INDOLINE DERIVATIVES AS INHIBITORS OF PERK

Title: INDOLINE DERIVATIVES AS INHIBITORS OF PERK

Abstract: The invention is directed to substituted indoline derivatives. Specifically, the invention is directed to compounds according to Formula 1 (I) wherein R1, R2 and R3 are defined herein. The compounds of the invention are inhibitors of PERK and can be useful in the treatment of cancer and diseases associated with activated unfolded protein response pathways, such as Alzheimer's disease, stroke, Type 1 diabetes, Parkinson disease, Huntington's disease, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, atherosclerosis, and arrhythmias, and more specifically cancers of the breast, colon, pancreas and lung. Accordingly, the invention is further directed to pharmaceutical compositions comprising a compound of the invention. The invention is still further directed to methods of inhibiting PERK activity and treatment of disorders associated therewith using a compound of the invention or a pharmaceutical composition comprising a compound of the invention.
INDOLINE DERIVATIVES AS INHIBITORS OF PERK

FIELD OF THE INVENTION

The present invention relates to substituted indoline derivatives that are inhibitors of the activity of the protein kinase R (PKR)-like ER kinase, PERK. The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using such compounds in the treatment of cancer and diseases associated with activated unfolded protein response pathways, such as Alzheimer's disease, stroke, Type 1 diabetes, Parkinson disease, Huntington's disease, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, atherosclerosis, and arrhythmias.

BACKGROUND OF THE INVENTION

The unfolded protein response (UPR) is a signal transduction pathway that allows cells to survive environmental stresses that perturb protein folding and maturation in the endoplasmic reticulum (ER) (Ma and Hendershot, 2004), (Feldman et al., 2005), (Koumenis and Wouters, 2006). Stress stimuli that activate UPR include hypoxia, disruption of protein glycosylation (glucose deprivation), depletion of luminal ER calcium, or changes in ER redox status (Ma and Hendershot, 2004), (Feldman et al., 2005). These perturbations result in the accumulation of unfolded or mis-folded proteins in the ER, which is sensed by resident ER membrane proteins. These proteins activate a coordinated cellular response to alleviate the impact of the stress and enhance cell survival. Responses include an increase in the level of chaperone proteins to enhance protein re-folding, degradation of the mis-folded proteins, and translational arrest to decrease the burden of proteins entering the ER. These pathways also regulate cell survival by modulating apoptosis (Ma and Hendershot, 2004), (Feldman et al., 2005), (Hamanaka et al., 2009) and autophagy (Rouschop et al.), and can trigger cell death under conditions of prolonged ER stress.

Three ER membrane proteins have been identified as primary effectors of the UPR: protein kinase R (PKR)-like ER kinase [PERK, also known as eukaryotic initiation factor 2A kinase 3 (eIF2AK3), or pancreatic eIF2a kinase (PEK)], inositol-requiring gene 1 α/β (IRE1), and activating transcription factor 6 (ATF6) (Ma and Hendershot, 2004). Under normal conditions these proteins are held in the inactive state by binding to the ER chaperone, GRP78 (BiP). Accumulation of unfolded proteins in the ER leads to release of GRP78 from these sensors resulting in their activation (Ma et al., 2002). PERK is a type I ER membrane protein containing a stress-sensing domain facing the ER lumen, a
transmembrane segment, and a cytosolic kinase domain (Shi et al., 1998), (Sood et al., 2000). Release of GRP78 from the stress-sensing domain of PERK results in oligomerization and autophosphorylation at multiple serine, threonine and tyrosine residues (Ma et al., 2001), (Su et al., 2008). The major substrate for PERK is the eukaryotic initiation factor 2a (eIF2a) at serine-51 (Marciniak et al., 2006). This site is also phosphorylated by other PERK family members [(general control non-derepressed 2 (GCN2), PKR, and heme-regulated kinase (HRI)] in response to different stimuli, and by pharmacological inducers of ER stress such as thapsigargin and tunicamycin. Phosphorylation of eIF2a converts it to an inhibitor of eIF2B, which hinders the assembly of the 40S ribosome translation initiation complex and consequently reduces the rate of translation initiation. Among other effects, this leads to a loss of cyclin D1 in cells resulting in arrest in the G1 phase of the cell division cycle (Brewer and Diehl, 2000), (Hamanaka et al., 2005). Paradoxically, translation of certain messages encoding downstream effectors of eIF2a, ATF4 and CHOP (C/EBP homologous protein; GADD153), which modulate cellular survival pathways, is actually increased upon ER stress. A second PERK substrate, Nrf2, regulates cellular redox potential, contributes to cell adaptation to ER stress, and promotes survival (Cullinan and Diehl, 2004). The normal function of PERK is to protect secretory cells from ER stress. Phenotypes of PERK knockout mice include diabetes, due to loss of pancreatic islet cells, skeletal abnormalities, and growth retardation (Harding et al., 2001), (Zhang et al., 2006), (Iida et al., 2007). These features are similar to those seen in patients with Wolcott-Rallison syndrome, who carry germline mutations in the PERK gene (Delepine et al., 2000). IRE1 is a transmembrane protein with kinase and endonuclease (RNAse) functions (Feldman et al., 2005) (Koumenis and Wouters, 2006). Under ER stress, it undergoes oligomerization and autophosphorylation, which activates the endonuclease to excise an intron from unspliced X-box binding protein 1 (XBP1) mRNA. This leads to the synthesis of truncated XBP1s, which activates transcription of UPR genes. The third effector of UPR, ATF6, is transported to the golgi upon ER stress, where it is cleaved by proteases to release the cytosolic transcription domain. This domain translocates to the nucleus and activates transcription of UPR genes (Feldman et al., 2005), (Koumenis and Wouters, 2006).

Tumor cells experience episodes of hypoxia and nutrient deprivation during their growth due to inadequate blood supply and aberrant blood vessel function (Brown and Wilson, 2004), (Blais and Bell, 2006). Thus, they are likely to be dependent on active UPR signaling to facilitate their growth. Consistent with this, mouse fibroblasts derived...
from PERK-/-, XBP1-/-, and ATF4-/- mice, and fibroblasts expressing mutant eIF2a show reduced clonogenic growth and increased apoptosis under hypoxic conditions in vitro and grow at substantially reduced rates when implanted as tumors in nude mice (Koumenis et al., 2002), (Romero-Ramirez et al., 2004), (Bi et al., 2005). Human tumor cell lines carrying a dominant negative PERK that lacks kinase activity also showed increased apoptosis in vitro under hypoxia and impaired tumor growth in vivo (Bi et al., 2005). In these studies, activation of the UPR was observed in regions within the tumor that coincided with hypoxic areas. These areas exhibited higher rates of apoptosis compared to tumors with intact UPR signaling. Further evidence supporting the role of PERK in promoting tumor growth is the observation that the number, size, and vascularity of insulinomas arising in transgenic mice expressing the SV40- T antigen in the insulin-secreting beta cells, was profoundly reduced in PERK -/- mice compared to wild-type control (Gupta et al., 2009). Activation of the UPR has also been observed in clinical specimens. Human tumors, including those derived from cervical carcinomas, glioblastomas (Bi et al., 2005), lung cancers (Jorgensen et al., 2008) and breast cancers (Ameri et al., 2004), (Davies et al., 2008) show elevated levels of proteins involved in UPR, compared to normal tissues. Therefore, inhibiting the unfolded protein response with compounds that block the activity of PERK and other components of the UPR is expected to have utility as anticancer agents and in the treatment of diseases associated with activated unfolded protein response pathways, such as Alzheimer’s disease, stroke and Type 1 diabetes.

Loss of endoplasmic reticulum homeostasis and accumulation of misfolded proteins can contribute to a number of disease states including cardiovascular and degenerative diseases (Paschen, 2004) such as: Alzheimer’s disease (Salminen e.t al., 2009 and O’Connor et. al. 2008), Parkinson disease, Huntington’s disease, amyotrophic lateral sclerosis (Kanekura et. al., 2009 and Nassif et. al. 2010), myocardial infarction, cardiovascular disease, atherosclerosis (McAlpine et. al, 2010), and arrhythmias. A PERK inhibitor is expected to have utility in the treatment of such cardiovascular and degenerative diseases in which the underlying pathology and symptoms are associated with dysregulation of the unfolded protein response.

References


Cullinan, S. B., and Diehl, J. A. (2004). PERK-dependent activation of Nrf2 contributes to redox homeostasis and cell survival following endoplasmic reticulum stress, J Biol Chem 279, 20108-17.


Ma, Y., and Hendershot, L. M. (2004). The role of the unfolded protein response in
tumour development: friend or foe?, Nat Rev Cancer 4, 966-77.


It is an object of the instant invention to provide novel compounds that are inhibitors of PERK.
It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

It is also an object of the present invention to provide a method for treating cancer, and diseases associated with activated unfolded protein response pathways, such as Alzheimer's disease, stroke, Type 1 diabetes, Parkinson disease, Huntington's disease, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, atherosclerosis, and arrhythmias, that comprises administering inhibitors of PERK activity.

**SUMMARY OF THE INVENTION**

The invention is directed to substituted indoline derivatives. Specifically, the invention is directed to compounds according to Formula (I):

![Diagram](image)

wherein $R^1$, $R^2$ and $R^3$ are defined below.

The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of PERK.

This invention also relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of a PERK inhibiting compound of Formula (I).

This invention also relates to a method of treating Alzheimer's disease, which comprises administering to a subject in need thereof an effective amount of a PERK inhibiting compound of Formula (I).
This invention also relates to a method of treating stroke, which comprises administering to a subject in need thereof an effective amount of a PERK inhibiting compound of Formula (I).

This invention also relates to a method of treating Type 1 diabetes, which comprises administering to a subject in need thereof an effective amount of a PERK inhibiting compound of Formula (I).

This invention also relates to a method of treating a disease state selected from: Parkinson disease, Huntington's disease, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, atherosclerosis, and arrhythmias, which comprises administering to a subject in need thereof an effective amount of a PERK inhibiting compound of Formula (I).

In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented PERK inhibiting compounds.

Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

Also included in the present invention are methods of co-administering the presently invented PERK inhibiting compounds with further active ingredients.

**DETAILED DESCRIPTION OF THE INVENTION**

This invention relates to novel compounds of Formula (I):

![Chemical Structure](image)
wherein:

$R^1$ is selected from:

- heteroaryl, and
- heteroaryl substituted with from one to five substituents independently selected from:
  - halo,
  - $\text{C-\text{-}6alkyl}$,
  - $\text{C-\text{-}4alkyloxy}$,
  - $\text{-OH}$,
  - hydroxy$\text{C-\text{-}4alkyl}$,
  - $\text{-COOH}$,
  - tetrazole,
  - $\text{-CF}_3$,
  - $\text{-C\text{-}4alkylO\text{-}Ci\text{-}4alkyl}$,
  - $\text{-CONH}_2$,
  - $\text{-CON(H)}\text{Ci\text{-}3alkyl}$,
  - $\text{-CH}_2\text{CH}_2\text{N(H)}\text{C(0)}\text{OCH}_2\text{aryl}$,
  - di$\text{Ci\text{-}4alkylaminoCi\text{-}4alkyl}$,
  - amino$\text{Ci\text{-}4alkyl}$,
  - $\text{-NO2}$,
  - $\text{-NH}_2$,
  - $\text{-N(H)}\text{Ci\text{-}3alkyl}$,
  - $\text{-N(Ci\text{-}3alkyl)}_2$,
  - $\text{-CN}$,

aryl,
aryl substituted with from one to three substituents independently selected from: $\text{C\text{-}4alkyl}$, di$\text{Ci\text{-}4alkylaminoCi\text{-}4alkyl}$, fluoro, chloro, bromo, iodo and $\text{-CF}_3$. 


heterocycloalkyl,
heterocycloalkyl substituted with from one to three substituents independently selected from: C-|-4alkyl, diCi-4alkylaminoC-|-4alkyl, fluoro, chloro, bromo, iodo and -CF3,
.Ci-4alkylheterocycloalkyl,
.Ci-4alkylheterocycloalkyl substituted with from one to three substituents independently selected from: C-|-4alkyl,
diCi-4alkylaminoC-|-4alkyl, fluoro, chloro, bromo, iodo and -CF3,
heteroaryl, and
heteroaryl substituted with from one to three substituents independently selected from: C-|-4alkyl, diCi-4alkylaminoC-|-4alkyl, fluoro, chloro, bromo, iodo and -CF3;

R2 is selected from:
aryl,
aryl substituted with form one to five substituents independently selected from: fluoro, chloro, bromo, iodo, C-|-4alkyl, C-|-4alkyloxy, -OH, -COOH, -CF3, -Ci-4alkyLOCi-4alkyl, -N02, -NH2 and -CN,
heteroaryl,
heteroaryl substituted with from one to five substituents independently selected from: fluoro, chloro, bromo, iodo, C-|-4alkyl, C-|-4alkyloxy, -OH, -COOH, -CF3, -Ci-4alkyLOCi-4alkyl, -N02, -NH2 and -CN,
cycloalkyi, and
cycloalkyi substituted with from one to five substituents independently selected from: fluoro, chloro, bromo, iodo, C-|-4alkyl, C-|-4alkyloxy, -OH, -COOH, -CF3, -Ci-4alkyLOCi-4alkyl, -N02, -NH2 and -CN; and

R3 is selected from: hydrogen, fluoro, chloro, bromo and iodo;

and salts thereof.
This invention also relates to pharmaceutically acceptable salts of the compounds of Formula (I).

For compounds of Formula (I), suitably R¹ is heteroaryl substituted with from one to three substituents independently selected from:

- halo,
- C-|-6alkyl,
- C-|-4alkyloxy,
- -OH,
- hydroxyC-|-4alkyl,
- -COOH,
- tetrazole,
- -CF₃,
- -CONH₂,
- -CON(H)Ci-3alkyl,
- -Ci-4alkylOCi-4alkyl,
- -CH₂CH₂N(H)C(0)OCH₂aryl,
- diCi-4alkylaminoCi-4alkyl,
- aminoCi-4alkyl,
- -NO₂,
- -NH₂,
- -N(H)Ci-3alkyl,
- -N(Ci-3alkyl)₂,
- -CN,
- aryl,
- aryl substituted with from one to three substituents independently selected from: Ci_4alkyl, diCi-4alkylaminoCi-4alkyl, fluoro, chloro, bromo, iodo and -CF₃,
heterocycloalkyl,
heterocycloalkyl substituted with from one to three substituents independently selected from: C-|-4alkyl, diCi-4alkylaminoC-|-4alkyl, fluoro, chloro, bromo, iodo and -CF3,
.Ci-4alkylheterocycloalkyl,
.Ci-4alkylheterocycloalkyl substituted with from one to three substituents independently selected from: C-|-4alkyl, diCi-4alkylaminoC-|-4alkyl, fluoro, chloro, bromo, iodo and -CF3, heteroaryl, and heteroaryl substituted with from one to three substituents independently selected from: C-|-4alkyl, diCi-4alkylaminoC-|-4alkyl, fluoro, chloro, bromo, iodo and -CF3.

For compounds of Formula (I), suitably R^1 is heteroaryl substituted with from one to three substituents independently selected from:
halo,
Ci-3alkyl,
C-|-3alkyloxy,
-OH,
-CONH2,
-CON(H)Ci-3alkyl,
-N(Ci-3alkyl) _2_,
-N(H)Ci-3alkyl, and
-NH$_2$.

For compounds of Formula (I), suitably R^1 is a substituted heteroaryl where the substituents are as described herein and the heteroaryl is selected from: pyrazole, pyrrole, isoxazole, pyridine, pyrimidine, pyridazine, and imidazole.
For compounds of Formula (I), suitably $R^1$ is a substituted pyrazole where the substituents are as described herein.

For compounds of Formula (I), suitably $R^1$ is substituted with from one to three substituents independently selected from:

- halo,
- $\text{Ci-3alkyl}$,
- $\text{C-|-3alkyloxy}$,
- $\text{-OH}$,
- $\text{-CONH}_2$,
- $\text{-CON(H)Ci-3alkyl}$,
- $\text{-N(Ci-3alkyl)}_2$,
- $\text{-N(H)Ci-3alkyl}$, and
- $\text{-NH}_2$.

For compounds of Formula (I), suitably $R^1$ is optionally substituted with one or two substituents independently selected from:

- halo,
- $\text{Ci-3alkyl}$,
- $\text{C-|-3alkyloxy}$,
- $\text{-OH}$,
- $\text{-CON(H)Ci-3alkyl}$,
- $\text{-N(Ci-3alkyl)}_2$,
- $\text{-N(H)Ci-3alkyl}$, and
- $\text{-NH}_2$. 
For compounds of Formula (I), suitably R² is selected from:

aryl,
aryl substituted with form one to three substituents independently selected from: halo, Ci-4alkyl, Ci-4alkyloxy, -OH, -COOH, -CF₃,
-Ci-4alkylOC-|-4alkyl, -N0₂, -NH₂ and -CN,
heteroaryl, and
heteroaryl substituted with from one to three substituents independently selected from: fluoro, chloro, bromo, iodo, C|-4alkyl, C|-4alkyloxy, -OH,
-COOH, -CF₃, -Ci-4alkylOCi-4alkyl, -N0₂, -NH₂ and -CN; and
R³ is selected from: hydrogen, fluoro and chloro.

Included in the presently invented compounds of Formula (I) are:

5-Amino-3-{1-[(2,5-difluorophenyl)acetyl]-2,3-dihydro-1H-indol-5-yl]-1-ethyl-1H-pyrazole-4-carboxamide;
1-Methyl-5-(methylamino)-3-(1-[[3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide;
5-amino-3-{1-[[3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indol-5-yl}-1-methyl-1H-pyrazole-4-carboxamide;
1-Methyl-3-{1-[[3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indol-5-yl}-1H-pyrazole-4-carboxamide;
5-Amino-3-(4-fluoro-1-[[3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide;
5-Amino-3-(4-fluoro-1-[[6-(trifluoromethyl)-2-pyridinyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide;
5-amino-3-(4-fluoro-1-[[6-methyl-2-pyridinyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide;
5-Amino-3-{1-[[3,5-dimethyl-1H-pyrazol-1-yl]acetyl]-4-fluoro-2,3-dihydro-1H-indol-5-yl]-1-methyl-1H-pyrazole-4-carboxamide;
5-Amino-1-methyl-3-(1-(2-(3-(trifluoromethyl)phenyl)acetyl)indolin-5-yl)-1 H-pyrazole-4-carboxamide;

5-Amino-1-methyl-3-(1-(2-(6-methylpyridin-2-yl)acetyl)indolin-5-yl)-1 H-pyrazole-4-carboxamide;

5-Amino-1-methyl-3-(1-(2-(6-(trifluoromethyl)pyridin-2-yl)acetyl)indolin-5-yl)-1 H-pyrazole-4-carboxamide; and

5-Amino-3-(1-(2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl)indolin-5-yl)-1-methyl-1 H-pyrazole-4-carboxamide.

and salts thereof including pharmaceutically acceptable salts thereof.

The skilled artisan will appreciate that salts, including pharmaceutically acceptable salts, of the compounds according to Formula I may be prepared. Indeed, in certain embodiments of the invention, salts including pharmaceutically-acceptable salts of the compounds according to Formula I may be preferred over the respective free or unsatled compound. Accordingly, the invention is further directed to salts, including pharmaceutically-acceptable salts, of the compounds according to Formula I.

The salts of the compounds of the invention are readily prepared by those of skill in the art.

The pharmaceutically acceptable salts of the compounds of the invention are readily prepared by those of skill in the art.

The compounds according to Formula I may contain one or more asymmetric centers (also referred to as a chiral center) and may, therefore, exist as individual enantiomers, diastereomers, or other stereoisomeric forms, or as mixtures thereof. Chiral centers, such as chiral carbon atoms, may be present in a substituent such as an alkyl group. Where the stereochemistry of a chiral center present in a compound of Formula I, or in any chemical structure illustrated herein, if not specified the structure is intended to encompass all individual stereoisomers and all mixtures thereof. Thus, compounds according to Formula I containing one or more chiral centers may be used as racemic
mixtures, enantiomerically enriched mixtures, or as enantiomerically pure individual stereoisomers.

The compounds according to Formula I may also contain double bonds or other centers of geometric asymmetry. Where the stereochemistry of a center of geometric asymmetry present in Formula I, or in any chemical structure illustrated herein, is not specified, the structure is intended to encompass the trans (E) geometric isomer, the cis (Z) geometric isomer, and all mixtures thereof. Likewise, all tautomeric forms are also included in Formula I whether such tautomers exist in equilibrium or predominately in one form.

The compounds of Formula I or salts, including pharmaceutically acceptable salts, thereof may exist in solid or liquid form. In the solid state, the compounds of the invention may exist in crystalline or noncrystalline form, or as a mixture thereof. For compounds of the invention that are in crystalline form, the skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates wherein water is the solvent that is incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The invention includes all such solvates.

The skilled artisan will further appreciate that certain compounds of Formula I or salts, including pharmaceutically acceptable salts thereof that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline structures). These different crystalline forms are typically known as "polymorphs." Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. In addition, one polymorph
may spontaneously convert to another polymorph under certain conditions. The invention includes all such polymorphs.

**Definitions**

"Alkyl" refers to a hydrocarbon chain having the specified number of "member atoms". For example, C-1-C4 alkyl refers to an alkyl group having from 1 to 4 member atoms. Alkyl groups may be saturated, unsaturated, straight or branched. Representative branched alkyl groups have one, two, or three branches. Alkyl includes methyl, ethyl, ethylene, propyl (n-propyl and isopropyl), butene, and butyl (n-butyl, isobutyl, and t-butyl).

"Alkoxy" refers to an -O-alkyl group wherein "alkyl" is as defined herein. For example, C-1-C4alkoxy refers to an alkoxy group having from 1 to 4 member atoms. Representative branched alkoxy groups have one, two, or three branches. Examples of such groups include methoxy, ethoxy, propoxy, and butoxy.

"Aryl" refers to an aromatic hydrocarbon ring. Aryl groups are monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring member atoms, wherein at least one ring system is aromatic and wherein each ring in the system contains 3 to 7 member atoms, such as phenyl, naphthalene, tetrahydronaphthalene and biphenyl. Suitably aryl is phenyl.

"Cycloalkyl" refers to a saturated or unsaturated non aromatic hydrocarbon ring having from three to seven carbon atoms. Cycloalkyl groups are monocyclic ring systems. For example, C3-C7 cycloalkyl refers to a cycloalkyl group having from 3 to 7 member atoms. Examples of cycloalkyl as used herein include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl and cyclohexenyl.

"Halo" refers to the halogen radicals fluoro, chloro, bromo, and iodo.

"Heteroaryl" refers to a monocyclic aromatic 4 to 8 member ring containing from 1 to 7 carbon atoms and containing from 1 to 4 heteroatoms, provided that when the number of
carbon atoms is 3, the aromatic ring contains at least two heteroatoms. Heteroaryl
groups containing more than one heteroatom may contain different heteroatoms.
Heteroaryl includes: pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl,
isothiazolyl, furanyl, furazanyl, thienyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl,
pyrazinyl, triazinyl, tetrazinyl. Suitably, "heteroaryl" includes: pyrazole, pyrrole, isoxazole,
pyridine, pyrimidine, pyridazine, and imidazole.

"Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic ring containing 4
to 12 member atoms, of which 1 to 11 are carbon atoms and from 1 to 6 are heteroatoms.
Heterocycloalkyl groups containing more than one heteroatom may contain different
heteroatoms. Heterocycloalkyl groups are monocyclic ring systems or a monocyclic ring
fused with an aryl ring or to a heteroaryl ring having from 3 to 6 member atoms.
Heterocycloalkyl includes: pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, pyranyl,
tetrahydropyranyl, dihydropyranyl, tetrahydrothienyl, pyrazolidinyl, oxazolidinyl, oxetany,
thiazolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, 1,3-
dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl,
1,3-oxazolidin-2-one, hexahydro-1 H-azepin, 4,5,6,7-tetrahydro-1 H-benzimidazol,
piperidinyl, 1,2,3,6-tetrahydro-pyridinyl and azetidinyl.

"Heteroatom" refers to a nitrogen, sulphur or oxygen atom.

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

As used herein the symbols and conventions used in these processes, schemes
and examples are consistent with those used in the contemporary scientific literature, for
example, the Journal of the American Chemical Society or the Journal of Biological
Chemistry. Standard single-letter or three-letter abbreviations are generally used to
designate amino acid residues, which are assumed to be in the L-configuration unless
otherwise noted. Unless otherwise noted, all starting materials were obtained from
commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

Ac (acetyl);
Ac_2O (acetic anhydride);

ACN (acetonitrile);
AIBN (azobisisobutyronitrile);
BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl);
BMS (borane-dimethyl sulphide complex);
Bn (benzyl);

Boc (tert-Butyloxycarbonyl);
Boc_2O (di-tert-butyl dicarbonate);
BOP (Benzotriazolyl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate);
CAN (ceric ammonium nitrate);
Cbz (benzyloxy carbonyl);

CSI (chlorosulfonyl isocyanate);
DABOO (1,4-Diazabicyclo[2.2.2]octane);
DAST ((Diethylamino)sulfur trifluoride);
DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene);
DCC (Dicyclohexyl Carbodiimide);

DOE (1,2-dichloroethane);
DCM (dichloromethane);

DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone);
ATP (adenosine triphosphate);

Bis-pinacolatodiboron (4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3,2-dioxaborolane);
BSA (bovine serum albumin);
C18 (refers to 18-carbon alkyl groups on silicon in HPLC stationary phase)

CHsCN (acetonitrile);
Cy (cyclohexyl);
DCM (dichloromethane);
DIPEA (Hunig's base, N-ethyl-N-(1-methylethyl)-2-propanamine);
DMAP (4-dimethylaminopyridine);
DME (1,2-dimethoxyethane);
DMF (A/-A/-dimethylformamide);
DMSO (dimethylsulfoxide);
DPPA (diphenyl phosphor yl azide);
EDC (N-(3-dimethylaminopropyl)-N'ethylcarbodiimide);
EDTA (ethylenediaminetetraacetic acid);
EtOAc (ethyl acetate);
EtOH (ethanol);
Et2O (diethyl ether);
HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
HATU (0-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate);
HOAt (1-hydroxy-7-azabenzotriazole); 
HOBt (1-hydroxybenzotriazole);
HOAc (acetic acid);
HPLC (high pressure liquid chromatography);
HMDS (hexamethyldisilazide);
Hunig's Base (N,N-Diisopropylethylamine);
IPA (isopropyl alcohol);
Indoline (2,3-dihydro-1H-indole) 
KHMDS (potassium hexamethyldisilazide) 
LAH (lithium aluminum hydride) 
LDA (lithium diisopropylamide) 
LHMDS (lithium hexamethyldisilazide)
MeOH (methanol);
MTBE (methyl tert-butyl ether);
mCPBA (m-chloroperbezoic acid);
NaHMDS (sodium hexamethyldisilazide);
NBS (N-bromosuccinimide);
PE (petroleum ether);
Pd$_2$(dba)$_3$ (Tris(dibenzylideneacetone)dipalladium(O);
Pd(dppf)Cl$_2$ ([1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(ll));
PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate);
PyBrOP (bromotripyrrolidinophosphonium hexafluorophosphate);
RPHPLC (reverse phase high pressure liquid chromatography);
SFC (supercritical fluid chromatography);
SGC (silica gel chromatography);
TEA (triethylamine);
TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl, free radical);
TFA (trifluoroacetic acid); and
THF (tetrahydrofuran).

All references to ether are to diethyl ether and brine refers to a saturated aqueous solution of NaCl.

**Compound Preparation**

The compounds according to Formula I are prepared using conventional organic synthetic methods. A suitable synthetic route is depicted below in the following general reaction schemes.

The skilled artisan will appreciate that if a substituent described herein is not compatible with the synthetic methods described herein, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired
intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999). In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful as an intermediate compound or is a desired substituent in a target compound.

As shown in Scheme 1, commercially available 5-bromoindoline 1 is acylated with a carboxylic acid using a coupling reagent (e.g., EDC, DCC or HATU) to form the amide bond in 2. Conversion of 2 to the boronate ester and subsequent Suzuki-Miyaura coupling with heteroaryl bromide A affords the product 3. The boronate ester (represented by 4) may be purified and isolated if desired and subjected to the Suzuki-Miyaura coupling in a separate synthetic procedure.

Scheme 1

The compounds of the invention can be prepared as shown in Scheme 2. The nitrogen of 5-bromoindoline 1 can be protected with the te/f-butylcarbamate (Boc) group to give 8. The analogous 4-F derivative can be prepared from 4-F indole via sodium cyanoborohydride reduction, N-Boc protection, followed by regioselective bromination with NBS. Transformation to the heteroaryl substituted indoline 9 is accomplished with or
without isolation of the intermediate boronate ester. Deprotection of the Boc group with HCl affords the indoline 10, which can be converted to 11 using a coupling reagent (e.g., EDC, DCC or HATU) to form the amide bond.

Scheme 2

Heteroaryl halide A is prepared as shown in Scheme 3. Dibromopyrazole 14 can be prepared from commercial 3-aminopyrazole-4-carbonitrile 12 using t-Bu nitrite in bromoform followed by bromine; alternatively dibromopyrazole 14 can be prepared by dibromination of commercial 1H-pyrazole-4-carbonitrile 15 with bromine. Intermediate 14 is alkylated with an alkyl iodide to form intermediate 16 which is treated with 2,4-dimethoxybenzylamine to install the 5-amino group of intermediate 17. Hydrolysis of the nitrile of intermediate 17 with sulfuric acid affords intermediate 18. 3-Aminopyrazole-4-carbonitrile 12 can be brominated with NBS to form intermediate 19 and following hydrolysis with sulfuric acid, gives intermediate 20. Treatment of dibromopyrazole 16 with 2,4-dimethoxybenzylamine overnight affords the 5-methylamino intermediate 21, and subsequent hydrolysis of the nitrile gives intermediate 22. Treatment of intermediate 17 with t-Bu nitrite affords bromopyrazole 23, and subsequent hydrolysis of the nitrile gives intermediate 24.
Methods of Use

The compounds according to Formula I and pharmaceutically acceptable salts thereof are inhibitors of PERK. These compounds are potentially useful in the treatment of conditions wherein the underlying pathology is attributable to (but not limited to) activation of the UPR pathway, for example, cancer and more specifically cancers of the breast, colon, and lung, pancreas and skin. Accordingly, in another aspect the invention is directed to methods of treating such conditions.
Suitably, the present invention relates to a method for treating or lessening the severity of breast cancer, including inflammatory breast cancer, ductal carcinoma, and lobular carcinoma.

Suitably the present invention relates to a method for treating or lessening the severity of colon cancer.

Suitably the present invention relates to a method for treating or lessening the severity of pancreatic cancer, including insulinomas, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, and glucagonoma.

Suitably the present invention relates to a method for treating or lessening the severity of skin cancer, including melanoma, including metastatic melanoma.

Suitably the present invention relates to a method for treating or lessening the severity of lung cancer including small cell lung cancer, non-small cell lung cancer, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

Suitably the present invention relates to a method for treating or lessening the severity of cancers selected from the group consisting of brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, head and neck, kidney, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid, lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, Immunoblastic large cell leukemia, mantle cell leukemia, multiple myeloma, megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia, malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer,
buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

Suitably the present invention relates to a method for treating or lessening the severity of pre-cancerous syndromes in a mammal, including a human, wherein the pre-cancerous syndrome is selected from: cervical intraepithelial neoplasia, monoclonal gammapathy of unknown significance (MGUS), myelodysplasia syndrome, aplastic anemia, cervical lesions, skin nevi (pre-melanoma), prostatic intraepithelial (intraductal) neoplasia (PIN), Ductal Carcinoma in situ (DCIS), colon polyps and severe hepatitis or cirrhosis.

Suitably the present invention relates to a method for treating or lessening the severity of additional diseases associated with UPR activation including: Type 1 diabetes, Alzheimer's disease, stroke, Parkinson disease, Huntington's disease, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, atherosclerosis, and arrhythmias.

The compounds of this invention inhibit angiogenesis which is implicated in the treatment of ocular diseases. *Nature Reviews Drug Discovery* 4, 711-712 (September 2005). Suitably the present invention relates to a method for treating or lessening the severity of ocular diseases/angiogenesis. In embodiments of methods according to the invention, the disorder of ocular diseases, including vascular leakage can be: edema or neovascularization for any occlusive or inflammatory retinal vascular disease, such as rubeosis irides, neovascular glaucoma, pterygium, vascularized glaucoma filtering blebs, conjunctival papilloma; choroidal neovascularization, such as neovascular age-related macular degeneration (AMD), myopia, prior uveitis, trauma, or idiopathic; macular edema, such as post surgical macular edema, macular edema secondary to uveitis including retinal and/or choroidal inflammation, macular edema secondary to diabetes, and macular edema secondary to retinovascular occlusive disease (i.e. branch and central retinal vein occlusion); retinal neovascularization due to diabetes, such as retinal vein occlusion, uveitis, ocular ischemic syndrome from carotid artery disease, ophthalmic or retinal artery occlusion, sickle cell retinopathy, other ischemic or occlusive neovascular retinopathies, retinopathy of prematurity, or Eale's Disease; and genetic disorders, such as Von-Hippel-Lindau syndrome.

In some embodiments, the neovascular age-related macular degeneration is wet age-related macular degeneration. In other embodiments, the neovascular age-related
macular degeneration is dry age-related macular degeneration and the patient is characterized as being at increased risk of developing wet age-related macular degeneration.

The methods of treatment of the invention comprise administering an effective amount of a compound according to Formula I or a pharmaceutically acceptable salt, thereof to a patient in need thereof.

The invention also provides a compound according to Formula I or a pharmaceutically-acceptable salt thereof for use in medical therapy, and particularly in cancer therapy. Thus, in further aspect, the invention is directed to the use of a compound according to Formula I or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a disorder characterized by activation of the UPR, such as cancer.

By the term "treating" and derivatives thereof as used herein, is meant prophylactic and therapeutic therapy. Prophylactic therapy is appropriate, for example, when a subject has a strong family history of cancer or is otherwise considered at high risk for developing cancer, or when a subject has been exposed to a carcinogen.

As used herein, the term "effective amount" and derivatives thereof means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" and derivatives thereof means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, "patient" or "subject" refers to a human or other animal. Suitably the patient or subject is a human.

The compounds of Formula I or pharmaceutically acceptable salts thereof may be administered by any suitable route of administration, including systemic administration. Systemic administration includes oral administration, and parenteral administration,
Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or infusion.

The compounds of Formula I or pharmaceutically acceptable salts thereof may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of the invention depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of the invention depend on the condition being treated, the severity of the condition being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change.

Additionally, the compounds of Formula I or pharmaceutically-acceptable salts thereof may be administered as prodrugs. As used herein, a "prodrug" of a compound of the invention is a functional derivative of the compound which, upon administration to a patient, eventually liberates the compound of the invention in vivo. Administration of a compound of the invention as a prodrug may enable the skilled artisan to do one or more of the following: (a) modify the onset of the compound in vivo; (b) modify the duration of action of the compound in vivo; (C) modify the transportation or distribution of the compound in vivo; (d) modify the solubility of the compound in vivo; and (e) overcome or overcome a side effect or other difficulty encountered with the compound. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, and the like for -COOH, and acetate maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics.
The compounds of Formula I and pharmaceutically acceptable salts thereof may be co-administered with at least one other active agent known to be useful in the treatment of cancer.

By the term "co-administration" as used herein is meant either simultaneous administration or any manner of separate sequential administration of a PERK inhibiting compound, as described herein, and a further active agent or agents, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment. The term further active agent or agents, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered by injection and another compound may be administered orally.

Typically, any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be co-administered in the treatment of cancer in the present invention. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimitabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; cell cycle signaling inhibitors; proteasome inhibitors; and inhibitors of cancer metabolism.

Examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented PERK inhibiting compounds are chemotherapeutic agents.
Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

Diterpenoids, which are derived from natural sources, are phase specific anti-cancer agents that operate at the G2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β-tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.


Cancer Chemotherapy Pocket Guide A 1998) related to the duration of dosing above a threshold concentration (50nM) (Kearns, CM. et. al., Seminars in Oncology, 3(6) p.16-23, 1995).

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-te/f-butyl ester, 13-ester with 5p-20-epoxy-1,2a,4,7p,10p, 13ot-hexahydrotax-1 1-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel q.v., prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree. The dose limiting toxicity of docetaxel is neutropenia.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

Vinblastine, vincaleukoblastine sulfate, is commercially available as VELBAN® as an injectable solution. Although, it has possible indication as a second line therapy of various solid tumors, it is primarily indicated in the treatment of testicular cancer and various lymphomas including Hodgkin's Disease; and lymphocytic and histiocytic lymphomas. Myelosuppression is the dose limiting side effect of vinblastine.

Vincristine, vincaleukoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosuppression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincaleukoblastine [R-(R',R')-2,3-dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable solution of vinorelbine tartrate (NAVELBINE®), is a semisynthetic vinca alkaloid. Vinorelbine is
indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung, advanced breast, and hormone refractory prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer. The primary dose limiting side effects of cisplatin are nephrotoxicity, which may be controlled by hydration and diuresis, and ototoxicity.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-0,0'], is commercially available as PARAPLATIN® as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma. Bone marrow suppression is the dose limiting toxicity of carboplatin.

Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulphydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant
lymphomas, multiple myeloma, and leukemias. Alopecia, nausea, vomiting and leukopenia are the most common dose limiting side effects of cyclophosphamide.

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Melphalan is indicated for the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. Bone marrow suppression is the most common dose limiting side effect of chlorambucil.

Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia. Bone marrow suppression is the most common dose limiting side effects of busulfan.

Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BICNU®. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas. Delayed myelosuppression is the most common dose limiting side effects of carmustine.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dacarbazine.

Antibiotic anti-neoplastics are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of
antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Dactinomycin, also known as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Dactinomycin is indicated for the treatment of Wilm's tumor and rhabdomyosarcoma. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dactinomycin.

Daunorubicin, (8S-cis)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,1 1-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as a liposomal injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi's sarcoma. Myelosuppression is the most common dose limiting side effect of daunorubicin.

Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,1 1-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas. Myelosuppression is the most common dose limiting side effect of doxorubicin.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of Streptomyces verticillus, is commercially available as BLENOXANE®. Bleomycin is indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas. Pulmonary and cutaneous toxicities are the most common dose limiting side effects of bleomycin.

Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G2 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA
strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-ethylidene-p-D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Etoposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of testicular and non-small cell lung cancers. Myelosuppression is the most common side effect of etoposide. The incidence of leucopenia tends to be more severe than thrombocytopenia.

Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-thenylidene-p-D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia in children. Myelosuppression is the most common dose limiting side effect of teniposide. Teniposide can induce both leucopenia and thrombocytopenia.

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mecaptopurine, thioguanine, and gemcitabine.

5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Myelosuppression and mucositis are dose limiting side effects of 5-fluorouracil. Other fluoropyrimidine analogs include 5-fluoro deoxyuridine (flouxuridine) and 5-fluorodeoxyuridine monophosphate.

Cytarabine, 4-amino-1-p-D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that
cytarabine exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2',2'-difluorodeoxycytidine (gemcitabine). Cytarabine induces leucopenia, thrombocytopenia, and mucositis.

Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®. Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression and gastrointestinal mucositis are expected side effects of mercaptopurine at high doses. A useful mercaptopurine analog is azathioprine.

Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of thioguanine administration. However, gastrointestinal side effects occur and can be dose limiting. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β-isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-phase and by blocking progression of cells through the G1/S boundary. Gemcitabine is indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of gemcitabine administration.

Methotrexate, N-[4[[2,4-diamino-6-pteridinyl] methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or
replication through the inhibition of dihydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin’s lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

Irinotecan HCl, (4S)-4,1-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®.

Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I - DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I : DNA : irinotecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of the colon or rectum. The dose limiting side effects of irinotecan HCl are myelosuppression, including neutropenia, and GI effects, including diarrhea.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1 H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I - DNA complex and prevents religation of singles strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer. The dose limiting side effect of topotecan HCl is myelosuppression, primarily neutropenia.
Also of interest, is the camptothecin derivative of Formula A following, including the racemic mixture (R,S) form as well as the R and S enantiomers:

![Chemical structure of camptothecin derivative](image)

known by the chemical name "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R,S)-camptothecin (racemic mixture) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R)-camptothecin (R enantiomer) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin (S enantiomer). Such compound as well as related compounds are described, including methods of making, in U.S. Patent Nos. 6,063,923; 5,342,947; 5,559,235; 5,491,237 and pending U.S. patent Application No. 08/977,217 filed November 24, 1997.

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children; aromatase inhibitors such as anastrozole, letrozole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestrins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5a-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the
release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagonists such as goserelin acetate and luprolide.

Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal transduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3 domain blockers, serine/threonine kinases, phosphotidylinositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor - I (IGFl) receptor, macrophage colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., Exp. Opin. Ther. Patents (2000) 10(6):803-818; Shawver et al DDT Vol 2, No. 2 February 1997; and Lofts, F. J. et al,

Suitably, the pharmaceutically active compounds of the invention are used in combination with a VEGFR inhibitor, suitably 5-[[4-[[2,3-dimethyl-2H-indazol-6-yl]methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide, or a pharmaceutically acceptable salt, suitably the monohydrochloride salt thereof, which is disclosed and claimed in International Application No. PCT/US01/49367, having an International filing date of December 19, 2001, International Publication Number WO02/05910 and an International Publication date of August 1, 2002, the entire disclosure of which is hereby incorporated by reference, and which is the compound of Example 69. 5-[[4-[[2,3-dimethyl-2H-indazol-6-yl]methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide can be prepared as described in International Application No. PCT/US01/49367.

Suitably, 5-[[4-[[2,3-dimethyl-2H-indazol-6-yl]methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide is in the form of a monohydrochloride salt. This salt form can be prepared by one of skill in the art from the description in International Application No. PCT/US01/49367, having an International filing date of December 19, 2001.

5-[[4-[[2,3-dimethyl-2H-indazol-6-yl]methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide is sold commercially as the monohydrochloride salt and is known by the generic name pazopanib and the trade name Votrient®.

Pazopanib is implicated in the treatment of cancer and ocular diseases/angiogenesis. Suitably the present invention relates to the treatment of cancer and ocular diseases/angiogenesis, suitably age-related macular degeneration, which method comprises the administration of a compound of Formula (I) alone or in combination with pazopanib.

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases for use in the present invention, which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell
SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (She, Crk, Nek, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), Journal of Pharmacological and Toxicological Methods. 34(3) 125-32.


Suitably, the pharmaceutically active compounds of the invention are used in combination with a MEK inhibitor. Suitably, N-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl]acetamide, or a pharmaceutically acceptable salt or solvate, suitably the dimethyl sulfoxide solvate, thereof, which is disclosed and claimed in International Application No. PCT/JP2005/01 1082, having an International filing date of June 10, 2005; International Publication Number WO 2005/121 142 and an International Publication date of December 22, 2005, the entire disclosure of which is hereby incorporated by reference. N-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl]acetamide, can be prepared as
described in United States Patent Publication No. US 2006/0014768, Published January 19, 2006, the entire disclosure of which is hereby incorporated by reference.

Suitably, the pharmaceutically active compounds of the invention are used in combination with a B-Raf inhibitor. Suitably, A/-(3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl)-2,6-difluorobenzenesulfonamide, or a pharmaceutically acceptable salt thereof, which is disclosed and claimed, in International Application No. PCT/US2009/042682, having an International filing date of May 4, 2009, the entire disclosure of which is hereby incorporated by reference. A/-(3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl)-2,6-difluorobenzenesulfonamide can be prepared as described in International Application No. PCT/US2009/042682.

Suitably, the pharmaceutically active compounds of the invention are used in combination with an Akt inhibitor. Suitably, N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide or a pharmaceutically acceptable salt thereof, which is disclosed and claimed in International Application No. PCT/US2008/053269, having an International filing date of February 7, 2008; International Publication Number WO 2008/098104 and an International Publication date of August 14, 2008, the entire disclosure of which is hereby incorporated by reference. N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide is the compound of example 224 and can be prepared as described in International Application No. PCT/US2008/053269.

Suitably, the pharmaceutically active compounds of the invention are used in combination with an Akt inhibitor. Suitably, A/-(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide or a pharmaceutically acceptable salt thereof, which is disclosed and claimed in International Application No. PCT/US2008/053269, having an International filing date of February 7, 2008; International Publication Number WO 2008/098104 and an International Publication date of August 14, 2008, the entire disclosure of which is hereby incorporated by reference. A/-(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide is the compound of example 96 and can be prepared as described in International Application No.
PCT/US2008/053269. Suitably, A/-[(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophencarboxamide is in the form of a hydrochloride salt. The salt form can be prepared by one of skill in the art from the description in International Application No. PCT/US2010/022323, having an International filing date of January 28, 2010.


Also of interest in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman and David Kerr, CRC press 1994, London.

Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras, thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), Journal of Biomedical Science. 7(4) 292-8; Ashby, M.N. (1998), Current Opinion in Lipidology. 9 (2) 99 - 102; and BioChim. Biophys. Acta, (19899) 1423(3):19-30.

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev., (2000), 26(4), 269-286); Herceptin ® erbB2 antibody (see Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kinases, Breast cancer Res., 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken, R.A. et al,

Non-receptor kinase angiogenesis inhibitors may also be useful in the present invention. Inhibitors of angiogenesis related VEGFR and TIE2 are discussed above in regard to signal transduction inhibitors (both receptors are receptor tyrosine kinases). Angiogenesis in general is linked to erbB2/EGFR signaling since inhibitors of erbB2 and EGFR have been shown to inhibit angiogenesis, primarily VEGF expression. Accordingly, non-receptor tyrosine kinase inhibitors may be used in combination with the compounds of the present invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin (alpha_v beta_3) that will inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with the disclosed compounds. (See Bruns CJ et al (2000), Cancer Res., 60: 2926-2935; Schreiber AB, Winkler ME, and Derynck R. (1986), Science, 232: 1250-1253; Yen L et al. (2000), Oncogene 19: 3460-3469).

Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of Formula (I). There are a number of immunologic strategies to generate an immune response. These strategies are generally in the realm of tumor vaccinations. The efficacy of immunologic approaches may be greatly enhanced through combined inhibition of signaling pathways using a small molecule inhibitor. Discussion of the immunologic/tumor vaccine approach against erbB2/EGFR are found in Reilly RT et al. (2000), Cancer Res. 60: 3569-3576; and Chen Y, Hu D, Eling DJ, Robbins J, and Kipps TJ. (1998), Cancer Res. 58: 1965-1971.

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of bcl-2 has therefore been linked to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the bcl-2 family (i.e., mcl-1). Therefore, strategies designed to downregulate the expression of bcl-2 in tumors have demonstrated clinical benefit and are now in Phase II/III trials, namely Genta’s G3139 bcl-2 antisense oligonucleotide. Such proapoptotic strategies using the antisense oligonucleotide strategy for bcl-2 are
Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania et al, Exp. Opin. Ther. Patents (2000) 10(2):215-230. Further, p21WAF1/CIP1 has been described as a potent and universal inhibitor of cyclin-dependent kinases (Cdks) (Ball et al., Progress in Cell Cycle Res., 3: 125 (1997)). Compounds that are known to induce expression of p21WAF1/CIP1 have been implicated in the suppression of cell proliferation and as having tumor suppressing activity (Richon et al., Proc. Nat Acad. Sci. U.S.A. 97(18): 10014-10019 (2000)), and are included as cell cycle signaling inhibitors. Histone deacetylase (HDAC) inhibitors are implicated in the transcriptional activation of p21WAF1/CIP1 (Vigushin et al., Anticancer Drugs, 13(1): 1-13 (Jan 2002)), and are suitable cell cycle signaling inhibitors for use herein.

Examples of such HDAC inhibitors include:


Vorinostat has the following chemical structure and name:

\[ /V\text{-hydroxy-A}^\prime\text{-phenyl-octanediamide} \]

Romidepsin, has the following chemical structure and name:

(1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-di(propan-2-yl)-2-oxa,12,13-dithia-5,8,20,23-tetrazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone


Panobinostat, has the following chemical structure and name:

(2£)-/V-hydroxy-3-[4-([2-(2-methyl-1/-/-indol-3-yl)ethyl]amino)methyl]phenyl]acrylamide

5. Valproic acid, has the following chemical structure and name:

\[ \text{CH}_3 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH} \quad \text{C} = \text{O} \quad \text{CH}_3 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{OH} \]

2-propylpentanoic acid


Mocetinostat, has the following chemical structure and name:

\[ \text{A} / (2\text{-Aminophenyl}) - 4 - [(4\text{-pyridin-3-ylpyrimidin-2-yl} \text{amino}) \text{methyl}] \text{ benzamide} \]
Further examples of such HDAC inhibitors are included in Bertrand European Journal of Medicinal Chemistry 45, (2010) 2095-2116, particularly the compounds of table 3 therein as indicated below.
Proteasome inhibitors are drugs that block the action of proteasomes, cellular complexes that break down proteins, like the p53 protein. Several proteasome inhibitors are marketed or are being studied in the treatment of cancer. Suitable proteasome inhibitors for use herein include:


Bortezomib has the following chemical structure and name.

![Chemical structure of Bortezomib](image)

\[
\text{[(1R)-3-methyl-1-\{(2S)-3-phenyl-2-[(pyrazin-2-ylcarbonyl)amino]propanoyl]amino\}butyl]boronic acid}
\]


Disulfiram has the following chemical structure and name.

![Chemical structure of Disulfiram](image)

1,1'-1",1"'-[disulfanediylbis(carbonothioylnitrilo)]tetraethane


Epigallocatechin gallate has the following chemical structure and name.

Salinosporamide A has the following chemical structure and name.

![Chemical Structure of Salinosporamide A](attachment:image.png)

(4R,5S)-4-(2-chloroethyl)-1-((1S)-cyclohex-2-enyl(hydroxy)methyl)-5-methyl-6-oxa-2-
azabicyclo3.2.0heptane-3,7-dione

Carfilzomib has the following chemical structure and name.

(S)-4-methyl-N-((S)-1 -(((S)-4-methyl- 1-(2-methyl-1-oxopentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide

The 70 kilodalton heat shock proteins (Hsp70s) and 90 kilodalton heat shock proteins (Hsp90s) are a families of ubiquitously expressed heat shock proteins. Hsp70s and Hsp90s are over expressed certain cancer types. Several Hsp70s and Hsp90s inhibitors are being studied in the treatment of cancer. Suitable Hsp70s and Hsp90s inhibitors for use in combination herein include:


17-AAG(Geldanamycin) has the following chemical structure and name.

17-(Allylamo)-17-demethoxygeldanamycin

2. Radicicol, including pharmaceutically acceptable salts thereof. (Lee et al., Mol Cell Endocrinol. 2002, 188,47-54)

Radicicol has the following chemical structure and name.
Inhibitors of cancer metabolism - Many tumor cells show a markedly different metabolism from that of normal tissues. For example, the rate of glycolysis, the metabolic process that converts glucose to pyruvate, is increased, and the pyruvate generated is reduced to lactate, rather than being further oxidized in the mitochondria via the tricarboxylic acid (TCA) cycle. This effect is often seen even under aerobic conditions and is known as the Warburg Effect.

Lactate dehydrogenase A (LDH-A), an isoform of lactate dehydrogenase expressed in muscle cells, plays a pivotal role in tumor cell metabolism by performing the reduction of pyruvate to lactate, which can then be exported out of the cell. The enzyme has been shown to be upregulated in many tumor types. The alteration of glucose metabolism described in the Warburg effect is critical for growth and proliferation of cancer cells and knocking down LDH-A using RNAi has been shown to lead to a reduction in cell proliferation and tumor growth in xenograft models.


High levels of fatty acid synthase (FAS) have been found in cancer precursor lesions. Pharmacological inhibition of FAS affects the expression of key oncogenes involved in both cancer development and maintenance.


Inhibitors of cancer metabolism, including inhibitors of LDH-A and inhibitors of fatty acid biosynthesis (or FAS inhibitors), are suitable for use in combination with the compounds of this invention.
In one embodiment, the cancer treatment method of the claimed invention includes the co-administration a compound of Formula (I) and/or a pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, cell cycle signaling inhibitors; proteasome inhibitors; and inhibitors of cancer metabolism.

Compositions

The pharmaceutically active compounds within the scope of this invention are useful as PERK inhibitors in mammals, particularly humans, in need thereof.

The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring PERK inhibition, which comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as PERK inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, t alc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a
syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical compositions are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of a PERK inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermal\textsuperscript{a}, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages, is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular PERK inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing PERK inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective PERK inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as a PERK inhibitor.
The invention also provides for the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in treating cancer.

The invention also provides for a pharmaceutical composition for use as a PERK inhibitor which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer, or compounds known to have utility when used in combination with a PERK inhibitor.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

EXAMPLES

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan
will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

Example 1

5-Amino-3-\{1-[(2,5-difluorophenyl)acetyl]-2,3-dihydro-1H-indol-5-yl]-1-ethyl-1H-pyrazole-4-carboxamide

\[
\begin{align*}
\text{5-Bromo-1H-pyrazole-4-carbonitrile} & \\
\text{To a solution containing 5-amino-1H-pyrazole-4-carbonitrile (5 g, 46.3 mmol) in bromoform (25 mL, 286 mmol) was added tert-butyl nitrite (16.50 mL, 139 mmol). The reaction was heated to 70 °C and stirred for 15 min. The reaction mixture was concentrated onto silica gel and purified by flash chromatography (0-60% ethyl acetate in hexanes) to afford 5-bromo-1H-pyrazole-4-carbonitrile (4.9 g, 28.5 mmol, 61%). LC-MS (ES) m/z = 172, 174 [M+H]^+.

3,5-Dibromo-1H-pyrazole-4-carbonitrile
To a solution of 5-bromo-1H-pyrazole-4-carbonitrile (5.92 g, 34.4 mmol) in ethanol (100 ml) was added sodium acetate (19.77 g, 241 mmol) in water (120 mL) followed by bromine (7.09 mL, 138 mmol). The reaction was stirred for 10 min, and then poured into water, extracted with ethyl acetate, washed with sat. sodium thiosulfate, dried over magnesium sulfate, filtered, and concentrated onto silica gel and purified by flash chromatography (silica gel, 0-50% ethyl acetate in hexanes), to afford 3,5-dibromo-1H-pyrazole-4-carbonitrile (6.15 g, 24.51 mmol, 71%) as a pale yellow solid. LC-MS (ES) m/z = 250, 252, 254 [M+H]^+.

Alternative method

3,5-Dibromo-1H-pyrazole-4-carbonitrile (from 1H-pyrazole-4-carbonitrile)
To 1H-pyrazole-4-carbonitrile (6.76 g, 52.2 mmol) were added ethanol (150 mL), water (225 mL) and sodium acetate (29.1 g, 355 mmol). The reaction was stirred until the solids completely dissolved, then bromine (10.75 mL, 209 mmol) was added dropwise, and the reaction stirred for 2 hours. The reaction was diluted with water then extracted with DCM (3 x 150 mL). The organic layers were combined then washed with saturated aqueous sodium thiosulfate (Na₂S₂O₃) and water was added until the DCM layer separated. The organic layer was then dried over MgSO₄, filtered and concentrated. The residue was dissolved in EtOAc. When all of the solid went into solution additional EtOAc was added to almost double the starting volume and hexane was added until the solution turned slightly cloudy. The mixture was allowed to stand for 0.5 hour then filtered. The filtrate was then concentrated to afford 3,5-Dibromo-1H-pyrazole-4-carbonitrile (8.9 g, 35.5 mmol, 68.0 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 15.02 (br. s., 1H).

3,5-Dibromo-1-ethyl-1H-pyrazole-4-carbonitrile

To a solution of 3,5-dibromo-1 H-pyrazole-4-carbonitrile (4 g, 15.94 mmol) in DMF (40 mL) was added sodium hydride (60 wt% in mineral oil, 0.701 g, 17.54 mmol) at 0 °C. The reaction was stirred for 5 min at 0 °C and then ethyl iodide (3.87 mL, 47.8 mmol) was added dropwise. The reaction was stirred for 48 h, quenched with aqueous NH₄Cl, extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated onto silica gel and purified by flash chromatography (silica gel, 0-50% ethyl acetate in hexanes), to afford 3,5-dibromo-1-ethyl-1H-pyrazole-4-carbonitrile (4.21 g, 15.09 mmol, 95%) as a pale yellow solid. LC-MS (ES) m/z = 278, 280, 282 [M+H]+.

5-Amino-3-bromo-1-ethyl-1H-pyrazole-4-carbonitrile

A solution containing 3,5-dibromo-1-ethyl-1 H-pyrazole-4-carbonitrile (3.16 g, 11.33 mmol) and 2,4-dimethoxybenzylamine (2.213 mL, 14.73 mmol) in N-Methyl-2-pyrrolidone(NMP) (5 mL) was heated at 180 °C for 2.5 hours on a heating block, then poured into aqueous NH₄Cl and 1 N HCl, extracted with CH₂Cl₂, dried over magnesium sulfate, filtered, then concentrated onto silica gel and purified by flash chromatography (silica gel, 0-50% ethyl acetate in hexanes), to afford 5-amino-3-bromo-1-ethyl-1H-pyrazole-4-carbonitrile (2.4 g, 11.33, 100%) as a pale yellow oil. LC-MS (ES) m/z = 215, 217 [M+H]+.

5-Amino-3-bromo-1-ethyl-1H-pyrazole-4-carboxamide
A solution containing 5-amino-3-bromo-1-ethyl-1H-pyrazole-4-carbonitrile (2440 mg, 11.35 mmol) in toluene (10 mL) and sulfuric acid (5 mL, 94 mmol) was heated at 60 °C for
3 hours. The reaction was chilled and quenched with NH₄OH carefully, the solution was made basic with 5 N NaOH, extracted with CH₂Cl₂ (5 x) and once with ethyl acetate/THF (1:1), dried over magnesium sulfate, filtered, concentrated onto silica gel and purified by flash chromatography (0-100% ethyl acetate in hexanes) to afford 5-amino-3-bromo-1-ethyl-1H-pyrazole-4-carboxamide (1.67 g) as a colorless solid. LC-MS (ES) m/z = 233, 235 [M+H]+.

5-bromo-1-[(2,5-difluorophenyl)acetyl]2,3-dihydro-1H-indole

To a mixture of (2,5-difluorophenyl)acetic acid (0.869 g, 5.05 mmol) and HATU (2.112 g, 5.55 mmol) in N,N-dimethylformamide (DMF) (10 mL) was added Hunig's base (0.882 mL, 5.05 mmol), and the resulting mixture was stirred for 15 minutes at room temperature. 5-bromo-2,3-dihydro-1 H-indole (1 g, 5.05 mmol) was added, and the reaction mixture was stirred at room temperature for 1 hour. The mixture was poured onto water, and the resulting aqueous mixture was filtered to afford 5-bromo-1-[(2,5-difluorophenyl)acetyl]-2,3-dihydro-1H-indole (1.6 g) as a tan solid. LC-MS(ES) m/z = 352, 354 [M+H]+.

1-[(2,5-difluorophenyl)acetyl]l-5-(4A,5,5-tetramethyl-1J,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole

In a sealed tube, to 5-bromo-1-[(2,5-difluorophenyl)acetyl]-2,3-dihydro-1 H-indole (3.5 g, 9.94 mmol), bis(pinacolato)diboron (3.03 g, 11.93 mmol) and potassium acetate (2.93 g, 29.8 mmol) was added 1,4-dioxane (15 mL) and the mixture was degassed with nitrogen for 10 minutes. PdCl₂(dppf)-CH₂Cl₂ (0.406 g, 0.497 mmol) was added and the reaction mixture was stirred for 48 hours at 100 °C. The mixture was cooled to room temperature. Ethyl acetate (300 mL) was poured onto the mixture, stirred, then filtered. The filtrate was poured into a separatory funnel. It was washed with brine, dried (MgSO₄), filtered and concentrated. Purified by Analogix silica Si90, gradient 0-40% EtOAc/hexane afforded 1-[(2,5-difluorophenyl)acetyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole as a white solid (2.01 g). LC-MS(ES) m/z = 400 [M+H]+.

5-Amino-3-[(1-[(2,5-difluorophenyl)acetyl]l-2,3-dihydro-1H-indol-5-yl]-1-ethyl-1H-pyrazole-4-carboxamide' TFA

A mixture of 5-amino-3-bromo-1-ethyl-1H-pyrazole-4-carboxamide (92 mg, 0.395 mmol), 1-[(2,5-difluorophenyl)acetyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro1H-indole (158 mg, 0.395 mmol), Pd₂(dba)₃ (18.07 mg, 0.020 mmol), potassium...
phosphate (K₃PO₄) (168 mg, 0.789 mmol), (t-Bu)₃PHBF₄ (11.45 mg, 0.039 mmol) in 1,4-dioxane (2 ml), water (660 µl) was heated in a microwave reactor at 120 ºC for 30 mins. The reaction was allowed to cool, and the organic layer removed by pipette. The aqueous layer was extracted with ethyl acetate (3 x 2 ml) and the combined organics were concentrated, redissolved in chloroform-methanol (95:5) and purified by flash chromatography (0-100% EtOAc in chloroform) to afford a white solid. The white solid was dissolved in DMSO and purified by RP-HPLC (25-55% ACN in H₂O, 0.1% TFA) to afford 5-amino-3-{1-[(2,5-difluorophenyl)acetyl]-2,3-dihydro-1H-indol-5-yl}-1-ethyl-1H-pyrazole-4-carboxamide·TFA (140 mg, 0.260 mmol, 65.7% yield) as a white solid.

Example 2

1-Methyl-5-(methylamino)-3-(1-[[3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide

3,5-Dibromo-1-methyl-1H-pyrazole-4-carbonitrile

A solution of 3,5-dibromo-1H-pyrazole-4-carbonitrile (1.85 g, 7.37 mmol) in N,N-dimethylformamide (DMF) (5 ml) under nitrogen was cooled to 0 ºC in an ice bath, then sodium hydride (60 wt% in mineral oil, 0.324 g, 8.11 mmol) was added portionwise. The reaction was let stir for 5 min at 0 ºC then iodomethane (1.383 ml, 22.12 mmol) was added dropwise. The reaction was allowed to warm to room temp and let stir over 1 hour. The reaction was quenched with saturated NH₄Cl solution then extracted with EtOAc (3 X 75 ml). The organics were combined then washed with saturated NaCl solution, dried over MgSO₄, filtered and concentrated to afford an amber colored oil. The oil was then purified by flash silica chromatography on a 200 g Analogix column with 0 to 100% EtOAc...
in hexane for 30 min to afford 3,5-dibromo-1-methyl-1H-pyrazole-4-carbonitrile (1.48 g, 5.59 mmol, 76 % yield) as an off-white solid. LC-MS(ES) m/z = 264, 266, 268 [M+H]+.

3-Bromo-1-methyl-5-(methylamino)-1H-pyrazole-4-carbonitrile

A mixture of 3,5-dibromo-1-methyl-1H-pyrazole-4-carbonitrile (1.16 g, 4.38 mmol) and 2,4-dimethoxybenzylamine (1.316 mL, 8.76 mmol) in N-methyl-2-pyrrolidone (NMP) (3 mL) was stirred at 180 °C in a sealed vessel overnight. The reaction was allowed to cool down to room temperature, and then was poured onto water and a red precipitate formed. The resulting mixture was filtered and the aqueous filtrate was extracted with EtOAc (3X). The organic layer was washed sequentially with saturated aqueous NH₄Cl solution, saturated aqueous NaHCO₃ solution, and brine, then dried (MgSO₄), filtered and concentrated to afford a residue. The red precipitate was treated with CH₂Cl₂ and filtered, then with CH₃OH and filtered. The combined filtrates were concentrated to afford a residue. The combined residues were purified by flash chromatography on SiO₂ (gradient: 100% hexane to 75% EtOAc) to afford 3-bromo-1-methyl-5-(methylamino)-1H-pyrazole-4-carbonitrile (168 mg) as a light yellow solid. LC-MS(ES) m/z = 215, 217 [M+H]+.

3-Bromo-1-methyl-5-(methylamino)-1H-pyrazole-4-carboxamide

A mixture of 3-bromo-1-methyl-5 -(methylamino)-1H-pyrazole-4-carboxamide (167 mg, 0.777 mmol) in toluene (10 mL) and concentrated sulfuric acid (5 mL, 94 mmol) was stirred for 3 hours at 60 °C. The reaction mixture was cooled to room temperature and poured slowly (caution: vigorous bubbling occurs) into saturated aqueous NaHCO₃. The resulting mixture was extracted with EtOAc (3x) and 20% IPA in CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography on SiO₂ (gradient: 100% hexanes to 100% EtOAc) to afford 3-bromo-1-methyl-5-(methylamino)-1H-pyrazole-4-carboxamide (87 mg) as a white solid. LC-MS(ES) m/z = 233, 235 [M+H]+.

5-bromo-1-[(3-(trifluoromethyl)phenyllacetyl)-2,3-dihydro-1H-indole

To 5-bromoindoline (5.0 g, 25.2 mmol, 1 equiv) and [3-(trifluoromethyl)phenyl]acetic acid (6.18 g, 30.3 mmol, 1.2 equiv) in 13 mL of DMF was added propylphosphonic anhydride (36.9 mL of a 1.71 M solution in DMF, 63.1 mmol, 2.5 equiv) followed by DIEA (8.82 mL, 50.5 mmol, 2 equiv). The reddish mixture became warm to touch and was cooled at once in an ice bath. After 30 minutes, the cooling bath was removed and the mixture was stirred at ambient temp. After 18 h, the mixture was diluted with 200 mL of EtOAc and
washed with 200 mL of water. The aqueous was extracted with 150 mL of EtOAc. The combined organics were dried over MgSO$_4$, filtered, and concentrated in vacuo to give a paste, which was taken up in ether and hexane to provide a suspension. The suspension was filtered. The solids were washed with hexane and then ether and dried under vacuum to afford crude product (6.17 g) which was redissolved in DCM (150 mL) and washed with water (50 mL). The organic was dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was triturated with DCM (5 mL) and ether (75 mL). The suspension was filtered, and the cake was washed with ether. The solids were dried under vacuum to afford 5-bromo-1-[[3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indole (4.73 g) as a light cream solid. The filtrate was concentrated in vacuo, and the residue was dissolved in DCM and absorbed onto a dryload cartridge. Purification was done on an SF40-150 g silica gel cartridge using gradient elution of 1% EtOAc in hexane to 45% EtOAc in hexane. The product peak eluted from 24-33% EtOAc. The product fractions were combined and concentrated in vacuo to afford as a brown sticky solid residue (2.80 g). The residue was triturated with DCM and ether. The suspension was filtered, and the cake was washed with ether. The solids were dried under vacuum to afford additional 5-bromo-1-[[3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indole (1.62 g) as an off-white solid. LC-MS (ES) m/z = 384, 386 [M+H]$^+$. $^1$H NMR (400 MHz, DMSO- $d_6$) $\delta$ ppm 3.20 (t, $J=8.5$ Hz, 2H), 4.00 (s, 2H), 4.23 (t, $J=8.6$ Hz, 2H), 7.32 (dd, $J=8.7$, 1.9 Hz, 1H), 7.45 (s, 1H), 7.53 - 7.70 (m, 4H), 7.96 (d, $J=8.6$ Hz, 1H).

5-(4A.5.5-tetramethyl-1.3.2-dioxaborolan-2-yl)-1-[f3-(trifluoromethyl)Dh enyl]acetyl]-2,3-dihydro-1H-indole

A mixture of 5-bromo-1-[[3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indole (8.50 g, 22.12 mmol, 1 equiv), bis(pinacolato)diboron (6.74 g, 26.5 mmol, 1.2 equiv), PdCl$_2$(dppf)-CH$_2$Cl$_2$ adduct (1.81 g, 2.21 mmol, 0.1 equiv) and potassium acetate (5.43 g, 55.3 mmol, 2.5 equiv) in 85 mL of dioxane in a 500 mL flask was degassed and backflushed with nitrogen. This process was repeated four times. The mixture was heated in an oil bath at 100 °C. After 20 hours, the dark black mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was partitioned between EtOAc (250 mL) and brine (40 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The solid residue was dissolved in DCM. About 1/5 was absorbed onto a dryload cartridge. Purification was done on an Analogix SF40-15 g silica gel cartridge using gradient elution of 1% EtOAc in hexane to 45% EtOAc in hexane. However, the dryload cartridge was plugged. About a half was injected into the silica gel
cartridge, and the desired product eluted from 24-30% EtOAc in hexane. The plugged dryload cartridge was flushed with 100 mL of 100% EtOAc to recover the rest of the injected sample, which was combined with the rest 4/5 of the original DCM sample solution. This mixture was concentrated in vacuo and re-dissolved in DCM (50 mL), and was added to a prep-packaged gravity column (250 g of coarse grade silica gel packed in 1% DCM in hexane). The column was eluted with 400 mL of 1% DCM in hexane, 400 mL of 1/3 DCM/hexane, 400 mL of 1/1 DCM/hexane, and then 400 mL 1/1 DCM/hexane portions each with 20 mL increment of EtOAc. The desired product eluted from 20 mL to 60 mL EtOAc fractions. The collected fractions (including the one from above Analogix prep) were combined and concentrated in vacuo to about 100 mL volume as a suspension. This suspension was filtered. The cake was washed with hexane (10 mL) and dried under vacuum for 18 hours to afford 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[(3-trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indole (5.98 g) as a white solid. LC-MS (ES) m/z = 432 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.28 (s, 12 H), 3.19 (t, J=8.5 Hz, 2 H), 4.02 (s, 2 H), 4.23 (t, J=8.6 Hz, 2 H), 7.48 (d, J=8.3 Hz, 1 H), 7.54 (s, 1 H), 7.56 - 7.69 (m, 14 H), 8.03 (d, J=8.1 Hz, 1 H).

1-Methyl-5-(methylamino)-3-[(3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide

A mixture of 3-bromo-1-methyl-5-(methylamino)-1/-/pyrazole-4-carboxamide (87 mg, 0.373 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[(3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indole (177 mg, 0.411 mmol), PdCl2(dppf)-CH2Cl2 (15.24 mg, 0.019 mmol) and saturated aqueous NaHCO3 (2 mL) in 6 mL of dioxane in a sealable tube was degassed and backflushed with nitrogen three times. The mixture was stirred and heated in an oil bath at 100 °C overnight. The mixture was cooled to room temperature, diluted with EtOAc and separated. The EtOAc layer was concentrated in vacuo to give a pale yellow solid. The solid was purified by flash silica chromatography 0%-100% EtOAc in hexane to afford a solid residue which was triturated with a mixture of 4 drops of CH2CN, and 0.5 mL of hexane. The solid was filtered and dried to afford 1-methyl-5-(methylamino)-3-[(3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1 H-pyrazole-4-carboxamide (13 mg) as an off-white solid. LC-MS(ES) m/z = 458 [M+H]+. 1H NMR (400 MHz, CHLOROFORM-d) δ 3.04 (d, J = 5.81 Hz, 3 H), 3.27 (t, J = 8.46 Hz, 2 H), 3.85 (s, 3 H), 3.89 (s, 2 H), 4.18 (t, J = 8.46 Hz, 2 H), 5.30 (br. s, 2 H), 6.77 - 6.83 (m, 1 H), 7.34 - 7.41 (m, 2 H), 7.47 - 7.59 (m, 4 H), 8.30 (d, J = 8.84 Hz, 1 H).
**Example 3**

5-amino-3-(1-([3-(trifluoromethyl)phenyl]acetyl)-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide

![Chemical Structure](image)

5-Amino-3-bromo-1H-pyrazole-4-carbonitrile

A 250 mL round bottom flask was charged with 5-amino-1H-pyrazole-4-carbonitrile (1.2 g, 11.1 mmol) in N,N-dimethylformamide (DMF) (30 mL) to give a colorless solution. It was cooled to 0 °C under nitrogen. NBS (1.98 g, 11.1 mmol) was added to the reaction mixture very slowly at 0 °C while stirring. The reaction was stirred at 0 °C for 1 hour. The reaction mixture was diluted with water (100 mL), the pH was adjusted to 8 from 5 using 3 N aqueous NaOH. The resulting solution was extracted with CH₂Cl₂ (2 x 250 mL) and the combined organics were concentrated and the residue was purified by flash chromatography on SiO₂ with 10-80% EtOAc in hexane for 30 minutes to afford 5-amino-3-bromo-1H-pyrazole-4-carbonitrile (1.4 g) as a yellow solid. LC-MS(ES) m/z = 187, 189 [M+H]⁺.

5-Amino-3-bromo-1H-pyrazole-4-carboxamide

A solution containing 5-amino-3-bromo-1H-pyrazole-4-carbonitrile (1.4 g) in toluene (10 mL) and concentrated sulfuric acid (2 mL, 37.5 mmol) was heated at 60 °C for 6 hours, then chilled and quenched with concentrated aqueous NH₄OH carefully, then the solution was made basic with 6 N aqueous NaOH. The mixture was concentrated in vacuo to dryness, and triturated with CH₂Cl₂/MeOH (100 mL/200 mL). The suspension was filtered, and the residue was washed by CH₂Cl₂ (50 mL), MeOH (100 mL). The filtrate was concentrated to 7 mL and this solution was purified by flash silica chromatography (50-100% EtOAc in hexane, 30 min, 100% EtOAc, 10 min) to afford 5-amino-3-bromo-1H-pyrazole-4-carboxamide (470 mg) as a white solid. LC-MS(ES) m/z = 205, 207 [M+H]⁺.
5-amino-3-(1-{3-(trifluoromethyl)phenyl}acetyl)-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide

A mixture of 5-amino-3-bromo-1H-pyrazole-4-carboxamide (104 mg, 0.507 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[3-(trifluoromethyl)phenyl]acetyl}-2,3-dihydro-1H-indole (230 mg, 0.533 mmol), Pd2dba3 (9.29 mg, 0.0102 mmol) and K3PO4 (234 mg, 1.015 mmol) in 6 mL of dioxane and 2 mL of water in a sealable tube was degassed and backflushed with nitrogen three times, followed by addition of tri-(t-butyl)phosphonium tetrafluoroborate (5.89 mg, 0.02 mmol). The mixture was degassed and backflushed with nitrogen four times. The mixture was sealed and heated in an oil bath at 100 °C for two days overnight. The mixture was cooled to room temperature, diluted with EtOAc and the layers separated. The EtOAc layer was concentrated in vacuo to give a pale yellow solid. The solid was purified by flash silica chromatography (SF 15-24 g at CH2Cl2-10% MeOH in CH2Cl2, the compound eluted at 7% MeOH in CH2Cl2) to afford a solid which was triturated with MeOH, filtered, and dried to afford 5-amino-3-(1-{3-(trifluoromethyl)phenyl}acetyl)-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide (6 mg, 0.014 mmol) as an off-white solid. LC-MS(ES) m/z = 458 [M+H]+. 1H NMR (400 MHz, CHLOROFORM-d+DMSO-d6) δ 3.23 (br. s., 2 H), 3.86 (br. s., 2 H), 4.15 (br. s., 2 H), 5.25 (br. s., 2 H), 5.43 (br. s., 2 H), 7.34 (br. s., 2 H), 7.39 - 7.61 (m, 4 H), 8.25 (br. s., 1 H), 10.82 - 11.54 (m, 1 H).

Example 4

1-Methyl-3-(1-{3-(trifluoromethyl)phenyl}acetyl)-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide

To 3,5-dibromo-1-methyl-1H-pyrazole-4-carbonitrile (4.5 g, 16.99 mmol) and [2,4-bis(methyloxy)phenyl]methylamine (3.69 g, 22.08 mmol) in a 20 mL sealable vial was added N-methyl-2-pyrrolidone (NMP) (10 mL). The vial was then sealed and heated in oil bath at 190 °C for 3 hours. The reaction was loaded directly on to a 200 g Analogix
column conditioned with hexane and purified by flash silica chromatography (gradient of 0 to 100% EtOAc in hexane over 50 min) to afford 5-amino-3-bromo-1-methyl-1H-pyrazole-4-carbonitrile (824 mg, 4.10 mmol, 24.13 % yield) as a yellow colored oil. LC-MS(ES) m/z = 201, 203 [M+H]+.

3-Bromo-1-methyl-1H-pyrazole-4-carbonitrile

To 5-amino-3-bromo-1-methyl-1H-pyrazole-4-carbonitrile (110 mg, 0.547 mmol) in tetrahydrofuran (THF) (5 mL) was added tert-butyl nitrite (0.130 mL, 1.094 mmol), and the reaction mixture was stirred at 50 °C for 3 hours. The reaction mixture was poured onto water and EtOAc. The organic layer was separated, and the aqueous layer was further extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated to afford crude 3-bromo-1-methyl-1H-pyrazole-4-carbonitrile (107 mg). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.90 (s, 3 H), 8.57 (s, 1 H).

3-Bromo-1-methyl-1H-pyrazole-4-carboxamide

To 3-bromo-1-methyl-1H-pyrazole-4-carbonitrile (107 mg, 0.575 mmol) in toluene (6 mL) was added concentrated H₂SO₄ (3 mL, 56.3 mmol), and the resulting mixture was stirred for 3 hours at 60 °C. The reaction was poured slowly in saturated aqueous NaHCO₃ (caution: gas evolution). The aqueous mixture was extracted with EtOAc (2X). The organics were washed with brine, dried (MgSO₄), filtered and concentrated. Flash chromatography on SiO₂ (gradient: 100% hexane to 100% EtOAc) afforded 3-bromo-1-methyl-1H-pyrazole-4-carboxamide (30 mg) as a white solid. LC-MS(ES) m/z = 204, 206 [M+H]+.

1-Methyl-3-(1-(3-(trifluoromethyl)Dhenyllacetyl)-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide

A mixture of 3-bromo-1-methyl-1H-pyrazole-4-carboxamide (30 mg, 0.147 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[(3-(trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indole (63.4 mg, 0.147 mmol) in 1,4-dioxane (3 mL) and saturated aqueous NaHCO₃ (1 mL) was "degassed" with nitrogen for 10 minutes. PdCl₂(dpdp)₂·CH₂Cl₂ adduct (6.00 mg, 7.35 μmol) was added, the vessel was sealed, and the reaction mixture was stirred overnight at 95 °C. The reaction was poured onto water, and the resulting mixture was filtered. The gray solid was purified by flash chromatography on SiO₂ (100% hexane to 100% EtOAc to 20% CH₃OH/EtOAc). The product fractions were combined and concentrated and the resulting residue was triturated with Et₂O to afford the desired
product (25 mg) as a purple solid. LC-MS(ES) m/z = 429 [M+H]^+. \textsuperscript{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.20 (t, J=8.34 Hz, 2 H), 3.86 (s, 3 H), 4.02 (s, 2 H), 4.25 (t, J=8.46 Hz, 2 H), 7.00 (br. s., 1 H), 7.34 (br. s., 1 H), 7.52 - 7.73 (m, 6 H), 7.99 (d, J=8.34 Hz, 1 H), 8.09 (s, 1 H).

**Example 5**

5-Amino-3-(4-fluoro-1-[(3-trifluoromethyl)phenyl]acetyl)-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide

![Chemical structure of 5-Amino-3-(4-fluoro-1-[(3-trifluoromethyl)phenyl]acetyl)-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide](image)

**5-Amino-3-bromo-1-methyl-1H-pyrazole-4-carboxamide**

To a solution of 5-amino-3-bromo-1-methyl-1H-pyrazole-4-carboxamide (1.2 g, 5.97 mmol) in toluene (15 mL) was added concentrated sulfuric acid (2 mL, 37.5 mmol). The bi-phasic reaction was stirred vigorously at 65 °C for 3 hours. The reaction was then quenched by slow addition to a saturated solution of NaHCO$_3$ then extracted with EtOAc (2 X 30 mL), DCM (2 X 3 mL) and THF:EtOAc (1:1, 2 X 30 mL). The organics were combined then washed with saturated NaCl solution, dried over MgSO$_4$, filtered and concentrated to form a solid. The solid was recrystallized with EtOAc and hexane to afford 5-amino-3-bromo-1-methyl-1H-pyrazole-4-carboxamide (1.22 g, 5.57 mmol, 93 % yield) as a white solid. LC-MS(ES) m/z = 219, 221 [M+H]^+.

**4-fluoro-2,3-dihydro-1H-indole**

To a stirred solution of 4-fluoro-1H-indole (950 mg, 7.03 mmol) in acetic acid (20 mL) at 12 °C under nitrogen was added sodium cyanoborohydride (1458 mg, 23.20 mmol) portionwise. The reaction was stirred at 12 °C for 2 hours and at room temperature overnight. The reaction was worked up by pouring into sodium hydroxide (10 N). The aqueous was extracted with diethyl ether (3 x 100 mL), and the combined organics dried over sodium sulfate. LCMS analysis at this point indicated presence of product and some...
acylated product, along with some acylated starting material. The crude was dissolved in
THF (10 mL) and treated with NaOH (6 N, 2 mL), then stirred at room temperature for 2
hours. The reaction was stirred overnight, but no change in LCMS was observed, so the
organic layer was removed, and the aqueous extracted with diethyl ether (2 x 10 mL), the
combined organics were dried over sodium sulfate. The dried solution was filtered and
concentrated, and the residue was purified by flash chromatography (0-25% EtOAc in
hexanes, 24-g silica gel column) to afford 4-fluoro-2,3-dihydro-1H-indole (510 mg, 3.72
mmol, 52.9 % yield) as a colorless oil. LC-MS(ES) m/z = 138 [M+H]+. 1H NMR (400
MHz, DMSO-d6) δ 2.94 (t, J = 8.72 Hz, 2 H), 3.48 (t, J = 8.59 Hz, 2 H), 3.72 (t, J = 8.59 Hz, 2 H), 5.79 (br. s., 1 H),
6.23 - 6.35 (m, 2 H), 6.87 - 6.99 (m, 1 H).

1,1-dimethylethyl 4-fluoro-2,3-dihydro-1H-indole-1-carboxylate
A solution of 4-fluoro-2,3-dihydro-1H-indole (500 mg, 3.65 mmol), Boc2O (0.846 mL, 3.65
mmol), DIEA (1.273 mL, 7.29 mmol), DMAP (44.5 mg, 0.365 mmol) was stirred at room
temperature overnight. The reaction mixture was poured into 0.1 N HCl (10 mL) and
extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over sodium
sulfate, filtered and concentrated to afford 1,1-dimethylethyl 4-fluoro-2,3-dihydro-1H-
indole-1-carboxylate (0.866 g, 100 % yield) as a colorless oil. LC-MS(ES) m/z = 182
[M+H-tBu]+. 1H NMR (400 MHz, DMSO-d6) δ 1.51 (s, 9 H), 3.08 (t, J = 8.72 Hz, 2 H), 3.97
(t, J = 8.72 Hz, 2 H), 6.77 (t, J = 8.72 Hz, 1 H), 7.11 - 7.26 (m, 1 H), 7.27 - 7.66 (m, 1 H).

1,1-dimethylethyl 5-bromo-4-fluoro-2,3-dihydro-1H-indole-1-carboxylate
To a solution of 1,1-dimethylethyl 4-fluoro-2,3-dihydro-1H-indole-1-carboxylate (0.866 g,
3.65 mmol) in dichloromethane (DCM) (10 mL) was added a solution of NBS (0.650 g,
3.65 mmol) in dichloromethane (DCM) (10 mL). The reaction was stirred overnight. The
reaction mixture was poured into saturated aqueous sodium bicarbonate (50 mL) and
extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over
sodium sulfate, filtered and concentrated. The residue was purified by flash
chromatography (0-30% EtOAc in hexanes, 24-g silica gel column) to afford 1,1-
dimethylethyl 5-bromo-4-fluoro-2,3-dihydro-1H-indole-1-carboxylate (1 g) as a (4:1 LCMS,
10:1 by 1H NMR) mixture with the starting material. The mixture was used without further
purification. LC-MS(ES) m/z = 260, 262 [M+H-t-Bu]+. 1H NMR (400 MHz, DMSO-d6) δ
1.51 (s, 9 H), 3.13 (t, J = 8.72 Hz, 2 H), 3.94 - 4.08 (m, 2 H), 7.26 - 7.63 (m, 2 H).
1. 1-dimethylethyl 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-1-carboxylate

A mixture of 1,1-dimethylethyl 5-bromo-4-fluoro-2,3-dihydro-1H-indole-1-carboxylate (1 g, 3.16 mmol), PdCl2(dpff)*CH2Cl2 adduct (0.129 g, 0.158 mmol), potassium acetate (0.776 g, 7.91 mmol) and bis(pinacolato)diboron (0.803 g, 3.16 mmol) in 1,4-dioxane (20 mL) was stirred at 100 °C overnight on a stirrer hot-plate. LCMS indicated complete conversion to the desired product. The reaction mixture was poured into 1:1 saturated aqueous NaCl: H2O (100 mL) and ethyl acetate (100 mL), shaken, and filtered through celite. The resulting mixture was separated and the aqueous layer was extracted with two additional portions of ethyl acetate (2 x 50 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (0-25% EtOAc in hexanes, 40 g silica gel column) to afford 1,1-dimethylethyl 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-1-carboxylate (660 mg, 57.4 % yield) as a pale yellow oil. LC-MS(ES) m/z = 308 [M+H-tBu]+. 1H NMR (400 MHz, DMSO-d6) δ 1.29 (s, 12 H), 1.51 (s, 9 H), 3.05 (t, J = 8.72 Hz, 2 H), 3.98 (t, J = 8.72 Hz, 2 H), 7.22 - 7.61 (m, 2 H).

2. 1-Dimethylethyl 5-[5-amino-4-(aminocarbonyl)-1-methyl-1H-pyrazol-3-yl]4-fluoro-2,3-dihydro-1H-indole-1-carboxylate

To 5-amino-3-bromo-1-methyl-1H-pyrazole-4-carboxamide (1.2 g, 5.48 mmol) was added 1,1-dimethylethyl 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-1-carboxylate (3.62 g, 7.67 mmol) in a 20 mL sealable vial. Then 1,4-dioxane (5 mL) and saturated NaHCO3 solution (7 mL) were added. The mixture was then bubbled with nitrogen gas for 10 min then Pd(Ph3P)4 (0.633 g, 0.548 mmol) was added and the mixture was bubbled with nitrogen for another 5 min. The mixture was then capped and heated on a hot plate at 85 °C overnight. Additional 1,1-dimethylethyl 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-1-carboxylate (0.5 g) and Pd(Ph3P)4 (100 mg) and 200 mg of solid NaHCO3 was added and the reaction was heated at 85 °C for 3 hours. Additional 1,1-dimethylethyl 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-1-carboxylate (0.5 g) and Pd(Ph3P)4 (100 mg) and 200 mg of solid NaHCO3 was added, and the reaction stirred overnight at 85 °C. The reaction was quenched with water (50 mL) then extracted with EtOAc (4 X 50 mL). The organics were combined then washed with saturated NaCl solution, dried over MgSO4, filtered and concentrated. The residual oil was then dissolved in DMF and loaded onto a 100 g Biotage SNAP column conditioned with hexane and purified by flash silica chromatography (0 to 100% EtOAc in hexane for 30 min then 15 min of 100% EtOAc) to
afford 1,1-dimethylethyl 5-[5-amino-4-(aminocarbonyl)-1-methyl-1H-pyrazol-3-yl]-4-fluoro-2,3-dihydro-1H-indole-1-carboxylate (1.5 g, 4.00 mmol, 72.9 % yield) as a light yellow oil. LC-MS(ES) m/z = 376 [M+H]+.

5-Amino-3-(4-fluoro-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide

To a solution of 1,1-dimethylethyl 5-[5-amino-4-(aminocarbonyl)-1-methyl-1H-pyrazol-3-yl]-4-fluoro-2,3-dihydro-1H-indole-1-carboxylate (1.5 g, 4.00 mmol) in 1,4-dioxane (10 mL) was added HCl (4 M, dioxane, 4 mL, 16.00 mmol). The reaction was stirred at room temperature overnight. The reaction was concentrated and the solid residue was triturated with diethyl ether and filtered to afford 5-amino-3-(4-fluoro-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide·HCl (900 mg, 2.89 mmol, 72.3 % yield) as a white solid. LC-MS(ES) m/z = 276 [M+H]+.

5-Amino-3-(4-fluoro-1-[(3-(trifluoromethyl)phenyllacetyl)-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide

A solution of 5-amino-3-(4-fluoro-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide (100 mg, 0.321 mmol), [3-(trifluoromethyl)phenyl]acetic acid (85 mg, 0.417 mmol) and HATU (134 mg, 0.353 mmol) in N,N-dimethylformamide (DMF) (2 mL) was cooled in an ice bath then DIEA (0.279 mL, 1.604 mmol) was added slowly. After addition the reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then loaded directly on to an Analogix 24 g column conditioned with hexane and then purified by flash silica chromatography (gradient of 0 to 100% EtOAc in hexane for 15 min then 15 min at 100% EtOAc). The fractions with the desired product were combined then transferred to 40 mL vial with MeCN. Water was added and the mixture was freeze-dried to isolate 5-amino-3-(4-fluoro-1-[(3-(trifluoromethyl)phenyllacetyl)-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide (60 mg, 0.130 mmol, 40.5 % yield) as a white solid. LC-MS(ES) m/z = 462 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 3.25 (t, J = 8.34 Hz, 2 H), 3.56 (s, 3 H), 4.03 (s, 2 H), 4.34 (t, J = 8.46 Hz, 2 H), 6.27 (br. s., 2 H), 7.20 (t, J = 7.83 Hz, 1 H), 7.55 - 7.66 (m, 3 H), 7.67 (s, 1 H), 7.90 (d, J = 8.34 Hz, 1 H). Two protons were not observed.
**Example 6**

5-Amino-3-(4-fluoro-1-[(6-(trifluoromethyl)-2-pyridinyl)acetyl]-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide

A solution of 5-amino-3-(4-fluoro-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide (100 mg, 0.321 mmol), 6-(trifluoromethyl)-2-pyridinyl]acetic acid (86 mg, 0.417 mmol) and HATU (134 mg, 0.353 mmol) in N,N-dimethylformamide (DMF) (2 mL) was cooled in an ice bath then DIEA (0.279 mL, 1.604 mmol) was added slowly. After addition, the reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction was then loaded directly onto an Analogix 24 g column conditioned with hexane and purified by flash silica chromatography (gradient of 0 to 100% EtOAc in hexane for 15 min then 15 min at 100% EtOAc). The fractions with the desired product were combined then transferred to 40 mL vial with MeCN. Water was added and the mixture was freeze-dried. The sample was repurified with same gradient to afford 5-amino-3-(4-fluoro-1-[(6-(trifluoromethyl)-2-pyridinyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide (62 mg, 95% purity) as a white solid. LC-MS(ES) m/z = 463 [M+H]⁺. ¹H NMR (400 MHz, DMSO-δ) δ 3.24 (t, J = 8.34 Hz, 2 H), 3.56 (s, 3 H), 4.21 (s, 2 H), 4.37 (t, J = 8.46 Hz, 2 H), 6.27 (s, 2 H), 7.20 (t, J = 7.83 Hz, 1 H), 7.70 (d, J = 7.83 Hz, 1 H), 7.82 (d, J = 7.58 Hz, 1 H), 7.87 (d, J = 8.34 Hz, 1 H), 8.09 (t, J = 7.83 Hz, 1 H). Two protons were not observed.

**Example 7**

5-amino-3-{4-fluoro-1-[(6-methyl-2-pyridinyl)acetyl]-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide
A solution of 5-amino-3-(4-fluoro-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide (100 mg, 0.321 mmol), (6-methyl-2-pyridinyl)acetic acid•TFA (111 mg, 0.417 mmol) and HATU (134 mg, 0.353 mmol) in N,N-dimethylformamide (DMF) (2 ml) was cooled in an ice bath then DIEA (0.279 ml, 1.604 mmol) was added slowly. After addition, the reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then loaded directly on to a Analogix 24 g column conditioned with hexane and purified by flash silica chromatography (3 min at 100% hexane then a gradient of 0 to 10% MeOH in DCM over 25 min). The fractions with the desired product were combined then concentrated. The solid was then triturated with EtOAc and hexane then filtered to afford 5-amino-3-{4-fluoro-1-[(6-methyl-2-pyridinyl)acetyl]-2,3-dihydro-1H-indol-5-yl}-1-methyl-1H-pyrazole-4-carboxamide (78 mg) as a white solid. LC-MS(ES) m/z = 409 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 2.45 (s, 3 H), 3.18 - 3.25 (m, 2 H), 3.56 (s, 3 H), 3.99 (s, 2 H), 4.34 (t, J = 8.59 Hz, 2 H), 6.27 (s, 2 H), 7.15 (dd, J = 7.58, 5.31 Hz, 2 H), 7.20 (t, J = 7.83 Hz, 1 H), 7.65 (t, J = 7.71 Hz, 1 H), 7.90 (d, J = 8.08 Hz, 1 H). Two protons were not observed.

Example 8

5-Amino-3-{1-[(3,5-dimethyl-1H-pyrazol-1-yl)acetyl]-4-fluoro-2,3-dihydro-1H-indol-5-yl]-1-methyl-1H-pyrazole-4-carboxamide

A solution of 5-amino-3-(4-fluoro-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide (100 mg, 0.321 mmol), (3,5-dimethyl-1H-pyrazol-1-yl)acetic acid (64.3 mg,
0.417 mmol) and HATU (134 mg, 0.353 mmol) in N,N-dimethylformamide (DMF) (2 mL) was cooled in an ice bath then DIEA (0.279 mL, 1.604 mmol) was added slowly. After addition, the reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then loaded directly on to a Analogix 24 g column conditioned with hexane and purified by flash silica chromatography (3 min at 100% hexane then a gradient of 0 to 10% MeOH in DCM over 25 min). The fractions with the desired product were combined then concentrated. The solid was triturated with EtOAc and hexane then filtered to afford 5-amino-3-{1-[(3,5-dimethyl-1H-pyrazol-1-yl)acetyl]-4-fluoro-2,3-dihydro-1H-indol-5-yl}-1-methyl-1H-pyrazole-4-carboxamide (60 mg, 0.146 mmol, 45.5 % yield) as a pink colored solid. LC-MS(ES) m/z = 412 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 2.09 (s, 3 H), 2.15 (s, 3 H), 3.25 (t, J = 8.46 Hz, 2 H), 3.56 (s, 3 H), 4.33 (t, J = 8.46 Hz, 2 H), 5.09 (s, 2 H), 5.85 (s, 1 H), 6.27 (s, 2 H), 7.22 (t, J = 7.83 Hz, 1 H), 7.85 (d, J = 8.08 Hz, 1 H). Two protons were not observed.

Example 9
5-Amino-1-methyl-3-(1-(2-(3-(trifluoromethyl)phenyl)acetyl)indol-5-yl)-1H-pyrazole-4-carboxamide

1,1-Dimethylethyl 5-bromo-2,3-dihydro-1H-indole-1-carboxylate
To a stirred solution of 5-bromo-2,3-dihydro-1 H-indole (30 g, 151 mmol) and DMAP (0.4 g, 3.27 mmol, 0.02 equiv) in 150 mL of MeCN at room temperature was added Boc₂O (43 g, 197 mmol, 1.3 equiv) in one portion. The mixture was stirred at room temperature. After 10 min, the mixture gradually became a suspension. After 3 hours, the suspension was filtered. The cake was washed with cold MeCN (60 mL), and dried under house vacuum for 5 hours to give 1,1-Dimethylethyl 5-bromo-2,3-dihydro-1 H-indole-1-carboxylate (ca. 28.5 g prior to drying). LCMS (ES) m/z = 244, 242 as prominent fragments. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.50 (s, 9 H), 3.06 (t, J=8.7 Hz, 2 H),
3.91 (t, J=8.7 Hz, 2 H), 7.31 (dd, J=8.5, 1.9 Hz, 1 H), 7.38 (s, 1 H), 7.51 - 7.71 (br s, 0.6 H).

1.1-Dimethylethyl 5-(4.4.5.5-tetramethyl-1.3.2-dioxaborolan-2-yl)-2.3-dihydro-1H-indole-1-carboxylate

A mixture of 1,1-dimethylethyl 5-bromo-2,3-dihydro-1H-indole-1-carboxylate (32 g, 107 mmol, 1 equiv), bis(pinacolato)diboron (32.7 g, 129 mmol, 1.2 equiv), PdCl_2(dppf)-CH_2Cl_2 (4.38 g, 15.37 mmol, 0.05 equiv) and potassium acetate (26.3 g, 268 mmol, 2.5 equiv) in 350 mL of dioxane in a 1 L flask was evacuated and backflushed with nitrogen, which was repeated five times. The mixture was heated at 100 °C for 18 hours. The mixture was filtered through Celite and washed with EtOAc (500 mL). The filtrate was concentrated in vacuo. The residue was partitioned between EtOAc (700 mL) and brine (300 mL). The organic was extracted with EtOAc (200 mL). The combined organic was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in DCM and split into 7 equal portions. Each was absorbed onto a dryload cartridge right before actual chromatography. Purification was done on 120 g silica gel cartridges using gradient elution of 1% EtOAc in hexane to 40% EtOAc in hexane. The desired product eluted from 17-24% EtOAc in hexane. The combined fractions were concentrated in vacuo to give a waxy cake in the recovery flask, which was broken up and dried under vacuum at room temperature for 20 hours to give the product (30.54 g, 82% yield) as a light yellow waxy solid. LC-MS (ES) m/z = 346 [M+H]^+, prominent fragment at 290 [M-55]^+. \(^1\)H NMR (400 MHz, DMSO-d_6) \(\delta\) ppm 1.27 (s, 12 H), 1.50 (s, 9 H), 3.05 (t, J=8.6 Hz, 2 H), 3.91 (t, J=8.7 Hz, 2 H), 7.43 - 7.52 (m, 2 H), 7.58 - 7.80 (br s, 1 H).

Tert-butyl 5-(5-amino-4-carbamoyl-1-methyl-1H-pyrazol-3-yl)indoline-1-carboxylate

A 20-mL sealable vial was charged with 5-amino-3-bromo-1-methyl-1 H-pyrazole-4-carboxamide (1 g, 4.57 mmol), 1,1-dimethylethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1 H-indole-1-carboxylate (2.207 g, 6.39 mmol), 1,4-dioxane (7 mL) and saturated NaHC0_3 solution (7 mL). The mixture was then bubbled with nitrogen gas for 10 min then Pd(Ph_3)P_4 (0.528 g, 0.457 mmol) was added and the mixture was bubbled with nitrogen for 5 min. The vial was then capped and heated on a hot plate at 85 °C overnight. The reaction was quenched with water (50 mL) then extracted with EtOAc (4 X 50 mL). The combined organics were washed with saturated NaCl solution, dried over MgS0_4, filtered and concentrated. The residual oil was then loaded with DMF onto a 100 g Biotage SNAP column conditioned with hexane and purified by flash silica.
chromatography (0 to 100% EtOAc in hexane for 30 min then 15 min of 100% EtOAc) to afford tert-butyl 5-(5-amino-4-carbamoyl-1-methyl-1H-pyrazol-3-yl)indoline-1-carboxylate (1.4 g, 3.92 mmol, 86 % yield) as an orange color oil. LC-MS(ES) m/z = 358 [M+H]+.

5-Amino-3-(indolin-5-yl)-1-methyl-1H-pyrazole-4-carboxamide, Hydrochloride
To tert-butyl 5-(5-amino-4-carbamoyl-1-methyl-1H-pyrazol-3-yl)indoline-1-carboxylate (1.4 g, 3.92 mmol) was added HCl (4 M, dioxane, 10 mL, 40.0 mmol). The reaction was allowed to stir for 4 hours at room temperature. The reaction was then concentrated, redissolved in MeOH (3 mL), then diethyl ether (20 mL) was added. A solid crashed out of solution and was isolated by filtration to afford 5-amino-3-(indolin-5-yl)-1-methyl-1H-pyrazole-4-carboxamide, hydrochloride (1 g, 3.40 mmol, 87 % yield) as light brown/yellow solid. LC-MS(ES) m/z = 258 [M+H]+.

5-Amino-1-methyl-3-(1-(2-(3-(trifluoromethyl)phenyl)acetyl)indolin-5-yl)-1H-pyrazole-4-carboxamide
To 5-amino-3-(indolin-5-yl)-1-methyl-1H-pyrazole-4-carboxamide, Hydrochloride (100 mg, 0.340 mmol), 2-(3-(trifluoromethyl)phenyl)acetic acid (90 mg, 0.443 mmol) and HATU (142 mg, 0.374 mmol) in a 40 mL vial was added N,N-dimethylformamide (DMF) (1.5 mL). The reaction was cooled in an ice bath, and then DIEA (0.296 mL, 1.702 mmol) was added dropwise. After addition the reaction was removed from ice bath and stirred at room temperature for 1 hour. The reaction solution was then loaded directly onto a double stacked (2X) 10 g Biotage SNAP columns first conditioned with hexane and purified by flash silica chromatography (4 min 100% hexane, then 3 min 100% DCM, then 0 to 10% MeOH in DCM for 20 min). The product fractions were combined and concentrated then transferred to a 40 mL vial and MeCN and water were added. The sample was freeze-dried to afford 5-amino-1-methyl-3-(1-(2-(3-(trifluoromethyl)phenyl)acetyl)indolin-5-yl)-1H-pyrazole-4-carboxamide (87 mg) as a white powder. LC-MS(ES) m/z = 444 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 3.22 (t, J = 8.46 Hz, 2 H), 3.55 (s, 3 H), 4.02 (s, 2 H), 4.26 (t, J = 8.59 Hz, 2 H), 6.28 (s, 2 H), 7.25 (d, J = 8.08 Hz, 1 H), 7.34 (s, 1 H), 7.54 - 7.66 (m, 3 H), 7.67 (s, 1 H), 8.07 (d, J = 8.34 Hz, 1 H). Two protons were not observed.
Example 10
5-Amino-1-methyl-3-(1-(2-(6-methylpyridin-2-yl)acetyl)indolin-5-yl)-1H-pyrazole-4-carboxamide

To 5-amino-3-(indolin-5-yl)-1-methyl-1H-pyrazole-4-carboxamide hydrochloride (100 mg, 0.340 mmol), 2-(6-methylpyridin-2-yl)acetic acid, trifluoroacetic acid salt (117 mg, 0.443 mmol) and HATU (142 mg, 0.374 mmol) in a 40 mL vial was added N,N-dimethylformamide (DMF) (1.5 mL). The reaction was cooled in an ice bath, and DIEA (0.296 mL, 1.702 mmol) was added dropwise. After addition, the reaction was removed from ice bath and stirred at room temperature for 1 hour. The reaction solution was then loaded directly onto a double stacked (2X) 10 g Biotage SNAP column first conditioned with hexane and purified by flash silica chromatography (4 min 100% hexane, then 3 min 100% DCM, then 0 to 10% MeOH in DCM for 20 min). The product fractions were combined and concentrated then transferred into a 40 mL vial and MeCN and water were added. The sample was freeze-dried to afford 5-amino-1-methyl-3-(1-(2-(6-methylpyridin-2-yl)acetyl)indolin-5-yl)-1H-pyrazole-4-carboxamide (70 mg) as a white powder. LC-MS(ES) m/z = 391 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 2.47 (s, 3H), 3.20 (t, J = 8.46 Hz, 2 H), 3.55 (s, 3 H), 4.02 (br. s., 2 H), 4.27 (t, J = 8.46 Hz, 2 H), 6.27 (br. s., 2 H), 7.20 (br. s., 2H), 7.25 (d, J = 8.59 Hz, 1 H), 7.34 (s, 1 H), 7.72 (br.s., 1 H), 8.07 (d, J = 8.34 Hz, 1 H). Two protons were not observed.

Example 11
5-Amino-1-methyl-3-(1-(2-(6-(trifluoromethyl)pyridin-2-yl)acetyl)indolin-5-yl)-1H-pyrazole-4-carboxamide

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To 5-amino-3-(indolin-5-yl)-1-methyl-1H-pyrazole-4-carboxamide, hydrochloride (100 mg, 0.340 mmol), 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid (91 mg, 0.443 mmol) and HATU (142 mg, 0.374 mmol) in a 40 ml vial was added N,N-dimethylformamide (DMF) (1.5 ml). The reaction was cooled in an ice bath, and then DIEA (0.296 ml, 1.702 mmol) was added dropwise. After addition, the reaction was removed from ice bath and stirred at room temperature for 1 hour. The reaction solution was then loaded directly onto a double stacked (2X) 10 g Biotage SNAP column first conditioned with hexane and purified by flash silica chromatography (4 min 100% hexane, then 3 min 100% DCM, then 0 to 10% MeOH in DCM for 20 min). The product fractions were combined and concentrated then transferred to a 40 ml vial and MeCN and water were added. The sample was freeze-dried to afford 5-amino-1-methyl-3-(1-(2-(6-(trifluoromethyl)pyridin-2-yl)acetyl)indolin-5-yl)-1H-pyrazole-4-carboxamide (112 mg) as a white powder. LC-MS(ES) m/z = 445 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 3.22 (t, J = 8.34 Hz, 2 H), 4.18 (s, 2 H), 4.28 (t, J = 8.46 Hz, 2 H), 6.26 (s, 2 H), 7.24 (d, J = 8.08 Hz, 1 H), 7.34 (s, 1 H), 7.69 (d, J = 7.83 Hz, 1 H), 7.81 (d, J = 7.83 Hz, 1 H), 8.01 - 8.10 (m, 2 H). Two protons were not observed. N-Methyl peak obscured by water peak.

Example 12

5-Amino-3-(1-(2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl)indolin-5-yl)-1-methyl-1H-pyrazole-4-carboxamide

To 5-amino-3-(indolin-5-yl)-1-methyl-1H-pyrazole-4-carboxamide, hydrochloride (100 mg,
0.340 mmol), 2-(3,5-dimethyl-1H-pyrazol-1-yl)acetic acid (68.2 mg, 0.443 mmol) and HATU (142 mg, 0.374 mmol) in a 40 ml vial was added N,N-dimethylformamide (DMF) (1.5 ml). The reaction was cooled in an ice bath, and then DIEA (0.296 ml, 1.702 mmol) was added dropwise. After addition, the reaction was removed from ice bath and stirred at room temperature for 1 hour. The reaction solution was then loaded directly onto a double stacked (2X) 10 g Biotage SNAP column first conditioned with hexane and purified by flash silica chromatography (4 min 100% hexane, then 3 min 100% DCM, then 0 to 10% MeOH in DCM for 20 min). The product fractions were combined and concentrated and the residue was purified by flash silica chromatography on a 10 g Biotage column conditioned with hexanes (3 min 100% hexane, then 0 to 100% EtOAC for 10 min then 0 to 10% MeOH in EtOAc). The product fractions were combined, concentrated, and then transferred to a 40 ml vial and MeCN and water was added. The sample was freeze-dried to afford 5-amino-3-{1-(2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl)indolin-5-yl)-1-methyl-1H-pyrazole-4-carboxamide (79 mg) as a white powder. LC-MS(ES) m/z = 394 [M+H]+.

1H NMR (400 MHz, DMSO-d6) δ 2.09 (s, 3 H), 2.16 (s, 3 H), 3.19 - 3.28 (m, 2 H), 3.55 (s, 3 H), 4.25 (t, J = 8.08 Hz, 2 H), 5.08 (s, 2 H), 5.84 (s, 1 H), 6.27 (s, 2 H), 7.26 (d, J = 8.08 Hz, 1 H), 7.36 (s, 1 H), 8.02 (d, J = 8.08 Hz, 1 H). Two protons were not observed.

**Example 13 - Capsule Composition**

An oral dosage form for administering the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>AMOUNTS</th>
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<tbody>
<tr>
<td>5-Amino-3-{1-[(2,5-difluorophenyl)acetyl]-2,3-dihydro-1 H-indol-5-yl]-1-ethyl-1 H-pyrazole-4-carboxamide (Compound of Example 1)</td>
<td>7 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>53 mg</td>
</tr>
<tr>
<td>Talc</td>
<td>16 mg</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>4 mg</td>
</tr>
</tbody>
</table>

**Example 14 - Injectable Parenteral Composition**

An injectable form for administering the present invention is produced by stirring 1.7% by weight of 1-Methyl-5-(methylamino)-3-{1-[(3-(trifluoromethyl)phenyl)acetyl]-2,3-dihydro-1 H-indol-5-yl]-1H-pyrazole-4-carboxamide (Compound of Example 2) in 10% by volume propylene glycol in water.
Example 15- Tablet Composition

The sucrose, calcium sulfate dihydrate and a PERK inhibitor as shown in Table II below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

Table II

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>AMOUNTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-amino-3-((3-(trifluoromethyl)phenyl)acetyl)-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide (Compound of Example 3)</td>
<td>12 mg</td>
</tr>
<tr>
<td>calcium sulfate dihydrate</td>
<td>30 mg</td>
</tr>
<tr>
<td>sucrose</td>
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<tr>
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Biological Activity

PKR-like Endoplasmic Reticulum Kinase (PERK) Assay (HTRF Format)

Source of the PERK enzyme: GST-PERK (536-1116) cytoplasmic domain was purchased from Invitrogen (www.invitrogen.com) catalogue#PV5106 (2011).

Source of substrate: elF2a: 6-His-Full-length human elF2a is purified from baculovirus expression in Sf9 insect cells. The elF2 protein is buffer exchanged by dialysis into PBS, chemically modified by NHS-LC-Biotin and then buffer exchanged by dialysis into 50 mM TRIS pH 7.2/250 mM NaCl/5 mM DTT. Protein is aliquoted and stored at -80oC.

Quench Solution: The quench solution is freshly prepared and when added to the reactions gives final concentrations of 4 nM elF2a phospho-ser51-Antibody (purchased from Millipore, catalogue #07-760, www.millipore.com), 4 nM Eu-1024 labeled anti-rabbit IgG (purchased from Perkin Elmer, catalogue#AD0083), 40 nM Streptavidin Surelight APC (purchased from Perkin Elmer, catalogue* AD0201) and 15mM EDTA.

Reactions were performed in black 384-well polystyrene low volume plates (Grenier, #784076) in a final volume of 10 µL. The reaction volume contains, in final concentrations, 10mM HEPES, 5mM MgCl2, 5µM ATP, 1mM DTT, 2mM CHAPS, 40 nM biotinylated-6-His-EF2a, and 0.4 nM GST-PERK (536-1116). Assays were performed by
adding GST-PERK solution to assay plates containing compounds and pre-incubated for 30 minutes at room temperature. The reaction is initiated by the addition of ATP and EIF2a substrate solution. Quench solution is added following a one hour incubation at room temperature. The plates are covered for 2 hours at room temperature prior to determination of signal. The resulting signal is quantified on a Viewlux Reader (PerkinElmer). The APC Signal is normalized to the Europium signal by transforming the data through an APC/Eu calculation.

Compounds under analysis were dissolved in DMSO to 1.0 mM and serially diluted 1 to 3 with DMSO through eleven dilutions. 0.1 µl of each concentration was transferred to the corresponding well of an assay plate. This creates a final compound concentration range from 0.00017 to 10 µM.

The data for concentration response curves were plotted as % Inhibition calculated with the data reduction formula $100\times(1-(U_1-C_2)/(C_1-C_2))$ versus concentration of compound where $U$ is the unknown value, $C_1$ is the average control value obtained for 1% DMSO, and $C_2$ is the average control value obtained for 0.1 M EDTA. Data were fitted with a curve described by:

$$ y = A + \frac{B - A}{1 + \left( \frac{10x}{10c} \right) D} $$

where $A$ is the minimum $y$, $B$ is the maximum $y$ concentration [M], $D$ is the slope factor, and $x$ is the log$_{10}$ of the compound. The results for each compound were recorded as pIC50s, calculated as follows:

$$ \text{pIC50} = -\log_{10}(K). $$

Abbreviations used:
APC, Allophycocyanin
ATP, adenosine triphosphate
BSA, bovine serum albumin
CHAPS, 3-[3-Cholamidopropyl)Dimethylammonio] -1-Propanesulfonate
DMSO, dimethyl sulfoxide
DTT, Dithiothreitol
EDTA, ethylenediaminetetraacetic acid
Eu, Europium
Compounds of the invention are tested for activity against PERK in the above assay.

All the compounds of the Examples were tested generally according to the above PERK enzyme assay and in at least one experimental run exhibited a pIC50 value: 
\[
> 6.9
\]
against PERK.

The compound of Example 1 was tested generally according to the above PERK enzyme assay and in at least one experimental run exhibited a pIC50 value of 8.4 against PERK.

In the above data, pIC50 is defined as -log(IC50) where the IC50 value is expressed in molar units.

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.
What is claimed is:

1. A compound according to Formula I:

   \[
   \begin{array}{c}
   \text{R}^2 \\
   \text{O} \\
   \text{\textbf{N}} \\
   \text{R}^1 \\
   \text{R}^3 \\
   \end{array}
   \]

   (I)

wherein:

- \( \text{R}^1 \) is selected from:
  - heteroaryl, and
  - heteroaryl substituted with from one to five substituents independently selected from:
    - halo,
    - C-|-6alkyl,
    - C-|-4alkyloxy,
    - -OH,
    - hydroxyC-|-4alkyl,
    - -COOH,
    - tetrazole,
    - -CF_3,
    - -Ci-4alkylOC-|-4alkyl,
    - -CONH2,
    - -CON(H)Ci-3alkyl,
    - -CH_2CH_2N(H)C(0)OCH_2aryl,
    - diCi-4alkylaminoC-|-4alkyl,
    - aminoCi-4alkyl,
-NO2,
-NH2,
-N(H)C-3alkyl,
-N(C-3alkyl)2,
-CN,
ad, aryl substituted with from one to three substituents independently selected from: C-|-4alkyl, diC-4alkylaminoC-4alkyl, fluoro, chloro, bromo, iodo and -CF3,
heterocycloalkyl,
heterocycloalkyl substituted with from one to three substituents independently selected from: C-|--4alkyl, diC-4alkylaminoC-4alkyl, fluoro, chloro, bromo, iodo and -CF3,
.Ci-4alkylheterocycloalkyl,
.Ci-4alkylheterocycloalkyl substituted with from one to three substituents independently selected from: C-|--4alkyl, diC-4alkylaminoC-4alkyl, fluoro, chloro, bromo, iodo and -CF3;

R2 is selected from:
aryl,
aryl substituted with from one to five substituents independently selected from: fluoro, chloro, bromo, iodo, Ci-4alkyl, Ci-4alkyloxy, -OH, -COOH, -CF3,
-Ci-4alkyloxyC-4alkyl, -N02, -NH2 and -CN,
heteroaryl,
heteroaryl substituted with from one to five substituents independently selected from: fluoro, chloro, bromo, iodo, C-|-4alkyl, C-|-4alkyloxy, -OH, -COOH, -CF₃, -Ci-4alkylOC-|-4alkyl, -N0₂, -NH₂ and -CN, cycloalkyl, and cycloalkyl substituted with from one to five substituents independently selected from: fluoro, chloro, bromo, iodo, C-|-4alkyl, C-|-4alkyloxy, -OH, -COOH, -CF₃, -Ci-4alkylOCi-4alkyl, -N0₂, -NH₂ and -CN; and

R³ is selected from: hydrogen, fluoro, chloro, bromo and iodo;
or a salt thereof including a pharmaceutically acceptable salt thereof.

2. A compound of Formula (I), as described in claim 1, wherein:

R¹ is heteroaryl substituted with from one to three substituents independently selected from:

halo,
Ci-3alkyl,
C-|-3alkyloxy,
-OH,
-CONH₂,
-CON(H)Ci-3alkyl,
-N(Ci-3alkyl)₂,
-N(H)Ci-3alkyl, and

-NH₂;

R² is selected from:

aryl,
aryl substituted with from one to three substituents independently selected from: halo, Ci-4alkyl, Ci-4alkyloxy, -OH, -COOH, -CF₃, -Ci-4alkylOC-|-4alkyl,
-NO₂, -NH₂ and -CN,

heteroaryl,
heteroaryl substituted with from one to three substituents independently selected from: fluoro, chloro, bromo, iodo, C-4alkyl, C-4alkyloxy, -OH,

-COOH, -CF₃, -Ci-4alkyloxy, -OH,

R³ is selected from: hydrogen, fluoro and chloro;
or a salt thereof including a pharmaceutically acceptable salt thereof.

3. A compound of Formula (I), as described in claim 1, wherein:

\[
\begin{align*}
  \text{R}^1 & \text{ is } \begin{array}{c}
    \text{substituted with from one to three substituents independently selected from:} \\
    \text{halo,} \\
    \text{Ci-3alkyl,} \\
    \text{C-3alkyloxy,} \\
    \text{-OH,} \\
    \text{-CONH₂,} \\
    \text{-CON(H)Ci-3alkyl,} \\
    \text{-N(Ci-3alkyl)₂,} \\
    \text{-N(H)Ci-3alkyl, and} \\
    \text{-NH₂;}
  \end{array} \\
  \text{R}^2 & \text{ is selected from:} \\
  \text{aryl,} \\
  \text{aryl substituted with form one to three substituents independently selected from:} \\
  \text{halo, Ci-4alkyl, Ci-4alkyloxy, -OH, -COOH, -CF₃, -Ci-4alkyloxy, -4alkyl,}
\end{align*}
\]
-NO₂, -NH₂ and -CN, heteroaryl, heteroaryl substituted with from one to three substituents independently selected from: fluoro, chloro, bromo, iodo, C-|−4alkyl, C-|−4alkyloxy, -OH, -COOH, -CF₃, -Ci-4alkylOC-|−4alkyl, -N0₂, -NH₂ and -CN; and

R³ is selected from: hydrogen, fluoro and chloro;
or a salt thereof including a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 selected from:

5-Amino-3-{|[(2,5-difluorophenyl)acetyl]-2,3-dihydro-1H-indol-5-yl}-1-ethyl-1H-pyrazole-4-carboxamide;

1-Methyl-5-(methylamino)-3-{|[(3-trifluoromethyl)phenyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide;

5-amino-3-{|[(3-trifluoromethyl)phenyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide; and

1-Methyl-3-{|[(3-trifluoromethyl)phenyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-1H-pyrazole-4-carboxamide;
or a salt thereof including a pharmaceutically acceptable salt thereof.

5. A compound of claim 1 selected from:

5-Amino-3-{|(4-fluoro-1-|[(3-trifluoromethyl)phenyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide;

5-Amino-3-{|(4-fluoro-1-|[(6-(trifluoromethyl)-2-pyridinyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide;

5-amino-3-{|(4-fluoro-1-|[(6-methyl-2-pyridinyl]acetyl]-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide;

5-Amino-3-{|[(3,5-dimethyl-1H-pyrazol-1-yl]acetyl]-4-fluoro-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrazole-4-carboxamide;
5-Amino-1-methyl-3-(1-(2-(3-(trifluoromethyl)phenyl)acetyl)indolin-5-yl)-1H-pyrazole-4-carboxamide;

5-Amino-1-methyl-3-(1-(2-(6-methylpyridin-2-yl)acetyl)indolin-5-yl)-1H-pyrazole-4-carboxamide;

5-Amino-1-methyl-3-(1-(2-(6-(trifluoromethyl)pyridin-2-yl)acetyl)indolin-5-yl)-1H-pyrazole-4-carboxamide; and

5-Amino-3-(1-(2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl)indolin-5-yl)-1-methyl-1H-pyrazole-4-carboxamide.

or a salt thereof including a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising a compound of Formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

7. A method of treating or lessening the severity of cancer, pre-cancerous syndromes and/or diseases associated with activated unfolded protein response pathways, such as Alzheimer's disease, stroke, Type 1 diabetes, Parkinson disease, Huntington's disease, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, atherosclerosis, and arrhythmias, in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula I, as described in claim 1 or a pharmaceutically acceptable salt thereof.

8. The method of claim 7 wherein the mammal is a human.

9. A method of treating or lessening the severity of cancer, pre-cancerous syndromes and/or diseases associated with activated unfolded protein response pathways, such as Alzheimer's disease, stroke, Type 1 diabetes, Parkinson disease, Huntington's disease, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, atherosclerosis, and arrhythmias, in a mammal in need thereof, which comprises
administering to such mammal a therapeutically effective amount of a compound of claim 5 or a pharmaceutically acceptable salt thereof.

10. The method of claim 9 wherein the mammal is a human.

11. The method according to claim 7 wherein said cancer is selected from: brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma and thyroid.

12. The method according to claim 9 wherein: said cancer is selected from brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma and thyroid.

13. Use of a compound of Formula (I), as described in claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or lessening the severity of cancer.

14. The method of inhibiting PERK activity in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula (I), as described in claim 1 or a pharmaceutically acceptable salt thereof.

15. The method of claim 14 wherein the mammal is a human.

16. A method of treating cancer in a mammal in need thereof, which comprises: administering to such mammal a therapeutically effective amount of
a) a compound of Formula (I), as described in claim 1 or a pharmaceutically acceptable salt thereof; and 
b) at least one anti-neoplastic agent.

17. The method claim 16, wherein the at least one anti-neoplastic agent is selected from the group consisting of: anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis, inhibitors, immunotherapeutic agents, proapoptotic agents, cell cycle signaling inhibitors, proteasome inhibitors, and inhibitors of cancer metabolism.

18. The method of claim 16, wherein the at least one anti-neoplastic agent is an anti-microtubule agent selected from diterpenoids and vinca alkaloids.

19. The method of claim 16, wherein the at least one anti-neoplastic agent is a diterpenoid.

20. The method of claim 16, wherein the at least one anti-neoplastic agent is a vinca alkaloid.

21. The method of claim 16, wherein the at least one anti-neoplastic agent is a platinum coordination complex.

22. The method of claim 16, wherein the at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

23. The method of claim 16, wherein the at least one anti-neoplastic agent is paclitaxel.

24. The method of claim 16, wherein the at least one anti-neoplastic agent is carboplatin.
25. The method of claim 16, wherein the at least one anti-neoplastic agent is vinorelbine.

26. The method of claim 16, wherein the at least one anti-neoplastic agent is a signal transduction pathway inhibitor.

27. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a growth factor receptor kinase selected from the group consisting of VEGFR2, TIE2, PDGFR, BTK, IGFR-1, TrkA, TrkB, TrkC, and c-fms.

28. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of rafk, akt, and PKC-zeta.

29. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the src family of kinases.

30. The method of claim 29, wherein the signal transduction pathway inhibitor is an inhibitor of c-src.

31. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.

32. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K, MEK and BRaf.
33. The method of claim 16, wherein the at least one anti-neoplastic agent is a cell cycle signaling inhibitor.

34. The method of claim 33, wherein the cell cycle signaling inhibitor is selected from inhibitors of the group CDK2, CDK4, and CDK6.

35. A pharmaceutical combination as claimed in claim 16 for use in therapy.


37. The method according to claim 7 wherein said cancer is selected from: breast cancer, inflammatory breast cancer, ductal carcinoma, lobular carcinoma, colon cancer, pancreatic cancer, insulinomas, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, skin cancer, melanoma, metastatic melanoma, lung cancer, small cell lung cancer, non-small cell lung cancer, squamous cell carcinoma, adenocarcinoma, large cell carcinoma, brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, head and neck, kidney, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, Immunoblastic large cell leukemia, mantle cell leukemia, multiple myeloma, megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland
cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

38. The method of claim 37 wherein the mammal is a human.

39. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable excipient and an effective amount of a compound of Formula (I) as described in claim 1 or a pharmaceutically acceptable salt thereof, which process comprises bringing the compound of Formula (I) or a pharmaceutically acceptable salt thereof into association with a pharmaceutically acceptable excipient.

40. The method according to claim 7 wherein said pre-cancerous syndrome is selected from: cervical intraepithelial neoplasia, monoclonal gammapathy of unknown significance (MGUS), myelodysplasia syndrome, aplastic anemia, cervical lesions, skin nevi (pre-melanoma), prostatic intraepithelial (intraductal) neoplasia (PIN), Ductal Carcinoma in situ (DCIS), colon polyps and severe hepatitis or cirrhosis.

41. The method of claim 16, wherein the at least one anti-neoplastic agent is pazopanib.

42. A method of treating or lessening the severity of ocular diseases in a human in need thereof, which comprises administering to such human a therapeutically effective amount of a compound of Formula I, as described in claim 1 or a pharmaceutically acceptable salt thereof.

43. A method according to claim 42 wherein the ocular disease is selected from: rubeosis irides; neovascular glaucoma; pterygium; vascularized glaucoma filtering blebs; conjunctival papilloma; choroidal neovascularization associated with age-related macular degeneration (AMD), myopia, prior uveitis, trauma, or idiopathic; macular edema; retinal neovascularization due to diabetes; age-related macular degeneration (AMD); macular degeneration (AMD); ocular ischemic syndrome from carotid artery disease; ophthalmic
or retinal artery occlusion; sickle cell retinopathy; retinopathy of prematurity; Eale’s Disease; and VonHippel-Lindau syndrome.

44. A method according to claim 42 wherein the ocular disease is selected form: age-related macular degeneration (AMD) and macular degeneration.
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D401/14 C07D403/04 C07D403/14 A61K31/44

**ADD.**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

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 practicable, search terms used)

EPO-Internal , CHEM ABS Data, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2007/026920 A2 (ASTELLAS PHARMA INC [JP]; SAWADA KOUZ0 ZENKO TATSUYA [JP]; TERA) 8 March 2007 (2007-03-08) example 47</td>
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<td>WO 2011/119663 A1 (GLAXOSMITHKLINE LLC [US]; AXTEN JEFFREY MICHAEL [US]; GRANT SETH WI LS0) 29 September 2011 (2011-09-29) example 130, first intermediate example 142, first intermediate</td>
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### Further documents are listed in the continuation of Box C. See patent family 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 application or patent 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
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- "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**

22 January 2015

**Date of mailing of the international search report**

09/02/2015

**Name and mailing address of the ISA**

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

Authorized officer

Bakboord, Joan

Form PCT/ISA/210 (second sheet) (April 2009)
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