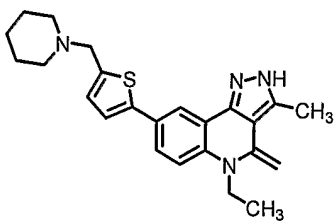
I-46



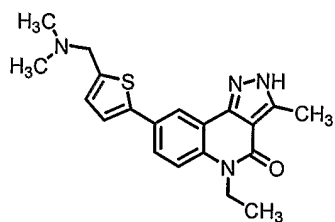
I-47



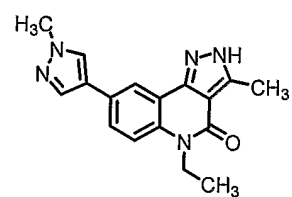
I-48



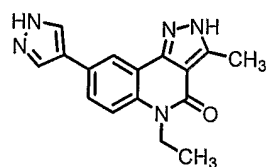
I-49



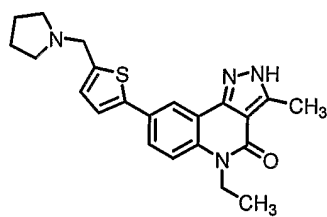
I-50



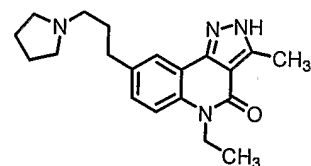
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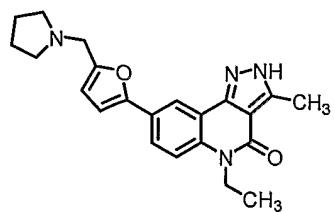
I-52



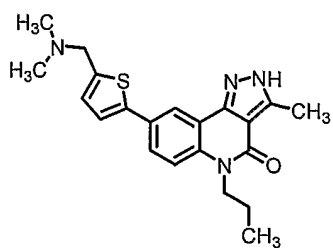
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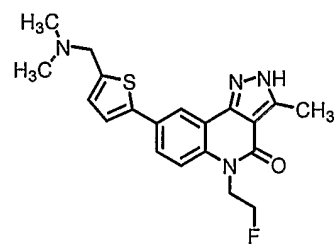
I-54



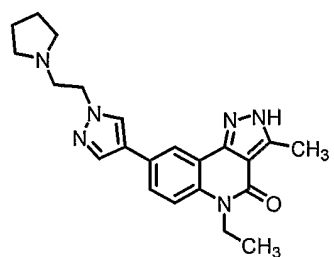
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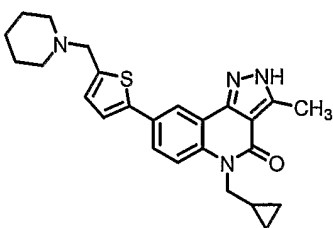
I-56



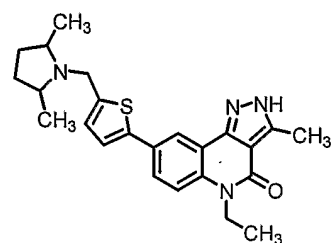
I-57



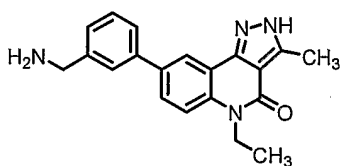
I-58



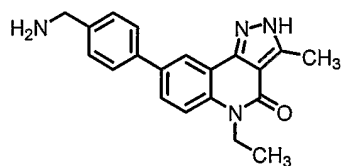
I-59



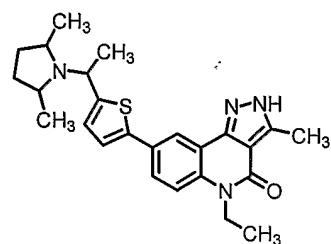
I-60



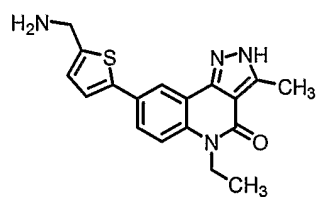
I-61



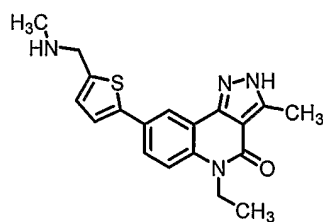
I-62



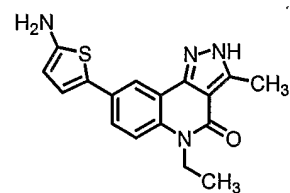
I-63



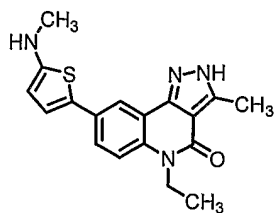
I-64



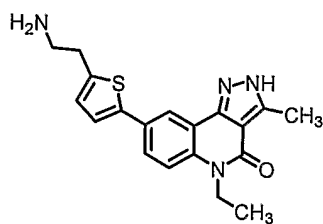
I-65



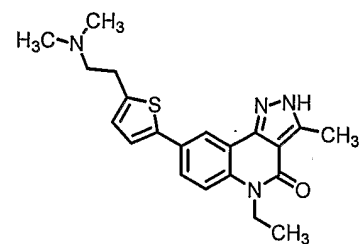
I-66



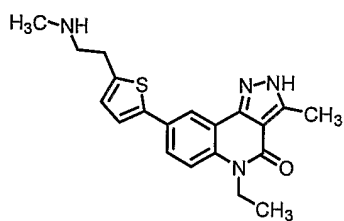
I-67



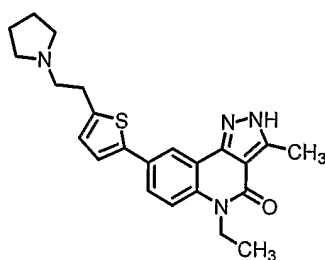
I-68



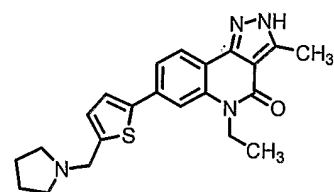
I-69



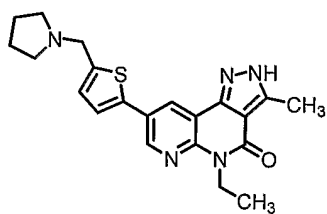
I-70



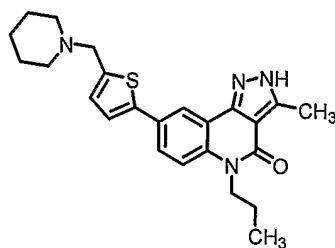
I-71



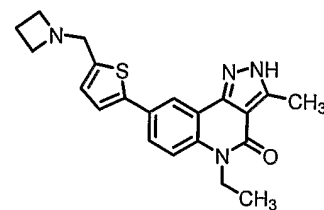
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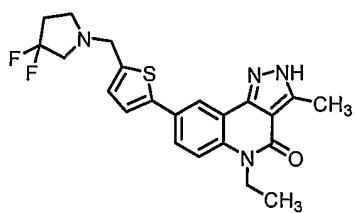
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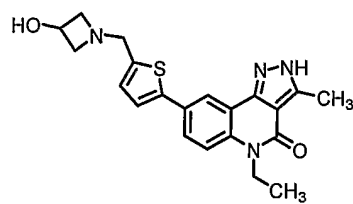
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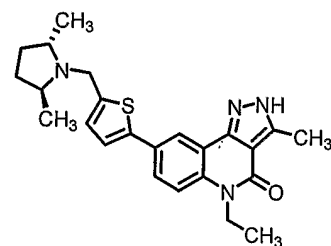
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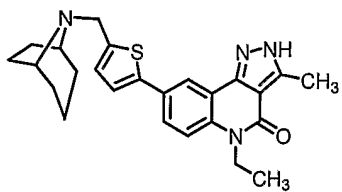
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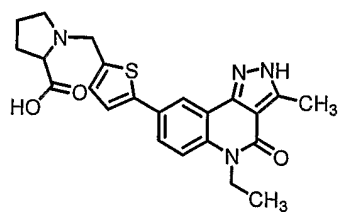
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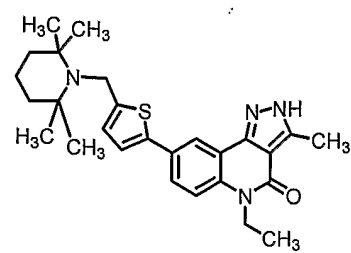
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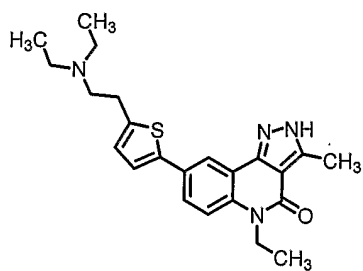
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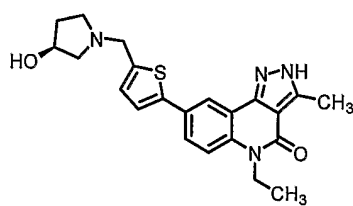
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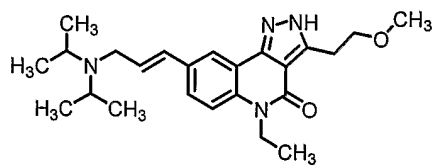
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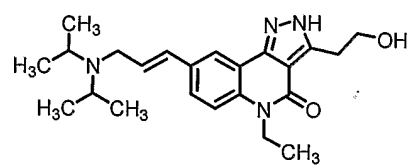
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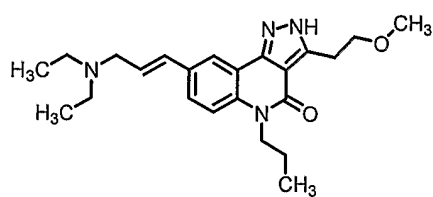
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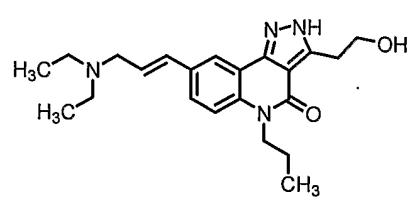
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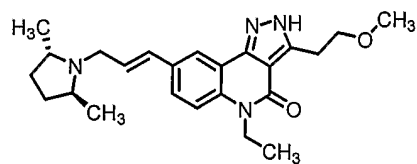
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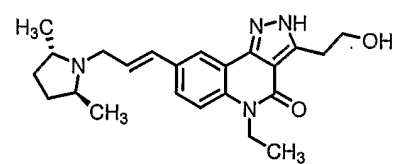
I-86



I-87



I-88



I-89

The Chk-1 inhibitors depicted in Table 1 above also may be identified by the following chemical names:

	Chemical Name
I-1:	8-[3-(diethylamino)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-2:	8-{3-[(2 <i>S</i> ,5 <i>S</i>)-2,5-dimethylpyrrolidin-1-yl]prop-1-yn-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-3:	8-{3-[(2 <i>R</i> ,5 <i>S</i>)-2,5-dimethylpyrrolidin-1-yl]prop-1-yn-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-4:	5-(2,2-difluoroethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-5:	5-(2-methoxyethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-6:	5-(cyclopropylmethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-7:	5-ethyl-3-methyl-8-(3-morpholin-4-ylprop-1-yn-1-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-8:	5-ethyl-3-methyl-8-[3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-9:	5-ethyl-3-methyl-8-(3-piperidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-10:	5-(2-fluoroethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-11:	8-[3-(dimethylamino)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-12:	3,5-dimethyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-13:	3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one

I-14:	5-ethyl-3-(2-methoxyethyl)-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-15:	8-(3-amino-3-methylbut-1-yn-1-yl)-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-16:	5-isobutyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-17:	5-(2-hydroxyethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-18:	5-(3-hydroxypropyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-19:	3-methyl-5-propyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-20:	3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-5-(2,2,2-trifluoroethyl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-21:	5-ethyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-22:	8-ethynyl-3,5-dimethyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-23:	8-(3-aminoprop-1-yn-1-yl)-3,5-dimethyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-24:	8-(3-hydroxyprop-1-yn-1-yl)-3,5-dimethyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-25:	5-ethyl-3-methyl-8-[(1E)-3-pyrrolidin-1-ylprop-1-en-1-yl]-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-26:	5-ethyl-3-methyl-8-[(1Z)-3-pyrrolidin-1-ylprop-1-en-1-yl]-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-27:	5-ethyl-3-methyl-8-(3-pyrrolidin-1-ylbut-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-28:	5-ethyl-3-methyl-8-(4-pyrrolidin-1-ylbut-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one
I-29:	5-ethyl-3-methyl-7-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one

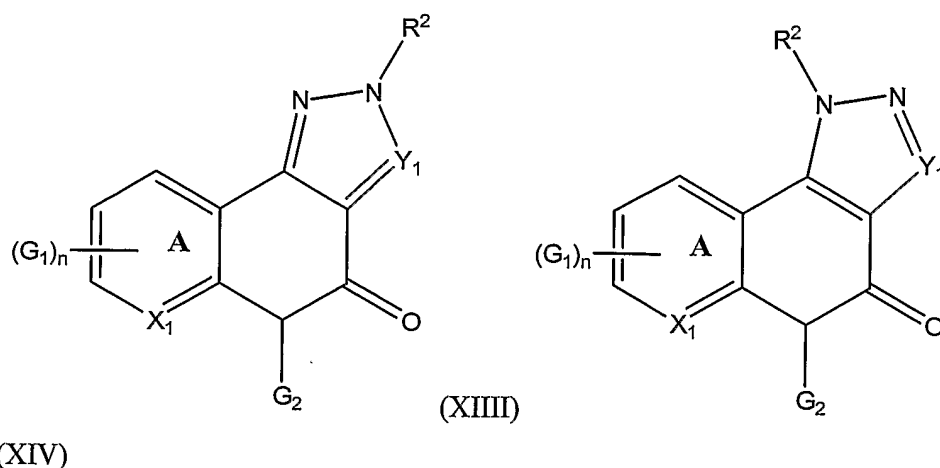
I-30:	8-[3-(3,3-difluoropyrrolidin-1-yl)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-31:	8-(3-azetidin-1-ylprop-1-yn-1-yl)-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-32:	5-ethyl-3-methyl-8-[3-(2,2,6,6-tetramethylpiperidin-1-yl)prop-1-yn-1-yl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-33:	8-[3-(8-azabicyclo[3.2.1]oct-8-yl)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-34:	1-[3-(5-ethyl-3-methyl-4-oxo-4,5-dihydro-2 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-8-yl)prop-2-yn-1-yl]pyrrolidine-2-carboxylic acid
I-35:	5-ethyl-3-methyl-8-(piperidin-2-ylethynyl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-36:	8-[3-(diisopropylamino)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-37:	8-{3-[(2 <i>R</i> ,6 <i>S</i>)-2,6-dimethylpiperidin-1-yl]prop-1-yn-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-38:	8-{3-[<i>tert</i> -butyl(isopropyl)amino]prop-1-yn-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-39:	8-[3-(<i>tert</i> -butylamino)-3-methylbut-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-40:	8-{(1 <i>E</i>)-3-[(2 <i>S</i> ,5 <i>S</i>)-2,5-dimethylpyrrolidin-1-yl]prop-1-en-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-41:	8-{(1 <i>E</i>)-3-[(2 <i>R</i> ,5 <i>S</i>)-2,5-dimethylpyrrolidin-1-yl]prop-1-en-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-42:	5-ethyl-3-methyl-7-(3-pyrrolidin-1-ylpropyl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-43:	8-[(1 <i>E</i>)-3-(diethylamino)prop-1-en-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-44:	8-[(1 <i>E</i>)-3-(diisopropylamino)prop-1-en-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-45:	8-{(1 <i>E</i>)-3-[benzyl(methyl)amino]prop-1-en-1-yl}-5-ethyl-3-methyl-2,5-

	dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-46:	8-{5-[(diethylamino)methyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-47:	5-(2-fluoroethyl)-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-48:	8-[5-(3,4-dihydroisoquinolin-2(1 <i>H</i>)-ylmethyl)-2-thienyl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-49:	5-ethyl-3-methyl-4-methylene-8-[5-(piperidin-1-ylmethyl)-2-thienyl]-4,5-dihydro-2 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinoline
I-50:	8-{5-[(dimethylamino)methyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-51:	5-ethyl-3-methyl-8-(1-methyl-1 <i>H</i> -pyrazol-4-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-52:	5-ethyl-3-methyl-8-(1 <i>H</i> -pyrazol-4-yl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-53:	5-ethyl-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-54:	5-ethyl-3-methyl-8-(3-pyrrolidin-1-ylpropyl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-55:	5-ethyl-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-furyl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-56:	8-{5-[(dimethylamino)methyl]-2-thienyl}-3-methyl-5-propyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-57:	8-{5-[(dimethylamino)methyl]-2-thienyl}-5-(2-fluoroethyl)-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-58:	5-ethyl-3-methyl-8-[1-(2-pyrrolidin-1-ylethyl)-1 <i>H</i> -pyrazol-4-yl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-59:	5-(cyclopropylmethyl)-3-methyl-8-[5-(piperidin-1-ylmethyl)-2-thienyl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-60:	8-{5-[(2,5-dimethylpyrrolidin-1-yl)methyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one

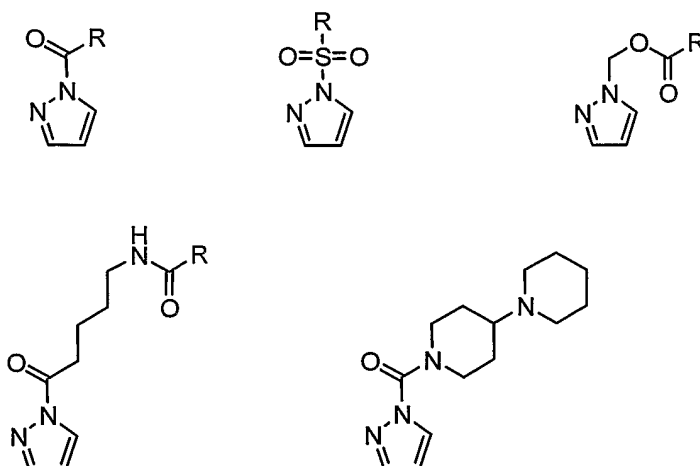
I-61:	8-[3-(aminomethyl)phenyl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-62:	8-[4-(aminomethyl)phenyl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-63:	8-{5-[1-(2,5-dimethylpyrrolidin-1-yl)ethyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-64:	8-[5-(aminomethyl)-2-thienyl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-65:	5-ethyl-3-methyl-8-{5-[(methylamino)methyl]-2-thienyl}-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-66:	8-(5-amino-2-thienyl)-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-67:	5-ethyl-3-methyl-8-[5-(methylamino)-2-thienyl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-on
I-68:	8-[5-(2-aminoethyl)-2-thienyl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-69:	8-{5-[2-(dimethylamino)ethyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-70:	5-ethyl-3-methyl-8-{5-[2-(methylamino)ethyl]-2-thienyl}-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-71:	5-ethyl-3-methyl-8-[5-(2-pyrrolidin-1-ylethyl)-2-thienyl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-72:	5-ethyl-3-methyl-7-[5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-73:	5-ethyl-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]-1,8-naphthyridin-4-one
I-74:	3-methyl-8-[5-(piperidin-1-ylmethyl)-2-thienyl]-5-propyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-75:	8-[5-(azetidin-1-ylmethyl)-2-thienyl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-76:	8-{5-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-thienyl}-5-ethyl-3-methyl-2,5-

	dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-77:	5-ethyl-8-{5-[(3-hydroxyazetidin-1-yl)methyl]-2-thienyl}-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-78:	8-(5-{[(2 <i>S</i> ,5 <i>S</i>)-2,5-dimethylpyrrolidin-1-yl]methyl}-2-thienyl)-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-79:	8-[5-(8-azabicyclo[3.2.1]oct-8-ylmethyl)-2-thienyl]-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-80:	1-{[5-(5-ethyl-3-methyl-4-oxo-4,5-dihydro-2 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-8-yl)-2-thienyl]methyl}pyrrolidine-2-carboxylic acid
I-81:	5-ethyl-3-methyl-8-{5-[(2,2,6,6-tetramethylpiperidin-1-yl)methyl]-2-thienyl}-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-82:	8-{5-[2-(diethylamino)ethyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-83:	5-ethyl-8-(5-{[(3 <i>S</i>)-3-hydroxypyrrolidin-1-yl]methyl}-2-thienyl)-3-methyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-84:	8-[(1 <i>E</i>)-3-(diisopropylamino)prop-1-en-1-yl]-5-ethyl-3-(2-methoxyethyl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-85:	8-[(1 <i>E</i>)-3-(diisopropylamino)prop-1-en-1-yl]-5-ethyl-3-(2-hydroxyethyl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-86:	8-[(1 <i>E</i>)-3-(diethylamino)prop-1-en-1-yl]-3-(2-methoxyethyl)-5-propyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-87:	8-[(1 <i>E</i>)-3-(diethylamino)prop-1-en-1-yl]-3-(2-hydroxyethyl)-5-propyl-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-88:	8-{(1 <i>E</i>)-3-[(2 <i>S</i> ,5 <i>S</i>)-2,5-dimethylpyrrolidin-1-yl]prop-1-en-1-yl}-5-ethyl-3-(2-methoxyethyl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one
I-89:	8-{(1 <i>E</i>)-3-[(2 <i>S</i> ,5 <i>S</i>)-2,5-dimethylpyrrolidin-1-yl]prop-1-en-1-yl}-5-ethyl-3-(2-hydroxyethyl)-2,5-dihydro-4 <i>H</i> -pyrazolo[4,3- <i>c</i>]quinolin-4-one

The depiction of R² in Structural Formula (I) indicates that R² is permissibly bonded to either of the nitrogen atoms in the pyrazolo or triazolo ring. Thus, Structural Formula (I) encompasses Structural Formula (XIII) and (XIV):



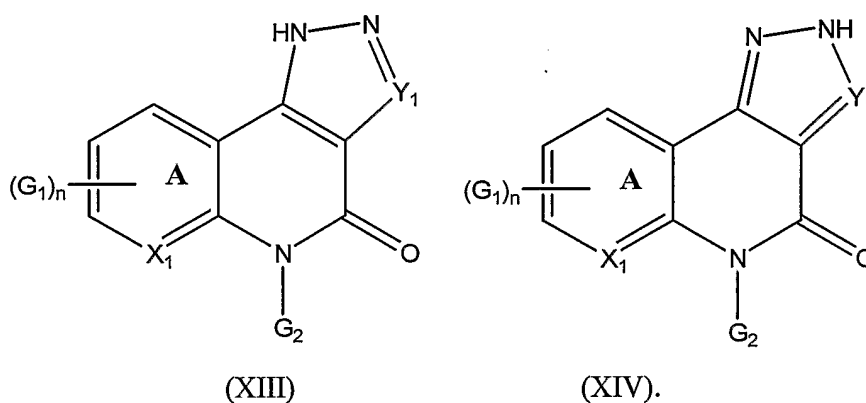
- R^2 in Structural Formulas (I), (VI) and (VII) is $-H$ or a group that is
- 5 cleavable *in vivo*. The term “cleavable *in vivo*” means that after the Chk-1 inhibitor is administered to a subject, at least half of the cleavable groups R^2 groups are converted to $-H$ before half of the administered Chk-1 inhibitor is cleared from the subject or metabolized to a form that is inactive with respect to Chk-1. A cleavable R^2 group can be converted to $-H$ either by hydrolysis or enzymatically. Examples of
- 10 suitable cleavable groups for R^2 include $-S(O)_2R$ to form a sulfonamide, $-C(O)-R$ to form an amide, $-C(O)-OR$ to form a carbamate and $-C(O)-NHR$ or $-C(O)-NR_2$ to form a urea, wherein R is an optionally substituted alkyl or an optionally substituted aryl group, (preferably an unsubstituted alkyl or an optionally substituted aryl group such as an optionally substituted phenyl group) or $-NR_2$ is a substituted or
- 15 unsubstituted heteroaryl or non-aromatic heterocyclic group. Specific examples of pyrazoles with cleavable groups are shown below:



When R^2 represents $-H$, two tautomeric forms of the molecule are possible.

By way of example, these two tautomeric forms are shown below for Structural

5 Formula (I):



It is to be understood that both tautomeric forms are contemplated for the Chk-1 inhibitors disclosed herein.

10 Some of the disclosed Chk-1 inhibitors contain one or more chiral centers. The presence of chiral centers in a molecule gives rise to stereoisomers. For example, a pair of optical isomers, referred to as “enantiomers”, exist for every chiral center in a molecule; and a pair of diastereomers exist for every chiral center in a compound having two or more chiral centers.

15 When a disclosed Chk-1 inhibitor is named or depicted by structure without indicating the stereochemistry, and the inhibitor has at least one chiral center, it is to be understood that the name or structure encompasses one enantiomer of inhibitor free from the corresponding optical isomer, a racemic mixture of the inhibitor and

mixtures enriched in one enantiomer relative to its corresponding optical isomer.

When a mixture is enriched in one enantiomer relative to its optical isomers, the mixture contains, for example, an enantiomeric excess of at least 50%, 75%, 90%, 95% 99% or 99.5%.

5 The enantiomers of the present invention may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one
10 enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. Where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step
15 is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

 When a disclosed Chk-1 is named or depicted by structure without indicating
20 the stereochemistry and has at least two chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diastereomeric pairs
25 in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s). When a mixture is enriched in one diastereomer or diastereomeric pair(s) relative to the other diastereomers or diastereomeric pair(s), the mixture is enriched with the depicted or referenced diastereomer or diastereomeric pair(s) relative to other diastereomers or diastereomeric pair(s) for the compound, for example, by a
30 molar excess of at least 50%, 75%, 90%, 95% 99% or 99.5%.

 The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization, and the individual

enantiomers within each pair may be separated as described above. In certain instances compounds of the present invention may be associated in isolated form with solvent or water, as in a "solvate" or "hydrate". References to the disclosed compounds or structural formulas depicting the disclosed compounds are meant to
5 include such solvates and hydrates.

An "aliphatic group" is non-aromatic, consists solely of carbon and hydrogen and may optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight-chained, branched or cyclic (i.e., "cycloaliphatic"). When straight-chained or branched, an aliphatic group typically
10 contains between about 1 and about 12 carbon atoms, typically between about 1 and about 6 carbon atoms, more typically between about 1 and about 4 carbon atoms. When cyclic, an aliphatic group typically contains between about 3 and about 12 carbon atoms, more typically between about 3 and about 7 carbon atoms. An aliphatic group may be optionally substituted at any "substitutable carbon atom". A
15 "substitutable carbon atom" in an aliphatic group is a carbon in an aliphatic group that is bonded to one or more hydrogen atoms. One or more hydrogen atoms can be optionally replaced with a suitable substituent group. A "haloaliphatic group" is an aliphatic group, as defined above, substituted with one or more halogen atoms. Suitable substituents on a substitutable carbon atom of an aliphatic group are the
20 same as those for an alkyl group.

A cycloaliphatic group can be monocyclic, fused bicyclic or bridged bicyclic. A fused bicyclic cycloaliphatic group comprises two cycloaliphic rings sharing two adjacent ring carbon atoms. A bridged bicyclic cycloaliphatic group comprises two cycloaliphic rings sharing three or four adjacent ring carbon atoms.
25 Examples of bridged bicyclic cycloaliphatic groups include bicyclodecyl, bicyclononyl, bicyclooctyl bicycloheptyl bicyclohexanyl and bicyclopentyl.

The term "alkyl" as used herein means saturated straight-chain, branched or cyclic hydrocarbons. When straight-chained or branched, an alkyl group is typically C₁₋₈, more typically C₁₋₆; when cyclic, an alkyl group is typically C₃₋₁₂, more
30 typically C₃₋₇. The terms "alkyl", "alkoxy", "hydroxyalkyl", "haloalkyl", "aralkyl", "alkoxyalkyl", "alkylamine", "dialkylamine", "alkylamino", "dialkylamino", "alkoxycarbonyl" and the like, used alone or as part of a larger moiety includes both

straight and branched saturated chains containing one to eight carbon atoms. The term "cycloalkyl" used alone or as part of a larger moiety shall include cyclic C₃-C₁₂ hydrocarbons which are completely saturated

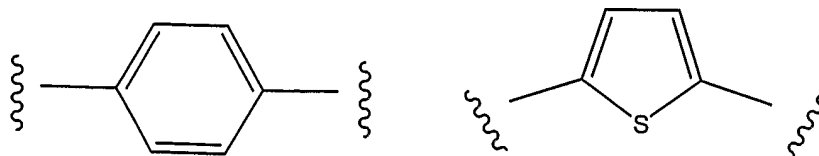
The term "alkoxy" means -O-alkyl, where alkyl is as defined above.

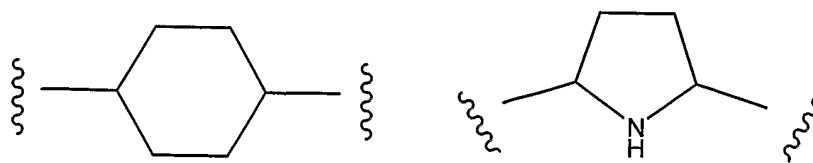
5 The terms "haloalkyl" and "haloalkoxy" means alkyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br or I. Preferably the halogen in a haloalkyl or haloalkoxy is F.

10 The term "acyl group" mean -C(O)R, wherein R is an optionally substituted alkyl group or aryl group (e.g., optionally substituted phenyl). R is preferably an unsubstituted alkyl group or phenyl.

A bivalent aliphatic group is an aliphatic group in a molecule bonded to two other groups by two of its carbon atoms, each carbon atom being connected by a single covalent bond. Examples of bivalent aliphatic groups include alkylidene groups and polymethylene groups. Suitable substituents for a bivalent aliphatic
15 group are the same as for an monovalent aliphatic group (i.e., an aliphatic group attached to another group in the molecule through a single covalent bond from one of its carbon atoms).

An "alkylene group" is represented by -[CH₂]_z-, wherein z is a positive integer, preferably from one to eight, more preferably from one to six. The terms
20 "arylene", "heterocyclene" and "carbocyclene"/"cycloalkylene" refer to aryl, non-aromatic heterocyclic or carbocyclic/cycloalkyl ring(s) in a molecule that are bonded to two other groups in the molecule through a single covalent from two of its ring atoms. Examples include phenylene [- (C₆H₄)-], thienylene [- (C₄H₂S)-], furanylene [- (C₄H₂O)-], pyrrolodinylenes [- (C₄H₅N)-] and cyclohexylene [- (C₆H₁₀)-]. By way of
25 example, the structure of 1,4-phenylene, 2,5-thienylene, 1,4 cyclohexylene and 2,5-pyrrolodinylenes are shown below:





An "alkylidene group" is an alkylene group in which one or more hydrogen atoms are optionally replaced with suitable substituents. Suitable substituents are as defined below for alkyl groups. Preferred substituents include alkyl, hydroxyl, alkoxy, amine, alkylamine, dialkylamine, spiro cycloalkyl, fused cycloalkyl and non-aromatic heterocyclic group. Additional preferred substituents include oxo, halo, hydroxyalkyl, alkoxyalkyl, aminoalkyl. V_3 , V_4 and V_5 are defined to be alkylidene groups. One of ordinary skill in the art will recognize that substitution of the alpha carbon atom of V_3 , V_4 and V_5 (, for example, the carbon atom bonded to R^{13}) with a hydroxyl, cyano or amine will result in a functional group which is not sufficiently stable for pharmaceutical use when certain values of R^{13} are selected. By way of example, when R^{13} is $-OH$ or $-CN$, substitution of the alpha carbon of V_3 with $-OH$ will result in $-CH(OH)OH$ and $-CH(OH)CN$, respectively, both of which are not sufficiently stable for pharmaceutical use. Such groups are not within the scope of the present invention. Thus, when R^{13} is, $-OR^{12}$, $-CN$, $-NR^{11}R^{12}$, $-NR^{11}CONR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NH-C(=NR^{11})NR^{11}R^{12}$, $-N=C(NR^{11}R^{12})_2$, $-NR^{11}SO_2R^{12}$, $-OC(O)R^{12}$, $-NR^{11}C(O)OR^{12}$, $-O-C(O)-OR^{12}$, $-OC(O)-NR^{11}R^{12}$, $-NR^{11}CO-CH(OR^{18})-R^{12}$, $-NR^{11}CO-CH(NR^{18}R^{18})-R^{12}$, $-NR^{11}CO-(CH_2)_nCH(NR^{18}R^{18})-R^{12}$, $-OC(O)-CH(OR^{18})-R^{12}$, $-OC(O)-CH(NR^{18}R^{18})-R^{12}$, $-NR^{11}CO-C(R^{19}R^{19})-OR^{12}$, $-NR^{11}CO-C(R^{19}R^{19})-NR^{11}R^{12}$, $-OC(O)-C(R^{19}R^{19})-OR^{12}$, $-OC(O)-C(R^{19}R^{19})-NR^{11}R^{12}$, $-NR^{11}-C(R^{12})-C(O)OR^{12}$, $-NR^{11}-C(R^{12})-C(O)NR^{11}R^{12}$, $-NR^{11}-C(R^{12})CH_2OR^{12}$, or $-NHC(O)NR^{11}R^{12}$, then the alpha carbon of V_3 and V_4 is preferably unsubstituted or optionally substituted with one or two methyl groups or a spiro cycloalkyl group.

A "spiro cycloalkyl" or "spiro non-aromatic heterocyclic" group is a cycloalkyl or non-aromatic heterocyclic group which shares one ring carbon atom with a carbon atom in an alkylene group or alkyl group, wherein the carbon atom being shared in the alkyl group is not a terminal carbon atom.

The term "oxo" means a group of the formula: $=O$.

The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heteroaryl or non-aromatic heterocyclic group. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR" (as in N-substituted pyrrolidinyl), wherein R" is a suitable substituent for the nitrogen atom in the ring of a non-aromatic nitrogen-containing heterocyclic group, as defined below.

10 The term "aromatic group" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", includes carbocyclic aromatic rings and heteroaryl rings. The term "aromatic group" may be used interchangeably with the terms "aryl", "aryl ring" "aromatic ring", "aryl group" and "aromatic group".

Carbocyclic aromatic ring groups have only carbon ring atoms (typically six to fourteen) and include monocyclic aromatic rings such as phenyl and fused polycyclic aromatic ring systems in which two or more carbocyclic aromatic rings are fused to one another. Examples include 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term "carbocyclic aromatic ring", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings (cycloalkyl or heterocyclic), such as in an indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

The term "heteroaryl", "heteroaromatic", "heteroaryl ring", "heteroaryl group" and "heteroaromatic group", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to heteroaromatic ring groups having five to fourteen members, including monocyclic heteroaromatic rings and polycyclic aromatic rings in which a monocyclic aromatic ring is fused to one or more other carbocyclic or heteroaromatic aromatic rings. Heteroaryl groups have one or more ring heteroatoms. Examples of heteroaryl groups include 2-furanyl, 3-furanyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-pyrazolyl, 4-pyrazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-

pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-triazolyl, 5-triazolyl, tetrazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolyl, indolyl, 5 isoindolyl, acridinyl, or benzisoxazolyl.

The term “non-aromatic heterocyclic group”, used alone or as part of a larger moiety as in “non-aromatic heterocyclalkyl group”, refers to non-aromatic ring systems typically having five to fourteen members, preferably five to ten, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, or S. A “nitrogen-containing non-aromatic heterocyclic group” is a non-aromatic heterocyclic group with at least one nitrogen ring atom, and can be monocyclic, fused bicyclic or bridged bicyclic. A fused bicyclic non-aromatic heterocyclic group comprises two non-aromatic rings, one of which is nitrogen containing, that share two adjacent ring atoms. A bridged bicyclic non-aromatic heterocyclic group comprises two non-aromatic rings, one of which is nitrogen containing, that share three or four adjacent ring atoms.

Examples of non-aromatic heterocyclic groups include 3-1H-benzimidazol-2-one, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, [1,3]-dioxalanyl, [1,3]-dithiolanyl, [1,3]-dioxanyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, *N*-azetidiny, 1-azetidiny, 2-azetidiny, *N*-oxazolidiny, 2-oxazolidiny, 4-oxazolidiny, 5-oxazolidiny, *N*-morpholiny, 2-morpholiny, 3-morpholiny, *N*-thiomorpholiny, 2-thiomorpholiny, 3-thiomorpholiny, *N*-pyrrolidiny, 2-pyrrolidiny, 3-pyrrolidiny, *N*-piperaziny, 2-piperaziny, *N*-piperidiny, 2-piperidiny, 3-piperidiny, 4-piperidiny, *N*-pyrrolidiny, 2-pyrrolidiny, 3-pyrrolidiny, 4-thiazolidiny, diazolony, *N*-substituted diazolony, 1-phthalimidiny, benzoxany, benzopyrrolidiny, benzopiperidiny, benzoxolany, benzothiolany, benzothianyl, tetrahydroquinoliny, tetrahydroisoquinoliny, azabicyclopentyl, azabicyclohexyl, azabicycloheptyl, azabicyclooctyl, azabicyclononyl, azabicyclodecyl, diazabicyclohexyl, diazabicycloheptyl, diazabicyclooctyl, diazabicyclononyl, and diazabicyclodecyl. Also included within the scope of the term “non-aromatic heterocyclic group”, as it is used herein, is a group in which a non-aromatic heteroatom-containing ring is

fused to one or more aromatic or non-aromatic rings, such as in an indoliny, chromanyl, phenanthridinyl, or tetrahydroquinoliny, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. The designation “*N*” on *N*-morpholiny, *N*-thiomorpholiny, *N*-pyrrolidiny, *N*-piperaziny and *N*-piperidiny indicates that the non-aromatic heterocyclic group is attached to the remainder of the molecule at the ring nitrogen atom.

An “aralkyl group”, “heteroaralkyl group” or “non-aromatic heterocyclalkyl” are an alkyl group substituted with an aryl, heteroaryl or non-aromatic heterocyclic group, respectively.

The term “ring atom” is an atom such as C, N, O or S that is in the ring of an aromatic group, cycloalkyl group or non-aromatic heterocyclic ring.

A “substitutable ring atom” in an aromatic group is a ring carbon or nitrogen atom bonded to a hydrogen atom. The hydrogen can be optionally replaced with a suitable substituent group. Thus, the term “substitutable ring atom” does not include ring nitrogen or carbon atoms which are shared when two rings are fused. In addition, “substitutable ring atom” does not include ring carbon or nitrogen atoms when the structure depicts that they are already attached to a moiety other than hydrogen. Thus, the carbon atom bonded to R^4 in Structural Formula (V) is not a “substitutable ring atom” within the meaning of the term, as it is used herein.

An aryl group (including, but not limited to, Ring A, and aryl groups represented by R^7 , R^{12} , R^{14} , R^{15} , R^{16} , R^{17} , R^{13a} , R^{13b} , Cy, NR^{11} , R^{12} , R^{50} , R^{61} , R^{201} , R^{202} and R^x) may contain one or more substitutable ring atoms, each bonded to a suitable substituent. Examples of suitable substituents on a substitutable ring carbon atom of an aryl group include halogen, R^0 , $-OR^0$, $-O(haloalkyl)$, $-SR^0$, trialkylsilyl, boronate, alkylboronate, dialkylboronate, $-NO_2$, $-CN$, $-N(R')_2$, $-NR'CO_2R^0$, $-NR'C(O)R^0$, $-NR'NR'C(O)R^0$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^0$, $-C(O)C(O)R^0$, $-C(O)CH_2C(O)R^0$, $-CO_2R^0$, $-C(O)R^0$, $-C(O)N(R^0)_2$, $-OC(O)R^0$, $-OC(O)N(R^0)_2$, $-S(O)_2R^0$, $-SO_2N(R')_2$, $-S(O)R^0$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^0$, $-C(=S)N(R')_2$, $-NR'-C(=NH)-N(R')_2$ and $-C(=NH)-N(R')_2$ or two adjacent ring carbon atoms may be substituted with 1,2-methylene-dioxy or 1,2-ethylene-dioxy.

Each R' is independently R^0 , $-CO_2R^0$, $-SO_2R^0$ or $-C(O)R^0$ or $-NR'R'$ is an optionally substituted non-aromatic nitrogen-containing heterocyclic group;

Each R^0 is independently hydrogen or an alkyl group, non-aromatic heterocyclic group or aromatic group and the alkyl, non-aromatic heterocyclic group and aromatic group represented by R^0 is optionally substituted with one or more independently selected groups represented by $R^\#$.

5 $R^\#$ is R^+ , $-OR^+$, $-O(\text{haloalkyl})$, $-SR^+$, $-NO_2$, $-CN$, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$, or $-C(=NH)-N(R^+)_2$.

10 R^+ is $-H$, a C1-C3 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, $-CN$, $-NO_2$, amine, alkylamine or dialkylamine; or $-N(R^+)_2$ is a non-aromatic heterocyclic group, provided that non-aromatic heterocyclic groups represented by R^+ and $-N(R^+)_2$ that comprise a secondary ring.
15 amine are optionally acylated or alkylated.

An alkyl or aliphatic group (including, but not limited to, groups represented by R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{11} , R^{12} , R^{14} , R^{15} , R^{16} , R^{18} , R^{19} , R^{20} , R^{52} , R^{53} , R^{62} , R^{63} , R^{200} , R^{201} , R^x , V_1 , V_3 , V_4 , V_5 , V_6 , T_0 , G_2 , W_1 , and $NR^{11}R^{12}$) or a non-aromatic heterocyclic group (including, but not limited to, non-aromatic heterocyclic groups
20 represented by R^7 , R^{12} , R^{13a} , R^{13b} , R^{50} , R^{51} , R^{52} , R^{61} , R^{201} , R^{202} , R^x , V_5 , Cy , $NR^{11}R^{12}$, $NR^{62}R^{62}$ and $-NR^{18}R^{18}$) may contain one or more substituents. Examples of suitable substituents for an alkyl or aliphatic group or a ring carbon of a non-aromatic heterocyclic group include those listed above for a substitutable carbon of an aryl and the following: $=O$, $=S$, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2$
25 (alkyl), $=NNHSO_2$ (alkyl), $=NR^*$, spiro cycloalkyl group or fused cycloalkyl group. Each R^* is independently selected from hydrogen, an unsubstituted alkyl group or a substituted alkyl group. Examples of substituents on the alkyl group represented by R^* include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy,
30 dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl. When R^1 is substituted with cycloalkyl or phenyl the cycloalkyl and phenyl are preferably unsubstituted.

Two rings are fused when they share two adjacent ring atoms. A cycloalkyl group or non-aromatic heterocyclic group is fused to an alkyl or alkylidene group when two adjacent ring carbons from the cycloalkyl group or non-aromatic heterocyclic group are also adjacent carbon atoms in the alkyl or alkylidene group.

5 A "substitutable ring atom" in a non-aromatic carbocyclic or nitrogen-containing non-aromatic heterocyclic group is a ring carbon or nitrogen atom that is bonded to at least one hydrogen atom. The hydrogen atom can therefore optionally be replaced with the substituent. The term "substitutable ring atom" therefore excludes ring nitrogen and carbon atoms that already have three (for nitrogen) and
10 four (for carbon) bonds to atoms other than hydrogen.

A preferred position for substitution of a non-aromatic nitrogen-containing heterocyclic group is the nitrogen ring atom. Suitable substituents on the nitrogen of a non-aromatic heterocyclic group or heteroaryl group include $-R^{\wedge}$, $-N(R^{\wedge})_2$, $-C(O)R^{\wedge}$, $-CO_2 R^{\wedge}$, $-C(O)C(O)R^{\wedge}$, $-C(O)CH_2 C(O)R^{\wedge}$, $-SO_2 R^{\wedge}$, $-SO_2 N(R^{\wedge})_2$,
15 $-C(=S)N(R^{\wedge})_2$, $-C(=NH)-N(R^{\wedge})_2$, and $-NR^{\wedge} SO_2 R^{\wedge}$; wherein $R^{\wedge}$ is hydrogen, an alkyl group, a substituted alkyl group, phenyl (Ph), substituted Ph, $-O(Ph)$, substituted $-O(Ph)$, $CH_2(Ph)$, or an unsubstituted heteroaryl or heterocyclic ring. Examples of substituents on the alkyl group or the phenyl ring represented by $R^{\wedge}$ include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl,
20 dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxy carbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl. Preferred substituents on a substitutable nitrogen atom of a nitrogen-containing heteroaryl or nitrogen-containing non-aromatic heterocyclic group include C1-C3 alkyl, C1-C3 acyl, C1-C3 alkylsulfonyl, $-OC(O)N(R')_2$, $-NR'C(O)OR'$, or $-NR'C(O)N(R')_2$ group, where
25 R' is H or C1-C3 alkyl.

Non-aromatic nitrogen containing heterocyclic rings that are substituted on a ring nitrogen and attached to the remainder of the molecule at a ring carbon atom are said to be *N*-substituted. For example, an *N*-alkyl-piperidinyl group is attached to the remainder of the molecule at the two, three or four position of the piperidinyl ring
30 and substituted at the ring nitrogen with an alkyl group. Non-aromatic nitrogen containing heterocyclic rings such as pyrazinyl that are substituted on a ring nitrogen and attached to the remainder of the molecule at a second ring nitrogen atom are said

to be *N'*-substituted-*N*-heterocycles. For example, an *N'*-acyl-*N*-pyrazinyl group is attached to the remainder of the molecule at one ring nitrogen atom and substituted at the second ring nitrogen atom with an acyl group.

5 Additionally, pharmaceutically acceptable salts of the compounds of the disclosed Chk-1 inhibitors are included in the present invention. For example, an acid salt of a compound containing an amine or other basic group can be obtained, by reacting the compound with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, perchloric acid and the like. Compounds with a quaternary ammonium group also contain a counteranion such as
10 chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid.

15 Salts of compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base. Such a pharmaceutically acceptable salt may be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium
20 salts, as well as salts made from physiologically acceptable organic bases such as trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, *N,N'*-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, *N*-benzyl- β -phenethylamine, dehydroabietylamine, *N,N'*-bisdehydroabietylamine,
25 glucamine, *N*-methylglucamine, collidine, quinine, quinoline, and basic amino acid such as lysine and arginine.

The disclosed Chk-1 inhibitors are advantageously administered to inhibit Chk-1 in a subject in whom a beneficial therapeutic or prophylactic effect can be achieved by inhibiting Chk-1, i.e., a subject in need of Chk-1 inhibition. A "subject"
30 is a mammal, preferably a human or an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep,

pigs, horses, and the like), and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

The disclosed Chk-1 inhibitors are particularly useful in therapeutic applications relating to a Chk-1-mediated disorder. As used herein, the term "Chk-1-mediated disorder" includes any disorder, disease or condition which is caused or characterized by an increase in Chk-1 expression or activity, or which requires Chk-1 activity. The term "Chk-1-mediated disorder" also includes any disorder, disease or condition in which inhibition of Chk-1 activity is beneficial.

Chk-1 inhibition can be used to achieve a beneficial therapeutic or prophylactic effect, for example, in subjects with a proliferative disorder. Non-limiting examples of proliferative disorders include chronic inflammatory proliferative disorders, e.g., psoriasis and rheumatoid arthritis; proliferative ocular disorders, e.g., diabetic retinopathy; benign proliferative disorders, e.g., hemangiomas; and cancer. As used herein, the term "cancer" refers to a cellular disorder characterized by uncontrolled or dysregulated cell proliferation, decreased cellular differentiation, inappropriate ability to invade surrounding tissue, and/or ability to establish new growth at ectopic sites. The term "cancer" includes, but is not limited to, solid tumors and bloodborne tumors. The term "cancer" encompasses diseases of skin, tissues, organs, bone, cartilage, blood, and vessels. The term "cancer" further encompasses primary and metastatic cancers.

Non-limiting examples of solid tumors that can be treated with the disclosed Chk-1 inhibitors include pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; hepatocellular cancer; lung cancer, including, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck; melanoma; neuroendocrine cancer, including metastatic neuroendocrine tumors; brain tumors, including, e.g., glioma, anaplastic oligodendroglioma, adult

glioblastoma multiforme, and adult anaplastic astrocytoma; bone cancer; and soft tissue sarcoma.

Non-limiting examples of hematologic malignancies that can be treated with the disclosed Chk-1 inhibitors include acute myeloid leukemia (AML); chronic
5 myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's disease (HD); non-Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma; T-cell lymphoma; multiple myeloma (MM); Waldenstrom's macroglobulinemia;
10 myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with excess blasts (RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes.

The disclosed Chk-1 inhibitors are particularly useful in the treatment of
15 cancers or cell types in which Chk-1 protein or activity is upregulated, including, without limitation, rapidly proliferating cells and drug-resistant cells (Shyjan et al., U.S. Patent No. 6,723,498 (2004)), as well as retinoblastomas such as Rb negative or inactivated cells (Gottifredi et al., Mol. Cell. Biol., 21:1066 (2001)), or where the ARF^{p14/p19} locus has been inactivated or misregulated. The disclosed Chk-1
20 inhibitors also are particularly useful in the treatment of cancers or cell types in which another checkpoint pathway has been mutated or abrogated, including, without limitation, cancers or cell types in which p53 or the p53 pathway has been inactivated or abrogated.

The disclosed Chk-1 inhibitors can be administered in conjunction with other
25 therapeutic agents, including anticancer agents. As used herein, the term "anticancer agent" refers to any agent that is administered to a subject with cancer for purposes of treating the cancer. Use of Chk-1 inhibitors for the treatment of cancer is particularly advantageous and can enhance the effectiveness of the treatment when:
1) combined with radiation therapy or chemotherapeutic agents that act by causing
30 damage to the genetic material of cells (collectively referred to herein as "DNA damaging agents"); 2) combined with agents which are otherwise cytotoxic to cancer cells during cell division; 3) combined with agents which are proteasome

inhibitors; 4) combined with agents which inhibit NF- κ B (e.g., IKK inhibitors) (Bottero et al., Cancer Res., 61:7785 (2001)); or 5) used with combinations of cancer drugs with which are not cytotoxic when administered alone, yet in combination produce a toxic effect. In preferred embodiments, a disclosed Chk-1 inhibitor is
5 combined with a DNA damaging agent.

Non-limiting examples of DNA damaging chemotherapeutic agents include topoisomerase I inhibitors (e.g., irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin); topoisomerase II inhibitors (e.g., etoposide, teniposide, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil,
10 busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics (e.g., 5-fluorouracil, capecitabine, gemcitabine, fludarabine, cytarabine, mercaptopurine,
15 thioguanine, pentostatin, and hydroxyurea).

Agents that disrupt cell replication include: paclitaxel, docetaxel, and related analogs; vincristine, vinblastin, and related analogs; thalidomide and related analogs (e.g., CC-5013 and CC-4047); protein tyrosine kinase inhibitors (e.g., imatinib mesylate and gefitinib); antibodies which bind to proteins overexpressed in cancers
20 and thereby downregulate cell replication (e.g., trastuzumab, rituximab, cetuximab, and bevacizumab); and other inhibitors of proteins or enzymes known to be upregulated, over-expressed or activated in cancers, the inhibition of which downregulates cell replication.

The disclosed Chk-1 inhibitors are also effective when used in combination
25 with DNA-damaging anti-cancer drugs and/or radiation therapy to treat subjects with multi-drug resistant cancers. A cancer is resistant to a drug when it resumes a normal rate of tumor growth while undergoing treatment with the drug after the tumor had initially responded to the drug. A tumor "responds to a drug" when it exhibits a decrease in tumor mass or a decrease in the rate of tumor growth. The
30 term "multi-drug resistant cancer" refers to cancer that is resistant to two or more drugs, often as many as five or more.

As such, an "effective amount" of the disclosed Chk-1 inhibitors is the quantity which inhibits Chk-1 when administered to a subject or which, when administered to a subject with cancer, slows tumor growth, ameliorates the symptoms of the disease and/or increases longevity. When used in combination with a DNA damaging agent, an effective amount of the Chk-1 inhibitor is the quantity at which a greater response is achieved when the Chk-1 inhibitor is co-administered with the DNA damaging anti-cancer drug and/or radiation therapy than is achieved when the DNA damaging anti-cancer drug and/or radiation therapy is administered alone. When used as a combination therapy, an "effective amount" of the DNA damaging agent is administered to the subject, which is a quantity that normally produces an anti-cancer effect.

A disclosed Chk-1 inhibitor can be co-administered with another therapeutic agent (e.g., DNA-damaging agent, agent that disrupts cell replication, proteasome inhibitor, NF- κ B inhibitor, or other anticancer agent) as part of the same pharmaceutical composition or, alternatively, as separate pharmaceutical compositions. When administered separately, the Chk-1 inhibitor can be administered prior to, at the same time as, or following administration of the other agent, provided that the enhancing effect of the Chk-1 inhibitor is retained.

The amount of Chk-1 inhibitor, DNA damaging anti-cancer drug and radiation dose administered to the subject will depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Effective dosages for commonly used anti-cancer drugs and radiation therapy are well known to the skilled person. Effective amounts of the disclosed Chk-1 inhibitors typically range between about 1 mg/mm² per day and about 10 grams/mm² per day, and preferably between 10 mg/mm² per day and about 5 grams/mm².

The Chk-1 inhibitors described herein, and the pharmaceutically acceptable salts, solvates and hydrates thereof can be used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The Chk-1 inhibitor will be present in such

pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein. Techniques for formulation and administration of the compounds of the instant invention can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995).

For oral administration, the Chk-1 inhibitor or salts thereof can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, pills, powders, syrups, solutions, suspensions and the like.

The tablets, pills, capsules, and the like contain from about 1 to about 99 weight percent of the active ingredient and a binder such as gum tragacanth, acacias, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

For parental administration the disclosed Chk-1 inhibitor, or salts thereof can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable salts of the compounds. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

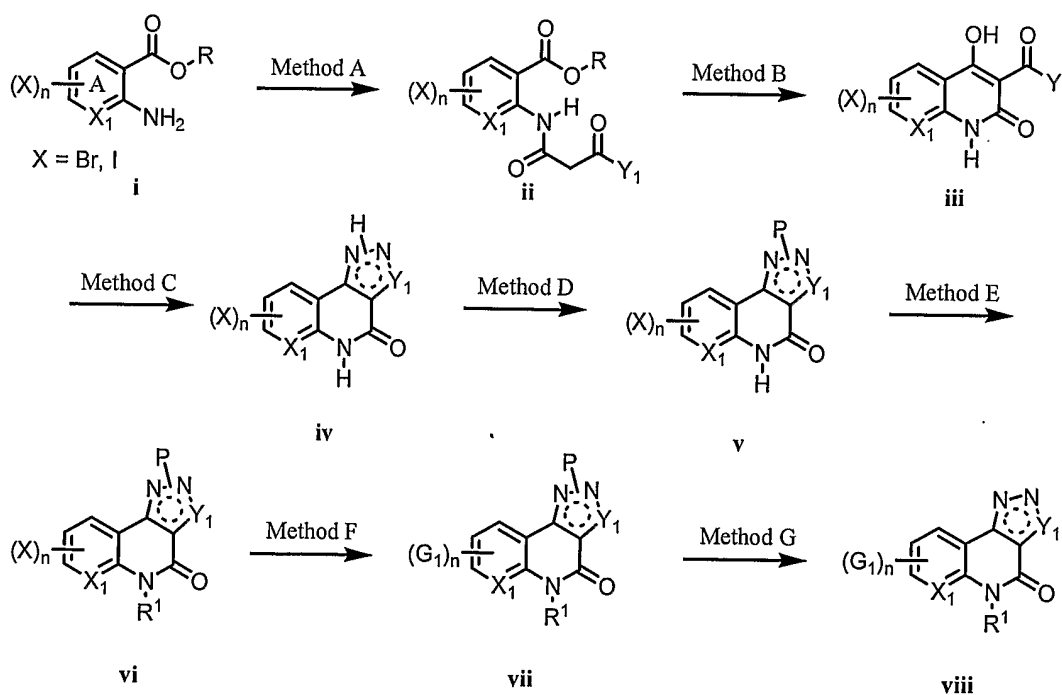
In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation, for example, subcutaneously or intramuscularly or by intramuscular injection. Thus, for example, as an emulsion in an acceptable oil, or

ion exchange resins, or as sparingly soluble derivatives, for example, as sparingly soluble salts.

Preferably disclosed Chk-1 inhibitors or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be any unit dosage form known in the art including, for example, a capsule, an IV bag, a tablet, or a vial. The quantity of active ingredient (viz., a compound of Structural Formula I, II or III or salts thereof) in a unit dose of composition is an effective amount and may be varied according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration which may be by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal and intranasal.

The disclosed Chk-1 inhibitors can be prepared by a variety of procedures one of which is illustrated in scheme 1.

Scheme 1: General route for the synthesis of 2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-ones.



Methods for the synthesis of 2-amino benzoates of formula **i** are known, and exemplary synthetic procedures are described in the Examples. Conversion of **i** to the amido-benzoate of formula **ii** can be accomplished by acylation of the aniline using a suitable acyl-transfer reagent as exemplified in Method A. Compound **iii** may be prepared by a subsequent cyclization reaction, which may be mediated by an appropriate acid or base. Conversion of the quinolone of formula **iii** to the fused pyrazole of formula **iv** may be performed by a reaction with hydrazine or substituted hydrazine according to Method C. A suitable protecting group P may then be introduced, allowing the formation of compounds of the formula **v** according to Method D. Protecting groups are selected so that they are suitable for the depicted transformations and can be removed following the synthesis with little or no loss of yield. The introduction and selective removal of protecting groups are taught, e.g., in Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (1991) the entire contents of which are incorporated herein by reference. Compound **vi** may be prepared by the alkylation of the quinolone ring with a suitable alkylating reagent and may be mediated by an appropriate acid or base according to Method E. Alternatively, a substituted 2-amino benzoate, with the R¹ substituent already in place, may be used in Method A in place of compound **i**.

Compound **vi** may then undergo a cross-coupling reaction with an appropriate reagent such as a boronic acid, stannane, organozinc, amine, or amide, typically in the presence of a transition metal catalyst, according to Method F. One of ordinary skill in the art will appreciate that compounds of formula **vi**, wherein X is -OSO₂CF₃, may be employed in the cross-coupling reaction in place of the halides depicted in Scheme 1. Such compounds may be prepared from the compounds of formula **i**, wherein X is a protected hydroxyl, according to Methods A-E, followed by deprotection of the hydroxyl and conversion to the triflate.

The coupled products of formula **vii** can be further alkylated, acylated, oxidized, reduced, or derivatized. Alternatively, the cross-coupling reaction of Method F can be performed prior to the alkylation reaction of Method E. Those of ordinary skill in the art will recognize the feasibility of carrying out many of the transformations depicted in Scheme 1 sequentially or in a differing order of steps.

The protecting group(s) may then be removed from compounds of the formula **vii** to afford the compounds of the formula **viii**, according to Method G.

EXAMPLES

Definitions

5	AcOH	acetic acid
	aq	aqueous
	ATP	adenosine triphosphate
	BSA	bovine serum albumin
	Boc	<i>tert</i> -butoxycarbonyl
10	DMF	<i>N,N</i> -dimethylformamide
	DCE	dichloroethane
	DCM	dichloromethane
	DMSO	dimethylsulfoxide
	DTT	dithiothreitol
15	EDTA	ethylenediaminetetraacetic acid
	EtOAc	ethyl acetate
	EtOH	ethanol
	eq	equivalents
	LCMS	liquid chromatography mass spectrum
20	MeOH	methanol
	MHz	megahertz
	MTT	methylthiazoletetrazolium
	rt	room temperature
	R _t	retention time
25	XTT	2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide inner salt
	WST	(4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzene disulfonate sodium salt
	PKA	cAMP-dependent protein kinase
30	TBTU	<i>O</i> -Benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
	TEA	triethylamine
	THF	tetrahydrofuran

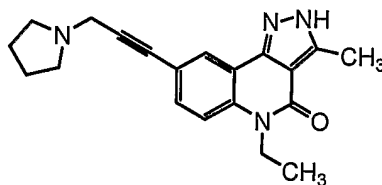
	h	hours
	min	minutes
	m/z	mass to charge
	MS	mass spectrum
5	HRMS	high resolution mass spectrum
	NMR	nuclear magnetic resonance

ANALYTICAL METHODS

- 10 LCMS: compounds were analysed on a Phenomenex Luna column (C18, 50 x 4.6 mm, 5 um) eluted with 5% acetonitrile/water/0.1% formic acid (mobile phase A) and 100% acetonitrile/0.1% formic acid (mobile phase B) with a flow rate of 1.5 ml/min. The 5 min cycle consisted of a gradient of 100% A to 100% B in 3.5 min; 100% B for 1 min; 100% B to 100% A in 0.1 min; then re-equilibration with mobile
15 phase A for 0.49 min.

NMR: proton spectra were recorded on a Bruker 300 or 400 MHz ultrashield spectrometer. Chemical shifts are reported relative to methanol (δ 3.31), dimethyl sulfoxide (δ 2.50), or chloroform (δ 7.26).

- 20 **Example 1:** Preparation of 5-Ethyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

**Step 1, Preparation of 5-Iodoisatoic Anhydride.**

- To a solution of 2-amino-5-iodobenzoic acid (50.09 g, 190.4 mmol) in 800.
25 mL anhydrous THF at rt was added triphosgene (19.1 g, 64.4 mmol). The solution was stirred at rt for 6 h, then stored at 0 °C for 16 h. The precipitate was filtered and washed with diethyl ether to give 40.32 g product. The filtrate was then concentrated and the residue was triturated with THF/ether (1:1) then filtered and washed with ether to give an additional 9.91 g product. The overall yield was
30 50.23 g.

Step 2, Preparation of Methyl 2-amino-5-iodobenzoate.

To a suspension of 5-iodoisatoic anhydride (50.23 g, 173.8 mmol) in 800 mL anhydrous methanol at rt was added 4-dimethylaminopyridine (1.97 g, 16.2 mmol). The mixture was then stirred at 80 °C for 4 h, then cooled to rt and the solvent was evaporated in vacuo. The residue was partitioned between EtOAc and 0.1 N HCl. The layers were separated and the organic phase was then washed with 0.1 N HCl (2 x), brine, then dried over sodium sulfate and concentrated in vacuo to give 47.06 g product as an off-white solid.

Step 3, Preparation of Methyl 2-(acetoacetylamino)-5-iodobenzoate.

A solution of methyl 2-amino-5-iodobenzoate (17.9 g, 64.6 mmol) and methylacetoacetate (7.0 mL, 64.6 mmol) in toluene (250 mL) was heated to reflux using a Soxhlet extractor filled with 3 angstrom molecular sieves. After 24 h, the molecular sieves were replaced, more methylacetoacetate (3.75 mL, 32.3 mmol) was added, and the solution was refluxed 2 days. Concentration in vacuo and wash with diethyl ether afforded 24.7 g (76%) of methyl 2-(acetoacetylamino)-5-iodobenzoate as an off-white powder. LCMS: $R_t = 1.70$ min, $[MH^+ 362.0]$.

Step 4, Preparation of 3-Acetyl-4-hydroxy-6-iodoquinolin-2(1H)-one.

To a suspension of methyl 2-(acetoacetylamino)-5-iodobenzoate (2.3 g, 6.37 mmol) in CH_3OH (64 mL) was added $NaOCH_3$ solution in CH_3OH (1.09 mL, 4.78 mmol) dropwise via syringe. The mixture was heated to 70 °C for 3 h then cooled to rt and diluted with 1.0 N HCl solution (50 mL) and filtered. The resulting solid was washed with H_2O (2x) and Et_2O (2x) and dried under high vacuum. A 91% yield of 3-acetyl-4-hydroxy-6-iodoquinolin-2(1H)-one was isolated as a white solid. LCMS: $R_t = 1.93$ min, $[MH^+ 330.0]$.

Step 5, Preparation of 8-Iodo-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

To a suspension of 3-acetyl-4-hydroxy-6-iodoquinolin-2(1H)-one (13.2 g, 40.0 mmol) in DMF (200 mL) was added hydrazine hydrate (5.8 mL, 120 mmol)

and the mixture was heated to reflux for 3 h. The solution was cooled to rt before it was carefully quenched with 1.0 N HCl solution (100 mL), stirred for 1 h and filtered. The filtered material was washed with H₂O (2x) and Et₂O (2x) before being dried under high vacuum to afford 9.45 g (73%) of 8-iodo-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one as a white solid. LCMS: *R*_t = 1.37 min, [MH⁺ 326.0].

Step 6, Preparation of 8-Iodo-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

10 A mixture of 8-iodo-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (9.9 g, 30.6 mmol), 3,4-dihydro-2*H*-pyran (11.0 mL, 122.3 mmol) and *p*-toluenesulfonic acid (0.6 g, 3.06 mmol) was heated to 90 °C for 18 h. Dilution of the mixture with Et₂O followed by filtration afforded 9.0 g (72%) of 8-iodo-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one
15 as a white powder. LCMS: *R*_t = 1.81 min, [MH⁺ 410.0].

Step 7, Preparation of 5-Ethyl-8-iodo-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

20 A mixture of 8-iodo-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (5.0 g, 12.2 mmol) and Cs₂CO₃ (19.9 g, 61.1 mmol) in DMF (122 mL) was stirred 10 min before ethyliodide (2.47 mL, 30.6 mmol) in DMF (5 mL) was added. The reaction mixture was heated to 90 °C and stirred for 1 h then cooled to rt. Dilution of the mixture with cold H₂O followed by filtration resulted in a white solid. The crude material was purified by crystallization in
25 EtOAc (100 mL) and hexane (200 mL) at 0 °C for 12 h. Crystals were filtered and dried to afford 4.38 g (83%) of 5-ethyl-8-iodo-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one as a white solid. LCMS: *R*_t = 2.20 min, [MH⁺ 438.3].

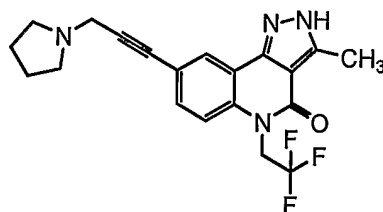
30 **Step 8,** Preparation of 5-Ethyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

To a solution of 5-ethyl-8-iodo-3-methyl-2-(tetrahydro-2H-pyran-2-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one (1.5 g, 3.43 mmol) in 35 mL DMF at rt was added dichlorobis(triphenylphosphine)palladium (84 mg, 0.12 mmol), copper iodide (52 mg, 0.274 mmol), and triethylamine (1.91 mL, 13.72 mmol). The solution was degassed, backfilled with Ar, and stirred at rt for 1 h. 1-Prop-2-yn-1-ylpyrrolidine (0.749 mL, 6.86 mmol) was then added and the solution was stirred at 60 °C for 16 h (for some alkynes the reaction was carried out at rt). The solution was then allowed to cool to rt, and was diluted with EtOAc and water. The organic phase was washed with water followed by brine, dried over sodium sulfate and the concentrated in vacuo. The residue was purified by silica gel chromatography (10-50% ethyl acetate in hexanes) to give 1.28 g product as a white solid (89%). LCMS: [MH⁺419.3].

Step 9, Preparation of 5-Ethyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

To a solution of 5-ethyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2-(tetrahydro-2H-pyran-2-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one (1.28 g, 3.05 mmol) in CH₃OH (100 mL) was added concentrated HCl (1.0 mL) and the reaction was stirred for 4 h. Concentration in vacuo afforded 1.32 g of 5-ethyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.29 (d, 1 H), 7.72 (dd, 1 H), 7.61 (d, 1H), 4.43 (s, 2 H), 4.37 (q, 2 H), 3.81-3.72 (m, 2 H), 3.41-3.33 (m, 2 H), 2.70 (s, 3 H), 2.31-2.05 (m, 4 H), 4.32 (t, 3 H). LCMS: R_t = 0.180 min, [MH⁺335.2].

Example 2: Preparation of 3-Methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-5-(2,2,2-trifluoroethyl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

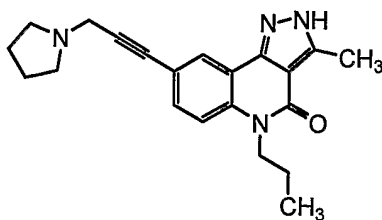


The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (300 MHz, DMSO- d_6) δ 8.40 (d, 1 H), 7.8-7.6 (m, 2 H), 5.30-5.10 (m, 2 H), 4.90 (s, 2 H), 3.60-3.39 (m, 2 H), 3.30 (s, 3 H), 2.60-2.55 (m, 2 H), 2.10-1.85 (m, 4 H). LCMS: R_t = 1.07 min, $[\text{MH}^+ 389.2]$.

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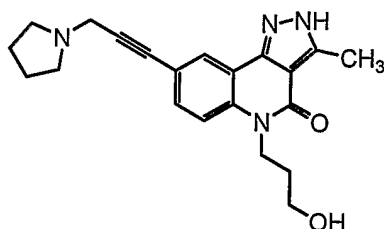
Example 3: Preparation of 3-Methyl-5-propyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

10 **Example 1.** ^1H NMR (400 MHz, DMSO- d_6) δ 7.92 (s, 1 H), 7.25 (d, 1 H), 7.17 (d, 1 H), 3.99 (d, 2 H), 3.77 (app t, 2 H), 3.20-3.11 (m, 2 H), 2.80-2.78 (m, 2 H), 2.15 (s, 3 H), 1.70-1.45 (m, 4 H), 1.25-1.15 (m, 2 H), 0.55 (t, 3 H). LCMS: R_t = 1.12 min, $[\text{MH}^+ 349.4]$.

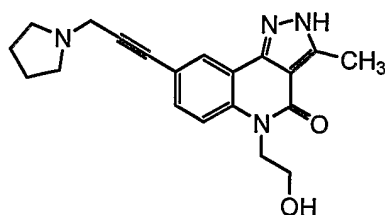
15 **Example 4:** Preparation of 5-(3-Hydroxypropyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

20 **Example 1.** ^1H NMR (400 MHz, DMSO- d_6) δ 7.32 (s, 1 H), 6.77-6.75 (m, 2 H), 3.57 (app t, 2 H), 2.90 (s, 2 H), 2.86 (t, 2 H), 2.02-1.98 (m, 4 H), 1.84 (s, 3 H), 1.12-1.07 (m, 6 H). LCMS: R_t = 0.92 min, $[\text{MH}^+ 365.4]$.

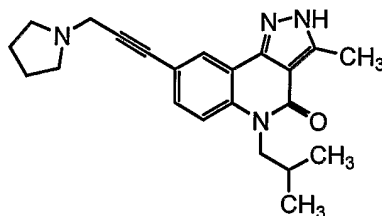
Example 5: Preparation of 5-(2-Hydroxyethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.69 (br s, 1 H), 8.15 (d, 1 H), 7.66-7.50 (m, 2 H), 4.87 (t, 1 H), 4.36-4.26 (m, 2 H), 3.66-3.61 (m, 4 H), 2.67-2.53 (m, 4 H), 1.78-1.71 (m, 4 H). LCMS: $R_t = 0.82$ min, $[\text{MH}^+ 351.5]$.

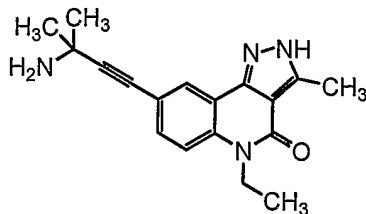
Example 6: Preparation of 5-Isobutyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.95 (br s, 1 H), 8.27 (s, 1 H), 7.72-7.52 (m, 2 H), 4.42 (d, 2 H), 4.16-4.10 (m, 2 H), 3.65-3.55 (m, 3 H), 3.24-3.15 (m, 2 H), 2.59 (s, 3 H), 2.15-1.90 (m, 4 H), 0.89 (d, 6 H). LCMS: $R_t = 1.15$ min, $[\text{MH}^+ 363.5]$.

Example 7: Preparation of 8-(3-Amino-3-methylbut-1-yn-1-yl)-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

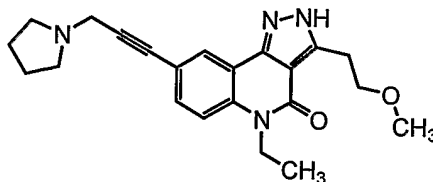


The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (400 MHz, CD_3OD) δ 8.25 (d, 1 H), 7.66 (dd, 1 H), 7.60 (d, 1

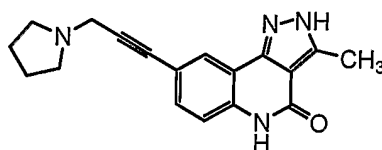
H), 4.38 (q, 2 H), 2.70 (s, 3 H), 1.77 (s, 6 H), 1.33 (t, 3 H). LCMS: R_t = 0.98 min, $[M2H^+310.2]$.

Example 8: Preparation of 5-Ethyl-3-(2-methoxyethyl)-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



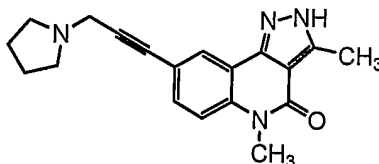
The title compound was prepared using analogous procedures as outlined in **Example 1**. ^1H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1 H), 7.72 (d, 1 H), 7.63 (d, 1 H), 4.42-4.36 (m, 4 H), 3.81 (t, 2 H), 3.56-3.47 (m, 4 H), 3.40-3.35 (m, 5 H), 2.19-2.14 (m, 4 H), 1.34 (t, 3 H). LCMS: R_t = 0.90 min, $[\text{MH}^+379.3]$.

Example 9: Preparation of 3-Methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in **Example 1**. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1 H), 7.55 (d, 1 H), 7.35 (d, 1 H), 2.68 (s, 2 H), 2.82-2.76 (m, 4 H), 2.71 (s, 3 H), 1.95-1.82 (m, 4 H). LCMS: R_t = 1.14 min, $[\text{MH}^+307.4]$.

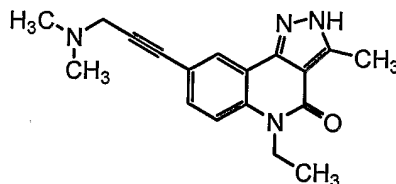
Example 10: Preparation of 3,5-Dimethyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in **Example 1**. ^1H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1 H), 7.70 (d, 1 H), 7.59 (d, 1

H), 4.30 (s, 2 H), 3.70 (s, 3 H), 3.52-3.39 (m, 4 H), 2.68 (s, 3 H), 2.18-2.10 (m, 4 H).
LCMS: R_t = 0.85 min, $[MH^+]$ 321.4].

Example 11: Preparation of 8-[3-(Dimethylamino)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



Step 1, Preparation of 5-Ethyl-8-(3-hydroxyprop-1-yn-1-yl)-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

To a solution of 5-ethyl-8-iodo-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (as prepared in **example 1**, 2.0 g, 4.57 mmol) in 45 mL DMF at rt was added dichlorobis(triphenylphosphine)palladium (112 mg, 0.159 mmol), copper iodide (69 mg, 0.366 mmol), and triethylamine (2.54 mL, 18.3 mmol). The solution was degassed with Ar, and stirred at rt for 1 h. Prop-2-yn-1-ol (0.533 mL, 9.15 mmol) was then added and the solution was stirred at 60 °C for 16 h (for some alkynes the reaction was carried out at rt). The solution was then allowed to cool to rt, and was diluted with EtOAc and water. The organic phase was washed with water followed by brine, dried over sodium sulfate and the concentrated in vacuo. The residue was purified by silica gel chromatography (0-100% ethyl acetate in hexanes) to give 1.5 g product as a white solid (89%). LCMS: $[MH^+]$ 366.4].

Step 2, Preparation of 3-[5-Ethyl-3-methyl-4-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-8-yl]prop-2-ynal.

To a solution of 5-ethyl-8-(3-hydroxyprop-1-yn-1-yl)-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (100 mg, 0.274 mmol) in DCM (3.0 mL) was added Dess-Martin periodinane (232 mg, 0.548 mmol). The reaction was stirred 1 h, diluted with DCM and washed with sodium thiosulfate (saturated aq solution), sodium bicarbonate, and brine. The solution was

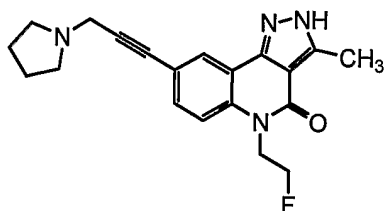
dried over magnesium sulfate, filtered, and concentrated. The crude residue was taken on to the next step with no further purification.

Step 3, Preparation of 8-[3-(Dimethylamino)prop-1-yn-1-yl]-5-ethyl-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

To a solution of 3-[5-ethyl-3-methyl-4-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-8-yl]prop-2-ynal (0.274 mmol) in DCE (3 mL) was added sodium triacetoxyborohydride (87 mg, 0.411 mmol) and dimethylamine (0.137 mL, 0.274 mmol). The reaction was stirred at 60 °C for 2 h, cooled, and diluted with EtOAc. The resulting solution was washed (sodium bicarbonate, brine), dried (magnesium sulfate), filtered, and concentrated. The crude residue was then purified by flash chromatography (gradient elution: 0-5% MeOH in DCM) to afford 73 mg as a white solid. LCMS: [MH⁺393.1].

Acidic deprotection as in **example 1**, step 9 provided the title compound. ¹H NMR (400 MHz, CD₃OD) δ 8.22 (s, 1 H), 7.66 (d, 1 H), 7.58 (d, 1 H), 4.38 (q, 2 H), 4.03 (s, 2 H), 2.80 (s, 6 H), 2.68 (s, 3 H), 1.35 (t, 3 H). LCMS: R_t = 0.86 min, [MH⁺309.0].

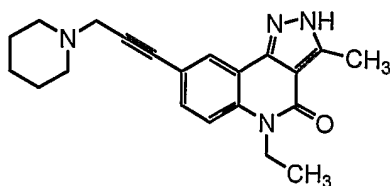
Example 12: Preparation of 5-(2-Fluoroethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 1. ¹H NMR (400 MHz, CD₃OD) δ 8.30 (s, 1 H), 7.69 (s, 2 H), 4.88-4.62 (m, 4 H), 4.45 (s, 2 H), 3.82-3.71 (m, 2 H), 3.45-3.33 (m, 2 H), 2.70 (s, 3 H), 2.32-2.05 (m, 4 H). LCMS: R_t = 0.98 min, [MH⁺353.4].

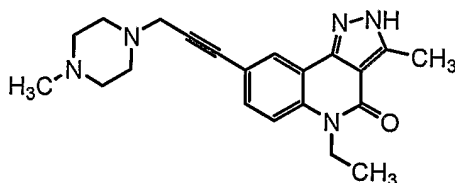
Example 13: Preparation of 5-Ethyl-3-methyl-8-(3-piperidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

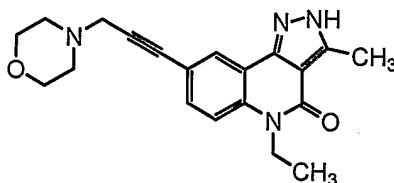
- Example 11.** ^1H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1 H), 7.72 (d, 1 H), 7.60 (d, 1 H), 4.38 (q, 2 H), 4.35 (s, 2 H), 3.75 (d, 2 H), 3.15 (app t, 2 H), 2.70 (s, 3 H), 2.05 (d, 2 H), 1.90-1.52 (m, 4 H), 1.32 (t, 3 H). LCMS: R_t = 0.91 min, $[\text{MH}^+ 349.1]$.

Example 14: Preparation of 5-Ethyl-3-methyl-8-[3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl]-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



- The title compound was prepared using analogous procedures as outlined in
- Example 11.** ^1H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1 H), 7.77 (d, 1 H), 7.60 (d, 1 H), 4.45 (s, 2 H), 4.39 (q, 2 H), 3.95-3.50 (m, 8 H), 3.04 (s, 3 H), 2.70 (s, 3 H), 1.32 (t, 3 H). LCMS: R_t = 0.88 min, $[\text{MH}^+ 364.1]$.

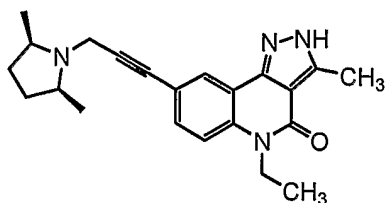
- Example 15:** Preparation of 5-Ethyl-3-methyl-8-(3-morpholin-4-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

- Example 11.** ^1H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1 H), 7.76 (d, 1 H), 7.61 (d, 1 H), 4.43 (s, 2 H), 4.38 (q, 2 H), 4.16 (d, 2 H), 3.86 (app t, 2 H), 3.70 (d, 2 H), 3.37 (d, 2 H), 2.70 (s, 3 H), 1.31 (t, 3 H). LCMS: R_t = 0.87 min, $[\text{MH}^+ 351.2]$.

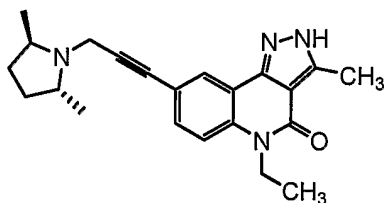
Example 16: Preparation of 8-{3-[(2*R*,5*S*)-2,5-Dimethylpyrrolidin-1-yl]prop-1-yn-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

5 **Example 11.** ¹H NMR (400 MHz, CD₃OD) δ 8.16 (s, 1 H), 7.62-7.50 (m, 2 H), 4.37 (q, 2 H), 3.82 (s, 2 H), 2.96-2.92 (m, 2 H), 2.65 (s, 3 H), 1.95-1.92 (m, 2 H), 1.48-1.39 (m, 2 H), 1.33 (t, 3 H), 1.28 (d, 6 H). LCMS: R_t = 0.99 min, [MH⁺363.5].

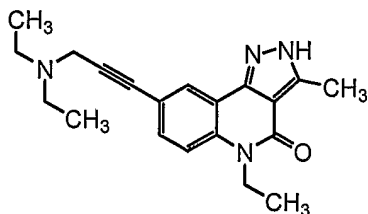
Example 17: Preparation of 8-{3-[(2*S*,5*S*)-2,5-Dimethylpyrrolidin-1-yl]prop-1-yn-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (racemic mixture of enantiomers).



The title compound was prepared using analogous procedures as outlined in

15 **Example 11.** ¹H NMR (400 MHz, CD₃OD) δ 8.16 (s, 1 H), 7.62-7.51 (m, 2 H), 4.36 (q, 2 H), 3.91-3.51 (abq, 2 H), 2.67 (s, 3 H), 2.18-2.05 (m, 2 H), 1.57-1.45 (m 2 H), 1.31 (t, 3 H), 1.16 (d, 6 H). LCMS: R_t = 1.00 min, [MH⁺363.5].

Example 18: Preparation of 8-[3-(Diethylamino)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



20

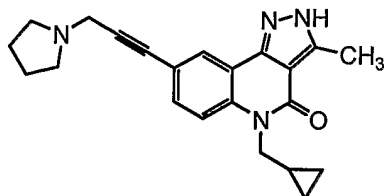
The title compound was prepared using analogous procedures as outlined in

Example 11. ¹H NMR (400 MHz, CD₃OD) δ 8.30 (s, 1 H), 7.75-7.55 (m, 2 H), 4.43

(s, 2 H), 4.39 (q, 2 H), 3.45 (q, 4 H), 2.69 (s, 3 H), 1.43 (t, 6 H), 1.32 (t, 3 H).

LCMS: R_t = 0.95 min, $[MH^+]$ 337.2].

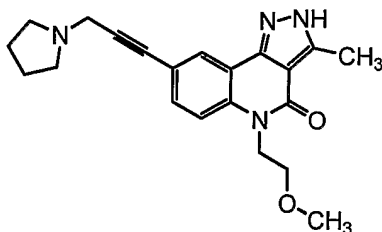
Example 19: Preparation of 5-(Cyclopropylmethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (300 MHz, CD_3OD) δ 8.27 (s, 1 H), 7.66-7.71 (m, 2 H), 4.43 (s, 2 H), 4.25 (d, 2 H), 3.73-3.80 (m, 2 H), 3.31-3.40 (m, 2 H), 2.67 (s, 3 H), 2.07-2.28 (m, 4 H), 1.24-1.32 (m, 1 H), 0.51-0.53 (m, 4 H). LCMS: R_t = 0.95 min, $[MH^+]$ 361.0].

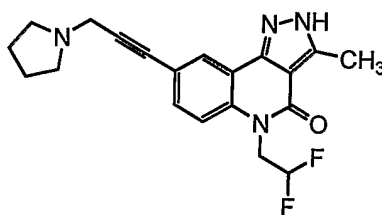
Example 20: Preparation of 5-(2-Methoxyethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (br s, 1 H), 7.47-7.53 (m, 2 H), 4.42-4.47 (m, 4 H), 3.95-4.00 (m, 2 H), 3.70-3.73 (m, 2 H), 3.30-3.38 (m, 5 H), 2.89 (s, 3 H), 2.25-2.30 (m, 4 H). LCMS: R_t = 0.86 min, $[MH^+]$ 365.0].

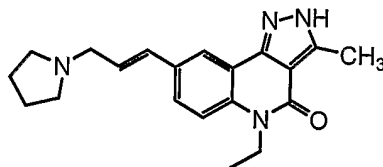
Example 21: Preparation of 5-(2,2-Difluoroethyl)-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (400 MHz, DMSO- d_6) δ 8.31 (d, 1 H), 7.64-7.81 (m, 2 H), 6.06-6.34 (m, 1 H), 4.72-4.83 (m, 2 H), 4.42 (s, 2 H), 3.30-3.67 (m, 4 H), 2.70 (s, 3 H), 2.11-2.77 (m, 4 H). LCMS: R_t = 0.98 min, $[\text{MH}^+]$ 371.0].

Example 22: Preparation of 5-Ethyl-3-methyl-8-[(1*E*)-3-pyrrolidin-1-ylprop-1-en-1-yl]-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



Step 1, Preparation of Methyl (2*E*)-3-[5-ethyl-3-methyl-4-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-8-yl]acrylate.

To a suspension of K_2CO_3 (2.37 g, 17.16 mmol) and tetra-*n*-butylammonium chloride (1.91 g, 6.86 mmol) in DMF (30 mL) was added H_2O (3 mL) and mixture was stirred for 20 min. To the suspension were added triphenylphosphine (0.18 g, 0.686 mmol), 5-ethyl-8-iodo-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (as prepared in **Example 1**, 3.0 g, 6.68 mmol) and methyl acrylate (1.24 mL, 13.37 mmol). DMF (50 mL) and H_2O (5 mL) were added to the suspension and the mixture was stirred for 15 min before palladium acetate (0.077 g, 0.343 mmol) was added and reaction mixture was heated to 50 $^\circ\text{C}$ for 2 h. Methyl acrylate (0.62 mL, 6.86 mmol) was added and mixture was stirred 12 h at 75 $^\circ\text{C}$. The reaction mixture was cooled to rt and cold H_2O was added followed by filtration affording 1.6 g (59%) of desired product methyl (2*E*)-3-[5-ethyl-3-methyl-4-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-8-yl]acrylate. LCMS: R_t = 1.89 min, $[\text{MH}^+]$ 396.2].

Step 2, Preparation of 5-Ethyl-8-[(1*E*)-3-hydroxyprop-1-en-1-yl]-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

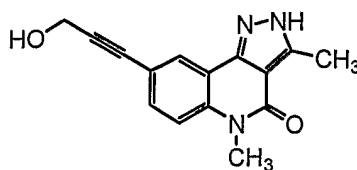
To a -78 °C suspension of methyl (2*E*)-3-[5-ethyl-3-methyl-4-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-8-yl]acrylate (0.25 g, 0.633 mmol) in THF (4 mL) was added lithium aluminum hydride (0.11 g, 1.27 mmol). The reaction mixture was stirred for 45 min, then quenched with H₂O (1 eq), 15% aq NaOH (1 eq), and H₂O (3 eq) all with vigorous stirring. Surplus of MgSO₄ was added and the mixture was filtered and washed with DCM. The crude material was purified by silica gel flash chromatography (0-40% EtOAc in hexanes) to afford 0.14 g (60%) of desired product 5-ethyl-8-[(1*E*)-3-hydroxyprop-1-en-1-yl]-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one. LCMS: *R*_t = 1.49 min, [MH⁺ 368.2].

Step 3, Preparation of (2*E*)-3-[5-Ethyl-3-methyl-4-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-8-yl]acrylaldehyde.

To a solution of 5-ethyl-8-[(1*E*)-3-hydroxyprop-1-en-1-yl]-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (0.088 g, 0.240 mmol) in DCM (5 mL) was added Dess-Martin periodinane (0.203 g, 0.480 mmol). The mixture was stirred 4 h at rt and poured into a saturated aq sodium thiosulfate solution. The organic phase was separated and washed with saturated aq NaHCO₃ solution (50 mL) and water (2x50 mL). The crude material was purified by silica gel flash chromatography (0-30% EtOAc in hexanes) to afford 0.065 g (74%) of desired product (2*E*)-3-[5-ethyl-3-methyl-4-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-8-yl]acrylaldehyde. LCMS: *R*_t = 1.73 min, [MH⁺ 366.3].

Reductive amination and acidic deprotection as in **Example 11** provided the title compound 5-ethyl-3-methyl-8-[(1*E*)-3-pyrrolidin-1-ylprop-1-en-1-yl]-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one as light yellow powder. ¹H NMR (400 MHz, CD₃OD) δ 8.25 (d, 1 H), 7.76 (dd, 1 H), 7.58 (d, 1 H), 7.02 (d, 1 H), 6.40-6.51 (m, 1 H), 4.33-4.40 (m, 2 H), 4.04 (d, 2 H), 3.62-3.71 (m, 2 H), 3.16-3.26 (m, 2 H), 2.68 (s, 3 H), 2.01-2.23 (m, 4 H), 1.30-1.35 (m, 3 H). LCMS: *R*_t = 0.84 min, [MH⁺ 337.5].

Example 23: Preparation of 8-(3-Hydroxyprop-1-yn-1-yl)-3,5-dimethyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

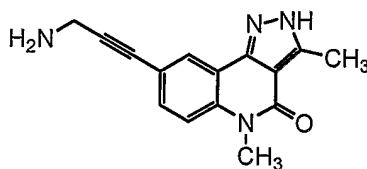


The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (300 MHz, DMSO- d_6) δ 8.17 (s, 1 H), 7.47-7.62 (m, 3 H), 4.32 (s, 2 H), 3.57 (s, 3 H), 2.55 (s, 3 H). LCMS: R_t = 1.17 min, $[\text{MH}^+ 268.1]$.

5

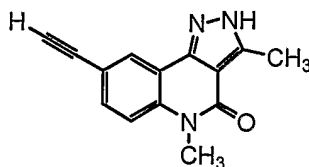
Example 24: Preparation of 8-(3-Aminoprop-1-yn-1-yl)-3,5-dimethyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

10 **Example 1.** ^1H NMR (300 MHz, D $_2$ O) δ 7.08 (d, 1 H), 6.94 (s, 1 H), 6.62 (d, 1 H), 4.07 (s, 2 H), 2.93 (s, 3 H), 2.20 (s, 3 H). LCMS: R_t = 0.86 min, $[\text{MH}^+ 250.1]$.

Example 25: Preparation of 8-Ethynyl-3,5-dimethyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

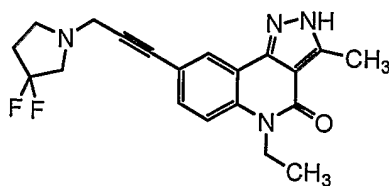


15

The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (300 MHz, DMSO- d_6) δ 8.21 (s, 1 H), 7.64 (d, 1 H), 7.51 (d, 1 H), 4.23 (s, 1 H), 3.58 (s, 3 H), 2.55 (s, 3 H). LCMS: R_t = 1.35 min, $[\text{MH}^+ 238.0]$.

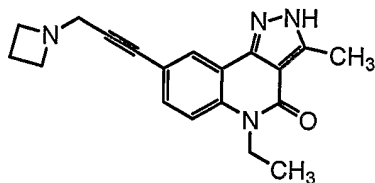
20 **Example 26:** Preparation of 8-[3-(3,3-Difluoropyrrolidin-1-yl)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

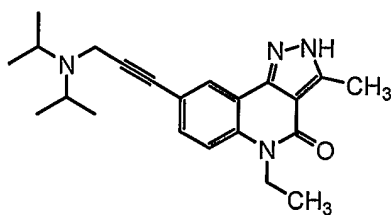
- Example 11.** ^1H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1 H), 7.68 (d, 1 H), 7.52 (d, 1 H), 4.52 (s, 2 H), 4.29 (q, 2 H), 4.05 (app t, 2 H), 3.88 (app t, 2 H), 2.80-2.62 (m, 2 H), 2.61 (s, 3 H), 1.28 (t, 3 H). LCMS: R_t = 1.25 min, $[\text{MH}^+ 372.2]$.

Example 27: Preparation of 8-(3-Azetidin-1-ylprop-1-yn-1-yl)-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



- The title compound was prepared using analogous procedures as outlined in
- Example 11.** ^1H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1 H), 7.70 (d, 1 H), 7.58 (d, 1 H), 4.40-4.25 (m, 8 H), 2.69 (s, 3 H), 2.68-2.48 (m, 2 H), 1.33 (t, 3 H). LCMS: R_t = 0.91 min, $[\text{MH}^+ 321.4]$.

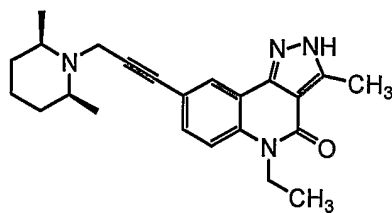
- Example 28:** Preparation of 8-[3-(Diisopropylamino)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

- Example 11.** ^1H NMR (400 MHz, CD_3OD) δ 8.30 (d, 1 H), 7.70 (dd, 1 H), 7.61 (d, 1 H), 4.45 (s, 2 H), 4.40 (q, 2 H), 3.99 (m, 2 H), 2.69 (s, 3 H), 1.52 (t, 12 H), 1.35 (t, 3 H). LCMS: R_t = 1.06 min, $[\text{MH}^+ 365.3]$.

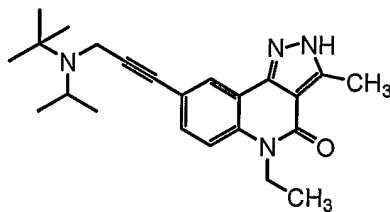
Example 29: Preparation of 8-{3-[(2*R*,6*S*)-2,6-Dimethylpiperidin-1-yl]prop-1-yn-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

5 **Example 11.** ^1H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1 H), 7.69 (d, 1 H), 7.60 (d, 1 H), 4.60 (q, 2 H), 4.53 (s, 2 H), 2.90 (s, 3 H), 2.17-2.13 (m, 2 H), 2.07-1.99 (m, 1 H), 1.90-1.71 (m, 3 H), 1.65-1.50 (m, 9 H). LCMS: R_t = 1.15 min, $[\text{MH}^+ 377.2]$.

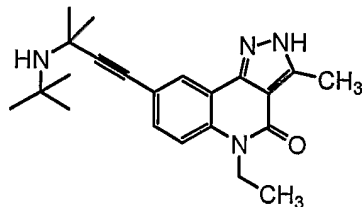
10 **Example 30:** Preparation of 8-{3-[*tert*-Butyl(isopropyl)amino]prop-1-yn-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 11. ^1H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1 H), 7.55 (s, 2 H), 4.37 (q, 2 H), 3.72 (s, 2 H), 3.48 (m, 1 H), 2.67 (s, 3 H), 1.15-1.08 (m, 12 H), 1.03 (d, 6 H).
15 LCMS: R_t = 1.11 min, $[\text{MH}^+ 379.5]$.

Example 31: Preparation of 8-[3-(*tert*-Butylamino)-3-methylbut-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

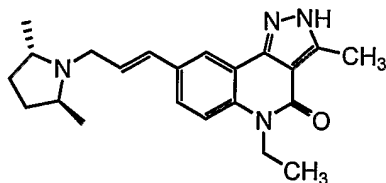


20 The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1 H), 7.62-7.60 (m, 2 H), 4.38

(q, 2 H), 2.69 (s, 3 H), 1.75 (s, 6 H), 1.52 (s, 9 H), 1.31 (t, 3 H). LCMS: R_t = 0.99 min, $[MH^+ 365.2]$.

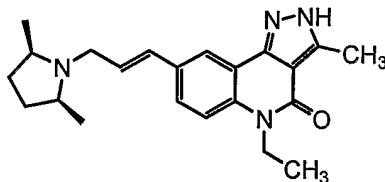
Example 32: Preparation of 8- $\{(1E)$ -3-[(2*S*,5*S*)-2,5-Dimethylpyrrolidin-1-yl]prop-1-en-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.
(racemic mixture of enantiomers)



The title compound was prepared using analogous procedures as outlined in

Example 22. ^1H NMR (400 MHz, DMSO) δ 10.14 (bs, 1H), 8.26 (s, 1H), 7.71 (d, 1H), 7.58 (d, 1H), 6.99 (d, 1H), 6.40-6.47 (m, 1H), 4.27-4.32 (m, 2H), 3.91-4.04 (m, 2H), 3.76-3.84 (m, 1H), 3.60-3.68 (m, 1H), 2.59 (s, 3H), 2.26-2.35 (m, 1H), 2.10-2.19 (m, 1H), 1.70-1.78 (m, 1H), 1.57-1.66 (m, 1H), 1.41 (d, 3H), 1.30 (d, 3H), 1.22 (t, 3H). LCMS: Method FA, R_t = 2.80 min, $[MH^+ 363.2]$.

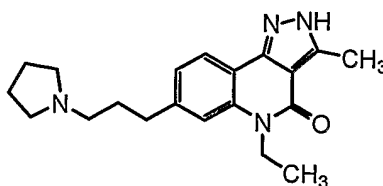
Example 33: Preparation of 8- $\{(1E)$ -3-[(2*R*,5*S*)-2,5-Dimethylpyrrolidin-1-yl]prop-1-en-1-yl}-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 22. ^1H NMR (400 MHz, DMSO) δ 9.46 (bs, 1H), 8.23 (s, 1H), 7.72-7.77 (m, 1H), 7.56-7.61 (m, 1H), 7.30 (d, 1H), 6.42-6.49 (m, 1H), 4.27-4.32 (m, 2H), 4.00-4.05 (m, 2H), 3.53-3.61 (m, 2H), 2.59 (s, 3H), 2.14-2.20 (m, 2H), 1.62-1.69 (m, 2H), 1.41-1.42 (m, 6H), 1.21 (t, 3H). LCMS: R_t = 2.80 min, $[MH^+ 363.2]$.

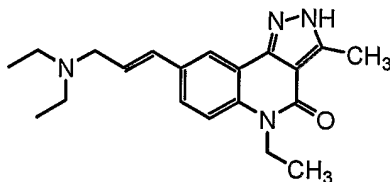
Example 34: Preparation of 5-Ethyl-3-methyl-7-(3-pyrrolidin-1-ylpropyl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 1. ^1H NMR (300 MHz, CD_3OD) δ 8.04 (d, 1H), 7.48 (bs, 1H), 7.24-7.27 (m, 1H), 4.36-4.43 (m, 2H), 3.62-3.69 (m, 2H), 3.21-3.26 (m, 2H), 3.02-3.11 (m, 2H), 2.87-2.92 (m, 2H), 2.67 (s, 3H), 1.96-2.19 (m, 6H), 1.30-1.35 (m, 3H). LCMS: R_t = 0.89 min, $[\text{MH}^+ 339.4]$.

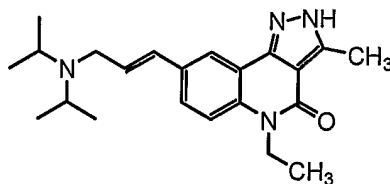
Example 35: Preparation of 8-[(1E)-3-(Diethylamino)prop-1-en-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 22. ^1H NMR (400 MHz, CD_3OD) δ 8.26 (bs, 1H), 7.76 (d, 1H), 7.60 (d, 1H), 7.01 (d, 1H), 6.36-6.43 (m, 1H), 4.37-4.42 (m, 2H), 3.91-3.93 (m, 2H), 3.18-3.24 (s, 3H), 2.69 (s, 3H), 1.32-1.38 (m, 10H). LCMS: R_t = 0.95 min, $[\text{MH}^+ 339.0]$.

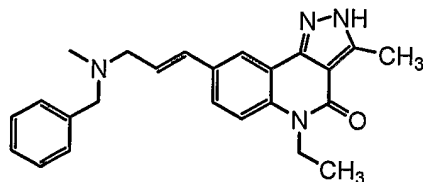
Example 36: Preparation of 8-[(1E)-3-(Diisopropylamino)prop-1-en-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

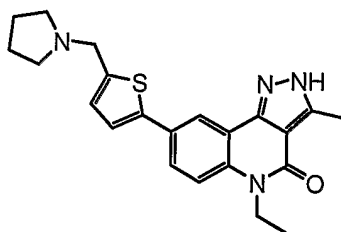
Example 22. ^1H NMR (400 MHz, CD_3OD) δ 8.28 (bs, 1H), 7.75-7.73 (m, 1H), 7.60-7.62 (m, 1H), 7.04 (d, 1H), 6.38-6.45 (m, 1H), 4.37-4.42 (m, 2H), 4.07 (d, 2H), 3.83-3.89 (m, 2H), 2.70 (s, 3H), 1.46-1.48 (m, 12H), 1.34 (t, 3H). LCMS: R_t = 0.98 min, $[\text{MH}^+ 365.6]$.

Example 37: Preparation of 8-[(1*E*)-3-[Benzyl(methyl)amino]prop-1-en-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



5 The title compound was prepared using analogous procedures as outlined in **Example 22**. ¹H NMR (400 MHz, DMSO) δ 11.11 (bs, 1H), 8.35 (s, 1H), 7.73 (dd, 1H), 7.62-7.64 (m, 3H), 7.49-7.51 (m, 3H), 4.23-4.52 (m, 6H), 2.83 (s, 3H), 2.59 (s, 3H), 1.21 (t, 3H). LCMS: R_t = 1.02 min, [MH⁺385.6].

10 **Example 38:** Preparation of 5-Ethyl-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



Step 1, Preparation of 5-[5-Ethyl-3-methyl-4-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-8-yl]thiophene-2-carbaldehyde.

15 To a solution of 5-ethyl-8-iodo-3-methyl-2-(tetrahydro-2*H*-pyran-2-yl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (as prepared in **example 1**, 1.5 g, 3.43 mmol) in THF (40 mL) and ethanol (10 mL) was added a saturated aq solution of sodium carbonate (1.0 mL). The reaction was then sparged with Ar for 20 min. 5-Formyl-2-thiopheneboronic acid (0.803 g, 5.15 mmol) and

20 tetrakis(triphenylphosphine) palladium (0.198 g, 0.17 mmol) were added to the solution and the reaction mixture was heated to 85 °C and stirred for 5 h. The mixture was then cooled to rt and the residue was diluted with EtOAc and washed with a saturated aq NaHCO₃ solution (50 mL) and water (2 x 50 mL). The organic layer was dried over MgSO₄, filtered and the solvent evaporated in vacuo. The crude

25 material was purified by silica gel chromatography (0-40% EtOAc in hexanes) to

afford 0.833 g of 5-[5-ethyl-3-methyl-4-oxo-2-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-8-yl]thiophene-2-carbaldehyde in 58% yield. LCMS: $R_t = 1.99$ min, $[MH^+ 422.3]$.

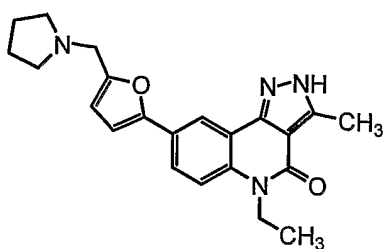
- 5 **Step 2**, Preparation of 5-Ethyl-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2-(tetrahydro-2H-pyran-2-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

To a solution of 5-[5-ethyl-3-methyl-4-oxo-2-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-2H-pyrazolo[4,3-c]quinolin-8-yl]thiophene-2-carbaldehyde (410 mg, 0.974 mmol) in DCE (10 mL) was added sodium triacetoxyborohydride (310 mg, 1.461 mmol) and pyrrolidine (0.081 mL, 0.974 mmol). The reaction was stirred at 10 60 °C for 2 h and cooled to rt. The reaction was diluted with EtOAc, washed with sodium bicarbonate (saturated aq solution) and brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography (gradient elution: 0-10% MeOH in DCM) to afford 325 mg of 5-ethyl-3-methyl-8-
15 [5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2-(tetrahydro-2H-pyran-2-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

Step 3, Preparation of 5-Ethyl-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

- 20 To a solution of 5-ethyl-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2-(tetrahydro-2H-pyran-2-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one (50 mg, 0.116 mmol) in MeOH (5 mL) was added 200 μ L of concentrated aq HCl. The reaction was stirred for 2 h and concentrated in vacuo. Purification via flash chromatography afforded 44 mg of the title compound. ^1H NMR (400 MHz, CD_3OD) δ 8.40 (d, 1 H), 7.88 (dd, 1 H), 7.61 (d, 1 H), 7.49 (d, 1 H), 7.38 (d, 1 H),
25 4.68 (s, 2 H), 4.38 (q, 2 H), 3.95-3.60 (m, 4 H), 2.69 (s, 3 H), 2.25-2.02 (m 4 H), 1.35 (t, 3 H). LCMS: $R_t = 0.95$ min, $[MH^+ 393.1]$.

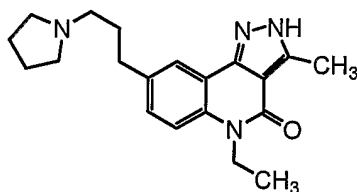
- Example 39**: Preparation of 5-Ethyl-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-furyl]-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.
30



The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1 H), 7.99 (d, 1 H), 7.62 (d, 2 H), 6.95 (d, 1 H), 6.82 (d, 1 H), 4.59 (s, 2 H), 4.38 (q, 2 H), 3.75-3.62 (m, 2 H), 3.40-3.28 (m, 2 H), 2.70 (s, 3 H), 2.30-2.05 (m, 4 H), 1.35 (t, 3 H). LCMS: R_t = 1.46 min, $[\text{MH}^+ 377.5]$.

Example 40: Preparation of 5-Ethyl-3-methyl-8-(3-pyrrolidin-1-ylpropyl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

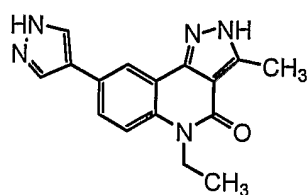


10

To a solution of 5-ethyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one (as prepared in **example 1**, 50 mg, 0.149 mmol) in MeOH (50 mL) was added 10 % Pd on carbon (20 mg). The suspension was degassed and backfilled with hydrogen (3 x) and stirred under ambient pressure for 1 h. The reaction was then filtered through a pad of Celite and concentrated. The crude residue was then purified via flash chromatography (gradient elution: 0-10% MeOH in DCM) to afford 48 mg of 5-ethyl-3-methyl-8-(3-pyrrolidin-1-ylpropyl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1 H), 7.52-7.50 (m, 2 H), 4.39 (q, 2 H), 3.25 (m, 4 H), 2.85 (t, 2 H), 2.65 (s, 3 H), 2.20-2.05 (m, 6 H), 1.35-1.28 (m, 5 H). LCMS: R_t = 0.88 min, $[\text{MH}^+ 339.3]$.

20

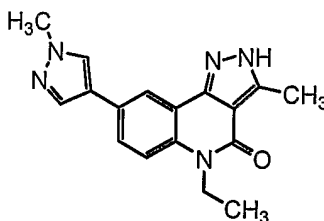
Example 41: Preparation of 5-Ethyl-3-methyl-8-(1H-pyrazol-4-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

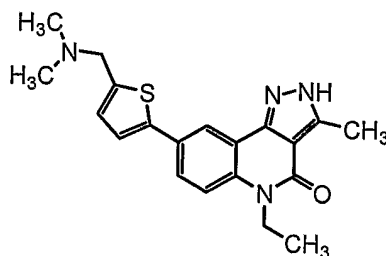
Example 38. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.37 (s, 1 H), 8.09 (s, 2 H), 7.81 (d, 1 H), 7.56 (d, 1 H), 4.30 (q, 2 H), 2.58 (s, 3 H), 1.24 (t, 3 H). LCMS: R_t = 1.13 min, $[\text{MH}^+ 294.2]$.

Example 42: Preparation of 5-Ethyl-3-methyl-8-(1-methyl-1H-pyrazol-4-yl)-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in
Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.29 (d, 2 H), 8.20 (s, 1 H), 7.82 (d, 1 H), 7.60 (d, 1 H), 4.38 (q, 2 H), 4.08 (s, 3 H), 2.70 (s, 3 H), 1.34 (t, 3 H). LCMS: R_t = 1.21 min, $[\text{MH}^+ 308.2]$.

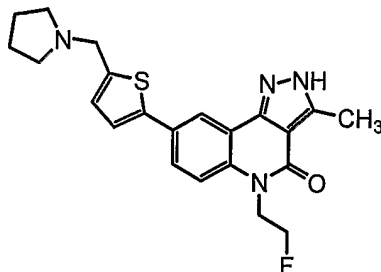
Example 43: Preparation of 8-{5-[(Dimethylamino)methyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

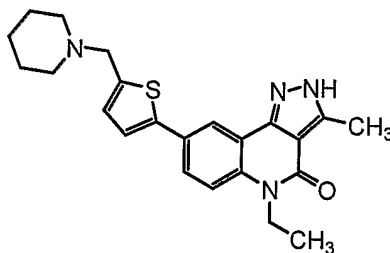
Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1 H), 7.90 (d, 1 H), 7.64 (d, 1 H), 7.51 (d, 1 H), 7.38 (d, 1 H), 4.62 (s, 2 H), 4.40 (q, 2 H), 2.95 (s, 6 H), 2.70 (s, 3 H), 1.37 (t, 3 H). HRMS: $[\text{MH}^+ 367.1605]$.

Example 44: Preparation of 5-(2-Fluoroethyl)-3-methyl-8-[5-(pyrrolidin-1-ylmethyl)-2-thienyl]-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



- 5 The title compound was prepared using analogous procedures as outlined in **Example 38**. ^1H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1 H), 7.85 (dd, 1 H), 7.70 (dd, 1 H), 7.49 (d, 1 H), 7.39 (d, 1 H), 4.88-4.62 (m, 6 H), 3.65-3.22 (m, 4 H), 2.68 (s, 3 H), 2.28-2.01 (m, 4 H). LCMS: R_t = 0.99 min, $[\text{MH}^+ 411.2]$.

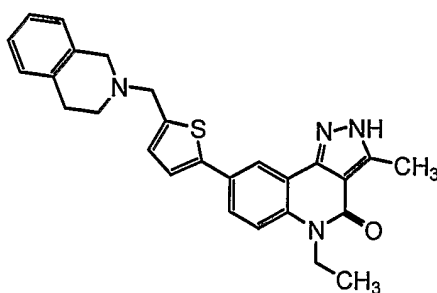
- 10 **Example 45:** Preparation of 5-Ethyl-3-methyl-4-methylene-8-[5-(piperidin-1-ylmethyl)-2-thienyl]-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline.



The title compound was prepared using analogous procedures as outlined in

- Example 38**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.43 (br s, 1 H), 7.86 (dd, 1 H), 7.64 (d, 1 H), 7.57 (d, 1 H), 7.40 (d, 1 H), 4.54 (d, 2 H), 4.28-4.34 (m, 2 H), 3.41 (d, 2 H), 2.86-2.95 (m, 2 H), 2.59 (s, 3 H), 1.78-1.87 (m, 3 H), 1.66-1.78 (m, 3 H), 1.23 (t, 3 H). LCMS: R_t = 1.05 min, $[\text{MH}^+ 322.4]$.

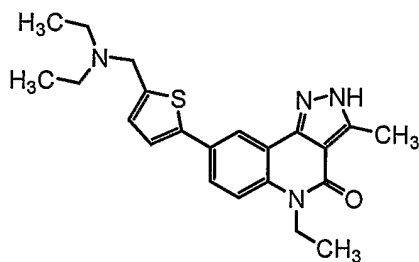
- Example 46:** Preparation of 8-[5-(3,4-Dihydroisoquinolin-2(1*H*)-ylmethyl)-2-thienyl]-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.47 (d, 1 H), 7.91 (dd, 1 H), 7.66 (d, 1 H), 7.54 (d, 1 H), 7.43 (d, 1 H), 7.27-7.36 (m, 3 H), 7.23 (d, 1 H), 4.79 (d, 2 H),
5 4.52 (d, 2 H), 4.45-4.38 (m, 2 H), 3.48 (m, 2 H), 3.24 (m, 2 H), 2.70 (s, 3 H), 1.36 (t, 3 H). LCMS: R_t = 1.15 min, $[\text{MH}^+ 355.0]$.

Example 47: Preparation of 8-{5-[(Diethylamino)methyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

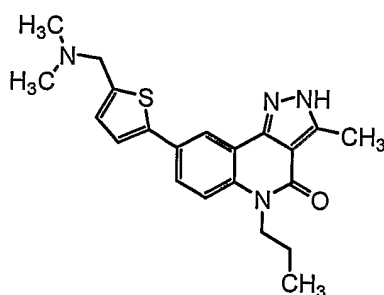


10

The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (300 MHz, CD_3OD) δ 8.43 (d, 1 H), 7.89 (dd, 1 H), 7.63 (d, 1 H), 7.50 (d, 1 H), 7.40 (d, 1 H), 4.65 (s, 2 H), 4.36-4.43 (m, 2 H), 3.24-3.65 (m, 4 H), 2.69 (s, 3 H), 1.40-1.44 (m, 6 H), 1.29-1.37 (m, 3 H). LCMS: R_t = 0.98 min,
15 $[\text{MH}^+ 395.0]$.

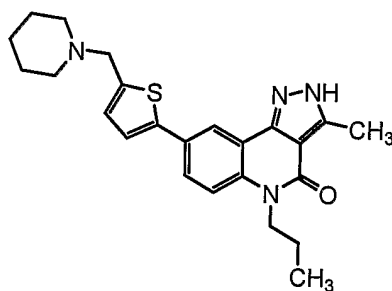
Example 48: Preparation of 8-{5-[(Dimethylamino)methyl]-2-thienyl}-3-methyl-5-propyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1 H), 7.89 (dd, 1 H), 7.60 (d, 1 H), 7.51 (d, 1 H), 7.38 (d, 1 H), 4.62 (s, 2 H), 4.29 (app t, 2 H), 2.95 (s, 6 H), 2.69 (s, 3 H), 1.85-1.70 (m, 2 H), 1.05 (t, 3 H). LCMS: $R_t = 1.054$ min, $[\text{MH}^+ 381.1]$.

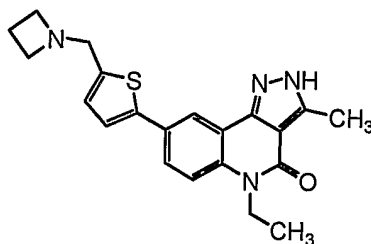
Example 49: Preparation of 3-Methyl-8-[5-(piperidin-1-ylmethyl)-2-thienyl]-5-propyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1 H), 7.88 (dd, 1 H), 7.60 (d, 1 H), 7.50 (d, 1 H), 7.37 (d, 1 H), 4.59 (s, 2 H), 4.28 (app t, 2 H), 3.59 (d, 2 H), 3.05 (app t, 2 H), 2.70 (s, 3 H), 2.08-1.95 (m, 2 H), 1.91-1.50 (m, 6 H), 1.05 (t, 3 H). LCMS: $R_t = 1.123$ min, $[\text{MH}^+ 421.2]$.

Example 50: Preparation of 8-[5-(Azetidin-1-ylmethyl)-2-thienyl]-3-methyl-5-propyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.

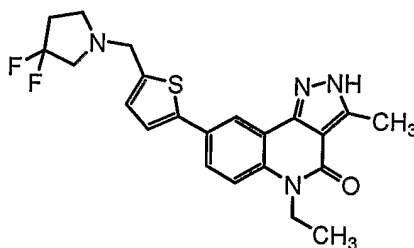


The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1 H), 7.77 (d, 1 H), 7.52 (d, 1 H), 7.29 (d, 1 H), 6.99 (d, 1 H), 4.35 (q, 2 H), 3.85 (s, 2 H), 3.41 (t, 4 H), 2.65 (s, 3 H), 2.20-2.10 (m, 2 H), 1.32 (t, 3 H). LCMS: R_t = 1.031 min, $[\text{MH}^+ 379.4]$.

5

Example 51: Preparation of 8-{5-[(3,3-Difluoropyrrolidin-1-yl)methyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

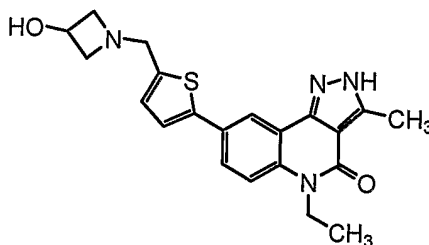


The title compound was prepared using analogous procedures as outlined in

10 **Example 38.** ^1H NMR (400 MHz, CD_3OD) δ 8.45-8.35 (m, 1 H), 7.92-7.80 (m, 1 H), 7.66-7.39 (m, 3 H), 4.90-4.71 (m, 2 H), 4.41-4.29 (m, 2 H), 4.10-3.75 (m, 3 H), 2.80-2.61 (m, 6 H), 1.40-1.29 (m, 3 H). LCMS: R_t = 1.28 min, $[\text{MH}^+ 429.4]$.

Example 52: Preparation of 5-Ethyl-8-{5-[(3-hydroxyazetidin-1-yl)methyl]-2-thienyl}-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.

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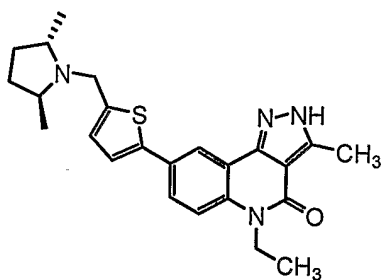


The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1 H), 7.90 (d, 1 H), 7.64 (d, 1 H), 7.47 (d, 1 H), 7.35 (d, 1 H), 4.77-4.62 (m, 3 H), 4.49-4.37 (m, 4 H), 4.09-4.00 (m, 2 H), 2.72 (s, 3 H), 1.37 (t, 3 H). LCMS: R_t = 0.92 min, $[\text{MH}^+ 322.3]$.

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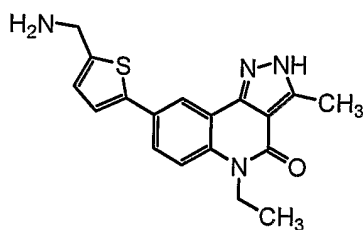
Example 53: Preparation of 8-(5-{[(2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl]methyl}-2-thienyl)-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (racemic mixture of enantiomers).



The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.34 (br s, 1 H), 7.85 (d, 1 H), 7.59 (d, 1 H), 7.41 (d, 1 H), 7.22 (d, 1 H), 4.35-4.40 (m, 4 H), 3.69 (br s, 1 H), 3.22 (br s, 1 H), 2.68 (s, 3 H), 2.18 (d, 2 H), 1.65 (d, 2 H), 1.31-1.36 (m, 9 H). LCMS: R_t = 1.05 min, $[\text{MH}^+ 421.0]$.

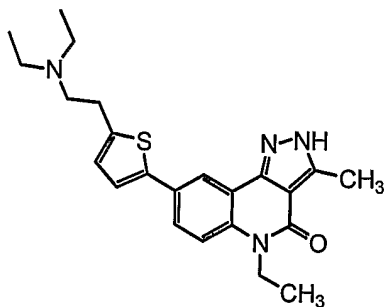
Example 54: Preparation of 8-[5-(Aminomethyl)-2-thienyl]-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.44 (d, 1H), 7.88 (dd, 1H), 7.64 (d, 1H), 7.44-7.45 (m, 1H), 7.26-7.27 (m, 1H), 4.38-4.44 (m, 4H), 2.70 (s, 3H), 1.34-1.38 (m, 3H). LCMS: R_t = 0.95 min, $[\text{MH}^+ 322.4]$.

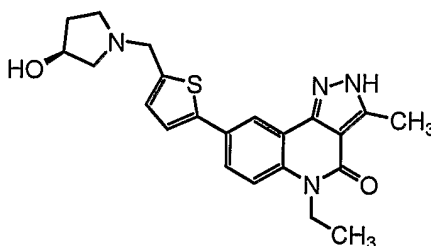
Example 55: Preparation of 8-{5-[2-(Diethylamino)ethyl]-2-thienyl}-5-ethyl-3-methyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, DMSO) δ 8.38-8.40 (m, 1H), 7.80-7.82 (m, 1H), 7.59-7.61 (m, 1H), 7.43-7.44 (m, 1H), 7.07-7.08 (m, 1H), 4.27-4.32 (m, 3H), 3.28-3.38 (m, 4H), 3.15-3.24 (m, 4H), 2.59 (s, 3H), 1.21-1.28 (m, 9H). LCMS: $R_t = 1.01$ min, $[\text{MH}^+ 409.0]$.

Example 56: Preparation of 5-Ethyl-8-(5-((3*S*)-3-hydroxypyrrolidin-1-yl)methyl)-2-thienyl)-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.



The title compound was prepared using analogous procedures as outlined in

Example 38. ^1H NMR (400 MHz, CD_3OD) δ 8.15-8.16 (m, 1H), 7.65 (dd, 1H), 7.38 (d, 1H), 7.19 (d, 1H), 6.93 (d, 1H), 4.37-4.42 (m, 1H), 4.22-4.28 (s, 2H), 3.79-3.88 (m, 2H), 2.80-2.92 (m, 2H), 2.58-2.67 (m, 5H), 2.13-2.22 (m, 1H), 1.73-1.80 (m, 1H), 1.29 (t, 3H). LCMS: $R_t = 0.97$ min, $[\text{MH}^+ 409.4]$.

Example 57 Biological Assays

Chk1 Expression & Purification:

Recombinant human Chk1 was expressed as a fusion protein with glutathione S-transferase at the amino-terminus (GST-Chk1) using standard baculovirus vectors and (Bac-to-Bac®) insect cell expression system purchased from GIBCO™ Invitrogen.

Recombinant protein expressed in insect cells was purified using glutathione sepharose (Amersham Biotech) using standard procedures described by the manufacturer.

Chk1 FlashPlate® kinase assay:

Assays (25 μ L) contained 8.7 nM GST-Chk1, 10 mM MES, 0.1 mM ethylene glycol-bis(β -aminoethylether)-N,N,N',N'-tetracetic acid (EGTA, pH 8.0), 2 mM DTT, 0.05% Tween 20, 3 μ M peptide substrate (Biotin-ILSRRPSYRKILND-free acid) (SEQ ID NO: 1), 1 μ M ATP, 0.4 uCi ^{33} P- γ -ATP (NEN), 4% DMSO. Reactions were incubated for 30 minutes at room temperature, terminated with 50 μ L of 50 mM EDTA and 90 μ L were transferred to streptavidin-coated FlashPlates® (NEN) and incubated for 1 hour at room temperature. Plates were washed with phosphate buffered saline containing 0.01% Tween-20 and 10 mM sodium pyrophosphate. Plates were dried, sealed with Topseal™ (NEN) and amount of ^{33} P incorporated into the peptide substrate measure using a Packard Topcount® NXT™ scintillation counter with standard settings.

Chk1 DELFIA® kinase assay:

Assays (25 μ L) utilized 6.4 nM GST-Chk1 containing 25 mM Tris, pH 8.5, 20% glycerol, 50 mM sodium chloride (NaCl), 0.1% Surfact-Amps® 20, 1 μ M peptide substrate (Biotin-GLYRSPSPMPEN-amide) (SEQ ID NO: 2), 2 mM DTT, 4% DMSO, 12.5 μ M ATP, 5 mM $MgCl_2$ and reacted for 30 minutes at room temperature. Reactions were terminated with 100 μ L of Stop buffer containing 1% BSA, 10 mM Tris, pH 8.0, 150 mM NaCl, 100 mM EDTA. Stopped reactions (100 μ L) were transferred to 96 well neutravidin plates (Pierce) to capture the biotin-peptide substrate during a 30 minute room temperature incubation. Wells were washed and reacted with 100 μ L PerkinElmer Wallac Assay Buffer containing 21.5 ng/ml anti-phospho-Ser216-Cdc25c rabbit polyclonal antibody from Cell Signaling Technology (Beverly, MA) and 292ng/ml europium labeled anti-rabbit-IgG for 1 hour at room temperature. Wells were washed and europium released from the bound antibody by addition of Enhancement Solution (100 μ L) (PerkinElmer Wallac) and detected using a Wallac Victor2™ using standard manufacturer settings.

Chk1 DELFIA® kinase assay:

Assays (25 μ L) utilized 2 nM GST-Chk1 containing 10 mM Tris, pH 7.5, 20% glycerol, 50 mM sodium chloride (NaCl), 0.01% Surfact-Amps® 20, 1 μ M peptide substrate (Biotin-GLYRSPSPMPEN-amide) (SEQ ID NO: 2), 0.1% BSA, 2 mM DTT, 4% DMSO, 600 μ M ATP, 10 mM $MgCl_2$ and reacted for 50 minutes at room temperature. Reactions were terminated with 100 μ L of Stop buffer containing 1% BSA, 10 mM Tris, pH 8.0, 150 mM NaCl, 100 mM EDTA. Stopped reactions (100 μ L) were transferred to 96 well NeutrAvidin plates (Pierce) to capture the biotin-peptide substrate during a 30 minute room temperature incubation. Wells were washed and reacted with 100 μ L PerkinElmer Wallac Assay Buffer containing 21.5 ng/ml anti-phospho-Ser216-Cdc25c rabbit polyclonal antibody from Cell Signaling Technology (Beverly, MA) and 292 ng/ml europium labeled anti-rabbit-IgG for 1 hour at room temperature. Wells were washed and europium released from the bound antibody by addition of Enhancement Solution (100 μ L) (PerkinElmer Wallac) and detected using a Perkin Elmer Wallac Envision™ 2100 multilabel reader using standard manufacturer settings.

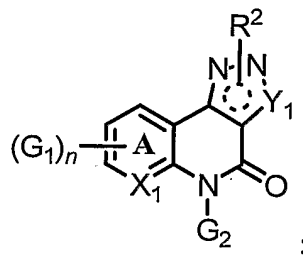
Compounds I-1 to I-25, I-30, I-31, I-36 to I-41, I-43 to I-47, I-49, I-50, I-53, I-55, I-56, I-74 to I-78, I-82 and I-83 were tested in this assay and exhibited IC_{50} values less than 500 nM. Compounds I-42, I-48, I-51, I-52 and I-54 exhibited IC_{50} values greater than 500 nM and less than 1 μ M.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound represented by the following structural formula:



Ring A is optionally substituted at any one or more substitutable ring carbon atoms;

Y_1 is N or CR^3 ;

G_2 is -H, or a C1-C8 aliphatic group optionally substituted with one or more fluoro, -OR¹², -CONR¹¹R¹², -COOR¹², cycloalkyl or phenyl, wherein the cycloalkyl and phenyl are optionally substituted with halo or alkyl;

R^2 is -H or a group that is cleavable *in vivo*;

R^3 is -H, halogen, alkyl, haloalkyl or -V₁-R⁷, wherein V₁ is a covalent bond or a C1-C4 alkylidene optionally substituted with one or more -OR¹⁴, -NR¹⁵R¹⁶, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, or with a spiro cycloalkyl group; R⁷ is -OR¹⁴, -SR¹⁴, -CONR¹⁵R¹⁶, -NR¹⁵R¹⁶, -NHC(O)NR¹⁵R¹⁶, -CN, -COOR¹⁴, -NHC(O)H, -NHC(O)R¹⁴, -OC(O)R¹⁴, -OC(O)NR¹⁵R¹⁶, -NHC(O)-OR¹⁴, -S(O)₂NR¹⁵R¹⁶, -S(O)₂(R¹⁴), boronate, alkyl boronate, -C(=NR¹⁴)-NR¹⁵R¹⁶, -NH-C(=NR¹⁴)NR¹⁵R¹⁶, -NH-C(=NR¹⁴)R¹⁴, an optionally substituted cycloaliphatic or non-aromatic heterocyclic group, or an optionally substituted aromatic group; R¹⁴ is -H, alkyl or an optionally substituted aromatic or aralkyl group; and R¹⁵ and R¹⁶ are independently -H, alkyl or an optionally substituted aromatic or aralkyl group; or -NR¹⁵R¹⁶ is an optionally substituted nitrogen-containing non-aromatic heterocyclic group;

X_1 is N, or CR^4 ;

R^4 is -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, -NO₂, C1-C3 alkoxy, C1-C3 haloalkoxy, -CN, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂, -NHC(O)O-(C1-C3 alkyl), -C(O)O-(C1-C3 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-C3 alkyl), -NHC(O)N(C1-C3 alkyl)₂, or -NHC(O)O-(C1-C3 alkyl);

each G_1 is independently - R^{13b} , - V_3-R^{13} , - V_3-R^{13a} , - $T_0-T_1-V_3-R^{13}$, - $T_0-T_1-V_3-R^{13a}$, - $T_0-T_1-R^{13a}$, - $T_0-Cy-V_4-R^{13}$, - $T_0-Cy-V_4-R^{13a}$, - $T_0-Cy-T_1-V_4-R^{13}$, - $T_0-Cy-T_1-V_4-R^{13a}$, T_0-Cy-R^{13} , or - T_0-Cy-R^{13a} ; or n is 2, one G_1 is (- T_2-R^{200})_x and the other G_1 is (- $T_3-V_5-R^{50}$)_y, x is 1 or 2, y is 0 or 1 and $x + y$ is 1 or 2; and

T_0 is absent, -CH₂-, -CH₂-CH₂-, or -CH₂-CH₂-CH₂-;

T_1 is -O-, -S-, -N(R⁶)-, -S(O)-, -SO₂-, -C(O)-, -OC(O)-, -C(O)O-, -N(R⁶)C(O)-, -C(O)N(R⁶)-, -SO₂N(R⁶)-, or -N(R⁶)SO₂;

T_2 is a covalent bond, -O-, -S-, -N(R⁶)-, -S(O)-, -SO₂-, -C(O)-, -OC(O)-, -C(O)O-, -N(R⁶)C(O)-, -C(O)N(R⁶)-, -SO₂N(R⁶)-, or -N(R⁶)SO₂;

T_3 is a covalent bond, -O-, -NH-, -C(O)O-, -C(O)- or -C(O)NH-;

Cy is an optionally substituted arylene group or an optionally substituted non-aromatic heterocyclene or non-aromatic carbocyclene group;

V_3 is an optionally substituted C1-C8 alkylidene, provided that V_3 is a C2-C8 alkylidene when T_1 is -O-, -N(R⁶)-, -C(O)O-, or -C(O)N(R⁶)- and R^{13} is -CN, -OR¹², -NR¹¹R¹², -NR¹¹C(O)R¹², -OC(O)R¹², -NR¹¹C(O)NR¹¹R¹², -OC(O)NR¹¹R¹² or -NR¹¹C(O)OR¹², and wherein V_3 is optionally substituted with alkyl, halo, haloalkyl, alkoxy, hydroxy, NR¹¹R¹² or oxo;

V_4 is an optionally substituted bivalent C1-C8 aliphatic group provided that V_4 is a C2-C8 aliphatic group when T_1 is -O-, -N(R⁶)-, -C(O)O-, or -C(O)N(R⁶)- and R^{13} is -CN, -OR¹², -NR¹¹R¹², -NR¹¹C(O)R¹², -OC(O)R¹², -NR¹¹C(O)NR¹¹R¹², -OC(O)NR¹¹R¹² or -NR¹¹C(O)OR¹², and wherein V_4 is optionally substituted with alkyl, halo, haloalkyl, alkoxy, hydroxy, NR¹¹R¹² or oxo;

V_5 is a covalent bond or a C1-C4 alkylidene, provided that V_5 is C2-C4 alkylidene when T_3 is -O-, -NH-, -C(O)O-, or -C(O)NH- and R^{50} is -CN, -

OH, $-\text{NR}^{51}\text{R}^{52}$, $-\text{NHC}(\text{O})\text{R}^{51}$, $-\text{OC}(\text{O})\text{R}^{51}$, $-\text{NHC}(\text{O})\text{NR}^{51}\text{R}^{52}$, $-\text{OC}(\text{O})\text{NR}^{51}\text{R}^{52}$, $-\text{NHC}(\text{O})\text{OR}^{51}$ or a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group wherein a C1-C4 alkylidene group represented by V_5 is optionally substituted with a spirocyclopropyl group or one or two methyl groups and wherein a C1-C4 alkylidene group represented by V_5 is optionally fused to a cyclopropyl group;

each R^6 is independently $-\text{H}$ or C1-C3 alkyl;

each R^{11} is independently $-\text{H}$ or a C1-C3 alkyl group;

each R^{12} is independently $-\text{H}$ or an optionally substituted alkyl, aromatic, aralkyl, non-aromatic heterocyclic or non-aromatic heterocyclalkyl group; or $-\text{NR}^{11}\text{R}^{12}$ is an optionally substituted aromatic or non-aromatic nitrogen-containing heterocyclic group;

R^{13} is $-\text{OR}^{12}$, $-\text{CN}$, $-\text{COOR}^{12}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{COR}^{12}$, $-\text{NH}-\text{C}(=\text{NR}^{11})\text{NR}^{11}\text{R}^{12}$, $-\text{N}=\text{C}(\text{NR}^{11}\text{R}^{12})_2$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{SO}_2\text{R}^{12}$, $-\text{OC}(\text{O})\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{12}$, $-\text{O}-\text{C}(\text{O})-\text{OR}^{12}$, $-\text{OC}(\text{O})-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{CO}-\text{CH}(\text{OR}^{18})-\text{R}^{12}$, $-\text{NR}^{11}\text{CO}-\text{CH}(\text{NR}^{18}\text{R}^{18})-\text{R}^{12}$, $-\text{NR}^{11}\text{CO}-(\text{CH}_2)_m\text{CH}(\text{NR}^{18}\text{R}^{18})-\text{R}^{12}$, $-\text{OC}(\text{O})-\text{CH}(\text{OR}^{18})-\text{R}^{12}$, $-\text{OC}(\text{O})-\text{CH}(\text{NR}^{18}\text{R}^{18})-\text{R}^{12}$, $-\text{NR}^{11}\text{CO}-\text{C}(\text{R}^{19}\text{R}^{19})-\text{OR}^{12}$, $-\text{NR}^{11}\text{CO}-\text{C}(\text{R}^{19}\text{R}^{19})-\text{NR}^{11}\text{R}^{12}$, $-\text{OC}(\text{O})-\text{C}(\text{R}^{19}\text{R}^{19})-\text{OR}^{12}$, $-\text{OC}(\text{O})-\text{C}(\text{R}^{19}\text{R}^{19})-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}-\text{C}(\text{R}^{12})-\text{C}(\text{O})\text{OR}^{12}$, $-\text{NR}^{11}-\text{C}(\text{R}^{12})-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}-\text{C}(\text{R}^{12})\text{CH}_2\text{OR}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{NHC}(\text{O})\text{NR}^{11}\text{R}^{12}$, or $-\text{C}(=\text{NR}^{11})-\text{NR}^{11}\text{R}^{12}$;

R^{13a} is an optionally substituted nitrogen-containing heteroaromatic group or a nitrogen-containing non-aromatic heterocyclic group;

R^{13b} is an optionally substituted nitrogen-containing heteroaromatic group or a nitrogen-containing non-aromatic heterocyclic group;

each R^{18} is independently $-\text{H}$, a C1-C3 alkyl group, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})-(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}-(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{N}-(\text{C1-C3 alkyl})_2$, $-\text{C}(\text{O})\text{O}-(\text{C1-C3 alkyl})$, $-\text{S}(\text{O})_2(\text{C1-C3 alkyl})$ or $-\text{NR}^{18}\text{R}^{18}$ taken together is a substituted or unsubstituted non-aromatic nitrogen-containing heterocyclic group;

each R^{19} is independently -H, a C1-C3 alkyl group or $-C(R^{19}R^{19})-$ taken together is a C3-C8 cycloalkyl group;

R^{50} is -CN, $-OR^{51}$, $-NR^{51}R^{52}$, $-C(O)NR^{51}R^{52}$, $-NHC(O)R^{51}$, $-NHC(O)NR^{51}R^{52}$, $-NHC(O)OR^{51}$, $-C(O)OR^{51}$ or an optionally substituted aromatic group or non-aromatic heterocyclic group;

each R^{51} and each R^{52} are independently -H or C1-C3 alkyl or $-NR^{51}R^{52}$ is an optionally substituted non-aromatic heterocyclic group;

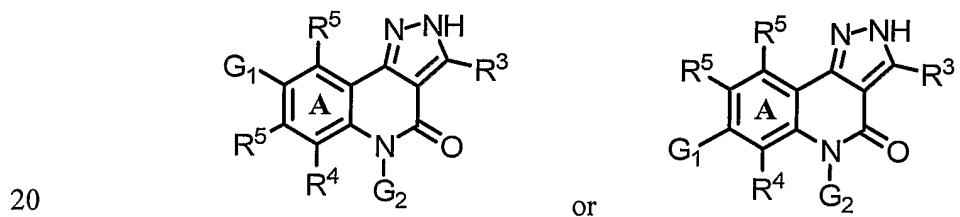
R^{200} is an optionally substituted C2-C4 alkenyl or C2-C4 alkynyl group;

m is 1 or 2; and

n is 1 or 2.

2. The compound of Claim 1 wherein each G_1 is independently $-R^{13b}$, $-V_3-R^{13}$, $-V_3-R^{13a}$, $-T_0-T_1-V_3-R^{13}$, $-T_0-T_1-V_3-R^{13a}$, $-T_0-T_1-R^{13a}$, $-T_0-Cy-V_4-R^{13}$, $-T_0-Cy-V_4-R^{13a}$, $-T_0-Cy-T_1-V_4-R^{13}$, $-T_0-Cy-T_1-V_4-R^{13a}$, T_0-Cy-R^{13} , or $-T_0-Cy-R^{13a}$.

3. The compound of Claim 2, wherein the compound is represented by any of the following structural formulae:



or a pharmaceutically acceptable salt thereof, wherein:

G_2 is C1-C4 alkyl, optionally substituted with fluoro or a C3-C8 cycloalkyl optionally substituted with halo or alkyl; and

- 25 each R^5 is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, $-NO_2$, C1-C3 alkoxy, C1-C3 haloalkoxy, -CN, $-NH_2$, C1-C3 alkylamino, C1-C3 dialkylamino, $-C(O)NH_2$, $-C(O)NH(C1-C3 \text{ alkyl})$, $-C(O)N(C1-C3 \text{ alkyl})_2$,

-NHC(O)O-(C1-C3 alkyl), -C(O)O-(C1-C3 alkyl), -NHC(O)NH₂,
 -NHC(O)NH(C1-C3 alkyl), -NHC(O)N(C1-C3 alkyl)₂, or -NHC(O)O-(C1-C3
 alkyl).

5 4. The compound of Claim 3, wherein:

 R³ is methyl, or ethyl; or R³ is V₁-R⁷, wherein V₁ is a C1-C2
 alkylidene and R⁷ is -OH, -OCH₃; or V₁ is a covalent bond and R⁷ is
 cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl; and

 R⁴ and each R⁵ are independently -H, halogen, C1-C3 alkyl, C1-C3
 10 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy.

5. The compound of claim 3, wherein

 G₁ is -R^{13b};

 R^{13b} is an optionally substituted imidazolyl, pyrrolyl, pyrazolyl,
 15 triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl,
 isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl or thiadiazolyl;

 each substitutable ring nitrogen atom of the group represented by
 R^{13b} is optionally substituted with a C1-C3 alkyl, C1-C3 acyl, C1-C3
 alkylsulfonyl, -OC(O)N(R')₂, -NR'C(O)OR', or -NR'C(O)N(R')₂ group;

20 each substitutable ring carbon atom of a non-aromatic ring in the group
 represented by R^{13b} is optionally substituted with a C1-C3 alkyl group,
 hydroxy, fluoro, oxo, -C(O)OH, -C(O)O(C1-C3 alkyl), C1-C3 alkoxy, -NH₂,
 C1-C3 alkylamino, C1-C3 dialkylamino, amido, C1-C3 alkylamido, C1-C3
 fluoroalkylamido, amino (C1-C3) alkyl, (C1-C3)alkylamino(C1-C3)alkyl,
 25 (C1-C3)dialkylamino(C1-C3)alkyl, hydroxy(C1-C3)alkyl, (C1-C3)alkoxy(C1-
 C3)alkyl;

 each substitutable ring carbon atom of an aromatic ring in the group
 represented by R^{13b} is optionally substituted with halo, hydroxy, cyano, C1-C3
 alkyl, C1-C3 fluoroalkyl, C1-C3 alkoxy, C1-C3 fluoroalkoxy, -NH₂, C1-C3
 30 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl),
 C(O)N(C1-C3 alkyl)₂, -NR'CO(C1-C3 alkyl), -NR'CO(C1-C3 haloalkyl),
 -NR'C(O)O(C1-C3 alkyl), -C(O)O(C1-C3 alkyl), -NR'C(O)NH₂,

-NR'C(O)NH(C1-C3 alkyl), -NR'C(O)N(C1-C3 alkyl)₂, -NR'C(O)O-(C1-C3 alkyl)-SH, -S(C1-C3 alkyl), -NO₂, -S(O)₂H, -S(O)₂(C1-C3 alkyl), -SO₂N(R')₂, -S(O)H, -S(O)(C1-C3 alkyl), -NR'S(O)₂NH₂, -NR'S(O)₂NH(C1-C3 alkyl), -NR'S(O)₂N(C1-C3 alkyl)₂, -NR'S(O)₂H or -NR'S(O)₂(C1-C3 alkyl); and

each R' is hydrogen or a C1-C3 alkyl group.

6. The compound of Claim 3, wherein G₁ is -V₃-R¹³, -V₃-R^{13a}, -T₀-T₁-V₃-R¹³, -T₀-T₁-V₃-R^{13a}, or -T₀-T₁-R^{13a}.

7. The compound of Claim 6, wherein:

V₃ is C1-C4 alkylidene;

R¹³ is -CN, -OR¹², -NR¹¹R¹², -NHC(O)R¹², -NHC(O)OR¹², -NHC(O)NR¹¹R¹², -NHC(O)OR¹², or -OC(O)R¹²;

each substitutable ring nitrogen atom of the group represented by R^{13a} is optionally substituted with a C1-C3 alkyl, C1-C3 acyl, C1-C3 alkylsulfonyl, -OC(O)N(R')₂, -NR'C(O)OR', or -NR'C(O)N(R')₂ group;

each substitutable ring carbon atom of a non-aromatic ring in the group represented by R^{13a} is optionally substituted with a C1-C3 alkyl group, hydroxy, fluoro, oxo, -C(O)OH, -C(O)O(C1-C3 alkyl), C1-C3 alkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, amido, C1-C3 alkylamido, C1-C3 fluoroalkylamido, amino (C1-C3) alkyl, (C1-C3)alkylamino(C1-C3)alkyl, (C1-C3)dialkylamino(C1-C3)alkyl, hydroxy(C1-C3)alkyl, (C1-C3)alkoxy(C1-C3)alkyl;

each substitutable ring carbon atom of an aromatic ring in the group represented by R^{13a} is optionally substituted with halo, hydroxy, cyano, C1-C3 alkyl, C1-C3 fluoroalkyl, C1-C3 alkoxy, C1-C3 fluoroalkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), C(O)N(C1-C3 alkyl)₂, -NR'CO(C1-C3 alkyl), -NR'CO(C1-C3 haloalkyl), -NR'C(O)O(C1-C3 alkyl), -C(O)O(C1-C3 alkyl), -NR'C(O)NH₂, -NR'C(O)NH(C1-C3 alkyl), -NR'C(O)N(C1-C3 alkyl)₂, -NR'C(O)O-(C1-C3

alkyl) -SH, -S(C1-C3 alkyl), -NO₂, -S(O)₂H, -S(O)₂(C1-C3 alkyl),
-SO₂N(R')₂, -S(O)H, -S(O)(C1-C3 alkyl), -NR'S(O)₂NH₂, -NR'S(O)₂NH(C1-
C3 alkyl), -NR'S(O)₂N(C1-C3 alkyl)₂, -NR'S(O)₂H or -NR'S(O)₂(C1-C3
alkyl); and

5 each R' is hydrogen or a C1-C3 alkyl group.

8. The compound of Claim 7, wherein:

T₀ is absent;

T₁ is -O- or -N(R⁶);

10 R³ is -H, methyl, ethyl, n-propyl, iso-propyl, C1-C3 haloalkyl or
V₁-R⁷, wherein V₁ is a covalent bond or a C1-C2 alkylidene optionally
substituted with one or two methyl groups or with a spiro cyclopropyl group;
and R⁷ is -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -CONH₂, -CONHCH₃,
-CON(CH₃)₂, -CN, -COOH, -COOCH₃, -NHC(O)H, -NHC(O)CH₃, -OC(O)H,
15 -OC(O)CH₃, -OC(O)NH₂, -OC(O)NHCH₃, C3-C6 cycloalkyl, furyl,
tetrahydrofuryl, N-piperazinyl, N'-alkyl-N-piperazinyl, N'-acyl-N-
piperazinyl, N-pyrrolidyl, N-piperidinyl or N-morpholinyl; and

R^{13a} is an optionally substituted non-aromatic heterocyclic group
selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azetidyl,
20 tetrahydrofuranyl, oxazolidinyl, thiomorpholinyl, tetrahydroquinolinyl,
tetrahydroisoquinolinyl, and azabicyclopentyl, azabicyclohexyl,
azabicycloheptyl, azabicyclooctyl, azabicyclononyl, azabicyclodecyl,
diazabicyclohexyl, diazabicycloheptyl, diazabicyclooctyl, diazabicyclononyl,
or diazabicyclodecyl or an optionally substituted heteroaromatic group
25 selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl,
pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl,
thiazolyl, isothiazolyl, and thiadiazolyl.

9. The compound of Claim 8, wherein:

R^3 is methyl, ethyl; or R^3 is V_1-R^7 , wherein V_1 is a C1-C2 alkylidene and R^7 is -OH, -OCH₃; or V_1 is a covalent bond and R^7 is cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl;

5 R^4 and each R^5 are independently -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy;

R^{13} is -OH, -CN, C1-C3 alkoxy, NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, C1-C3 hydroxyalkyl, or C1-C3 haloalkylamino; and

10 R^{13a} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-thiomorpholinyl, *N*-azetidiny, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, *N*-tetrahydroquinoliny, *N*-tetrahydroisoquinoliny and 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl or an
15 optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl.

20 10. The compound of Claim 3, wherein G_1 is $-T_0-Cy-V_4-R^{13}$, $-T_0-Cy-V_4-R^{13a}$, $-T_0-Cy-T_1-V_4-R^{13}$, $-T_0-Cy-T_1-V_4-R^{13a}$, T_0-Cy-R^{13} , or $-T_0-Cy-R^{13a}$.

11. The compound of claim 10, wherein:

T_0 is absent;

25 V_4 is C1-C4 alkylidene, alkenylidene or alkynylidene group optionally substituted with C1-C3 alkyl;

R^{13} is -CN, -OR¹², -NR¹¹R¹², -NHC(O)R¹², -NHC(O)OR¹², -NHC(O)NR¹¹R¹², -NHC(O)OR¹², or -OC(O)R¹²;

30 each substitutable ring nitrogen atom of the group represented by R^{13a} or Cy is optionally substituted with a C1-C3 alkyl, C1-C3 acyl, C1-C3 alkylsulfonyl, -OC(O)N(R')₂, -NR'C(O)OR', or -NR'C(O)N(R')₂ group;

each substitutable ring carbon atom of a non-aromatic ring in the group represented by R^{13a} or Cy is optionally substituted with a C1-C3 alkyl group, hydroxy, fluoro, oxo, -C(O)OH, -C(O)O(C1-C3 alkyl), C1-C3 alkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, amido, C1-C3 alkylamido, C1-C3 fluoroalkylamido, amino (C1-C3) alkyl, (C1-C3)alkylamino(C1-C3)alkyl, (C1-C3)dialkylamino(C1-C3)alkyl, hydroxy(C1-C3)alkyl, (C1-C3)alkoxy(C1-C3)alkyl;

each substitutable ring carbon atom of an aromatic ring in the group represented by R^{13a} or Cy is optionally substituted with halo, hydroxy, cyano, C1-C3 alkyl, C1-C3 fluoroalkyl, C1-C3 alkoxy, C1-C3 fluoroalkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), C(O)N(C1-C3 alkyl)₂, -NR'CO(C1-C3 alkyl), -NR'CO(C1-C3 haloalkyl), -NR'C(O)O(C1-C3 alkyl), -C(O)O(C1-C3 alkyl), -NR'C(O)NH₂, -NR'C(O)NH(C1-C3 alkyl), -NR'C(O)N(C1-C3 alkyl)₂, -NR'C(O)O-(C1-C3 alkyl)-SH, -S(C1-C3 alkyl), -NO₂, -S(O)₂H, -S(O)₂(C1-C3 alkyl), -SO₂N(R')₂, -S(O)H, -S(O)(C1-C3 alkyl), -NR'S(O)₂NH₂, -NR'S(O)₂NH(C1-C3 alkyl), -NR'S(O)₂N(C1-C3 alkyl)₂, -NR'S(O)₂H or -NR'S(O)₂(C1-C3 alkyl); and

each R' is hydrogen or a C1-C3 alkyl group.

20

12. The compound of Claim 11, wherein:

V_4 is C1-C4 alkylidene;

R^3 is -H, methyl, ethyl, n-propyl, iso-propyl, C1-C3 haloalkyl or V_1-R^7 , wherein V_1 is a covalent bond or a C1-C2 alkylidene optionally substituted with one or two methyl groups or with a spiro cyclopropyl group; and R^7 is -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -CONH₂, -CONHCH₃, -CON(CH₃)₂, -CN, -COOH, -COOCH₃, -NHC(O)H, -NHC(O)CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)NH₂, -OC(O)NHCH₃, C3-C6 cycloalkyl, furyl, tetrahydrofuryl, N-piperazinyl, N'-alkyl-N-piperazinyl, N'-acyl-N-piperazinyl, N-pyrrolidyl, N-piperidinyl or N-morpholinyl;

30

R^{13a} is an optionally substituted non-aromatic heterocyclic group selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azetidiny,

5 tetrahydrofuranyl, oxazolidinyl, thiomorpholinyl, tetrahydroquinoliny, tetrahydroisoquinoliny and azabicyclopentanyl, azabicyclohexanyl, azabicycloheptanyl, azabicyclononanyl, azabicyclodecanyl, diazabicyclohexanyl, diazabicycloheptanyl, diazabicyclooctanyl, diazabicyclononanyl, or diazabicyclodecanyl or an optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl; and

10 Cy is an optionally substituted phenylene, pyrrolylene, thienylene, furanylene, imidazolylene, triazolylene, tetrazolylene oxazolylene, isoxazolylene, oxadiazolylene, pyrazolylene, pyridinylene, pyrimidylene, pyrazinylene, thiazolylene, cyclopropylene, cyclopentylene, cyclohexylene, cycloheptylene, piperidinylene, piperazinylene, pyrrolidinylene, pyrazolidinylene, imidazolidinylene, tetrahydrofuranylene, 15 tetrahydrothienylene, isooxazolidinylene, oxazolidinylene, isothiazolidinylene, thiazolidinylene, oxathiolanylene, dioxolanylene, or dithiolanylene.

13. The compound of Claim 12, wherein:

20 R^3 is methyl or ethyl; or R^3 is V_1-R^7 , wherein V_1 is a C1-C2 alkylidene and R^7 is -OH, -OCH₃; or V_1 is a covalent bond and R^7 is cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl;

R^{13} is -OH, -CN, C1-C3 alkoxy, or $NR^{11}R^{12}$, where R^{11} is -H or a C1-C3 alkyl group and R^{12} is -H, an optionally substituted alkyl, or an optionally substituted non-aromatic heterocyclic group, or $NR^{11}R^{12}$ is an optionally substituted aromatic or non-aromatic nitrogen containing heterocyclic group;

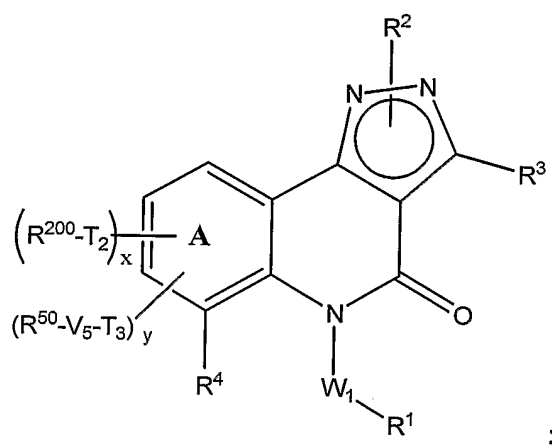
25 R^{13a} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-thiomorpholinyl, *N*-azetidiny, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, *N*-tetrahydroquinoliny, *N*-tetrahydroisoquinoliny and 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl or an 30

optionally substituted heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl;

5 Cy is [2,5]thienylene or [2,5]furanylene; and

R⁴ and each R⁵ are independently -H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, or C1-C3 haloalkoxy.

14. The compound of Claim 1 wherein the compound is represented by
10 the following structural formula:



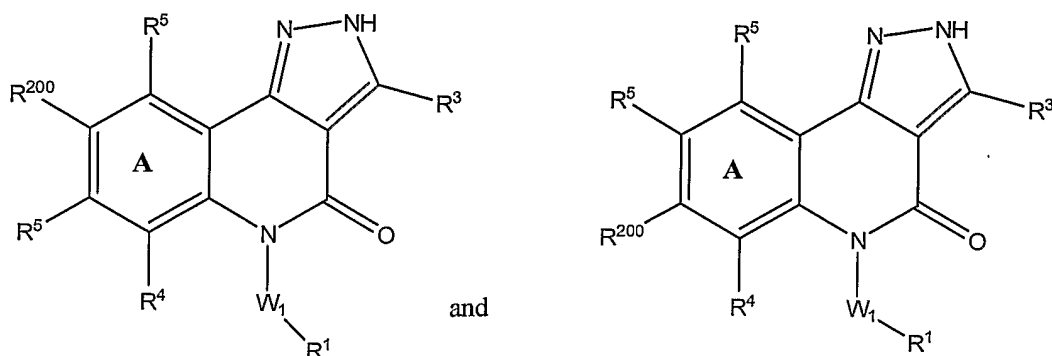
wherein:

Ring A is optionally substituted at any one or more substitutable ring carbon atoms; and

15 R¹ is -H, -CONR¹¹R¹², -COOR¹², fluoro, or a cycloalkyl optionally substituted with halo or alkyl and W₁ is a linear C1-C6 alkylidene chain or R¹ is -OR¹² W₁ is a linear C2-C6 alkylidene group wherein the alkylidene group represented by W₁ is optionally substituted with one or more -CH₃ or fluoro groups; or -W₁-R¹ is -H.

20

15. The compound of Claim 14, wherein the compound is represented by a structural formula selected from:



wherein:

5 R^3 is -H, methyl, ethyl, n-propyl, iso-propyl, C1-C3 haloalkyl, or V_1-R^7 , wherein V_1 is a covalent bond or a C1-C2 alkylidene optionally substituted with one or two methyl groups or with a spiro cyclopropyl group; R^7 is -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -CONH₂, -CONHCH₃,
 10 -CON(CH₃)₂, -CN, -COOH, -COOCH₃, -NHC(O)H, -NHC(O)CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)NH₂, -OC(O)NHCH₃, -OC(O)N(CH₃)₂, -NHC(O)NH₂,
 -NHC(O)NH(CH₃), -NHC(O)N(CH₃)₂, -NHC(O)OCH₃, C3-C6 cycloalkyl, furyl, tetrahydrofuryl, N-piperazinyl, N'-alkyl-N-piperazinyl, N'-acyl-N-piperazinyl, N-pyrrolidyl, N-piperidinyl or N-morpholinyl;

15 each R^5 is independently H, halogen, C1-C3 alkyl, C1-C3 haloalkyl, -NO₂, C1-C3 alkoxy, C1-C3 haloalkoxy, -CN, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂, -NHC(O)O-(C1-C3 alkyl), -C(O)O-(C1-C3 alkyl), -NHC(O)NH₂,
 -NHC(O)NH(C1-C3 alkyl), -NHC(O)N(C1-C3 alkyl)₂, or -NHC(O)O-(C1-C3 alkyl);

20 R^{200} is $-C\equiv CR^{201}$, $-CH=CHR^{201}$, $-C\equiv C-(C(R^{20}R^{20}))_pR^{202}$, or $-CH=CH-(C(R^{20}R^{20}))_pR^{202}$;

R^{201} is -H, alkyl, haloalkyl, hydroxyalkyl, CO₂R⁵¹, or an optionally substituted aromatic group or non-aromatic heterocyclic group;

25 R^{202} is -H, -CN, -OR⁵¹, -OC(O)NR⁵¹R⁵², -OC(O)R⁵¹, -NR⁵¹R⁵², -C(O)NR⁵¹R⁵², -NR⁵¹C(O)R⁵¹, -NR⁵¹C(O)NR⁵¹R⁵², -NR⁵¹C(O)OR⁵¹,

-NR⁵¹S(O)₂R^x, -S(O)₂NR⁵¹, -CO₂R⁵¹ or an optionally substituted aromatic group or non-aromatic heterocyclic group;

each R²⁰ is independently -H or C1-C3 alkyl;

R^x is alkyl or an optionally substituted aromatic group or non-aromatic heterocyclic group;

p is 1 or 2;

each substitutable ring nitrogen atom in an aromatic or non-aromatic heterocyclic group represented by R²⁰¹ or R²⁰² is optionally substituted with a C1-C3 alkyl, C1-C3 acyl, C1-C3 alkylsulfonyl, -OC(O)N(R')₂, -NR'C(O)OR', or -NR'C(O)N(R')₂ group;

each substitutable ring carbon atom of a non-aromatic heterocyclic group represented by R²⁰¹ or R²⁰² is optionally substituted with a C1-C3 alkyl group, hydroxy, fluoro, oxo, -C(O)OH, -C(O)O(C1-C3 alkyl), C1-C3 alkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, amido, C1-C3 alkylamido, C1-C3 fluoroalkylamido, amino (C1-C3) alkyl, (C1-C3)alkylamino(C1-C3)alkyl, (C1-C3)dialkylamino(C1-C3)alkyl, hydroxy(C1-C3)alkyl, (C1-C3)alkoxy(C1-C3)alkyl;

each substitutable ring carbon atom of an aromatic group represented by R²⁰¹ or R²⁰² is optionally substituted with halo, hydroxy, cyano, C1-C3 alkyl, C1-C3 fluoroalkyl, C1-C3 alkoxy, C1-C3 fluoroalkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl), C(O)N(C1-C3 alkyl)₂, -NR'CO(C1-C3 alkyl), -NR'CO(C1-C3 haloalkyl), -NR'C(O)O(C1-C3 alkyl), -C(O)O(C1-C3 alkyl), -NR'C(O)NH₂, -NR'C(O)NH(C1-C3 alkyl), -NR'C(O)N(C1-C3 alkyl)₂, -NR'C(O)O-(C1-C3 alkyl)-SH, -S(C1-C3 alkyl), -NO₂, -S(O)₂H, -S(O)₂(C1-C3 alkyl), -SO₂N(R')₂, -S(O)H, -S(O)(C1-C3 alkyl), -NR'S(O)₂NH₂, -NR'S(O)₂NH(C1-C3 alkyl), -NR'S(O)₂N(C1-C3 alkyl)₂, -NR'S(O)₂H or -NR'S(O)₂(C1-C3 alkyl); and

each R' is independently hydrogen or a C1-C3 alkyl group.

16. The compound of Claim 15, wherein:

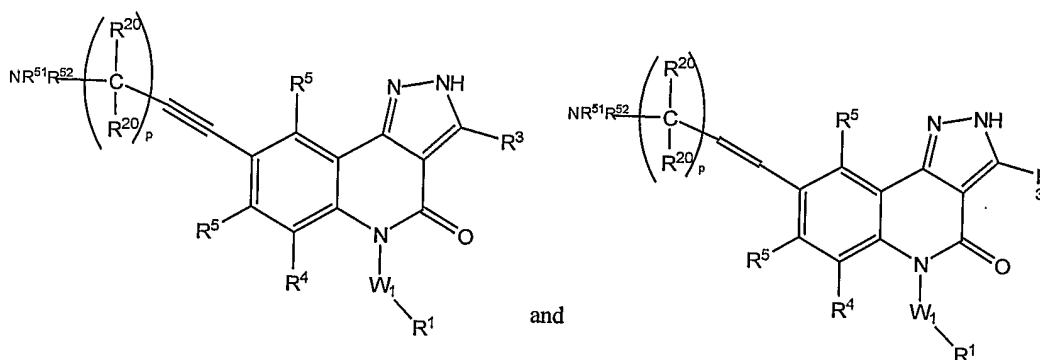
R^3 is methyl, or ethyl; or R^3 is V_1-R^7 , wherein V_1 is a C1-C2 alkylidene and R^7 is -OH, -OCH₃; or wherein V_1 is a covalent bond and R^7 is cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl;

R^4 and each R^5 are independently -H, halogen, -CH₃, halomethyl, -OCH₃, or haloalkoxy;

R^{201} is an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-azetidiny, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 2-azetidiny, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 3-azetidiny, 4-piperidinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, *N*-tetrahydroquinoliny, *N*-tetrahydroisoquinoliny, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl; and

R^{202} is -CN, -OH, C1-C3 alkoxy, -NH₂, C1-C3 alkylamino, C1-C3 dialkylamino, an optionally substituted non-aromatic heterocyclic group selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl, 2-morpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, *N*-tetrahydroquinoliny, *N*-tetrahydroisoquinoliny, 3-oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl.

17. The compound of Claim 15, wherein the compound is represented by a structural formula selected from :



18. The compound of Claim 17, wherein:

R^3 is methyl, or ethyl; or R^3 is V_1-R^7 , wherein V_1 is a C1-C2 alkylidene and R^7 is -OH, -OCH₃; or wherein V_1 is a covalent bond and R^7 is -cyclopropyl, cyclopentyl, furyl or tetrahydrofuryl;

5 R^4 and each R^5 are independently -H, halogen, -CH₃, halomethyl, -OCH₃, or haloalkoxy;

R^{200} is $-C\equiv C-R^{203}$ or $-C=CHR^{203}$;

R^{203} has the formula $-V_6-R^{60}$, $-V_6-R^{61}$, $-T_{11}-V_6-R^{60}$, or $-T_{11}-V_6-R^{61}$;

10 V_6 is a C1-C4 alkylidene, wherein V_6 is optionally substituted with alkyl, halo, haloalkyl, alkoxy, hydroxy, $NR^{11}R^{12}$ or oxo;

T_{11} is -S(O)-, -S(O)₂-, -C(O)-, -C(O)O-, -C(O)N(R⁶)-, or -SO₂N(R⁶)-;

15 R^{60} is -OR¹², -CN, -COOR¹², -NR¹¹R¹², -NR¹¹CONR¹¹R¹², -NR¹¹COR¹², -NH-C(=NR¹¹)NR¹¹R¹², -N=C(NR¹¹R¹²)₂, -SO₂NR¹¹R¹², -NR¹¹SO₂R¹², -OC(O)R¹², -NR¹¹C(O)OR¹², -O-C(O)-OR¹², -OC(O)-NR¹¹R¹², -NR¹¹CO-CH(OR⁶²)-R¹², -NR¹¹CO-CH(NR⁶²R⁶²)-R¹², -NR¹¹CO-(CH₂)₂CH(NR⁶²R⁶²)-R¹², -OC(O)-CH(OR⁶²)-R¹², -OC(O)-CH(NR⁶²R⁶²)-R¹², -NR¹¹CO-C(R⁶²R⁶³)-OR¹², -NR¹¹CO-C(R⁶³R⁶³)-NR¹¹R¹², -OC(O)-C(R⁶³R⁶³)-OR¹², -OC(O)-C(R⁶³R⁶³)-NR¹¹R¹², -NR¹¹-C(R¹²)-C(O)OR¹², -NR¹¹-C(R¹²)-C(O)NR¹¹R¹², -NR¹¹-C(R¹²)CH₂OR¹², -C(O)NR¹¹R¹², -NHC(O)NR¹¹R¹², or -C(=NR¹¹)-NR¹¹R¹²;

R^{61} is an optionally substituted nitrogen-containing heteroaromatic group or a nitrogen-containing non-aromatic heterocyclic group;

25 each R^{62} is independently -H, a C1-C3 alkyl group, -C(O)H, -C(O)-(C1-C3 alkyl), -C(O)NH₂, -C(O)NH-(C1-C3 alkyl), -C(O)N-(C1-C3 alkyl)₂, -C(O)O-(C1-C3 alkyl), -S(O)₂(C1-C3 alkyl) or -NR⁶²R⁶² taken together is a substituted or unsubstituted non-aromatic nitrogen-containing heterocyclic group;

30 each R^{63} is independently -H, a C1-C3 alkyl group or -C(R⁶³R⁶³)- taken together is a C3-C8 cycloalkyl group; and

z is an integer from 1 to 4.

19. The compound of Claim 18, wherein:

R^{60} is -CN, -OR¹², -NR¹¹R¹², -NHC(O)R¹², -NHC(O)OR¹²,
-NHC(O)NR¹¹R¹², -NHC(O)OR¹², or -OC(O)R¹²;

5 R^{61} is an optionally substituted non-aromatic heterocyclic group
selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azetidiny,
tetrahydrofuranyl, oxazolidinyl, thiomorpholinyl, tetrahydroquinolinyl,
tetrahydroisoquinolinyl and azabicyclopentanyl, azabicyclohexanyl,
azabicycloheptanyl, azabicyclononanyl, azabicyclodecanyl,
10 diazabicyclohexanyl, diazabicycloheptanyl, diazabicyclooctanyl,
diazabicyclononanyl, or diazabicyclodecanyl or an optionally substituted
heteroaromatic group selected from imidazolyl, pyrrolyl, pyrazolyl, triazolyl,
tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl,
isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl;

15 each substitutable ring nitrogen atom of the group represented by R^{61}
is optionally substituted with a C1-C3 alkyl, C1-C3 acyl, C1-C3
alkylsulfonyl, -OC(O)N(R')₂, -NR'C(O)OR', or -NR'C(O)N(R')₂ group;

each substitutable ring carbon atom of a non-aromatic ring in the
group represented by R^{61} is optionally substituted with a C1-C3 alkyl group,
hydroxy, fluoro, oxo, -C(O)OH, -C(O)O(C1-C3 alkyl), C1-C3 alkoxy, -NH₂,
20 C1-C3 alkylamino, C1-C3 dialkylamino, amido, C1-C3 alkylamido, C1-C3
fluoroalkylamido, amino (C1-C3) alkyl, (C1-C3)alkylamino(C1-C3)alkyl,
(C1-C3)dialkylamino(C1-C3)alkyl, hydroxy(C1-C3)alkyl, (C1-
C3)alkoxy(C1-C3)alkyl;

25 each substitutable ring carbon atom of an aromatic ring in the group
represented by R^{61} is optionally substituted with halo, hydroxy, cyano,
C1-C3 alkyl, C1-C3 fluoroalkyl, C1-C3 alkoxy, C1-C3 fluoroalkoxy, -NH₂,
C1-C3 alkylamino, C1-C3 dialkylamino, -C(O)NH₂, -C(O)NH(C1-C3 alkyl),
C(O)N(C1-C3 alkyl)₂, -NR'CO(C1-C3 alkyl), -NR'CO(C1-C3 haloalkyl),
-NR'C(O)O(C1-C3 alkyl), -C(O)O(C1-C3 alkyl), -NR'C(O)NH₂,
30 -NR'C(O)NH(C1-C3 alkyl), -NR'C(O)N(C1-C3 alkyl)₂, -NR'C(O)O-(C1-
C3 alkyl) -SH, -S(C1-C3 alkyl), -NO₂, -S(O)₂H, -S(O)₂(C1-C3 alkyl),
-SO₂N(R')₂, -S(O)H, -S(O)(C1-C3 alkyl), -NR'S(O)₂NH₂,

-NR'S(O)₂NH(C1-C3 alkyl), -NR'S(O)₂N(C1-C3 alkyl)₂, -NR'S(O)₂H or -NR'S(O)₂(C1-C3 alkyl); and

each R' is hydrogen or a C1-C3 alkyl group.

- 5 20. The compound of Claim 19, wherein:
 R⁶⁰ is NH₂, C1-C3 alkylamino, or C1-C3 dialkylamino; and
 R⁶¹ is an optionally substituted non-aromatic heterocyclic group
 selected from *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, *N*-piperazinyl,
 N-azetidiny, *N*-thiomorpholinyl, 2-pyrrolidinyl, 2-piperidinyl, 2-piperazinyl,
 10 2-morpholinyl, 2-thiomorpholinyl, 3-pyrrolidinyl, 3-piperidinyl, 3-
 morpholinyl, 3-thiomorpholinyl, 4-piperidinyl, tetrahydroquinolinyl,
 tetrahydroisoquinolinyl, *N*-tetrahydroquinolinyl *N*-tetrahydroisoquinolinyl 3-
 oxo-*N*-8-azabicyclo[3.2.1]octyl or *N*-8-azabicyclo[3.2.1]octyl.
- 15 21. A compound selected from:
 8-[3-(diethylamino)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4*H*-
 pyrazolo[4,3-*c*]quinolin-4-one;
 8-{3-[(2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl]prop-1-yn-1-yl}-5-ethyl-3-methyl-
 2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one;
 20 5-ethyl-3-methyl-8-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-2,5-dihydro-4*H*-
 pyrazolo[4,3-*c*]quinolin-4-one;
 5-ethyl-3-methyl-8-[(1*E*)-3-pyrrolidin-1-ylprop-1-en-1-yl]-2,5-dihydro-4*H*-
 pyrazolo[4,3-*c*]quinolin-4-one;
 8-[3-(diisopropylamino)prop-1-yn-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4*H*-
 25 pyrazolo[4,3-*c*]quinolin-4-one;
 8-{3-[(2*R*,6*S*)-2,6-dimethylpiperidin-1-yl]prop-1-yn-1-yl}-5-ethyl-3-methyl-
 2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one;
 8-{3-[*tert*-butyl(isopropyl)amino]prop-1-yn-1-yl}-5-ethyl-3-methyl-2,5-
 dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one;
 30 8-{(1*E*)-3-[(2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl]prop-1-en-1-yl}-5-ethyl-3-
 methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one;

- 8-[(1*E*)-3-(diethylamino)prop-1-en-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one;
- 8-[(1*E*)-3-(diisopropylamino)prop-1-en-1-yl]-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one; and
- 5 8-(5-{[(2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl]methyl}-2-thienyl)-5-ethyl-3-methyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.
22. A compound selected from:
- 10 8-[(1*E*)-3-(diisopropylamino)prop-1-en-1-yl]-5-ethyl-3-(2-methoxyethyl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one; and
- 8-{(1*E*)-3-[(2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl]prop-1-en-1-yl}-5-ethyl-3-(2-hydroxyethyl)-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one.
23. A method of treating a proliferative disorder in a subject comprising
- 15 administering an effective amount of the Chk-1 inhibitor of Claim 1.
24. The method of claim 23, wherein the proliferative disorder is a cancer.
25. The method of claim 24, wherein the cancer is one in which a checkpoint
- 20 pathway has been mutated or upregulated.
26. The method of claim 25, wherein the Chk-1 inhibitor is administered in combination with another therapeutic agent.
- 25 27. The method of claim 26, wherein the Chk-1 inhibitor and the other therapeutic agent are administered as part of the same pharmaceutical composition.
28. The method of claim 27, wherein the Chk-1 inhibitor and the other
- 30 therapeutic agent are administered as separate pharmaceutical compositions, and the Chk-1 inhibitor is administered prior to, at the same time as, or following administration of the other agent.

29. The method of claim 28, wherein the other therapeutic agent is an anticancer agent.
- 5 30. The method of claim 29, wherein the anticancer agent is selected from the group consisting of DNA damaging agents; cytotoxic agents; agents that disrupt cell replication; proteasome inhibitors; and NF- κ B inhibitors.
- 10 31. The method of claim 30, wherein the anticancer agent is a DNA damaging agent.
- 15 32. The method of claim 31, wherein the DNA damaging agent is selected from the group consisting of radiation therapy, topoisomerase I inhibitors, topoisomerase II inhibitors, alkylating agents, DNA intercalators, and nucleoside mimetics.
- 20 33. A method of treating a proliferative disorder in a subject comprising administering an effective amount of the Chk-1 inhibitor of any one of Claims 2 to 22.
34. A pharmaceutical composition comprising the compound of Claim 1 and at least one pharmaceutically acceptable carrier or diluent.

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SEQUENCE LISTING

<110> Millennium Pharmaceuticals, Inc.
Boyle, Robert George
Imogai, Hassan Julien
Cherry, Michael
Humphries, Alfred John
Navarro, Eva Figueroa
Owen, David Rodney
Dales, Natalie A.
LaMarche, Matthew J.
Cullis, Courtney
Gould, Alexandra E.
Greenspan, Paul D.

<120> CHK-1 INHIBITORS

<130> 1855.2070004

<150> 60/575,159
<151> 2004-05-28

<150> 60/634,359
<151> 2004-12-08

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<223> Biotin labelled peptide substrate

2/2

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/018745

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 C07D519/00 A61K31/4745 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2005/028474 A (MILLENNIUM PHARMACEUTICALS, INC; BOYLE, ROBERT, GEORGE; IMOAI, HASSAN) 31 March 2005 (2005-03-31) examples	1-34
Y	WO 01/46199 A (ELI LILLY AND COMPANY; WANG, QIUPING; BONJOUKLIAN, ROSANNE; COHEN, JEF) 28 June 2001 (2001-06-28) claims	1-34
Y	WO 01/27116 A (ELI LILLY AND COMPANY; BONJOUKLIAN, ROSANNE; JOHNSON, DOUGLAS, WEBB; L) 19 April 2001 (2001-04-19) examples	1-34
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the International search

26 October 2005

Date of mailing of the international search report

08/11/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fazzi, R

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/018745

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BIPUL BARUAH ET AL.: "1,2-Diaryl-1-ethanone and pyrazolo[4,3-c]quinoline-4-one as novel selective cyclooxygenase-2-inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 2, January 2004 (2004-01), pages 445-448, XP002351193 page 446 -----	1-34
A	EL-HOSSAIN ALI MOHAMED ET AL.: "Synthesis and behaviour of 2,4-dichloro-6-methylquinoline and 4-chloro-6-methyl-2(1H)quinolone towards some nucleophilic reagents" J. SERB. CHEM. SOC., vol. 58, no. 10, 1993, pages 737-743, XP009056091 page 739 -----	1-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/018745

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 23-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/018745

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2005028474	A	31-03-2005	NONE	
WO 0146199	A	28-06-2001	AT 282623 T AU 2251901 A CA 2395513 A1 DE 60016039 D1 DE 60016039 T2 EP 1250340 A1 ES 2233487 T3 JP 2003518125 T PT 1250340 T	15-12-2004 03-07-2001 28-06-2001 23-12-2004 11-08-2005 23-10-2002 16-06-2005 03-06-2003 29-04-2005
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