Title: 3-HETEROCYCLYL SUBSTITUTED 5-TRIFLUOROMETHYL OXADIAZOLES AS HISTONE DEACETYLASE 6 (HDAC6) INHIBITORS

Abstract: The present invention is directed to substituted 5-trifluoromethyl oxadiazole compounds of generic formula (I) (I) or a pharmaceutically acceptable salt thereof. In particular, the invention is directed to a class of aryl and heteroaryl substituted 5-trifluoromethyl oxadiazole compounds of formula I which may be useful as HDAC6 inhibitors for treating cellular proliferative diseases, including cancer, neurodegenerative diseases, such as schizophrenia and stroke, as well as other diseases.
TITLE OF THE INVENTION

3-HETEROCYCLYL SUBSTITUTED 5-TRIFLUOROMETHYL OXADIAZOLES AS HISTONE DEACETYLASE 6 (HDAC6) INHIBITORS

BACKGROUND OF THE INVENTION

Histone deacetylases (HDACs) and histone acetyl transferases (HATs) determine the pattern of histone acetylation, which together with other dynamic sequential post-translational modifications might represent a 'code' that can be recognised by non-histone proteins forming complexes involved in the regulation of gene expression. This and the ability of histone deacetylases (HDACs) to also modify non-histonic substrates and participate in multi-protein complexes contributes to the regulation of gene transcription, cell cycle progression and differentiation, genome stability and stress responses.

Eleven members of the HDAC family have been identified in humans, which share a conserved catalytic domain and are grouped into two classes: class I (1, 2, 3, 8), homologous to yeast Rpd3; class IIa (4, 5, 7, 9) and IIb (6, 10), homologous to yeast Hdal. HDAC11 shares homologies with both classes, but is at the same time distinct from all the other ten subtypes. Interest in these enzymes is growing because HDAC inhibitors (HDACi) are promising therapeutic agents against cancer and other diseases. The first generation of HDACi were discovered from cell-based functional assays and only later identified as HDAC class I/II inhibitors. Present HDAC inhibitors are pan-specific or poorly selective. Those that entered clinical trials all show similar adverse effects, mainly fatigue, anorexia, hematologic and GI-toxicity, that becomes dose-limiting in clinical trials.

HDAC6 is one of the best characterized deacetylase enzymes regulating many important biological processes via the formation of complexes with specific client proteins. In contrast to other deacetylases, HDAC6 has unique substrate specificity for nonhistone proteins such as α-tubulin, Hsp90, cortactin and peroxiredoxins. The diverse function of HDAC6 in conjunction with published data over the past few years suggest it could serve as a potential therapeutic target for the treatment of a wide range of diseases and may be overexpressed or deregulated in various cancers, neurodegenerative diseases and inflammatory disorders. Despite extensive efforts, very few HDAC6-selective inhibitors have been identified. The majority of the reported compounds use the hydroxamic acid pharmacophore as the zinc-binding group. See WO2013080120, WO2013008162, WO2013066835, WO2013066839, WO2013066831, WO2013066833, WO2013006408, WO2011088192, WO2011088181, J. Kalin et al., J. Med Chem 2013, 56, 6297-6313; and Simoes-Pires, et al., Molecular Neurodegeneration 2013 8:7.
See also WO2016031815 containing compounds that have not used the hydroxamic acid pharmacophore as the zinc-binding group.

To date, HDAC inhibitors that have been approved for use by the FDA can be divided into two categories: 1) non-selective pan HDAC inhibitors such as vorinostat (SAHA); and 2) HDAC inhibitors such as entinostat that only target Class I HDACs. Consequently, the potential advantage of isoform-selective inhibitors over pan-HDAC inhibitors is based both in terms of efficacy and toxicity. The development of potent and highly selective HDAC inhibitors would be critical for better understanding of the cellular pathways related to their therapeutic effects, while also providing a reasonable basis to explore synergistic interactions with other clinically active compounds. It is also valuable because it is expected that the selective inhibition of a mostly cytoplasmic HDAC6 should avoid toxicity resulting from inhibition of other HDACs mainly involved in epigenetic modulation.

SUMMARY OF THE INVENTION

The invention is directed to a class of heterocyclic ring substituted 5-trifluoromethyl oxadiazole compounds of formula I below, their salts, pharmaceutical compositions comprising them, diagnostic and therapeutic uses and processes for making such compounds. In particular, the invention is directed to a class of aryl and heteroaryl substituted 5-trifluoromethyl oxadiazole compounds of formula I which may be useful as HDAC6 inhibitors for treating cellular proliferative diseases, including cancer, neurodegenerative diseases, such as schizophrenia and stroke, as well as other diseases. Uses for the claimed compounds include treating autoimmune diseases and/or inflammatory diseases (e.g., inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis, Sjogren’s syndrome, Behcet’s disease, systemic erythematodes etc), graft-versus-host disease (GVHD), cellular proliferative diseases, including cancer (e.g., multiple myeloma, leukemia, uterus smooth muscle sarcoma, prostate cancer, intestinal cancer, lung cancer, cachexia, bone marrow fibrosis, etc.), central nervous system diseases, including neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, schizophrenia and stroke, amongst other diseases.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to substituted 5-trifluoromethyl oxadiazole compounds of generic formula (I)

\[
\begin{align*}
\text{F}_3&\text{C} \\
\text{N} &\text{---} \\
\text{Y} &\text{---} \\
\text{R}^1 &\text{---} \\
\text{N} &\text{---}
\end{align*}
\]

(I)
or a pharmaceutically acceptable salt thereof wherein;

Y is a five membered heterocyclyl optionally substituted with 1 to 3 groups of \( R^2 \), or

\[
\frac{3}{2} - \frac{3}{2} Y R^1
\]

is represented by structural formula (a):

(a)

--- represent double bond(s) in the ring which may be present or absent;

\( R^1 \) represents \(-C_{1-6}alkyl\), \(-(CHR)pC_{4-10} heterocyclyl\), \(-C(O)(CHR)pC_{4-10} heterocyclyl\), or \(-(CHR)pC_{6-10} aryl\), said alkyl, aryl and heterocyclyl optionally substituted with 1 to 3 groups of \( R^a \);

\( X^3 \) and \( X^4 \) independently represent \(-N \) or \(-CH-\);

\( X^5 \) represents \(-S-, -SO-, -SO_2-, -N=, -NR^2-, -CH-, \) or \(-CH_2-\);

\( X^6 \) and \( X^7 \) independently represent \(-CR^2, -C(R^3)_, -N=, \) or \(-NR^2-\);

\( R^2 \) represents hydrogen, \(-C_{1-6}alkyl\), \(-C(O)OC_{1-6}alkyl\), \(-S(O)C_{6-10}aryl\), \(-(CH_2)pC_{6-10}aryl\), said alkyl and aryl optionally substituted with 1 to 3 groups of \( R^a \), or

when \( X^6 \) and \( X^7 \) are either \(-CR^2, -C(R^3)_, \) or \(-NR^2-\), then adjacent \( R^2 \) groups of \( X^6 \) and \( X^7 \) can combine with the atoms to which they are attached to form phenyl or \( C_{5-6}heteroaryl \) said phenyl and heteroaryl optionally substituted with 1 to 3 groups of \( R^a \);

\( G^1 \) and \( G^2 \) independently may be absent when \( r \) is 0, or are selected from \(-N-, -NH-, -NC_{1-6}alkyl, -NC(O)C_{1-6}alkyl, -C(O)C_{6-10}aryl, -C(O)C_{4-10}heterocyclyl, -C=O, -CH-, \) and \(-CH_2; \) said alkyl, aryl and heterocyclyl optionally substituted with 1 to 3 groups of \( R^a \);

\( R^a \) is selected from the group consisting of \( C_{1-6}alkyl \), halo, CN, \( =O, -SO_2C_{1-6}alkyl, C_{3-6}cycloalkyl, -C_{1-6}alkylOR, -(CH_2)pC_{6-10} aryl, -(CH_2)pC_{5-10} heteroaryl, \) and \(-C_{1-4}haloalkyl, \) said aryl and heteroaryl optionally substituted with 1 to 3 groups of \( C_{1-6} \) alkyl,

Each \( p \) represents 0-4,
each r represents 0-1, when r is 0 for both G₁ and G₂ a bond exist between X² and the carbon atom in the ring containing X₄, said carbon atom being the one linked to G₂ if r for G₂ was 1.

An embodiment of this invention is realized when Y is a five membered heterocyclyl selected from the group consisting of optionally substituted thiophenyl, thiazolyl, isothiazolyl, isoxazolyl, oxazolyl, imidazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiazolyl, pyrrolidinyl, tetrahydrofuranyl, and furanyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted thiophenyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted isothiazolyl or thiazolyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted imidazolyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted pyrazolyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted triazolyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted oxadiazolyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted thiadiazolyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted pyrrolidinyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted isoxazolyl or oxazolyl. A further subembodiment of this aspect of the invention is realized when Y is optionally substituted tetrahydrofuranyl or furanyl.

Another embodiment of this invention is realized when R₁ is optionally substituted –C₁₋₆alkyl. A subembodiment of this aspect of the invention is realized when R₁ is selected from the group consisting of optionally substituted methyl, ethyl, propyl, isopropyl, butyl, pentyl, and the like.

Another embodiment of this invention is realized when R₁ is optionally substituted -(CHR)ₚ₋₄-C₁₋₁₀ heterocyclyl. A subembodiment of this aspect of the invention is realized when R₁ is selected from the group consisting of optionally substituted pyrrolidinonyl, piperidonyl, morpholinyl, pyridyl, triazolyl, and pyrrolidinyl. A further subembodiment of this aspect of the invention is realized when R₁ is optionally substituted pyrrolidinonyl. Another subembodiment of this aspect of the invention is realized when R₁ is optionally substituted morpholinonyl. Another subembodiment of this aspect of the invention is realized when R₁ is optionally substituted pyridyl. Another subembodiment of this aspect of the invention is realized when R₁ is optionally substituted triazolyl. Another subembodiment of this aspect of the invention is realized when R₁ is optionally substituted pyrrolidinyl. Still another embodiment of this aspect of the invention is realized when R₁ is unsubstituted. Yet another embodiment of this aspect of the invention is realized when R₁ is substituted with 1,
2, or 3 groups of $R^a$ selected from $C_{1-6}$alkyl, halo, -C$_{1-6}$alkylOH, or -(CH$_2$)$_p$C$_6$-10 aryl. A subembodiment of this aspect of the invention is realized when the aryl is selected from phenyl, and CH$_2$phenyl.

Another embodiment of this invention is realized when \[ \frac{2}{5} \cdot Y \rightarrow R^1 \] is represented by formula (a) and $r$ is 0 for both $G^1$ and $G^2$. A further subembodiment of the invention where $r$ is 0 for both $G^1$ and $G^2$ is realized when $X^4$ is N and $X^3$ is CH. A further subembodiment of the invention where $r$ is 0 for both $G^1$ and $G^2$ is realized when $X^4$ is CH and $X^3$ is N. A further subembodiment of the invention when $r$ is 0 for both $G^1$ and $G^2$ and $X^4$ is N is realized when $X^3$, $X^6$, and $X^7$ together with $X^4$ and the other atoms of the ring form a group selected from pyrrolopyridinyl, said groups optionally substituted optionally substituted with 1 to 3 groups of R. A further subembodiment of the invention where $r$ is 0 for both $G^1$ and $G^2$ is realized when $X^4$ is -CH. A further subembodiment of the invention when $r$ is 0 for both $G^1$ and $G^2$ and $X^4$ is CH is realized when $X^3$, $X^6$, $X^8$, and $X^7$ together with $X^4$ and the other atoms of the ring form a group selected from indolyl, isoindolyl, benztriazolyl, benzthiazolyl, benzimidazolyl, and benzoazolyl, said groups optionally substituted optionally substituted with 1 to 3 groups of R. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted indolyl. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted benzotriazolyl. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted benzoazolyl. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted benzoazolyl. Still a further subembodiment of this aspect of the invention is realized when $R^2$ is selected from the group consisting of CH$_3$, C(O)OC(CH$_3$)$_3$, (CH$_2$)$_n$phenyl, S(O)$_2$phenyl, said phenyl optionally substituted with 1 to 3 groups of $R^a$.

An embodiment of this invention is realized when \[ \frac{2}{5} \cdot Y \rightarrow R^1 \] is represented by formula (a) where $r$ is 0 for one of $G^1$ and $G^2$ and $r$ is 1 for the other. A further subembodiment of the invention when $r$ is 0 for one of $G^1$ and $G^2$ and 1 for the other and $X^4$ is CH is realized when $X^3$, $X^6$, and $X^7$ together with $X^4$ and the other atoms of the ring form a group selected from quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, dihydroisoquinolinyl, said groups optionally substituted with 1 to 3 groups of $R^a$. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted quinolinyl. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted tetrahydroisoquinolinyl. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted dihydroisoquinolinyl.
An embodiment of this invention is realized when \( \frac{1}{2} Y \rightarrow R^1 \) is represented by formula (a) where \( r \) is 1 for both \( G^1 \) and \( G^2 \). A subembodiment of this aspect of the invention is realized when \( X^6 \) and \( X^7 \) are either \(-CR^2\), \(-C(R')_2\), or \(-NR^2\), and adjacent \( R^2 \) groups of \( X^6 \) and \( X^7 \) combine with the atoms to which they are attached to form phenyl or \( C_5\)-heteroaryl thereby forming a tricyclic group, said phenyl and heteroaryl optionally substituted with 1 to 3 groups of \( R^a \). A further subembodiment of this aspect of the invention is realized when \( r \) is 1 for both \( G^1 \) and \( G^2 \), and \( G^1 \) and \( G^2 \), \( X^4 \), \( X^5 \), \( X^6 \), and \( X^7 \) combine with the other atoms of the ring to form a group selected from benzothiazipine, dihydribenzothiazipine dioxide, dihydribenzothiazipine oxide, dihydribenzothiazipinone oxide, dibenzothiepine dioxide, dibenzothiepine dioxide, and dibenzothiopine oxide, said groups optionally substituted with 1 to 3 groups of \( R^a \). A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted benzothiazipine. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted dihydribenzothiazipine dioxide. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted dihydribenzothiazipine oxide. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted dihydribenzothiazipinone oxide. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted dibenzothiepine dioxide. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted dibenzothiepine dioxide. A subembodiment of this aspect of the invention is realized when formula (a) is optionally substituted dibenzothiopine oxide.

Another embodiment of the claimed invention of formula I is realized by structural formula II:

![Formula II](image)

or a pharmaceutically acceptable salt thereof, wherein

\( Y^1 \) is represented by structural formula
Wherein R¹ is as originally described. A subembodiment of this aspect of the invention is realized when Y' is (a'). Another subembodiment of this aspect of the invention is realized when Y' is (b'). Another subembodiment of this aspect of the invention is realized when Y' is (c'). Another subembodiment of this aspect of the invention is realized when Y' is (d'). Another subembodiment of this aspect of the invention is realized when Y' is (e'). Another subembodiment of this aspect of the invention is realized when Y' is (f'). Another subembodiment of this aspect of the invention is realized when Y' is (g'). Another subembodiment of this aspect of the invention is realized when Y' is (h'). Another subembodiment of this aspect of the invention is realized when Y' is (i'). Another subembodiment of this aspect of the invention is realized when Y' is (j'). Another subembodiment of this aspect of the invention is realized when Y' is (k').

Another embodiment of the claimed invention of formula I is realized by structural formula III:

\[
\text{III}
\]

or a pharmaceutically acceptable salt thereof, wherein

[Y-R¹] is represented by structural formulas (m), (n) and (o)
\[ G^1, G^2, X^5 \text{ and } R^a \text{ are as originally described and } Z \text{ is N or CH.} \] A subembodiment of this aspect of the invention is realized when \([Y-R^1]\) is (m) and

\[ X^5, G^2 \text{ and } G^1, \text{ respectively, are represented as:} \]

1. \( \text{SO}_2, \text{NR}^2, \text{CH}_2; \)
2. \( \text{SO}, \text{NR}^2, \text{C(O)}; \)
3. \( \text{SO}, \text{NR}^2, \text{CH}_2; \)
4. \( \text{SO}, \text{C(O)}, \text{NR}^2; \) and
5. \( \text{S, NR}^2, \text{CH}_2. \)

Another subembodiment of the invention of formula III where \([Y-R^1]\) is (m) is realized when \(R^2\) is selected from the group consisting of \(-C_{1-6} \text{alkyl, or -C(O)OC}_{1-6} \text{alkyl, -S(O)O}_{2-C_{6-10} \text{aryl,} \}
(\text{CH}_2)_n \text{C}_{6-10} \text{aryl, said alkyl and heteroaryl optionally substituted with 1 to 3 groups of } R^a. \) A further subembodiment of this aspect of the invention is realized when \(R^2\) is selected from the group consisting of \(\text{CH}_3, \text{C(O)OC(CH}_3)_3, (\text{CH}_2)_n \text{phenyl, said phenyl optionally substituted with 1 to 3 groups of } R^a. \)

A subembodiment of this aspect of the invention is realized when \([Y-R^1]\) is (n) or (o) and

\[ X^5, G^2 \text{ and } G^1, \text{ respectively, are represented as:} \]

1. \( \text{S, N, CH;} \)
2. \( \text{SO}_2, \text{CH, CH;} \)
3. \( \text{SO, CH, CH;} \) and
4. \( \text{SO, N, CH.} \)

Another subembodiment of the invention of formula III where \([Y-R^1]\) is (n) or (o) is realized when \(R^2\) is selected from the group consisting of \(-C_{1-6} \text{alkyl, or -C(O)OC}_{1-6} \text{alkyl, -S(O)O}_{2-C_{6-10} \text{aryl,} \}
(\text{CH}_2)_n \text{C}_{6-10} \text{aryl, said alkyl and heteroaryl optionally substituted with 1 to 3 groups of } R^a. \) A further subembodiment of this aspect of the invention is realized when \(R^2\) is selected from the group consisting of \(\text{CH}_3, \text{C(O)OC(CH}_3)_3, (\text{CH}_2)_n \text{phenyl, said phenyl optionally substituted with 1 to 3 groups of } R^a. \)

The compounds of the present invention may have asymmetric centers, chiral axes and chiral planes, and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. (See E.L.)

Absolute stereochemistry is illustrated by the use of hashed and solid wedge bonds. As shown in Illus-I and Illus-II. Accordingly, the methyl group of Illus-I is emerging from the page of the paper and the ethyl group in Illus-II is descending into the page, where the cyclohexene ring resides within the plane of the paper. It is assumed that the hydrogen on the same carbon as the methyl group of Illus-I descends into the page and the hydrogen on the same carbon as the ethyl group of Illus-II emerges from the page. The convention is the same where both a hashed and solid rectangle are appended to the same carbon as in Illus-III, the Methyl group is emerging from the plane of the paper and the ethyl group is descending into the plane of the paper with the cyclohexene ring in the plane of the paper.

As is conventional, unless otherwise noted in accompanying text, ordinary "stick" bonds or "wavy" bonds indicate that all possible stereochemistry is represented, including, pure compounds, mixtures of isomers, and racemic mixtures.

As described herein, unless otherwise indicated, the use of a compound in treatment means that an amount of the compound, generally presented as a component of a formulation that comprises other excipients, is administered in aliquots of an amount, and at time intervals, which provides and maintains at least a therapeutic serum level of at least one pharmaceutically active form of the compound over the time interval between dose administration.

When any variable (e.g. aryl, heterocycle, R1, R2 etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds, is chemically feasible and/or valency permits.

As used herein, unless otherwise specified, the terms in the paragraphs immediately below have the indicated meanings.

"Alkoxy" means a moiety of the structure: alkyl-O- (i.e., the bond to the substrate moiety is through the oxygen), wherein the alkyl portion of the moiety is as defined below for alkyl; non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isoproxy, n-butoxy and heptoxy.

"Alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms.

"Halogen" or "halo" means fluoro, chloro, bromo and iodo.
"Cycloalkyl" is intended to include cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Preferably, cycloalkyl is C₃-C₁₀ cycloalkyl. Examples of such cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

"Aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl rings include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocyclyl, heterocycle or heterocyclic represents a stable 5- to 7-membered monocyclic or stable 8- to 14-membered bicyclic or tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term heterocyclyl, heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzodioxolyl, benzimidazolyl, benzisoxazolyl, benzofurazan-1-yl, benzopyranyl, benzothiopyranyl, benzo furyl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoazolyl, chroman-1-yl, cinnolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, furopyridinyl, imidazolidinyl, imidazolyl, indolyl, indolyl, iso chromanyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolopyridinyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, pyrrolopyridinyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydropyran, tetrahydroisquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholiny sulf oxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl, and triazolyl.

Preferably, heterocyclyl is selected from furopyridinyl, imidazolyl, indolyl, isoquinolinyl, iso thi azolyl, morpholinyl, naphthyridinyl, oxadiazolyl, piperidinyl, piperazinyl, pyridinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolopyridinyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, pyrrolopyridinyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydropyran, tetrahydroisquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholiny sulf oxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl, and triazolyl.

"Heteroaryl" means any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples
of such heteroaryl rings include, but are not limited to, imidazolyl, indolyl, indolyl, isochromanyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, tetrahydropyrroloquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thiophenyl, thienyl, triazolyl and the like.

"Effective amount" or "therapeutically effective amount" is meant to describe the provision of an amount of at least one compound of the invention or of a composition comprising at least one compound of the invention which is effective in treating or inhibiting a disease or condition described herein, and thus produce the desired therapeutic, ameliorative, inhibitory or preventative effect. For example, in treating cellular proliferative diseases or central nervous system diseases or disorders with one or more of the compounds described herein "effective amount" (or "therapeutically effective amount") means, for example, providing the amount of at least one compound of Formula I that results in a therapeutic response in a patient afflicted with a central nervous system disease or disorder ("condition"), including a response suitable to manage, alleviate, ameliorate, or treat the condition or alleviate, ameliorate, reduce, or eradicate one or more symptoms attributed to the condition and/or long-term stabilization of the condition, for example, as may be determined by the analysis of pharmacodynamic markers or clinical evaluation of patients afflicted with the condition.

The phrase "at least one" used in reference to the number of components comprising a composition, for example, "at least one pharmaceutical excipient" means that one member of the specified group is present in the composition, and more than one may additionally be present. Components of a composition are typically aliquots of isolated pure material added to the composition, where the purity level of the isolated material added into the composition is the normally accepted purity level for a reagent of the type.

"at least one" used in reference to substituents on a compound or moiety appended to the core structure of a compound means that one substituent of the group of substituents specified is present, and more than one substituent may be bonded to any of the chemically accessible bonding points of the core.

Whether used in reference to a substituent on a compound or a component of a pharmaceutical composition the phrase "one or more", means the same as "at least one".

As used herein, the term "patient" and "subject" means an animal, such as a mammal (e.g., a human being) and is preferably a human being.

"prodrug" means compounds that are rapidly transformed, for example, by hydrolysis in blood, in vivo to the parent compound, e.g., conversion of a prodrug of Formula A to a
compound of Formula A, or to a salt thereof; a thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference; the scope of this invention includes prodrugs of the novel compounds of this invention.

Unsatisfed valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have a hydrogen atom or atoms of sufficient number to satisfy the valences.

One or more compounds of the invention may also exist as, or optionally be converted to, a solvate. Preparation of solvates is generally known. Thus, for example, M. Cairn et al., J. Pharmaceutical Sci., 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, and hemisolvate, including hydrates (where the solvent is water or aqueous-based) and the like are described by E. C. van Tonder et al., AAPS PharmSciTech., 5(1), article 12 (2004); and A. L. Bingham et al., Chem. Commun., 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (for example, an organic solvent, an aqueous solvent, water or mixtures of two or more thereof) at a higher than ambient temperature, and cooling the solution, with or without an antisolvent present, at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I.R. spectroscopy, show the presence of the solvent (including water) in the crystals as a solvate (or hydrate in the case where water is incorporated into the crystalline form).

The term “substituted” means that one or more of the enumerated substituents can occupy one or more of the bonding positions on the substrate typically occupied by "-H"; provided that such substitution does not exceed the normal valency rules for the atom in the bonding configuration presented in the substrate, and that the substitution ultimate provides a stable compound, which is to say that such substitution does not provide compounds with mutually reactive substituents located geminal or vicinal to each other; and wherein the substitution provides a compound sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture.

Where optional substitution of a moiety is described (e.g. "optionally substituted") the term means that if substituents are present, one or more of the enumerated (or default substituents for the specified substrate, for example, hydrogen on an alkyl or aromatic moiety) can be present on the substrate in a bonding position normally occupied by the default substituent, for example, a hydrogen atom, in accordance with the definition of "substituted" presented herein.
As used herein, unless otherwise specified, the preceding terms used to describe moieties, whether comprising the entire definition of a variable portion of a structural representation of a compound of the invention or a substituent appended to a variable portion of a structural representation of a group of compounds of the invention have the following meanings, and unless otherwise specified, the definitions of each term (i.e., moiety or substituent) apply when that term is used individually or as a component of another term (e.g., the definition of aryl is the same for aryl and for the aryl portion of arylalkyl, alkylaryl, arylalkynyl moieties, and the like); moieties are equivalently described herein by structure, typographical representation or chemical terminology without intending any differentiation in meaning, for example, the chemical term "acyl", defined below, is equivalently described herein by the term itself, or by typographical representations "R'-(C=O)-" or "R'-C(O)-", or by the structural representation: \[
\text{\begin{ceq}}
\text{R'-(C=O)-} \\
\text{-}
\text{\end{ceq}}
\].

The term “pharmaceutical composition” as used herein encompasses both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent as described herein, along with any pharmaceutically inactive excipients. As will be appreciated by the ordinarily skilled artisan, excipients are any constituent which adapts the composition to a particular route of administration or aids the processing of a composition into a dosage form without itself exerting an active pharmaceutical effect. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said “more than one pharmaceutically active agents”. The bulk composition is material that has not yet been formed into individual dosage units.

This invention also includes the compounds of this invention in isolated and purified form obtained by routine techniques.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates and prodrugs of the compounds of Formula I, are intended to be included in the present invention. Certain compounds of the invention may exist in different isomeric forms (e.g., enantiomers, diastereoisomers, atropisomers). The inventive compounds include all isomeric forms thereof, both in pure form and admixtures of two or more, including racemic mixtures.

In the same manner, unless indicated otherwise, presenting a structural representation of any tautomeric form of a compound which exhibits tautomerism is meant to include all such tautomeric forms of the compound. Accordingly, where compounds of the invention, their salts, and solvates and prodrugs thereof, may exist in different tautomeric forms or in equilibrium among such forms, all such forms of the compound are embraced by, and included within the
scope of the invention. Examples of such tautomers include, but are not limited to, ketone/enol tautomeric forms, imine-enamine tautomeric forms, and for example heteroaromatic forms such as the following moieties:

\[
\text{H} \quad \text{and} \quad \text{OH}
\]

All stereoisomers of the compounds of the invention (including salts and solvates of the inventive compounds and their prodrugs), such as those which may exist due to asymmetric carbons present in a compound of the invention, and including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may be isolated in a pure form, for example, substantially free of other isomers, or may be isolated as an admixture of two or more stereoisomers or as a racemate. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms “salt”, “solvate” “prodrug” and the like, is intended to equally apply to salts, solvates and prodrugs of isolated enantiomers, stereoisomer pairs or groups, rotamers, tautomers, or racemates of the inventive compounds.

Where diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by known methods, for example, by chiral chromatography and/or fractional crystallization, simple structural representation of the compound contemplates all diastereomers of the compound. As is known, enantiomers may also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher’s acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individually isolated diastereomers to the corresponding purified enantiomers.

Included in the instant invention is the free base of compounds of Formula I, as well as the pharmaceutically acceptable salts and stereoisomers thereof. The formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for example, by S. Berge et al., Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; in The Orange Book (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich Stahl, Camille G. Wermuth (Eds.), Handbook of Pharmaceutical Salts: Properties, Selection, and Use, (2002) Int'l. Union of
Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference.

The present invention contemplates all available salts, including salts which are generally recognized as safe for use in preparing pharmaceutical formulations and those which may be formed presently within the ordinary skill in the art and are later classified as being "generally recognized as safe" for use in the preparation of pharmaceutical formulations, termed herein as "pharmacologically acceptable salts".

Some of the specific compounds exemplified herein are the protonated salts of amine compounds. Compounds of Formula I with a heterocycle ring containing 2 or more N atoms may be protonated on any one, some or all of the N atoms. The term "free base" refers to the amine compounds in non-salt form. The encompassed pharmacologically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmacologically acceptable salts of the free form of compounds of Formula I. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmacologically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylactic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. Preferably, a pharmaceutically acceptable salt of this invention contains 1 equivalent of a compound of formula (I) and 1, 2 or 3 equivalent of an inorganic or organic acid.
More particularly, pharmaceutically acceptable salts of this invention are the trifluoroacetate or the chloride salts, especially the trifluoroacetate salts.

When the compound of the present invention is acidic, suitable “pharmaceutically acceptable salts” refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganese salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N-di-benzylethylendiamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylendiamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripolyamine, tromethamine and the like.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

The present invention also embraces isotopically-labeled compounds of the present invention which are structurally identical to those recited herein, but for the fact that a statistically significant percentage of one or more atoms in that form of the compound are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number of the most abundant isotope usually found in nature, thus altering the naturally occurring abundance of that isotope present in a compound of the invention. Examples of isotopes that can be preferentially incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, iodine, fluorine and chlorine, for example, but not limited to: \( ^2H \), \( ^3H \), \( ^{11}C \), \( ^{13}C \), \( ^{14}C \), \( ^{13}N \), \( ^{15}N \), \( ^{15}O \), \( ^{17}O \), \( ^{18}O \), \( ^{31}P \), \( ^{32}P \), \( ^{35}S \), \( ^{18}F \), and \( ^{36}Cl \), \( ^{123}I \) and \( ^{125}I \). It will be appreciated that other isotopes may be incorporated by known means also.

Certain isotopically-labeled compounds of the invention (e.g., those labeled with \( ^3H \), \( ^{11}C \) and \( ^{14}C \) are recognized as being particularly useful in compound and/or substrate tissue distribution assays using a variety of known techniques. Tritiated (i.e., \( ^3H \) and carbon-14 (i.e., \( ^{14}C \) isotopes are particularly preferred for their ease of preparation and detection. Further, substitution of a naturally abundant isotope with a heavier isotope, for example, substitution of
protium with deuterium (i.e., $^2\text{H}$) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the reaction

Schemes and/or in the Examples herein below, by substituting an appropriate isotopically labeled reagent for a non-isotopically labeled reagent, or by well-known reactions of an appropriately prepared precursor to the compound of the invention which is specifically prepared for such a “labeling” reaction. Such compounds are included also in the present invention.

The compounds of the invention can be used in a method of treatment of the human or animal body by therapy.


The compounds of the invention are used to treat cellular proliferation diseases. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), neurodegenerative diseases, schizophrenia and stroke.

The compounds, compositions and methods provided herein are particularly deemed useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. In particular, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (duodenal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis
(seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfrona (osteoartilaginous exostoses), benign chordoma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiomasarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma], mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-theal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for treating cellular proliferation diseases.

The present invention also provides a method for the treatment of cellular proliferation diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the instant invention may also be useful in the treatment or prevention of neurodegenerative diseases, including, but not limited to, polyglutamine-expansion-related neurodegeneration, Huntington's disease, Kennedy's disease, spinocerebellar ataxia, dentatorubral-pallidoluysian atrophy (DRPLA), protein-aggregation-related neurodegeneration, Machado-Joseph's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spongiform encephalopathy, a prion-related disease and multiple sclerosis (MS).
Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for treating or preventing neurodegenerative diseases.

The present invention also provides a method for treating or preventing neurodegenerative diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of mental retardation, in particular “X chromosome-linked mental retardation” and “Rubinstein-Taybi syndrome”.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing mental retardation.

The present invention also provides a method for treating or preventing mental retardation, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of schizophrenia.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing schizophrenia.

The present invention also provides a method for treating or preventing schizophrenia, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.


Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing inflammatory diseases.

The present invention also provides a method for treating or preventing inflammatory diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the present invention are also useful in the inhibition of smooth muscle cell proliferation and/or migration and are thus useful in the prevention and/or treatment of restenosis, for example after angioplasty and/or stent implantation.
Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing restenosis.

The present invention also provides a method for treating or prevention restenosis, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

In one embodiment, smooth muscle cell proliferation and/or migration is inhibited and restenosis is prevented and/or treated by providing a stent device having one or more of the compounds of the instant invention in or on the stent device, e.g. coated onto the stent device. The stent device is designed to controllably release the compounds of the invention, thereby inhibiting smooth muscle cell proliferation and/or migration and preventing and/or treating restenosis.

Stenosis and restenosis are conditions associated with a narrowing of blood vessels. Stenosis of blood vessels generally occurs gradually over time. Restenosis, in contrast, relates to a narrowing of blood vessels following an endovascular procedure, such as balloon angioplasty and/or stent implantation, or a vascular injury.

Balloon angioplasty is typically performed to open a stenotic blood vessel; stenting is usually performed to maintain the patency of a blood vessel after, or in combination with, balloon angioplasty. A stenotic blood vessel is opened with balloon angioplasty by navigating a balloon-tipped catheter to the site of stenosis, and expanding the balloon tip effectively to dilate the occluded blood vessel. In an effort to maintain the patency of the dilated blood vessel, a stent may be implanted in the blood vessel to provide intravascular support to the opened section of the blood vessel, thereby limiting the extent to which the blood vessel will return to its occluded state after release of the balloon catheter. Restenosis is typically caused by trauma inflicted during angioplasty, effected by, for example, balloon dilation, atherectomy or laser ablation treatment of the artery. For these procedures, restenosis occurs at a rate of about 30% to about 60% depending on the vessel location, lesion length and a number of other variables. This reduces the overall success of the relatively non-invasive balloon angioplasty and stenting procedures.

Restenosis is attributed to many factors, including proliferation of smooth muscle cells (SMC). SMC proliferation is triggered by the initial mechanical injury to the intima that is sustained at the time of balloon angioplasty and stent implantation. The process is characterized by early platelet activation and thrombus formation, followed by SMC recruitment and migration, and, finally, cellular proliferation and extracellular matrix accumulation. Damaged endothelial cells, SMCs, platelets, and macrophages secrete cytokines and growth factors which promote restenosis. SMC proliferation represents the final common pathway leading to neointimal hyperplasia. Therefore, anti-proliferative therapies aimed at inhibiting specific
regulatory events in the cell cycle may constitute the most reasonable approach to restenosis after angioplasty.

The compounds of the invention may also be used as immunosuppressants or immunomodulators and can accordingly be used in the treatment or prevention of immune response or immune-mediated responses and diseases such as systemic lupus erythematosus (SLE) and acute or chronic transplant rejection in a recipient of an organ, tissue or cell transplant, (see WO 05/013958).

Examples of autoimmune diseases for which the compounds of the invention may be employed include autoimmune hematological disorders (including hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, thyroiditis, Hashimoto's thyroiditis, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, atopic dermatitis, vasculitis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including ulcerative colitis and Crohn's disease) endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), diabetes type II and the disorders associated therewith, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis (with and without nephrotic syndrome, including idiopathic nephrotic syndrome or minimal change nephropathy), juvenile dermatomyositis, infectious, auto-antibody mediated diseases, aplastic anemia, Evan's syndrome, autoimmune hemolytic anemia, infectious diseases causing aberrant immune response and/or activation, such as traumatic or pathogen induced immune disregulation, including for example, that which are caused by hepatitis B and C infections, staphylococcus aureus infection, viral encephalitis, sepsis, parasitic diseases wherein damage is induced by inflammatory response (e.g. leprosy); and circulatory diseases, such as arteriosclerosis, atherosclerosis, polyarteritis nodosa and myocarditis.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for the treatment or prevention of immune disorders.

The present invention also provides a method for treating or preventing immune disorders, which method comprises administration to a patent in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of other diseases such as diabetes, cardiovascular disorders, asthma, cardiac hypertrophy and heart failure, (see Cell (2002), 110:479-488).

The compounds of this invention may be administered to mammals, preferably humans, either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In one
embodiment, the compounds of this invention may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium croscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethylene glycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide
with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monoleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monoooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's blood stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant
compound. In order to maintain such a constant concentration, a continuous intravenous
delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™
model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or
oleaginous suspension for intramuscular and subcutaneous administration. This suspension may
be formulated according to the known art using those suitable dispersing or wetting agents and
suspending agents which have been mentioned above. The sterile injectable preparation may
also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent
or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are
conventionally employed as a solvent or suspending medium. For this purpose any bland fixed
oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as
oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of suppositories for rectal
administration of the drug. These compositions can be prepared by mixing the drug with a
suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal
temperature and will therefore melt in the rectum to release the drug. Such materials include
cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols
of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the
compound of Formula I are employed. (For purposes of this application, topical application
shall include mouth washes and gurgles.)

The compounds for the present invention can be administered in intranasal form via
topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using
those forms of transdermal skin patches well known to those of ordinary skill in the art. To be
administered in the form of a transdermal delivery system, the dosage administration will, of
course, be continuous rather than intermittent throughout the dosage regimen.

When a compound according to this invention is administered into a human subject, the
daily dosage will normally be determined by the prescribing physician with the dosage generally
varying according to the age, weight, sex and response of the individual patient, as well as the
severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a
mammal undergoing treatment for cancer. Administration generally occurs in an amount
between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably
of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The instant compounds are also useful in combination with known therapeutic agents and
anti-cancer agents. Thus, this invention provides combinations of compounds of formula (I) and
known therapeutic agents and/or anti-cancer agents for simultaneous, separate or sequential
administration. For example, instant compounds are useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the 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. Such anti-cancer agents include, but are not limited to, the following: other HDAC inhibitors, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

In an embodiment, the instant compounds are also useful in combination with known anti-cancer agents including the following: other HDAC inhibitors, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

Examples of “other HDAC inhibitors” include suberoylanilide hydroxamic acid (SAHA), LAQ824, LBH589, PXD101, MS275, FK228, valproic acid, butyric acid and CI-994.

“Estrogen receptor modulators” refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy)-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]- phenyl-2,2-dimethylpropanoate, 4,4’-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazine, and SH646.

“Androgen receptor modulators” refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

“Retinoid receptor modulators” refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-(4’-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

“Cytotoxic/cytostatic agents” refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell’s functioning or inhibit or interfere
with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonerin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibospidium chloride, pumitepa, lobaplatin, satraplatin, proflromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum(II)]tetrachloride, diarizidinylpermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisanitrene, mitoxantrone, pirarubicin, pinafide, valrubcin, amrubcin, antineoplaston, 3’-deamino-3’-morpholino-13-deoxy-10-hydroxycuraminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylisulphonyl-daunorubicin (see WO 00/50032).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin, bortezomib, epoxomicin and peptide aldehydes such as MG 132, MG 115 and PSI.

In an embodiment, the compounds of the present invention may be used in combination with other HDAC inhibitors such as SAHA and proteasome inhibitors.

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3’,4’-didehydro-4’-deoxy-8’-norvincaleukoblastine, docetaxel, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-\(N\)-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, \(N\),\(N\)-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hyacantine, irinotecan, rubitecan, 6-ethoxypropionyl-3’,4’-O-exo-benzylidene-chartreusin, 9-methoxy-\(N\),\(N\)-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyran[3’,4’:b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(\(N\)-isopropylamino)ethyl]-20S-camptothecin, BNP1350, BNP11100, BNP80915, BNP80942, etoposide phosphate, teniposide, sobuzoxane, 2’-dimethylamino-2’-deoxy-etoposide, GL331, \(N\)-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-
dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino][ethyl]-5-[4-hydroxy-3,5-dimethoxy-phenyl]-5,5a,6,8,8a,9-hexahydrofuro(3’,4’:6,7)naptho(2,3-d)-1,3-dioxol-6-one, 2,3-(methyleneedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benz[o]glsoguoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethyl]amino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in the prior art.

“Inhibitors of kinesins involved in mitotic progression” include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK) (in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1.

“Antiproliferative agents” includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, palitrexid, emitefur, tiazofurin, dectabine, nolatrexed, pemetrexed, nelzarabine, 2’-deoxy-2’-methylidenecytidine, 2’-fluoromethylene-2’-deoxy cytidine, N-[5-(2,3-dihydrobenzofuryl)sulfonyl]-N’-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxatidine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(5S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flourouracil, alanosine, 11-acetyl-8-(carbamoyloxy methyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.07,4)-tetradeca-2,4,6,9-ti en-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2’-cyano-2’-deoxy-N4-palmitoyl-l-B-D-arabinofuranosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

“HMG-CoA reductase inhibitors” refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®), simvastatin (ZOCOR®), pravastatin (PRAVACHOL®), fluvastatin (LESCOL®) and atorvastatin (LIPTOR®). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry &
Industry, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

“Prenyl-protein transferase inhibitor” refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer (1999), 35(9):1394-1401.


Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in Clin. Chem. La. Med. (2000) 38:679-692). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see Thromb. Haemost. (1998) 80:10-23), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see Thrombosis Res. (2001) 101:329-354).
TAF1a inhibitors have been described in PCT Publication WO 03/013,526 and U.S. Ser. No. 60/349,925 (filed January 18, 2002).

“Agents that interfere with cell cycle checkpoints” refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosopiridin, flavoipiridol, CYC202 (Cyclacel) and BMS-387032.

“Inhibitors of cell proliferation and survival signaling pathway” refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR (for example those disclosed in WO 03/059951), inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K (for example LY294002), serine/threonine kinases, inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779 and Ariad AP23573). Such agents include small molecule inhibitor compounds and antibody antagonists.

“Apoptosis inducing agents” include activators of TNF receptor family members (including the TRAIL receptors).

The invention also encompasses combinations with NSAID’s which are selective COX-2 inhibitors. For purposes of this specification NSAID’s which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC50 for COX-2 over IC50 for COX-1 evaluated by cell or microsomal assays.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are 5-chloro-3-(4-methylsulfanyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX® and BEXTRA® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranipimase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyloxi)iranyl]-1-oxaspiro[2.5]oct-6-yl(chloroacetetyl)carbamate, acetyldinanaline, 5-amino-1-[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carboxylbis[imino-N-methyl-4,2-pyrrolcarboxylimin0[N-methyl-4,2-pyrrole]-carboxylimin0]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).
As used above, “integrin blockers” refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αvβ3 integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αvβ5 integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the αvβ3 integrin and the αvβ5 integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the αvβ6, αvβ8, α1β1, α2β1, α5β1, α6β1 and α6β4 integrins. The term also refers to antagonists of any combination of αvβ3, αvβ5, αvβ6, αvβ8, α1β1, α2β1, β5α1, α6β1 and α6β4 integrins.

Some specific examples of tyrosine kinase inhibitors include 1-N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[2,4-dimethylpyrrol-5-yl]methylidenediindolin-2-one, 17-(allylamo)-17-demethoxy geldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxy]quinoxaline, N-(3-ethylphenyl)-6,7-bis(2-methoxy ethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolol[1,2,3-fg:3',2',1'-kl]pyrrole[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5-6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenylamino)-6,7-dimethoxyquinoxaline, 4-(4′-hydroxyphenyl)amino-6,7-dimethoxy quinoxaline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamide, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malignancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see J. Cardiovasc. Pharmacol. (1998) 31:909-913; J. Biol. Chem. (1999) 274:9116-9121; Invest. Ophthalmol Vis. Sci. (2000) 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (Arch. Ophthalmol. (2001) 119:709-717). Examples of PPAR-γ agonists and PPAR-γ/δ agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GIZ26570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid, and 2(8R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid.
Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with anti-viral agents (such as nucleoside analogs including ganciclovir for the treatment of cancer.

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (Am J Hum Genet (1997) 61:785-789) and Kufe et al (Cancer Medicine, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," Gene Therapy, August (1998) 5(8):1105-13), and interferon gamma (J Immunol (2000) 164:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zanisetro, GABA receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S. Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In an embodiment, an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis that may result upon administration of the instant compounds.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Pat. No. 5,719,147.
A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous erythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, cladronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from: other HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an anti-viral agent, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.
The term “treating cancer” or “treatment of cancer” refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl-fumagillo, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a compound selected from: other HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an anti-viral agent, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with a COX-2 inhibitor.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula I and a compound selected from: other HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an anti-viral agent, an inhibitor of cell proliferation and survival.
signaling, an agent that interferes with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

These and other aspects of the invention will be apparent from the teachings contained herein.

The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of the invention.

The compounds described herein can be prepared according to the procedures of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

All temperatures are degrees Celsius unless otherwise noted. Mass spectra (MS) were measured by electrospray ion-mass spectroscopy (ESI). $^1$H NMR spectra were recorded at 400-500 MHz. Compounds described herein were synthesized as a racemic mixture unless otherwise stated in the experimental procedures.

In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
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<tr>
<td>Anal.</td>
<td>analytical</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>$n$-BuLi</td>
<td>$n$-butyl lithium</td>
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<tr>
<td>br</td>
<td>broad</td>
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<tr>
<td>calc.</td>
<td>calculated</td>
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<tr>
<td>$m$-CPBA</td>
<td>3-chloroperoxybenzoic acid</td>
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DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE = dichloroethane
DCM = dichloromethane
DEA = diethylamine
DIEA = N,N-diisopropylethylamine
DIPEA = N,N-diisopropylethylamine
DMA = N,N-dimethylethylamine
DMF = dimethylformamide
DMSO = dimethyl sulfoxide
ESI = electrospray ionization
EtOAc = ethyl acetate
EtOH = ethanol
HATU = 1-[(bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium3-oxid hexafluorophosphate
Hex = hexanes
HPLC = high-pressure liquid chromatography
IPA = iso-propyl alcohol
IPAc = iso-propyl acetate
KF = Karl-Fischer titration (to determine water content)
KOt-Bu = potassium tert-butoxide
LCMS = liquid chromatography-mass spectrometry
LiHMDS = lithium hexamethyl silazane
m = multiplet
MeCN = acetonitrile
MeOH = methyl alcohol
MPa = milipascal
MS = mass spectroscopy
MTBE = methyl tert-butyl ether
NHS = normal human serum
NMR = nuclear magnetic resonance spectroscopy
PE = petroleum ether
Piv = pivalate, 2,2-dimethylpropanoyl
Pd/C = palladium on carbon
q = quartet
rt = room temperature
s = singlet
sat. aq. = saturated aqueous
SEM-Cl = 2-(trimethylsilyl)ethoxymethyl chloride
SFC = supercritical fluid chromatography
t = triplet
THF = THF
TFA = trifluoroacetic acid
TFAA = trifluoroacetic anhydride
TLC = thin-layer chromatography
p-TsOH = para-toluene sulfonic acid
THF = tetrahydrofuran
wt% = percentage by weight
Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

REACTION SCHEMES

The compounds of the present invention can be prepared readily according to the following Schemes and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthetic procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail. The general procedures for making the compounds claimed in this invention can be readily understood and appreciated by one skilled in the art from viewing the following Schemes.

Scheme 1 illustrates a general strategy for preparing the 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl compounds of the present invention in which a nitrile intermediate (1.1) is heated with hydroxylamine to give the hydroxamidine product 1.2. Cyclization of 1.2 with TFAA in the presence of potassium carbonate then provides the 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl product 1.3.

SCHEME 1
Scheme 2 depicts methods of preparing nitrile intermediates of the present invention. Nitrile intermediate 2.3 is prepared by a cross-coupling reaction of bromide 2.1 with lactam 2.2 using copper or a palladium catalyst and a suitable base. For the preparation of nitrile intermediate 2.6, heating morpholine 2.5 with bromide 2.4 in the presence of potassium carbonate in the absence of catalyst is sufficient to effect the cross-coupling reaction.

**SCHEME 2**

For the preparation of certain nitrile intermediates of the present invention, ester or carboxylic acid starting materials are utilized, as illustrated in Scheme 3. For example, in the synthesis of intermediate 3.5, deprotonation of 3.2 with sodium hydride followed by heating with chloride 3.1 furnishes ester 3.3. Treatment of 3.3 with ammonia provides amide 3.4, which is dehydrated with trifluoroacetic anhydride and triethylamine to give nitrile intermediate 3.5. For the preparation of nitrile intermediate 3.8, carboxylic acid 3.6 is coupled with ammonia under HATU conditions to furnish amide 3.7. Dehydration of amide 3.7 using TFAA in the presence of pyridine then affords nitrile 3.8.

**SCHEME 3**
The following examples are presented to further illustrate compounds of the invention, but, with reference to the general formula presented above, they are not presented as limiting the invention to these specifically exemplified compounds.

**EXAMPLE 1**

3-(1-(Phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole

**Step A:** 1-(Phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile

To a stirred suspension of 1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (200 mg, 1.40 mmol) in dichloromethane (5 mL) was added triethylamine (0.60 mL, 4.2 mmol) followed by
benzenesulfonyl chloride (0.27 mL, 2.1 mmol) and the resulting mixture was stirred at ambient temperature for 72 h. The reaction mixture was diluted with dichloromethane (10 mL) and washed with water (5 mL x 2). The dichloromethane layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness in vacuo. The crude residue was purified by flash silica gel chromatography (ISCO CombiFlash Rf Purification System®; 12 g SepaFlash® Silica Flash Column, eluting with a 4-50% ethyl acetate in hexanes gradient) to afford the title compound as a solid. MS (ESI) m/z [M+H]^+; 284.2.

**Step B: (Z)-N'-Hydroxy-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-5-carboximidamide**

To a stirred suspension of 1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (170 mg, 0.600 mmol) in a mixture of ethanol (2 mL) and water (1 mL) was added 50% aqueous hydroxylamine solution (1.0 mL, 16 mmol). The resulting homogeneous solution was heated to 50 °C for 15 h, cooled to ambient temperature and extracted with ethyl acetate (10 mL x 3). The combined ethyl acetate extracts were washed with brine (5 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness in vacuo to afford the title compound as a solid. MS (ESI) m/z [M+H]^+; 317.2.

**Step C: 3-(1-(Phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole**

To a stirred suspension of (Z)-N'-hydroxy-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-5-carboximidamide (190 mg, 0.601 mmol) in dichloromethane (3 mL) cooled to 0 °C under an atmosphere of nitrogen was added neat trifluoracetic anhydride (0.13 mL, 0.90 mmol) in one portion. The cooling bath was removed and the resulting solution was stirred for 2 h with gradual warming to ambient temperature. Neat triethylamine (0.34 mL, 2.4 mmol) was then added in one portion and the resulting solution was allowed to stir for 17 h. The reaction mixture was evaporated to dryness in vacuo and the residue was dissolved in dichloromethane (5 mL) and washed with a saturated aqueous sodium bicarbonate solution (5 mL). The layers were separated and the dichloromethane layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness in vacuo. The crude residue was purified by flash silica gel chromatography (ISCO CombiFlash Rf Purification System®; 12 g SepaFlash® Silica Flash Column, eluting with a 0-50% ethyl acetate in hexanes gradient) to afford the title compound as a solid.

$^1$H NMR (500 MHz, CDCl₃): δ 9.16 (d, J = 1.8 Hz, 1 H), 8.57 (d, J = 1.8 Hz, 1 H), 8.24
(d, J = 7.9 Hz, 1 H), 7.85 (t, J = 4.0 Hz, 1 H), 7.63-7.60 (m, 1 H), 7.56-7.48 (m, 3 H), 6.71 (d, J = 4.0 Hz, 1 H); MS (ESI) m/z [M+H]^+ 395.3.

**EXAMPLE 2**

**tert-Butyl 6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate**

The title compound was prepared from tert-butyl 6-cyano-3,4-dihydroisoquinoline-2(1H)-carboxylate according to the procedures outlined for the preparation of Example 1, steps B and C. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.92 (dd, J = 11.8, 3.8 Hz, 2H), 7.25 (d, J = 3.4 Hz, 1H), 4.64 (s, 2H), 3.69 (s, 2H), 2.92 (t, J = 6.0 Hz, 2H), 1.50 (s, 9H); MS (ESI) m/z [M+H+CH$_3$CN]^+ 370.3.

**EXAMPLE 3**

**5-Phenyl-1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiophen-2-ylpyrrolidin-2-one**

**Step A: 5-(2-Oxo-5-phenylpyrrolidin-1-yl)thiophene-2-carbonitrile**

5-Phenylpyrrolidin-2-one (300 mg, 1.86 mmol) was added to a mixture of 5-bromothiophene-2-carbonitrile (350 mg, 1.86 mmol), potassium carbonate (772 mg, 5.58 mmol), (1R,2R)-N$_2$N$_2$-dimethylcyclohexane-1,2-diamine (291 mg, 2.047 mmol) and copper(I) iodide (354 mg, 1.861 mmol) in 1,4-dioxane (4 mL) at 11 °C. After complete addition, the suspension was heated at 130 °C for 18 h under N$_2$. After cooling to room temperature, the mixture was filtered through diatomaceous earth and the filtrate was diluted with EtOAc (20 mL). The organic layer was washed with H$_2$O (20 mL). The water layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous
Na₂SO₄. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, PE:EtOAc=3:1) to give 5-(2-oxo-5-phenylpyrrolidin-1-yl)thiophene-2-carbonitrile as an oil. ESI-MS m/z [M+H]⁺: 269.1.

**Step B:** (Z)-N'-Hydroxy-5-(2-oxo-5-phenylpyrrolidin-1-yl)thiophene-2-carboximidamide

A mixture of 5-(2-oxo-5-phenylpyrrolidin-1-yl)thiophene-2-carbonitrile (91 mg, 0.34 mmol), hydroxylamine hydrochloride (47.1 mg, 0.678 mmol) and triethylamine (0.095 mL, 0.68 mmol) in EtOH (10 mL) was heated at 50 °C for 12 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, then diluted with H₂O (10 mL). The water layer was extracted with EtOAc (10 mL x 2). The collected organic layers was was washed with brine (10 mL), dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound as an oil. The crude product was used for the next step without further purification. ESI-MS m/z [M+H]⁺: 302.1.

**Step C:** 5-Phenyl-1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiophen-2-yl)pyrrolidin-2-one

TFAA (0.223 mL, 1.58 mmol) was added to a stirred mixture of potassium carbonate (87 mg, 0.63 mmol) and (Z)-N'-hydroxy-5-(2-oxo-5-phenylpyrrolidin-1-yl)thiophene-2-carboximidamide (95 mg, 0.32 mmol) in 1,4-dioxiane (3 mL) at 15 °C, and the resulting mixture was stirred at 15 °C for 16 h. The mixture was diluted with water (20 mL) and extracted ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Phenomenex Synergi C18 250 x 21.2mm, 4um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 30-60%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 5-phenyl-1-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiophen-2-yl)pyrrolidin-2-one as an solid. ¹H NMR (400 MHz, CD₂OD): δ 2.01 - 2.14 (m, 1H) 2.60 - 2.72 (m, 1H) 2.74 - 2.90 (m, 2H) 5.38 - 5.56 (m, 1H) 6.37 (d, J=4.2 Hz, 1H) 7.27 (s, 3H) 7.34 - 7.41 (m, 2H) 7.54 (d, J=4.2 Hz, 1H); ESI-MS m/z [M+H]⁺: 380.0.

**EXAMPLE 4**

- 41 -
6-Phenyl-1-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiophen-2-yl)piperidin-2-one

Step A: 5-(2-Oxo-6-phenylpiperidin-1-yl)thiophene-2-carbonitrile

5-Bromothiophene-2-carbonitrile (805 mg, 4.28 mmol) was added to a mixture of 6-phenylpiperidin-2-one (500 mg, 2.85 mmol), (1S,2S)-cyclohexane-1,2-diamine (326 mg, 2.85 mmol), potassium phosphate tribasic (1.21 g, 5.71 mmol) and copper(I) iodide (543 mg, 2.85 mmol) in 1,4-dioxane (20 mL) at 11 °C. The resulting suspension was heated at 120 °C for 20 h under N₂. After cooling to room temperature, the mixture was filtered through diatomaceous earth and the filtrate was diluted with EtOAc (30 mL). The organic layer was washed with H₂O (20 mL). The water layer was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with a Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water (containing 0.1%TFA, v/v), mobile phase B: acetonitrile, gradient: 36-66% B, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give the title compound as an solid. MS (ESI) m/z [M+H]⁺: 283.1.

Step B: (Z)-N-Hydroxy-5-(2-oxo-6-phenylpiperidin-1-yl)thiophene-2-carboximidamide

Hydroxylamine hydrochloride (21.7 mg, 0.312 mmol) was added to a mixture of 5-(2-oxo-6-phenylpiperidin-1-yl)thiophene-2-carbonitrile (44 mg, 0.16 mmol) and triethylamine (0.043 mL, 0.31 mmol) in EtOH (2 mL) at 10 °C. After the addition was complete, the mixture was heated at 80 °C for 2 h. After the starting material was consumed, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between H₂O (10 mL) and EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound as a solid, which was used for the next step directly without further purification. ESI-MS m/z [M+H]⁺: 316.1.
Step C: 6-Phenyl-1-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiophen-2-yl)piperidin-2-one

To a mixture of (Z)-N'-hydroxy-5-(2-oxo-6-phenylpiperidin-1-yl)thiophene-2-carboximidamide (76 mg, 0.14 mmol) and pyridine (0.035 mL, 0.43 mmol) in anhydrous toluene (2 mL) was added TFAA (0.061 mL, 0.43 mmol) at 0 °C, and the resulting mixture was stirred at 110 °C for 2 h. After the starting material was consumed completely, the mixture was concentrated under reduced pressure, then diluted with H2O (10 mL). The aqueous mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na2SO4. The residue was purified by prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 250x21.2mmx4um using water and acetonitrile as the eluents, mobile phase A: water (containing 0.1%TFA, v/v), mobile phase B: acetonitrile. gradient: 49-79% B, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give the title compound as an oil. 1H NMR (400 MHz, CD3OD): δ ppm 7.52 (d, J=4.19 Hz, 1H) 7.33 - 7.40 (m, 2H) 7.25 - 7.31 (m, 1H) 7.22 (br d, J=7.3 Hz, 2H) 6.55 (d, J=4.2 Hz, 1H) 5.61 (br s, 1H) 2.76 - 2.85 (m, 2H) 2.39 - 2.51 (m, 1H) 2.16 (br d, J=11.25 Hz, 1H) 1.71 - 1.82 (m, 2H); ESI-MS m/z [M+H]+: 394.0.

EXAMPLE 5

6-Phenyl-1-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiiazol-2-yl)piperidin-2-one

Step A: 2-(2-Oxo-6-phenylpiperidin-1-yl)thiazole-5-carbonitrile

A solution of 2-bromothiazole-5-carbonitrile (259 mg, 1.37 mmol), 6-phenylpiperidin-2-one (200 mg, 1.14 mmol), cesium carbonate (558 mg, 1.71 mmol), XantPhos (52.8 mg, 0.091 mmol), and Pd(PPh3)4 (132 mg, 0.114 mmol) in dioxane (3 mL) in a sealed tube was heated at 125 °C for 18 h under N2. The reaction mixture was cooled to room temperature and partitioned between water (20 mL) and ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na2SO4, filtered and concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters...
XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 38-68%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 2-(2-oxo-6-phenylpiperidin-1-yl)thiazole-5-carbonitrile as a solid. ESI-MS m/z [M+H]^+: 284.0.

5 **Step B**: (Z)-N'-Hydroxy-2-(2-oxo-6-phenylpiperidin-1-yl)thiazole-5-carboximidamide

![Chemical Structure]

A mixture of 2-(2-oxo-6-phenylpiperidin-1-yl)thiazole-5-carbonitrile (30 mg, 0.11 mmol), hydroxylamine hydrochloride (36.8 mg, 0.529 mmol) and triethylamine (0.074 mL, 0.53 mmol) in EtOH (5 mL) was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, then diluted with H2O (10 mL). The water layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na2SO4. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was used for the next step without further purification. ESI-MS m/z [M+H]^+: 317.0.

15 **Step C**: 6-Phenyl-1-(5-(5-(trifluoromethyl)-1,2,4-oxadiazo)-3-yl)thiazol-2-yl)piperidin-2-one

![Chemical Structure]

TFAA (0.067 mL, 0.47 mmol) was added to a stirred mixture of potassium carbonate (26.2 mg, 0.190 mmol) and (Z)-N'-hydroxy-2-(2-oxo-6-phenylpiperidin-1-yl)thiazole-5-carboximidamide (30 mg, 0.095 mmol) in 1,4-dioxane (10 mL) at 25 °C, and the resulting mixture was stirred at 25 °C for 3 h. Sodium bicarbonate (aq) (15 mL) was added, and the aqueous mixture was extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na2SO4, filtered and concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Phenomenex Synergi C18 150x30mmx4um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 59-79%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 6-phenyl-1-(5-(5-(trifluoromethyl)-1,2,4-oxadiazo-3-yl)thiazol-2-yl)piperidin-2-one as a solid. 1H NMR (400 MHz, CD3OD): δ 8.08 (s, 1H), 7.37-7.27 (m, 2H), 7.23 (d, J=7.3 Hz, 1H), 7.13 (d, J=7.5 Hz, 2H), 6.24 (br. s., 1H), 2.88-2.78 (m, 2H), 2.48-2.34 (m, 1H), 2.23 (d, J=2.4 Hz, 1H), 1.83-1.67 (m, 2H); ESI-MS m/z [M+H]^+: 395.0.
EXAMPLE 6

3-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydropyridine[β,γ][1,4]thiazepine 5,5-dioxide

\[
\begin{align*}
\text{HN} & \quad \text{N} \\
\text{SO} & \quad \text{N} \\
\text{O} & \quad \text{F} \\
\end{align*}
\]

5 Step A: 10,11-Dihydrodibenzo[β,γ][1,4]thiazepine-3-carboxamide 5,5-dioxide

To a solution of 10,11-dihydropyridine[β,γ][1,4]thiazepine-3-carboxylic acid 5,5-dioxide (600 mg, 2.07 mmol, described in US4263207), diisopropylethylamine (1.09 mL, 6.22 mmol) and HATU (1183 mg, 3.11 mmol) in DMF (15 mL) was added ammonium chloride (444 mg, 8.30 mmol) at 0 °C. The mixture was stirred at 20 °C for 16 h. Water (100 mL) was added and aqueous mixture was extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 16-46%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 10,11-dihydropyridine[β,γ][1,4]thiazepine-3-carboxamide 5,5-dioxide as a solid. ESI-MS m/z [M+H]⁺: 289.1.

20 Step B: 10-(2,2,2-Trifluoroacetyl)-10,11-dihydropyridine[β,γ][1,4]thiazepine-3-carbonitrile 5,5-dioxide

To a mixture of 10,11-dihydropyridine[β,γ][1,4]thiazepine-3-carboxamide 5,5-dioxide (460 mg, 1.595 mmol) and pyridine (252 mg, 3.19 mmol) in anhydrous DCM (15 mL) was added 2,2,2-trifluoroacetic anhydride (1.01 mg, 4.79 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then at 18 °C for 16 h. The mixture was concentrated under reduced pressure and then diluted with H₂O (100 mL). The water layer was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated under reduced pressure to
give 10-(2,2,2-trifluoroacetyl)-10,11-dihydridibenzo[6,7][1,4]thiazepine-3-carbonitrile 5,5-dioxide as an oil. ESI-MS m/z [M+23+41]^+: 430.1.

**Step C:** (Z)-N'-Hydroxy-10,11-dihydridibenzo[6,7][1,4]thiazepine-3-carboximidamide 5,5-dioxide

A mixture of 10-(2,2,2-trifluoroacetyl)-10,11-dihydridibenzo[6,7][1,4]thiazepine-3-carbonitrile 5,5-dioxide (548 mg, 1.50 mmol), hydroxylamine hydrochloride (208 mg, 2.99 mmol) and triethylamine (303 mg, 2.99 mmol) in EtOH (15 mL) was heated at 80 °C for 16 h. After cooling to the room temperature, the mixture was concentrated under reduced pressure and diluted with H2O (80 mL). The aqueous mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na2SO4. The mixture was filtered and the filtrate was concentrated under reduced pressure to give (Z)-N'-hydroxy-10,11-dihydridibenzo[6,7][1,4]thiazepine-3-carboximidamide 5,5-dioxide as a solid. ESI-MS m/z [M+H]^+: 304.1.

**Step D:** 3-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydridibenzo[6,7][1,4]thiazepine 5,5-dioxide

(Z)-N'-hydroxy-10,11-dihydridibenzo[6,7][1,4]thiazepine-3-carboximidamide 5,5-dioxide (440 mg, 1.451 mmol) and methyl 2,2,2-trifluoroacetate (371 mg, 2.90 mmol) were dissolved in a mixture of toluene (10 mL) and DMF (1 mL). Potassium carbonate (301 mg, 2.176 mmol) was added, and the resulting mixture was heated at 80 °C for 16 h. After cooling to the room temperature, the mixture was concentrated under reduced pressure. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 32-62%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydridibenzo[6,7][1,4]thiazepine 5,5-dioxide as a solid. 1H NMR (400 MHz, CDCl3) δ ppm 8.77 (s, 1H), 8.37 (d, J=7.8 Hz, 1H), 7.98 (d, J=8.2 Hz, 1H), 7.54 (d, J=7.8 Hz, 1H), 7.25 - 7.32 (m, 1H), 6.78 (s, 1H), 6.57 (d, J=8.2 Hz, 1H), 5.05 (s, 2H); ESI-MS m/z [M+H]^+: 382.1.
**EXAMPLE 7**

10-Methyl-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydribenzo[b,f][1,4]thiazepine 5,5-dioxide

![Chemical Structure](image)

A mixture of formaldehyde (4.72 mg, 0.157 mmol) and 3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydribenzo[b,f][1,4]thiazepine 5,5-dioxide (20 mg, 0.052 mmol) in AcOH (1 mL) was stirred at 20 °C. After 30 min, sodium triacetoxborohydride (22.2 mg, 0.105 mmol) was added to the mixture and the reaction was stirred at 20 °C for 16 h. The mixture was filtered, washed with EtOAc (20 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 46-76%, 0-10 min; 100%B, 10.5-12.5 min; 5%B, 13-15 min) to give 10-methyl-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydribenzo[b,f][1,4]thiazepine 5,5-dioxide as an oil. $^1$H NMR (400MHz, CDCl$_3$): $\delta$ ppm 8.83 (d, $J$=1.6 Hz, 1H), 8.32 - 8.44 (m, 1H), 8.14 (dd, $J$=8.2, 1.6 Hz, 1H), 7.57 (d, $J$=7.8 Hz, 1H), 7.41 (br t, $J$=1.6 Hz, 1H), 6.74 - 6.92 (m, 2H), 5.03 - 5.15 (m, 2H), 3.22 (s, 3H); ESI-MS m/z [M+H]$^+$: 396.0.

**EXAMPLE 8**

10-Isobutyl-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydribenzo[b,f][1,4]thiazepine 5,5-dioxide

![Chemical Structure](image)

A mixture of isobutyaldehyde (37.8 mg, 0.524 mmol) and 3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydribenzo[b,f][1,4]thiazepine 5,5-dioxide (20 mg, 0.052 mmol) in THF (1 mL) was stirred at 20 °C. After 30 min, sodium borohydride (9.92 mg, 0.262 mmol) and TFA (8.08 µL, 0.105 mmol) were added to the mixture and the reaction was stirred at 20 °C for 16 h. Water (20 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18
EXAMPLE 9

\[
\text{1-(5,5-Dioxido-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzolo[\beta,\gamma][1,4]thiazepin-10(11H)-yl)ethanone}
\]

A mixture of acetyl chloride (12.4 mg, 0.157 mmol), 3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydropyridinobenzol[\beta,\gamma][1,4]thiazepin-5,5-dioxide (30 mg, 0.079 mmol) and pyridine (0.013 mL, 0.16 mmol) in toluene (0.5 mL) was heated at 80 °C for 16 h. After cooling to the room temperature, the mixture was concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 40-70%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 1-(5,5-dioxido-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[\beta,\gamma][1,4]thiazepin-10(11H)-yl)ethanone as an oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) ppm 8.99 (d, \(J=1.6\) Hz, 1H), 8.17 - 8.31 (m, 2H), 7.76 - 7.86 (m, 1H), 7.65 (br d, \(J=1.0\) Hz, 1H), 7.45 - 7.57 (m, 2H), 6.16 - 6.64 (m, 1H), 4.02 - 4.57 (m, 1H), 2.05 - 2.08 (m, 1H), 2.01 (s, 2H); ESI-MS \(m/z\) [M+H+1]: 465.1.

EXAMPLE 10

\[
\text{(5,5-Dioxido-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzolo[\beta,\gamma][1,4]thiazepin-10(11H)-yl)(phenyl)methanone}
\]

A mixture of pyridine (2.24 µL, 0.052 mmol), benzoyl chloride (14.7 mg, 0.104 mmol) and 3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydropyridinobenzol[\beta,\gamma][1,4]thiazepin-5,5-dioxide (30 mg, 0.079 mmol) in toluene (0.5 mL) was heated at 80 °C for 16 h. After cooling to the room temperature, the mixture was concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 40-70%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give (5,5-dioxido-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[\beta,\gamma][1,4]thiazepin-10(11H)-yl)(phenyl)methanone as an oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) ppm 8.99 (d, \(J=1.6\) Hz, 1H), 8.17 - 8.31 (m, 2H), 7.76 - 7.86 (m, 1H), 7.65 (br d, \(J=1.0\) Hz, 1H), 7.45 - 7.57 (m, 2H), 6.16 - 6.64 (m, 1H), 4.02 - 4.57 (m, 1H), 2.05 - 2.08 (m, 1H), 2.01 (s, 2H); ESI-MS \(m/z\) [M+H+1]: 465.1.
dioxide (20 mg, 0.052 mmol) in toluene (2 mL) was heated at 80 °C for 16 h. After cooling to room temperature, the mixture was concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 22-52%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give (5,5-dioxido-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f][1,4]thiazepin-10(11H)-yl)(phenyl)methanone as an oil. ^1H NMR (400 MHz, CDCl3): δ ppm 9.01 (d, J=1.6 Hz, 1H), 8.29 (dd, J=8.0, 1.76 Hz, 1H), 8.16 (dd, J=5.8, 3.6 Hz, 1H), 7.52 - 7.60 (m, 3H), 7.43 (dd, J=5.8, 3.4 Hz, 2H), 7.29 (s, 1H), 7.22 (br d, J=7.6 Hz, 2H), 6.97 - 7.04 (m, 1H), 4.90 - 6.18 (m, 2H). ESI-MS m/z [M+H]^+ : 486.1.

EXAMPLE 11

(5,5-Dioxido-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f][1,4]thiazepin-10(11H)-yl)(morpholino)methanone

A solution of bis(trichloromethyl)carbonate (23.4 mg, 0.079 mmol) in DCM (0.5 mL) was added to a solution of 3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-1,11-dihydrodibenzo[b,f][1,4]thiazepine-5,5-dioxide (20 mg, 0.052 mmol) and pyridine (0.025 mL, 0.315 mmol) in DCM (1 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 15 h. The mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and extracted with DCM (3 x 10 mL). The combined organic fractions were washed with hydrochloric acid (1 M, 10 mL), dried (Na2SO4), and concentrated under reduced pressure. The residue was dissolved in DCM (1 mL) and morpholine (0.046 mL, 0.524 mmol) and DIEA (0.018 mL, 0.105 mmol) were added successively to the solution at 0 °C. The resulting mixture was stirred for 2 h at 20 °C. The mixture was partitioned between water (20 mL) and DCM (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na2SO4), and concentrated under reduced pressure. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 42-72%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give (5,5-dioxido-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f][1,4]thiazepin-10(11H)-yl)(morpholino)methanone as an oil. ^1H NMR (400 MHz, CDCl3) δ ppm 8.91 - 9.05 (m, 1H), 8.25 (s, 1H), 8.16 - 8.22 (m, 1H), 7.68 - 7.75 (m, 1H),
7.49 (br d, J=7.8 Hz, 2H), 7.27 - 7.34 (m, 1H), 5.29 (s, 2H), 3.52 (br s, 4H), 3.35 (br d, J=4.7 Hz, 4H); ESI-MS m/z [M+H]^+: 495.0.

**EXAMPLE 12**

3-(10,11-Dihydrodibenzoz[b,f][1,4]thiazepin-3-yl)-5-(trifluoromethyl)-1,2,4-oxadiazone

**Step A: 10,11-Dihydrodibenzoz[b,f][1,4]thiazepine-3-carboxamide**

To a solution of 10,11-dihydrodibenzoz[b,f][1,4]thiazepine-3-carboxylic acid (200 mg, 0.777 mmol, described in US4263207), diisoproylethylamine (0.679 mL, 3.89 mmol) and HATU (443 mg, 1.166 mmol) in DMF (3 mL) was added ammonium chloride (208 mg, 3.89 mmol) at 0 °C. The reaction was stirred at 20 °C for 2 h. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on an EG instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%NH3.H2O-ACN), gradient: 21-51%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 10,11-dihydrodibenzoz[b,f][1,4]thiazepine-3-carboxamide as a solid. ESI-MS m/z [M+H]^+: 257.1.

**Step B: 10-(2,2,2-Trifluoroacetyl)-10,11-dihydrodibenzoz[b,f][1,4]thiazepine-3-carbonitrile**

To a mixture of 10,11-dihydrodibenzoz[b,f][1,4]thiazepine-3-carboxamide (130 mg, 0.507 mmol) and pyridine (80 mg, 1.0 mmol) in anhydrous DCM (4 mL) was added 2,2,2-trifluoroacetic anhydride (320 mg, 1.52 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then at 18 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was diluted with H2O (30 mL). The water layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na2SO4, and concentrated under reduced pressure to give 10-(2,2,2-trifluoroacetyl)-10,11-dihydrodibenzoz[b,f][1,4]thiazepine-3-carbonitrile as an oil. ESI-MS m/z [M+H]^+: 376.1.
Step C: \((Z)-N^\prime\)-hydroxy-10-(2,2,2-trifluoroacetyl)-10,11-dihydridibenzo[b,f][1,4]thiazepine-3-carboximidamide

A mixture of 10-(2,2,2-trifluoroacetyl)-10,11-dihydridibenzo[b,f][1,4]thiazepine-3-carbonitrile (152 mg, 0.409 mmol), hydroxylamine hydrochloride (63.2 mg, 0.909 mmol) and triethylamine (92 mg, 0.91 mmol) in EtOH (3 mL) was heated at 80 °C for 16 h. After cooling to the room temperature, the mixture was concentrated under reduced pressure, then diluted with H₂O (50 mL). The aqueous mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give \((Z)-N^\prime\)-hydroxy-10-(2,2,2-trifluoroacetyl)-10,11-dihydridibenzo[b,f][1,4]thiazepine-3-carboximidamide as a solid. ESI-MS m/z [M+H]⁺: 368.0.

Step D: 3-(10,11-Dihydridibenzo[b,f][1,4]thiazepin-3-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole

A mixture of potassium carbonate (55.1 mg, 0.399 mmol), \((Z)-N^\prime\)-hydroxy-10-(2,2,2-trifluoroacetyl)-10,11-dihydridibenzo[b,f][1,4]thiazepine-3-carboximidamide (122 mg, 0.332 mmol) and methyl 2,2,2-trifluoroacetate (85 mg, 0.66 mmol) in toluene (2 mL) and DMF (0.2 mL) was heated at 80 °C for 16 h. After cooling to room temperature, the mixture was concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 35-65%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 3-(10,11-dihydridibenzo[b,f][1,4]thiazepin-3-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole as an oil. \(^1\)H NMR (400 MHz, CDCl₃): δ ppm 8.11 (d, J=1.4 Hz, 1H), 7.89 (dd, J=8.0, 1.6 Hz, 1H), 7.59 - 7.68 (m, 1H), 7.40 (br dd, J=6.4, 1.7 Hz, 4H), 5.65 - 5.78 (m, 1H), 4.28 - 4.42 (m, 1H); ESI-MS m/z [M+H]⁺: 350.0.

EXAMPLE 13
3-(dibenzo[b,f][1,4]thiazepin-3-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole
Example 13, 3-(dibenzo[b,f][1,4]thiazepin-3-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole, was prepared according to the procedures described above.

**EXAMPLE 14**

3-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-5-oxide

$mCPBA$ (35.2 mg, 0.163 mmol) (80%) was added slowly to a mixture of 3-(10,11-dihydrodibenzo[b,f][1,4]thiazepin-3-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole (57 mg, 0.16 mmol) in $CH_2Cl_2$ (5 mL) at -78 °C. The mixture was stirred at -78 °C for 2 h. Saturated aqueous sodium bicarbonate solution (20 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by reverse-phase prep-HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 32-52%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-5-oxide as a solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ ppm 8.45 (s, 1H), 8.21 (br d, $J=1.6$ Hz, 1H), 7.62 - 7.71 (m, 1H), 7.41 - 7.47 (m, 1H), 7.17 - 7.22 (m, 1H), 6.80 - 6.88 (m, 1H), 6.51 - 6.58 (m, 1H), 4.94 - 5.04 (m, 1H), 4.63 - 4.75 (m, 1H); ESI-MS $m/z$ [M+H]$^+$; 366.1.

**EXAMPLE 15**

7-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydrodibenzo[b,f][1,4] thiazepine 5,5-dioxide

**Step A:** 10,11-Dihydrodibenzo[b,f][1,4]thiazepine-7-carboxamide 5,5-dioxide

To a solution of 10,11-dihydrodibenzo[b,f][1,4]thiazepine-7-carboxylic acid 5,5-dioxide (200 mg, 0.691 mmol, described in US4263207), disopropylethylamine (0.604 mL, 3.46 mmol)
and HATU (394 mg, 1.037 mmol) in DMF (5 mL) was added ammonium chloride (185 mg, 3.46 mmol) at 0 °C. The reaction was stirred at 20 °C for 16 h. The reaction mixture was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with YM-Actus Pro C18 150x30 5u using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 17-47%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 10,11-dihydridibenzo[β,γ][1,4]thiazepine-7-carboxamide 5,5-dioxide as a solid. ESI-MS m/z [M+H]^+: 289.1.

**Step B:** 10,11-Dihydridibenzo[β,γ][1,4]thiazepine-7-carbonitrile 5,5-dioxide

![Diagram](image)

2,2,2-Trifluoroacetic anhydride (284 mg, 1.35 mmol) was added to a stirred mixture of 10,11- dihydridibenzo[β,γ][1,4]thiazepine-7-carboxamide 5,5-dioxide (130 mg, 0.451 mmol) and pyridine (0.109 mL, 1.35 mmol) in DCM (10 mL) at 0 °C, and the resulting mixture was stirred at 15 °C for 16 h. Water (20 mL) was added at 0 °C, and the resulting mixture was extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give 10,11- dihydridibenzo[β,γ][1,4] thiazepine-7-carbonitrile 5,5-dioxide as a solid.

**Step C:** (Z)-N'-Hydroxy-10,11-dihydridibenzo[β,γ][1,4]thiazepine-7-carboximidamide 5,5-dioxide

![Diagram](image)

A mixture of 10,11-dihydridibenzo[β,γ][1,4]thiazepine-7-carbonitrile 5,5-dioxide (120 mg, 0.444 mmol), hydroxylamine hydrochloride (154 mg, 2.22 mmol) and triethylamine (0.309 mL, 2.22 mmol) in EtOH (10 mL) was heated at 80 °C for 30 min. After cooling to room temperature, the mixture was concentrated under reduced pressure, then diluted with H₂O (20 mL). The aqueous mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give N-hydroxy-10,11-dihydridibenzo[β,γ][1,4]thiazepine-7-carboximidamide 5,5-dioxide as a solid. ESI-MS m/z [M+H]^+: 304.0.

**Step D:** 7-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydridibenzo[β,γ][1,4]thiazepine 5,5-dioxide

- 53 -
A mixture of potassium carbonate (45.4 mg, 0.328 mmol), methyl 2,2,2-trifluoroacetate (70.1 mg, 0.547 mmol) and N-hydroxy-10,11-dihydrodibenzo[b,f][1,4]thiazepine-7-carboximidamide 5,5-dioxide (83 mg, 0.27 mmol) in toluene (2 mL) and DMF (0.2 mL) was heated at 80 °C for 16 h. After cooling to room temperature, the mixture was concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Phenomenex Synergi C18 250x21.2mmx4um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 50-70%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 7-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine 5,5-dioxide as an oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) = 8.69 (d, \(J=2.0\) Hz, 1H), 8.00 (d, \(J=7.9\) Hz, 1H), 7.89 (dd, \(J=2.1, 8.7\) Hz, 1H), 7.65 - 7.59 (m, 1H), 7.47 (t, \(J=7.7\) Hz, 1H), 7.34 (d, \(J=7.3\) Hz, 1H), 6.60 (d, \(J=8.6\) Hz, 1H), 5.01 (br s, 3H); ESI-MS m/z [M+H]\(^+\): 382.0.

**EXAMPLE 16**

10-Methyl-7-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f][1,4]thiazepin-11(10H)-one 5-oxide

**Step A:** 11-Oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-7-carboxamide 5-oxide

To a solution of 11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-7-carboxylic acid 5-oxide (200 mg, 0.696 mmol, described in US4263207), disopropylethylamine (0.608 mL, 3.48 mmol) and HATU (529 mg, 1.392 mmol) in DMF (5 mL) was added ammonium hydroxide (186 mg, 3.48 mmol) at 0 °C. The mixture was stirred at 20 °C for 4 h, then purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with YMC-Actus Pro C18 150x30 5u using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 3-33%, 0-10 min; 100% B, 10.5-12.5 min;
5% B, 13-15 min) to give 11-oxo-10,11-dihydropyrazolo[1,5-c][1,4]thiazepine-7-carboxamide 5-oxide as a solid. ESI-MS m/z [M+H]^+: 287.0.

**Step B: 11-Oxo-10,11-dihydropyrazolo[1,5-c][1,4]thiazepine-7-carbonitrile 5-oxide**

2,2,2-Trifluoroacetic anhydride (242 mg, 1.15 mmol) was added to a mixture of 11-oxo-10,11-dihydropyrazolo[1,5-c][1,4]thiazepine-7-carboxamide 5-oxide (110 mg, 0.384 mmol) and pyridine (91 mg, 1.2 mmol) in DCM (10 mL) at 0 °C. The resulting mixture was stirred at 15 °C for 16 h. Water (20 mL) was added at 0 °C, and the aqueous mixture was extracted with DCM (30 mL x 2). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give 11-oxo-10,11-dihydropyrazolo[1,5-c][1,4]thiazepine-7-carbonitrile 5-oxide as a solid. ESI-MS m/z [M-H]^-: 269.1.

**Step C: (Z)-5-Hydroxy-11-oxo-10,11-dihydropyrazolo[1,5-c][1,4]thiazepine-7-carboximidamide 5-oxide**

A mixture of 11-oxo-10,11-dihydropyrazolo[1,5-c][1,4]thiazepine-7-carbonitrile 5-oxide (100 mg, 0.373 mmol), hydroxylamine hydrochloride (130 mg, 1.86 mmol) and triethylamine (0.260 mL, 1.86 mmol) in EtOH (10 mL) was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, then diluted with H₂O (20 mL). The aqueous mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give (Z)-5-hydroxy-11-oxo-10,11-dihydropyrazolo[1,5-c][1,4]thiazepine-7-carboximidamide 5-oxide as a solid. ESI-MS m/z [M-H]^-: 302.0.

**Step D: 10-Methyl-7-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenz[5,f][1,4]thiazepin-11(10H)-one 5-oxide**
A mixture of potassium carbonate (33.0 mg, 0.239 mmol), methyl 2,2,2-trifluoroacetate (51.0 mg, 0.398 mmol) and N-hydroxy-11-oxo-10,11-dihydropyrido[b,f][1,4]thiazepine-7-carboximidamide 5-oxide (60 mg, 0.20 mmol) in toluene (2 mL) and DMF (0.2 mL) was heated at 80 °C for 16 h. After cooling to the room temperature, the mixture was concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Phenomenex Synergi C18 250x21.2mmx4um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1% TFA-ACN), gradient: 25-55%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 10-methyl-7-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenz[b,f][1,4]thiazepin-11(10H)-one 5-oxide as a solid. 1H NMR (400 MHz, CDCl3) δ ppm 3.60 (s, 3H) 7.36 - 7.51 (m, 2H) 7.59 (br t, J=7.2 Hz, 1H) 7.78 (br d, J=7.7 Hz, 2H) 8.11 (br d, J=8.2 Hz, 1H) 8.44 (s, 1H); ESI-MS m/z [M+H]+: 394.1.

EXAMPLE 17

(R)-3-Phenyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiazol-2-yl)morpholine

Step A: (R)-2-(3-Phenylmorpholinoo)thiazole-5-carbonitrile

Potassium carbonate (0.762 g, 5.51 mmol) was added to a mixture of 2-bromothiazole-5-carbonitrile (0.417 g, 2.21 mmol) and (R)-3-phenylmorpholine (0.30 mg, 1.8 mmol) in NMP (2.0 mL). The resulting mixture was heated 130 °C under microwave irradiation for 1 h. The mixture was cooled, diluted with water (10 mL), and extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried (Na2SO4) and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®, 4 g SepaFlash® Silica Flash Column, Eluent of 0-30% EA/PE gradient @ 40 mL/min) to give (R)-2-(3-phenylmorpholinoo)thiazole-5-carbonitrile as an oil. ESI-MS m/z [M+H]+: 272.0.

Step B: (R,Z)-N°-Hydroxy-2-(3-phenylmorpholinoo)thiazole-5-carboximidamide
A mixture of (R)-2-(3-phenylmorpholinoo)thiazole-5-carbonitrile (0.5 g, 1.843 mmol), hydroxylamine hydrochloride (0.256 g, 3.69 mmol) and triethylamine (0.514 mL, 3.69 mmol) in EtOH (10 mL) was heated at 80 °C for 12 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, then diluted with H2O (10 mL). The aqueous mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na2SO4 and concentrated under reduced pressure to give the title compound as an oil. ESI-MS m/z [M+H]+: 305.1.

Step C: (R)-3-Phenyl-4-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiazol-2-yl)morpholine

To a a mixture of (R,Z)-N'-hydroxy-2-(3-phenylmorpholinoo)thiazole-5-carboximidamide (100 mg, 0.33 mmol) in dioxane (3 mL) was added potassium carbonate (91 mg, 0.66 mmol) and TFAA (273 mg, 1.3 mmol) at 0 °C. After addition the reaction mixture was stirred at 12 °C for 17 h. The mixture was concentrated under reduced pressure, then diluted with H2O (10 mL). The aqueous mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na2SO4 and concentrated under reduced pressure. The residue was purified by reverse-phase Prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 250x21.2mmx4um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 31-61%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give the (R)-3-phenyl-4-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiazol-2-yl)morpholine as a solid. 1H NMR (400 MHz, CDCl3): δ ppm 3.68 - 3.87 (m, 4H) 3.98 - 4.07 (m, 2H) 4.27 (dd, J=12.0, 2.0 Hz, 1H) 4.93 (br s, 1H) 7.24 - 7.35 (m, 3H) 7.37 - 7.43 (m, 2H) 7.99 (s, 1H); ESI-MS m/z [M+H]+: 383.1.

EXAMPLE 18

3-Fluoro-7-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f]thiepine 5-

oxide

Step A: 7-Fluorodibenzo[b,f]thiepine-3-carboxamide 5-oxide
To a solution of 7-fluorodibenzo[\(b,f\)]thiepine-3-carboxylic acid 5-oxide (500 mg, 1.73 mmol, described in US 4536507), diisopropylethylamine (0.909 mL, 5.20 mmol) and HATU (1.32 g, 3.47 mmol) in DMF (10 mL) was added NH\(_4\)Cl (186 mg, 3.47 mmol) at 0 °C. The reaction was stirred at 28 °C for 12 h. The resulting mixture was acidified with aqueous HCl solution (1 N) to pH 5. Water (20 mL) was added, and aqueous mixture was extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO\(^\text{®}\); 4 g SepaFlash\(^\text{®}\) Silica Flash Column, Eluent of 0-40% EA/PE gradient @ 35 ml/min) to give 7-fluorodibenzo[\(b,f\)]thiepine-3-carboxamide 5-oxide as a solid. ESI-MS m/z [M+CN]\(^+\): 329.0.

**Step B: 7-Fluorodibenzo[\(b,f\)]thiepine-3-carbonitrile 5-oxide**

2,2,2-Trifluoroacetic anhydride (110 mg, 0.522 mmol) was added to a mixture of 7-fluorodibenzo[\(b,f\)]thiepine-3-carboxamide 5-oxide (50 mg, 0.174 mmol, described in US4536507) and pyridine (0.042 mL, 0.522 mmol) in THF (5 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 16 h. Water (20 mL) was added, and the aqueous mixture was extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Agela ASB 150x25mmx5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 37-67%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 7-fluorodibenzo[\(b,f\)]thiepine-3-carbonitrile 5-oxide as a solid. ESI-MS m/z [M+H]\(^+\): 269.9.

**Step C: (Z)-7-Fluoro-N\(^{\text{-}}\)hydroxydibenzo[\(b,f\)]thiepine-3-carboximidamide 5-oxide**
A mixture of 7-fluorodibenzo [b,f]thiopine-3-carbonitrile 5-oxide (75 mg, 0.28 mmol), hydroxylamine hydrochloride (77 mg, 1.1 mmol) and triethylamine (0.155 mL, 1.11 mmol) in EtOH (10 mL) was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, then diluted with H2O (20 mL). The aqueous mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na2SO4, and concentrated under reduced pressure to give (Z)-7-fluoro-N-hydroxydibenzo [b,f]thiopine-3-carboximidamide 5-oxide as a white solid. ESI-MS m/z [M+H]+: 303.0.

**Step D: 3-Fluoro-7-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f]thiopine 5-oxide**

![Chemical Structure]

2,2,2-Trifluoroacetic anhydride (0.388 mL, 2.75 mmol) was added to a stirred mixture of potassium carbonate (76 mg, 0.55 mmol) and (Z)-7-fluoro-N-hydroxydibenzo[b,f]thiopine-3-carboximidamide 5-oxide (83 mg, 0.28 mmol) in 1,4-dioxane (10 mL) at 25 °C and the mixture was stirred at 25 °C for 16 h. Water (20 mL) was added and the aqueous mixture was extracted with ethyl acetate (30 ml x 2). The combined organic layers were washed with brine (20 mL), dried over Na2SO4, filtered and concentrated. The residue was purified by reverse prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Phenomenex Synergi C18 150x30mmx4um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 55-85%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 3-fluoro-7-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f]thiopine 5-oxide as a solid. 1H NMR (400 MHz, CDCl3): δ 8.62 (s, 1H), 8.14 (d, J=7.8 Hz, 1H), 7.66 (dd, J=2.3, 7.8 Hz, 1H), 7.49 (d, J=8.2 Hz, 1H), 7.36 (dd, J=5.1, 8.2 Hz, 1H), 7.22 - 7.15 (m, 2H), 7.11 (dt, J=2.3, 8.0 Hz, 1H); ESI-MS m/z [M+H]+: 381.0.

**EXAMPLE 19**

![Chemical Structure]

3-(5-(Pyridin-3-yl)thiophen-2-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole

**Step A: 5-(Pyridin-3-yl)thiophene-2-carbonitrile**

- 59 -
To a glass vial containing a magnetic stir bar is added the 5-bromothiophene-2-carbonitrile (200 mg, 1.06 mmol) and the vial is purged with argon. To the vial was added a solution of Pd(PPh₃)₄ (24.6 mg, 0.021 mmol) in dimethoxyethane (2 mL) and sodium carbonate (1.06 mL, 2.13 mmol) (2M), and the vial was once again purged with argon. The resultant solution was stirred at room temperature for 5 min when a slurry/solution of pyridin-3-ylboronic acid (157 mg, 1.28 mmol) in EtOH (2 mL) was added, the vial was purged with argon and capped, and the mixture was heated at 90 °C and stirred for 1 h. The solution was cooled to room temperature and filtered through a pad of Celite (washing with dichloromethane, 50 mL) into a flask containing anhydrous magnesium sulfate (5 g). The solution was dried for 10 min and filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®, 4g SepaFlash® Silica Flash Column, Eluent of 0–50% EA/PE gradient @ 40 ml/min) to give 5-(pyridin-3-yl)thiophene-2-carbonitrile as a solid. ESI-MS m/z [M+H]⁺: 187.0.

**Step B:** \((Z)-N^\text{1}-\text{Hydroxy-5-}(\text{pyridin-3-yl})\text{thiophene-2-carboximidamide}

\[
\begin{align*}
\text{N} & \text{O} \\
\text{N} & \text{H}_2
\end{align*}
\]

A mixture of 5-(pyridin-3-yl)thiophene-2-carbonitrile (270 mg, 1.45 mmol), hydroxylamine hydrochloride (302 mg, 4.35 mmol) and triethylalmine (0.606 mL, 4.35 mmol) in EtOH (10 mL) was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, then diluted with H₂O (20 mL). The water layer was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated under reduced pressure to give \((Z)-N^\text{1}-\text{hydroxy-5-}(\text{pyridin-3-yl})\text{thiophene-2-carboximidamide as a white solid. ESI-MS m/z [M+H]⁺:} \ 220.0.

**Step C:** 3-(5-(Pyridin-3-yl)thiophen-2-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole

\[
\begin{align*}
\text{N} & \text{CF}_3 \\
\text{S} & \text{N} - \text{O}
\end{align*}
\]

2,2,2-Trifluoroacetic anhydride (0.986 ml, 6.98 mmol) was added to a mixture of potassium carbonate (193 mg, 1.40 mmol) and \((Z)-N^\text{1}-\text{hydroxy-5-}(\text{pyridin-3-yl})\text{thiophene-2-carboximidamide (153 mg, 0.698 mmol) in 1,4-dioxane (10 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 2.5 h. Water (20 mL) was added and the mixture was extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase prep-HPLC
(preparative HPLC on a GILSON 281 instrument fitted with Phenomenex Synergi C18 150x30mmx4um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 35-95%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 3-(5-(pyridin-3-yl)thiophen-2-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole as a solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.94 (br. s., 1H), 8.60 (d, \(J=3.1\) Hz, 1H), 7.97 (d, \(J=7.8\) Hz, 1H), 7.87 (d, \(J=3.9\) Hz, 1H), 7.48 - 7.38 (m, 2H); LC/MS : MS (ESI) m/z: 297.9 [M+H]\(^+\).

**EXAMPLE 20**

\[
\text{3-(5-(1-Benzyl-1H-1, 2, 3-triazol-4-yl)thiophen-2-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole}
\]

![Chemical Structure](image)

**Step A: 5-(1-Benzyl-1H-1,2,3-triazol-4-yl)thiophene-2-carbonitrile**

A mixture of PdCl\(_2\)(DTBPF) (82 mg, 0.13 mmol), 1-benzyl-4-bromo-1H-1, 2,3-triazole (300 mg, 1.26 mmol), (5-cyanothiophen-2-yl)boronic acid (231 mg, 1.51 mmol) and potassium phosphate tribasic (2.52 ml, 1M) in isopropanol (2 ml) was heated at 85 °C under microwave irradiation for 30 min. The mixture was cooled and partitioned between water (20 ml) and ethyl acetate (30 ml x 2). The combined organic layers were washed with brine (20 ml), dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO\(^\text{®}\); 4 g SepaFlash\(^\text{®}\) Silica Flash Column, Eluent of 0-50% EA/PE gradient @ 35 ml/min) to give 5-(1-benzyl-1H-1, 2, 3-triazol-4-yl)thiophene-2-carbonitrile as a solid. ESI-MS m/z [M+H]\(^+\): 267.0.

**Step B: (Z)-5-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N'-hydroxythiophene-2-carboximidamide**

A mixture of 5-(1-benzyl-1H-1, 2, 3-triazol-4-yl) thiophene-2-carbonitrile (41 mg, 0.15 mmol), hydroxylamine hydrochloride (42.8 mg, 0.616 mmol) and triethylamine (0.107 mL, 0.770 0.770 mmol) in EtOH (5 ml) was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, The residue was diluted with H\(_2\)O (15 ml) and the aqueous mixture was extracted with EtOAc (30 ml x 2). The combined organic layers
were washed with brine (15 mL) and dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give (Z)-5-(1-benzyl-1H-1, 2, 3-triazol-4-yl)-N'-hydroxythiophene-2-carboximidamide (crude) as a solid. ESI-MS m/z [M+H]⁺: 300.0.

5 Step C: 3-(5-(1-Benzyl-1H-1, 2, 3-triazol-4-yl)thiophen-2-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole

\[
\begin{align*}
\text{CF}_3 \\
\text{N} \\
\text{S} \\
\text{N} \\
\text{S} \\
\text{N} \\
\end{align*}
\]

2,2,2-Trifluoroacetic anhydride (0.500 mL, 3.54 mmol) was added to a stirred mixture of potassium carbonate (46.2 mg, 0.334 mmol) and (Z)-5-(1-benzyl-1H-1,2,3-triazol-4-yl)-N'-hydroxythiophene-2-carboximidamide (50 mg, 0.17 mmol) in 1,4-dioxane (10 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 3 h. Water (20 mL) was added and the aqueous mixture was extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (20 ml), dried over Na₂SO₄, filtered and concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Phenomenex Synergi C18 150x30mmx4um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 56-76%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 3-(5-(1-benzyl-1H-1, 2,3-triazol-4-yl)thiophen-2-yl)-5- (trifluoromethyl)-1,2,4-oxadiazole as a solid. ¹H NMR (400 MHz, CDCl₃): δ 7.75 (d, J=3.9 Hz, 1H), 7.60 (s, 1H), 7.33 (br. s., 4H), 7.28 - 7.23 (m, 2H), 5.52 (s, 2H); ESI-MS m/z [M+H]⁺: 378.0.

The following examples in TABLE 1 were prepared according to the identified procedures from the examples above using the appropriate commercially available starting materials.

### TABLE 1

<table>
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<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>Stereochemistry</th>
<th>[M+H]⁺</th>
<th>Procedure (Example)</th>
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<td><img src="image" alt="Structure" /></td>
<td>3-(1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(trifluoromethyl)-1,2,4-</td>
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<td>1 STEP B AND C</td>
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<td>Name</td>
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<td>3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f][thiepine 5,5-dioxide</td>
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<td>10-ethyl-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydrodibenzo[bd][1,4]thiazepine 5,5-dioxide</td>
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<td>3-(1-benzyl-1H-benzo[d][1,2,3]triazol-5-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole</td>
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<td>1, STEPS B AND C</td>
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<td>low ionization</td>
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</tbody>
</table>

**EXAMPLE 32**

5-Phenyl-1-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-1H-imidazol-2-yl)pyrrolidin-2-one

5. **Step A:** Ethyl 2-(2-oxo-5-phenylpyrrolidin-1-yl)oxazole-5-carboxylate

![Ethyl 2-chlorooxazole-5-carboxylate](image)

Ethyl 2-chlorooxazole-5-carboxylate (457 mg, 2.61 mmol) was added to a mixture of 5-phenylpyrrolidin-2-one (350 mg, 2.17 mmol) and sodium hydride (100 mg, 2.61 mmol) in THF (10 mL) at 0 °C, and the resulting mixture was stirred at 15 °C for 17 h. The mixture was diluted with saturated aqueous NH₄Cl solution (20 mL) at 0 °C, then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (saturated, 30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, PE: EA= 2:1 ) to give ethyl 2-(2-oxo-5-phenylpyrrolidin-1-yl)oxazole-5-carboxylate as a solid. ESI-MS m/z [M+H]^+: 301.0.

10. **Step B:** 2-(2-Oxo-5-phenylpyrrolidin-1-yl)-1H-imidazole-5-carboxamide
A mixture of 2-(2-oxo-5-phenylpyrrolidin-1-yl)oxazole-5-carboxylate (200 mg, 0.666 mmol) in a solution of saturated NH₃ in ethanol (30 mL) was stirred at 16 °C for 17 h. The mixture was concentrated under reduced pressure to give 2-(2-oxo-5-phenylpyrrolidin-1-yl)-1H-imidazole-5-carboxamide as a solid.

**Step C: 2-(2-Oxo-5-phenylpyrrolidin-1-yl)-1H-imidazole-5-carbonitrile**

Triethylamine (168 mg, 1.66 mmol) and 2,2,2-trifluoroacetic anhydride (233 mg, 1.11 mmol) were added to a mixture of 2-(2-oxo-5-phenylpyrrolidin-1-yl)-1H-imidazole-5-carboxamide (150 mg, 0.555 mmol) in DCM (4 mL) at 20 °C. The mixture was sealed and heated at 80 °C for 17 h, then cooled and concentrated under reduced pressure. The residue was diluted with H₂O (50 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, PE: EA = 2 : 1) to give 2-(2-oxo-5-phenylpyrrolidin-1-yl)-1H-imidazole-5-carbonitrile as a solid. ESI-MS m/z [M+H]^+: 253.0.

**Step D: (Z)-N'-hydroxy-2-(2-oxo-5-phenylpyrrolidin-1-yl)-1H-imidazole-5-carboximidamide**

A mixture of 2-(2-oxo-5-phenylpyrrolidin-1-yl)-1H-imidazole-5-carbonitrile (90 mg, 0.36 mmol), hydroxylamine hydrochloride (99 mg, 1.4 mmol) and triethylamine (144 mg, 1.43 mmol) in ethanol (15 mL) was heated at 80 °C for 2 h, then cooled and concentrated under reduced pressure. The residue was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give (Z)-N'-hydroxy-2-(2-oxo-5-phenylpyrrolidin-1-yl)-1H-imidazole-5-carboximidamide as a solid.
Step E: 5-Phenyl-1-(5-(trifluoromethyl)-1,2,4-oxadiazo1-3-yl)-1H-imidazol-2-yl)pyrrolidin-2-one

2,2,2-Trifluoroacetic anhydride (155 mg, 0.736 mmol) was added to a mixture of (Z)-N'-hydroxy-2-(2-oxo-5-phenylpyrrolidin-1-yl)-1H-imidazole-5-carboximidamide (70 mg, 0.245 mmol) and K$_2$CO$_3$ (102 mg, 0.736 mmol) in dioxane (1.5 mL) at 15 °C. The resulting mixture was stirred at 15 °C for 17 h, then partitioned between water (8 mL) and EtOAc (10 mL x 3). The combined organic layers were washed with brine (8 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0–10% EA/PE gradient @ 40 mL/min) to give 5-phenyl-1-(5-(trifluoromethyl)-1,2,4-oxadiazo1-3-yl)-1H-imidazol-2-yl)pyrrolidin-2-one as a solid. $^1$H NMR (400 MHz, CDCl$_3$): δ ppm 3.12 - 2.52 (m, 4H), 4.93 (br s, 1H), 7.36 - 7.47 (m, 5H), 7.57 (s, 1H). ESI-MS m/z [M+H]+: 364.1.

EXAMPLE 33

5-Phenyl-1-(2-(5-(trifluoromethyl)-1,2,4-oxadiazo1-3-yl)thiazol-5-yl)pyrrolidin-2-one

Step A: Ethyl 5-(2-oxo-5-phenylpyrrolidin-1-yl)thiazo1e-2-carboxylate

A solution of 5-phenylpyrrolidin-2-one (500 mg, 3.10 mmol), ethyl 5-bromothiazo1e-2-carboxylate (732 mg, 3.10 mmol), copper(I) iodide (59.1 mg, 0.310 mmol), N1,N2-dimethylcyclohexane-1,2-diamine (44.1 mg, 0.310 mmol), and K$_2$CO$_3$ (1715 mg, 12.41 mmol) in
dioxane (8 mL) was heated under nitrogen in a sealed tube at 125 °C for 18 h. The mixture was cooled, diluted with water (20 mL), and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, and concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a Gilson 281 instrument fitted with Agela ASB 150*25mm*5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 31-61%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give ethyl 5-(2-oxo-5-phenylpyrrolidin-1-yl) thiazole-2-carboxylate as a solid. ESI-MS m/z [M+H]+: 317.0.

5-Phenyl-1-(2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiazol-5-yl)pyrrolidin-2-one

The title compound, 5-phenyl-1-(2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiazol-5-yl)pyrrolidin-2-one, was prepared from ethyl 5-(2-oxo-5-phenylpyrrolidin-1-yl)thiazole-2-carboxylate in analogy to the procedures described for the preparation of Example 32, steps B through E. 1H NMR (400 MHz, CD₃OD) δ 7.46 - 7.40 (m, 1H), 7.38 - 7.30 (m, 2H), 7.38 - 7.30 (m, 1H), 7.38 - 7.30 (m, 1H), 7.38 - 7.30 (m, 1H), 5.52 (dd, J=3.5, 8.3 Hz, 1H), 2.96 - 2.71 (m, 1H), 2.96 - 2.71 (m, 1H), 2.20 - 2.11 (m, 1H). ESI-MS m/z [M+H]+: 381.0.

EXAMPLE 34

3-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole

Step A: 4-Bromo-3-methyl-1-phenyl-1H-pyrazole

A mixture of K₂CO₃ (858 mg, 6.21 mmol), 4-bromo-3-methyl-1H-pyrazole (500 mg, 3.11 mmol) and (2-bromoethyl)benzene (690 mg, 3.73 mmol) in DMF (20 mL) was stirred at 15 °C for 16 h. The mixture was partitioned between and H₂O (100 mL) and EtOAc (3 x 50 mL).
The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCOS®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% EtOAc/PE gradient @ 20 mL/min) to give 4-bromo-3-methyl-1-phenethyl-1H-pyrazole as an oil. ESI-MS m/z [M+H]⁺: 264.9/266.9.

**Step B: 3-Methyl-1-phenethyl-1H-pyrazole-4-carbonitrile**

\[
\text{\begin{center}
\includegraphics[width=0.3\textwidth]{molecule.png}
\end{center}}
\]

A mixture of 4-bromo-3-methyl-1-phenethyl-1H-pyrazole (180 mg, 0.679 mmol), Zn(CN)₂ (96 mg, 0.82 mmol) and bis(tri-tert-butylphosphine)palladium(0) (35 mg, 0.068 mmol) in NMP (5 mL) was heated at 150 °C for 30 mins under microwave irradiation. The mixture was cooled, diluted with H₂O (50 mL), and extracted with ethyl acacetate (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give 3-methyl-1-phenethyl-1H-pyrazole-4-carbonitrile as an oil. ESI-MS m/z [M+H]⁺: 212.1.

**Step C: (Z)-N'-Hydroxy-3-methyl-1-phenethyl-1H-pyrazole-4-carboximidamide**

\[
\text{\begin{center}
\includegraphics[width=0.3\textwidth]{molecule.png}
\end{center}}
\]

A mixture of triethylamine (0.104 mL, 1.14 mmol), hydroxylamine hydrochloride (79 mg, 1.1 mmol) and 3-methyl-1-phenethyl-1H-pyrazole-4-carbonitrile (120 mg, 0.568 mmol) in EtOH (8 mL) was heated at 80 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. The residue was diluted with H₂O (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give (Z)-N'-hydroxy-3-methyl-1-phenethyl-1H-pyrazole-4-carboximidamide as an oil.

**Step D: 3-(3-Methyl-1-phenethyl-1H-pyrazol-4-yl)-5-( trifluoromethyl)-1,2,4-oxadiazole**

\[
\text{\begin{center}
\includegraphics[width=0.3\textwidth]{molecule.png}
\end{center}}
\]
A mixture of (Z)-N'-hydroxy-3-methyl-1-phenethyl-1H-pyrazole-4-carboximidamide (125 mg, 0.512 mmol), K₂CO₃ (141 mg, 1.02 mmol) and TFAA (0.217 mL, 1.53 mmol) in dioxane (10 mL) was stirred at 15 °C for 16 h. The mixture was partitioned between ethyl acetate (50 mL) and water (30 mL). The organic layer was washed with brine (30 mL), dried over Na₂SO₄, and concentrated. The residue was purified by SFC (Column: OJ(250mm x 30mm, 5μm), mobile phase: A: CO₂ B: Methanol (0.1%NH₃·H₂O EtOH), gradient: from 10% to 40% of B in 5.5 min and hold 10% for 3 min, then 5% of B for 1.5 min flow rate: 2.5mL/min, column temperature: 40 °C) to give 3-(3-methyl-1-phenethyl-1H-pyrazol-4-yl)-5-(trifluoromethyl)-1,2,4-oxadiazone as an oil. ¹H NMR (400 MHz, CD₃OD) δ 8.01 (s, 1H), 7.24 - 7.17 (m, 3H), 7.01 (dd, J=2.0, 7.2 Hz, 2H), 4.90 (s, 2H), 4.37 (t, J=6.6 Hz, 2H), 3.12 (t, J=6.6 Hz, 2H), 2.13 (s, 3H). ESI-MS m/z [M+H]⁺: 323.1.

**EXAMPLE 35**

3-(2-Benzylimidazo[1,2-a]pyridin-7-yl)-5-(trifluoromethyl)-1,2,4-oxadiazone

Step A: 2-(Chloromethyl)imidazo[1,2-a]pyridine-7-carbonitrile

1,3-Dichloropropan-2-one (1.39 g, 10.9 mmol) was added to a mixture of 2-aminoisonicotinonitrile (1.00 g, 8.39 mmol) in EtOH (5 mL) and DME (6 mL). The resulting mixture was stirred at 25 °C for 1 h, then heated at 90 °C for 16 h. The mixture was cooled and concentrated under reduced pressure. The residue was partitioned between water (50 mL) and EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give 2-(chloromethyl)imidazo [1,2-a] pyridine-7-carbonitrile as an oil. MS (ESI) m/z [M+H]⁺: 192.1.

Step B: 2-Benzylimidazo[1,2-a]pyridine-7-carbonitrile
To a solution of K$_2$CO$_3$ (216 mg, 1.57 mmol), phenylboronic acid (127 mg, 1.04 mmol) and 2-(chloromethyl)imidazo[1,2-a]pyridine-7-carbonitrile (100 mg, 0.522 mmol) in a mixture of dioxane (2 mL) and water (0.5 mL) was added Pd(PPh$_3$)$_2$Cl$_2$ (60 mg, 0.052 mmol) at 25 °C. The resulting mixture was heated at 105 °C for 16 h. The mixture was partitioned between water (30 mL) and DCM (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a Gilson 281 instrument fitted with Waters XSELECT C18 150 x 30mm, 5um using water and acetonitrile as the eluents, mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN), gradient: 10-40%, 0-10 min; 100% B, 10.5-12.5 min; 5% B, 13-15 min) to give 2-benzylimidazo[1,2-a]pyridine-7-carbonitrile as an oil. MS (ESI) m/z [M+H]+: 234.1.

**Step C:** (Z)-2-Benzyl-N'-hydroxyimidazo[1,2-a]pyridine-7-carboximidamide

To a solution of 2-benzylimidazo[1,2-a]pyridine-7-carbonitrile (100 mg, 0.429 mmol) in EtOH (4 mL) was added triethylamine (0.299 mL, 2.14 mmol) and hydroxylamine hydrochloride (89 mg, 1.3 mmol) at 25 °C. The resulting mixture was heated at 80 °C for 1 h, then cooled and concentrated to give the (Z)-2-benzyl-N'-hydroxyimidazo[1,2-a]pyridine-7-carboximidamide as a yellow solid. MS (ESI) m/z [M+H]+: 267.1.

**Step D:** 3-(2-Benzylimidazo[1,2-a]pyridin-7-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole

2,2,2-Trifluoroacetic anhydride (3.53 mL, 12.2 mmol) and K$_2$CO$_3$ (101 mg, 0.732 mmol) was added to a mixture of (Z)-2-benzyl-N'-hydroxyimidazo[1,2-a]pyridine-7-carboximidamide (130 mg, 0.488 mmol) in dioxane (1.5 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 16 h, then partitioned between water (20 mL) and ethyl acetate (3 x 10 mL). The combined
organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by reverse-phase prep-HPLC (preparative HPLC on a Gislon 281 instrument fitted with a Waters XSELECT C18 150 x 30mm, 5µm using water and acetonitrile as the eluents, mobile phase A: water (containing 0.1% TFA, v/v), mobile phase B: acetonitrile, gradient: 23-53% B, 0-10 min; 100% B, 10.5 - 12.5 min; 5% B, 13 -15 min) to give 3-(2- benzylimidazo[1,2-a]pyridin-7-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole as an oil. ¹H NMR (400 MHz, CDCl₃) δ 4.33 (s, 2H) 7.30-7.44 (m, 6H) 7.81 (dd, J=7.0, 1.0 Hz, 1H) 8.34 (d, J=7.0 Hz, 1H) 8.81 (s, 1H). MS (ESI) m/z [M+H]⁺: 345.1.

Assays
Methods for HDAC Enzymatic Assays:

Compound potencies were determined versus HDAC 1, 2, 3, 5, 6, and 8 isoforms with in vitro assays that measured inhibition of cleavage of a Fluor-de-Lys substrate.

HDAC1, 2, 3, and 6 reagents: FLAG-tagged HDACs 1, 2, 3, and 6 were prepared in-house by protein expression in HEK293F cells followed by anti-FLAG affinity purification. Assays were performed with buffer containing 20 mM HEPES, pH 8.0 [Boston BioProducts, catalog #BB-104, 1M stock], 137 mM NaCl [Sigma, catalog #S5150, 5M stock], 2.7 mM KCl [BioChemika, catalog #87526, 4M stock], 1 mM MgCl₂ [Fluka, catalog #63020, 1M stock], and 0.05% BSA (Fraction V) [Invitrogen, catalog #15260, 7.5% stock]. In addition to the above buffer ingredients, TCEP [CalBiochem, catalog #580561, 500 mM stock] was added at a final concentration of 0.5 mM to the buffer for the HDAC6 assays. HDAC 1, 2, 3, and 6 enzymes were run at the final concentrations of 0.3 nM, 1.5 nM, 0.3 nM, and 1.333 nM, respectively. Fluor-de-Lys substrate [BioMol Research Laboratories, catalog #KI-104], used to evaluate enzyme activity, was added at the final concentrations of 20 uM, 40 uM, 20 uM, and 2.5 uM for HDACs 1, 2, 3, and 6. To enable detection of the signal, Developer [BioMol Research Laboratories, catalog #KI-105] was added at a 1:250 dilution to the stop solution, which also included 10 uM SAHA [Sigma, catalog # SML0061] to ensure complete termination of the reaction.

HDAC5 reagents: N-terminal GST tagged HDAC5 was purchased from BPS Bioscience [catalog # 50045]. Assays were performed with buffer containing 20 mM HEPES, pH 8.0 [Boston BioProducts, catalog #BB-104, 1M stock], 137 mM NaCl [Sigma, catalog #S5150, 5M stock], 2.7 mM KCl [BioChemika, catalog #87526, 4M stock], 1 mM MgCl₂ [Fluka, catalog #63020, 1M stock], and 0.05% BSA (Fraction V) [Invitrogen, catalog #15260,
7.5% stock]. The HDAC5 enzyme was run at the final concentration of 0.447 nM. Boc-Lys(TFA)-AMC substrate [Bachem, catalog #I-1985.0050], used to evaluate enzyme activity, was added at the final concentration of 60 uM. To enable detection of the signal, Developer II [BioMol Research Laboratories, catalog #KI-176] was added at a 1:200 dilution to the stop solution, which also included 20 uM trichostatin A (TSA) [Sigma, catalog # T8552] to ensure complete termination of the reaction.

HDAC8 reagents: HDAC8 was purchased from Enzo Life Sciences [catalog # BML-SE145]. Assays were performed with buffer containing 20 mM HEPES, pH 8.0 [Boston BioProducts, catalog #BB-104, 1M stock], 100 mM NaCl [Sigma, catalog #S5150, 5M stock], 20 mM KCl [BioChemika, catalog #87526, 4M stock], 1 mM MgCl2 [Fluka, catalog #63020, 1M stock], 0.05% BSA (Fraction V) [Invitrogen, catalog #15260, 7.5% stock], and 0.1% n-Octyl-β-D-glucopyranoside (N-OG) [Anatrace, catalog #0311, 10% stock]. The HDAC8 enzyme was run at the final concentration of 1.333 nM. Fluor-de-Lys substrate [BioMol Research Laboratories, catalog #KI-178], used to evaluate enzyme activity, was added at the final concentration of 200 uM. To enable detection of the signal, Developer II [BioMol Research Laboratories, catalog #KI-176] was added at a 1:200 dilution to the stop solution, which also included 20 uM SAHA [Sigma, catalog # SML0061] to ensure complete termination of the reaction.

Assay protocol: In brief, compounds were titrated in 100% DMSO via acoustic dispensing directly to the assay plate using the ECHO 550 [Labcyte]. HDAC enzymes at the concentrations indicated above were added in assay buffer to the assay plates containing the compounds using a Combi [Thermo Scientific]. The wells were mixed, and the plates were allowed to pre-incubate at room temperature for 3 hours. After the 3 hours, the appropriate substrate, at the concentrations indicated above, was added to the wells using a Combi. The wells were mixed, and the plates were allowed to incubate at room temperature for 1 hour. After the 1 hour, the appropriate Developer/stop solution was added to the wells using a Combi. The wells were mixed, and the plates were allowed to incubate at room temperature for 1 hour. The plates were then read on the EnVision [Perkin Elmer] using 380 nm excitation and 460 nm emission. Data were analyzed using 4P curve fitting with Activity Base [IDBS] software.

TABLE 2 displays the HDAC inhibitory activity of representative HDAC isoforms for the illustrated examples.
<table>
<thead>
<tr>
<th>Example</th>
<th>HDAC Isoform IC50 (nM)</th>
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<tr>
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<tr>
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<td>Example</td>
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</table>

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.
What is claimed is:

1. A compound of formula (I):

\[
\begin{align*}
\text{F}_3\text{C} & \equiv \text{N} \\
\text{O} & \equiv \text{N} \\
\text{Y} & - \text{R}^1
\end{align*}
\]

(I)

or a pharmaceutically acceptable salt thereof wherein;

Y is a five membered heterocycl1 optionally substituted with 1 to 3 groups of R², or

\[
\begin{align*}
\text{\textsuperscript{\textfrac{1}{2}}}\text{Y} & - \text{R}^1
\end{align*}
\]

is represented by structural formula (a):

(a)

--- represent double bond(s) in the ring which may be present or absent;

R¹ represents \(-\text{C}_{1-6}\)alkyl, \(-(\text{CHR})_p\text{C}_{4-10}\) heterocycl1, \(-(\text{O})\,(\text{CHR})_p\text{C}_{4-10}\) heterocycl1, or \(\text{C}_{6-10}\) aryl, said alkyl, aryl and heterocycl1 optionally substituted with 1 to 3 groups of R²;

X³ and X⁴ independently represent \(-\text{N}\) or \(-\text{CH}-\);

X⁵ represents \(-\text{S}\), \(-\text{SO}\), \(-\text{SO}_2\), \(-\text{N}\), \(-\text{NR}^2\), \(-\text{CH}_2\), or \(-\text{CH}_2-\);

X⁶ and X⁷ independently represent \(-\text{CR}^2\), \(-\text{C}(\text{R}^2)_2\), \(-\text{N}\), or \(-\text{NR}^2\);

R² represents hydrogen, \(-\text{C}_{1-6}\)alkyl, \(-\text{C}(\text{O})\text{OC}_{1-6}\)alkyl, \(-\text{S}(\text{O})_2\text{C}_{6-10}\)aryl, \(-\text{(CH}_2)_n\text{C}_{6-10}\)aryl, said alkyl and aryl optionally substituted with 1 to 3 groups of R²; or

when X⁶ and X⁷ are either \(-\text{CR}^2\), \(-\text{C}(\text{R}^2)_2\), or \(-\text{NR}^2\), then adjacent R² groups of X⁶ and X⁷ can combine with the atoms to which they are attached to form phenyl or C₅-₆heteroaryl said phenyl and heteroaryl optionally substituted with 1 to 3 groups of R²;
G¹ and G² independently may be absent when r is 0, or are selected from -N, -NH, -NC₁₋₆alkyl, -NC(O)C₁₋₆alkyl, -C(O)C₆₋₁₀aryl, -C(O)C₄₋₁₀heterocycyl, -C=O, -CH-, and -CH₂.; said alkyl, aryl and heterocycyl optionally substituted with 1 to 3 groups of Rᵃ;

Rᵃ is selected from the group consisting of C₁₋₆alkyl, halo, CN, =O, -SO₂C₁₋₆alkyl, C₃₋₆cycloalkyl, -C₁₋₆alkylOR, -(CH₂)ₚC₆₋₁₀aryl, -(CH₂)ₚC₅₋₁₀heteroaryl, and -C₁₋₄haloalkyl, said aryl and heteroaryl optionally substituted with 1 to 3 groups of C₁₋₆alkyl,

Each p represents 0-4,

10 each r represents 0-1.

2. The compound according to claim 1 wherein Y is a five membered heterocycyl selected from the group consisting of optionally substituted thiophenyl, thiazolyl, isothiazolyl, isoxazolyl, oxazolyl, imidazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiazadiazolyl, pyrrolidinyl, tetrahydronfuranyl, and furanyl or a pharmaceutically acceptable salt thereof.

3. The compound according to any one of claims 1 and 2 wherein Y is optionally substituted thiophenyl or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1 and 2 wherein Y is optionally substituted isothiazolyl or thiazolyl or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1 and 2 wherein Y is optionally substituted imidazolyl, pyrazolyl, triazolyl, oxadiazolyl, isoxazolyl, oxazolyl, pyrrolidinyl, thiazadiazolyl, tetrahydronfuranyl, and furanyl or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1 to 5 wherein R¹ is optionally substituted -(CHR)pC₄₋₁₀heterocycyl, said heterocycyl selected from the group consisting of optionally substituted pyrrolidinonyl, piperidonyl, morpholinyln, benzimidazolyl, pyridyl, triazolyl, and pyrrolidinyl or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1 wherein \( \frac{3}{2}Y \) is represented by formula (a) and r is 0 for both G¹ and G² or a pharmaceutically acceptable salt thereof.

8. The compound according to claims 1 and 7 wherein r is 0 for both G¹ and G², X⁴ is N, and X³, X⁵, X⁶, and X⁷ together with X⁴ and the other atoms of the ring form a group selected from pyrrolopypyridinyl, said groups optionally substituted with 1 to 3 groups of R² or a pharmaceutically acceptable salt thereof.

9. The compound according to claims 1 and 7 wherein r is 0 for both G¹ and G², X⁴ is -CH₃, X³, X⁵, X⁶, and X⁷ together with X⁴ and the other atoms of the ring form a group selected from indolyl, isoindolyl, benztriazolyl, benzthiazolyl, and benzoxazolyl, said groups optionally substituted with 1 to 3 groups of R² or a pharmaceutically acceptable salt thereof.
10. The compound according to claim 9 wherein R² is selected from the group consisting of CH₃, C(O)OC(CH₃)₃, (CH₂)₃phenyl, S(O)₂phenyl, said phenyl optionally substituted with 1 to 3 groups of R⁸.

11. The compound according to claim 1 wherein \(\frac{3}{2}Y\to R¹\) is represented by formula (a), r is 0 for one of G¹ and G² and 1 for the other, or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 1 and 11 wherein r is 0 for one of G¹ and G² and 1 for the other, X¹ is CH and X³, X⁵, X⁶, and X⁷ together with X⁴ and the other atoms of the ring form a group selected from quinolinyl, isoquinolinyl, dihydroisoquinolinyl, said groups optionally substituted with 1 to 3 groups of R⁸, or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 1 wherein \(\frac{3}{2}Y\to R¹\) is represented by formula (a) where r is 1 for both G¹ and G², or a pharmaceutically acceptable salt thereof.

14. The compound according to claims 1 and 13 wherein r is 1 for both G¹ and G² and G¹, G², X³, X⁴, X⁵, X⁶, and X⁷ combine with the other atoms of the ring to form a group selected from benzothiazepine, dihydridobenzothiazepine dioxide, dihydridobenzothiazepine oxide, dihydridobenzothiazepine oxide, dibenzothiepin dioxide, dibenzothiepin dioxide, and dibenzothiepin dioxide, said groups optionally substituted with 1 to 3 groups of R⁸, or a pharmaceutically acceptable salt thereof.

15. The compound according to any one of claims 1 to 6 represented by structural formula II:

\[
\text{II}
\]

or a pharmaceutically acceptable salt thereof, wherein

\(Y\) is represented by structural formula
and R¹ is as originally described.

16. The compound according to any one of claims 1, 13 and 14 represented by structural formula III:

\[
\begin{array}{c}
\text{III} \\
\text{F₃C=N-O=}[Y-R¹]
\end{array}
\]

or a pharmaceutically acceptable salt thereof, wherein

[Y-R¹] is represented by structural formulas (m), (n) and (o)

\[
\begin{align*}
\text{(m)} & \quad \text{(n)} \\
\text{(o)} & \\
\end{align*}
\]

G¹, G², X⁵ and R²⁰ are as originally described and Z is N or CH.

17. The compound according to any one of claims 1, and 16 wherein [Y-R¹] is (m) and

X⁵, G² and G¹, respectively, are represented as:

1) SO₂, NR³, CH₃;
2) SO₂, NR³, C(O);
3) SO, NR³, CH₃;
4) SO, C(O), NR²; and
5) S, NR², CH₂ or a pharmaceutically acceptable salt thereof.

18. The compound according to claims 16 and 17 wherein [Y-R¹] is (m) is realized when R² is selected from the group consisting of -C₁₆₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋₃₋三分之一
3-(dibenzo[b,f][1,4]thiazepin-3-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole,
7-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydrödibenzo[b,f][1,4] thiazepine 5,5-dioxide,
10-Methyl-7-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f][1,4] thiazepine 11(10H)-one 5-oxide,
(R)-3-Phenyl-4-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiazol-2-yl)morpholine,
3-Fluoro-7-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f]thiepine 5-oxide,
3-(5-(Pyridin-3-yl)thiophen-2-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole,
3-(5-(1-Benzyl-1H-1,2,3-triazol-4-yl)thiophen-2-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole,
3-(1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole,
3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f]thiepine 5,5-dioxide,
9-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzo[6,7]thiepin[2,3-b]pyridine 11,11-dioxide,
3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f][1,4]thiazepin-11(10H)-one 5,5-dioxide,
3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)dibenzo[b,f][1,4]thiazepine 5-oxide,
10-ethyl-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-10,11-dihydrödibenzo[b,f][1,4]thiazepine 5,5-dioxide,
4-phenyl-1-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiophen-2-yl)pyrrolidin-2-one,
3-(1-benzyl-1H-benzo[d][1,2,3]triazol-5-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole,
5-phenyl-1-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiazol-2-yl)pyrrolidin-2-one;
(tetrahydrofuran-2-yl)(6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydrösoquolinolin-
2(1H)-yl)methanone;
3-(2-(methylsulfonyl)-1,2,3,4-tetrahydrosoquolinolin-6-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole;
5-Phenyl-1-(5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-1H-imidazol-2-yl)pyrrolidin-2-one;
5-Phenyl-1-(2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiazol-5-yl)pyrrolidin-2-one;
3-(5-Methyl-1-phenethyl-1H-pyrazol-4-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole;
3-(2-Benzylimidazol[1,2-a]pyridin-7-yl)-5-(trifluoromethyl)-1,2,4-oxadiazole;
or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a compound of any previous claim, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof for use in therapy.

24. The use of a compound of any one of claims 1 to 22 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing a disease ameliorated by modulating HDAC activity.
25. The use of a compound of any one of claims 1 to 22 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing cellular proliferation diseases, neurodegenerative diseases, mental retardation, schizophrenia, inflammatory diseases, restenosis, immune disorders, diabetes, cardiovascular disorders or asthma.

26. A method for treating or preventing cellular proliferation diseases, neurodegenerative diseases, mental retardation, schizophrenia, inflammatory diseases, restenosis, immune disorders, diabetes, cardiovascular disorders or asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound or composition of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof.
### INTERNATIONAL SEARCH REPORT

#### A. CLASSIFICATION OF SUBJECT MATTER
- **IPC(B)**: C07D 413/14, A61K 31/4245, A61K 31/444 (2017.01)
- **CPC**: C07D 413/04, A61K 31/506, A61K 31/4439, C07D 413/14

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#### B. FIELDS SEARCHED
- Minimum documentation searched (classification system followed by classification symbols)
- **See Search History Document**

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 2015/0038534 A1 (Tempero Pharmaceuticals, Inc.) 05 February 2015 (05.02.2015); para [0546]</td>
<td>1.5</td>
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<td>A</td>
<td>WO 2013/066833 A1 (GLAXOSMITHKLINE LLC) 10 May 2013 (10.05.2013); pg. 21, In 7-8</td>
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<td>A</td>
<td>&quot;Pubchem CID 2781559&quot; Create Date: 19 July 2005 (19.07.2005) Date Accessed: 18 August 2017 (18.08.2017); pg. 4, compound listed</td>
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<td>A</td>
<td>WO 2013/008162 A1 (NOVARTIS AG) 17 January 2013 (17.01.2013); entire document</td>
<td>1.5</td>
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<td>A</td>
<td>WO 2013/080120 A1 (NOVARTIS AG) 06 June 2013 (06.06.2013); entire document</td>
<td>1.5</td>
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- **Date of mailing of the international search report**: 27 OCT 2017

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- **Authorized officer**: Lee W. Young
- **PCT Helpdesk**: 571-272-4300
- **PCT Ops**: 571-272-7774

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Form PCT/ISA/210 (second sheet) (January 2015)
INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6, 8-10, 12, 14-20, 22-26
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see supplemental page)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5

Remark on Protest ☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-5, 7, 11, 13 and 21 directed to compounds having the general formula of claim 1, formula (I). The compound of claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by the first formula of claim 1, formula (I), wherein Y is a five membered heterocyclic and R1 is C1 alkyl. It is believed that claims 1-5 read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the *group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, represented by the first formula of claim 1, formula (I), wherein Y-R1 is structural formula a, X3 and X4 are N; X5 is S; X6 and X7 are CR2 and R2 is hydrogen; G1 and G2 are absent; r is 0 (i.e., claims 1 and 7).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula I, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a compound of formula 1.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 2015/336941 A1 to Dart Neuroscience (Cayman) Ltd., (hereinafter Dart). Dart discloses a compound of formula (I) wherein Y is a five membered heterocyclic and R1 is -C(O)(CH)<sub>p</sub>C6 heterocyclic and p is 0 (para [0436]: compound listed).

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Note: Claims 6, 8-10, 12, 14-20, 22-26 have been found to be unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).