

MODULATORS OF MITOCHONDRIAL DNA REPLICATION

PRIORITY CLAIM

[0001] This application claims the benefit of U.S. provisional application no. 63/526,814, filed July 14, 2023, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Embodiments of the invention relate to novel DNA polymerase γ (POL γ) modulators, their pharmaceutically acceptable salts, and pharmaceutical compositions thereof. Embodiments of the invention also relate to methods of using such compounds and compositions, including to modulate POL γ .

BACKGROUND OF THE INVENTION

[0003] Human mitochondria contain multiple copies of a circular, double-stranded (ds) DNA genome (mtDNA), and a dedicated DNA replication machinery is required for maintaining the mitochondrial genome. POL γ is the replicative polymerase essential for maintaining the mtDNA. POL γ is a heterotrimer in human cells with one catalytic subunit (POL γ A) and two accessory subunits (POL γ B). POL γ A belongs to the family A DNA polymerases. POL γ A is 1239 amino acids in length and consists of three distinct regions: an N-terminal exonuclease domain connected by a linker domain to the C-terminal polymerase domain. The accessory POL γ B is 485 amino acids in length and the crystal structures of both mouse and human POL γ B have revealed the protein as a dimer with high similarities to aminoacyl tRNA synthetases. POL γ B acts as a processivity factor, which increases the affinity of the polymerase for DNA and promotes tighter nucleotide binding, thereby increasing the polymerase rate. *See, e.g.,* Gustafsson, C.M., *et al.*, "Maintenance and expression of mammalian mitochondrial DNA," *Annu. Rev. Biochem.*, 85:133-160 (2016) (Gustafsson 2016) and Farge, G., *et al.*, "The accessory subunit B of DNA polymerase γ is required for mitochondrial replisome function," *Nucleic Acids Res.*, 35:902-911 (2007).

[0004] A primary biological role of POL γ is to replicate the mitochondrial genome. However, POL γ cannot replicate the ds mtDNA alone. It acts together with a DNA helicase (TWINKLE) and the mitochondrial single-stranded DNA-binding protein (mtSSB). TWINKLE is 684 amino acids in length and forms a hexamer in solution. TWINKLE travels

in front of POL γ during mtDNA replication, unwinding the dsDNA and creating a single-stranded (ss) DNA template that POL γ can utilize. The mtSSB is 148 amino acids in length and is active as a tetramer. It binds to ssDNA, protects this DNA against nucleases, and prevents secondary structure formation so POL γ can use ssDNA as a template to synthesize dsDNA. The mtSSB enhances mtDNA synthesis by increasing the processivity of POL γ and also stimulates TWINKLE's helicase activity. POL γ cannot initiate DNA synthesis de novo, as it needs a short RNA primer to initiate DNA synthesis. In mitochondria, the mitochondrial RNA polymerase (POLRMT) has a dual function; it acts as an RNA polymerase involved in mtDNA transcription but it also synthesizes the primers needed to initiate mtDNA replication from mitochondrial origins of replication. *See, e.g., Gustafsson 2016.*

[0005] The mitochondrial genome encodes subunits of the oxidative phosphorylation (OXPHOS) system. The OXPHOS system is composed of four respiratory chain complexes, which are responsible for electron transport and generation of the proton gradient across the mitochondrial inner membrane. ATP synthase uses this proton gradient to produce ATP. *See, e.g., id.* The biogenesis of the OXPHOS system is under dual genetic control and requires the concerted expression of nuclear DNA and mtDNA encoded genes. Mitochondria contain multiple copies of ds mtDNA, which encodes 2 ribosomal RNAs (mt-rRNAs), 22 transfer RNAs (mt-tRNAs), and 11 messenger RNAs (mt-mRNAs) producing 13 protein subunits of OXPHOS complexes I, III, IV, and ATP synthase (sometime referred to as complex V). The biogenesis of the OXPHOS system is critically dependent on the mtDNA-encoded subunits as they typically have key catalytic roles or are core subunits for OXPHOS assembly. Similar to the nuclear genome, expression of mammalian mtDNA requires several essential steps, including genome maintenance, replication, transcription, RNA maturation, and translation. All proteins involved in these processes are encoded in the nuclear genome, translated in the cytosol, and imported into the mitochondrial network. It is estimated that approximately one quarter of the ~1200 nucleus-encoded mitochondrial proteins are devoted to the control of mtDNA gene expression in mammals. *See, e.g., Shokolenko, I.N., et al., "Mitochondrial transcription in mammalian cells," Front. Biosci. (Landmark Ed.), 22:835-853 (2017).* POL γ is required for mtDNA synthesis and is thus essential for biogenesis of the OXPHOS system, resulting in ATP production. ATP production is in turn vital for energy homeostasis in the cell.

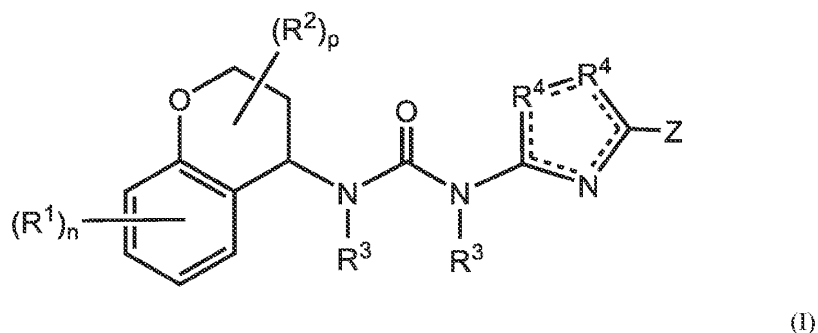
[0006] There are over 300 POL γ mutations correlated to a broad clinical spectrum of neurodegenerative and mitochondrial diseases. *See, e.g., Rahman, S., et al., "POLG-related disorders and their neurological manifestations," Nat. Rev. Neurol., 15:40-52 (2019) (Rahman 2019).* Many disease-causing variants of POL γ are associated with decreased replication processivity of the mtDNA replication machinery, leading to replication stalling.

[0007] In view of the numerous and varied roles of POL γ , the need exists for potent and specific compounds that increase the processivity of POL γ .

SUMMARY OF THE INVENTION

[0008] Provided are compounds, pharmaceutically acceptable salts of the compounds, and pharmaceutical compositions comprising the compounds or their salts for increasing the processivity of POL γ .

[0009] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (I):



wherein:

R¹ is selected from the group consisting of H, C₁-C₃ alkyl, Cl, F, CN, and O-C₁-C₆ alkyl optionally substituted with one or more halogen;

R² is H or C₁-C₃ alkyl optionally substituted with OR⁵;

R³ is each independently H or C₁-C₄ alkyl optionally substituted with one or more halogen or OH;

R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;

Z is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkene, NR⁵R⁶, SR⁵, C(O)R⁵, C(O)R⁷, C(O)OR⁵, C(O)NR⁵R⁶, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, aryl-heterocyclyl, aryl-heteroaryl, and sulfonamide, wherein the C₁-C₆ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, phenyl, OR⁵, halogen, C(O)NR⁵R⁶, NR⁵R⁶, NR⁵-C(O)CH₃, SO₂R⁵, NH-SO₂R⁵, heterocyclyl, aryl, heteroaryl, and aryl-heteroaryl, wherein cycloalkyl is optionally substituted with one or more groups each independently selected from the group consisting of F, C₁-C₃ alkyl-OH, C₁-C₃ alkyl-O-C₁-C₃ alkyl, C(O)OR⁵, C(O)NR⁵R⁵, NR⁵R⁵, and NR⁵-C(O)CH₃, wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR⁵, keto, C₃-C₆ cycloalkyl, C(O)CH₃, C(O)NR⁵R⁵, NH-C(O)R⁵, NH-SO₂R⁵, and C₁-C₄ alkyl that is optionally substituted with one or more F or OH, wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

- C₁-C₄ alkyl that is optionally substituted with one or more groups each independently selected from the group consisting of F, OH, and NR⁵R⁶,
- C₃-C₆ cycloalkyl that is substituted with NR⁵R⁶,
- halogen,
- CN,
- OR⁵,
- C(O)NR⁵R⁶,
- NR⁵R⁶,
- SO₂R⁶,
- SO₂NR⁵R⁶,
- SO(NH)R⁵,
- S(NR)(NH)R⁵,
- P(O)R⁵R⁵, and
- 4- or 5,6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more groups

independently selected from the group consisting of F, Cl, OR⁵, CN, C₁-C₄ alkyl, oxo, and NR⁵R⁶,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, C(O)NR⁵R⁶, OR⁵, NR⁵R⁶, oxo, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₄ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, OR⁵, and C(O)NR⁵R⁶; wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with a group selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁-C₅ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₅ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

R⁷ is cycloalkyl optionally substituted with one or more halogens;

n is 1-4;

p is 1-2;

with the proviso that a compound selected from the group consisting of:

(*S*)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2*H*-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea,

and

1-(5-cyclopropylthiazol-4-yl)-3-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)urea, is excluded.

[0010] Further embodiments of the present invention are compounds of formula (I) and their pharmaceutically acceptable salts wherein one or more hydrogen is substituted with a deuterium atom.

[0011] Additional embodiments of the invention are pharmaceutical compositions comprising a compound of the invention, a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0012] The term “alkyl” as used herein refers to both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms in a specified range. For example the term “C₁-C₇ alkyl” means linear or branched chain alkyl groups, including all possible isomers, having 1, 2, 3, 4, 5, 6, or 7 carbon atoms. Furthermore, alkyl groups allow for substituents to be located on any of the carbon atoms. For example, a substituted C₃ alkyl group allows for the substituent to be located on any one, or more, of the three carbon atoms.

[0013] The term “alkoxy” or “alkoxyl” as used herein refers to an -O-alkyl group. For example, the term “C₁-C₄ alkoxy” means -O-C₁-C₄ alkyl. In certain embodiments, alkoxy may be represented by “OR” wherein R is an optionally substituted alkyl group. Examples of alkoxy include methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), and the like.

[0014] The term “azole” as used herein refers to a class of five-membered heterocyclic compounds containing a nitrogen atom and at least one other non-carbon atom (i.e., nitrogen, sulfur, or oxygen) as part of the ring. Examples of azole rings include, but not limited to, pyrrole, furazan, pyrazole, thiazole, oxazole, triazole, thiadiazole, oxadiazole, imidazole, 1,2 pyrazole, 2,3 thiazole, 2,4 thiazole, 2,3 oxazole, 1,2,4 triazole, 1,2,4 thiadiazole, and 1,2,4 oxadiazole.

[0015] The term “halogen” or “halo” as used herein refers any of the six nonmetallic elements that constitute Group 17 (Group VIIa) of the periodic table. The halogen elements include, but are not limited to, fluorine or fluoro (F), chlorine or chloro (Cl), bromine or bromo (Br), and iodine or iodo (I).

[0016] The term “cycloalkyl” as used herein refers to a completely saturated or partially unsaturated cyclic group that includes monocyclic or multicyclic ring system. In certain embodiments, cycloalkyl groups contain 3 to 14 carbon atoms in the ring system (“C₃-C₁₄ cycloalkyl”). In certain embodiments, each of the cycloalkyl rings may contain one or more

double or triple bonds. Examples of cycloalkyl include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.0]hexane, octahydro-1*H*-indene, decahydronaphthalene, and tetradecahydroanthracene.

[0017] The term “heterocyclyl” refers to a cycloalkyl group, as described above, in which at least one or more heteroatoms are present in a ring that includes, but is not limited to, nitrogen (N), oxygen (O), and sulfur (S) atoms, wherein the heteroatom may be oxidized, e.g., NO, SO, SO₂, SO₄, and the N may be quaternized. In certain embodiments, heterocyclyl groups contain 3 to 14 atoms in the ring system (“3- to 14-membered heterocyclyl”). Heterocyclyl can be attached to the core structure via a ring carbon atom or a ring heteroatom. Typical monocyclic heterocyclyl rings include, but are not limited to, azetidiny, pyrrolidyl, oxetanyl, pyrazoliny, imidazoliny, imidazolidiny, oxazolidiny, isoxazolidiny, thiazolidiny, isothiazolidiny, tetrahydrofuryl, piperidyl, piperaziny, hexahydroazepiny, 4-piperidonyl, tetrahydropyrany, morpholiny, thiomorpholiny, 1,3-dioxany, and tetrahydro-1,1-dioxythienyl.

[0018] The term “aryl” as used herein refers to a monocyclic or multicyclic ring system having the characteristics of a conjugated pi-electron system. In certain embodiments, aryl groups contain 4 to 14 carbon atoms in the ring system (“C₄-C₁₄ aryl”). Fused aryl groups may include an aryl ring (e.g., a phenyl ring) fused to another aryl ring. Examples, without limitation, of aryl groups include phenyl, biphenyl, naphthalenyl, anthracenyl, and phenantherenyl.

[0019] The term “heteroaryl” or “heteroaromatic” as used herein refers to an aryl group, as described above, containing one or more heteroatoms that includes, but is not limited to, N, O, and S atoms, wherein the heteroatom may be oxidized, e.g., NO, SO, SO₂, SO₄, and the N may be quaternized. In certain embodiments, heteroaryl or heteroaromatic groups contain 4 to 14 atoms in the ring system (“4- to 14-membered heteroaryl”). Examples, without limitation, include pyridyl, pyrrolyl, pyraziny, pyrimidiny, pyridaziny, triaziny, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl (*i.e.*, 1,2,3-triazolyl or 1,2,4-triazolyl), tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl (*i.e.*, 1,2,3-, 1,2,4-, 1,2,5-(furazanyl), or 1,3,4-isomers), oxatriazolyl, thiazolyl, isothiazolyl, thiadiazolyl, benzofuran, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoxadiazolyl, benzpyraziny, indolyl,

indazolyl, indoliziny, pteridiny, puriny, phthalaziny, quinazoliny, quinoliny, and quinoliziny.

[0020] The term “aryl-cycloalkyl” as used herein refers to an aryl group, as defined above, that is fused to a cycloalkyl group, as defined above, by any two or more atoms in the ring. In certain embodiments, aryl-cycloalkyl groups contain 6 to 14 atoms in the ring system (“6- to 14-membered aryl-cycloalkyl”). Aryl-cycloalkyl can be attached to the core structure via a ring carbon atom on the aryl ring or on the cycloalkyl ring. Examples of aryl-cycloalkyl include, but are not limited to, indane, indene, tetrahydronaphthalene, 1,4-dihydronaphthalene, and bicyclo[4.2.0]octa-1,3,5-triene.

[0021] The term “aryl-heteroaryl” as used herein refers to an aryl group, as defined above, that is fused to a heteroaryl group, as defined above. Examples of aryl-heteroaryl include quinoline, quinazoline, quinoxaline, and benzofuran.

[0022] The term “heteroaryl-cycloalkyl” as used herein refers to a heteroaryl group, as defined above, which is fused to a cycloalkyl group, as defined above, by any two or more atoms in the ring. In certain embodiments, heteroaryl-cycloalkyl groups contain 6 to 14 atoms in the ring system (“6- to 14-membered heteroaryl-cycloalkyl”). Heteroaryl-cycloalkyl can be attached to the core structure via a ring carbon atom or heteroatom on the aryl ring or via a carbon atom on the cycloalkyl ring. Examples of heteroaryl-cycloalkyl include, but are not limited to, 1,4,5,6-tetrahydrocyclopenta[b]pyrrole, 4,5,6,7-tetrahydro-1*H*-indole, 2,3-cyclopentenopyridine, and 5,6,7,8-tetrahydroquinoline.

[0023] The term “aryl-heterocyclyl” as used herein refers to an aryl group, as defined above, which is fused to a heterocyclyl group, as defined above, by any two or more atoms in the ring. In certain embodiments, aryl-heterocyclyl groups contain 6 to 14 atoms in the ring system (“6- to 14-membered aryl-heterocyclyl”). Aryl-heterocyclyl can be attached to the core structure via a ring carbon atom on the aryl ring or a ring carbon atom or heteroatom on the heterocyclyl ring. Examples of aryl-heterocyclyl include, but are not limited to, benzopyran, chromane, 4*H*-chromene, isochromane, thiochromane, isothiochromane, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, 2,3-dihydrobenzofuran, 1,3-dihydroisobenzofuran, 2,3-dihydrobenzo[b]thiophene, 1,3-dihydrobenzo[c]thiophene, indoline, isoindoline, and benzdioxane.

[0024] The term “heteroaryl-heterocyclyl” as used herein refers to a heteroaryl group, as defined above, which is fused to a heterocyclyl group, as defined above, by any two or more atoms in the ring. In certain embodiments, heteroaryl-heterocyclyl groups contain 6 to 14 atoms in the ring system (“6- to 14-membered heteroaryl-heterocyclyl”). Heteroaryl-heterocyclyl can be attached to the core structure via a ring carbon atom or heteroatom on the aryl ring or a ring carbon atom or heteroatom on the heterocyclyl ring. Examples of aryl-heterocyclyl include, but are not limited to 2,3-dihydro-1 λ^2 ,6 λ^2 -pyrrolo[2,3-*b*]pyrrole, 4,7-dihydro-5*H*-1 λ^2 ,6 λ^2 -pyrrolo[2,3-*c*]pyridine, 5,7-dihydro-6 λ^2 -pyrrolo[3,4-*b*]pyridine, and 3,4-dihydro-2*H*-1 λ^2 -1,8-naphthyridine.

[0025] The term “optionally substituted” or “optional substituents” as used herein means that the groups are either unsubstituted or substituted with one or more of the substituents specified. When the groups are substituted with more than one substituent, the substituents may be the same or different. Furthermore, when using the terms “independently,” “independently are,” and “independently selected from” means that the groups may be the same or different.

[0026] The term “deuterium” as used herein refers to an isotope of hydrogen that has one proton and one neutron in its nucleus and that has twice the mass of ordinary hydrogen. Deuterium herein is represented by the symbol “D”.

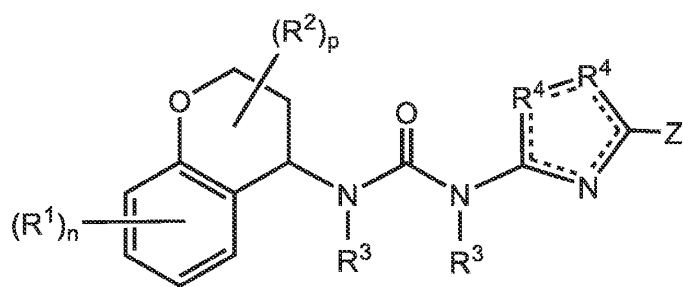
[0027] The term “deuterated” by itself or used to modify a compound or group as used herein refers to the presence of at least one deuterium atom attached to carbon. For example, the term “deuterated compound” refers to a compound which contains one or more carbon-bound deuterium(s). In a deuterated compound of the present invention, when a particular position is designated as having deuterium, it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015%.

[0028] The term “undeuterated” or “non-deuterated” as used herein refers to the ratio of deuterium atoms of which is not more than the natural isotopic deuterium content, which is about 0.015%; in other words, all hydrogen are present at their natural isotopic percentages. Unless otherwise stated, when a position is designated specifically as “H” or “hydrogen”, the position is understood to have hydrogen at its natural abundance isotopic composition.

[0029] The term “pharmaceutically acceptable salt” as used herein refers to a salt that is not biologically or otherwise undesirable (*e.g.*, not toxic or otherwise harmful). A salt of a compound of the invention is formed between an acid and a basic group of the compound, or a base and an acidic group of the compound. For example, when the compounds of the invention contain at least one basic group (*i.e.*, groups that can be protonated), the invention includes the compounds in the form of their acid addition salts with organic or inorganic acids such as, for example, but not limited to, salts with hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, benzenesulfonic acid, acetic acid, citric acid, glutamic acid, lactic acid, and methanesulfonic acid. When compounds of the invention contain one or more acidic groups (*e.g.*, a carboxylic acid), the invention includes the pharmaceutically acceptable salts of the compounds formed with, but not limited to, alkali metal salts, alkaline earth metal salts or ammonium salts. Examples of such salts include, but are not limited to, sodium salts, potassium salts, calcium salts, magnesium salts, or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine, or amino acids. Additional examples of such salts can be found in Stahl, P. H. *et al.*, Handbook of Pharmaceutical Salts: Properties, Selection, and Use, 2nd Revised Edition, Wiley, 2011.

Compounds

[0030] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (I):



(I)

wherein:

R^1 is selected from the group consisting of H, C_1 - C_3 alkyl, Cl, F, CN, and O- C_1 - C_6 alkyl optionally substituted with one or more halogen;

R^2 is H or C_1 - C_3 alkyl optionally substituted with OR^5 ;

R^3 is each independently H or C_1 - C_4 alkyl optionally substituted with one or more halogen or OH;

R^4 is $C-R^5$ or S, wherein one R^4 is $C-R^5$ and the other R^4 is S;

Z is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkene, NR^5R^6 , SR^5 , $C(O)R^5$, $C(O)R^7$, $C(O)OR^5$, $C(O)NR^5R^6$, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, aryl-heterocyclyl, aryl-heteroaryl, and sulfonamide, wherein the C_1 - C_6 alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, phenyl, OR^5 , halogen, $C(O)NR^5R^6$, NR^5R^6 , $NR^5-C(O)CH_3$, SO_2R^5 , $NH-SO_2R^5$, heterocyclyl, aryl, heteroaryl, and aryl-heteroaryl, wherein cycloalkyl is optionally substituted with one or more groups each independently selected from the group consisting of F, C_1 - C_3 alkyl-OH, C_1 - C_3 alkyl-O- C_1 - C_3 alkyl, $C(O)OR^5$, $C(O)NR^5R^5$, NR^5R^5 , and $NR^5-C(O)CH_3$, wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5 , keto, C_3 - C_6 cycloalkyl, $C(O)CH_3$, $C(O)NR^5R^5$, $NH-C(O)R^5$, $NH-SO_2R^5$, and C_1 - C_4 alkyl that is optionally substituted with one or more F or OH, wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

- C_1 - C_4 alkyl that is optionally substituted with one or more groups each independently selected from the group consisting of F, OH, and NR^5R^6 ,
- C_3 - C_6 cycloalkyl that is substituted with NR^5R^6 ,
- halogen,
- CN,
- OR^5 ,
- $C(O)NR^5R^6$,
- NR^5R^6 ,
- SO_2R^6 ,
- $SO_2NR^5R^6$,

SO(NH)R⁵,
 S(NR)(NH)R⁵,
 P(O)R⁵R⁵, and

4- or 5,6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more groups independently selected from the group consisting of F, Cl, OR⁵, CN, C₁-C₄ alkyl, oxo, and NR⁵R⁶,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, C(O)NR⁵R⁶, OR⁵, NR⁵R⁶, oxo, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₄ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, OR⁵, and C(O)NR⁵R⁶; wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with a group selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁-C₅ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₅ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

R⁷ is cycloalkyl optionally substituted with one or more halogens;

n is 1-4;

p is 1-2;

with the proviso that a compound selected from the group consisting of:

(S)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2H-pyran-4-yl)thiazol-2-yl)urea,
 1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,
 1-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea,
 and
 1-(5-cyclopropylthiazol-4-yl)-3-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)urea, is excluded.

[0031] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (I) wherein:

R^1 is selected from the group consisting of H, Cl, F, and O- C_1 alkyl optionally substituted three halogens;

R^2 is H;

R^3 is H;

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;

Z is selected from the group consisting of C_1 - C_3 alkyl, C_2 alkene, NR^5R^6 , SR^5 , $C(O)R^5$, $C(O)R^7$, $C(O)OR^5$, $C(O)NR^5R^6$, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, and sulfonamide,

wherein the C_1 - C_3 alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, cyclobutyl optionally substituted with one or more F, OR^5 , halogen, NR^5R^6 , and $NH-SO_2R^5$,

wherein cycloalkyl is optionally substituted with one or more groups each independently selected from the group consisting of F, CH_2-OH , CH_2-O-CH_3 , and $C(O)OR^5$,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5 , and C_1 alkyl optionally substituted with one or more F,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C_1 - C_3 alkyl that is optionally substituted with NR^5R^6 ,

halogen,

CN,

OR^5 ,

$C(O)NR^5R^6$,

SO_2R^6 ,

$SO_2NR^5R^6$,

$SO(NH)R^5$,

$S(NR)(NH)R^5$,

$P(O)R^5R^5$, and

5-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more oxo,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, cyclobutyl optionally substituted with one or more OH or F, CN, C(O)NR⁵R⁶, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₃ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, and OR⁵;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with one or more groups selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

R⁷ is cyclobutyl optionally substituted with one or more halogens;

n is 1;

p is 1;

with the proviso that a compound selected from the group consisting of:

(S)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2H-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea,

and

1-(5-cyclopropylthiazol-4-yl)-3-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)urea, is

excluded.

[0032] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (I) wherein:

R¹ is selected from the group consisting of H, Cl, and F;

R² is H;

R³ is H;

R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;

Z C₁-C₃ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, OR⁵, halogen, and NR⁵R⁶,
 R⁵ is independently H or C₁ alkyl;
 R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;
 n is 1; and
 p is 1.

[0033] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (I) wherein:

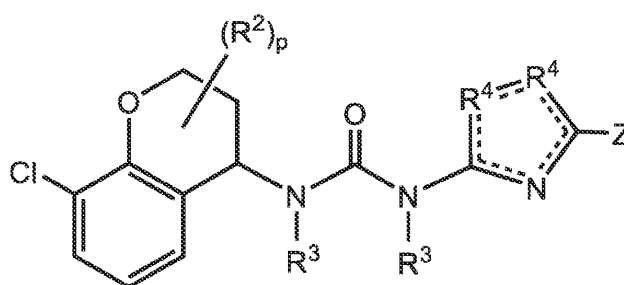
R¹ is selected from the group consisting of H, Cl, and F;
 R² is H;
 R³ is H;
 R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;
 Z is aryl substituted with one or more groups selected from the group consisting of:
 halogen,
 C(O)NR⁵R⁶, and
 SO₂NR⁵R⁶;
 R⁵ is independently H or C₁ alkyl;
 R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;
 n is 1; and
 p is 1.

[0034] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (I) wherein:

R¹ is selected from the group consisting of H, Cl, and F;
 R² is H;
 R³ is H;
 R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;

Z heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR⁵, and C₁ alkyl optionally substituted with one or more F, R⁵ is independently H or C₁ alkyl;
 n is 1; and
 p is 1.

[0035] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II):



(II)

wherein:

R² is H or C₁-C₃ alkyl optionally substituted with OR⁵;

R³ is each independently H or C₁-C₄ alkyl optionally substituted with one or more halogen or OH;

R⁴ is C-R⁵ or S, wherein one R³ is C-R⁵ and the other R³ is S;

Z is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkene, NR⁵R⁶, SR⁵, C(O)R⁵, C(O)R⁷, C(O)OR⁵, C(O)NR⁵R⁶, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, aryl-heterocyclyl, and aryl-heteroaryl,

wherein the C₁-C₆ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, phenyl, OR⁵, halogen, C(O)NR⁵R⁶, NR⁵R⁶, NR⁵-C(O)CH₃, SO₂R⁵, NH-SO₂R⁵, heterocyclyl, aryl, heteroaryl, and aryl-heteroaryl,

wherein cycloalkyl is optionally substituted with one or more groups each independently selected from the group consisting of F, C₁-C₃ alkyl-OH, C₁-C₃ alkyl-O-C₁-C₃ alkyl, C(O)OR⁵, C(O)NR⁵R⁵, NR⁵R⁵, and NR⁵-C(O)CH₃,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR⁵, keto, C₃-C₆ cycloalkyl, C(O)CH₃, C(O)NR⁵R⁵, NH-C(O)R⁵, NH-SO₂R⁵, and C₁-C₄ alkyl that is optionally substituted with one or more F or OH,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C₁-C₄ alkyl that is optionally substituted with one or more groups each independently selected from the group consisting of F, OH, and NR⁵R⁶,

C₃-C₆ cycloalkyl that is substituted with NR⁵R⁶,

halogen,

CN,

OR⁵,

C(O)NR⁵R⁶,

NR⁵R⁶,

SO₂R⁶,

SO₂NR⁵R⁶,

SO(NH)R⁵,

S(NR)(NH)R⁵,

P(O)R⁵R⁵, and

4- or 5,6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more groups independently selected from the group consisting of F, Cl, OR⁵, CN, C₁-C₄ alkyl, oxo, and NR⁵R⁶,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, C(O)NR⁵R⁶, OR⁵, NR⁵R⁶, oxo, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₄ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, OR⁵, and C(O)NR⁵R⁶;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with a group selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁-C₅ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₅ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

R⁷ is cycloalkyl optionally substituted with one or more halogens;

p is 1-2;

with the proviso that a compound selected from the group consisting of:

(S)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2H-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea,

and

1-(5-cyclopropylthiazol-4-yl)-3-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)urea, is

excluded.

[0036] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R² is H;

R³ is H;

R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;

Z is selected from the group consisting of C₁-C₃ alkyl, NR⁵R⁶, SR⁵, C(O)NR⁵R⁶, cycloalkyl, heterocyclyl, aryl, and heteroaryl,

wherein the C₁-C₃ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, OR⁵, halogen, and NR⁵R⁶,

wherein cycloalkyl is optionally substituted with one or more F;

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR⁵, and C₁ alkyl optionally substituted with one or more F,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C₁-C₃ alkyl that is optionally substituted with NR⁵R⁶,

halogen,

CN,

OR⁵,

C(O)NR⁵R⁶,

SO₂R⁶,

SO₂NR⁵R⁶,

SO(NH)R⁵,

S(NR)(NH)R⁵,

P(O)R⁵R⁵, and

5-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more oxo,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, CN, C(O)NR⁵R⁶, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₃ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, and OR⁵;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with one or more groups selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

p is 1;

with the proviso that a compound selected from the group consisting of:

(S)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2H-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea,

and

1-(5-cyclopropylthiazol-4-yl)-3-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)urea, is excluded.

[0037] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R^2 is H;

R^3 is H;

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;

Z is C₁-C₃ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, OR⁵, halogen, and NR⁵R⁶,

R^5 is independently H or C₁ alkyl;

R^6 is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen; and

p is 1.

[0038] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R^2 is H;

R^3 is H;

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;

Z is aryl substituted with one or more groups selected from the group consisting of:
halogen,
C(O)NR⁵R⁶, and
SO₂NR⁵R⁶;

R^5 is independently H or C₁ alkyl;

R^6 is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen; and

p is 1.

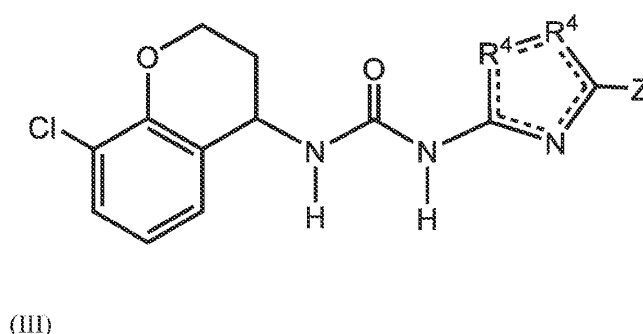
[0039] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R^2 is H;

R^3 is H;

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;
 Z is heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5 , and C_1 alkyl optionally substituted with one or more F,
 R^5 is independently H or C_1 alkyl; and
 p is 1.

[0040] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (III):



wherein:

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;
 Z is selected from the group consisting of C_1 - C_3 alkyl, C_1 - C_6 alkene, NR^5R^6 , SR^5 , $C(O)R^5$, $C(O)R^7$, $C(O)OR^5$, $C(O)NR^5R^6$, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, and sulfonamide,

wherein the C_1 - C_3 alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, OR^5 , halogen, NR^5R^6 , and $NH-SO_2R^5$, wherein cycloalkyl is optionally substituted with one or more F, C_1 - C_3 alkyl-OH, C_1 - C_3 alkyl-O- C_1 - C_3 alkyl, $C(O)OR^5$,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5 , and C_1 alkyl optionally substituted with one or more F, wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C₁-C₃ alkyl that is optionally substituted with NR⁵R⁶,

halogen,

CN,

OR⁵,

C(O)NR⁵R⁶,

SO₂R⁶,

SO₂NR⁵R⁶,

SO(NH)R⁵,

S(NR)(NH)R⁵,

P(O)R⁵R⁵, and

5-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more oxo,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, C(O)NR⁵R⁶, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₃ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, and OR⁵;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with one or more groups selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

R⁷ is cycloalkyl optionally substituted with one or more halogens;

with the proviso that a compound selected from the group consisting of:

(*S*)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2*H*-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea,

and

1-(5-cyclopropylthiazol-4-yl)-3-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)urea, is excluded.

[0041] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (III) wherein:

- R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;
- Z is C₁-C₃ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, OR⁵, halogen, and NR⁵R⁶,
- R⁵ is independently H or C₁ alkyl; and
- R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen.

[0042] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

- R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;
- Z is NR⁵R⁶;
- R⁵ is independently H or C₁ alkyl; and
- R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen.

[0043] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

- R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;
- Z is C(O)NR⁵R⁶;
- R⁵ is independently H or C₁ alkyl; and
- R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen.

[0044] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;
 Z is cycloalkyl is optionally substituted with one or more F; and
 R^5 is independently H or C₁ alkyl.

[0045] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;
 Z is heterocyclyl that optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR⁵, and C₁ alkyl optionally substituted with one or more F;
 and
 R^5 is independently H or C₁ alkyl.

[0046] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;
 Z is aryl that is optionally substituted with one or more groups selected from the group consisting of:
 C₁-C₃ alkyl that is optionally substituted with NR⁵R⁶,
 halogen,
 CN,
 OR⁵,
 C(O)NR⁵R⁶,
 SO₂R⁶,
 SO₂NR⁵R⁶,
 SO(NH)R⁵,
 S(NR)(NH)R⁵,
 P(O)R⁵R⁵, and
 5-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more oxo;
 R^5 is independently H or C₁ alkyl; and

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen.

[0047] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;
Z is heteroaryl that is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, CN, C(O)NR⁵R⁶, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₃ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, and OR⁵;
R⁵ is independently H or C₁ alkyl; and
R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen.

[0048] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;
Z is aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with one or more groups selected from the group consisting of OR⁵, Cl, and F; and
R⁵ is independently H or C₁ alkyl.

[0049] In embodiments, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (II) wherein:

R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;
Z is aryl-heteroaryl optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵; and
R⁵ is independently H or C₁ alkyl.

[0050] In embodiments, R^1 is H, C₁-C₃ alkyl, Cl, F, CN, and O-C₁-C₆ alkyl optionally substituted with one or more halogen. In embodiments, R^1 is H. In embodiments, R^1 is C₁-C₃ alkyl. In embodiments, R^1 is C₁ alkyl. In embodiments, R^1 is C₂ alkyl. In embodiments, R^1 is C₃ alkyl. In embodiments, R^1 is Cl. In embodiments, R^1 is Cl. In embodiments, R^1 is CN. In embodiments, R^1 is OCH₃. In embodiments, R^1 is OCF₃.

[0051] In embodiments, R^2 is H or C₁-C₃ alkyl substituted with OH or OCH₃. In embodiments, R^2 is H. In embodiments, R^2 is C₁ alkyl substituted with OH. In embodiments, R^2 is C₂ alkyl substituted with OH. R^2 is C₃ alkyl substituted with OH. In embodiments, R^2 is C₁ alkyl substituted with OCH₃. In embodiments, R^2 is C₂ alkyl substituted with OCH₃. R^2 is C₃ alkyl substituted with OCH₃.

[0052] In embodiments, R^3 is independently H or C₁-C₄ alkyl optionally substituted with one or more halogen or OH. In embodiments, R^3 is H. In embodiments, R^3 is C₁ alkyl optionally substituted with one or more halogen. In embodiments, R^3 is C₁ alkyl optionally substituted with one or more OH. In embodiments, R^3 is C₂ alkyl optionally substituted with one or more halogen. In embodiments, R^3 is C₂ alkyl optionally substituted with one or more OH. In embodiments, R^3 is C₃ alkyl optionally substituted with one or more halogen. In embodiments, R^3 is C₃ alkyl optionally substituted with one or more OH. In embodiments, R^3 is C₄ alkyl optionally substituted with one or more halogen. In embodiments, R^3 is C₄ alkyl optionally substituted with one or more OH.

[0053] In embodiments, R^4 is independently H or C₁-C₄ alkyl. In embodiments, R^4 is H. In embodiments, R^4 is C₁ alkyl. In embodiments, R^4 is H or C₂ alkyl. In embodiments, R^4 is C₃ alkyl. In embodiments, R^4 is C₄ alkyl.

[0054] In embodiments, Z is C₁-C₆ alkyl, NR⁵R⁶, C(O)NR⁵R⁶, cycloalkyl, heterocyclyl, aryl, heteroaryl, aryl-heterocyclyl, or aryl-heteroaryl. In embodiments, Z is C₁-C₆ alkyl optionally substituted with cyclopropyl. In embodiments, Z is C₁-C₆ alkyl optionally substituted with phenyl. In embodiments, Z is C₁-C₆ alkyl optionally substituted with OR⁵. In embodiments, Z is C₁-C₆ alkyl optionally substituted with halogen. In embodiments, Z is C₁-C₆ alkyl optionally substituted with C(O)NR⁵R⁶. In embodiments, Z is C₁-C₆ alkyl optionally substituted with NR⁵R⁵. In embodiments, Z is C₁-C₆ alkyl optionally substituted with NR⁵-C(O)CH₃. In embodiments, Z is C₁-C₆ alkyl optionally substituted with SO₂R⁵. In embodiments, Z is C₁-C₆ alkyl optionally substituted with heterocyclyl. In embodiments, Z is

C₁-C₆ alkyl optionally substituted with aryl. In embodiments, Z is C₁-C₆ alkyl optionally substituted with heteroaryl. In embodiments, Z is C₁-C₆ alkyl optionally substituted with aryl-heteroaryl.

[0055] In embodiments, Z is NR⁵R⁶. In embodiments, Z is C(O)NR⁵R⁶.

[0056] In embodiments, Z is cycloalkyl optionally substituted with one or more groups each independently selected from the group consisting of F, C(O)NR⁵R⁵, NR⁵R⁵, and NR⁵-C(O)CH₃. In embodiments, Z is cycloalkyl optionally substituted with one or more F. In embodiments, Z is cycloalkyl optionally substituted with one or more C(O)NR⁵R⁵. In embodiments, Z is cycloalkyl optionally substituted with one or more NR⁵R⁵. In embodiments, Z is cycloalkyl optionally substituted with one or more NR⁵-C(O)CH₃.

[0057] In embodiments, Z is heterocyclyl that optionally contains another heteroatom that is N or O and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR⁵, keto, C₃-C₆ cycloalkyl, C(O)CH₃, C(O)NR⁵R⁵, and C₁-C₄ alkyl that is optionally substituted with one or more F or OH. In embodiments, Z is heterocyclyl that contains another heteroatom that is N. In embodiments, Z is heterocyclyl that contains another heteroatom that is O. In embodiments, Z is heterocyclyl that is substituted with one or more F. In embodiments, Z is heterocyclyl that is substituted with one or more OR⁵. In embodiments, Z is heterocyclyl substituted with one or more keto. In embodiments, Z is heterocyclyl substituted with one or more C₃-C₆ cycloalkyl. In embodiments, Z is heterocyclyl substituted with one or more C(O)CH₃. In embodiments, Z is heterocyclyl substituted with one or more C(O)NR⁵R⁵. In embodiments, Z is heterocyclyl substituted with one or more C₁-C₄ alkyl that is optionally substituted with one or more OH. In embodiments, Z is heterocyclyl substituted with one or more C₁-C₄ alkyl that is optionally substituted with one or more F.

[0058] In embodiments, Z is aryl that is optionally substituted with one or more C₁-C₄ alkyl that is optionally substituted with one or more F, OH, or NR⁵R⁶. In embodiments, Z is aryl that is substituted with one or more C₁-C₄ alkyl that is substituted with one or more F. In embodiments, Z is aryl that is substituted with one or more C₁-C₄ alkyl that is substituted with one or more OH. In embodiments, Z is aryl that is substituted with one or more C₁-C₃ alkyl that is substituted with one or more NR⁵R⁶.

[0059] In embodiments, Z is aryl that is optionally substituted with one or more C₃-C₆ cycloalkyl that is substituted with NR⁵R⁶.

[0060] In embodiments, Z is aryl that is substituted with one or more halogen. In embodiments, Z is aryl that is substituted with one or more CN. In embodiments, Z is aryl that is substituted with one or more OR⁵. In embodiments, Z is aryl that is substituted with one or more C(O)NR⁵R⁶. In embodiments, Z is aryl that is optionally substituted with one or more NR⁵R⁶. In embodiments, Z is aryl that is substituted with one or more SO₂R⁵. In embodiments, Z is aryl that is substituted with one or more SO₂NR⁵R⁶. In embodiments, Z is aryl that is optionally substituted with one or more SO(NH)R⁵. In embodiments, Z is aryl that is optionally substituted with one or more S(NR)(NH)R⁵. In embodiments, Z is aryl that is optionally substituted with one or more P(O)R⁵R⁵.

[0061] In embodiments, Z is aryl that is substituted with a 4- or 6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is substituted with one or more F. In embodiments, Z is aryl that is substituted with a 4- or 6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is substituted with one or more Cl. In embodiments, Z is aryl that is substituted with a 4- or 6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is substituted with one or more OR⁵. In embodiments, Z is aryl that is substituted with a 4- or 6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is substituted with one or more CN. In embodiments, Z is aryl that is substituted with a 4- or 6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is substituted with one or more C₁-C₄ alkyl. In embodiments, Z is aryl that is substituted with a 4- or 6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, that is substituted with one or more oxo. In embodiments, Z is aryl that is substituted with a 4- or 6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, that is substituted with NR⁵R⁵.

[0062] In embodiments, Z is heteroaryl that is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, CN, C(O)NR⁵R⁶, OR⁵, NR⁵R⁶, oxo, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₄ alkyl optionally substituted with one or more groups independently selected from the group consisting of F,

NR^5R^6 , OR^5 , and $\text{C(O)NR}^5\text{R}^6$. In embodiments, Z is heteroaryl that is optionally substituted with one or more cyclopropyl. In embodiments, Z is heteroaryl that is optionally substituted with one or more CN. In embodiments, Z is heteroaryl that is substituted with one or more $\text{C(O)NR}^5\text{R}^5$. In embodiments, Z is heteroaryl that is substituted with one or more OR^5 . In embodiments, Z is heteroaryl that is substituted with one or more NR^5R^5 . In embodiments, Z is heteroaryl that is substituted with one or more oxo. In embodiments, Z is heteroaryl that is substituted with one or more SO_2R^6 . In embodiments, Z is heteroaryl that is substituted with one or more 4- to 6-membered heterocyclic ring. In embodiments, Z is heteroaryl that is substituted with one or more C_1 - C_4 alkyl optionally substituted with F. In embodiments, Z is heteroaryl that is substituted with one or more C_1 - C_4 alkyl optionally substituted with NR^5R^6 . In embodiments, Z is heteroaryl that is substituted with one or more C_1 - C_4 alkyl optionally substituted with $\text{C(O)NR}^5\text{R}^6$.

[0063] In embodiments, Z is aryl-heterocyclyl optionally substituted with Cl, F or C_1 - C_4 alkyl that is optionally substituted with OR^5 , Cl or F. In embodiments, Z is aryl-heterocyclyl substituted with one or more Cl. In embodiments, Z is aryl-heterocyclyl substituted with one or more F. In embodiments, Z is aryl-heterocyclyl substituted with one or more C_1 - C_4 alkyl that is optionally substituted with OR^5 . In embodiments, Z is aryl-heterocyclyl substituted with one or more C_1 - C_4 alkyl that is optionally substituted with Cl. In embodiments, Z is aryl-heterocyclyl substituted with one or more C_1 - C_4 alkyl that is optionally substituted with F.

[0064] In embodiments, Z is aryl-heteroaryl optionally substituted with C_1 - C_3 alkyl that is optionally substituted with OR^5 .

[0065] In embodiments, R^5 is H or C_1 - C_5 alkyl. In embodiments, R^5 is H. In embodiments, R^5 is C_1 alkyl. In embodiments, R^5 is C_2 alkyl. In embodiments, R^5 is C_3 alkyl. In embodiments, R^5 is C_4 alkyl. In embodiments, R^5 is C_5 alkyl.

[0066] In embodiments, R^6 is H, cyclopropyl, and C_1 - C_5 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5 , OR^5 , and halogen. In embodiments, R^6 is H. In embodiments, R^6 is cyclopropyl. In embodiments, R^6 is C_1 - C_5 alkyl optionally substituted with one or more NR^5R^5 . In embodiments, R^6 is C_1 - C_5 alkyl optionally substituted with one or more OR^5 . In embodiments, R^6 is C_1 - C_5 alkyl optionally substituted with one or more halogen.

[0067] In embodiments, n is 1-4. In embodiments, n is 1. In embodiments, n is 2. In embodiments, n is 3. In embodiments, n is 4.

[0068] In embodiments, p is 1-2. In embodiments, p is 1. In embodiments, p is 2.

[0069] In embodiments, compounds are identified in Table 1.

Table 1

No.	Chemical Name	Structure
1	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
2	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
3	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[2-(dimethylamino)thiazol-4-yl]urea	
4	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[4-[4-(pyrrolidin-2-yl)phenyl]thiazol-2-yl]urea	
5	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[4-[4-(pyrrolidin-2-yl)phenyl]thiazol-2-yl]urea	
6	1-(2-(1-(2-aminopropyl)-1 <i>H</i> -pyrazol-3-yl)thiazol-4-yl)-3-((<i>S</i>)-8-chlorochroman-4-yl)urea	
7	1-(2-(1-(2-aminopropyl)-1 <i>H</i> -pyrazol-3-yl)thiazol-4-yl)-3-((<i>S</i>)-8-chlorochroman-4-yl)urea	
8	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(1-ethyl-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
9	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(pyridin-2-yl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
10	(S)-1-(8-chlorochroman-4-yl)-3-(2-(pyridin-4-yl)thiazol-4-yl)urea	
11	(S)-1-(8-chlorochroman-4-yl)-3-(2-phenylthiazol-4-yl)urea	
12	(S)-1-(8-fluorochroman-4-yl)-3-(2-phenylthiazol-4-yl)urea	
13	(S)-1-(chroman-4-yl)-3-(2-phenylthiazol-4-yl)urea	
14	(S)-1-(8-chlorochroman-4-yl)-3-(2-(pyridin-3-yl)thiazol-4-yl)urea	
15	1-[(4S)-8-chlorochroman-4-yl]-3-(2-cyclopropylthiazol-4-yl)urea	
16	1-[(4S)-8-chlorochroman-4-yl]-3-[2-(1-methylpyrazol-4-yl)thiazol-4-yl]urea	
17	1-[(4S)-8-chlorochroman-4-yl]-3-[2-(4-methylsulfonylphenyl)thiazol-4-yl]urea	
18	1-[(4S)-8-chlorochroman-4-yl]-3-[2-[4-(methylsulfonyl)phenyl]thiazol-4-yl]urea	
19	1-[(4S)-8-chlorochroman-4-yl]-3-[2-(3-methylsulfonylphenyl)thiazol-4-yl]urea	
20	4-[4-[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-N-methyl-benzamide	

No.	Chemical Name	Structure
21	5-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-N-methyl-pyridine-2-carboxamide	
22	1-[(4S)-8-chlorochroman-4-yl]-3-[2-[3-(methylsulfamoyl)phenyl]thiazol-4-yl]urea	
23	methyl 4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluorobenzoate	
24	4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzamide	
25	4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]benzamide	
26	4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzamide	
27	4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzamide	
28	1-[(4S)-8-chlorochroman-4-yl]-3-[2-(1-methylpyrazol-3-yl)thiazol-4-yl]urea	
29	1-[(4S)-8-chlorochroman-4-yl]-3-[2-(4-cyanophenyl)thiazol-4-yl]urea	
30	5-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]pyridine-2-carboxamide	
31	1-[(4S)-8-chlorochroman-4-yl]-3-[2-[1-(2,2-difluoroethyl)pyrazol-4-yl]thiazol-4-yl]urea	

No.	Chemical Name	Structure
32	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]thiazol-4-yl]urea	
33	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[2-(5-cyano-2-pyridyl)thiazol-4-yl]urea	
34	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazol-4-yl]urea	
35	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[2-[1-(2,2,2-trifluoroethyl)pyrazol-3-yl]thiazol-4-yl]urea	
36	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[4-(4-cyanophenyl)thiazol-2-yl]urea	
37	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[4-(4-methylsulfonylphenyl)thiazol-2-yl]urea	
38	1-[4-[4-(1-amino-1-methyl-ethyl)phenyl]thiazol-2-yl]-3-[(4 <i>S</i>)-8-chlorochroman-4-yl]urea	
39	1-[2-[1-[2-aminopropyl]pyrazol-4-yl]thiazol-4-yl]-3-[(4 <i>S</i>)-8-chlorochroman-4-yl]urea	
40	1-[2-[1-[2-aminopropyl]pyrazol-4-yl]thiazol-4-yl]-3-[(4 <i>S</i>)-8-chlorochroman-4-yl]urea	
41	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[2-[4-[pyrrolidin-2-yl]phenyl]thiazol-4-yl]urea	
42	1-[(4 <i>S</i>)-8-chlorochroman-4-yl]-3-[2-[4-[pyrrolidin-2-yl]phenyl]thiazol-4-yl]urea	

No.	Chemical Name	Structure
43	1-((<i>S</i>)-chroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
44	1-((<i>S</i>)-chroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
45	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(pyrrolidin-1-yl)thiazol-4-yl)urea	
46	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(3-hydroxy-3-methylpyrrolidine-1-yl)thiazol-4-yl)urea	
47	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(3-hydroxy-3-methylpyrrolidin-1-yl)thiazol-4-yl)urea	
48	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-((<i>S</i>)-3-methoxypyrrolidin-1-yl)thiazol-4-yl)urea	
49	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-((<i>R</i>)-3-methoxypyrrolidin-1-yl)thiazol-4-yl)urea	
50	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(3,3-difluoropyrrolidin-1-yl)thiazol-4-yl)urea	
51	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-((<i>R</i>)-3-hydroxypyrrolidin-1-yl)thiazol-4-yl)urea	
52	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-((<i>S</i>)-3-hydroxypyrrolidin-1-yl)thiazol-4-yl)urea	
53	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
54	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl)thiazol-4-yl)urea	
55	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(1-(oxetan-3-yl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
56	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(3-fluoro-4-(methylsulfonyl)phenyl)thiazol-4-yl)urea	
57	(<i>S</i>)-1-(2-(4-((2-aminoethyl)sulfonyl)phenyl)thiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	
58	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-(pyrrolidin-3-yl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
59	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-(pyrrolidin-3-yl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
60	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(1-methyl-1 <i>H</i> -1,2,3-triazol-4-yl)thiazol-4-yl)urea	
61	(<i>S</i>)-1-(8-fluorochroman-4-yl)-3-(2-(1-(tetrahydro-2 <i>H</i> -pyran-4-yl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
62	(<i>S</i>)-1-(2-(1-ethyl-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)-3-(8-fluorochroman-4-yl)urea	
63	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(4-((trifluoromethyl)sulfonyl)phenyl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
64	(S)-1-(8-chlorochroman-4-yl)-3-(2-(4-((2-(methylamino)ethyl)sulfonyl)phenyl)thiazol-4-yl)urea	
65	1-((S)-8-chlorochroman-4-yl)-3-(2-(1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)thiazol-4-yl)urea	
66	1-((S)-8-chlorochroman-4-yl)-3-(2-(1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)thiazol-4-yl)urea	
67	(S)-1-(8-chlorochroman-4-yl)-3-(2-(4-methylpiperazin-1-yl)thiazol-4-yl)urea	
68	1-((S)-8-chlorochroman-4-yl)-3-(2-((R)-3-hydroxypiperidin-1-yl)thiazol-4-yl)urea	
69	(S)-1-(8-chlorochroman-4-yl)-3-(2-(piperidin-1-yl)thiazol-4-yl)urea	
70	(S)-1-(8-chlorochroman-4-yl)-3-(2-(morpholinothiazol-4-yl)urea	
71	(S)-1-(8-chlorochroman-4-yl)-3-(2-(4-(dimethylphosphoryl)phenyl)thiazol-4-yl)urea	
72	(S)-1-(8-chlorochroman-4-yl)-3-(2-(1-cyclopropyl-1H-imidazol-4-yl)thiazol-4-yl)urea	
73	(S)-1-(8-chlorochroman-4-yl)-3-(2-(5-(methylsulfonyl)pyridin-2-yl)thiazol-4-yl)urea	
74	(S)-1-(8-chlorochroman-4-yl)-3-(2-(2-methyl-2H-1,2,3-triazol-4-yl)thiazol-4-yl)urea	

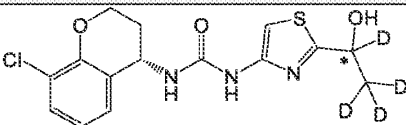
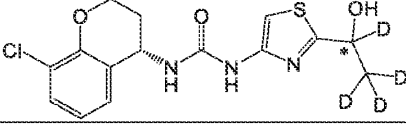
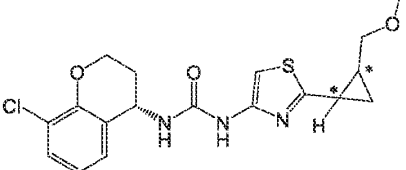
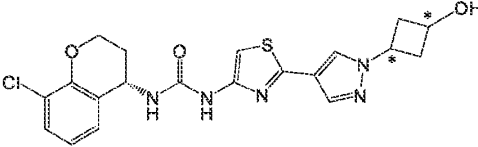
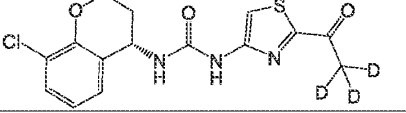
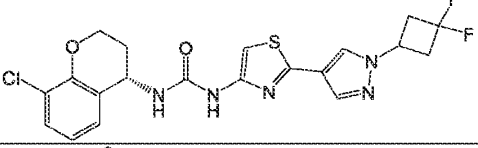
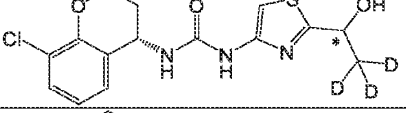
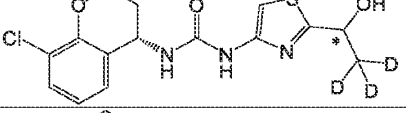
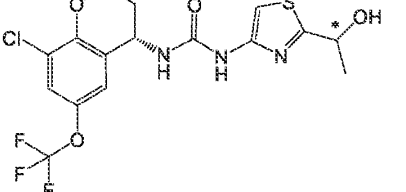
No.	Chemical Name	Structure
75	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(2,2,2-trifluoro-1-hydroxyethyl)thiazol-4-yl)urea	
76	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(2,2,2-trifluoro-1-hydroxyethyl)thiazol-4-yl)urea	
77	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-(2-hydroxypropyl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
78	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-(2-hydroxypropyl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
79	1-((<i>S</i>)-8-fluorochroman-4-yl)-3-(2-(3-hydroxypyrrolidin-1-yl)thiazol-4-yl)urea	
81	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(4-((2-(dimethylamino)ethyl)sulfonyl)phenyl)thiazol-4-yl)urea	
82	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(2-hydroxypropan-2-yl)thiazol-4-yl)urea	
83	1-(2-(1-amino-2,2,2-trifluoroethyl)thiazol-4-yl)-3-((<i>R</i>)-8-chlorochroman-4-yl)urea	
85	1-((<i>R</i>)-8-fluorochroman-4-yl)-3-(2-(3-hydroxypyrrolidin-1-yl)thiazol-4-yl)urea	
87	1-(2-(1-aminoethyl)thiazol-4-yl)-3-((<i>R</i>)-8-chlorochroman-4-yl)urea	
88	1-(2-(1-aminoethyl)thiazol-4-yl)-3-((<i>R</i>)-8-chlorochroman-4-yl)urea	
89	1-((<i>R</i>)-chroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
91	1-((<i>R</i>)-8-fluorochroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
92	1-((<i>R</i>)-8-fluorochroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
93	1-((<i>S</i>)-8-fluorochroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
94	1-((<i>S</i>)-8-fluorochroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
95	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(4-(4-(cyclopropylsulfonyl)phenyl)thiazol-2-yl)urea	
96	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(4-(4-(ethylsulfonyl)phenyl)thiazol-2-yl)urea	
97	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(4-(4-(<i>S</i> -methylsulfonimidoyl)phenyl)thiazol-2-yl)urea	
98	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(4-(3-(<i>S</i> -methylsulfonimidoyl)phenyl)thiazol-2-yl)urea	
99	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(4-(5-(methylsulfonyl)pyridin-2-yl)thiazol-2-yl)urea	
100	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(4-(3-(<i>N</i> ,1-dimethyl-1-phenyl-λ ⁶ -sulfanediimine)thiazol-2-yl)urea	
101	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(4-(3-(1-oxido-4-oxo-3,4-dihydro-2 <i>H</i> -1 <i>H</i> ,2,5-thiadiazol-1-yl)phenyl)thiazol-2-yl)urea	

No.	Chemical Name	Structure
102	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(isopropylamino)thiazol-4-yl)urea	
105	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(1-methyl-1 <i>H</i> -imidazol-4-yl)thiazol-4-yl)urea	
106	1-((<i>S</i>)-chroman-4-yl)-3-(2-(3-hydroxypyrrolidin-1-yl)thiazol-4-yl)urea	
108	1-((<i>R</i>)-8-chlorochroman-4-yl)-3-(4-(1-hydroxyethyl)thiazol-2-yl)urea	
109	1-((<i>R</i>)-8-chlorochroman-4-yl)-3-(4-(1-hydroxyethyl)thiazol-2-yl)urea	
110	1-((<i>R</i>)-8-chlorochroman-4-yl)-3-(2-(cyclopropyl(hydroxy)methyl)thiazol-4-yl)urea	
111	1-((<i>R</i>)-8-chlorochroman-4-yl)-3-(2-(cyclopropyl(hydroxy)methyl)thiazol-4-yl)urea	
113	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(4-cyanophenyl)-5-methylthiazol-4-yl)urea	
114	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(4-(4-cyanophenyl)-5-methylthiazol-2-yl)urea	
115	1-((<i>S</i>)-8-chlorochroman-4-yl-4- <i>d</i>)-3-(2-((<i>R</i>)-1-hydroxyethyl-2,2,2- <i>d</i> ₃)thiazol-4-yl)urea	
116	1-((<i>S</i>)-8-chlorochroman-4-yl-4- <i>d</i>)-3-(2-((<i>S</i>)-1-hydroxyethyl-2,2,2- <i>d</i> ₃)thiazol-4-yl)urea	

No.	Chemical Name	Structure
117	(S)-1-(2-(acetyl- <i>d</i> ₃)thiazol-4-yl)-3-(8-chlorochroman-4-yl)-4-urea	
118	(S)-1-(8-chlorochroman-4-yl)-3-(2-vinylthiazol-4-yl)urea	
119	(S)-1-(2-acetylthiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	
120	(S)-1-(8-chlorochroman-4-yl)-3-(2-(3,3-difluorocyclobutane-1-carbonyl)thiazol-4-yl)urea	
121	(S)-1-(2-(bicyclo[1.1.1]pentan-1-yl)thiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	
122	1-(2-(bicyclo[1.1.1]pentan-1-yl)(hydroxy)methyl)thiazol-4-yl)-3-((S)-8-chlorochroman-4-yl)urea	
123	1-(2-(bicyclo[1.1.1]pentan-1-yl)(hydroxy)methyl)thiazol-4-yl)-3-((S)-8-chlorochroman-4-yl)urea	
124	(S)-1-(2-(bicyclo[1.1.1]pentane-1-carbonyl)thiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	
125	1-((S)-8-chlorochroman-4-yl)-3-(2-((3,3-difluorocyclobutyl)(hydroxy)methyl)thiazol-4-yl)urea	
126	1-((S)-8-chlorochroman-4-yl)-3-(2-((3,3-difluorocyclobutyl)(hydroxy)methyl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
127	(<i>S</i>)-1-(2-(1-acetylazetidin-3-yl)thiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	
128	1-(2-acetylthiazol-4-yl)-3-(8-chloro-4-methylchroman-4-yl)urea	
129	1-(2-acetylthiazol-4-yl)-3-(8-chloro-4-methylchroman-4-yl)urea	
130	1-(2-acetylthiazol-4-yl)-3-((3 <i>R</i> ,4 <i>R</i>)-8-chloro-3-methylchroman-4-yl)urea	
131	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl-1,2,2,2- <i>d</i> ₄)thiazol-4-yl)urea	
132	1-(2-acetylthiazol-4-yl)-3-((2 <i>S</i> ,4 <i>S</i>)-8-chloro-2-methylchroman-4-yl)urea	
133	1-(2-acetylthiazol-4-yl)-3-((3 <i>S</i> ,4 <i>S</i>)-8-chloro-3-methylchroman-4-yl)urea	
134	1-(2-acetylthiazol-4-yl)-3-((2 <i>R</i> ,4 <i>S</i>)-8-chloro-2-methylchroman-4-yl)urea	
135	1-(2-acetylthiazol-4-yl)-3-((3 <i>S</i> ,4 <i>R</i>)-8-chloro-3-methylchroman-4-yl)urea	
136	1-(2-acetylthiazol-4-yl)-3-((3 <i>R</i> ,4 <i>S</i>)-8-chloro-3-methylchroman-4-yl)urea	

No.	Chemical Name	Structure
137	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl-1,2,2,2- <i>d</i> ₄)thiazol-4-yl)urea	
138	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl-1,2,2,2- <i>d</i> ₄)thiazol-4-yl)urea	
139	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(2-(methoxymethyl)cyclopropyl)thiazol-4-yl)urea	
140	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-(3-hydroxycyclobutyl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
141	(<i>S</i>)-1-(2-(acetyl- <i>d</i> ₃)thiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	
142	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(1-(3,3-difluorocyclobutyl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
143	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl-2,2,2- <i>d</i> ₃)thiazol-4-yl)urea	
144	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl-2,2,2- <i>d</i> ₃)thiazol-4-yl)urea	
145	1-((<i>S</i>)-8-chloro-6-(trifluoromethoxy)chroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
146	1-((<i>S</i>)-8-chloro-6-(trifluoromethoxy)chroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
147	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(2-(hydroxymethyl)cyclopropyl)thiazol-4-yl)urea	
148	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(2-(hydroxymethyl)cyclopropyl)thiazol-4-yl)urea	
149	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(2-(hydroxymethyl)cyclopropyl)thiazol-4-yl)urea	
150	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(2-(hydroxymethyl)cyclopropyl)thiazol-4-yl)urea	
151	<i>N</i> -(1-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)ethyl)methanesulfonamide	
152	<i>N</i> -(1-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)ethyl)methanesulfonamide	
153	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(5,6-dihydro-4 <i>H</i> -pyrrolo[1,2- <i>b</i>]pyrazol-3-yl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
154	(<i>S</i>)-1-(2-acetylthiazol-4-yl)-3-(8-chloro-6-(trifluoromethoxy)chroman-4-yl)urea	
155	2-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)cyclopropane-1-carboxylic acid	
156	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl-1- <i>d</i>)thiazol-4-yl)urea	
157	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl-1- <i>d</i>)thiazol-4-yl)urea	
158	(<i>S</i>)-1-(2-acetylthiazol-4-yl)-3-(8-chloro-6-methoxychroman-4-yl)urea	
159	1-((<i>S</i>)-8-chloro-6-methoxychroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
160	1-((<i>S</i>)-8-chloro-6-methoxychroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
161	(<i>R</i>)-1-(2-acetylthiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	

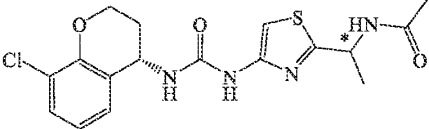
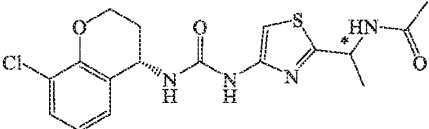
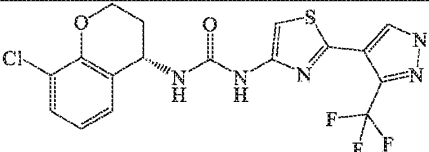
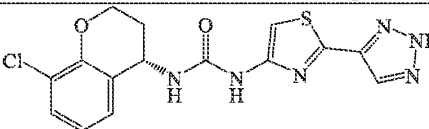
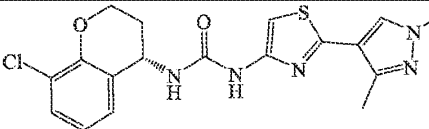
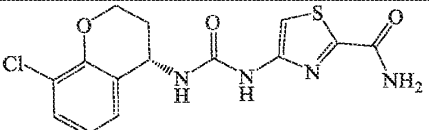
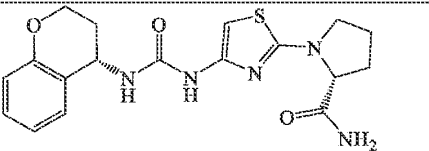
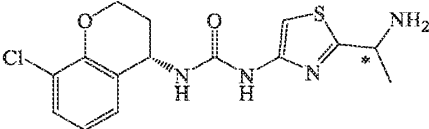
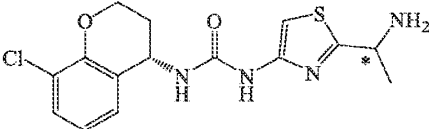
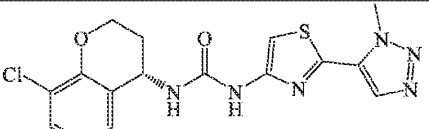
No.	Chemical Name	Structure
162	(<i>S</i>)-4-(3-(8-chlorochroman-4-yl)ureido)thiazole-2-carboxylic acid	
163	methyl (<i>S</i>)-4-(3-(8-chlorochroman-4-yl)ureido)thiazole-2-carboxylate	
164	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1,2-dihydroxyethyl)thiazol-4-yl)urea	
165	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(6-oxo-1,6-dihydropyridin-3-yl)thiazol-4-yl)urea	
166	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1,2-dihydroxyethyl)thiazol-4-yl)urea	
167	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(3-hydroxyoxetan-3-yl)thiazol-4-yl)urea	
168	(<i>S</i>)-1-(2-(azetidin-3-yl)thiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	
169	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(3-fluorooxetan-3-yl)thiazol-4-yl)urea	
170	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(oxetan-3-yl)thiazol-4-yl)urea	
171	1-(8-chloro-4-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
172	1-(8-chloro-4-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
173	1-(8-chloro-4-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
174	1-(8-chloro-4-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
175	1-(8-chloro-3-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
176	1-(8-chloro-3-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
177	1-(8-chloro-3-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
178	1-(8-chloro-3-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
179	1-(8-chloro-3-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
180	1-(8-chloro-3-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
181	1-((S)-8-chlorochroman-4-yl)-3-(2-(1-methoxyethyl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
182	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-methoxyethyl)thiazol-4-yl)urea	
183	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(methylthio)thiazol-4-yl)urea	
184	1-((4 <i>S</i>)-8-chloro-3-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
185	1-((4 <i>S</i>)-8-chloro-3-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
186	1-((<i>R</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
187	1-((<i>R</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
188	1-((4 <i>S</i>)-8-chloro-2-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
189	1-((4 <i>S</i>)-8-chloro-2-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
190	1-((4 <i>S</i>)-8-chloro-2-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
191	1-((4 <i>S</i>)-8-chloro-2-methylchroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	
192	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(methoxymethyl)thiazol-4-yl)urea	
193	2-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)- <i>N</i> -methylcyclopropane-1-carboxamide	
194	2-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)- <i>N</i> -methylcyclopropane-1-carboxamide	
195	2-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)cyclopropane-1-carboxamide	
196	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxy-2-methylpropyl)thiazol-4-yl)urea	
197	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxy-2-methylpropyl)thiazol-4-yl)urea	
198	2-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)- <i>N</i> -methylcyclopropane-1-carboxamide	

No.	Chemical Name	Structure
199	2-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)- <i>N</i> -methylcyclopropane-1-carboxamide	
200	2-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)- <i>N</i> -methylcyclopropane-1-carboxamide	
201	2-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)cyclopropane-1-carboxamide	
202	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(5-methyl-1-(oxetan-3-yl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
203	2-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)- <i>N</i> -methylcyclopropane-1-carboxamide	
204	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxypropyl)thiazol-4-yl)urea	
205	1-((<i>S</i>)-8-chlorochroman-4-yl)-3-(2-(1-hydroxypropyl)thiazol-4-yl)urea	
206	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(3-methyl-1-(oxetan-3-yl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
207	(<i>S</i>)-1-(2-(4-(2-aminopropan-2-yl)phenyl)thiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	

No.	Chemical Name	Structure
208	<i>N</i> -(1-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)ethyl)acetamide	
209	<i>N</i> -(1-(4-(3-((<i>S</i>)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)ethyl)acetamide	
210	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
211	(<i>S</i>)-1-(2-(2 <i>H</i> -1,2,3-triazol-4-yl)thiazol-4-yl)-3-(8-chlorochroman-4-yl)urea	
212	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(1,3-dimethyl-1 <i>H</i> -pyrazol-4-yl)thiazol-4-yl)urea	
213	(<i>S</i>)-4-(3-(8-chlorochroman-4-yl)ureido)thiazole-2-carboxamide	
214	(<i>R</i>)-1-(4-(3-((<i>S</i>)-chroman-4-yl)ureido)thiazol-2-yl)pyrrolidine-2-carboxamide	
215	1-(2-(1-aminoethyl)thiazol-4-yl)-3-((<i>S</i>)-8-chlorochroman-4-yl)urea	
216	1-(2-(1-aminoethyl)thiazol-4-yl)-3-((<i>S</i>)-8-chlorochroman-4-yl)urea	
217	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-(1-methyl-1 <i>H</i> -1,2,3-triazol-5-yl)thiazol-4-yl)urea	

No.	Chemical Name	Structure
218	(<i>S</i>)-4-(3-(8-chlorochroman-4-yl)ureido)- <i>N</i> -methylthiazole-2-carboxamide	
219	<i>N</i> -((<i>R</i>)-1-(4-(3-((<i>S</i>)-chroman-4-yl)ureido)thiazol-2-yl)pyrrolidin-3-yl)methanesulfonamide	
220	(<i>S</i>)-1-(2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)thiazol-4-yl)-3-(chroman-4-yl)urea	
221	<i>N</i> -((<i>R</i>)-1-(4-(3-((<i>S</i>)-chroman-4-yl)ureido)thiazol-2-yl)pyrrolidin-3-yl)acetamide	
222	(<i>S</i>)-1-(8-chlorochroman-4-yl)-3-(2-((2-methoxyethyl)(methyl)amino)thiazol-4-yl)urea	
223	<i>N</i> -((<i>S</i>)-1-(4-(3-((<i>S</i>)-chroman-4-yl)ureido)thiazol-2-yl)pyrrolidin-3-yl)methanesulfonamide	
224	<i>N</i> -((<i>S</i>)-1-(4-(3-((<i>S</i>)-chroman-4-yl)ureido)thiazol-2-yl)pyrrolidin-3-yl)acetamide	
225	1-((<i>R</i>)-chroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea	

[0070] The compounds of the present invention may contain asymmetric carbon atoms (sometimes as the result of a deuterium atom) and thereby can exist as either individual stereoisomers or mixtures of the enantiomers or mixtures of diastereomers. Accordingly, a compound of the present invention may exist as either a racemic mixture, a mixture of diastereomers, or as individual stereoisomers that are substantially free of other stereoisomers. Synthetic, separation, or purification methods to be used to obtain an enantiomer of a given compound are known in the art and are applicable for obtaining the compounds identified herein.

[0071] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound. Carbon atoms labelled with * refer to a carbon atom that is chiral but the absolute stereochemistry has not been determined.

[0072] The compounds of the present invention may contain double bonds that may exist in more than one geometric isomer. Examples of such double bonds are carbon-carbon double bonds which form alkenes. In the case of carbon-carbon double bonds, the geometric isomers may be E or Z isomers.

[0073] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the geometric isomerism and has one or more possible geometric isomers, it is understood to represent all possible geometric isomers of the compound.

[0074] Certain compounds of the present invention may be able to exist as tautomers. All tautomeric forms of these compounds, whether isolated individually or in mixtures, are within the scope of the present invention. For example, in instances where an —OH substituent is permitted on a heteroaromatic ring and ketoenol tautomerism is possible, it is understood that the substituent might in fact be present, in whole or in part, in the oxo (=O) form.

[0075] In certain embodiments, hydrogen atoms may be replaced with deuterium. The deuterium isotope content at a the deuterium substituted position may be is greater than the natural isotopic deuterium content (0.015%), more preferably greater than 50%, more preferably greater than 60%, more preferably greater than 75%, more preferably greater than 90%, more preferably greater than 95%, more preferably greater than 97%, more preferably greater than 99%. It will be understood that some variation of natural isotopic abundance may occur in any compound depending upon the source of the reagents used in the synthesis. Thus, a preparation of undeuterated compounds may inherently contain small amounts of deuterated isotopologues, such amounts being insignificant as compared to the degree of stable isotopic substitution of the deuterated compounds of the invention. *See, e.g.*, Gannes, L.Z., et al., *Comp Biochem. Physiol. Mol. Integr. Physiol.*, 119:725 (1998). Replacement of hydrogen with deuterium may affect the activity, toxicity, and pharmacokinetics (e.g., absorption, distribution, metabolism, and excretion ("ADME")) of some drugs. For instance,

such replacement may alter the chemical stability and biochemical reactivity of a compound through kinetic isotope effects. Because of the increased mass of deuterium relative to hydrogen, epimerization at stereogenic carbons may be slowed down when hydrogen is replaced with deuterium. See Pirali, T. et al., *J. Med. Chem.*, 62:5276-97 (2019).

Additionally, the presence of deuterium may affect how a molecule interacts with enzymes, thereby impacting enzyme kinetics. While in certain cases the increased mass of deuterium as compared to hydrogen can stabilize a compound and thereby improve activity, toxicity, or half-life, such impact is not predictable. In other instances deuteration may have little to no impact on these properties, or may affect them in an undesirable manner. Whether and/or how such replacement will impact drug properties can only be determined if the drug is synthesized, evaluated, and compared to its non-deuterated counterpart. See Fukuto, J.M., et al., *J. Med. Chem.*, 34:2871-76 (1991). Because some drugs have multiple sites of metabolism or more than one active sites for binding to a target, it is unpredictable as to which sites may benefit by deuterium replacement or to what extent isotope enrichment is necessary to produce a beneficial effect.

EXAMPLES

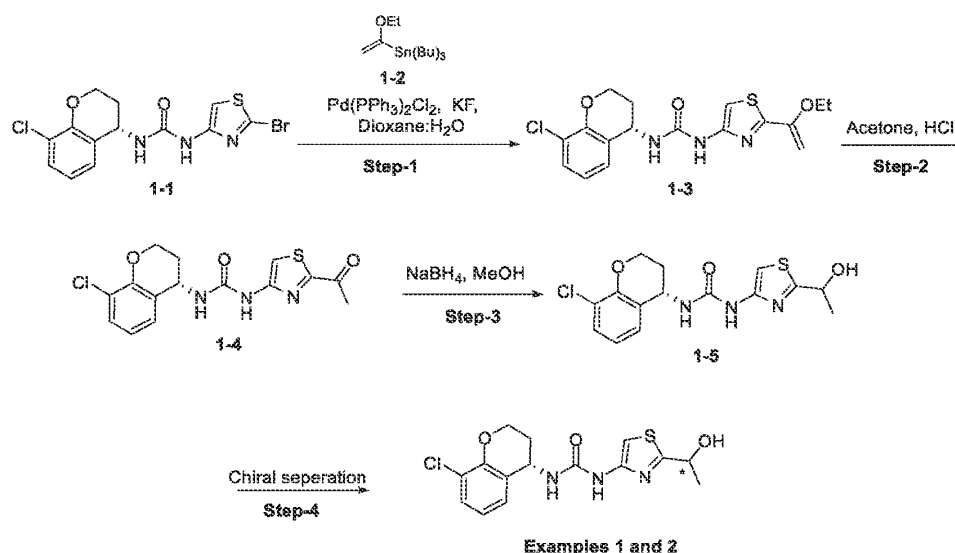
[0076] The examples below further illustrate embodiments of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

[0077] The structures of the compounds are confirmed by mass spectrometry and/or NMR, where peaks assigned to the characteristic protons in the title compound are presented where appropriate. ¹H NMR shift (δ) are given in parts per million (ppm) down field from an internal reference standard.

[0078] The abbreviations used herein are known to a person of ordinary skill in the art. A partial list of abbreviations that may be used herein include: acetonitrile (CH₃CN or MeCN or ACN), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (Pd(dppf)Cl₂ complex with CH₂Cl₂), bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium (II) (Pd(amphos)Cl₂), calculated (Calcd.), cerium chloride (CeCl₃), cesium carbonate (Cs₂CO₃), cesium fluoride (CsF), copper acetate (Cu(OAc)₃), copper bromide (CuBr), copper (I) oxide (Cu₂O), degrees Celsius (°C), deuterium (*d*), dichloromethane (DCM, CH₂Cl₂), dichloroethane (DCE), *N,N*-

diisopropylethylamine (DIPEA), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), *N,N'*-disuccinimidylcarbonate (DSC), di-*tert*-butyl decarbonate (Boc₂O), ethyl acetate (EtOAc), ethanol (EtOH), hour (h), iodobenzene diacetate (PhI(OAc)₂), *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU), high performance liquid chromatography (HPLC), lithium hydroxide monohydrate (LiOH·H₂O), megahertz (MHz), methanol (MeOH, CH₃OH), methyl lithium (MeLi), minutes (min), nuclear magnetic resonance (NMR), palladium on carbon (Pd/C), pounds per square inch (PSI), potassium carbonate (K₂CO₃), potassium hydroxide (KOH), potassium phosphate (K₃PO₄), pyridine (Pyr), liquid chromatography-mass spectrometry (LCMS), methanesulfonyl chloride (MsCl), room/ambient temperature (RT), sodium bicarbonate (NaHCO₃), sodium borohydride (NaBH₄), sodium hydride (NaH), sodium hydroxide (NaOH), sodium sulfate (Na₂SO₄), *N*-bromosuccinimide (NBS), sodium *tert*-butoxide (NaO^tBu), supercritical fluid chromatography (SFC), tetrabutylammonium tribromide (TBAH), tetrahydrofuran (THF), thin layer chromatography (TLC), triethylamine (Et₃N, TEA), palladium-tetrakis(triphenylphosphine) (Pd(PPh₃)₄), and water (H₂O).

Example 1 and Example 2: Synthesis of 1-((*S*)-8-chlorochroman-4-yl)-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea



* Absolute stereochemistry not determined

[0079] **Step-1: 1-[(4S)-8-chlorochroman-4-yl]-3-[2-(1-ethoxyvinyl)thiazol-4-yl]urea (1-3):** To a stirred solution of 1-(2-bromothiazol-4-yl)-3-[(4S)-8-chlorochroman-4-yl]urea **1-1** (0.50 g, 1.29 mmol) in 1,4-dioxane (10 mL) was added tributyl(1-ethoxyvinyl)tin **1-2** (0.53 mL, 1.54 mmol) followed by KF (0.22 g, 3.86 mmol) at RT. The reaction mixture was purged with nitrogen for 15 min and then *bis*(triphenylphosphine)palladium (II) chloride (0.09 g, 0.12 mmol) was added into it. The reaction mixture was heated at 110 °C for 6 h. After completion, reaction mixture was filtered through Celite bed. Organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by CombiFlash (20% EtOAc/heptane) to afford 1-[(4S)-8-chlorochroman-4-yl]-3-[2-(1-ethoxyvinyl)thiazol-4-yl]urea **1-3** (0.35 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.22 (s, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.26 - 7.20 (m, 2H), 6.90 (t, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 5.07 (s, 1H), 4.98 - 4.90 (m, 1H), 4.44 (br s, 1H), 4.41 - 4.36 (m, 1H), 4.28 - 4.19 (m, 1H), 3.96 (q, *J* = 6.9 Hz, 2H), 2.13 (dd, *J* = 5.1, 8.3 Hz, 1H), 2.03 - 1.94 (m, 1H), 1.32 (t, *J* = 6.9 Hz, 3H); LCMS: [M+H]⁺ = 380.

[0080] **Step-2: 1-(2-acetylthiazol-4-yl)-3-[(4S)-8-chlorochroman-4-yl]urea (1-4):** To a stirred solution of 1-[(4S)-8-chlorochroman-4-yl]-3-[2-(1-ethoxyvinyl)thiazol-4-yl]urea **1-3** (0.35 g, 0.82 mmol) in acetone (5 mL) was added concentrated HCl (1.00 mL, 33.30 mmol). Reaction mixture was stirred at RT for 1 h. After completion, reaction mixture was quenched with saturated NaHCO₃ solution, extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 1-(2-acetylthiazol-4-yl)-3-[(4S)-8-chlorochroman-4-yl]urea **1-4** (0.30 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.48 (br s, 1H), 7.71 (s, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 4.96 (d, *J* = 5.5 Hz, 1H), 4.38 (d, *J* = 7.9 Hz, 1H), 4.24 (t, *J* = 8.8 Hz, 1H), 2.57 (s, 3H), 2.12 (br s, 1H), 1.98 (br s, 1H); LCMS: [M+H]⁺ = 352.

[0081] **Step-3: 1-[(4S)-8-chlorochroman-4-yl]-3-[2-(1-hydroxyethyl)thiazol-4-yl]urea (1-5):** To a stirred solution of 1-(2-acetylthiazol-4-yl)-3-[(4S)-8-chlorochroman-4-yl]urea **1-4** (0.30 g, 0.76 mmol) in ethanol (8 mL) was added NaBH₄ (0.13 g, 3.45 mmol) at 0 °C and the reaction mixture was stirred at 40 °C for 4 h. After completion, reaction mixture was concentrated under reduced pressure and product was quenched with H₂O, extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product obtained was purified by reverse phase CombiFlash to afford

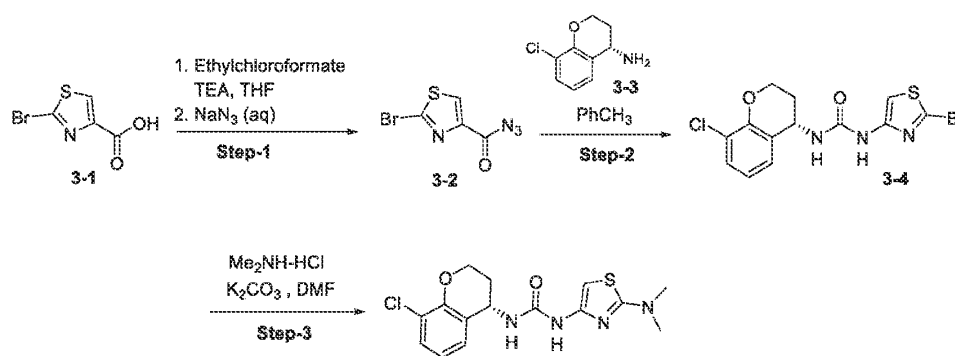
1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(1-hydroxyethyl)thiazol-4-yl]urea **1-5** (0.13 g). LCMS: $[M+H]^+ = 354$.

[0082] **Step-4: 1-[(*S*)-8-chlorochroman-4-yl]-3-(2-(1-hydroxyethyl)thiazol-4-yl)urea (Examples 1 and 2):** Racemic compound of **1-5** 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(1-hydroxyethyl)thiazol-4-yl]urea (0.13 g) was submitted for chiral-HPLC separation to afford **Example 1** (0.04 g) and **Example 2** (0.01 g). The absolute stereochemistry of these products was not determined.

[0083] **Example 1:** ^1H NMR (400 MHz, DMSO- d_6) δ = 9.01 (s, 1H), 7.32 (dd, J = 1.3, 7.9 Hz, 1H), 7.25 - 7.20 (m, 1H), 7.05 (s, 1H), 6.90 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.02 (d, J = 5.3 Hz, 1H), 4.98 - 4.90 (m, 1H), 4.89 - 4.80 (m, 1H), 4.43 - 4.33 (m, 1H), 4.28 - 4.20 (m, 1H), 2.17 - 2.09 (m, 1H), 2.05 - 1.92 (m, 1H), 1.40 (d, J = 6.4 Hz, 3H); LCMS: $[M+H]^+ = 354$.

[0084] **Example 2:** ^1H NMR (400 MHz, DMSO- d_6) δ = 9.00 (s, 1H), 7.32 (dd, J = 1.3, 7.9 Hz, 1H), 7.23 (d, J = 7.1 Hz, 1H), 7.05 (s, 1H), 6.90 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.01 (d, J = 5.3 Hz, 1H), 4.97 - 4.90 (m, 1H), 4.89 - 4.80 (m, 1H), 4.44 - 4.35 (m, 1H), 4.29 - 4.18 (m, 1H), 2.19 - 2.05 (m, 1H), 2.03 - 1.93 (m, 1H), 1.40 (d, J = 6.5 Hz, 3H); LCMS: $[M+H]^+ = 354$.

Example 3: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(dimethylamino)thiazol-4-yl]urea

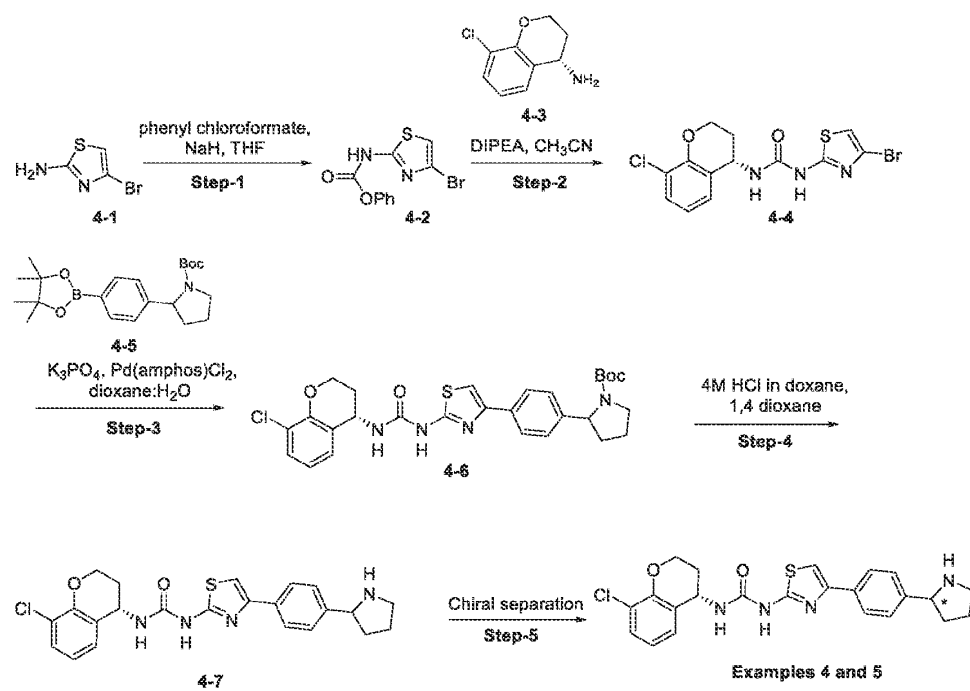


[0085] **Step-1: 2-bromothiazole-4-carbonyl azide (3-2):** To a suspension of 2-bromothiazole-4-carboxylic acid **3-1** (2.50 g, 12.00 mmol) in THF (5 mL) was added TEA (2.0 mL, 14.4 mmol) at 0 °C followed by ethyl chloroformate (1.4 mL, 14.4 mmol). Reaction mixture was stirred at RT for 1 h. To the above reaction mixture was added aqueous solution of sodium azide (5.86 g, 90.1 mmol) and stirred at RT for 2 h. After completion, reaction mixture was diluted with H₂O and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain 2-bromothiazole-4-carbonyl azide **3-2** (2.40 g). LCMS: [M+H]⁺ = 205.

[0086] **Step-2: 1-(2-bromothiazol-4-yl)-3-[(4S)-8-chlorochroman-4-yl]urea (3-4):** A solution of 2-bromothiazole-4-carbonyl azide **3-2** (2.40 g, 10.3 mmol) in toluene (20 mL) was stirred at 90 °C for 15 min under N₂ atmosphere. To the above reaction mixture was added (4S)-8-chlorochroman-4-amine hydrochloride **3-3** (2.27 g, 10.3 mmol) and stirred at 90 °C for 12 h. After completion, reaction mixture was concentrated under reduced pressure to obtain a product which was purified by CombiFlash column chromatography to obtain 1-(2-bromothiazol-4-yl)-3-[(4S)-8-chlorochroman-4-yl]urea **3-4** (2.00 g). LCMS: [M+H]⁺ = 390.

[0087] **Step-3: 1-[(4S)-8-chlorochroman-4-yl]-3-[2-(dimethylamino)thiazol-4-yl]urea (Example 3):** To a stirred solution of dimethylamine HCl (0.01 g, 0.15 mmol) in DMF (3 mL) was added K₂CO₃ (0.08 g, 0.64 mmol) and stirred for 15 min. To this was added 1-(2-bromothiazol-4-yl)-3-[(4S)-8-chlorochroman-4-yl]urea **3-4** (0.05 g, 0.12 mmol) and the reaction mixture was stirred at 90 °C for 4 h. After completion, the reaction mixture was quenched with ice cold water, extracted with EtOAc. Combined organic layer was washed with brine solution, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The product was purified by CombiFlash (50% EtOAc/*n*-heptane) to afford **Example 3** (0.01 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.74 (s, 1H), 7.32 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 6.90 (t, *J* = 1.0 Hz, 2H), 6.21 (s, 1H), 4.95 - 4.85 (m, 1H), 4.43 - 4.34 (m, 1H), 4.26 - 4.17 (m, 1H), 2.95 (s, 6H), 2.18 - 2.06 (m, 1H), 2.01 - 1.90 (m, 1H); LCMS: [M+H]⁺ = 353.

Example 4 and Example 5: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[4-[4-(pyrrolidin-2-yl)phenyl]thiazol-2-yl]urea



* Absolute stereochemistry not determined

[0088] **Step-1: phenyl *N*-(4-bromothiazol-2-yl)carbamate (4-2):** To a stirred solution of 4-bromothiazol-2-amine **4-1** (0.20 g, 1.12 mmol) in THF (5 mL) was added NaH (60% in mineral oil, 0.04 g, 1.68 mmol) at 0 °C followed by phenyl chloroformate (0.15 mL, 1.23 mmol). The reaction mixture was stirred at 25 °C for 12 h. After completion, reaction was quenched with cold H₂O, extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product obtained was purified by CombiFlash (50% EtOAc/heptane) to afford **4-2** phenyl *N*-(4-bromothiazol-2-yl)carbamate (0.15 g). ¹H NMR: (400 MHz, DMSO-*d*₆) δ = 12.60 (br s, 1H), 7.48 - 7.43 (m, 2H), 7.34 - 7.22 (m, 4H); LCMS: [M+H]⁺ = 301.

[0089] **Step-2: 1-(4-bromothiazol-2-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea (4-4):** To a stirred solution of phenyl *N*-(4-bromothiazol-2-yl)carbamate **4-2** (0.20 g, 0.66 mmol) in MeCN (5 mL) was added DIPEA (0.35 mL, 2.01 mmol) followed by (4*S*)-8-chlorochroman-4-amine hydrochloride **4-3** (0.14 g, 0.66 mmol). The reaction mixture was stirred at 80 °C for

4 h. After completion, the reaction mixture was diluted with water, extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by CombiFlash (30% EtOAc/heptane) to afford 1-(4-bromothiazol-2-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea **4-4** (0.26 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 10.51 (br s, 1H), 7.34 (dd, J = 1.3, 7.9 Hz, 1H), 7.22 (dd, J = 0.6, 7.8 Hz, 1H), 7.16 - 7.12 (m, 2H), 6.91 (t, J = 7.8 Hz, 1H), 4.98 - 4.93 (m, 1H), 4.40 - 4.34 (m, 1H), 4.30 - 4.23 (m, 1H), 2.17 - 2.10 (m, 1H), 2.08 - 2.01 (m, 1H); LCMS: $[\text{M}+\text{H}]^+ = 390$.

[0090] **Step-3: *tert*-butyl 2-[4-[2-[[[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-4-yl]phenyl]pyrrolidine-1-carboxylate (4-6):** To a stirred solution of 1-(4-bromothiazol-2-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea **4-4** (0.70 g, 1.80 mmol) in 1,4-dioxane (7 mL) and water (3 mL) was added *tert*-butyl 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-1-carboxylate **4-5** (0.84 g, 2.25 mmol) followed by potassium phosphate (1.14 g, 5.40 mmol) at RT and the reaction mixture was purged with N_2 for 10 min. To this was added $\text{Pd}(\text{amphos})\text{Cl}_2$ (0.25 g, 0.36 mmol) and the reaction mixture was again purged with N_2 for 5 min. The reaction mixture was heated at 100 °C for 16 h. After completion, reaction mixture was diluted with H_2O and extracted with EtOAc. Combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by CombiFlash (40% EtOAc/heptane) to afford desired product which was again purified by reverse phase column chromatography to afford *tert*-butyl 2-[4-[2-[[[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-4-yl]phenyl]pyrrolidine-1-carboxylate **4-6** (0.20 g) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 10.44 (br s, 1H), 7.77 (d, J = 6.4 Hz, 2H), 7.43 (s, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.18 (d, J = 7.5 Hz, 3H), 6.92 (t, J = 7.8 Hz, 1H), 4.99 (q, J = 6.2 Hz, 1H), 4.86 - 4.68 (m, 1H), 4.45 - 4.35 (m, 1H), 4.27 (t, J = 8.2 Hz, 1H), 3.58 - 3.42 (m, 2H), 2.33 - 2.13 (m, 2H), 2.07 (s, 1H), 1.86 - 1.69 (m, 3H), 1.41 - 1.07 (m, 9H); LCMS: $[\text{M}+\text{H}]^+ = 555$.

[0091] **Step-4: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[4-(4-pyrrolidin-2-ylphenyl)thiazol-2-yl]urea (4-7):** To a stirred solution of *tert*-butyl 2-[4-[2-[[[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-4-yl]phenyl]pyrrolidine-1-carboxylate **4-6** (0.17 g, 0.30 mmol) in 1,4-dioxane (5 mL) was added 4M HCl in 1,4-dioxane (4 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The product was triturated with EtOAc to afford 1-[(4*S*)-8-chlorochroman-4-yl]-3-[4-(4-pyrrolidin-2-ylphenyl)thiazol-2-yl]urea **4-7** (0.15 g). ^1H NMR: (400 MHz,

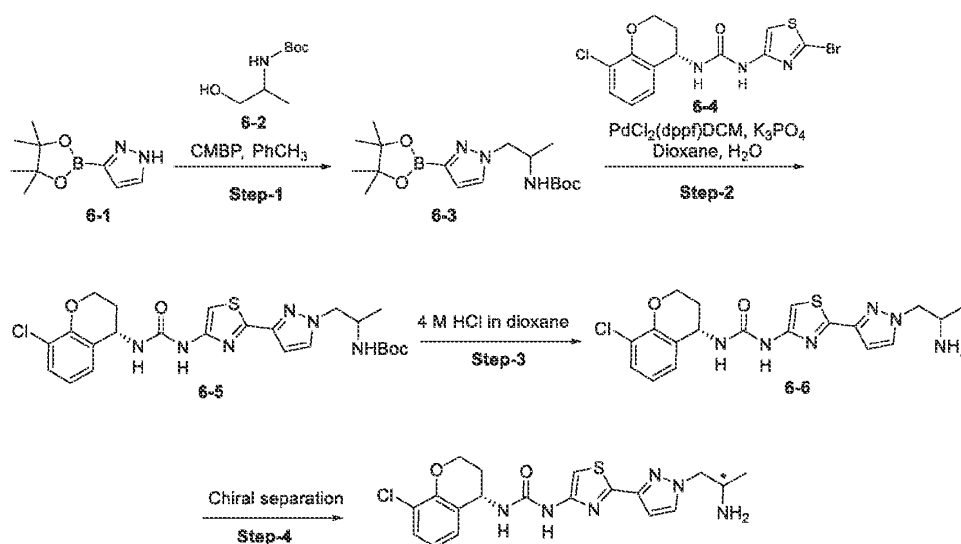
DMSO-*d*₆) δ = 10.55 (br s, 1H), 9.76 (br s, 1H), 8.83 (br s, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.58 - 7.51 (m, 2H), 7.39 - 7.32 (m, 2H), 7.25 (d, J = 7.7 Hz, 1H), 6.92 (t, J = 7.8 Hz, 1H), 4.99 (d, J = 6.4 Hz, 1H), 4.56 (br s, 1H), 4.44 - 4.36 (m, 1H), 4.33 - 4.24 (m, 1H), 3.57 (s, 1H), 3.40 - 3.27 (m, 2H), 2.38 (d, J = 5.5 Hz, 1H), 2.18 - 2.00 (m, 4H), LCMS: $[M+H]^+ = 455$.

[0092] **Step-5: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[4-[4-(pyrrolidin-2-yl)phenyl]thiazol-2-yl]urea (Examples 4 and 5):** 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-pyrrolidin-2-ylphenyl)thiazol-4-yl]urea **4-7** (0.15 g) was submitted for chiral-HPLC separation to afford **Example 4** (0.04 g) and **Example 5** (0.02 g). The absolute stereochemistry of these products was not determined.

[0093] **Example 4:** ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.75 (d, J = 8.3 Hz, 2H), 7.41 (s, 1H), 7.37 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 1.3 Hz, 1H), 7.27 - 7.22 (m, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.92 (t, J = 7.8 Hz, 1H), 4.98 (q, J = 6.3 Hz, 1H), 4.45 - 4.35 (m, 1H), 4.33 - 4.22 (m, 1H), 4.04 (t, J = 7.6 Hz, 1H), 3.06 - 2.99 (m, 1H), 2.94 - 2.85 (m, 1H), 2.22 - 2.00 (m, 3H), 1.83 - 1.68 (m, 2H), 1.54 - 1.42 (m, 1H); LCMS: $[M+H]^+ = 456$.

[0094] **Example 5:** ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.26 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.46 - 7.39 (m, 3H), 7.34 (dd, J = 1.3, 7.9 Hz, 2H), 7.25 (d, J = 7.1 Hz, 1H), 6.92 (t, J = 7.8 Hz, 1H), 4.99 (q, J = 6.3 Hz, 1H), 4.44 - 4.35 (m, 1H), 4.33 - 4.25 (m, 1H), 4.23 - 4.18 (m, 1H), 3.17 - 3.09 (m, 1H), 3.06 - 2.97 (m, 1H), 2.25 - 2.12 (m, 2H), 2.10 - 2.01 (m, 1H), 1.91 - 1.79 (m, 2H), 1.72 - 1.61 (m, 1H); LCMS: $[M+H]^+ = 456$.

Example 6 and Example 7: Synthesis of 1-(2-(1-(2-aminopropyl)-1H-pyrazol-3-yl)thiazol-4-yl)-3-((S)-8-chlorochroman-4-yl)urea



Examples 6 and 7

* Absolute stereochemistry not determined

[0095] **Step-1: *tert*-butyl (1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propan-2-yl)carbamate (6-3):** To a stirred solution of *tert*-butyl *N*-(2-hydroxy-1-methyl-ethyl)carbamate **6-2** (0.50 g, 2.85 mmol) in toluene (8 mL) was added 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole **6-1** (0.66 g, 3.42 mmol) and the reaction mixture was purged with nitrogen for 10 min. To this was added cyanomethylenetriethylphosphorane (0.75 mL, 2.85 mmol) and the resulting reaction mixture was stirred at 80 °C for 12 h. After completion, the reaction mixture was evaporated under reduced pressure to afford *tert*-butyl *N*-[1-methyl-2-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]ethyl]carbamate **6-3** (1.00 g). LCMS: $[M+H]^+ = 270$.

[0096] **Step-2: *tert*-butyl (1-(3-(4-(3-((*S*)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)-1H-pyrazol-1-yl)propan-2-yl)carbamate (6-5):** To a stirred solution of 1-(2-bromothiazol-4-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea **6-4** (0.50 g, 1.13 mmol) in 1,4-dioxane (15 mL) and water (1.5 mL) was added *tert*-butyl *N*-[1-methyl-2-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]ethyl]carbamate **6-3** (1.19 g, 3.40 mmol) followed by K_3PO_4 (0.72 g, 3.40 mmol) at RT and the reaction mixture was purged with N_2 for 15 min. To this

was added Pd(dppf)Cl₂ complex with DCM (0.04 g, 0.05 mmol) and the reaction mixture was stirred at 85 °C for 2 h. After completion, reaction mixture was quenched with H₂O and filtered through Celite bed. The filtrate was extracted with the EtOAc, combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by CombiFlash to afford *tert*-butyl 1-(3-(4-(3-((*S*)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)-1*H*-pyrazol-1-yl)propan-2-yl)carbamate **6-5** (0.15 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.07 (s, 1H), 7.48 (s, 1H), 7.36 - 7.20 (m, 3H), 6.98 (d, *J* = 7.4 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.72 (br s, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 4.98 - 4.91 (m, 1H), 4.57 (dd, *J* = 4.6, 12.9 Hz, 1H), 4.38 (d, *J* = 6.5 Hz, 2H), 4.24 (t, *J* = 9.0 Hz, 1H), 3.97 - 3.90 (m, 1H), 2.17 - 2.10 (m, 1H), 1.97 (s, 1H), 1.26 - 1.13 (m, 9H), 0.97 (d, *J* = 6.5 Hz, 2H); LCMS: [M+H]⁺ = 533.

[0097] **Step-3: 1-(2-(1-(2-aminopropyl)-1*H*-pyrazol-3-yl)thiazol-4-yl)-3-((*S*)-8-chlorochroman-4-yl)urea (6-6):** To a stirred solution of *tert*-butyl 1-(3-(4-(3-((*S*)-8-chlorochroman-4-yl)ureido)thiazol-2-yl)-1*H*-pyrazol-1-yl)propan-2-yl)carbamate **6-5** (0.15 g, 0.16 mmol) in DCM (1.5 mL), 4.0 M HCl in dioxane (0.006 g, 0.16 mmol) was added at 0 °C. Reaction mixture was stirred at 25 °C for 1 h. After completion, the reaction mixture was evaporated under reduced pressure. The product was washed with EtOAc and concentrated under reduced pressure to afford 1-(2-(1-(2-aminopropyl)-1*H*-pyrazol-3-yl)thiazol-4-yl)-3-((*S*)-8-chlorochroman-4-yl)urea **6-6** (0.11 g). LCMS: [M+H]⁺ = 433.

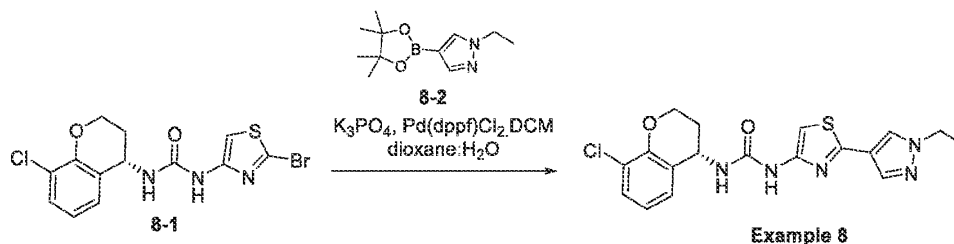
[0098] **Step-4: 1-(2-(1-(2-aminopropyl)-1*H*-pyrazol-3-yl)thiazol-4-yl)-3-((*S*)-8-chlorochroman-4-yl)urea (Examples 6 and 7):** 1-[2-[1-(2-aminopropyl)pyrazol-3-yl]thiazol-4-yl]-3-[(4*S*)-8-chlorochroman-4-yl]urea **6-6** (0.11 g) was submitted to chiral-HPLC separation to afford **Example 6** (0.01 g) and **Example 7**. The absolute stereochemistry of these products was not determined.

[0099] **Example 6:** ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.45 (s, 1H), 7.59 (d, *J* = 2.1 Hz, 1H), 7.38 - 7.30 (m, 2H), 7.25 (dd, *J* = 0.7, 7.7 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 2.1 Hz, 1H), 5.87 - 5.63 (m, 2H), 5.01 - 4.92 (m, 1H), 4.55 (d, *J* = 6.3 Hz, 2H), 4.45 - 4.36 (m, 1H), 4.30 - 4.22 (m, 1H), 3.53 - 3.41 (m, 1H), 2.20 - 2.10 (m, 1H), 2.06 - 1.94 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 3H) LCMS: [M+H]⁺ = 434.

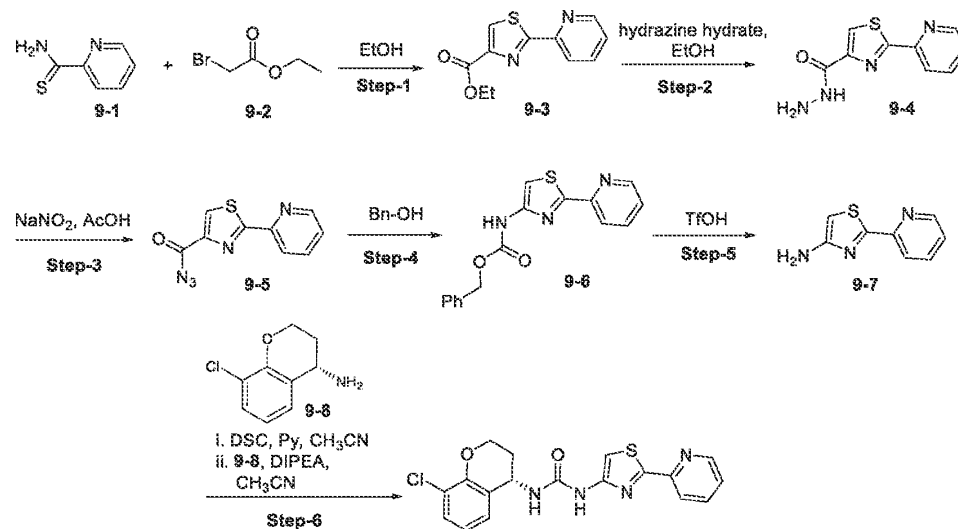
[0100] **Example 7:** ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.21 (s, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.36 - 7.31 (m, 2H), 7.26 (d, *J* = 7.4 Hz, 1H), 6.97 - 6.89 (m, 2H), 6.78 (d, *J* = 2.0 Hz,

1H), 4.96 (q, $J = 6.2$ Hz, 1H), 4.40 (d, $J = 5.6$ Hz, 3H), 4.29 - 4.22 (m, 1H), 3.23 (d, $J = 6.4$ Hz, 1H), 2.21 - 2.10 (m, 1H), 2.08 - 1.98 (m, 1H), 0.92 (d, $J = 6.5$ Hz, 3H); LCMS: $[M+H]^+ = 434$.

Example 8: Synthesis of (S)-1-(8-chlorochroman-4-yl)-3-(2-(1-ethyl-1H-pyrazol-4-yl)thiazol-4-yl)urea



[0101] **Step-1: 1-[(4-{S})]-8-chlorochroman-4-yl]-3-[2-(1-ethylpyrazol-4-yl)thiazol-4-yl]urea (Example 8):** To a stirred solution of 1-(2-bromothiazol-4-yl)-3-[(4S)-8-chlorochroman-4-yl]urea **8-1** (0.20 g, 0.51 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was added K_3PO_4 (0.32 g, 1.54 mmol) followed by 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **8-2** (0.13 g, 0.61 mmol) and the reaction mixture was degassed with argon for 30 min. To this was added $Pd(dppf)Cl_2 \cdot DCM$ (0.02 g, 0.02 mmol) at RT. The reaction mixture was stirred at 90 °C for 4 h. After completion of reaction, the reaction mixture was filtered with Celite bed. The filtrate was diluted with H_2O and extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the compound which was purified using combi-flash (50% EtOAc/n-heptane) to afford **Example 8** (0.06 g). 1H NMR (400 MHz, $DMSO-d_6$) $\delta = 9.14$ (s, 1H), 8.26 (s, 1H), 7.82 (s, 1H), 7.33 (dd, $J = 1.3, 7.9$ Hz, 1H), 7.26 - 7.22 (m, 1H), 7.05 (s, 1H), 6.94 - 6.84 (m, 2H), 4.98 - 4.91 (m, 1H), 4.44 - 4.35 (m, 1H), 4.28 - 4.21 (m, 1H), 4.17 (q, $J = 7.3$ Hz, 2H), 2.20 - 2.09 (m, 1H), 2.06 - 1.93 (m, 1H), 1.39 (t, $J = 7.3$ Hz, 3H), LCMS: $[M+H]^+ = 404$.

Example 9: Synthesis of 1-[(4S)-8-chlorochroman-4-yl]-3-[2-(2-pyridyl)thiazol-4-yl]urea**Example 9**

[0102] **Step-1: ethyl 2-(2-pyridyl)thiazole-4-carboxylate (9-3):** To a stirred solution of ethyl 3-bromo-2-oxopropanoate **9-2** (1.40 mL, 10.90 mmol) in ethanol (15 mL) was added pyridine-2-carbothioamide **9-1** (1.50 g, 10.90 mmol) at RT. Resulting mixture was stirred at 70 °C for 12 h. After completion of the reaction, reaction mixture was concentrated under reduced pressure. Material was dissolved in ethyl acetate. Organic layer was washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product was purified by column chromatography (2% MeOH/DCM) to afford ethyl 2-(2-pyridyl)thiazole-4-carboxylate **9-3** (2.20 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 1.33 (t, *J* = 8.0 Hz, 3H), 4.35 (q, *J* = 6.8 Hz, 2 H), 7.55 (t, *J* = 8.0 Hz, 1H), 8.00 (t, *J* = 7.2 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.60 (s, 1H), 8.66 (d, *J* = 4.4 Hz 1H); LCMS: [M+H]⁺ = 235.

[0103] **Step-2: 2-(2-pyridyl)thiazole-4-carbohydrazide (9-4):** To a stirred solution of ethyl 2-(2-pyridyl)thiazole-4-carboxylate **9-3** (2.00 g, 8.45 mmol) in ethanol (35 mL) was added hydrazine hydrate (2.00 mL, 50.70 mmol) at RT. The resulting reaction mixture was stirred at 100 °C for 16 h. After completion of reaction, reaction mixture was diluted in ice water to get the solid which was filtered and dried under reduced pressure to afford 2-(2-pyridyl)thiazole-4-carbohydrazide **9-4** (1.50 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.81 - 9.76 (m, 1H), 8.65

(br s, 1H), 8.36 - 8.28 (m, 2H), 8.06 - 8.00 (m, 1H), 7.57 - 7.52 (m, 1H), 4.62 - 4.55 (m, 2H); LCMS: $[M+H]^+ = 221$.

[0104] **Step-3: 2-(2-pyridyl)thiazole-4-carbonyl azide (9-5):** To a stirred solution of 2-(2-pyridyl)thiazole-4-carbohydrazide **9-4** (1.10 g, 4.99 mmol) in acetic acid (15 mL) was added sodium nitrite (0.48 g, 6.99 mmol) at 0 °C for 30 min followed by at RT for 2 h. After completion of reaction, reaction mixture was quenched with ice water to get the solid which was filtered and dried under reduced pressure to afford 2-(2-pyridyl)thiazole-4-carbonyl azide **9-5** (0.80 g).

[0105] **Step-4: benzyl *N*-[2-(2-pyridyl)thiazol-4-yl]carbamate (9-6):** A solution of 2-(2-pyridyl)thiazole-4-carbonyl azide **9-5** (0.90 g, 3.89 mmol) in benzyl alcohol (BnOH) (15 mL, 58.40 mmol) was stirred at 110 °C for 12 h. After completion of reaction, reaction mixture was concentrated under the reduced pressure. Product was purified by silica gel flash chromatography using (20% EtOAc/*n*-heptane) to afford benzyl *N*-[2-(2-pyridyl)thiazol-4-yl]carbamate **9-6** (0.60 g). LCMS: $[M+H]^+ = 312$.

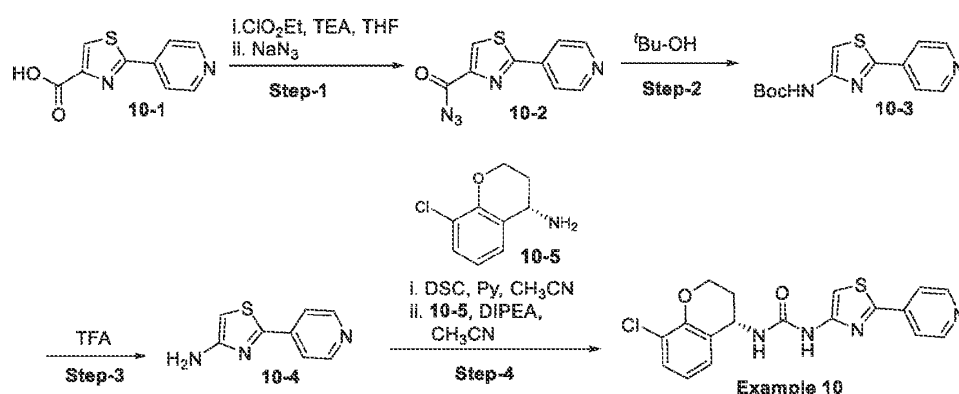
[0106] **Step-5: 2-(2-pyridyl)thiazol-4-amine (9-7):** A solution of benzyl *N*-[2-(2-pyridyl)thiazol-4-yl]carbamate **9-6** (0.60 g, 1.93 mmol) in trifluoromethanesulfonic acid (3.00 mL, 34.00 mmol) was stirred at RT for 2 h. After completion of reaction, reaction mixture was quenched with saturated NaHCO₃ solution and extracted with DCM. Combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get 2-(2-pyridyl)thiazol-4-amine **9-7** (0.11 g); ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.57 - 8.55 (m, 1H), 7.97 - 7.94 (m, 1H), 7.92 - 7.88 (m, 1H), 7.43 - 7.39 (m, 1H), 3.31 (1H), 5.48 (s, 2H); LCMS: $[M+H]^+ = 178$.

[0107] **Step-6: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(2-pyridyl)thiazol-4-yl]urea (Example 52):** To a stirred solution of 2-(2-pyridyl)thiazol-4-amine **9-7** (0.06 g, 0.33 mmol) in MeCN (3 mL) was added *N,N'*-disuccinimidyl carbonate (0.04 g, 0.16 mmol) followed by pyridine (0.02 mL, 0.33 mmol) at RT and the resulting reaction mixture was stirred at RT for 20 min. To this was added (4*S*)-8-chlorochroman-4-amine **9-8** (0.06 g, 0.33 mmol) followed by DIPEA (0.18 mL, 1.02 mmol) at 0 °C. The reaction mixture was stirred at RT for 1 h. After completion of reaction, reaction mixture was diluted with water and extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get a product that was purified by reverse phase flash

chromatography to afford 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(2-pyridyl)thiazol-4-yl]urea

Example 9 (0.07 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.26 (s, 1H), 8.61 (d, J = 3.9 Hz, 1H), 7.99 - 7.93 (m, 2H), 7.51 - 7.46 (m, 1H), 7.38 - 7.25 (m, 3H), 6.95 - 6.88 (m, 2H), 4.97 (d, J = 5.7 Hz, 1H), 4.45 - 4.38 (m, 1H), 4.30 - 4.23 (m, 1H), 2.15 (d, J = 4.4 Hz, 1H), 2.03 (d, J = 4.4 Hz, 1H). LCMS: $[\text{M}+\text{H}]^+ = 387$.

Example 10: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-pyridyl)thiazol-4-yl]urea



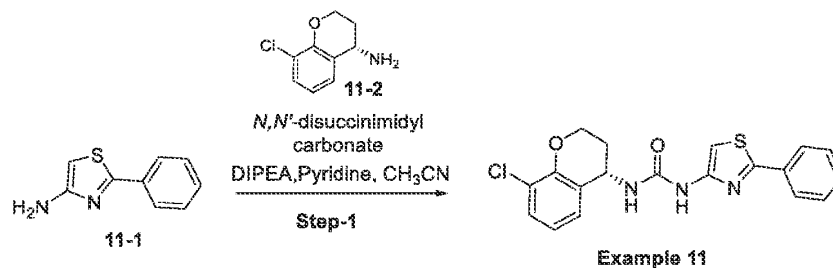
[0108] **Step-1: 2-(4-pyridyl)thiazole-4-carbonyl azide (10-2):** To a stirred solution of 2-(4-pyridyl)thiazole-4-carboxylic acid **10-1** (0.50 g, 2.38 mmol) in THF (5 mL) was added TEA (0.67 mL, 4.75 mmol) followed by ethyl chloroformate (0.35 mL, 3.56 mmol) at 0 °C. Reaction mixture was stirred at RT for 2 h. To this was added sodium azide (0.78 g, 11.90 mmol) at RT. The reaction mixture was stirred at RT for 4 h. After completion of the reaction, reaction mixture was diluted with water and was extracted by ethyl acetate. Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 2-(4-pyridyl)thiazole-4-carbonyl azide **10-2** (0.50 g), which was used as such for the next reaction. LCMS: $[\text{M}+\text{H}]^+ = 232$.

[0109] **Step-2: tert-butyl N-[2-(4-pyridyl)thiazol-4-yl]carbamate (10-3):** A solution of 2-(4-pyridyl)thiazole-4-carbonyl azide **10-2** (0.33 g, 1.30 mmol) in *tert*-butanol (6 mL) was stirred at 100 °C for 12 h. After completion of reaction, reaction mixture was concentrated under reduced pressure. The product was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The product was purified by the CombiFlash (30%

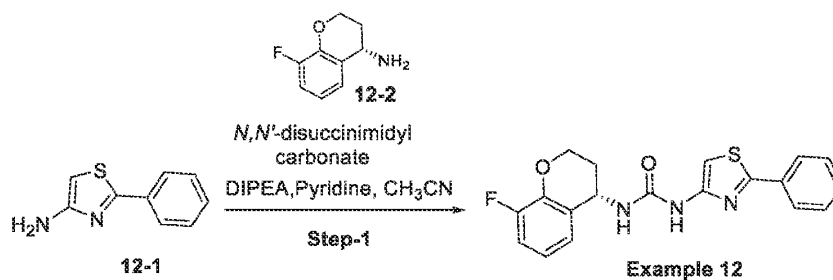
EtOAc/*n*-Heptane) to afford *tert*-butyl *N*-[2-(4-pyridyl)thiazol-4-yl]carbamate **10-3** (0.20 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.32 (s, 1H), 9.07 (s, 1H), 8.65 (d, *J* = 3.2 Hz, 1H), 8.21 (d, *J* = 8 Hz, 1H) 7.55 - 7.52 (m, 1H), 7.35 (s, 1H), 1.48 (s, 9H); LCMS: [M+H]⁺ = 277.

[0110] **Step-3: 2-(4-pyridyl)thiazol-4-amine (10-4):** To a stirred solution of *tert*-butyl *N*-[2-(4-pyridyl)thiazol-4-yl]carbamate **10-3** (0.38 g, 1.36 mmol) in DCM (5 mL) was added TFA (0.32 mL, 4.07 mmol) at 0 °C. Reaction was stirred at RT for 4 h. After completion of the reaction, reaction mixture was directly concentrated under reduced pressure to afford 2-(4-pyridyl)thiazol-4-amine (0.20 g), which was used such as for the next reaction. LCMS: [M+H]⁺ = 178.

[0111] **Step-4: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-pyridyl)thiazol-4-yl]urea (Example 10):** To stirred solution of 2-(4-pyridyl)thiazol-4-amine **10-4** (0.18 g, 0.96 mmol) in MeCN (6 mL) was added *N,N'*-disuccinimidyl carbonate (0.25 g, 0.96 mmol) followed by pyridine (0.08 mL, 0.96 mmol) at RT. The resulting reaction mixture was stirred at RT for 30 min. To this was added DIPEA (0.52 mL, 2.89 mmol) followed by (4*S*)-8-chlorochroman-4-amine.HCl **10-5** (0.22 g, 0.96 mmol) at 0 °C and reaction was stirred at 0 °C for 4 h. After completion of the reaction, reaction mixture was concentrated under reduced pressure. Material was dissolved in EtOAc. Organic layer was washed with 2N HCl, H₂O, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product obtained was purified by CombiFlash (30% EtOAc/hexane) to afford 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-pyridyl)thiazol-4-yl]urea **Example 10** (0.13 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.36 (br s, 1H), 8.71 - 8.67 (m, 2H), 7.81 - 7.78 (m, 2H), 7.46 (s, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 6.94 - 6.89 (m, 2H), 5.00 - 4.94 (m, 1H), 4.40 (d, *J* = 5.9 Hz, 1H), 4.27 (d, *J* = 7.8 Hz, 1H), 2.21 - 2.11 (m, 1H), 2.07 - 1.99 (m, 1H); LCMS: [M+H]⁺ = 387.

Example 11: Synthesis of (S)-1-(8-chlorochroman-4-yl)-3-(2-phenylthiazol-4-yl)urea

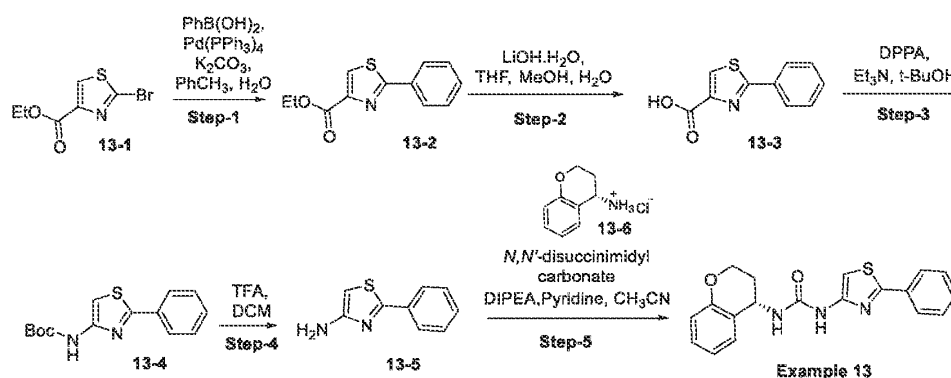
[0112] **Step-1:** To a stirred solution of 2-phenylthiazol-4-amine **11-1** (0.08 g, 0.45 mmol) in MeCN (2 mL) was added pyridine (0.03 mL, 0.45 mmol) followed by *N,N'*-disuccinimidyl carbonate (0.12 g, 0.45 mmol) and the resulting reaction mixture was stirred at RT for 30 min. To this solution was added (4*S*)-8-chlorochroman-4-amine **11-2** (0.08 g, 0.45 mmol) followed by DIPEA (0.24 mL, 1.36 mmol) and the reaction mixture was stirred at RT for 12 h. After completion, the reaction mixture was concentrated under reduced pressure. The product was dissolved in EtOAc and washed with water and brine solution. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by preparative HPLC to afford **Example 11** (0.02 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.25 (s, 1H), 7.89 - 7.82 (m, 2H), 7.52 - 7.46 (m, 3H), 7.37 - 7.32 (m, 1H), 7.26 (br s, 2H), 6.96 - 6.89 (m, 2H), 5.00 - 4.93 (m, 1H), 4.45 - 4.38 (m, 1H), 4.29 - 4.22 (m, 1H), 2.20 - 1.98 (m, 2H); LCMS: [M+H]⁺ = 386.

Example 12: Synthesis of (S)-1-(8-fluorochroman-4-yl)-3-(2-phenylthiazol-4-yl)urea

[0113] **Step-1:** To a stirred solution of 2-phenylthiazol-4-amine **12-1** (0.07 g, 0.40 mmol) in MeCN (2 mL) was added pyridine (0.03 mL, 0.40 mmol) followed by *N,N'*-disuccinimidyl carbonate (0.10 g, 0.40 mmol) and the resulting reaction mixture was stirred at RT for 30

min. To this solution was added (4*S*)-8-fluorochroman-4-amine **12-2** (0.07 g, 0.40 mmol) followed by DIPEA (0.21 mL, 1.19 mmol) and reaction was stirred at RT for 12 h. After completion, the reaction mixture was concentrated under reduced pressure. The product was dissolved in EtOAc and washed with water and brine solution. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by preparative HPLC to afford **Example 12** (0.02 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.26 (br s, 1H), 7.85 (d, 2H), 7.48 (br s, 3H), 7.26 (s, 1H), 7.15 - 7.08 (m, 2H), 6.95 - 6.86 (m, 2H), 4.96 (d, 1H), 4.36 (br s, 1H), 4.22 (t, 1H), 2.15 (d, 1H), 2.02 (d, 1H); LCMS: [M+H]⁺ = 370.

Example 13: Synthesis of (*S*)-1-(chroman-4-yl)-3-(2-phenylthiazol-4-yl)urea



[0114] **Step-1: ethyl 2-phenylthiazole-4-carboxylate (13-2):** To a degassed solution of ethyl 2-bromothiazole-4-carboxylate **13-1** (0.50 g, 2.12 mmol), phenylboronic acid (0.39 g, 3.18 mmol) and K₂CO₃ (0.73 g, 5.29 mmol) in toluene (8 mL) and water (2 mL) was added Pd(PPh₃)₄ (0.25 g, 0.21 mmol) and the reaction mixture was stirred at 100 °C for 14 h. After completion, the reaction mixture was quenched with H₂O, extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The product obtained was purified by CombiFlash (20% EtOAc/hexane) to afford **13-2** (0.30 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 7.99 (d, 2H), 7.54 (br s, 3H), 4.39 - 4.32 (m, 2H), 1.34 (t, 3H); LCMS: [M+H]⁺ = 234.

[0115] **Step-2: 2-phenylthiazole-4-carboxylic acid (13-3):** To a stirred solution of **13-2** (0.20 g, 0.86 mmol) in THF/MeOH/H₂O (4:1:1, 6 mL) was added LiOH.H₂O (0.11 g, 2.57 mmol) and the reaction mixture was stirred at RT for 12 h. After completion, the reaction

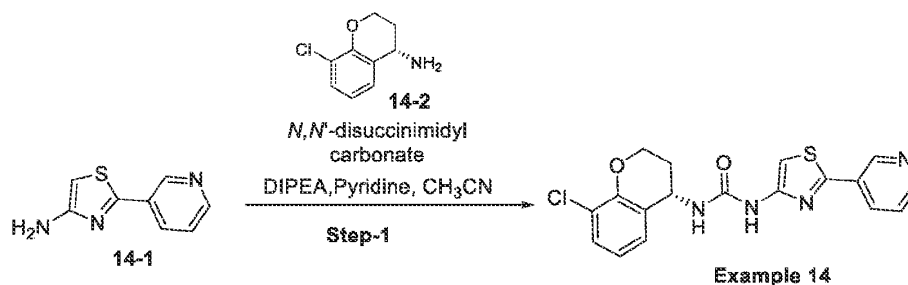
mixture was concentrated and diluted with H₂O. The pH was adjusted with 2N HCl and the precipitated solid was filtered and dried under reduced pressure to afford **13-3** (0.10 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.11 (bs, 1H), 8.49 (s, 1H), 7.98 - 7.97 (m, 2H), 7.53 (br s, 3H); LCMS: [M+H]⁺ = 205.

[0116] **Step-3: *tert*-butyl (2-phenylthiazol-4-yl)carbamate (13-4):** To a stirred solution of **13-3** (0.20 g, 0.98 mmol) in *tert*-butanol (2 mL) was added triethylamine (0.27 mL, 1.95 mmol) followed by diphenylphosphoryl azide (0.27 mL, 1.27 mmol) and the reaction mixture was stirred at 90 °C for 12 h. After completion, the reaction was quenched with H₂O and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The product obtained was purified by CombiFlash chromatography (20% EtOAc/hexane) to afford **13-4** (0.07 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.27 (br s, 1H), 7.88 - 7.86 (m, 2H), 7.52 - 7.46 (m, 3H), 7.25 (s, 1H), 1.47 (s, 9H); LCMS: [M-56]⁺ = 221.

[0117] **Step-4: 2-phenylthiazol-4-amine (13-5):** To a stirred solution of **13-4** (0.40 g, 1.45 mmol) in DCM (2 mL) was added TFA (0.69 g, 5.79 mmol) at 0 °C and the resulting mixture was stirred at RT for 4 h. After completion, the reaction mixture was concentrated under reduced pressure. The product was triturated with diethyl ether and *n*-pentane to afford **13-5** (0.30 g, TFA salt), which was used directly for the next reaction.

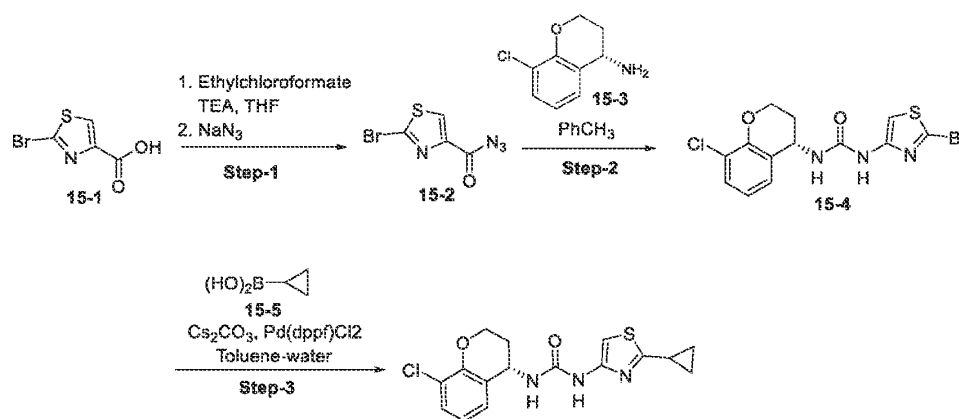
[0118] **Step-5: (S)-1-(chroman-4-yl)-3-(2-phenylthiazol-4-yl)urea (Example 13):** To a stirred solution of (4S)-chroman-4-amine **13-6** (0.09 g, 0.567 mmol) in MeCN (2 mL) was added pyridine (0.09 mL, 1.13 mmol) followed by *N,N'*-disuccinimidyl carbonate (0.15 g, 0.57 mmol) and the resulting reaction mixture was stirred at RT for 30 min. To this solution was added 2-phenylthiazol-4-amine **13-5** (0.10 g, 0.57 mmol) followed by DIPEA (0.30 mL, 1.70 mmol) and the reaction mixture was stirred at RT for 12 h. After completion, the reaction mixture was concentrated under reduced pressure. The product was dissolved in EtOAc and washed with water and brine solution. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by preparative HPLC to afford **Example 13** (0.01 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.25 - 9.20 (m, 1H), 7.85 (d, 2H), 7.47 (br s, 3H), 7.30 - 7.24 (m, 2H), 7.20 - 7.14 (m, 1H), 6.93 - 6.87 (m, 2H), 6.83 - 6.78 (m, 1H), 4.94 - 4.87 (m, 1H), 4.31 - 4.24 (m, 1H), 4.17 - 4.10 (m, 1H), 2.17 - 2.07 (m, 1H), 1.99 (br s, 1H); LCMS: [M+H]⁺ = 352.

Example 14: Synthesis of (S)-1-(8-chlorochroman-4-yl)-3-(2-(pyridin-3-yl)thiazol-4-yl)urea



[0119] **Step-1:** To a stirred solution of 2-(3-pyridyl)thiazol-4-amine **14-1** (0.30 g, 1.69 mmol) in MeCN (10 mL) was added pyridine (0.14 mL, 1.69 mmol), *N,N'*-disuccinimidyl carbonate (0.43 g, 1.69 mmol) and the reaction mixture was stirred at RT for 45 min. To this solution was added DIPEA (0.89 mL, 5.08 mmol) and (4*S*)-8-chlorochroman-4-amine hydrochloride **14-2** (0.37 g, 1.69 mmol) and the reaction mixture was stirred at RT for 4 h. After completion, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The product was purified by preparative HPLC to afford **Example 14** (0.04 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.34 (br s, 1H), 9.06 (br s, 1H), 8.65 (d, 1H), 8.21 (d, 1H), 7.56 - 7.50 (m, 1H), 7.39 - 7.30 (m, 2H), 7.26 (d, 1H), 6.95 - 6.88 (m, 2H), 4.97 (d, 1H), 4.45 - 4.37 (m, 1H), 4.30 - 4.23 (m, 1H), 2.22 - 2.11 (m, 1H), 2.07 - 1.97 (m, 1H); LCMS: [M+H]⁺ = 387.

Example 15: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-(2-cyclopropylthiazol-4-yl)urea



Example 15

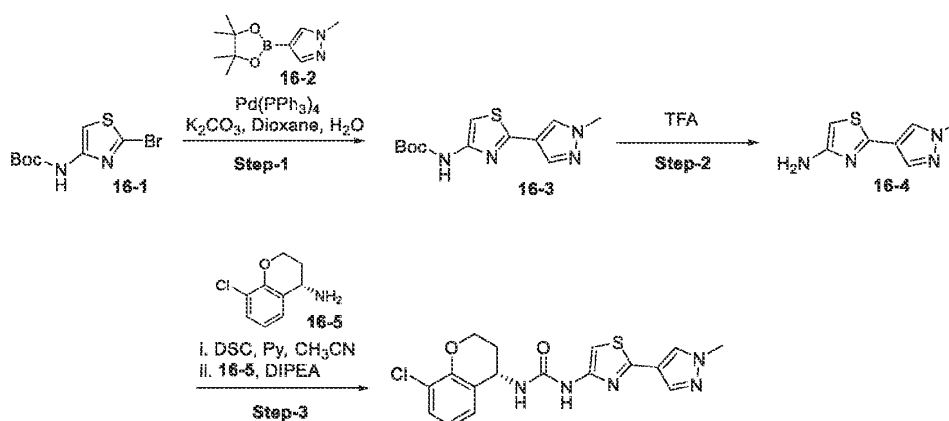
[0120] **Step-1: 2-bromothiazole-4-carbonyl azide (15-2):** To a suspension of 2-bromothiazole-4-carboxylic acid **15-1** (2.50 g, 12.0 mmol) in THF (5 mL) was added TEA (2.00 mL, 14.40 mmol) at 0 °C followed by ethyl chloroformate (1.40 mL, 14.4 mmol). Reaction mixture was stirred at RT for 1 h. To the above reaction mixture was added aqueous solution of sodium azide (5.86 g, 90.10 mmol) and stirred at RT for 2 h. After completion, reaction mixture was diluted with H₂O and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain 2-bromothiazole-4-carbonyl azide **15-2** (2.40 g). LCMS: [M+H]⁺ = 205.

[0121] **Step-2: 1-(2-bromothiazol-4-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea (15-4):** A solution of 2-bromothiazole-4-carbonyl azide **15-2** (2.50 g, 10.7 mmol) in toluene (20 mL) was stirred at 90 °C for 15 min. To the above reaction mixture was added (4*S*)-8-chlorochroman-4-amine hydrochloride **15-3** (2.36 g, 10.70 mmol) and stirred at 90 °C for 12 h. After completion, reaction mixture was concentrated under reduced pressure to obtain a product which was purified by CombiFlash to obtain **15-4** 1-(2-bromothiazol-4-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea (1.90 g). LCMS: [M+H]⁺ = 390.

[0122] **Step-3: 1-[(4*S*)-8-chlorochroman-4-yl]-3-(2-cyclopropylthiazol-4-yl)urea (Example 15):** To a stirred solution of 1-(2-bromothiazol-4-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea **15-4** (0.18 g, 0.476 mmol) in toluene (3 mL) and water (1 mL) was added cesium

carbonate (0.31 g, 0.95 mmol) followed by cyclopropylboronic acid **15-5** (0.06 g, 0.71 mmol) at RT. The reaction mixture was purged with argon for 5 min. To this was added Pd(dppf)Cl₂ (0.07 g, 0.09 mmol) and again purged with argon for 5 min. The reaction mixture was stirred at 80 °C for 12 h. After completion of reaction, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by prep-HPLC to afford **Example 15** (0.04 g). ¹H NMR: (400 MHz, DMSO-*d*₆) δ = 9.01 (s, 1H), 7.32 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.23 - 7.20 (m, 1H), 6.93 - 6.87 (m, 2H), 6.79 (d, *J* = 7.9 Hz, 1H), 4.92 (q, *J* = 1.0 Hz, 1H), 4.42 - 4.35 (m, 1H), 4.26 - 4.19 (m, 1H), 2.34 - 2.25 (m, 1H), 2.17 - 2.07 (m, 1H), 2.01 - 1.93 (m, 1H), 1.10 - 1.03 (m, 2H), 0.89 - 0.84 (m, 2H); LCMS: [M+H]⁺ = 350.

Example 16: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(1-methylpyrazol-4-yl)thiazol-4-yl]urea



Example 16

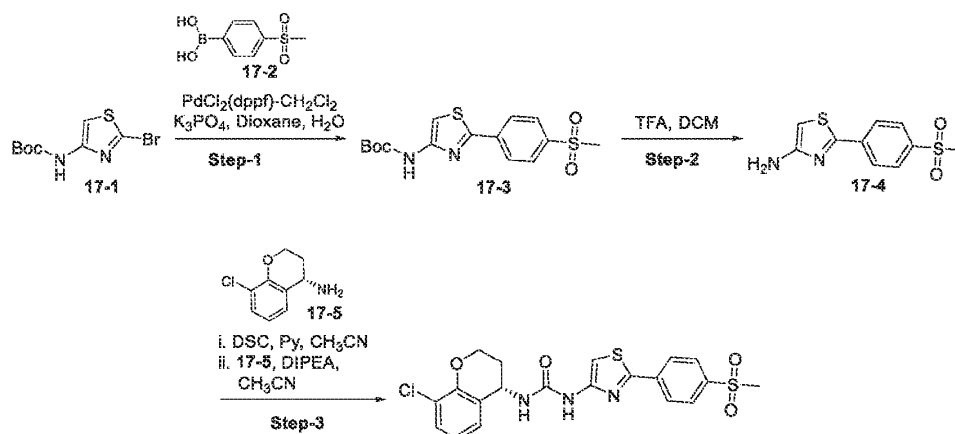
[0123] **Step-1: (*tert*-butyl *N*-[2-(1-methylpyrazol-3-yl)thiazol-4-yl]carbamate (16-3):** To a degassed solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **16-1** (0.30 g, 1.07 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **16-2** (0.33 g, 1.61 mmol) in 1,4-dioxane (12 mL) and water (4 mL) was added K₂CO₃ (0.44 g, 3.22 mmol) followed by Pd(PPh₃)₄ (0.12 g, 0.10 mmol). Reaction mixture was stirred at 90 °C for 16 h. After completion, the reaction mixture was quenched with H₂O and extracted with EtOAc. Combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and

concentrated under reduced pressure. The product was purified by the CombiFlash column (55% EtOAc/*n*-heptane) to afford (*tert*-butyl *N*-[2-(1-methylpyrazol-3-yl)thiazol-4-yl]carbamate **16-3** (0.27 g). LCMS: (M+H)⁺ = 281.

[0124] **Step-2: 2-(1-methylpyrazol-4-yl)thiazol-4-amine (16-4):** A mixture of *tert*-butyl *N*-[2-(1-methylpyrazol-3-yl)thiazol-4-yl]carbamate **16-3** (0.01 g, 0.03 mmol) and TFA (0.10 mL) was stirred at 0 °C for 15 min followed by at RT for 4 h. After completion, reaction mixture was concentrated under reduced pressure to afford 2-(1-methylpyrazol-4-yl)thiazol-4-amine **16-4** (0.01 g, TFA salt) which was used directly for the next reaction.

[0125] **Step-3: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(1-methylpyrazol-4-yl)thiazol-4-yl]urea (Example 16):** To a stirred solution of (4*S*)-8-chlorochroman-4-amine hydrochloride **16-5** (0.25 g, 1.15 mmol) in MeCN (10 mL) was added pyridine (0.20 mL, 2.31 mmol). The resulting reaction mixture was stirred at RT for 30 min. To this was added 2-(1-methylpyrazol-4-yl)thiazol-4-amine hydrochloride **16-4** (0.17 g, 0.80 mmol) followed by DIPEA (0.85 mL, 4.61 mmol) and the reaction mixture was stirred at 27 °C for 2 h. After completion, reaction mixture was quenched with H₂O, extracted with DCM. Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by prep HPLC to afford **Example 16** (0.05 g). ¹HNMR (400 MHz, DMSO-*d*₆) δ = 9.15 (s, 1H), 8.22 (s, 1H), 7.81 (d, *J* = 0.8 Hz, 1H), 7.33 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.05 (s, 1H), 6.95 - 6.81 (m, 2H), 4.98 - 4.92 (m, 1H), 4.43 - 4.37 (m, 1H), 4.28 - 4.23 (m, 1H), 3.88 (s, 3H), 2.18 - 2.12 (m, 1H), 2.04 - 1.99 (m, 1H); LCMS: [M+H]⁺ = 390.

Example 17: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-methylsulfonylphenyl)thiazol-4-yl]urea



Example 17

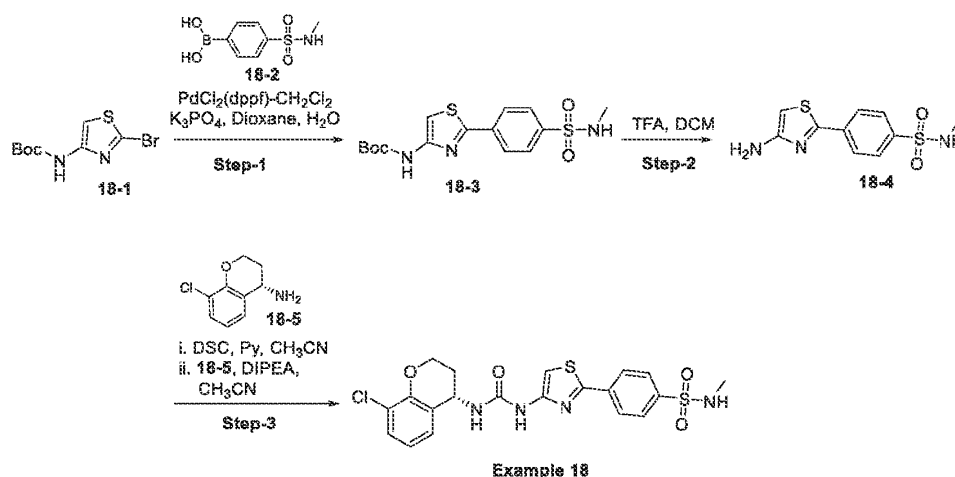
[0126] **Step-1: *tert*-butyl *N*-[2-(4-methylsulfonylphenyl)thiazol-4-yl]carbamate (17-3):** To a stirred solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **17-1** (0.50 g, 1.79 mmol) in 1,4-dioxane (2 mL) was added (4-methylsulfonylphenyl)boronic acid **17-2** (0.53 g, 2.69 mmol) followed by K_3PO_4 (1.14 g, 5.37 mmol) in water (0.5 mL) at RT. The reaction mixture was purged with argon for 20 min and then added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (0.08 g, 0.10 mmol) at RT. The reaction was stirred at 100 °C for 2 h. After completion, reaction was quenched with H_2O , extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by CombiFlash chromatography (40% EtOAc/heptane) to afford *tert*-butyl *N*-[2-(4-methylsulfonylphenyl)thiazol-4-yl]carbamate **17-3** (0.40 g). 1H NMR (400 MHz, $DMSO-d_6$) δ = 10.38 (br s, 1H), 8.14 - 8.11 (m, 2H), 8.06 - 8.03 (m, 2H), 7.41 (s, 1H), 3.26 (s, 3H), 1.48 (s, 9H); LCMS: $[M+H]^+ = 355$.

[0127] **Step-2: 2-(4-methylsulfonylphenyl)thiazol-4-amine (17-4):** To a stirred solution of *tert*-butyl *N*-[2-(4-methylsulfonylphenyl)thiazol-4-yl]carbamate **17-3** (0.20 g, 0.56 mmol) in DCM (2 mL) was added TFA (0.32 g, 2.82 mmol) at 0 °C. Reaction mixture was stirred at RT for 1 h. After completion, the reaction was quenched with saturated $NaHCO_3$ and aqueous layer was extracted with EtOAc. Combined organic layer was washed with brine solution,

dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Product was triturated from heptane to afford 2-(4-methylsulfonylphenyl)thiazol-4-amine **17-4** (0.08 g, TFA salt) which was used directly for the next reaction. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.08 - 8.05 (m, 2H), 8.00 - 7.97 (m, 2H), 6.10 (s, 1H), 5.60 (br s, 2H), 3.25 (s, 3H); LCMS: $[\text{M}+\text{H}]^+ = 255$.

[0128] **Step-3: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-methylsulfonylphenyl)thiazol-4-yl]urea (Example 17):** To a stirred solution of 2-(4-methylsulfonylphenyl)thiazol-4-amine **17-4** (0.08 g, 0.32 mmol) in MeCN (8 mL) was added *N,N'*-disuccinimidyl carbonate (0.25 g, 0.98 mmol) followed by pyridine (0.05 g, 0.65 mmol) at RT. The resulting mixture was stirred at RT for 15 min. To this was added (4*S*)-8-chlorochroman-4-amine **17-5** (0.06 g, 0.32 mmol) followed by DIPEA (0.05 mL, 0.32 mmol) and stirred at RT for 4 h. After completion, reaction mixture was diluted with H_2O and extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by CombiFlash chromatography (40% EtOAc/heptane) to afford **Example 17** (0.02 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.36 (s, 1H), 8.13 - 8.10 (m, 2H), 8.04 - 8.02 (m, 2H), 7.43 (s, 1H), 7.34 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.26 (d, $J = 7.9$ Hz, 1H), 6.94 - 6.90 (m, 2H), 5.00 - 4.94 (m, 1H), 4.44 - 4.38 (m, 1H), 4.29 - 4.23 (m, 1H), 3.26 (s, 3H), 2.20 - 2.12 (m, 1H), 2.06 - 2.00 (m, 1H); LCMS: $(\text{M}+\text{H})^+ = 464$.

Example 18: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[4-(methylsulfonyl)phenyl]thiazol-4-yl]urea



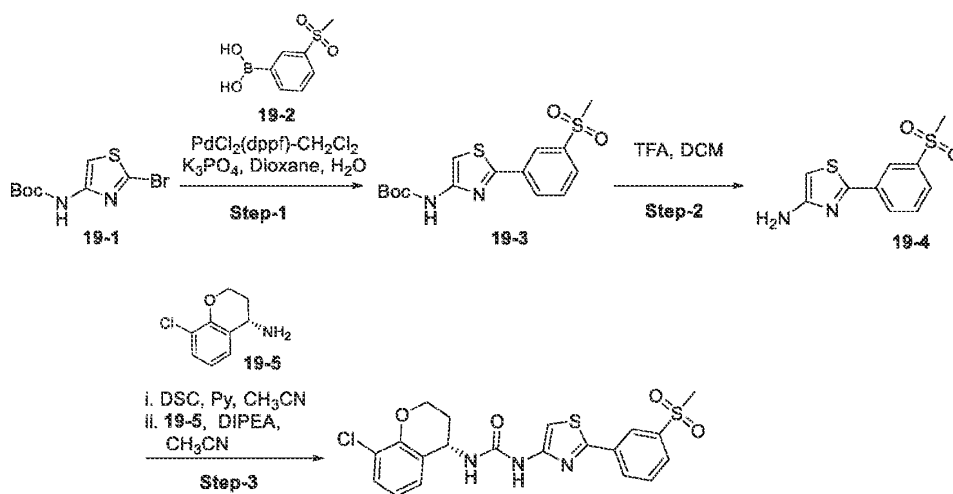
[0129] **Step-1: *tert*-butyl *N*-[2-[4-(methylsulfamoyl) phenyl] thiazol-4-yl] carbamate (18-3):** To a stirred solution of [4-(methylsulfamoyl) phenyl] boronic acid **18-2** (0.57 g, 2.69 mmol) in 1, 4 dioxane (8 mL) and water (2 mL) was added *tert*-butyl *N*-(2-bromothiazol-4-yl) carbamate **18-1** (0.50 g, 1.79 mmol) followed by K₃PO₄ (1.14 g, 5.37 mmol) and the reaction mixture was degassed for 15 min. To the resulting reaction mixture was added Pd(dppf)Cl₂ complex with dichloromethane (0.26 g, 0.35 mmol) and degassed for 10 min. The reaction mixture was stirred at 100 °C for 4 h. After completion, reaction mixture was quenched with H₂O, extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The product obtained was purified by CombiFlash (20% EtOAc/hexane) to afford *tert*-butyl *N*-[2-[4-(methylsulfamoyl) phenyl] thiazol-4-yl] carbamate **18-3** (0.50 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.36 (br s, 1H), 8.08 (d, *J* = 8.3 Hz, 2H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 4.4 Hz, 1H), 7.39 (s, 1H), 2.45 (d, *J* = 3.9 Hz, 3H), 1.48 (s, 9H).

[0130] **Step-2: 4-(4-aminothiazol-2-yl)-*N*-methyl-benzenesulfonamide (18-4):** A mixture of *tert*-butyl *N*-[2-[4-(methylsulfamoyl) phenyl] thiazol-4-yl] carbamate **18-3** (0.40 g, 1.08 mmol) and TFA (8.00 mL) was stirred at 0 °C for 1 h. After completion, reaction mixture was concentrated under reduced pressure. The product was quenched with saturated NaHCO₃ solution, extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 4-(4-aminothiazol-2-yl)-*N*-methyl-benzenesulfonamide **18-4** (0.30 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.53- 7.50 (m, 1H), 6.07 (s, 1H), 5.57 (s, 2H), 2.44 (d, *J* = 85.2 Hz, 3H); LCMS: [M+H]⁺ = 270.

[0131] **Step-3: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[4-(methylsulfamoyl) phenyl] thiazol-4-yl]urea (Example 18):** To a stirred solution of 4-(4-aminothiazol-2-yl)-*N*-methyl-benzenesulfonamide **18-4** (0.15 g, 0.55 mmol) in MeCN (5 mL) was added *N,N*-disuccinimidyl carbonate (0.14 g, 0.55 mmol) followed by pyridine (0.04 mL, 0.55 mmol). Reaction mixture was stirred at RT for 45 min. Reaction mixture was cooled to 0 °C, was added DIEPA (0.29 mL, 1.65 mmol) followed by (4*S*)-8-chlorochroman-4-aminehydrochloride **18-5** (0.12 g, 0.55 mmol) and stirred at 0 °C for 3 h. After completion, reaction mixture was quenched with H₂O and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to yield product. The product was purified by

CombiFlash (20% EtOAc/*n*-heptane) to afford **Example 18** (0.09 g). ^1H NMR (400 MHz, DMSO- d_6) δ = 9.34 (s, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 7.57 (q, J = 5.0 Hz, 1H), 7.40 (s, 1H), 7.34 (dd, J = 1.4, 7.9 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 6.92 (t, J = 7.8 Hz, 2H), 4.97 (q, J = 6.1 Hz, 1H), 4.44 - 4.38 (m, 1H), 4.28 - 4.23 (m, 1H), 2.44 (d, J = 5.0 Hz, 3H), 2.19 - 2.13 (m, 1H), 2.06 - 2.02 (m, 1H); LCMS: $[\text{M}+\text{H}]^+ = 479$.

Example 19: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(3-methylsulfonylphenyl)thiazol-4-yl]urea



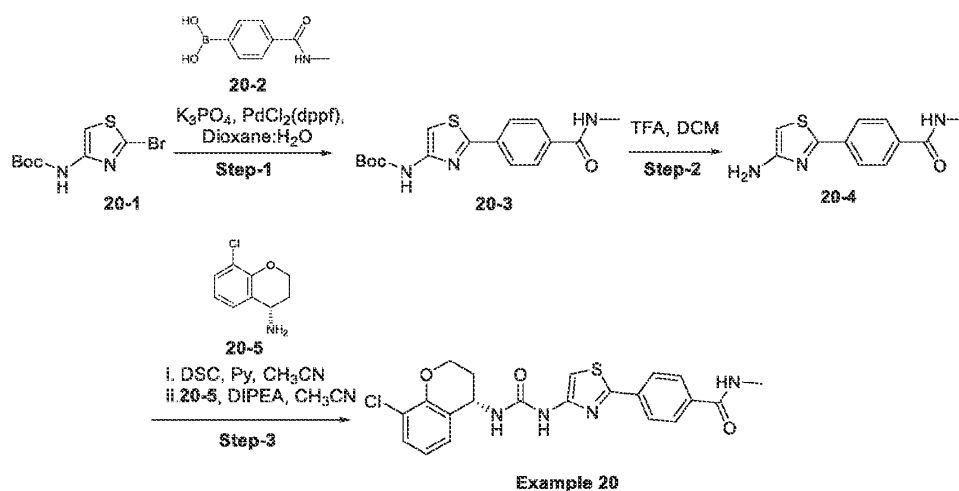
Example 19

[0132] **Step-1: *tert*-butyl *N*-[2-(3-methylsulfonylphenyl)thiazol-4-yl]carbamate (**19-3**):** To a stirred solution of (3-methylsulfonylphenyl)boronic acid **19-2** (0.04 g, 0.21 mmol) in 1,4-dioxane (2 mL) and H_2O (0.5 mL) were added *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **19-1** (0.05 g, 0.17 mmol) and K_3PO_4 (0.11 g, 0.53 mmol) at RT. The reaction mixture was purged with argon gas for 30 min. To the resulting reaction mixture was added (1,1-*bis*(diphenylphosphino)ferrocene)palladium (II) dichloride (0.03 g, 0.03 mmol) at RT and resulting mixture was degassed for 10 min. The reaction mixture was maintained at 80 °C for 3 h. After completion, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford *tert*-butyl *N*-[2-(3-methylsulfonylphenyl)thiazol-4-yl]carbamate **19-3** (0.04 g). LCMS: $[\text{M}+\text{H}]^+ = 299$.

[0133] **Step-2: 2-(3-methylsulfonylphenyl)thiazol-4-amine (19-4):** To a stirred solution of *tert*-butyl *N*-[2-(3-methylsulfonylphenyl)thiazol-4-yl]carbamate **19-3** (0.50 g, 1.41 mmol) in DCM (2 mL) was added TFA (1.10 mL, 14.10 mmol) at 0 °C. Reaction mixture was stirred at RT for 4 h. After completion, the reaction mixture was quenched with sodium bicarbonate solution and extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford 2-(3-methylsulfonylphenyl)thiazol-4-amine **19-4** (0.33 g, TFA salt). LCMS: [M+H]⁺ = 255.

[0134] **Step-3: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(3-methylsulfonylphenyl)thiazol-4-yl]urea (Example 19):** To a stirred solution of compound 2-(3-methylsulfonylphenyl)thiazol-4-amine **19-4** (0.10 g, 0.39 mmol) in MeCN (3 mL) was added pyridine (0.03 mL, 0.39 mmol) followed by *N,N*-disuccinimidyl carbonate (0.10 g, 0.40 mmol) and reaction mixture was stirred at RT for 15 min. To this was added (4*S*)-8-chlorochroman-4-amine hydrochloride **19-5** (0.08 g, 0.39 mmol) followed by DIPEA (0.22 mL, 1.18 mmol) and the reaction was stirred at RT for 4 h. After completion, reaction mixture was quenched with H₂O and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain product. The product was purified by prep-HPLC to afford **Example 19** (0.06 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.40 (s, 1H), 8.36 (t, *J* = 1.6 Hz, 1H), 8.20 - 8.17 (m, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.39 (s, 1H), 7.34 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.97 (q, *J* = 6.4 Hz, 1H), 4.43 - 4.38 (m, 1H), 4.28 - 4.24 (m, 1H), 3.29 (s, 3H), 2.19 - 2.14 (m, 1H), 2.07 - 2.01 (m, 1H); LCMS: [M+H]⁺ = 464.

Example 20: Synthesis of 4-[4-[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-N-methyl-benzamide



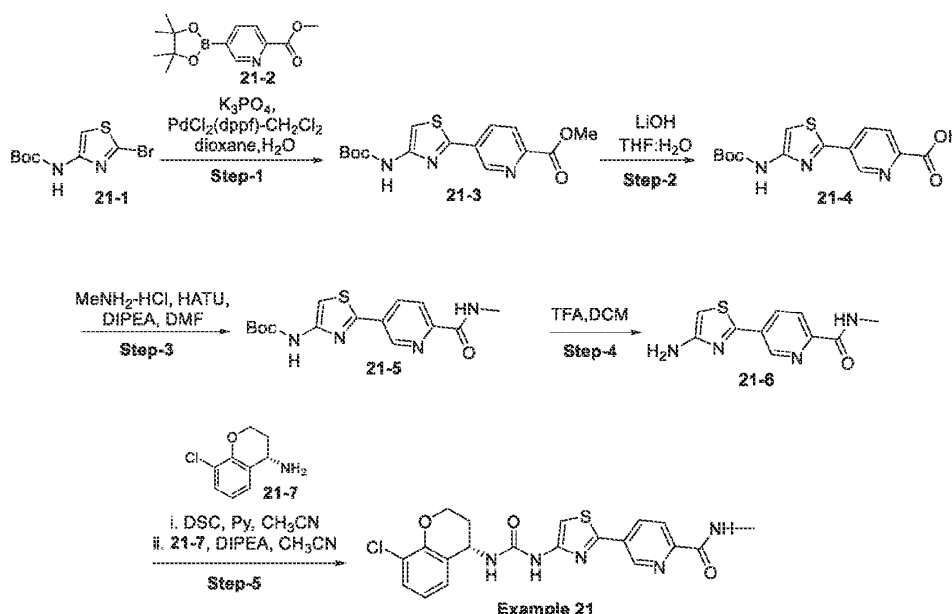
[0135] **Step-1: *tert*-butyl *N*-[2-[4-(methylcarbamoyl)phenyl]thiazol-4-yl]carbamate (20-3):** To a stirred solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **20-1** (0.50 g, 1.79 mmol) and [4-(methylcarbamoyl)phenyl]boronic acid **20-2** (0.38 g, 2.15 mmol) in 1,4-dioxane (10 mL), potassium phosphate (1.14 g, 5.37 mmol) was added dissolved in water (2 mL) and the reaction mixture was purged with argon for 30 min. To the resulting reaction mixture, Pd(dppf)Cl₂-DCM (0.08 g, 0.107 mmol) was added and the reaction mixture was again purged with argon for 20 min. The reaction mixture was stirred at 100 °C for 16 h. After completion of reaction, the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was diluted with cold water and extracted with ethyl acetate. Combined organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by silica gel column chromatography (60% EtOAc/hexane) to afford *tert*-butyl *N*-[2-[4-(methylcarbamoyl)phenyl]thiazol-4-yl]carbamate **20-3** (0.55 g). LCMS: [M+H]⁺ = 334.

[0136] **Step-2: 4-(4-aminothiazol-2-yl)-*N*-methyl-benzamide (20-4):** A solution of *tert*-butyl *N*-[2-[4-(methylcarbamoyl)phenyl]thiazol-4-yl]carbamate **20-3** (0.38 g, 1.14 mmol) in TFA (0.44 mL, 5.70 mmol) was stirred at 30 °C for 1 h. After completion of reaction, the reaction mixture was concentrated under reduced pressure, pH 8 was adjusted with NaHCO₃ solution and the aqueous layer was extracted with ethyl acetate. Combined organic layer was

dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash column chromatography (80% EtOAc/Heptane) to afford 4-(4-aminothiazol-2-yl)-*N*-methyl-benzamide **20-4** (0.20 g). LCMS: $[\text{M}+\text{H}]^+ = 234$.

[0137] **Step-3: 4-[4-[[[(4*S*)-8-chlorochroman-4-yl]carbamoylemino]thiazol-2-yl]-*N*-methyl-benzamide (Example 20):** To a stirred solution of 4-(4-aminothiazol-2-yl)-*N*-methyl-benzamide **20-4** (0.09 g, 0.40 mmol) in MeCN (2 mL) was added pyridine (0.06 mL, 0.81 mmol) followed by *N,N*-disuccinimidyl carbonate (0.10 g, 0.40 mmol) at RT and reaction mixture was stirred for 15 min. To this was added (4*S*)-8-chlorochroman-4-amine hydrochloride **20-5** (0.09 g, 0.40 mmol) followed by DIPEA (0.30 mL, 1.63 mmol) and the resulting reaction mixture was stirred at RT for 4 h. After completion, reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by prep-HPLC to afford **Example 20** (0.01 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) $\delta = 9.30$ (s, 1H), 8.54 (q, $J = 4.2$ Hz, 1H), 7.93 (s, 4H), 7.35 - 7.32 (m, 2H), 7.26 (d, $J = 7.8$ Hz, 1H), 6.94 - 6.90 (m, 2H), 4.99 - 4.94 (m, 1H), 4.43 - 4.38 (m, 1H), 4.28 - 4.23 (m, 1H), 2.80 (d, $J = 4.5$ Hz, 3H), 2.19 - 2.14 (m, 1H), 2.06 - 2.01 (m, 1H); LCMS: $[\text{M}+\text{H}]^+ = 443$.

Example 21: Synthesis of 5-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-*N*-methyl-pyridine-2-carboxamide



[0138] **Step-1: methyl 5-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]pyridine-2-carboxylate (21-3):** To a degassed solution of methyl 5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carboxylate **21-2** (0.14 g, 0.537 mmol), *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **21-1** (0.10 g, 0.35 mmol) and K_3PO_4 (0.22 g, 1.07 mmol) in 1,4-dioxane (4 mL) and water (1 mL), $PdCl_2(dppf)$ complex with dichloromethane (0.05 g, 0.07 mmol) was added and the reaction mixture was stirred at 100 °C for 14 h. After completion, reaction was quenched with H_2O , aqueous layer was extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The product was purified by CombiFlash to afford methyl 5-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]pyridine-2-carboxylate **21-3** (0.03 g). 1H NMR (400 MHz, $DMSO-d_6$) δ = 10.44 (br s, 1H), 9.19 (br s, 1H), 8.41 - 8.39 (m, 1H), 8.18 - 8.16 (m, 1H), 7.46 (s, 1H), 3.91 (s, 3H), 1.48 (s, 9H); LCMS: $[M+H]^+ = 336$.

[0139] **Step-2: 5-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]pyridine-2-carboxylic acid (21-4):** To a solution of methyl 5-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]pyridine-2-

carboxylate **21-3** (0.30 g, 0.89 mmol) in THF (6 mL):methanol (2 mL):water (2 mL) was added LiOH.H₂O (0.11 g, 2.68 mmol) and the reaction mixture was stirred at RT for 2 h. After completion, reaction mixture was concentrated. The product was diluted with H₂O, pH was adjusted with 2N HCl and precipitated solid was filtered, dried under reduced pressure to afford 5-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]pyridine-2-carboxylic acid **21-4** (0.20 g). LCMS: [M+H]⁺ = 322.

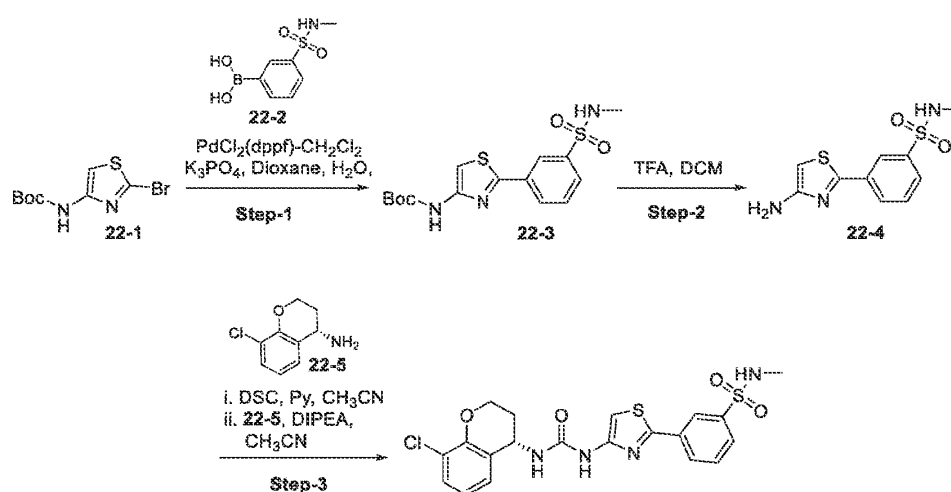
[0140] **Step-3: *tert*-butyl *N*-[2-[6-(methylcarbamoyl)-3-pyridyl]thiazol-4-yl]carbamate (21-5):** To a stirred solution of 5-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]pyridine-2-carboxylic acid **21-4** (0.20 g, 0.62 mmol) in DMF (2 mL) was added methylamine hydrochloride (0.06 g, 0.93 mmol) followed by addition of HATU (0.35 g, 0.93 mmol) and the reaction mixture was stirred at RT for 12 h. After completion, reaction mixture was quenched by addition of water and precipitated solid was filtered, dried under reduced pressure to afford *tert*-butyl *N*-[2-[6-(methylcarbamoyl)-3-pyridyl]thiazol-4-yl]carbamate **21-5** (0.13 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.38 (br s, 1H), 9.08 (s, 1H), 8.81 (br s, 1H), 8.40 - 8.38 (m, 1H), 8.14 - 8.12 (m, 1H), 7.46 - 7.42 (m, 1H), 2.84 (m, 3H), 1.48 (s, 9H); LCMS: [M+H]⁺ = 335.

[0141] **Step-4: 5-(4-aminothiazol-2-yl)-*N*-methyl-pyridine-2-carboxamide (21-6):** A mixture of *tert*-butyl *N*-[2-[6-(methylcarbamoyl)-3-pyridyl]thiazol-4-yl]carbamate **21-5** (0.13 g, 0.38 mmol) and TFA (0.59 mL, 7.78 mmol) was stirred at 0 °C for 10 min followed by at RT for 1 h. After completion, reaction mixture was concentrated under reduced pressure. The product **21-6** was triturated using diethyl ether and used directly for the next reaction. LCMS: [M+H]⁺ = 235.

[0142] **Step-5: 5-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-*N*-methyl-pyridine-2-carboxamide (Example 21):** To a stirred solution of 5-(4-aminothiazol-2-yl)-*N*-methyl-pyridine-2-carboxamide **21-6** (0.07 g, 0.299 mmol) in MeCN (2 mL) was added pyridine (0.07 mL, 0.89 mmol) followed by *N,N'*-disuccinimidyl carbonate (0.07 g, 0.30 mmol). Resulting reaction mixture was stirred at RT for 20 min. To this was added (4*S*)-8-chlorochroman-4-amine **21-7** (0.05 g, 0.29 mmol) followed by DIPEA (0.16 mL, 0.89 mmol) and reaction mixture was stirred at 30 °C for 4 h. After completion, reaction mixture was concentrated under reduced pressure and product obtained was dissolved in EtOAc. Organic layer was washed with 2N HCl, H₂O, brine solution, dried over anhydrous Na₂SO₄

and concentrated under reduced pressure. The product was purified by prep-HPLC to afford **Example 21** (0.003 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.40 (s, 1H), 9.08 (d, J = 1.6 Hz, 1H), 8.83 (d, J = 5.1 Hz, 1H), 8.39 (dd, J = 2.2, 8.2 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.45 (s, 1H), 7.34 (dd, J = 1.2, 7.9 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 6.94 - 6.87 (m, 2H), 5.01 - 4.93 (m, 1H), 4.43 - 4.38 (m, 1H), 4.29 - 4.22 (m, 1H), 2.84 (d, J = 4.9 Hz, 3H), 2.19 - 2.15 (m, 1H), 2.07 - 2.03 (m, 1H); LCMS: $[\text{M}+\text{H}]^+ = 445$.

Example 22: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[3-(methylsulfamoyl)phenyl]thiazol-4-yl]urea



Example 22

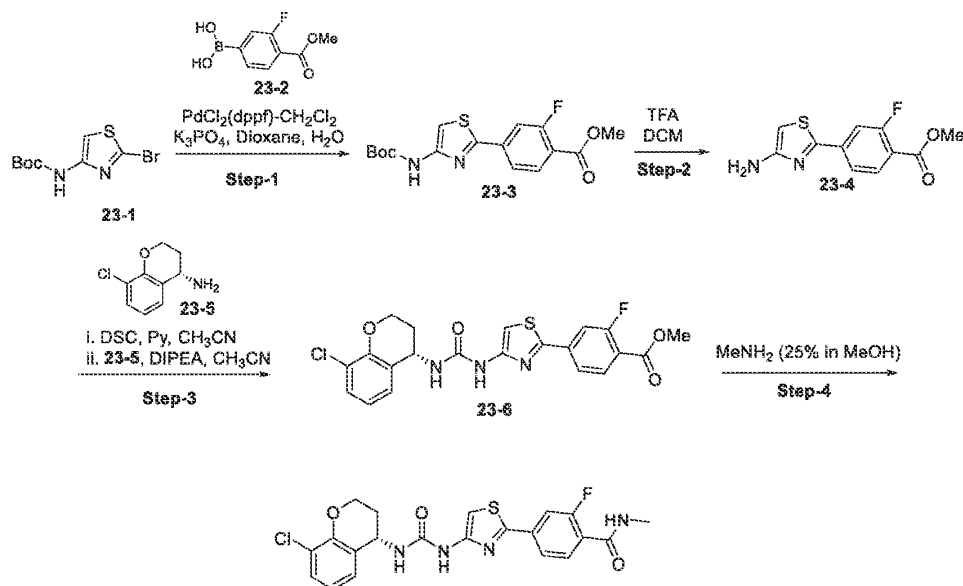
[0143] **Step-1: *tert*-butyl *N*-[2-[3-(methylsulfamoyl)phenyl]thiazol-4-yl]carbamate (**22-3**):** To a stirred solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **22-1** (0.50 g, 1.79 mmol) and [3-(methylsulfamoyl)phenyl]boronic acid **22-2** (0.38 g, 1.79 mmol) in 1,4-dioxane (10 mL), K_3PO_4 (1.14 g, 5.37 mmol) was added dissolved in water (5 mL) and the reaction mixture was purged with argon for 30 min. To the resulting reaction mixture, $\text{Pd}(\text{dppf})\text{Cl}_2$ complex with dichloromethane (0.29 g, 0.35 mmol) was added and the reaction mixture was again purged with argon for 20 min. The reaction mixture was stirred at 100 °C for 16 h. After completion of reaction, the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was diluted with cold water and extracted with ethyl acetate. Combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and

concentrated under reduced pressure to afford *tert*-butyl *N*-[2-[3-(methylsulfamoyl)phenyl]thiazol-4-yl]carbamate **22-3** (0.50 g). LCMS: $[M+H]^+ = 370$.

[0144] **Step-2: 3-(4-aminothiazol-2-yl)-*N*-methyl-benzenesulfonamide (22-4):** To a stirred solution of *tert*-butyl *N*-[2-[3-(methylsulfamoyl)phenyl]thiazol-4-yl]carbamate **22-3** (0.10 g, 0.27 mmol) was added TFA (0.21 mL, 2.71 mmol) at 0 °C and the reaction mixture was stirred at that temperature for 1 h. After completion, reaction mixture was concentrated under reduced pressure. The product was quenched with saturated NaHCO₃ solution, aqueous layer was extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 3-(4-aminothiazol-2-yl)-*N*-methyl-benzenesulfonamide **22-4** (0.07 g). LCMS: $[M+H]^+ = 270$.

[0145] **Step-3: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[3-(methylsulfamoyl)phenyl]thiazol-4-yl]urea (Example 22):** To a stirred solution of 3-(4-aminothiazol-2-yl)-*N*-methyl-benzenesulfonamide **22-4** (0.07 g, 0.26 mmol) in MeCN (5 mL) was added pyridine (0.04 g, 0.52 mmol) followed by *N,N'*-disuccinimidyl carbonate (0.06 g, 0.26 mmol). The resulting mixture was stirred at 25 °C for 30 min. To this was added (4*S*)-8-chlorochroman-4-amine **22-5** (0.04 g, 0.26 mmol) followed by DIPEA (0.10 g, 0.78 mmol) and the reaction mixture was stirred at 25 °C for 12 h. After completion, reaction mixture was concentrated under reduced pressure. The product was diluted with water and solid obtained was filtered, dried under reduced pressure. The product was purified by prep HPLC to afford **Example 22** (0.01 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.39 (s, 1H), 8.26 (t, *J* = 1.6 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 5.1 Hz, 1H), 7.76 - 7.71 (m, 1H), 7.61 (d, *J* = 5.0 Hz, 1H), 7.38 (s, 1H), 7.34 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.25 (d, *J* = 7.0 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 4.97 (q, *J* = 6.3 Hz, 1H), 4.43 - 4.38 (m, 1H), 4.29 - 4.23 (m, 1H), 2.44 (d, *J* = 5.0 Hz, 3H), 2.19 - 2.14 (m, 1H), 2.06 - 2.02 (m, 1H); LCMS: $[M+H]^+ = 479$.

Example 23: Synthesis of methyl 4-[4-[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoate



Example 23

[0146] **Step-1: methyl 4-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]-2-fluoro-benzoate (23-3):** To a stirred solution of (3-fluoro-4-methoxycarbonyl-phenyl)boronic acid **23-2** (0.42 g, 2.15 mmol) and *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **23-1** (0.50 g, 1.79 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was added K_3PO_4 (1.14 g, 5.37 mmol) and the reaction mixture was degassed for 30 min. To the resulting reaction mixture was added (1,1'-*bis*(diphenylphosphino)ferrocene)palladium (II) dichloride (0.29 g, 0.35 mmol) and degassed for another 10 min. The reaction mixture was stirred at 80 °C for 16 h. After completion, reaction was quenched with H_2O , extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Product obtained was purified by CombiFlash (5-10% EtOAc/Hexane) to afford methyl 4-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]-2-fluoro-benzoate **23-3** (0.40 g). 1H NMR: (400 MHz, $DMSO-d_6$) δ = 10.37 (br s, 1H), 8.03 - 7.99 (m, 1H), 7.84 - 7.77 (m, 2H), 7.43 (s, 1H), 3.88 (s, 3H), 1.48 (s, 9H). LCMS: $[M+H]^+ = 297$.

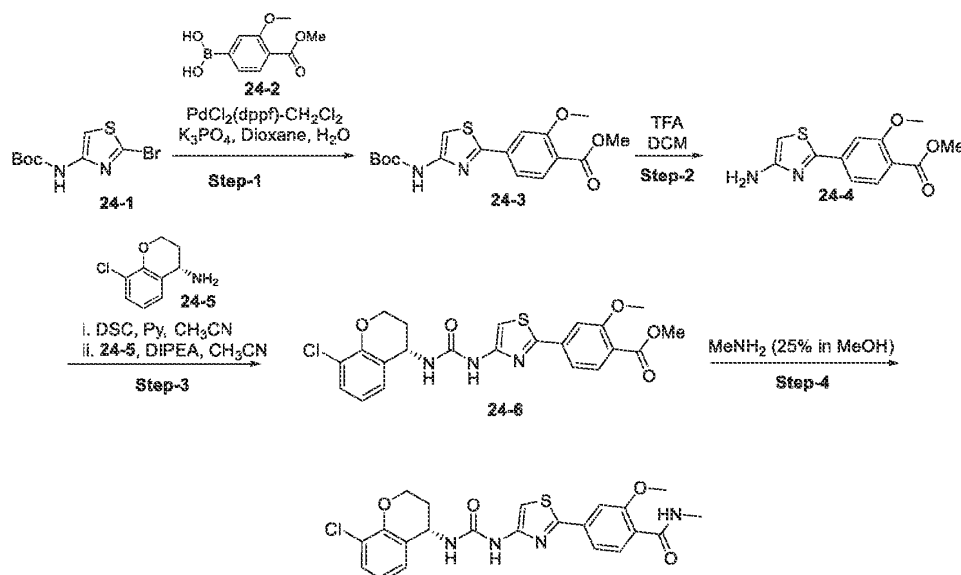
[0147] **Step-2: methyl 4-(4-aminothiazol-2-yl)-2-fluoro-benzoate (23-4):** A solution of methyl 4-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]-2-fluoro-benzoate **23-3** (1.00 g, 2.84

mmol) in TFA (10 mL) was stirred at 0 °C for 2 h. After completion, reaction mixture was concentrated under reduced pressure. Product obtained was triturated using pentane to afford methyl 4-(4-aminothiazol-2-yl)-2-fluoro-benzoate **23-4** (0.50 g). LCMS: $[M+H]^+ = 253$.

[0148] **Step-3: methyl 4-[4-[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoate (23-6):** To a stirred solution of methyl 4-(4-aminothiazol-2-yl)-2-fluoro-benzoate **23-4** (0.20 g, 0.79 mmol) in MeCN (5 mL) was added *N,N*-disuccinimidyl carbonate (0.20 g, 0.793 mmol) followed by pyridine (0.06 mL, 0.79 mmol) and the reaction mixture was stirred at RT for 40 min. Reaction mixture was cooled to 0 °C and DIEPA (0.42 mL, 2.38 mmol) was added followed by (4S)-8-chlorochroman-4-amine hydrochloride **23-5** (0.17 g, 0.793 mmol). The reaction mixture was stirred at 0 °C for 4 h. After completion, reaction mixture was concentrated under reduced pressure and product was dissolved in EtOAc. Organic layer was washed with 2N HCl, H₂O, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product obtained was purified by CombiFlash (20% EtOAc/Hexane) to afford methyl 4-[4-[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoate **23-6** (0.20 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.33 (s, 1H), 7.99 (s, 1H), 7.81 - 7.75 (m, 2H), 7.44 (s, 1H), 7.29 (dd, *J* = 6 Hz, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 7.6 Hz, 2H), 4.96 (s, 1H), 4.39 (s, 1H), 4.25 (s, 1H), 3.87 (s, 3H), 2.14 (s, 1H), 2.03 (s, 1H); LCMS: $(M+H)^+ = 462$.

[0149] **Step-4: 4-[4-[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-N-methyl-benzamide (Example 23):** A solution of methyl 4-[4-[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoate **23-6** (0.05 g, 0.12 mmol) in methylamine in methanol (7.00 mL) was stirred at RT for 12 h. After completion, solid was filtered under vacuum. The product solid was purified by prep HPLC to afford **Example 23** (0.01 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.30 (s, 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 7.77 - 7.68 (m, 3H), 7.38 (s, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 6.94 - 6.91 (m, 2H), 4.96 (q, *J* = 6.4 Hz, 1H), 4.44 - 4.38 (m, 1H), 4.29 - 4.20 (m, 1H), 2.79 (d, *J* = 4.4 Hz, 3H), 2.19 - 2.12 (m, 1H), 2.06 - 1.99 (m, 1H); LCMS: $[M+H]^+ = 461$.

Example 24: Synthesis of 4-[4-[(4*S*)-8-chlorochroman-4-yl] carbamoyl amino] thiazol-2-yl]-2-methoxy-benzamide



Example 24

[0150] **Step-1: methyl 4-[4-(*tert*-butoxycarbonylamino) thiazol-2-yl]-2-methoxy-benzoate (24-3):** To a degassed solution of *tert*-butyl *N*-(2-bromothiazole-4-yl)carbamate **24-1** (1.00 g, 3.58 mmol), **24-2** (3-methoxy-4-methoxycarbonyl-phenyl)boronic acid (1.13 g, 5.37 mmol) and K_3PO_4 (2.28 g, 10.7 mmol) in 1,4-dioxane (21 mL):water (7 mL) (3:1) was added $Pd(dppf)Cl_2$ (0.16 g, 0.21 mmol) and the reaction mixture was purged with argon for 10 min. Reaction mixture was stirred at 100 °C for 2 h. After completion, the organic layer was separated. The aqueous layer was extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield product which was purified by CombiFlash (30% EtOAc/*n*-heptane) to afford methyl 4-[4-(*tert*-butoxycarbonylamino) thiazol-2-yl]-2-methoxy-benzoate **24-3** (0.98 g). 1H NMR (400 MHz, $DMSO-d_6$) δ = 10.31 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 1.46 (s, 9H); LCMS: $[M+H]^+$ = 309.

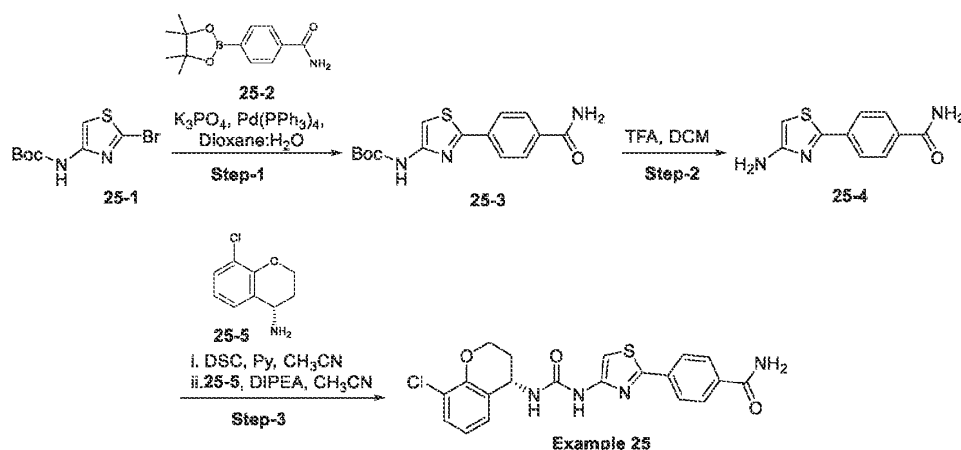
[0151] **Step-2: [2-(3-methoxy-4-methoxycarbonyl-phenyl) thiazol-4-yl]ammonium, 2,2,2-trifluoroacetate (24-4):** A solution of methyl 4-[4-(*tert*-butoxycarbonylamino) thiazol-2-yl]-2-methoxy-benzoate **24-3** (0.35 g, 0.96 mmol) in TFA (3.5 mL) was stirred at 0 °C for 2 h.

After completion, reaction mixture was concentrated under reduced pressure. The product was washed with diethyl ether to afford [2-(3-methoxy-4-methoxycarbonyl-phenyl)thiazol-4-yl]ammonium-2,2,2-trifluoroacetate salt **24-4** (0.30 g). ^1H NMR (400 MHz, DMSO- d_6) δ = 7.73 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 6.26 (s, 1H), 3.89 (s, 3H), 3.79 (s, 3H); LCMS: $[\text{M}+\text{H}]^+ = 265$.

Step-3: methyl 4-[4-[[4*S*]-8-chlorochroman-4-yl] carbamoyl amino] thiazol-2-yl]-2-methoxy-benzoate (24-6**):** To a stirred solution of *N,N'*-disuccinimidyl carbonate (0.11 g, 0.46 mmol) in MeCN (8 mL) was added pyridine (0.07 mL, 0.92 mmol) followed by methyl 4-(4-aminothiazol-2-yl)-2-methoxy-benzoate **24-4** (0.12 g, 0.46 mmol) and the reaction mixture was stirred at RT for 1 h. To this was added DIPEA (0.24 mL, 1.39 mmol) followed by (4*S*)-8-chlorochroman-4-amine **24-5** (0.08 g, 0.46 mmol) and stirred at RT for 45 min. After completion, reaction mixture was concentrated under reduced pressure. The product was dissolved in EtOAc, organic layer was washed with H₂O, brine, dried over anhydrous Na₂SO₄. The organic layer was concentrated under reduced pressure to afford methyl 4-[4-[[4*S*]-8-chlorochroman-4-yl] carbamoylamino] thiazol-2-yl]-2-methoxy-benzoate **24-6** (0.22 g). LCMS: $[\text{M}+\text{H}]^+ = 474$.

[0152] **Step-4: 4-[4-[[4*S*]-8-chlorochroman-4-yl] carbamoyl amino] thiazol-2-yl]-2-methoxy-benzamide (Example 24):** A solution of methyl 4-[4-[[4*S*]-8-chlorochroman-4-yl] carbamoyl amino] thiazol-2-yl]-2-methoxy-benzoate **24-6** (0.07 g, 0.14 mmol) in 25% methylamine in methanol (8 mL) was stirred at RT for 16 h. After completion, solid was filtered. The product solid was purified by prep HPLC to afford **Example 24** (0.01 g). ^1H NMR (400 MHz, DMSO- d_6) δ = 9.39 (s, 1H), 8.19 (d, J = 4.4 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.52 - 7.48 (m, 2H), 7.35 - 7.32 (m, 2H), 7.25 (d, J = 7.3 Hz, 1H), 6.94 - 6.87 (m, 2H), 5.01 - 4.94 (m, 1H), 4.44 - 4.39 (m, 1H), 4.28 - 4.23 (m, 1H), 3.94 (s, 3H), 2.81 (d, J = 4.4 Hz, 3H), 2.18 - 2.13 (m, 1H), 2.05 - 2.01 (m, 1H); LCMS: $[\text{M} + \text{H}]^+ = 473$.

Example 25: Synthesis of 4-[4-[[4-(8-chlorochroman-4-yl)]carbamoylamino]thiazol-2-yl]benzamide



[0153] **Step-1: *tert*-butyl *N*-[2-(4-carbamoylphenyl)thiazol-4-yl]carbamate (25-3):** To a stirred solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **25-1** (0.60 g, 2.15 mmol) and (4-carbamoylphenyl)boronic acid **25-2** (0.53 g, 3.22 mmol) in 1,4-dioxane (10mL), potassium phosphate (1.37 g, 6.45 mmol) was added dissolved in water (3mL) and the reaction mixture was purged with argon for 30 min. To the resulting reaction mixture, PdCl₂(dppf) (0.09 g, 0.129 mmol) was added and the reaction mixture was again purged with argon for 20 min. The reaction mixture was stirred at 100 °C for 16 h. After completion of reaction, the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was diluted with cold water and extracted with ethyl acetate. Combined organic layer was washed with water and brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by silica gel column chromatography (60 % EtOAc/hexane) to afford *tert*-butyl *N*-[2-(4-carbamoylphenyl)thiazol-4-yl]carbamate **25-3** (450 mg). LCMS: [M+H]⁺ = 264.

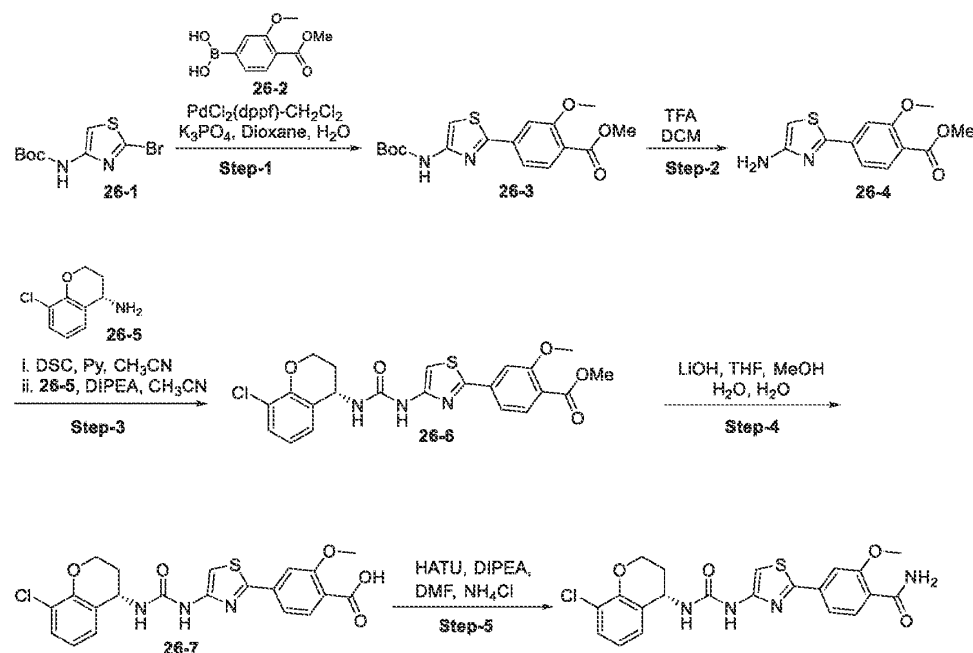
[0154] **Step-2: 4-(4-aminothiazol-2-yl)benzamide (25-4):** To a stirred solution of *tert*-butyl *N*-[2-(4-carbamoylphenyl)thiazol-4-yl]carbamate **25-3** (0.10 g, 0.31 mmol) in DCM (2 mL) maintained at 0 °C was added TFA (0.24 mL, 3.13 mmol). The reaction was stirred at RT for 4 h. After completion, reaction mixture was concentrated under reduced pressure. Product obtained was triturated using diethyl ether and pentane, dried well to afford 4-(4-

aminothiazol-2-yl)benzamide **25-4** (0.08 g) which was used directly for the next reaction.

LCMS: $[M+H]^+ = 220$.

[0155] **Step-3: 4-[4-[[*(4S)*-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]benzamide (Example 25):** To a stirred solution of 4-(4-aminothiazol-2-yl)benzamide **25-4** (0.07 g, 0.35 mmol) in MeCN (3 mL) was added *N,N'*-disuccinimidyl carbonate (0.09 g, 0.35 mmol) followed by pyridine (0.02 mL, 0.35 mmol). The resulting reaction mixture was stirred at RT for 45 min. To this was added DIPEA (0.19 mL, 1.06 mmol) followed by (*4S*)-8-chlorochroman-4-amine hydrochloride **25-5** (0.07 g, 0.35 mmol) and the reaction mixture was stirred at 30 °C for 1 h. After completion, reaction mixture was concentrated under reduced pressure and product obtained was dissolved in EtOAc. Organic layer was washed with 2N HCl, H₂O, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product obtained was purified by prep-HPLC to afford **Example 25** (0.06 g). ¹HNMR (400 MHz, DMSO-*d*₆) δ = 9.30 (s, 1H), 8.07 (br s, 1H), 7.99 - 7.90 (m, 4H), 7.47 (br s, 1H), 7.36 - 7.32 (m, 2H), 7.26 (d, *J* = 7.1 Hz, 1H), 6.95 - 6.90 (m, 2H), 4.97 (q, *J* = 6.1 Hz, 1H), 4.44 - 4.37 (m, 1H), 4.29 - 4.24 (m, 1H), 2.20 - 2.12 (m, 1H), 2.06 - 1.97 (m, 1H); LCMS: $[M+H]^+ = 429$.

Example 26: Synthesis of 4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzamide



Example 26

[0156] **Step-1: methyl 4-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]-2-methoxybenzoate (26-3):** To a degassed solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **26-1** (1.00 g, 3.58 mmol), **26-2** (3-methoxy-4-methoxycarbonyl-phenyl)boronic acid (1.12 g, 5.37 mmol) and K_3PO_4 (2.5 mL, 10.7 mmol) in 1,4-dioxane (10 mL) and water (2.5 mL) (3:1) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.15 g, 0.21 mmol) and argon was again purged for 10 min. Reaction was stirred at 100 °C for 2 h. After completion, the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by CombiFlash (30% EtOAc/*n*-heptane) to afford methyl 4-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]-2-methoxybenzoate **26-3** (0.92 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 10.33 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.36 (s, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 1.47 (s, 9H); LCMS: $[\text{M}+\text{H}]^+ = 365$.

[0157] **Step-2: methyl 4-(4-aminothiazol-2-yl)-2-methoxybenzoate (26-4):** A solution of methyl 4-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]-2-methoxybenzoate **26-3** (0.92 g, 2.46

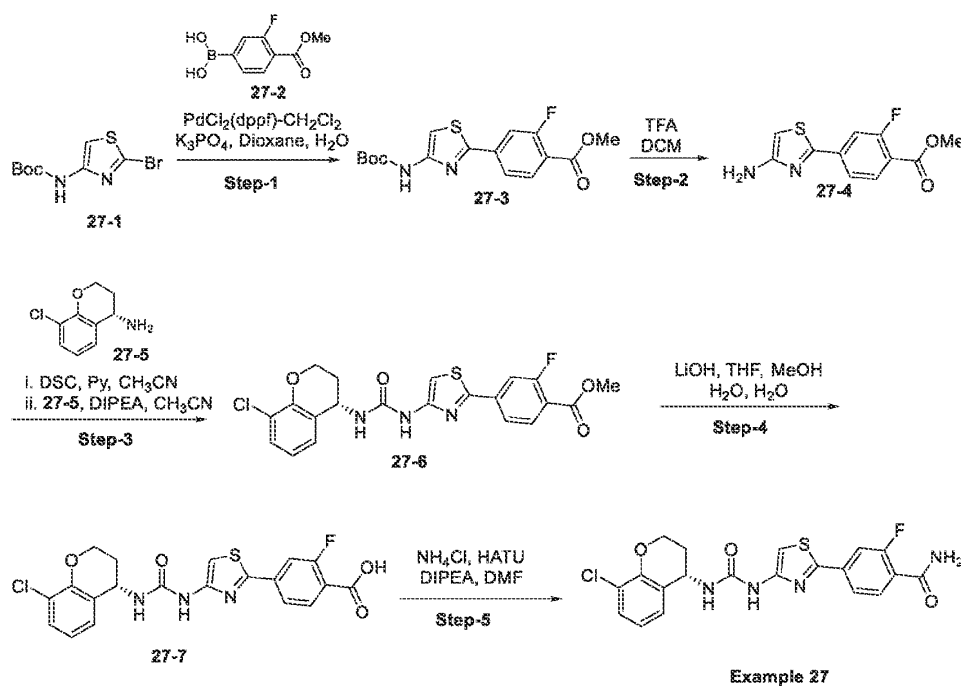
mmol) in TFA (9.0 mL) was stirred at 0 °C for 1 h. After completion, reaction mass was concentrated under reduced pressure. The product obtained was washed with diethyl ether to afford methyl 4-(4-aminothiazol-2-yl)-2-methoxybenzoate **26-4** (0.75 g, TFA salt). The product was used directly for the next reaction without any further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.73 (d, *J* = 7.6 Hz, 1H), 7.53 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 6.21 (s, 1H), 4.61 (br s, 2H), 3.89 (s, 3H), 3.79 (s, 3H); LCMS: [M+H]⁺ = 266.

[0158] **Step-3: methyl 4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzoate (26-6):** To a stirred solution of *N,N'*-disuccinimidyl carbonate (0.06 g, 0.26 mmol) in MeCN (4 mL) were added pyridine (0.04 mL, 0.53 mmol) and methyl 4-(4-aminothiazol-2-yl)-2-methoxybenzoate, TFA salt **26-4** (0.10 g, 0.265 mmol) and stirred at RT for 1 h. To the reaction mixture was added DIPEA (0.19 mL, 1.06 mmol) followed by (4*S*)-8-chlorochroman-4-amine hydrochloride **26-5** (0.05 g, 0.26 mmol) and stirred at RT for 45 min. After completion, reaction mass was concentrated under reduced pressure. The product was dissolved in EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford methyl 4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzoate **26-6** (0.08 g) ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.40 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.54 (s, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.37 (s, 1H), 7.33 - 7.25 (dd, *J* = 7.2 Hz, *J* = 8.0 Hz, 2H), 6.93 - 6.85 (m, 2H), 4.97 (d, *J* = 8.0 Hz, 1H), 4.42 - 4.25 (m, 2H), 3.89 (s, 3H), 3.80 (m, 3H), 2.17 - 1.98 (m, 2H); LCMS: [M+H]⁺ = 474.

[0159] **Step-4: 4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzoic acid (26-7):** To a stirred solution of methyl 4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzoate **26-6** (0.10 g, 0.21 mmol) in methanol (1 mL), THF (3 mL) and water (1 mL) was added LiOH.H₂O (0.08 g, 2.11 mmol) at 0 °C and the reaction mixture was stirred at RT for 3 h. After completion, reaction mass was concentrated under reduced pressure. The product obtained was dissolved in H₂O. The aqueous layer was acidified with dilute HCl to pH 2-3. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzoic acid **26-7** (0.06 g). LCMS: [M+H]⁺ = 460.

[0160] **Step-5: 4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzamide (Example 26):** To a stirred solution of 4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-methoxy-benzoic acid **26-7** (0.16 g, 0.348 mmol) in DMF (3 mL) was added HATU (0.19 g, 0.52 mmol) and DIPEA (0.18 mL, 1.04 mmol) followed by NH_4Cl (0.09 g, 1.74 mmol) and the reaction mixture was stirred at RT for 16 h. After completion, reaction mixture was quenched with ice-cold H_2O . The precipitated solid was filtered under vacuum to afford **Example 26** (0.01 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.40 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.68 (br s, 1H), 7.61 (br s, 1H), 7.53 - 7.48 (m, 2H), 7.35 - 7.31 (m, 2H), 7.25 (d, J = 7.3 Hz, 1H), 6.94 - 6.85 (m, 2H), 5.01 - 4.94 (m, 1H), 4.44 - 4.38 (m, 1H), 4.29 - 4.24 (m, 1H), 3.95 (s, 3H), 2.19 - 2.12 (m, 1H), 2.06 - 2.00 (m, 1H); LCMS: $[\text{M}+\text{H}]^+ = 459$.

Example 27: Synthesis of 4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzamide



[0161] **Step-1: methyl 4-[4-(tert-butoxycarbonylamino)thiazol-2-yl]-2-fluoro-benzoate (27-3):** To a degassed solution of *tert*-butyl *N*-(2-bromothiazol-4-yl) carbamate **27-1** (1.00 g, 3.58 mmol) was added (3-fluoro-4-methoxycarbonyl-phenyl)boronic acid **27-2** (0.85 g, 4.30

mmol) followed by K_3PO_4 (2.28 g, 10.7 mmol) in 1,4-dioxane (10 mL) and water (2 mL). To the resulting reaction mixture was added (1,1'-bis(diphenylphosphino)ferrocene) palladium (II) dichloride (0.17 g, 0.21 mmol) and degassed for 10 min. The reaction mixture was stirred at 80 °C for 2 h. After completion, reaction mixture was passed through Celite bed, the Celite bed was washed with EtOAc. The organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Product obtained was purified by CombiFlash (20% EtOAc/hexane) to afford methyl 4-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]-2-fluoro-benzoate **27-3** (0.80 g). 1H NMR: (400 MHz, $DMSO-d_6$) δ = 10.38 (br s, 1H), 8.03 - 7.99 (m, 1H), 7.83 - 7.75 (m, 2H), 7.42 (s, 1H), 3.87 (s, 3H), 1.48 (s, 9H); LCMS: $[M+H]^+ = 352$.

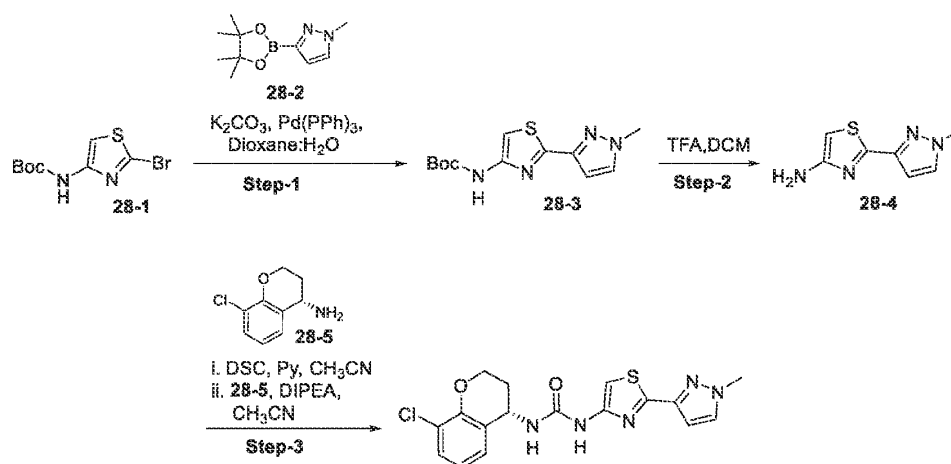
[0162] **Step-2: methyl 4-(4-aminothiazol-2-yl)-2-fluoro-benzoate (27-4):** A solution of methyl 4-[4-(*tert*-butoxycarbonylamino)thiazol-2-yl]-2-fluoro-benzoate **27-3** (1.00 g, 2.84 mmol) in TFA (10 mL) was stirred at 0 °C for 2 h. After completion, reaction mixture was concentrated under reduced pressure. Product obtained was triturated with pentane to afford methyl 4-(4-aminothiazol-2-yl)-2-fluoro-benzoate **27-4** (0.50 g) which was used directly for the next reaction. LCMS: $[M+H]^+ = 253$.

[0163] **Step-3: methyl 4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoate (27-6):** To a stirred solution of methyl 4-(4-aminothiazol-2-yl)-2-fluoro-benzoate **27-4** (0.20 g, 0.79 mmol) in MeCN (5 mL) was added *N,N*-disuccinimidyl carbonate (0.20 g, 0.79 mmol) followed by pyridine (0.06 mL, 0.79 mmol). Reaction mixture was stirred at RT for 40 min. Reaction mixture was cooled to 0 °C and was added DIEPA (0.42 mL, 2.38 mmol) followed by (4*S*)-8-chlorochroman-4-amine hydrochloride **27-5** (0.17 g, 0.79 mmol) and stirred at 0 °C for 4 h. After completion, reaction mixture was concentrated under reduced pressure and product was dissolved in EtOAc. Organic layer was washed with 2N HCl, H_2O , brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Product obtained was purified by CombiFlash (20% EtOAc/hexane) to afford methyl 4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoate **27-6** (0.20 g). 1H NMR (400 MHz, $DMSO-d_6$) δ = 9.33 (s, 1H), 7.99 (s, 1H), 7.81 - 7.75 (m, 2H), 7.44 (s, 1H), 7.29 (dd, $J = 6$ Hz, $J = 7.6$ Hz, 2H), 6.92 (d, $J = 7.6$ Hz, 2H), 4.96 (s, 1H), 4.39 (s, 1H), 4.25 (s, 1H), 3.87 (s, 3H), 2.14 (s, 1H), 2.03 (s, 1H); LCMS: $[M+H]^+ = 462$.

[0164] **Step-4: 4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoic acid (27-7):** To a stirred solution of methyl 4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoate **27-6** (0.30 g, 0.64 mmol) in THF (9 mL), methanol (6 mL) and water (3 mL) was added LiOH.H₂O (0.27 g, 6.48 mmol). Reaction mixture was stirred at RT for 12 h. After completion, reaction mixture was concentrated, product was diluted with H₂O and the pH was adjusted with 2N HCl. Solid obtained was filtered, dried under reduced pressure to afford 4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoic acid **27-7** (0.10 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.40 (br s, 1H), 9.34 (s, 1H), 7.97 (t, *J* = 7.8 Hz, 1H), 7.75 (dd, *J* = 8.4, 20.0 Hz, 2H), 7.43 - 7.25 (m, 3H), 6.97 - 6.90 (m, 2H), 4.96 (d, *J* = 6.0 Hz, 1H), 4.42 - 4.26 (m, 2H), 2.16 - 2.02 (m, 2H); LCMS: [M+H]⁺ = 448.

[0165] **Step-5: 4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzamide (Example 27):** To a stirred solution of 4-[4-[[[(4S)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]-2-fluoro-benzoic acid **27-7** (0.16 g, 0.34 mmol) in DMF (6 mL) were added DIPEA (0.18 mL, 1.00 mmol) and HATU (0.19 g, 0.50 mmol) followed by NH₄Cl (0.09 g, 1.67 mmol) at 0 °C. Reaction mixture was stirred at RT for 4 h. After completion, reaction mixture was quenched with H₂O, extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product obtained was purified by prep HPLC to afford **Example 27** (0.02 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.32 (s, 1H), 7.79 - 7.70 (m, 5H), 7.39 (s, 1H), 7.34 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 6.95 - 6.91 (m, 2H), 4.96 (q, *J* = 6.3 Hz, 1H), 4.43 - 4.37 (m, 1H), 4.29 - 4.23 (m, 1H), 2.20 - 2.13 (m, 1H), 2.07 - 1.98 (m, 1H); LCMS: [M+H]⁺ = 447.

Example 28: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(1-methylpyrazol-3-yl)thiazol-4-yl]urea



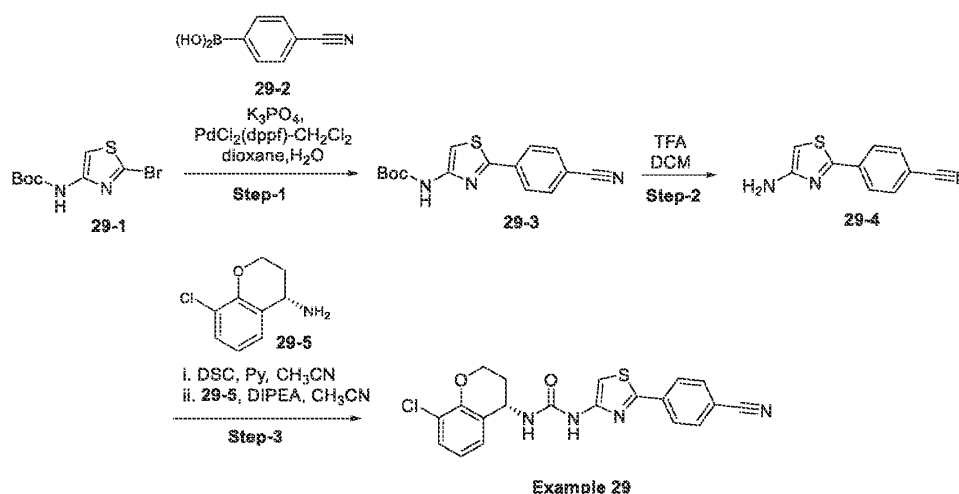
Example 28

[0166] **Step-1: *tert*-butyl *N*-[2-(1-methylpyrazol-3-yl)thiazol-4-yl]carbamate (28-3):** To a degassed solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **28-1** (0.30 g, 1.07 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **28-2** (0.33 g, 1.61 mmol) and K₂CO₃ (0.44 g, 3.22 mmol) in 1,4-dioxane (12 mL) and water (4 mL) was added Pd(PPh₃)₄ (0.12 g, 0.10 mmol) and argon was again purged for 10 min. Reaction mixture was stirred at 90 °C for 16 h. After completion, the reaction mixture was quenched with H₂O and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The product was purified by CombiFlash (55% EtOAc/*n*-heptane) to afford (*tert*-butyl *N*-[2-(1-methylpyrazol-3-yl)thiazol-4-yl]carbamate **28-3** (0.27 g). LCMS: [M+H]⁺ = 281.

[0167] **Step-2: (2-(1-methylpyrazol-3-yl)thiazol-4-amine (28-4):** A mixture of *tert*-butyl *N*-[2-(1-methylpyrazol-3-yl)thiazol-4-yl]carbamate **28-3** (0.27 g, 0.96 mmol) and TFA (0.80 mL) was stirred at 0 °C for 1 h followed by at RT for 4 h. After completion, reaction mixture was concentrated under reduced pressure. Product obtained was triturated with pentane to afford (2-(1-methylpyrazol-3-yl)thiazol-4-amine **28-4** (0.20 g, TFA salt) which was used directly for the next reaction. LCMS: [M+H]⁺ = 181.

[0168] **Step-3: (1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(1-methylpyrazol-3-yl)thiazol-4-yl]urea (Example 28):** To a stirred solution of 2-(1-methylpyrazol-3-yl)thiazol-4-amine **28-4** (0.07 g, 0.38 mmol) in MeCN (2 mL) was added pyridine (0.14 mL, 1.59 mmol) followed by *N,N'*-disuccinimidyl carbonate (0.09 g, 0.37 mmol). Resulting reaction mixture was stirred at RT for 30 min. To this was added (4*S*)-8-chlorochroman-4-amine **28-5** (0.08 g, 0.37 mmol) followed by DIPEA (0.03 mL, 0.16 mmol) and reaction was stirred at 30 °C for 1 h. After completion, reaction was quenched with H₂O, extracted with EtOAc. Organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product obtained was purified by CombiFlash (30% EtOAc in hexanes) to afford **Example 28** (0.38 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.22 (s, 1H), 7.82 (d, *J* = 2.3 Hz, 1H), 7.33 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.12 (s, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 4.95 (q, *J* = 6.3 Hz, 1H), 4.43 - 4.37 (m, 1H), 4.27 - 4.22 (m, 1H), 3.89 (s, 3H), 2.18 - 2.10 (m, 1H), 2.04 - 1.97 (m, 1H); LCMS: [M+H]⁺ = 390.

Example 29: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-cyanophenyl)thiazol-4-yl]urea



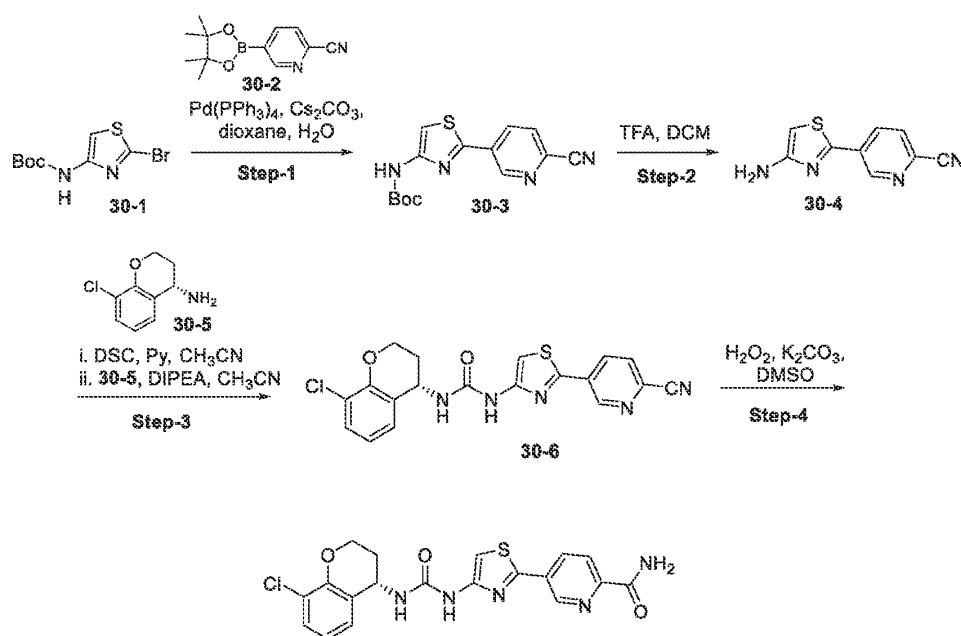
[0169] **Step-1: tert-butyl N-[2-(4-cyanophenyl)thiazol-4-yl]carbamate (29-3):** To a stirred solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **29-1** (1.00 g, 3.58 mmol) in 1,4-dioxane (20 mL), water (5 mL) were added (4-cyanophenyl)boronic acid **29-2** (0.79 g, 5.37 mmol) and K₃PO₄ (2.28 g, 10.70 mmol) at RT and purged with N₂ for 15 min. To the above

was added $\text{PdCl}_2(\text{dppf})_2$ complex with dichloromethane (0.18 g, 0.21 mmol) under same condition and reaction mixture was heated at 100 °C for 2 h. After completion, reaction mixture was quenched with H_2O and filtered through Celite bed. The filtrate was extracted with EtOAc and combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by CombiFlash (70% EtOAc/Heptane) to afford *tert*-butyl *N*-[2-(4-cyanophenyl)thiazol-4-yl]carbamate **29-3** (0.60 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 10.38 (br s, 1H), 8.06 - 8.03 (m, 2H), 7.98 - 7.95 (m, 2H), 7.42 (s, 1H), 1.48 (s, 9H).

[0170] **Step-2: 4-(4-aminothiazol-2-yl)benzonitrile (29-4):** To a stirred solution of *tert*-butyl *N*-[2-(4-cyanophenyl)thiazol-4-yl]carbamate **29-3** (0.18 g, 0.59 mmol) in DCM (4 mL) was added TFA (2 mL) at 0 °C drop wise. Reaction mixture was stirred at RT for 2 h. After completion of reaction, reaction mixture was concentrated under reduced pressure to afford 4-(4-aminothiazol-2-yl)benzonitrile **29-4** (0.12 g). LCMS: $[\text{M}+\text{H}]^+ = 202$.

[0171] **Step-3: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-cyanophenyl)thiazol-4-yl]urea (Example 29):** To a stirred solution of 4-(4-aminothiazol-2-yl)benzonitrile **29-4** (0.12 g, 0.53 mmol) in MeCN (2 mL) maintained at 0 °C was added pyridine (0.04 mL, 0.53 mmol) followed by *N,N'*-disuccinimidyl carbonate (0.13 g, 0.53 mmol). Resulting reaction mixture was stirred at RT for 1 h. To this was added (4*S*)-8-chlorochroman-4-amine hydrochloride **29-5** (0.11 g, 0.53 mmol) followed by DIPEA (0.29 mL, 1.59 mmol) and reaction mixture was stirred at RT for 1 h. After completion, reaction mixture was concentrated under reduced pressure. The product was quenched with H_2O and extracted with ethyl acetate. Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product obtained was purified by CombiFlash (40% EtOAc/Heptane) to afford **Example 29** 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-cyanophenyl)thiazol-4-yl]urea (0.01 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.33 (s, 1H), 8.06 - 8.02 (m, 2H), 7.97 - 7.92 (m, 2H), 7.44 (s, 1H), 7.34 (dd, J = 1.2, 7.9 Hz, 1H), 7.26 (d, J = 7.1 Hz, 1H), 6.94 - 6.90 (m, 2H), 4.96 (q, J = 6.4 Hz, 1H), 4.44 - 4.36 (m, 1H), 4.30 - 4.23 (m, 1H), 2.18 - 2.02 (m, 2H); LCMS: $[\text{M}+\text{H}]^+ = 411$.

Example 30: Synthesis of 5-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]pyridine-2-carboxamide



Example 30

[0172] **Step-1: *tert*-butyl *N*-[2-(6-cyano-3-pyridyl)thiazol-4-yl]carbamate (30-3):** To a stirred solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **30-1** (1.50 g, 5.37 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile **30-2** (2.47 g, 10.7 mmol) and Cs_2CO_3 (6.99 g, 21.5 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (0.37 g, 0.322 mmol) at RT. The reaction mixture was stirred at 120 °C for 12 h. After completion of the reaction, the reaction mixture was cooled and quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product obtained was purified with CombiFlash chromatography (45 % EtOAc/*n*-heptane) to afford *tert*-butyl *N*-[2-(6-cyano-3-pyridyl)thiazol-4-yl]carbamate **30-3** (0.23 g). LCMS: $[\text{M}-\text{H}]^- = 301$.

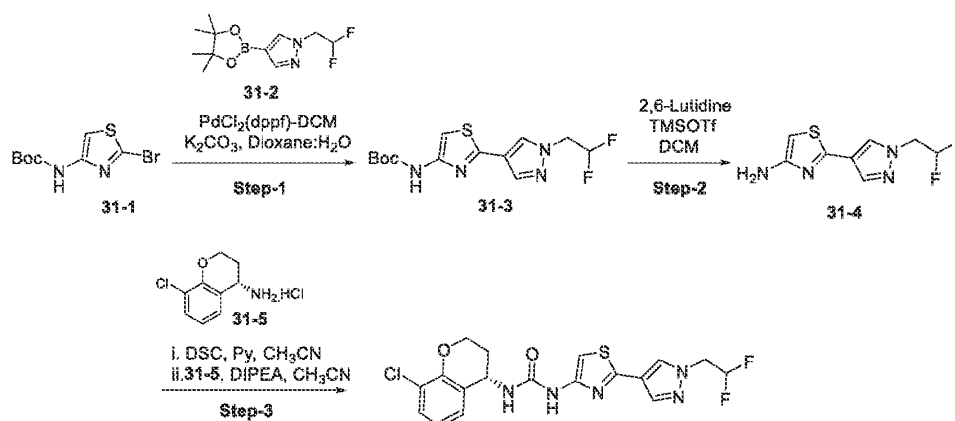
[0173] **Step-2: 5-(4-aminothiazol-2-yl)pyridine-2-carbonitrile (30-4):** To a stirred solution of *tert*-butyl *N*-[2-(6-cyano-3-pyridyl)thiazol-4-yl]carbamate **30-3** (0.14 g, 0.46 mmol) in DCM (5 mL) was added TFA (0.18 mL, 2.32 mmol) at 0 °C and the resulting reaction

mixture was stirred at RT for 4 h. After completion, reaction mixture was concentrated under reduced pressure. The product was triturated with diethyl ether and *n*-pentane to afford 5-(4-aminothiazol-2-yl)pyridine-2-carbonitrile **30-4** (0.11 g). LCMS: $[M+H]^+ = 203$.

[0174] **Step-3: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(6-cyano-3-pyridyl)thiazol-4-yl]urea (30-6):** To a stirred solution of 5-(4-aminothiazol-2-yl)pyridine-2-carbonitrile **30-4** (0.17 g, 0.84 mmol) in MeCN (4 mL) were added pyridine (0.14 mL, 1.68 mmol) and *N,N'*-disuccinimidyl carbonate (0.21 g, 0.84 mmol) and the reaction mixture was stirred at RT for 1 h. To the resulting reaction mixture (4*S*)-8-chlorochroman-4-amine hydrochloride **30-5** (0.18 g, 0.84 mmol) was added followed by DIPEA (0.59 mL, 3.36 mmol) and stirred at RT for 45 min. After completion, reaction mixture was concentrated under reduced pressure and product obtained was dissolved in EtOAc. Combined organic layer was washed with 2N HCl solution, water and brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Product was purified by column chromatography (40% EtOAc/Heptane) to afford 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(6-cyano-3-pyridyl)thiazol-4-yl]urea **30-6** (0.20 g). LCMS: $[M+H]^+ = 412$.

[0175] **Step-4: 5-[4-[[[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]pyridine-2-carboxamide (Example 30):** To a stirred solution of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(6-cyano-3-pyridyl)thiazol-4-yl]urea **30-6** (0.13 g, 0.31 mmol) in DMSO (3 mL) was added 30 % hydrogen peroxide (1.1 mL, 0.94 mmol) solution followed by potassium carbonate (0.17 g, 1.26 mmol) at RT. Reaction mixture was stirred at 30 °C for 1 h. After completion of reaction, reaction mixture was diluted with water and the precipitate was filtered out. The solid was washed with methanol and dried under vacuum to afford **Example 30** (0.12 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.38 (s, 1H), 9.08 (d, J = 1.8 Hz, 1H), 8.38 (dd, J = 2.3, 8.3 Hz, 1H), 8.18 - 8.12 (m, 2H), 7.74 (br s, 1H), 7.45 (s, 1H), 7.34 (dd, J = 1.1, 7.9 Hz, 1H), 7.26 (d, J = 7.4 Hz, 1H), 6.95 - 6.88 (m, 2H), 4.97 (q, J = 6.3 Hz, 1H), 4.44 - 4.37 (m, 1H), 4.29 - 4.25 (m, 1H), 2.20 - 2.12 (m, 1H), 2.07 - 2.01 (m, 1H); LCMS: $[M+H]^+ = 430$.

Example 31: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[1-(2,2-difluoroethyl)pyrazol-4-yl]thiazol-4-yl]urea



Example 31

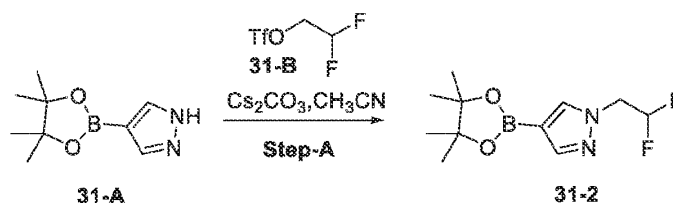
[0176] **Step-1: *tert*-butyl *N*-[2-[1-(2,2-difluoroethyl)pyrazol-4-yl]thiazol-4-yl]carbamate (31-3):** To a stirred solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **31-1** (0.50 g, 1.79 mmol) and 1-(2,2-difluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **31-2** (0.46 g, 1.79 mmol) in 1,4-dioxane (3 mL) and water (2 mL) was added potassium carbonate (0.74 g, 5.37 mmol). Reaction mixture was degassed with argon for 30 min. To this was added [1,1'-bis (diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (0.07 g, 0.08 mmol) and the reaction mixture was further degassed with argon for 10 min. Reaction mixture was stirred at 90 °C for 9 h. After completion, the reaction mixture was filtered through Celite. The filtrate was diluted with ice-cold water and extracted with EtOAc. Combined organic layer was washed with H₂O and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by CombiFlash (30% EtOAc/Hexane) to afford *tert*-butyl *N*-[2-[1-(2,2-difluoroethyl)pyrazol-4-yl]thiazol-4-yl]carbamate **31-3** (0.30 g). LCMS: [M+H]⁺ = 275.

[0177] **Step-2: 2-[1-(2,2-difluoroethyl)pyrazol-4-yl]thiazol-4-amine (31-4):** To a stirred solution of *tert*-butyl *N*-[2-[1-(2,2-difluoroethyl)pyrazol-4-yl]thiazol-4-yl]carbamate **31-3** (0.25 g, 0.75 mmol) in DCM (5 mL) maintained at 0 °C was added 2,6-lutidine (0.26 mL, 2.27 mmol) followed by trimethylsilyl trifluoromethanesulfonate (0.28 mL, 1.51 mmol) at RT. Reaction mixture was stirred at RT for 2 h. After completion, reaction mixture was concentrated under reduced pressure. Product obtained was triturated using diethyl ether to

afford 2-[1-(2,2-difluoroethyl)pyrazol-4-yl]thiazol-4-amine **31-4** (0.10 g) which was used directly for the next step. LCMS: $[M+H]^+ = 231$.

[0178] **Step-3: 1-[(4S)-8-chlorochroman-4-yl]-3-[2-[1-(2,2-difluoroethyl)pyrazol-4-yl]thiazol-4-yl]urea (Example 31):** To a stirred solution of 2-[1-(2,2-difluoroethyl)pyrazol-4-yl]thiazol-4-amine **31-4** (0.05 g, 0.22 mmol) in MeCN (3 mL) was added pyridine (0.04 mL, 0.43 mmol) at 0 °C followed by *N,N'*-disuccinimidyl carbonate (0.06 g, 0.23 mmol) at RT. Resulting reaction mixture was stirred at RT for 30 min. To this was added (4S)-8-chlorochroman-4-amine **31-5** (0.04 g, 0.23 mmol) followed by DIPEA (0.16 mL, 0.86 mmol) and the reaction was stirred at 30 °C for 2 h. After completion, reaction mixture was concentrated under reduced pressure. The product was quenched with H₂O and extracted with 10 % MeOH/DCM. Combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product obtained was purified by CombiFlash (10 % MeOH/DCM) to afford **Example 31** (0.01 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.18 (s, 1H), 8.33 (s, 1H), 7.94 (d, *J* = 0.6 Hz, 1H), 7.33 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.27 - 7.22 (m, 1H), 7.10 (s, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.59 - 6.24 (m, 1H), 5.00 - 4.90 (m, 1H), 4.77 - 4.64 (m, 2H), 4.44 - 4.39 (m, 1H), 4.29 - 4.22 (m, 1H), 2.20 - 2.10 (m, 1H), 2.06 - 1.97 (m, 1H); LCMS: $[M+H]^+ = 440$.

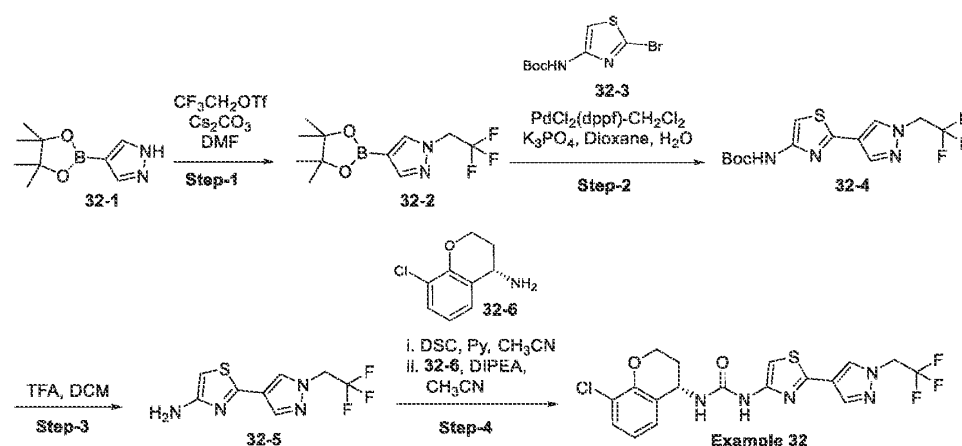
Synthesis of 31-2:



[0179] **Step-A: 1-(2,2-difluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (31-2):** To a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole **31-A** (1.00 g, 5.15 mmol) in MeCN (20 mL) was added cesium carbonate (4.20 g, 12.9 mmol) followed by 2,2-difluoroethyl trifluoromethanesulfonate **31-B** (0.80 mL, 5.67 mmol) at RT. Resulting reaction mixture was stirred at RT for 2 h. After completion, reaction mixture was concentrated under reduced pressure, filtered on Celite bed and washed with EtOAc. The product was purified by CombiFlash (30 % EtOAc/Heptane) to afford 1-(2,2-

difluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole **31-2** (1.00 g). LCMS: $[M+H]^+ = 259$.

Example 32: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]thiazol-4-yl]urea



[0180] **Step-1: 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)pyrazole (32-2):** To a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole **32-1** (0.50 g, 2.58 mmol) in DMF (7 mL) was added Cs_2CO_3 (2.09 g, 6.44 mmol) at 0 °C followed by addition of 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.45 mL, 3.09 mmol) and the reaction mixture was stirred at RT for 16 h. After completion of reaction, the reaction mixture was filtered, diluted with water and extracted with ethyl acetate. Organic layer was washed with water, brine and dried over anhydrous Na_2SO_4 . The organic layer was concentrated under reduced pressure. The product obtained was purified by CombiFlash chromatography (50% EtOAc/n-heptane) to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)pyrazole **32-2** (0.23 g).

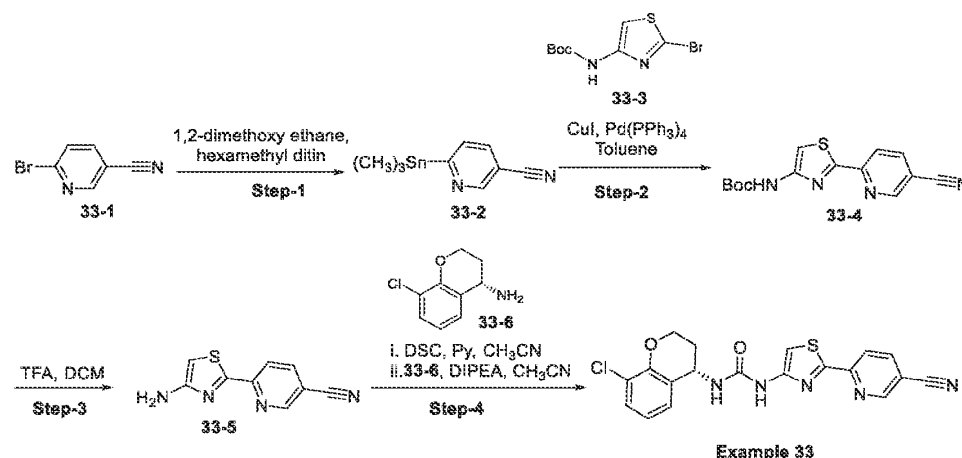
Step-2: *tert*-butyl *N*-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]thiazol-4-yl]carbamate (32-4): To a stirred solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **32-3** (0.15 g, 0.53 mmol) in 1,4-dioxane (3 mL) and water (0.75 mL) were added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)pyrazole **32-2** (0.22 g, 0.80 mmol), tripotassium phosphate (0.34 g, 1.61 mmol) at RT and purged with argon for 15 min. To this was added

Pd(dppf)Cl₂ complex with DCM (0.02 g, 0.03 mmol) and reaction mixture was stirred at 110 °C for 2 h. After completion, reaction mixture was filtered, diluted with water and extracted with ethyl acetate. Organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by CombiFlash (30% EtOAc/heptane) to afford *tert*-butyl *N*-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]thiazol-4-yl]carbamate **32-4** (0.15 g). LCMS: [M+H]⁺ = 293 (M-*t*Bu).

[0181] **Step-3: 2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]thiazol-4-amine (32-5):** A solution of *tert*-butyl *N*-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]thiazol-4-yl]carbamate **32-4** (0.10 g, 0.28 mmol) in TFA (2 mL) was stirred at 0 °C for 15 min followed by at RT for 2 h. After completion, reaction mixture was concentrated, product was quenched with aqueous Na₂CO₃ solution and aqueous layer was extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]thiazol-4-amine **32-5** (0.07 g). LCMS: [M+H]⁺ = 249.

[0182] **Step-4: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]thiazol-4-yl]urea (Example 32):** To a stirred solution of 2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]thiazol-4-amine **32-5** (0.07 g, 0.28 mmol) in MeCN (3 mL) was added pyridine (0.05 mL, 0.56 mmol) followed by *N,N'*-disuccinimidyl carbonate (0.07 g, 0.28 mmol) at 0 °C. Resulting reaction mixture was stirred at RT for 1 h. To this was added (4*S*)-8-chlorochroman-4-amine **32-6** (0.06 g, 0.28 mmol) followed by DIPEA (0.15 mL, 0.85 mmol) and reaction mixture was stirred at 25 °C for 1 h. After completion, reaction mixture was quenched with H₂O and extracted with ethyl acetate. Combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product obtained was purified by CombiFlash (60% EtOAc/heptane) to afford **Example 32** (0.01 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.19 (s, 1H), 8.39 (s, 1H), 8.00 (s, 1H), 7.33 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.13 (s, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.20 (q, *J* = 9.0 Hz, 2H), 4.95 (q, *J* = 6.2 Hz, 1H), 4.43 - 4.37 (m, 1H), 4.28 - 4.22 (m, 1H), 2.19 - 2.11 (m, 1H), 2.05 - 1.97 (m, 1H); LCMS: [M+H]⁺ = 458.

Example 33: Synthesis of 1-[(4S)-8-chlorochroman-4-yl]-3-[2-(5-cyano-2-pyridyl)thiazol-4-yl]urea



[0183] **Step-1: 6-(trimethylstannyl)pyridine-3-carbonitrile (33-2):** To a degassed solution of 6-bromopyridine-3-carbonitrile **33-1** (1.07 g, 5.85 mmol) in 1,2-dimethoxy ethane (10 mL) was added hexamethyl ditin (1.2 mL, 5.85 mmol) and the reaction mixture was purged with argon for 15 min. To the above reaction mixture was added Pd(PPh₃)₄ (0.33 g, 0.28 mmol) and heated at 100 °C for 48 h. After completion, reaction mixture was diluted with EtOAc and filtered through Celite. The filtrate was concentrated under reduced pressure to afford 6-(trimethylstannyl)pyridine-3-carbonitrile **33-2** (0.80 g).

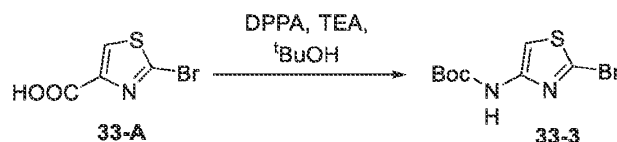
[0184] **Step-2: *tert*-butyl *N*-[2-(5-cyano-2-pyridyl)thiazol-4-yl]carbamate (33-4):** To a degassed solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **33-3** (0.65 g, 2.33 mmol) in toluene (10 mL) was added 6-(trimethylstannyl)pyridine-3-carbonitrile **33-2** (0.75 g, 2.79 mmol) and CuI (0.04 g, 0.23 mmol) followed by Pd(PPh₃)₄ (0.26 g, 0.23 mmol). Reaction mixture was stirred at 110 °C for 16 h. After completion, reaction mixture was diluted with EtOAc and filtered through Celite. The filtrate was concentrated under reduced pressure to obtain a product which was purified by CombiFlash (15% EtOAc/n-heptane) to afford *tert*-butyl *N*-[2-(5-cyano-2-pyridyl)thiazol-4-yl]carbamate **33-4** (0.05 g). LCMS: [M+H]⁺ = 247.

Step-3: 6-(4-aminothiazol-2-yl)pyridine-3-carbonitrile (33-5): To a stirred solution of *tert*-butyl *N*-[2-(5-cyano-2-pyridyl)thiazol-4-yl]carbamate **33-4** (0.05 g, 0.16 mmol) in DCM (1 mL) was added TFA (0.5 mL) at 0 °C and the reaction mixture was stirred at RT for 1 h.

After completion, reaction mixture was concentrated under reduced pressure. The product was neutralized by NaHCO_3 solution. The precipitated solid was filtered under reduced pressure to afford 6-(4-aminothiazol-2-yl)pyridine-3-carbonitrile **33-5** (0.03 g). LCMS: $[\text{M}+\text{H}]^+ = 203$.

[0185] **Step-4: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(5-cyano-2-pyridyl)thiazol-4-yl]urea (Example 33):** To a stirred solution of *N,N'*-disuccinimidy carbonate (0.04 g, 0.17 mmol) in MeCN (3 mL) was added pyridine (0.01 mL, 0.17 mmol) followed by 6-(4-aminothiazol-2-yl)pyridine-3-carbonitrile **33-5** (0.03 g, 0.17 mmol) and the reaction mixture was stirred at RT for 45 min. To the above was added DIPEA (0.09 mL, 0.51 mmol) followed by (4*S*)-8-chlorochroman-4-amine hydrochloride **33-6** (0.03 g, 0.173 mmol) and the reaction mixture was stirred at RT for 1 h. After completion, reaction mixture was concentrated under reduced pressure. The product was washed with ice-cold water and the precipitated solid was filtered under reduced pressure. The solid was triturated with MeOH and hexane to afford **Example 33** (0.01 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.35 (s, 1H), 9.05 (d, J = 1.3 Hz, 1H), 8.42 (dd, J = 2.0, 8.3 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.55 (s, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 6.94 - 6.89 (m, 2H), 5.01 - 4.92 (m, 1H), 4.45 - 4.36 (m, 1H), 4.29 - 4.22 (m, 1H), 2.21 - 2.09 (m, 1H), 2.07 - 1.96 (m, 1H). LCMS: $[\text{M}+\text{H}]^+ = 412$.

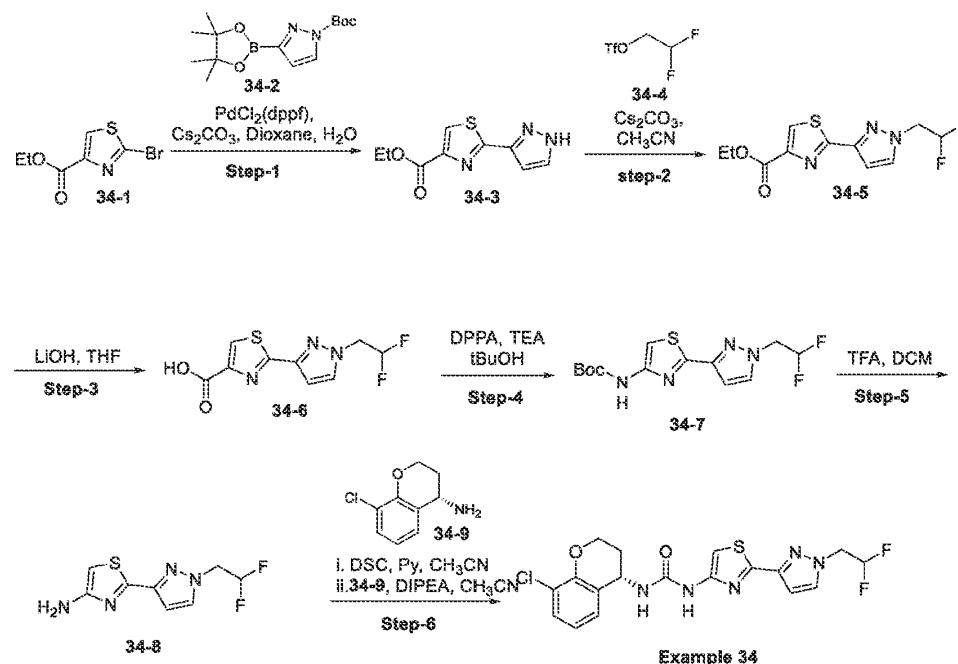
Preparation of 33-3:



[0186] **Step-1: *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate (33-3):** To a stirred solution of 2-bromothiazole-4-carboxylic acid **33-A** (10.00 g, 48.1 mmol) in *tert*-butanol (100 mL) was added TEA (7.90 mL, 57.7 mmol) followed by dropwise addition of DPPA (16 mL, 62.5 mmol) at RT. The resulting solution was heated at 80 °C for 12 h. After completion, the reaction mass was concentrated under reduced pressure. The product was diluted with water and extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield product which was purified by CombiFlash (8% EtOAc/n-heptane) to afford *tert*-butyl *N*-(2-bromothiazol-4-

yl)carbamate **33-3** (4.20 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 10.31 (s, 1H), 7.20 (s, 1H), 1.45 (s, 9H); LCMS: $[\text{M}+\text{H}]^+ = 225$.

Example 34: Synthesis of 1-[(4S)-8-chlorochroman-4-yl]-3-[2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazol-4-yl]urea



[0187] **Step-1: ethyl 2-(1-*tert*-butoxycarbonylpyrazol-3-yl)thiazole-4-carboxylate (34-3):**

To a degassed solution of *bis*(triphenylphosphine)palladium (II) dichloride (0.29 g, 0.42 mmol), cesium carbonate (4.14 g, 12.7 mmol) and *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-1-carboxylate **34-2** (1.24 g, 4.24 mmol) in 1,4-dioxane (3.5 mL) and water (1.5 mL) was added ethyl 2-bromothiazole-4-carboxylate **34-1** (1.00 g, 4.24 mmol). The reaction mixture was heated at 100 °C for 3 h. After completion, the reaction mixture was filtered through Celite bed. The filtrate was diluted with H_2O , aqueous layer was extracted with EtOAc. Combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The product was purified by CombiFlash (50% EtOAc/*n*-heptane) to afford ethyl 2-(1-*tert*-butoxycarbonylpyrazol-3-yl)thiazole-4-carboxylate **34-3** (0.80 g). LCMS: $[\text{M}+\text{H}]^+ = 224$.

[0188] Step-2: ethyl 2-[1-(2,2-difluoroethyl) pyrazol-3-yl] thiazole-4-carboxylate (34-5):

To a stirred solution of ethyl 2-[1-(2,2-difluoroethyl)thiazole-4-carboxylate **34-3** (0.30 g, 1.34 mmol) in MeCN (6 mL) was added Cs₂CO₃ (0.87 g, 2.69 mmol) followed by 2,2-difluoroethyl trifluoromethanesulfonate **34-4** (0.31 g, 1.47 mmol) and the reaction mixture was stirred at 27 °C for 3 h. After completion, the reaction mixture quenched with H₂O, extracted with EtOAc. Combined organic layer was washed with brine solution, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The product was purified by CombiFlash (50% EtOAc/*n*-heptane) to afford ethyl 2-[1-(2,2-difluoroethyl) pyrazol-3-yl] thiazole-4-carboxylate **34-5** (0.24 g). LCMS: [M+H]⁺ = 288.

[0189] Step-3: 2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazole-4-carboxylic acid (34-6):

To a stirred solution of ethyl 2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazole-4-carboxylate **34-5** (0.27 g, 0.96 mmol) in THF (3 mL), methanol (2 mL) and water (1.5 mL) was added lithium hydroxide monohydrate (0.12 g, 2.87 mmol) and the reaction mixture was stirred at 28 °C for 12 h. After completion, reaction mixture was concentrated under reduced pressure. The product was diluted with H₂O and washed with EtOAc. Then aqueous layer pH was adjusted with 2N HCl. Precipitated solid was filtered and dried under reduced pressure to afford 2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazole-4-carboxylic acid **34-6** (0.21 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.18 - 12.85 (m, 1H), 8.42 (s, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 6.88 - 6.83 (m, 1H), 6.58 - 6.28 (m, 1H), 4.79 - 4.70 (m, 2H); LCMS: [M+H]⁺ = 260.

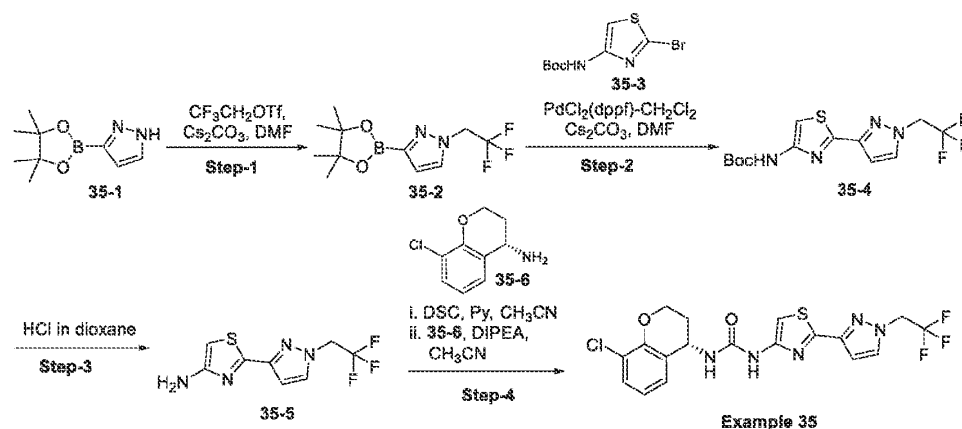
[0190] Step-4: tert-butyl N-[2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazol-4-yl]carbamate (34-7):

To a stirred solution of 2-[1-(2,2-difluoroethyl) pyrazol-3-yl] thiazole-4-carboxylic acid **34-6** (0.20 g, 0.77 mmol) in *tert*-butanol (3 mL) was added TEA (0.14 mL, 1.00 mmol) followed by dropwise addition of DPPA (0.20 mL, 0.92 mmol) at RT. The resulting mixture was heated at 80 °C for 12 h. After completion, the reaction mass was concentrated under reduced pressure. The product was diluted with water and extracted with EtOAc. Combined organic layer was washed with brine solution, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The product was purified via CombiFlash (20% EtOAc/*n*-heptane) to afford *tert*-butyl N-[2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazol-4-yl]carbamate **34-7** (0.23 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.22 (br s, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.19 - 7.14 (m, 1H), 6.73 - 6.69 (m, 1H), 6.56 - 6.26 (m, 1H), 4.76 - 4.66 (m, 2H), 1.46 (s, 9H); LCMS: [M+H]⁺ = 275.

[0191] **Step-5: 2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazol-4-amine (34-8):** To a stirred solution of *tert*-butyl *N*-[2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazol-4-yl] carbamate **34-7** (0.10 g, 0.30 mmol) in DCM (3 mL) was added TFA (0.28 mL, 3.63 mmol) at 0 °C and reaction mixture was stirred at 28 °C for 3 h. After completion, the reaction mixture was concentrated under reduced pressure. The product was quenched with H₂O, extracted with EtOAc. Combined organic layer was washed with brine solution, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to yield 2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazol-4-amine **34-8** (0.12 g). LCMS: [M+H]⁺ = 231.

[0192] **Step-6: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazol-4-yl]urea (Example 34):** To a stirred solution of 2-[1-(2,2-difluoroethyl)pyrazol-3-yl]thiazol-4-amine **34-8** (0.06 g, 0.28 mmol) in MeCN (3 mL) was added pyridine (0.04 mL, 0.56 mmol) followed by *N,N'*-disuccinimidyl carbonate (0.07 g, 0.28 mmol) and the reaction mixture was stirred at 27 °C for 45 min. To this was added (4*S*)-8-chlorochroman-4-amine hydrochloride **34-9** (0.06 g, 0.28 mmol) followed by DIPEA (0.15 mL, 0.84 mmol) and reaction mixture was stirred at 27 °C for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The product was dissolved in EtOAc. Organic layer was washed with H₂O and brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by prep HPLC to afford **Example 34** (0.01 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.28 (s, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.19 (s, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 6.43 (t, *J* = 3.0 Hz, 1H), 5.01 - 4.93 (m, 1H), 4.79 - 4.67 (m, 2H), 4.45 - 4.38 (m, 1H), 4.31 - 4.22 (m, 1H), 2.19 - 2.11 (m, 1H), 2.03 (dd, *J* = 2.4, 6.5 Hz, 1H); LCMS: [M+H]⁺ = 440.

Example 35: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[1-(2,2,2-trifluoroethyl)pyrazol-3-yl]thiazol-4-yl]urea



[0193] **Step-1: 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)pyrazole (35-2):** To a stirred solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole **35-1** (2.00 g, 10.3 mmol) in DMF (15 mL) was added Cs_2CO_3 (6.72 g, 20.6 mmol) at RT followed by 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.8 mL, 12.40 mmol) dropwise at 0 °C and the reaction mixture was stirred at RT for 12 h. After completion of starting material, the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. Combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by CombiFlash chromatography (10% EtOAc/*n*-heptane) to obtain 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)pyrazole **35-2** (2.00 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 7.88 (d, J = 2.3 Hz, 1H), 6.61 (d, J = 2.3 Hz, 1H), 5.19 (q, J = 9.1 Hz, 2H), 1.27 (s, 12H).

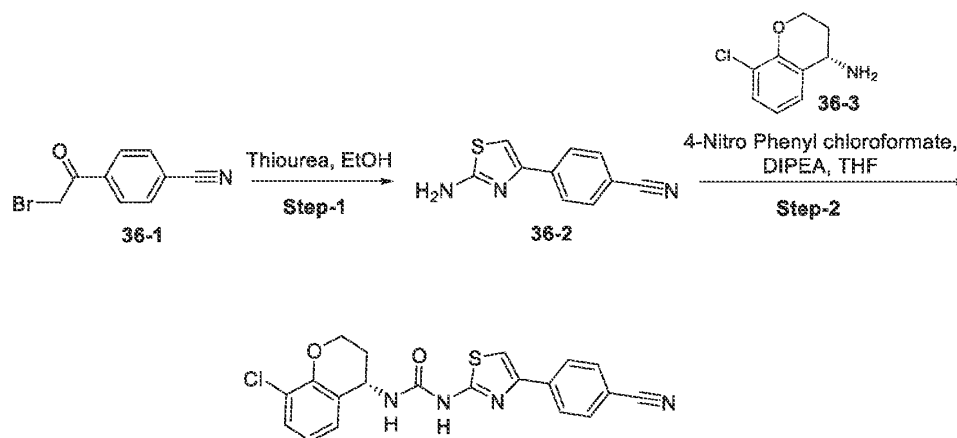
[0194] **Step-2: *tert*-butyl *N*-[2-[1-(2,2,2-trifluoroethyl)pyrazol-3-yl]thiazol-4-yl]carbamate (35-4):** To a stirred solution of *tert*-butyl *N*-(2-bromothiazol-4-yl)carbamate **35-3** (0.70 g, 2.51 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)pyrazole **35-2** (0.83 g, 3.01 mmol) and Cs_2CO_3 (4.08 g, 12.5 mmol) in DMF (8 mL), nitrogen was purged for 10 min. To the resulting reaction mixture was added $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ (0.41 g, 0.50 mmol) and reaction mixture was irradiated under microwave at 100 °C for 30 min. After completion, reaction mixture was filtered through

Celite bed. Cold water was added and aqueous layer was extracted with EtOAc. Organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by CombiFlash (30% EtOAc/Heptane) to afford *tert*-butyl *N*-[2-[1-(2,2,2-trifluoroethyl)pyrazol-3-yl]thiazol-4-yl]carbamate **35-4** (0.70 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.26 (br s, 1H), 7.99 (d, *J* = 2.4 Hz, 1H), 7.19 (s, 1H), 6.75 (d, *J* = 2.5 Hz, 1H), 5.25 (q, *J* = 9.1 Hz, 2H), 1.47 (s, 9H). LCMS: [M+H]⁺ = 349.

[0195] **Step-3: 2-[1-(2,2,2-trifluoroethyl)pyrazol-3-yl]thiazol-4-amine hydrochloride (35-5):** A solution of *tert*-butyl *N*-[2-[1-(2,2,2-trifluoroethyl)pyrazol-3-yl]thiazol-4-yl]carbamate **35-4** (0.25 g, 0.71 mmol) in HCl in dioxane (4.5 mL, 59.4 mmol) was stirred at 0 °C for 15 min followed by at RT for 1 h. After completion, reaction mixture was concentrated under reduced pressure. The product was triturated with diethyl ether and filtered. The solid was dried under reduced pressure to afford 2-[1-(2,2,2-trifluoroethyl)pyrazol-3-yl]thiazol-4-amine hydrochloride **35-5** (0.20 g). LCMS: [M+H]⁺ = 249.

[0196] **Step-4: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[1-(2,2,2-trifluoroethyl)pyrazol-3-yl]thiazol-4-yl]urea (Example 35):** To a stirred solution of 2-[1-(2,2,2-trifluoroethyl)pyrazol-3-yl]thiazol-4-amine hydrochloride **35-5** (0.13 g, 0.52 mmol) in MeCN (5 mL) was added *N,N'*-disuccinimidyl carbonate (0.13 g, 0.52 mmol) followed by pyridine (0.08 mL, 1.05 mmol) and the resulting reaction mixture was stirred at RT for 50 min. To this was added (4*S*)-8-chlorochroman-4-amine **35-6** (0.09 g, 0.52 mmol) followed by DIPEA (0.27 mL, 1.57 mmol) and reaction mixture was stirred at 0 °C for 2 h. After completion, reaction mixture was concentrated under reduced pressure and product obtained was dissolved in EtOAc. Organic layer was washed with 2N HCl solution, water and brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product was purified by prep-HPLC to afford **Example 35** (0.03 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.27 (s, 1H), 7.99 (d, *J* = 2.4 Hz, 1H), 7.33 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.20 (s, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 5.25 (q, *J* = 9.1 Hz, 2H), 4.99 - 4.92 (m, 1H), 4.43 - 4.38 (m, 1H), 4.28 - 4.22 (m, 1H), 2.19 - 2.11 (m, 1H), 2.05 - 1.99 (m, 1H); LCMS: [M+H]⁺ = 458.

Example 36: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[4-(4-cyanophenyl)thiazol-2-yl]urea



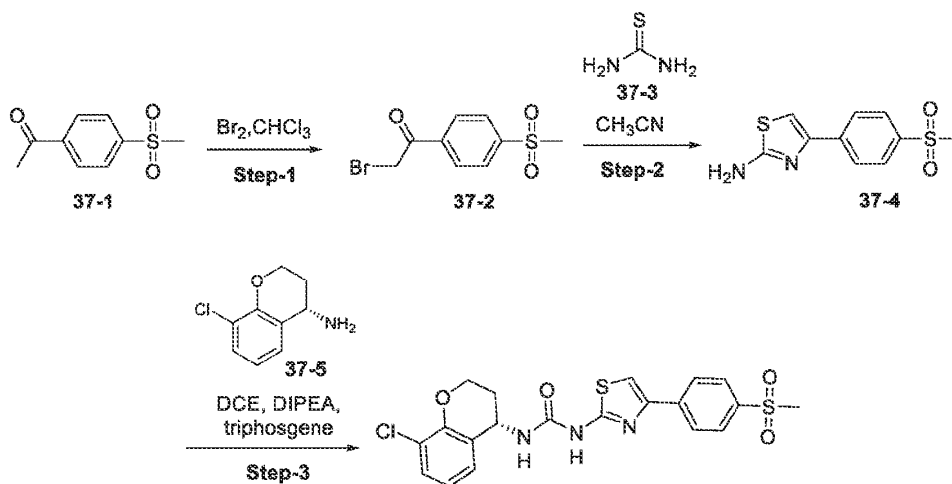
Example 36

[0197] **Step-1: 4-(5-aminothiazol-2-yl)benzonitrile (**36-2**):** To a stirred solution of 4-(2-bromoacetyl)benzonitrile **36-1** (1.12 g, 5.00 mmol) in ethanol (10 mL) was added thiourea (0.57 g, 7.50 mmol) at RT and the reaction mixture was refluxed for 2 h. After completion of reaction, reaction mixture was concentrated under reduced pressure. The product was added into NaHCO₃ solution and filtered. The solid obtained was dried under vacuum to get 4-(5-aminothiazol-2-yl)benzonitrile **36-2** (0.60 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.97 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.33 (s, 1H), 7.18 (s, 2H); LCMS: [M+H]⁺ = 202.

[0198] **Step-2: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[4-(4-cyanophenyl)thiazol-2-yl]urea (**Example 36**):** To a stirred solution of 4-nitro phenyl chloroformate (0.22 g, 1.09 mmol) in THF (5 mL) was added DIPEA (0.40 mL, 2.27 mmol) and the reaction mixture was cooled to 0 °C. To this was added 4-(2-aminothiazol-4-yl)benzonitrile **36-2** (0.36 g, 1.82 mmol) and the reaction mixture was stirred at 0 °C for 30 min. To the resulting reaction mixture was added (4*S*)-8-chlorochroman-4-amine hydrochloride **36-3** (0.20 g, 0.90 mmol) and stirred at 50 °C for 16 h. After completion, reaction mixture was cooled to RT and quenched with methanol. Reaction mixture was concentrated under reduced pressure. The product was purified by prep HPLC to afford **Example 36** (0.01 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.55 (br s, 1H), 8.05 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 1H), 7.37 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.94 (t, *J* = 7.8 Hz, 1H), 5.01 (q, *J* =

6.3 Hz, 1H), 4.44 - 4.38 (m, 1H), 4.32 - 4.26 (m, 1H), 2.22 - 2.13 (m, 1H), 2.11 - 2.04 (m, 1H); LCMS: $[M+H]^+ = 411$.

Example 37: Synthesis of (1-[(4*S*)-8-chlorochroman-4-yl]-3-[4-(4-methylsulfonylphenyl)thiazol-2-yl]urea



Example 37

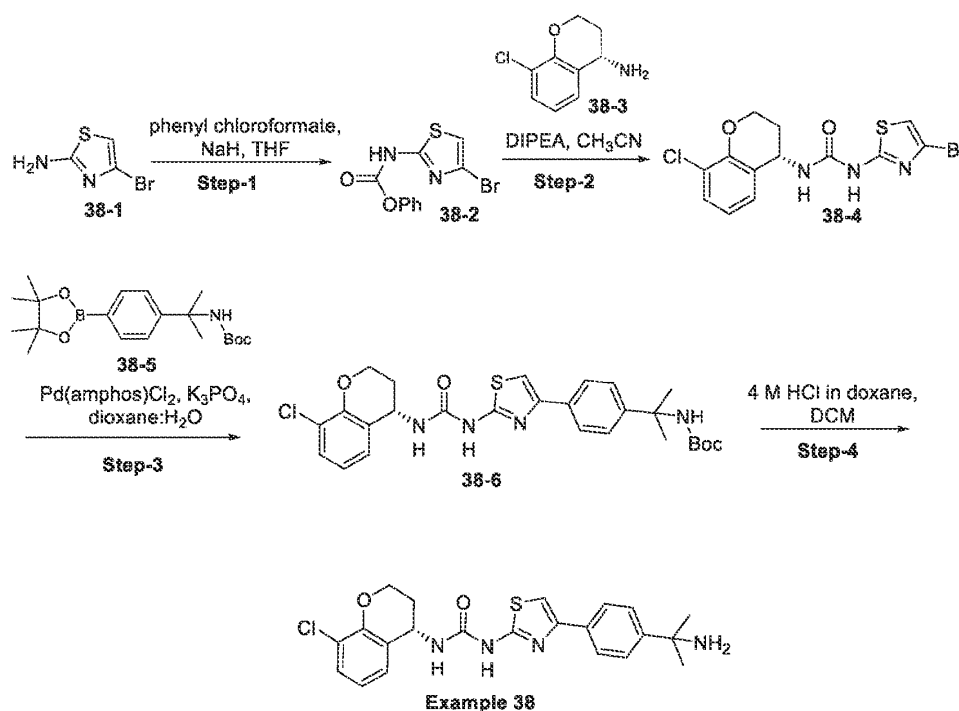
[0199] **Step-1: 2-bromo-1-(4-methylsulfonylphenyl)ethanone (37-2):** To a stirred solution of 1-(4-methylsulfonylphenyl)ethanone 37-1 (1.00 g, 5.04 mmol) in chloroform (20 mL) was added bromine (0.26 mL, 5.04 mmol) at 0 °C and the reaction mixture was stirred at RT for 16 h. After completion, reaction was quenched with saturated $Na_2S_2O_3$ solution, aqueous layer was extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The compound was purified by CombiFlash (15% EtOAc/hexane) to afford 2-bromo-1-(4-methylsulfonylphenyl)ethanone 37-2 (0.80 g). 1H NMR (400 MHz, $DMSO-d_6$) δ = 8.23- 8.21 (m, 2H), 8.11- 8.09 (m, 2H), 5.01 (s, 2H), 3.31 (s, 3H); LCMS: $[M+H]^+ = 277$.

[0200] **Step-2: 5-(4-methylsulfonylphenyl)thiazol-2-amine (37-4):** To a stirred solution of 2-bromo-1-(4-methylsulfonylphenyl)ethanone 37-2 (0.20 g, 0.72 mmol) in MeCN (5 mL) was added thiourea 37-3 (0.54 g, 7.22 mmol) and the reaction mixture was heated at 80 °C for 14 h. After completion, reaction was quenched with H_2O , aqueous layer was extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4

and concentrated under reduced pressure. The compound was purified by CombiFlash (40% EtOAc/hexane) to afford 5-(4-methylsulfonylphenyl)thiazol-2-amine **37-4** (0.05 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.23 - 8.21 (m, 2H), 7.98 - 7.96 (m, 2H), 7.53 - 7.49 (m, 1H), 7.18 - 7.16 (m, 1H), 6.51 - 6.49 (m, 1H), 6.11 (br s, 2H), 3.30 (s, 3H).

[0201] **Step-3: (1-[(4S)-8-chlorochroman-4-yl]-3-[4-(4-methylsulfonylphenyl)thiazol-2-yl]urea (Example 37):** To a stirred solution of 5-(4-methylsulfonylphenyl)thiazol-2-amine **37-4** (0.20 g, 0.78 mmol) in DCE (4 mL) was added DIPEA (0.43 mL, 2.36 mmol) and resulting reaction mixture was stirred at RT for 10 min. The reaction mixture was cooled to 0 °C and was added triphosgene (0.11 g, 0.39 mmol) followed by (4S)-8-chlorochroman-4-amine **37-5** (0.14 g, 0.78 mmol). Resulting reaction mixture was stirred at 80 °C for 2 h. After completion, reaction mixture was concentrated under reduced pressure and product obtained was dissolved in EtOAc. Organic layer was washed with H_2O , brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The compound was purified by prep-HPLC to afford **Example 37** (0.01 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 10.54 (s, 1H), 8.10 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H), 7.78 (s, 1H), 7.35 (dd, J = 1.2, 7.8 Hz, 1H), 7.25 (d, J = 7.1 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 6.92 (t, J = 7.8 Hz, 1H), 4.99 (q, J = 6.5 Hz, 1H), 4.44 - 4.36 (m, 1H), 4.32 - 4.25 (m, 1H), 3.23 (s, 3H), 2.19 - 2.13 (m, 1H), 2.10 - 2.03 (m, 1H); LCMS: $[\text{M}+\text{H}]^+ = 464$.

Example 38: Synthesis of 1-[4-[4-(1-amino-1-methyl-ethyl)phenyl]thiazol-2-yl]-3-[(4S)-8-chlorochroman-4-yl]urea



[0202] **Step-1: phenyl *N*-(4-bromothiazol-2-yl)carbamate (38-2):** To a stirred solution of 4-bromothiazol-2-amine **38-1** (2.00 g, 11.20 mmol) in THF (20 mL) was added NaH (60% mineral oil, 0.53 g, 22.30 mmol) at 0 °C. The reaction mixture was stirred at same temperature for 30 min. To the resulting reaction mixture was added phenyl chloroformate (1.60 mL, 13.10 mmol) and stirred at 25 °C for 12 h. After completion, reaction mixture was quenched with ice cold water and extracted with EtOAc. Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by CombiFlash (20 % EtOAc/heptane) to afford phenyl *N*-(4-bromothiazol-2-yl)carbamate **38-2** (0.53 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.58 (s, 1H), 7.43 - 7.41 (m, 2H), 7.32 - 7.24 (m, 4H); LCMS: [M+H]⁺ = 301.

[0203] **Step-2: 1-(4-bromothiazol-2-yl)-3-[(4S)-8-chlorochroman-4-yl]urea (38-4):** To a stirred solution of phenyl *N*-(4-bromothiazol-2-yl)carbamate **38-2** (0.53 g, 1.77 mmol) in MeCN (8 mL) was added DIPEA (0.93 mL, 5.32 mmol) followed by (4S)-8-chlorochroman-

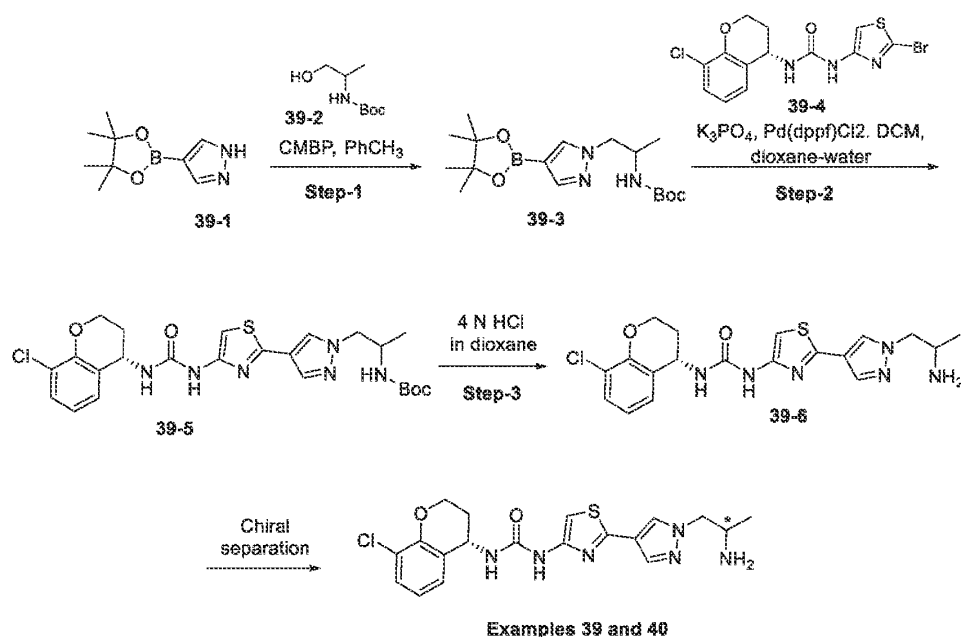
4-amine hydrochloride **38-3** (0.39 g, 1.77 mmol) at RT. The reaction mixture was stirred at 80 °C for 4 h. After completion, the reaction mixture was concentrated under reduced pressure. The product was purified by CombiFlash (30 % EtOAc/heptane) to afford 1-(4-bromothiazol-2-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea **38-4** (0.50 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.50 (br s, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.16 - 7.11 (m, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 4.99 - 4.91 (m, 1H), 4.42 - 4.34 (m, 1H), 4.30 - 4.23 (m, 1H), 2.19 - 2.10 (m, 1H), 2.09 - 2.01 (m, 1H); LCMS: [M+H]⁺ = 390.

[0204] **Step-3: *tert*-butyl *N*-[1-[4-[2-[[[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-4-yl]phenyl]-1-methyl-ethyl]carbamate (**38-6**)**: To a stirred solution of 1-(4-bromothiazol-2-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea **38-4** (0.25 g, 0.64 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was added *tert*-butyl *N*-[1-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl]carbamate **38-5** (0.29 g, 0.80 mmol), tri potassium phosphate (0.40 g, 1.93 mmol) at RT and the reaction mixture was purged with N₂ for 10 min. To the resulting reaction mixture was added Pd(amphos)Cl₂ (0.09 g, 0.12 mmol) and again purged with N₂ for 5 min. Then the reaction mixture was heated at 100 °C for 16 h. After completion, reaction mixture was diluted with H₂O and extracted with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by CombiFlash (60 % ethyl acetate/heptane) to afford *tert*-butyl *N*-[1-[4-[2-[[[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-4-yl]phenyl]-1-methyl-ethyl]carbamate **38-6** (0.15 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.43 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.40 (s, 1H), 7.34 - 7.32 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.15 - 7.10 (m, 2H), 6.92 (t, *J* = 8.0 Hz, 1H), 4.99 - 4.98 (m, 1H), 4.39 - 4.25 (m, 2H), 2.16 - 2.07 (m, 2H), 1.49 (s, 6H), 1.33 (s, 9H); LCMS: [M+H]⁺ = 543.

[0205] **Step-4: 1-[4-[4-(1-amino-1-methyl-ethyl)phenyl]thiazol-2-yl]-3-[(4*S*)-8-chlorochroman-4-yl]urea (Example 38)**: To a stirred solution of *tert*-butyl *N*-[1-[4-[2-[[[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-4-yl]phenyl]-1-methyl-ethyl]carbamate **38-6** (0.05 g, 0.09 mmol) in DCM (1 mL) was added 4.0M HCl in 1,4-dioxane (0.83 mL, 24.00 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After completion, the reaction mixture was concentrated under reduced pressure to remove the solvent. The product was triturated with EtOAc, pentane and concentrated under reduced pressure to afford **Example 38** (0.03 g) ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.54 (s, 1H),

8.50 (br s, 3H), 7.90 (d, $J = 8.5$ Hz, 2H), 7.61 - 7.52 (m, 3H), 7.38 - 7.30 (m, 2H), 7.28 - 7.21 (m, 1H), 6.92 (t, $J = 7.8$ Hz, 1H), 4.99 (q, $J = 6.6$ Hz, 1H), 4.44 - 4.37 (m, 1H), 4.32 - 4.24 (m, 1H), 2.22 - 2.12 (m, 1H), 2.09 - 2.01 (m, 1H), 1.64 (s, 6H); LCMS: $[M+H]^+ = 444$.

Example 39 and Example 40: Synthesis of 1-[2-[1-[2-aminopropyl]pyrazol-4-yl]thiazol-4-yl]-3-[(4*S*)-8-chlorochroman-4-yl]urea



* Absolute stereochemistry not determined

[0206] **Step-1: *tert*-butyl *N*-[1-methyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]ethyl]carbamate (39-3):** To a stirred solution of *tert*-butyl *N*-(2-hydroxy-1-methyl-ethyl)carbamate **39-2** (3.00 g, 17.10 mmol) in toluene (20 mL) was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole **39-1** (3.99 g, 20.5 mmol) followed by cyanomethylenetriethylphosphorane (4.5 mL, 17.1 mmol) at RT and the reaction mixture was stirred at 90 °C for 16 h. After completion, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to obtain a product which was purified by CombiFlash (80% EtOAc/*n*-heptane) to afford *tert*-butyl *N*-[1-methyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]ethyl]carbamate **39-3** (0.75 g). LCMS: $[M+H]^+ = 352$.

[0207] **Step-2: *tert*-butyl *N*-[2-[4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]pyrazol-1-yl]-1-methyl-ethyl]carbamate (39-5):** To a degassed solution of 1-(2-bromothiazol-4-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea **39-4** (0.20 g, 0.50 mmol) and *tert*-butyl *N*-[1-methyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]ethyl]carbamate **39-3** (0.26 g, 0.61 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added K₃PO₄ (0.32 g, 1.53 mmol) followed by Pd(dppf)Cl₂ complex in DCM (0.02 g, 0.02 mmol). Reaction mixture was stirred at 90 °C for 3 h. After completion, reaction mixture was filtered through Celite, diluted with EtOAc. The organic layer was washed with H₂O, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to yield product which was purified by CombiFlash to afford *tert*-butyl *N*-[2-[4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]pyrazol-1-yl]-1-methyl-ethyl]carbamate **39-5** (0.05 g). LCMS: [M+H]⁺ = 533.

[0208] **Step-3: 1-[2-[1-(2-aminopropyl)pyrazol-4-yl]thiazol-4-yl]-3-[(4*S*)-8-chlorochroman-4-yl]urea (39-6):** A solution of *tert*-butyl *N*-[2-[4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]pyrazol-1-yl]-1-methyl-ethyl]carbamate **39-5** (0.11 g, 0.20 mmol) in 4M HCl in dioxane (1.0 mL) was stirred at 0 °C for 1 h. After completion, reaction mixture was concentrated under reduced pressure. The product was triturated with Et₂O to afford 1-[2-[1-(2-aminopropyl)pyrazol-4-yl]thiazol-4-yl]-3-[(4*S*)-8-chlorochroman-4-yl]urea **39-6** (0.08 g). LCMS: [M+H]⁺ = 433.

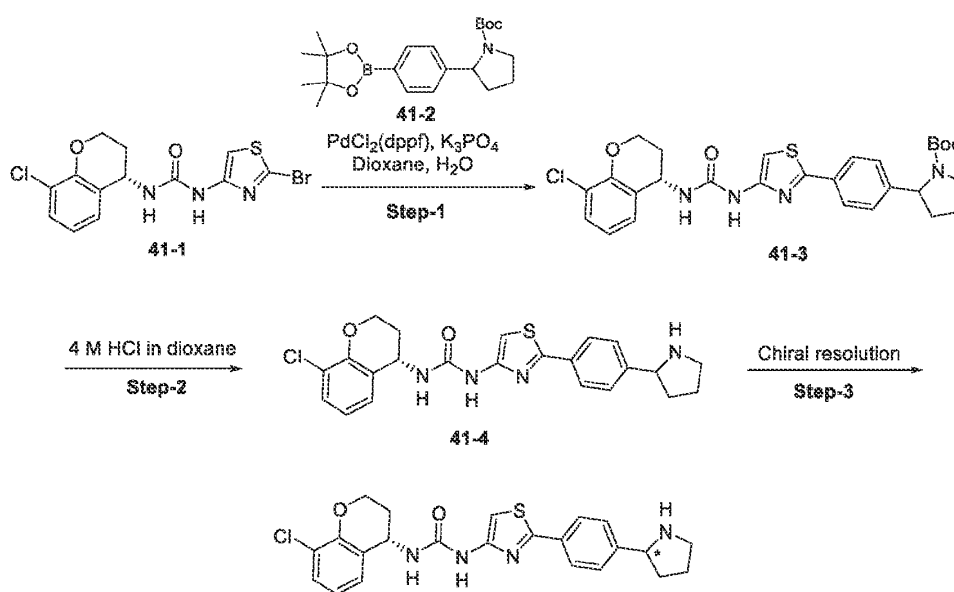
[0209] **Step-4: 1-[2-[1-[2-aminopropyl]pyrazol-4-yl]thiazol-4-yl]-3-[(4*S*)-8-chlorochroman-4-yl]urea (Examples 39 and 40):** 1-[2-[1-(2-aminopropyl)pyrazol-4-yl]thiazol-4-yl]-3-[(4*S*)-8-chlorochroman-4-yl]urea **39-6** (0.08 g, 0.19 mmol) was submitted to chiral-HPLC separation to afford **Example 39** (0.01 g) and **Example 40** (0.01 g). The absolute stereochemistry of these products was not determined.

[0210] **Example 39:** ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.15 (s, 1H), 8.23 (s, 1H), 7.84 (s, 1H), 7.33 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.05 (s, 1H), 6.94 - 6.85 (m, 2H), 4.95 (q, *J* = 1.0 Hz, 1H), 4.44 - 4.36 (m, 1H), 4.29 - 4.19 (m, 1H), 3.98 (dd, *J* = 4.6, 6.1 Hz, 2H), 3.22 (q, *J* = 1.0 Hz, 1H), 2.19 - 2.10 (m, 1H), 2.04 - 1.97 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H); LCMS: [M+H]⁺ = 433.

[0211] **Example 40:** ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.15 (s, 1H), 8.23 (s, 1H), 7.84 (s, 1H), 7.33 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.26 - 7.22 (m, 1H), 7.05 (s, 1H), 6.94 - 6.86 (m, 2H),

4.95 (q, $J = 1.0$ Hz, 1H), 4.43 - 4.37 (m, 1H), 4.28 - 4.20 (m, 1H), 4.07 - 3.92 (m, 2H), 3.22 (q, $J = 1.0$ Hz, 1H), 2.20 - 2.10 (m, 1H), 2.05 - 1.96 (m, 1H), 0.95 (d, $J = 6.4$ Hz, 3H);
LCMS: $[M+H]^+ = 433$.

Example 41 and Example 42: Synthesis of 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[4-[pyrrolidin-2-yl]phenyl]thiazol-4-yl]urea



Examples 41 and 42

* Absolute stereochemistry not determined

[0212] **Step-1: *tert*-butyl 2-[4-[4-[[[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]phenyl]pyrrolidine-1-carboxylate (**41-3**):** To a degassed solution of 1-(2-bromothiazol-4-yl)-3-[(4*S*)-8-chlorochroman-4-yl]urea **41-1** (0.16 g, 0.43 mmol) and *tert*-butyl 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-1-carboxylate **41-2** (0.24 g, 0.64 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was added K_3PO_4 (0.30 mL, 1.29 mmol) followed by $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.01 g, 0.02 mmol) and the reaction mixture was purged with argon for 10 min. Reaction was stirred at 100 °C for 2 h. After completion, the reaction mixture was filtered off through Celite bed. The filtrate was diluted with EtOAc. The organic layer was washed with H_2O , brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a product which was purified with CombiFlash (20% EtOAc/*n*-heptane) to afford *tert*-butyl 2-[4-[4-[[[(4*S*)-8-chlorochroman-4-

yl]carbamoylamino]thiazol-2-yl]phenyl]pyrrolidine-1-carboxylate **41-3** (0.21 g). ^1H NMR (400 MHz, DMSO- d_6) δ = 9.26 (s, 1H), 7.79 (s, 2H), 7.46 - 7.15 (m, 5H), 6.92 (d, J = 5.5 Hz, 2H), 4.96 (d, J = 4.6 Hz, 1H), 4.87 - 4.71 (m, 1H), 4.40 (s, 1H), 4.26 (d, J = 8.3 Hz, 1H), 3.51 (d, J = 14.8 Hz, 2H), 2.33 (s, 1H), 2.14 (d, J = 4.6 Hz, 1H), 2.03 (s, 1H), 1.83 (s, 2H), 1.71 (s, 1H), 1.48 - 1.04 (m, 9H); LCMS: $[\text{M}+\text{H}]^+ = 555$.

[0213] **Step-2: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-pyrrolidin-2-ylphenyl)thiazol-4-yl]urea hydrochloride (41-4):** A solution of *tert*-butyl 2-[4-[4-[(4*S*)-8-chlorochroman-4-yl]carbamoylamino]thiazol-2-yl]phenyl]pyrrolidine-1-carboxylate **41-3** (0.20 g, 0.34 mmol) in 4.0 M HCl in dioxane (2.0 mL) was stirred at 0 °C for 1 h. After completion, reaction mixture was concentrated under reduced pressure. The product was triturated with EtOAc to obtain **41-4** 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-pyrrolidin-2-ylphenyl)thiazol-4-yl]urea hydrochloride (0.17 g). LCMS: $[\text{M}+\text{H}]^+ = 455$.

[0214] **Step-3: 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-[4-[pyrrolidin-2-yl]phenyl]thiazol-4-yl]urea (Examples 41 and 42):** 1-[(4*S*)-8-chlorochroman-4-yl]-3-[2-(4-pyrrolidin-2-ylphenyl)thiazol-4-yl]urea **41-4** (0.21 g) was submitted for chiral-HPLC separation to afford **Example 41** (0.05 g) and **Example 42** (0.02 g). The absolute stereochemistry of these products was not determined.

[0215] **Example 41:** ^1H NMR (400 MHz, DMSO- d_6) δ = 9.25 (s, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.34 (dd, J = 1.3, 7.9 Hz, 1H), 7.27 - 7.24 (m, 1H), 7.21 (s, 1H), 6.96 - 6.85 (m, 2H), 4.96 (q, J = 6.1 Hz, 1H), 4.45 - 4.36 (m, 1H), 4.29 - 4.21 (m, 1H), 4.08 (t, J = 7.6 Hz, 1H), 3.06 - 2.96 (m, 1H), 2.95 - 2.85 (m, 1H), 2.23 - 2.07 (m, 2H), 2.07 - 1.96 (m, 1H), 1.84 - 1.67 (m, 2H), 1.53 - 1.41 (m, 1H); LCMS: $[\text{M}+\text{H}]^+ = 455$.

[0216] **Example 42:** ^1H NMR (400 MHz, DMSO- d_6) δ = 9.25 (s, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.34 (dd, J = 1.3, 7.9 Hz, 1H), 7.27 - 7.24 (m, 1H), 7.21 (s, 1H), 6.96 - 6.87 (m, 2H), 5.01 - 4.91 (m, 1H), 4.45 - 4.36 (m, 1H), 4.30 - 4.20 (m, 1H), 4.09 (t, J = 7.6 Hz, 1H), 3.07 - 2.97 (m, 1H), 2.96 - 2.86 (m, 1H), 2.21 - 2.08 (m, 2H), 2.07 - 1.97 (m, 1H), 1.82 - 1.68 (m, 2H), 1.53 - 1.41 (m, 1H); LCMS: $[\text{M}+\text{H}]^+ = 455$.

BIOLOGICAL/BIOCHEMICAL EVALUATION**DNA polymerization assay to monitor effects on human POL γ and five disease-causing mutant variants of human POL γ .**

[0217] The ability of small molecules to stimulate the polymerase activity of POL γ was analyzed in a quantitative fluorescence SYBR Green I assay with fluorescence intensity (FI) readout.

[0218] In the presence of dNTPs, human POL γ and mutant derivatives thereof were incubated with single-stranded, circular M13mp18 ssDNA hybridized to a short DNA oligonucleotide that functions as a primer for initiation of DNA synthesis. POL γ and mutant derivatives thereof will extend the primer and use the M13mp18 molecule as a template to synthesize long stretches of double-stranded DNA. SYBR Green I, which is a double-stranded DNA-binding dye, was used to quantify formation of double-stranded DNA in the reaction. When bound to double-stranded DNA, SYBR Green I fluorescence increases by up to 100-fold.

[0219] The assay was performed in the 384-well plate format. Upon addition of compounds, changes in double-stranded DNA synthesis activity can be monitored by following effects on fluorescent intensity.

[0220] Proteins used in the polymerization assays were wild type POL γ A (POL γ A:WT) and mutant derivatives thereof in which an Alanine in position 467 of the amino acids sequence had been changed to Threonine (POL γ A:A467T), a Glycine in position 848 of the amino acids sequence had been changed to Serine (POL γ A:G848S), an Arginine in position 309 of the amino acids sequence had been changed to Cysteine (POL γ A:R309C), or a Tyrosine in position 955 of the amino acid sequence had been changed to Cysteine (POL γ A:Y955C). W748S substitution arises because of a G to C mutation at position 2243 in exon 13. The W748S mutation is generally found *in cis* with the E1143G polymorphism, which is caused by an A to G transition at nucleotide 3428 in exon 21 of POL γ . The reactions also contained the accessory POL γ B subunit, and the human mitochondrial single stranded DNA binding protein (mtSSB).

[0221] The protein mixture used in the assays contained POL γ A or a mutant derivative (1 nM), POL γ B (1.3 nM, concentration calculated as a dimer), 25 mM Tris-HCl (pH 8.0), 0.1

mg/mL bovine serum albumin, 1 mM Bond-Breaker TCEP solution (pH 7), 25 mM NaCl, and 0.02% Triton X-100.

[0222] The primed circular ssDNA template used in the polymerization assay was generated by hybridizing circular, single-stranded DNA from M13mp18 with a 20 nucleotides long oligonucleotide (5'-GTA AAA CGA CGG CCA GTG CC-3') using a Bio-Rad T100 Thermal Cycler.

[0223] The DNA template mixture used in the assay contained 0.5 nM primed M13 mp18 ssDNA, 400 nM mtSSB, 0.1 mM Tris-HCl (pH 8.0), 0.1 mM dNTP, 10 mM MgCl₂, 0.1 mg/mL BSA, 1 mM Bond-Breaker TCEP solution, and 0.02% Triton X-100. The DNA template mixture for the wild type protein contained either 100 μM dNTP or 0.1 μM dNTP, the latter being designated with an * in Table 2.

[0224] Microplates with compounds (0.1 μL in each well) to be tested in the assay were prepared from 10 mM compound stocks in 100% DMSO, and equal amounts of DMSO without any compound were added to positive and negative control wells.

[0225] The protein mixture was dispensed (5 μL into each well) into compound plates and incubated at 37 °C for 15 minutes. After incubation, 5 μL of the DNA template mixture was dispensed into each well. The plates were then incubated at 37 °C for 2 hours.

[0226] During incubation, a combined stop buffer and detection reagent solution was prepared. The buffer contained 25 mM EDTA (pH 8.0), 0.02% Triton X-100, and SYBR Green I diluted 10,000 X (for fluorescent readout). EDTA will stop the enzymatic reaction by chelating magnesium ions.

[0227] After the incubation period, SYBR Green I solution was added (10 μL) to the screening plates and the plates were incubated at room temperature in the dark for 20 minutes before the fluorescent signal was read between 485-520 nm on a microtiter plate reader. The compound concentrations for half maximum activity (AC₅₀) are provided in Table 2.

Table 2: AC₅₀ Values for POL γ Activators on Human POL γ and Human Mutant POL γ .

No.	A467T AC ₅₀ (μ M)	G848S AC ₅₀ (μ M)	W748S+ E1143G (μ M)	R309C AC ₅₀ (μ M)	Y955C AC ₅₀ (μ M)	WT AC ₅₀ (μ M)
1	2	0.2	0.2	0.2	0.09	0.02*
2	3	0.3	0.6	0.3	0.1	0.04*
3	0.9	100	100	100	100	2*
4	4	2	0.5	0.6	0.2	0.5*
5	10	0.4	0.4	-	-	0.07
6	10	10	-	-	-	2*
7	15	17	9	5	5	3*
8	0.5	0.04	0.05	-	-	0.02
9	0.2	0.07	0.005	0.01	0.009	0.007
10	0.5	0.1	0.01	0.003	0.005	0.02
11	0.2	0.6	0.04	0.03	0.009	0.01
12	3	2	0.1	3	0.5	0.5
13	4	6	0.08	0.7	0.3	0.2
14	0.9	0.9	0.09	0.1	0.04	0.05
15	1	0.1	0.04	0.04	<0.003	0.01*
16	0.5	0.3	0.08	0.2	0.03	0.02
17	0.1	0.05	0.04	0.009	0.01	0.005
18	0.2	0.009	0.01	0.002	0.008	<0.003
19	0.4	0.3	0.1	0.1	0.02	0.03
20	0.2	0.07	0.1	0.2	0.03	0.01
21	0.9	0.4	0.4	0.8	0.3	0.09
22	1	0.04	0.1	1	0.1	0.03
23	0.03	0.05	0.03	0.04	0.02	0.02
24	10	0.1	0.1	0.1	0.04	-
25	0.1	0.03	0.04	0.08	0.03	0.006
26	0.6	0.04	0.09	0.2	0.02	0.2
27	0.2	<0.003	0.06	0.04	0.03	0.005
28	0.2	0.04	0.03	0.03	0.01	0.01
29	0.5	0.3	<0.003	0.2	0.05	0.01
30	1	0.5	0.06	0.04	0.05	0.04
31	1	0.1	0.04	<0.003	<0.003	0.03
32	0.3	0.1	0.05	0.02	<0.003	0.02
33	0.6	0.3	0.1	0.4	0.06	0.009
34	3	2	3	5	1	0.5
35	1	0.3	0.09	0.05	0.02	0.02
36	2	1	0.5	0.06	-	0.6*
37	0.3	0.2	0.06	0.2	0.1	0.04*
38	9	3	2	-	-	-
39	3	1	0.4	0.07	0.1	0.05*
40	4	0.4	0.2	0.1	0.08	0.04*
41	2	0.1	0.2	0.2	0.04	0.02*

No.	A467T AC50 (μ M)	G848S AC50 (μ M)	W748S+ E1143G (μ M)	R309C AC50 (μ M)	Y955C AC50 (μ M)	WT AC50 (μ M)
42	0.6	0.5	<0.003	<0.003	0.02	0.01*
43	6	5	3.4	-	-	0.4
44	7	10	4	-	-	3
45	3	2	30	4	5	0.4*
46	0.1	0.01	0.02	0.01	<0.003	-
47	0.08	0.01	0.01	0.01	0.008	0.01*
48	0.5	0.04	0.06	0.03	0.03	0.01*
49	0.2	0.04	0.04	0.03	0.02	-
50	0.2	0.06	0.04	0.04	0.02	0.01*
51	0.04	0.004	0.01	0.006	0.007	0.001
52	0.5	0.1	0.07	0.1	0.03	0.1*
53	1	0.2	0.2	-	-	0.1
54	2	0.3	0.3	-	-	0.1
55	0.05	0.01	0.01	0.01	0.001	0.003
56	0.1	0.02	-	-	-	-
57	10	0.06	-	-	-	-
58	1	0.1	0.4	0.2	0.05	0.06
59	2	10	-	-	-	-
60	0.7	0.4	0.3	-	-	0.07
61	10	5	-	-	-	-
62	10	0.6	-	-	-	0.2
63	0.8	0.1	-	-	-	0.1
64	5	0.2	-	-	-	-
65	0.3	0.02	-	-	-	0.01
66	0.5	0.04	-	-	-	0.007
67	0.6	0.1	-	-	-	-
68	0.2	0.01	-	-	-	-
69	0.3	0.07	-	-	-	0.1
70	3	0.1	-	-	-	0.07
71	0.4	0.1	0.1	-	-	0.1
72	0.04	0.002	-	-	-	-
73	0.08	0.02	-	-	-	-
74	0.1	0.04	0.1	0.05	0.01	0.03
75	10	0.6	-	-	-	0.3
76	10	10	-	-	-	0.2
77	2	0.1	-	-	-	0.1
78	1	0.1	-	-	-	0.02
79	1.4	0.1	0.1	0.1	0.02	0.4
81	2	0.3	-	-	-	0.1
82	8	0.4	0.4	-	-	0.1
83	-	-	-	-	-	-
85	10	2	-	-	-	10
87	6	1	0.7	-	-	0.3

No.	A467T AC50 (μ M)	G848S AC50 (μ M)	W748S+ E1143G (μ M)	R309C AC50 (μ M)	Y955C AC50 (μ M)	WT AC50 (μ M)
88	10	2	0.3	-	-	0.2
89	10	10	10	-	-	10
91	10	10	3	-	-	10
92	10	10	10	-	-	10
93	10	10	2	-	-	0.2
94	10	10	2	-	-	1
95	10	10	-	-	-	-
96	10	0.07	0.07	-	-	0.05
97	10	0.3	-	-	-	-
98	10	1	-	-	-	-
99	10	0.2	0.2	-	-	0.1
100	9	0.8	1	-	-	0.2
101	10	1.6	1	-	-	0.3
102	-	-	-	-	-	-
105	0.05	0.005	0.008	-	-	0.03
106	0.4	0.2	0.2	0.2	0.1	0.05
108	10	2	10	-	-	1
109	10	10	4	10	1	0.8
110	10	7	2	-	-	10
111	10	8	6	-	-	5
113	10	10	-	-	-	-
114	10	10	-	-	-	-
115	4	0.3	0.3	-	-	0.02
116	1	0.2	0.2	-	-	0.03
117	3	0.3	0.2	-	-	0.06
118	3	0.5	0.2	-	-	0.05
119	2	0.6	0.3	-	-	0.1
120	1	0.2	-	-	-	-
121	0.6	0.06	-	-	-	-
122	3	0.3	-	-	-	-
123	2	0.2	-	-	-	-
124	0.4	0.04	-	-	-	-
125	3	0.3	-	-	-	-
126	2	0.3	-	-	-	-
127	4	0.4	-	-	-	-
128	10	3	-	-	-	-
129	10	10	-	-	-	-
130	0.6	0.06	-	-	-	0.01
131	4	0.8	0.5	-	-	0.1
132	10	0.5	0.6	-	-	-
133	6	0.6	-	-	-	-
134	10	10	-	-	-	-
135	10	10	10	-	-	10

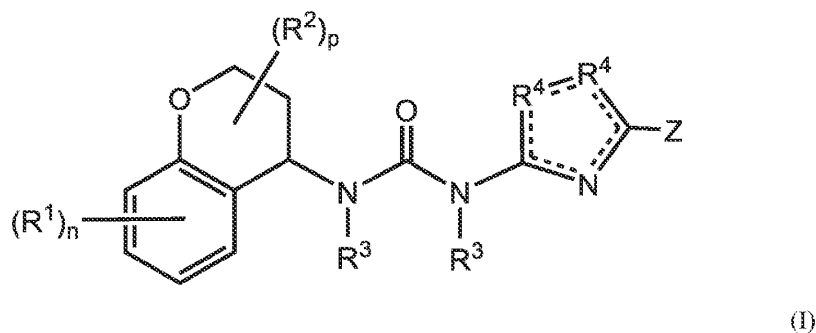
No.	A467T AC50 (μ M)	G848S AC50 (μ M)	W748S+ E1143G (μ M)	R309C AC50 (μ M)	Y955C AC50 (μ M)	WT AC50 (μ M)
136	1	0.1	0.2	-	-	0.05
137	2	0.4	0.3	-	-	0.1
138	1	0.3	0.1	-	-	0.05
139	0.3	0.07	0.07	-	-	0.03
140	0.4	0.03	0.02	-	-	0.01
141	2	0.5	0.3	-	-	0.05
142	0.2	0.05	0.05	-	-	0.02
143	10	0.2	0.2	-	-	0.1
144	2	0.3	0.3	-	-	0.1
145	10	2	6	-	-	1.4
146	5	0.5	0.8	-	-	0.3
147	0.1	0.008	0.005	-	-	0.002
148	2	0.07	0.1	-	-	0.03
149	7	0.9	0.7	-	-	0.15
150	7	1	1	-	-	0.2
151	10	1	3	-	-	4.3
152	10	1	0.5	-	-	0.5
153	7	0.05	0.03	-	-	0.1
154	10	2	10	-	-	10
155	10	0.6	0.3	-	-	0.01
156	2	0.3	0.4	-	-	0.07
157	1	0.1	0.2	-	-	0.04
158	10	5	10	-	-	1.3
159	10	10	10	-	-	1.6
160	10	2	2	-	-	1
161	6	3	2	-	-	-
162	10	10	10	-	-	10
163	2	0.6	0.5	-	-	0.2
164	3	5	-	-	-	0.5
165	0.4	0.1	-	-	-	0.04
166	1	2	-	-	-	0.4
167	7	0.3	-	-	-	-
168	6	5	-	-	-	-
169	3	0.7	-	-	-	-
170	2	0.8	-	-	-	-
171	10	10	-	-	-	-
172	10	10	-	-	-	-
173	10	3	-	-	-	-
174	10	1	-	-	-	-
175	0.7	0.3	-	-	-	-
176	1	0.1	-	-	-	-
177	10	10	-	-	-	-
178	10	10	-	-	-	-

No.	A467T AC50 (μ M)	G848S AC50 (μ M)	W748S+ E1143G (μ M)	R309C AC50 (μ M)	Y955C AC50 (μ M)	WT AC50 (μ M)
179	2	0.7	-	-	-	-
180	3	0.3	-	-	-	-
181	6	1	-	-	-	-
182	6	1	-	-	-	-
183	1	0.08	-	-	-	-
184	1	0.3	-	-	-	-
185	1	0.1	-	-	-	-
186	10	10	-	-	-	-
187	10	5	-	-	-	-
188	10	10	-	-	-	-
189	10	10	-	-	-	-
190	10	1	-	-	-	-
191	10	10	-	-	-	-
192	4	0.8	-	-	-	-
193	10	6	-	-	-	-
194	10	10	-	-	-	-
195	7	1	-	-	-	-
196	0.5	0.06	-	-	-	-
197	2	0.2	-	-	-	-
198	10	3	-	-	-	-
199	10	0.4	-	-	-	-
200	1	0.07	-	-	-	-
201	2	0.1	-	-	-	-
202	0.2	0.01	-	-	-	-
203	2	0.2	-	-	-	-
204	3	0.2	-	-	-	-
205	2	0.1	-	-	-	-
206	1	0.09	-	-	-	-
207	0.3	0.02	-	-	-	-
208	10	2	-	-	-	-
209	10	9	-	-	-	-
210	10	0.3	-	-	-	-
211	0.3	0.03	-	-	-	-
212	0.9	0.1	-	-	-	-
213	10	2	-	-	-	-
214	10	10	-	-	-	-
215	6	1	-	-	-	-
216	10	2	-	-	-	-
217	10	0.6	-	-	-	-
218	6	2	-	-	-	-
219	5	2	-	-	-	-
220	10	3	-	-	-	-
221	10	2	-	-	-	-

No.	A467T AC50 (μ M)	G848S AC50 (μ M)	W748S+ E1143G (μ M)	R309C AC50 (μ M)	Y955C AC50 (μ M)	WT AC50 (μ M)
222	0.7	0.06	-	-	-	-
223	10	3	-	-	-	-
224	10	2	-	-	-	-
225	10	10	-	-	-	-

CLAIMS

1. A compound having the structure of formula (I), or a pharmaceutically acceptable salt thereof,



wherein:

R^1 is selected from the group consisting of H, C_1 - C_3 alkyl, Cl, F, CN, and O- C_1 - C_6 alkyl optionally substituted with one or more halogen,

R^2 is H or C_1 - C_3 alkyl optionally substituted with OR^5 ;

R^3 is each independently H or C_1 - C_4 alkyl optionally substituted with one or more halogen or OH;

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;

Z is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkene, NR^5R^6 , SR^5 , $C(O)R^5$, $C(O)R^7$, $C(O)OR^5$, $C(O)NR^5R^6$, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, aryl-heterocyclyl, aryl-heteroaryl, and sulfonamide,

wherein the C_1 - C_6 alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, phenyl, OR^5 , halogen, $C(O)NR^5R^6$, NR^5R^6 , NR^5 - $C(O)CH_3$, SO_2R^5 , NH - SO_2R^5 , heterocyclyl, aryl, heteroaryl, and aryl-heteroaryl,

wherein cycloalkyl is optionally substituted with one or more groups each independently selected from the group consisting of F, C_1 - C_3 alkyl-OH, C_1 - C_3 alkyl-O- C_1 - C_3 alkyl, $C(O)OR^5$, $C(O)NR^5R^5$, NR^5R^5 , and NR^5 - $C(O)CH_3$,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5 , keto, C_3 - C_6 cycloalkyl, $C(O)CH_3$, $C(O)NR^5R^5$, NH -

$C(O)R^5$, $NH-SO_2R^5$, and C_1-C_4 alkyl that is optionally substituted with one or more F or OH,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C_1-C_4 alkyl that is optionally substituted with one or more groups each independently selected from the group consisting of F, OH, and NR^5R^6 ,

C_3-C_6 cycloalkyl that is substituted with NR^5R^6 ,

halogen,

CN,

OR^5 ,

$C(O)NR^5R^6$,

NR^5R^6 ,

SO_2R^6 ,

$SO_2NR^5R^6$,

$SO(NH)R$,

$S(NR)(NH)R$,

$P(O)R^5R^5$, and

4- or 5,6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more groups independently selected from the group consisting of F, Cl, OR^5 , CN, C_1-C_4 alkyl, oxo, and NR^5R^6 ,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, $C(O)NR^5R^6$, OR^5 , NR^5R^6 , oxo, SO_2R^6 , a 4- to 6-membered heterocyclic ring, and C_1-C_4 alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR^5R^6 , OR^5 , and $C(O)NR^5R^6$;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C_1-C_4 alkyl that is optionally substituted with a group selected from the group consisting of OR^5 , Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C_1-C_3 alkyl that is optionally substituted with OR^5 ;

R^5 is independently H or C_1-C_5 alkyl;

R^6 is selected from the group consisting of H, cyclopropyl, and C_1 - C_5 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5 , OR^5 , and halogen;

R^7 is cycloalkyl optionally substituted with one or more halogens;

n is 1-4;

p is 1-2;

with the proviso that a compound selected from the group consisting of:

(*S*)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2*H*-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea,

and

1-(5-cyclopropylthiazol-4-yl)-3-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)urea, is excluded.

2. The compound according to claim 1, wherein:

R^1 is selected from the group consisting of H, Cl, F and $O-C_1$ alkyl optionally substituted three halogens;

R^2 is H;

R^3 is H;

R^4 is $C-R^5$ or S, wherein one R^4 is $C-R^5$ and the other R^4 is S;

Z is selected from the group consisting of C_1 - C_3 alkyl, C_2 alkene, NR^5R^6 , SR^5 , $C(O)R^5$, $C(O)R^7$, $C(O)OR^5$, $C(O)NR^5R^6$, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, and sulfonamide.

wherein the C_1 - C_3 alkyl is optionally substituted with one or more groups each

independently selected from the group consisting of cyclopropyl, cyclobutyl

optionally substituted with one or more F, OR^5 , halogen, NR^5R^6 , and $NH-SO_2R^5$,

wherein cycloalkyl is optionally substituted with one or more groups each independently

selected from the group consisting of F, CH_2-OH , CH_2-O-CH_3 , and $C(O)OR^5$,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is

optionally substituted with one or more groups each independently selected from the

group consisting of F, OR^5 , and C_1 alkyl optionally substituted with one or more F,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C₁-C₃ alkyl that is optionally substituted with NR⁵R⁶,

halogen,

CN,

OR⁵,

C(O)NR⁵R⁶,

SO₂R⁶,

SO₂NR⁵R⁶,

SO(NH)R,

S(NR)(NH)R,

P(O)R⁵R⁵, and

5-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more oxo,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, cyclobutyl optionally substituted with one or more OH or F, CN, C(O)NR⁵R⁶, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₃ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, and OR⁵;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with one or more groups selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

R⁷ is cyclobutyl optionally substituted with one or more halogens;

n is 1; and

p is 1.

3. The compound according to claim 1, wherein:

R¹ is selected from the group consisting of H, Cl, and F;

R^2 is H;

R^3 is H;

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;

Z C₁-C₃ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, OR⁵, halogen, and NR⁵R⁶,

R^5 is independently H or C₁ alkyl;

R^6 is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

n is 1; and

p is 1.

4. The compound according to claim 1, wherein:

R^1 is selected from the group consisting of H, Cl, and F;

R^2 is H;

R^3 is H;

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;

Z is aryl substituted with one or more groups selected from the group consisting of:
halogen,

C(O)NR⁵R⁶, and

SO₂NR⁵R⁶;

R^5 is independently H or C₁ alkyl;

R^6 is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

n is 1; and

p is 1.

5. The compound according to claim 1, wherein:

R^1 is selected from the group consisting of H, Cl, and F;

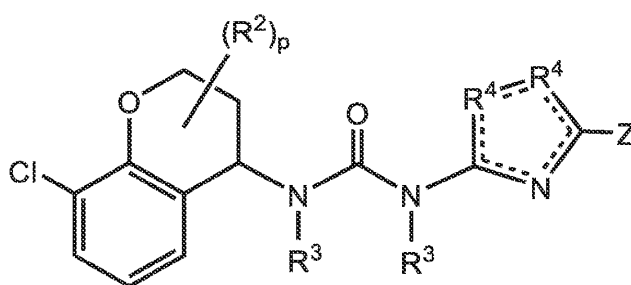
R^2 is H;

R^3 is H;

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;

- Z heterocyclcyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR⁵, and C₁ alkyl optionally substituted with one or more F, R⁵ is independently H or C₁ alkyl;
 n is 1; and
 p is 1.

6. A compound having the structure of formula (II), or a pharmaceutically acceptable salt thereof,



(II)

wherein:

- R² is H or C₁-C₃ alkyl optionally substituted with OR⁵;
 R³ is each independently H or C₁-C₄ alkyl optionally substituted with one or more halogen or OH;
 R⁴ is C-R⁵ or S, wherein one R³ is C-R⁵ and the other R³ is S;
 Z is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkene, NR⁵R⁶, SR⁵, C(O)OR⁵, C(O)R⁷, C(O)OR⁵, C(O)NR⁵R⁶, cycloalkyl, heterocyclcyl, aryl, heteroaryl, aryl-heterocyclcyl, aryl-heteroaryl, and sulfonamide,
 wherein the C₁-C₆ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, phenyl, OR⁵, halogen, heterocyclcyl, C(O)NR⁵R⁶, NR⁵R⁶, NR⁵-C(O)CH₃, SO₂R⁵, NH-SO₂R⁵, aryl, heteroaryl, and aryl-heteroaryl,
 wherein cycloalkyl is optionally substituted with one or more groups each independently selected from the group consisting of F, C₁-C₃ alkyl-OH, C₁-C₃ alkyl-O-C₁-C₃ alkyl, C(O)OR⁵, C(O)NR⁵R⁵, NR⁵R⁵, and NR⁵-C(O)CH₃,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR⁵, keto, C₃-C₆ cycloalkyl, C(O)CH₃, C(O)NR⁵R⁵, NH-C(O)R⁵, NH-SO₂R⁵, and C₁-C₄ alkyl that is optionally substituted with one or more F or OH,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C₁-C₄ alkyl that is optionally substituted with one or more groups each independently selected from the group consisting of F, OH, and NR⁵R⁶,
 C₃-C₆ cycloalkyl that is substituted with NR⁵R⁶,
 halogen,
 CN,
 OR⁵,
 C(O)NR⁵R⁶,
 NR⁵R⁶,
 SO₂R⁶,
 SO₂NR⁵R⁶,
 SO(NH)R,
 S(NR)(NH)R,
 P(O)R⁵R⁵, and
 4- or 5,6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more groups independently selected from the group consisting of F, Cl, OR⁵, CN, C₁-C₄ alkyl, oxo, and NR⁵R⁶,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, C(O)NR⁵R⁶, OR⁵, NR⁵R⁶, oxo, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₃ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, OR⁵, and C(O)NR⁵R⁶;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with a group selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁-C₅ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₅ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

R⁷ is cycloalkyl optionally substituted with one or more halogens;

p is 1-2;

with the proviso that a compound selected from the group consisting of:

(S)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2H-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea,

and

1-(5-cyclopropylthiazol-4-yl)-3-((3R,4R)-3-(hydroxymethyl)chroman-4-yl)urea, is

excluded.

7. The compound according to claim 6, wherein:

R² is H;

R³ is H;

R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;

Z is selected from the group consisting of C₁-C₃ alkyl, C₂ alkene, NR⁵R⁶, SR⁵, C(O)R⁵, C(O)R⁷, C(O)OR⁵, C(O)NR⁵R⁶, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, and sulfonamide.

wherein the C₁-C₃ alkyl is optionally substituted with one or more groups each

independently selected from the group consisting of cyclopropyl, cyclobutyl

optionally substituted with one or more F, OR⁵, halogen, NR⁵R⁶, and NH-SO₂R⁵,

wherein cycloalkyl is optionally substituted with one or more groups each independently

selected from the group consisting of F, CH₂-OH, CH₂-O-CH₃, and C(O)OR⁵;

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is

optionally substituted with one or more groups each independently selected from the

group consisting of F, OR⁵, and C₁ alkyl optionally substituted with one or more F,

wherein aryl is optionally substituted with one or more groups selected from the group

consisting of:

C₁-C₃ alkyl that is optionally substituted with NR⁵R⁶,

halogen,

CN,

OR⁵,

C(O)NR⁵R⁶,

SO₂R⁶,

SO₂NR⁵R⁶,

SO(NH)R,

S(NR)(NH)R,

P(O)R⁵R⁵, and

5-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more oxo,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, cyclobutyl optionally substituted with one or more OH or F, CN, C(O)NR⁵R⁶, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₃ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, and OR⁵;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with one or more groups selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

R⁷ is cyclobutyl optionally substituted with one or more halogens; and

p is 1.

8. The compound according to claim 6, wherein:

R² is H;

R³ is H;

R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;
Z C₁-C₃ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, OR⁵, halogen, and NR⁵R⁶,
 R^5 is independently H or C₁ alkyl;
 R^6 is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen; and
p is 1.

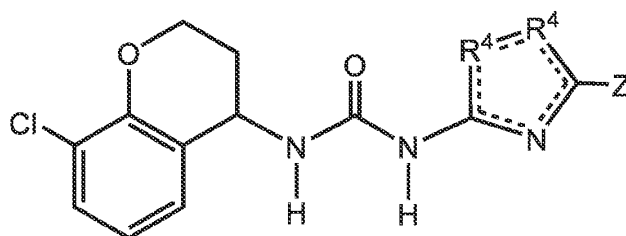
9. The compound according to claim 1, wherein:

R^2 is H;
 R^3 is H;
 R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;
Z is aryl substituted with one or more groups selected from the group consisting of:
halogen,
C(O)NR⁵R⁶, and
SO₂NR⁵R⁶;
 R^5 is independently H or C₁ alkyl;
 R^6 is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen; and
p is 1.

10. The compound according to claim 1, wherein:

R^2 is H;
 R^3 is H;
 R^4 is C- R^5 or S, wherein one R^4 is C- R^5 and the other R^4 is S;
Z heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR⁵, and C₁ alkyl optionally substituted with one or more F,
 R^5 is independently H or C₁ alkyl; and
p is 1.

11. A compound having the structure of formula (III), or a pharmaceutically acceptable salt thereof,



(III)

wherein:

R^4 is $C-R^5$ or S, wherein one R^4 is $C-R^5$ and the other R^4 is S;

Z is selected from the group consisting of C_1 - C_3 alkyl, C_1 - C_6 alkene, NR^5R^6 , SR^5 , $C(O)R^5$, $C(O)R^7$, $C(O)OR^5$, $C(O)NR^5R^6$, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, and sulfonamide,

wherein the C_1 - C_3 alkyl is optionally substituted with one or more groups each

independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, OR^5 , halogen, NR^5R^6 , and $NH-SO_2R^5$,

wherein cycloalkyl is optionally substituted with one or more F, C_1 - C_3 alkyl-OH, C_1 - C_3 alkyl-O- C_1 - C_3 alkyl, $C(O)OR^5$,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is

optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5 , and C_1 alkyl optionally substituted with one or more F,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C_1 - C_3 alkyl that is optionally substituted with NR^5R^6 ,

halogen,

CN,

OR^5 ,

$C(O)NR^5R^6$,

SO_2R^6 ,

$SO_2NR^5R^6$,

SO(NH)R,

S(NR)(NH)R,

P(O)R⁵R⁵, and

5-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more oxo,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, C(O)NR⁵R⁶, SO₂R⁶, a 4- to 6-membered heterocyclic ring, and C₁-C₃ alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR⁵R⁶, and OR⁵;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C₁-C₄ alkyl that is optionally substituted with one or more groups selected from the group consisting of OR⁵, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C₁-C₃ alkyl that is optionally substituted with OR⁵;

R⁵ is independently H or C₁ alkyl;

R⁶ is selected from the group consisting of H, cyclopropyl, and C₁-C₃ alkyl optionally substituted with one or more groups selected from the group consisting of NR⁵R⁵, OR⁵, and halogen;

R⁷ is cycloalkyl optionally substituted with one or more halogens;

with the proviso that a compound selected from the group consisting of:

(*S*)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2*H*-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea,

and

1-(5-cyclopropylthiazol-4-yl)-3-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)urea, is

excluded.

12. The compound according to claim 11, wherein:

R⁴ is C-R⁵ or S, wherein one R⁴ is C-R⁵ and the other R⁴ is S;

Z is C₁-C₃ alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, OR⁵, halogen, and NR⁵R⁶,

R^5 is independently H or C_1 alkyl; and

R^6 is selected from the group consisting of H, cyclopropyl, and C_1 - C_3 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5 , OR^5 , and halogen.

13. The compound according to claim 11, wherein:

R^4 is $C-R^5$ or S, wherein one R^4 is $C-R^5$ and the other R^4 is S;

Z is NR^5R^6 ;

R^5 is independently H or C_1 alkyl; and

R^6 is selected from the group consisting of H, cyclopropyl, and C_1 - C_3 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5 , OR^5 , and halogen.

14. The compound according to claim 11, wherein:

R^4 is $C-R^5$ or S, wherein one R^4 is $C-R^5$ and the other R^4 is S;

Z is $C(O)NR^5R^6$;

R^5 is independently H or C_1 alkyl; and

R^6 is selected from the group consisting of H, cyclopropyl, and C_1 - C_3 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5 , OR^5 , and halogen.

15. The compound according to claim 11, wherein:

R^4 is $C-R^5$ or S, wherein one R^4 is $C-R^5$ and the other R^4 is S;

Z is cycloalkyl is optionally substituted with one or more F; and

R^5 is independently H or C_1 alkyl.

16. The compound according to claim 11, wherein:

R^4 is $C-R^5$ or S, wherein one R^4 is $C-R^5$ and the other R^4 is S;

Z is heterocyclyl that optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5 , and C_1 alkyl optionally substituted with one or more F; and

R^5 is independently H or C_1 alkyl.

17. The compound according to claim 11, wherein:

R^4 is $C-R^5$ or S, wherein one R^4 is $C-R^5$ and the other R^4 is S;

Z is aryl that is optionally substituted with one or more groups selected from the group consisting of:

C_1 - C_3 alkyl that is optionally substituted with NR^5R^6 ,

halogen,

CN,

OR^5 ,

$C(O)NR^5R^6$,

SO_2R^6 ,

$SO_2NR^5R^6$,

$SO(NH)R$,

$S(NR)(NH)R$,

$P(O)R^5R^5$, and

5-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more oxo;

R^5 is independently H or C_1 alkyl; and

R^6 is selected from the group consisting of H, cyclopropyl, and C_1 - C_3 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5 , OR^5 , and halogen.

18. The compound according to claim 11, wherein:

R^4 is $C-R^5$ or S, wherein one R^4 is $C-R^5$ and the other R^4 is S;

Z is heteroaryl that is optionally substituted with one or more groups each independently selected from the group consisting of cyclopropyl, CN, $C(O)NR^5R^6$, SO_2R^6 , a 4- to 6-membered heterocyclic ring, and C_1 - C_3 alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR^5R^6 , and OR^5 ;

R^5 is independently H or C_1 alkyl; and

R^6 is selected from the group consisting of H, cyclopropyl, and C_1 - C_3 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5 , OR^5 , and halogen.

