

COMPOUNDS AND USE THEREOF IN THE EXPANSION OF STEM CELLS AND/OR PROGENITOR CELLS

CROSS REFERENCE TO RELATED APPLICATION

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This application claims benefit of US provisional application 62/581,149 filed November 3, 2017, the content of which is entirely incorporated herein by reference.

FIELD OF THE DISCLOSURE

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The invention relates to compounds as described herein and pharmaceutical compositions containing them. Also, the invention relates to methods for expanding stem cells and/or progenitor cells (HPCs) and methods for treating a hematopoietic disorder/malignancy, an autoimmune disease and/or an inherited immunodeficient disease.

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BACKGROUND OF THE DISCLOSURE

The three sources of hematopoietic stem cells (HSCs) are the bone marrow, mobilized peripheral blood and the umbilical cord blood (UCB). HSCs are used in the transplantation setting (autologous or allogeneic) which constitutes one of the most effective treatment strategies for achieving cures in patients with hematologic malignancies, bone marrow failure conditions, a variety of congenital diseases of global concern (e.g. sickle cell anemia and thalassemia) and autoimmune diseases such as lupus. However, this opportunity for life-saving or life-improving treatment is not available to many thousands of people worldwide due to an inability to amplify these cells *ex vivo* sufficiently to make the procedure safe and successful. More particularly, for every 3 patients, one will forego the opportunity for transplant because no human leucocyte antigen (HLA) identical donor can be found. Another proportion of patients will not have access to transplantation simply because too few HSCs are available in the graft (i.e. cord blood or autologous) for successful transplant. The safety and efficacy of marrow transplant is directly dependent on the number of HSCs and HPCs available for engrafting. The more that can be infused, the more rapidly is hematologic function restored, and the shorter is the window of risk for infection due to lack of granulocytes or of bleeding due to lack of platelets. The challenge in providing sufficient HSCs is further escalated where non-myeloablative

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conditioning is preferred such as in the context of gene therapy for major inherited blood disorders (the major genetic cause of morbidity and mortality worldwide).

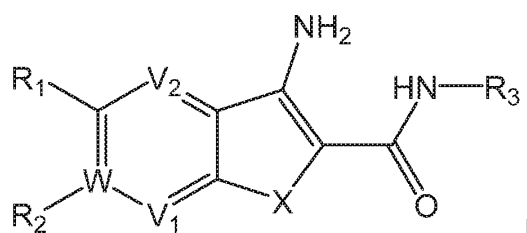
In adults, HSCs mainly reside in the bone marrow (BM) and must be mobilized to enter the circulation prior to being collected by apheresis, either for autologous or allogeneic hematopoietic stem cell transplantation (HSCT). The collection of an adequate number of CD34+ cells, a surrogate marker of (HSCs), is paramount because the dose of CD34+ cells influences the success and rate of hematopoietic recovery. Several reports suggest that a higher infused CD34+ cell dose is independently predictive of improved survival.

Allogeneic HSCT with BM or mobilized peripheral blood stem cells (mPBSC) is another transplantation alternative. However, about one third to one fourth of the patients who are eligible for this type of transplant cannot find a suitable donor. For those who get transplanted, there is a high frequency of transplant related mortality due to graft-versus-host disease, relapse or graft rejection; and a risk of immunodeficiency for prolonged periods of time. Alternatively, umbilical cord blood has been shown as a valid option in allogeneic HSCT. However, a single cord blood (CB) unit typically provides insufficient HSCs for an adult patient for a rapid and efficient recovery.

There is thus a need for novel strategies for increasing the expansion of stem cells, progenitor cells, or both stem cells and progenitor cells.

SUMMARY OF THE DISCLOSURE

An aspect relates to a compound of formula I



or a pharmaceutically acceptable salt thereof, wherein R₁, R₂, R₃, V₁, V₂, X, and W are as defined herein.

A further aspect relates to a pharmaceutical composition comprising a compound as defined herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5 A further aspect relates to a pharmaceutical composition comprising stem cells and/or progenitor cells expanded by a compound or method as defined herein.

In an aspect, there is provided a method of expanding stem cells and/or progenitor cells, as defined herein.

10 A further aspect relates to a cell population obtainable/ obtained by a method as defined herein.

In an aspect, there is provided a method of treating a hematopoietic disorder/malignancy, an autoimmune disease and/or an inherited immunodeficient disease as defined herein.

15 A further aspect relates to a method of treating a hematopoietic disorder/malignancy, an autoimmune disease and/or an inherited immunodeficient disease, comprising administering a compound or a pharmaceutically acceptable salt thereof as defined herein to a subject in need thereof.

20 A further aspect relates to a method of treating a patient receiving an organ transplant, more particularly a solid organ transplant.

BRIEF DESCRIPTION OF THE FIGURES

25 Reference is now made to the accompanying figures in which:

Fig.1A depicts the fold expansion of total cells and CD34+ cells in the different culture conditions compared to fresh samples, as well as the proportions of CD34+ cells in the different culture conditions;

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Fig.1B depicts the fold expansion of CD34+CD45RA-, CD34+CD45RA+ and CD34+CD201+ cells in the different culture conditions compared to fresh samples;

Fig.1C depicts the proportions of CD34+CD45RA-, CD34+CD45RA+ and CD34+CD201+ cells in the different culture conditions;

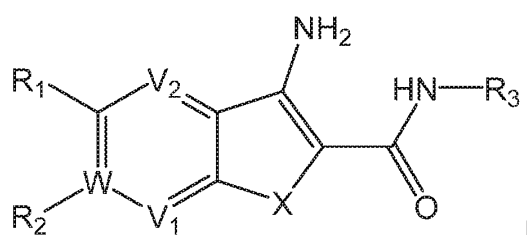
Fig.1D depicts the cell composition in percentages of different cell types in the different culture conditions;

Fig.2A shows the engraftment (as the percentage of human CD45+ cells in bone marrow aspirate) of human cord blood cells from fresh samples or in vitro expanded-samples in the different culture conditions; and

Fig.2B show the proportions of myeloid and lymphoid cells in engrafted human cord blood cells in mice.

DETAILED DESCRIPTION OF THE DISCLOSURE

In one embodiment, there is provided a compound of formula I



or a pharmaceutically acceptable salt thereof, wherein

X is O or S;

V1 is N or CH;

V2 is N or CH;

W is N or C;

wherein not more than one of said V1, V2 and W is N;

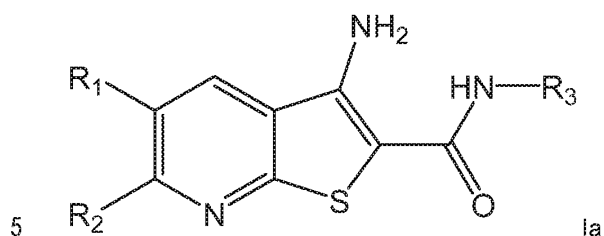
R₁ is halo, alkyl, fluoroalkyl, cycloalkyl, alkynyl, alkenyl, cyano, or COOR_a, wherein R_a is an alkyl;

R₂ is H, alkyl or R₂ is absent when W is N;

or R₁ and R₂ are attached together with the aromatic ring atoms to form a carbocyclic ring;

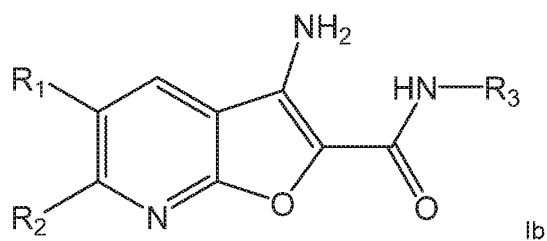
R₃ is an optionally substituted phenyl, an optionally substituted 5- or 6-membered heteroaryl, or an optionally substituted fused bicyclic heteroaryl.

In one embodiment, said compound is a compound of formula Ia



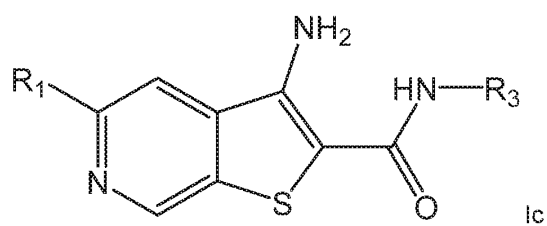
wherein R₁, R₂ and R₃ are as defined herein.

In one embodiment, said compound is a compound of formula Ib



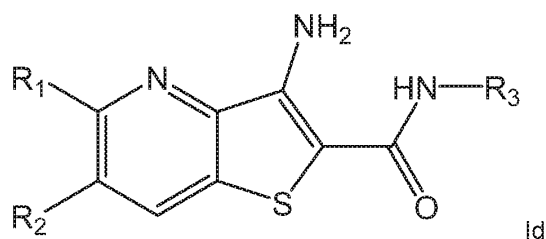
10 wherein R₁, R₂ and R₃ are as defined herein.

In one embodiment, said compound is a compound of formula Ic



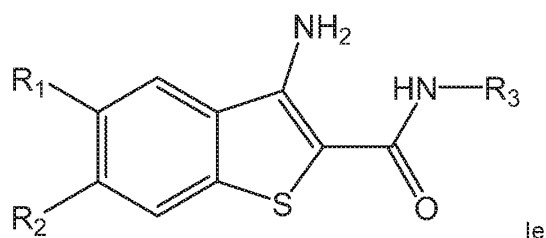
wherein R₁ and R₃ are as defined herein.

In one embodiment, said compound is a compound of formula Id



wherein R_1 , R_2 and R_3 are as defined herein.

In one embodiment, said compound is a compound of formula Ie



5 wherein R_1 , R_2 and R_3 are as defined herein.

In one embodiment, R_1 is halo, C1-6alkyl, C1-6fluoroalkyl, C3-6cycloalkyl, C2-3alkynyl, C2-3alkenyl, cyano, or COORa wherein Ra is a C1-6alkyl.

In one embodiment, R_1 is halo, C1-3alkyl, C1-3fluoroalkyl, C3-6cycloalkyl, C2-3alkynyl, C2-3alkenyl, cyano, or COORa wherein Ra is a C1-3alkyl.

10 In one embodiment, R_1 is F, Cl, Br, Me, Et, iPr, n-Pr, CF₃, cyclopropyl, CCH, CH=CMe, cyano, or COOEt.

In one embodiment, R_1 is F, Me, Et, iPr, n-Pr, CF₃, cyclopropyl, CCH, CH=CMe, cyano, or COOEt.

In one embodiment, R_1 is Me, CF₃, or joined to R_2 to form (CH₂)₃₋₅ ring.

15 In one embodiment, R_1 is Me or CF₃, preferably CF₃.

In one embodiment, R_2 is H, or C1-6alkyl.

In one embodiment, R_2 is H, or C1-3alkyl.

In one embodiment, R_2 is H or Me, preferably H.

In one embodiment, R_2 is H, methyl, ethyl, i-propyl or n-propyl; or preferably H or methyl.

In one embodiment, R_1 and R_2 are attached together to form $(CH_2)_{3-5}$.

5 In one embodiment, R_3 is an optionally mono or disubstituted phenyl, an optionally monosubstituted 5- or 6-membered heteroaryl, or an optionally monosubstituted fused bicyclic heteroaryl.

In one embodiment, R_3 is an optionally mono or disubstituted phenyl at any of positions 3, 4 and 5 of said phenyl, an optionally monosubstituted 5- or 6-membered heteroaryl, or an optionally monosubstituted fused bicyclic heteroaryl of 9 or 10 members.

10 In one embodiment, R_3 is an unsubstituted phenyl, a phenyl monosubstituted at position 4, a phenyl monosubstituted at position 3, a phenyl disubstituted at positions 3 and 4, or a phenyl disubstituted at positions 3 and 5.

In one embodiment, R_3 is an unsubstituted or monosubstituted heteroaryl selected from pyridinyl, pyrimidinyl, thiazolyl, benzothiazolyl, isoquinolinyl, quinolinyl, thienyl and indazolyl.

15 In one embodiment, R_3 is an unsubstituted or monosubstituted heteroaryl selected from 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-thiazolyl, 6-benzothiazolyl, 5-isoquinolinyl, 3-quinolinyl, 4-quinolinyl, 5-quinolinyl, 6-quinolinyl, 3-thienyl and 5-indazolyl.

In one embodiment, R_3 is an unsubstituted or monosubstituted heteroaryl selected from 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, and 3-thienyl.

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In one embodiment, when R_3 is substituted phenyl, said substituent is halo, optionally substituted C1-3alkyl, -O-C1-3fluoroalkyl, -O-C1-3alkyl, -O-benzyl, -O-phenyl, -S-C1-3alkyl, sulfonamide, C1-3fluoroalkyl, -COO-C1-3alkyl, carboxamide, amino, phenyl, 5- or 6-membered heteroaryl or two substituents of R_3 form together $-O(CH_2)_{3-5}O-$ wherein the substituent of said
25 optionally substituted C1-3alkyl is OH, OMe, CN, or COOEt.

In one embodiment, when R_3 is substituted phenyl, said substituent is halo, optionally substituted C1-3alkyl, -O-C1-3fluoroalkyl, -O-C1-3alkyl, -O-benzyl, -O-phenyl, -S-C1-3alkyl, -
SO₂NH(C1-3alkyl) -SO₂N(C1-3alkyl)₂, -SO₂NH₂, C1-3fluoroalkyl, -COO-C1-3alkyl, -CONH(C1-

3alkyl), -CON(C1-3alkyl)₂, -CONH₂, -NH(C1-3alkyl), -N(C1-3alkyl)₂, -NH₂, phenyl or 5- or 6-membered heteroaryl; or two substituents of R₃ form together -O(CH₂)O- or -O(CH₂CH₂)O- ; wherein the substituent of said optionally substituted C1-3alkyl is OH, OMe, CN, or COOEt.

5 In one embodiment, when R₃ is substituted phenyl, said substituent is F, Cl, Br, Me, Et, CH₂OH, CH₂OMe, CH₂CH₂OH, CH₂CH₂OMe, CH₂CN, CH₂COOEt, OCF₃, OCHF₂, -OMe, -O-benzyl, -O-phenyl, -SMe, -SO₂NH₂, CF₃, COOMe, -CONHMe, -CONH₂, -NH₂, 3-pyridinyl, 4- pyridinyl, or two substituents of R₃ form together form -O(CH₂)O- or -O(CH₂CH₂)O-.

10 In one embodiment, when R₃ is substituted phenyl, said substituent is halo, -S-C1-3alkyl, -O-C1-3fluoroalkyl, -O-C1-3alkyl or two substituents of R₃ form together -O(CH₂)₃₋₅O-.

In one embodiment, when R₃ is phenyl substituted at position 4 with H, F, Cl, Br, Me, Et, OMe, OEt, SMe or CF₃.

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In one embodiment, when R₃ is phenyl substituted at position 3 with H, F, Cl, Br, Me, or OMe.

In one embodiment, when R₃ is phenyl substituted at position 3 and 4 together form -CH₂O-, or -OCH₂CH₂O-.

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In one embodiment, when R₃ is substituted heteroaryl, said substituent is halo, optionally substituted C1-3alkyl, -O-C1-3fluoroalkyl, -O-C1-3alkyl, -O-benzyl, -O-phenyl, -S-C1-3alkyl, -SO₂NH(C1-3alkyl), -SO₂N(C1-3alkyl)₂, -SO₂NH₂, C1-3fluoroalkyl, -COO-C1-3alkyl, -CONH(C1-3alkyl), -CON(C1-3alkyl)₂, -CONH₂, -NH(C1-3alkyl), -N(C1-3alkyl)₂, -NH₂, phenyl or 5- or 6-membered heteroaryl; or two substituents of R₃ form together -O(CH₂)O- or -O(CH₂CH₂)O- ; wherein the substituent of said optionally substituted C1-3alkyl is OH, OMe, CN, or COOEt.

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In one embodiment, when R₃ is substituted heteroaryl, said substituent is F, Cl, Br, Me, Et, CH₂OH, CH₂OMe, CH₂CH₂OH, CH₂CH₂OMe, CH₂CN, CH₂COOEt, OCF₃, OCHF₂, -OMe, -O-benzyl, -O-phenyl, -SMe, -SO₂NH₂, CF₃, COOMe, -CONHMe, -CONH₂, -NH₂, 3-pyridinyl, 4-pyridinyl, or two substituents of R₃ form together form -O(CH₂)O- or -O(CH₂CH₂)O-.

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In one embodiment, when R₃ is substituted heteroaryl, such as 2-, 3-, 4-pyridyl or thienyl, said substituent is halo, C1-3alkyl, or -O-C1-3alkyl, preferably R₃ is 4-pyridinyl or 3-thienyl.

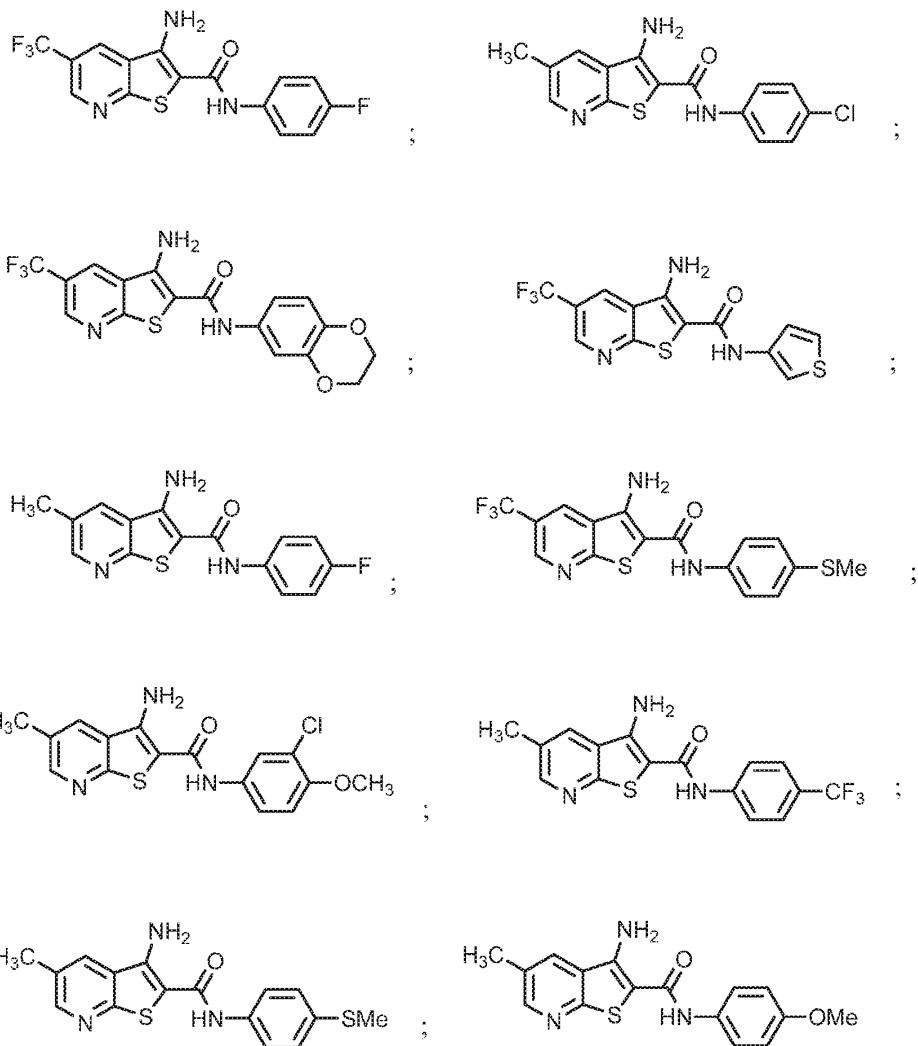
In one embodiment, in formula I, or in any of formula Ia to Ie, preferably in formula Ia and Ie, R₁ is C1-6alkyl, C1-6fluoroalkyl, R₂ is H or R₁ is joined to R₂ to form (CH₂)₃₋₅, R₃ is an unsubstituted phenyl, a phenyl monosubstituted at position 4, a phenyl monosubstituted at position 3, a phenyl disubstituted at positions 3 and 4, or a phenyl disubstituted at positions 3 and 5 or R₃ is an unsubstituted or monosubstituted heteroaryl selected from pyridinyl, pyrimidinyl, thiazolyl, benzothiazolyl, isoquinolinyl, quinolinyl, thienyl and indazolyl.

In one embodiment, in formula I, or in any of formula Ia to Ie, preferably in formula Ia and Ie, R₁ is halo, C1-3alkyl, C1-3fluoroalkyl, C3cycloalkyl, C2-3alkynyl, C2-3alkenyl, cyano, or COORa wherein Ra is a C1-3alkyl, preferably R₁ is Me, CF₃, or joined to R₂ to form (CH₂)₃₋₅ ring; R₂ is H, R₃ is an unsubstituted phenyl, a phenyl monosubstituted at position 4, a phenyl monosubstituted at position 3, a phenyl disubstituted at positions 3 and 4, or a phenyl disubstituted at positions 3 and 5 wherein said phenyl substituent(s) is F, Cl, Br, Me, Et, CH₂OH, CH₂OMe, CH₂CH₂OH, CH₂CH₂OMe, CH₂CN, CH₂COOEt, OCF₃, OCHF₂, -OMe, -O-benzyl, -O-phenyl, -SMe, -SO₂NH₂, CF₃, COOMe, -CONHMe, -CONH₂, -NH₂, 3-pyridinyl, 4-pyridinyl, or two substituents of R₃ together form -O(CH₂)O- or -O(CH₂CH₂)O- or R₃ is an unsubstituted or monosubstituted heteroaryl selected from 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, and 3-thienyl, wherein said substituent is halo, C1-3alkyl, or -O-C1-3alkyl.

In one embodiment, in formula I, or in any of formula Ia to Ie, preferably in formula Ia, R₁ is C1-3alkyl, or C1-3fluoroalkyl, preferably R₁ is Me; R₂ is H, R₃ is a phenyl monosubstituted at position 4, or a phenyl disubstituted at positions 3 and 4, wherein said phenyl substituent(s) is F, Cl, Br, Me, Et, CH₂OH, CH₂OMe, CH₂CH₂OH, CH₂CH₂OMe, CH₂CN, CH₂COOEt, OCF₃, OCHF₂, -OMe, -O-benzyl, -O-phenyl, -SMe, -SO₂NH₂, CF₃, COOMe, -CONHMe, -CONH₂, -NH₂, 3-pyridinyl, 4-pyridinyl, or two substituents of R₃ together form -O(CH₂)O- or -O(CH₂CH₂)O-, preferably said phenyl substituent is F, -Cl, -SMe, -OMe, CF₃ or two substituents form -O(CH₂CH₂)O-, or R₃ is an unsubstituted or monosubstituted heteroaryl selected from 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, and 3-thienyl, preferably said heteroaryl is an unsubstituted 3-thienyl.

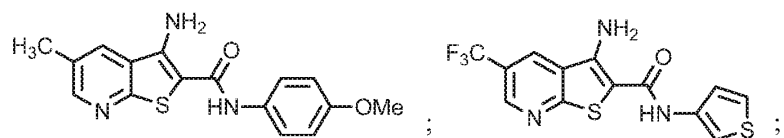
In one embodiment, compound of formula I is compounds of Tables 1 or 2.

In one embodiment, compound of formula I is



or a pharmaceutically acceptable salt thereof.

5 In one embodiment, compound of formula I is



or a pharmaceutically acceptable salt thereof.

The methods as defined herein enjoy the use of the full scope of the compounds as contemplated by the inventors. The compounds that are excluded from the scope of the claimed compounds are those defined by the following provisos or as enumerated below.

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Generic proviso 1: when V1 is N, X is S, R₁ and R₂ together form (CH₂)₃₋₅ and R₃ is phenyl, then said phenyl is other than i) unsubstituted phenyl or ii) phenyl substituted at position 4 by F, Cl or OMe, for example when said compound is of formula I or Ia.

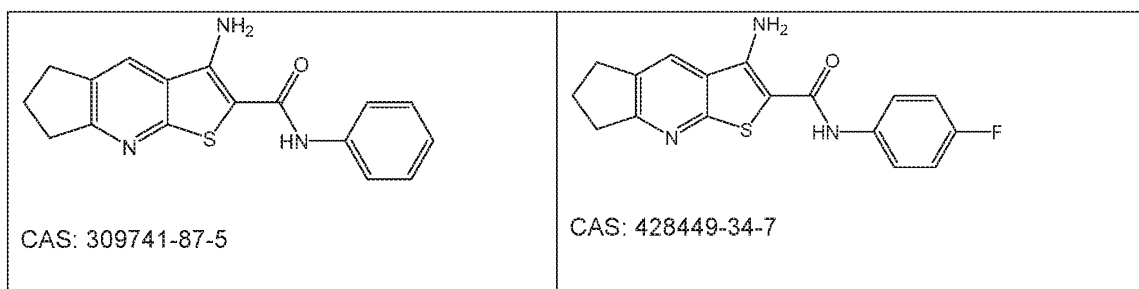
- 10 Generic proviso 1a: where V1 is N, X is S, R₁ and R₂ together form (CH₂)₃₋₅, R₃ is optionally substituted 5- or 6-membered heteroaryl, or an optionally substituted fused bicyclic heteroaryl, a phenyl monosubstituted at position 3, phenyl disubstituted at positions 3 and 4, a phenyl disubstituted at positions 3 and 5, a phenyl monosubstituted at position 4 by Br, optionally substituted C1-3alkyl, -O-C1-3fluoroalkyl, -O-C2-3alkyl, -O-benzyl, -O-phenyl, -S-C1-3alkyl, -
- 15 SO₂NH(C1-3alkyl), -SO₂N(C1-3alkyl)₂, -SO₂NH₂, C1-3fluoroalkyl, -COO-C1-3alkyl, -CONH(C1-3alkyl), -CON(C1-3alkyl)₂, -CONH₂, -NH(C1-3alkyl), -N(C1-3alkyl)₂, or -NH₂, for example when said compound is of formula I or Ia.

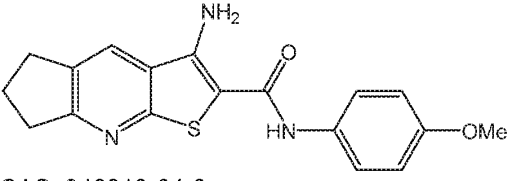
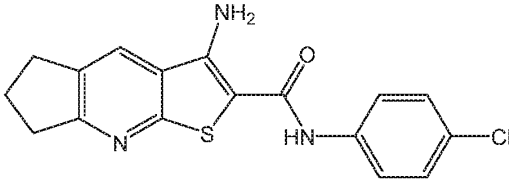
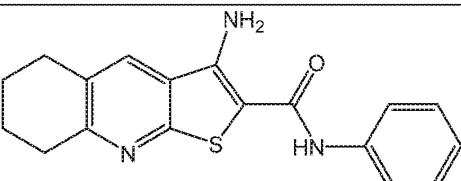
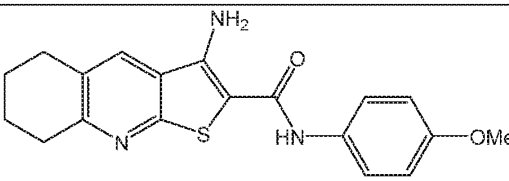
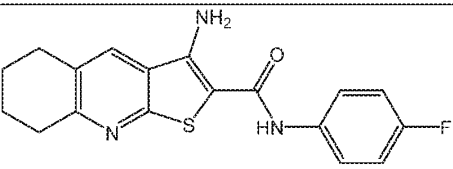
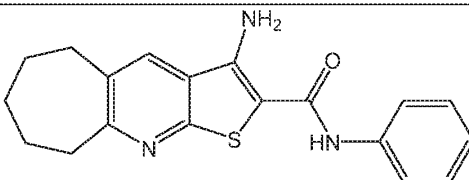
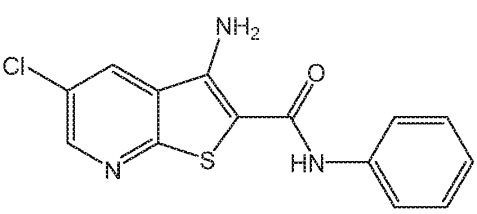
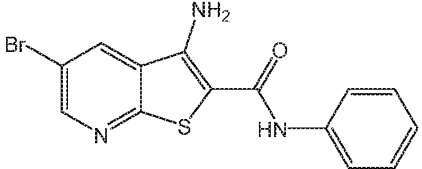
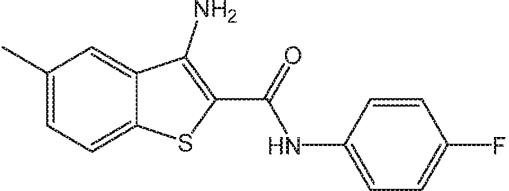
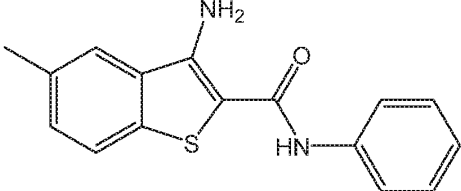
- 20 Generic proviso 2: when V1 is N, X is S, R₃ is unsubstituted phenyl and R₂ is H, then R₁ is other than Cl or Br, for example when said compound is of formula I or Ia.

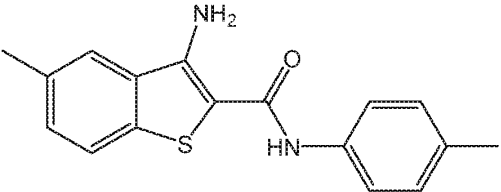
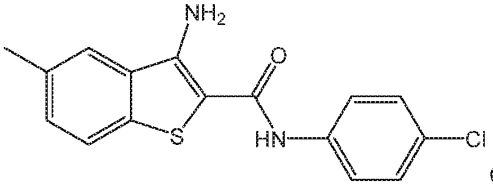
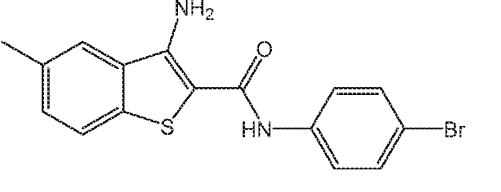
- Generic proviso 3: when V1 and V2 are CH, W is C, X is S, R₂ is H, R₁ is CH₃ and R₃ is phenyl, then said phenyl is other than i) unsubstituted phenyl or ii) phenyl substituted at position 4 by F, Cl, Br or Me, for example when said compound is of formula I or Ia.

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Alternatively, the compounds that are excluded from the scope of the claimed compounds are:



 CAS: 340813-04-9	 CAS: 428444-64-8
 CAS: 361198-68-7	 CAS: 340813-02-7
 CAS: 428451-61-0	 CAS: 298219-02-0
 CAS: 1628934-21-3	 CAS: 1628934-24-6
 CAS: 1927343-65-4	 CAS: 1927344-00-0

 CAS: 1942440-87-0	 CAS: 1962685-12-6
 CAS: 1939271-31-4	

When there is a sulfur atom present (such as a core ring atom), the sulfur atom can be at different oxidation levels, ie. S, SO, or SO₂. All such oxidation levels are within the scope of the present disclosure. When there is a nitrogen atom present, the nitrogen atom can be at different oxidation levels, i.e. N or NO. All such oxidation levels are within the scope of the present disclosure.

The term "alkyl", as used herein, unless otherwise defined is understood as referring to a saturated, monovalent unbranched or branched hydrocarbon chain. Examples of alkyl groups include, but are not limited to, C1-10 alkyl groups, provided that branched alkyls comprise at least 3 carbon atoms, such as C3-10. Straight alkyl may have 1 to 6 or preferably 1 to 3 carbon atoms; whereas branched alkyl comprise C3-6. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl and decyl.

The term "alkenyl" is meant to include alkyl residues in which one or more single bond(s) is replaced by a double bond.

The term "alkynyl" is meant to include alkyl residues in which one or more single bond(s) is replaced by a triple bond.

5 The term "fluoroalkyl" is meant to include alkyls in which one or more hydrogen atom is replaced by a fluoride atom of all alkyls defined above: straight or branched fluoroalkyls and straight or branched lower fluoroalkyls, such as trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, dichloromethyl, chloromethyl, trifluoroethyl, difluoroethyl, fluoroethyl.

10 The term "cycloalkyl" represents optionally substituted cyclic alkyl moiety having 3 to 10 carbon atoms. Examples of "cycloalkyl" groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

15 The term "carbocyclic ring" in the definition of R_1 and R_2 preferably refers to an alkyl chain forming a ring with the aromatic ring atoms to which they are attached, even more preferably the carbocyclic ring refers to a chain $(CH_2)_{3-5}$ forming a ring with the aromatic ring atoms to which they are attached.

20 The term "heteroaryl" represents a 5 to 11 membered aromatic cyclic moiety wherein said cyclic moiety is comprising at least one heteroatom selected from oxygen (O), sulfur (S) or nitrogen (N). Heteroaryls may be monocyclic or polycyclic rings. Heteroaryls may be 5 to 6 membered monocyclic ring or 5 membered monocyclic ring or 6 membered monocyclic ring. Heteroaryls may be fused 6,6, or 5,6 bicyclic rings. When heteroaryl is a polycyclic ring, the rings comprise at least one ring comprising the heteroatom and the other rings may be cycloalkyl, aryl or heterocycle and the point of attachment may be on any available atom. This term includes
25 without limitation, for example, furyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolyl and indazolyl.

30 There is also provided pharmaceutically acceptable salts of the compounds of the present disclosure. What is meant by the term pharmaceutically acceptable salts of the compounds is that they are derived from pharmaceutically acceptable inorganic and organic acids and bases.

For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, perchloric and the like, as well

as salts prepared from organic acids such as formic, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, benzenesulphonic, naphthalene 2 sulphonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic
5 and the like.

Other salts, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the disclosure and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal,
10 alkaline earth metal or ammonium salts.

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

20 In one embodiment there is provided a pharmaceutical composition comprising a compound as defined herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In one embodiment there is provided a pharmaceutical composition comprising stem cells
25 and/or progenitor cells expanded by a compound or method as defined herein.

The pharmaceutical composition may be further comprising a buffer solution or a an additional pharmaceutically active component, such as an antibiotic.

30 In one embodiment the pharmaceutical composition as defined herein, is for intravenous administration.

In one embodiment there is provided a method of expanding stem cells and/or progenitor cells, (such as hematopoietic stem and/or progenitor cells) the method comprising contacting a

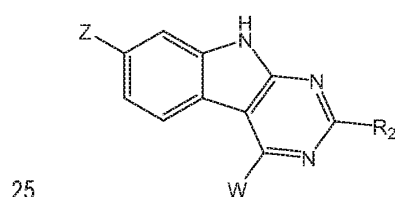
starting cell population and at least one compound or a pharmaceutically acceptable salt thereof as defined herein.

5 In one embodiment of the methods herein, said methods are comprising the steps of contacting stem cells and/or progenitor cells (such as hematopoietic stem and/or progenitor cells) with a compound for expanding stem cells and/or progenitor cells and at least one compound or a pharmaceutically acceptable salt thereof as defined herein.

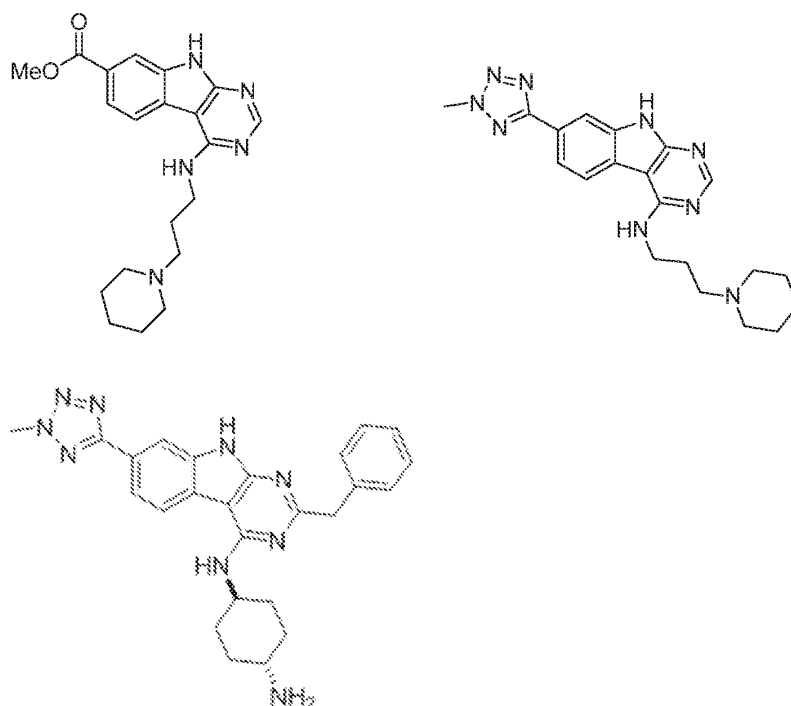
10 In one embodiment of the methods herein, said methods are comprising the steps of contacting stem cells and/or progenitor cells (such as hematopoietic stem and/or progenitor cells) with a first compound for expanding stem cells and/or progenitor cells, expanding the cells for a first period of time, adding at least one compound or a pharmaceutically acceptable salt thereof as defined herein and expanding the cells further for a second period of time.

15 In one embodiment of the methods herein, said methods are comprising the steps of contacting stem cells and/or progenitor cells (such as hematopoietic stem and/or progenitor cells) with a first compound for expanding stem cells and/or progenitor cells, expanding the cells for a first period of time, substantially removing said first compound (e.g. by washing the expanded cells with an appropriate wash medium), contacting said cells expanded from said first period of time
20 with at least one compound or a pharmaceutically acceptable salt thereof as defined herein and expanding the cells further for a second period of time.

A (first) compound for expanding stem cells, other than a compound of this invention (formula I, or Ia-Ie) may be a compound of formula



such as those described in WO 2013/110198 (PCT/CA2013/050052), the content of which is incorporated herein by reference in its entirety. In particular, the compound may be one of the following:



The method of expanding stem cells and/or progenitor cells as defined herein, may further be comprising at least one cell expanding agent.

5

In one embodiment of the method of expanding hematopoietic stem cells and/or progenitor cells as defined herein, said cell expanding agent is an agonist antibody against the Thrombopoietin (TPO) receptor (for example, VB22B sc(Fv)2 as detailed in patent publication WO 2007/145227, and the like); a cytokine such as SCF, IL-6, Flt-3 ligand, TPO or a TPO mimetic (for example, such as described in WO/2007/022269; WO/2007/009120; WO/2004/054515; WO/2003/103686; WO/2002/085343; WO/2002/049413; WO/2001/089457; WO/2001/039773; WO/2001/034585; WO/2001/021180; WO/2001/021180; WO/2001/017349; WO/2000/066112; WO/2000/035446; WO/2000/028987; WO/2008/028645; and the like, which are incorporated herein by reference); granulocyte colony stimulating factor (G-CSF); granulocyte macrophage colony stimulating factor (GM-CSF); a prostaglandin or a prostaglandin receptor agonist (for example, prostaglandin E2 receptor-1 (EP-1) agonist, prostaglandin E2 receptor-2 (EP-2) agonist, prostaglandin E2 receptor-3 (EP-3) agonist and prostaglandin E2 receptor-4 (EP-4) agonists, as detailed in patent publication WO/2008/073748 which is incorporated herein by

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reference); tetraethylenepentamine (TEPA); Notch-ligands (Delta-1); and/or a WNT agonist. These publications and their content are incorporated herein by reference.

5 Preferably the cell expanding agent is selected from Interleukin-3 (IL-3), Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), Thrombopoietin (TPO), FMS-Like Tyrosine Kinase 3 Ligand (FLT3-L), Stem Cell Factor (SCF), Interleukin-6 (IL-6) and a combination thereof.

10 The cell expanding agent may be SCF, FLT3-L, TPO, IL-6 or a combination thereof. In one embodiment of the method of expanding stem cells (such as hematopoietic stem cells) and/or progenitor cells as defined herein, said cell expanding agent, is StemRegenin 1 (SR1).

15 In one embodiment there is provided a method of modulating (antagonizing) the activity of aryl hydrocarbon receptor, comprising contacting stem cells and progenitor cells with a compound as defined herein.

20 In one embodiment there is further provided a method of increasing the number of stem cells and progenitor cells; said method comprising contacting the cells with a compound capable of antagonizing the activity and/or expression of aryl hydrocarbon receptor and/or a downstream effector of aryl hydrocarbon receptor pathway, wherein said compound is a compound as defined herein.

25 In one embodiment there is provided a method of expanding stem cells (such as hematopoietic stem cells) and/or progenitor cells as defined herein, wherein hematopoietic stem cells and/or progenitor cells are human hematopoietic stem and progenitor cells.

30 In one embodiment there is provided a method of expanding CD34+ stem cells and/or progenitor cells as defined herein, wherein CD34+ stem cells and/or progenitor cells are human hematopoietic stem and progenitor cells.

In one embodiment the starting cell population is comprising CD34+ cells harvested from mobilized peripheral blood (mPB), bone marrow (BM) or umbilical cord blood (UCB). In one embodiment, the starting cell population is human CD34+ stem cells and/or progenitor cells.

In one embodiment the starting cell population includes CD34+ cells harvested from umbilical cord blood (UCB).

5 In one embodiment the starting cell population consists essentially of CD34+ cells, for example purified from one or two umbilical cord blood units.

10 The expanded cells may then be washed to remove the compound or composition of invention and/or any other component of the cell culture and resuspended in an appropriate cell suspension medium for short term use or in a long-term storage medium, for example a medium suitable for cryopreservation.

15 A preferred method of administration of expanded cells or a composition comprising said expanded cells is intravenous infusion. The number of cells transfused will take into consideration factors such as sex, age, weight, the types of disease or disorder, stage of the disorder, the percentage of the desired cells in the cell population and the amount of cells needed to produce a therapeutic benefit. In one particular embodiment, the composition is administered by intravenous infusion and comprises at least $\geq 0.3 \times 10^5$ CD34⁺/ kg or $> 2 \times 10^6$ CD34⁺ for cord blood and 2.5×10^5 CD34⁺/ kg or more for bone marrow or mobilized peripheral blood cells.

20 Expanded stem cells (such as hematopoietic stem cells) and/or hematopoietic progenitor cells may be infused by drip, for example, in the case of treatment of leukemia, into patients pretreated with an anticancer drug, total body irradiation or an immunosuppressive drug for eradication of cancer cells or for facilitation of donor cell engraftment. The disease to be treated, 25 the pretreatment and the cell transplantation method are selected appropriately by the person in charge. The engraftment of so transplanted hematopoietic stem cells and/or hematopoietic progenitor cells in the recipient, the recovery of hematopoiesis, the presence of side effects of the transplantation and the therapeutic effect of the transplantation can be judged by an ordinary assay used in transplantation therapy.

30 In one embodiment of the method of expanding stem cells and/or progenitor cells as defined herein, said method is in vivo, in vitro or ex vivo, in particular, the method is ex vivo or in vitro.

In one embodiment, there is provided a cell population as expanded by a method as defined herein.

5 In one embodiment, there is provided a method of treating a hematopoietic disorder/malignancy, an autoimmune disease and/or an inherited immunodeficient disease, comprising administering expanded stem cells (such as hematopoietic stem cells) as defined herein to a subject in need thereof or expanding hematopoietic stem cells by a method as defined herein and administering said expanded stem cells to a subject in need thereof.

10 There is further provided a cell population with expanded HSCs, obtainable or obtained by the expansion method described above. In one specific embodiment, such cell population is resuspended in a pharmaceutically acceptable medium suitable for administration to a mammalian host, thereby providing a therapeutic composition.

15 There is further provided a method of treating a hematopoietic disorder/malignancy, an autoimmune disease and/or an inherited immunodeficient disease, comprising administering a compound or a pharmaceutically acceptable salt thereof as defined herein to a subject in need thereof.

20 In one embodiment, of the methods as defined herein, the hematopoietic disorder/malignancy, the autoimmune disease and/or the inherited immunodeficient disease comprise bone marrow failure conditions, a congenital diseases (such as sickle cell anemia and thalassemia), lupus, acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, myeloproliferative disorders, myelodysplastic syndromes, multiple
25 myeloma, non-Hodgkin's lymphoma, Hodgkin's disease, aplastic anemia, pure red cell aplasia, hemoglobinuria, Fanconi anemia, thalassemia, sickle cell anemia, Wiskott-Aldrich syndrome, inborn errors of metabolism (such as Gaucher disease).

In one embodiment, there is provided a method of treating a patient receiving an organ from a
30 transplantation (ex. solid organ transplantation), comprising administering expanded stem cells (such as hematopoietic stem cells) as defined herein to said patient or expanding hematopoietic stem cells by a method as defined herein and administering said expanded hematopoietic stem cells to said patient. In a further embodiment, the expanded cells are bone marrow cells from the organ donor.

Regarding the method of treating a patient receiving an organ from a transplantation (ex. solid organ transplantation), reference can be made to Basak GW et al., Am J Transplant 2015 PMID:25648262; Elahimehr R et al., Transplant Rev (Orlando) 2016, PMID:27553809
5 and Marino Granados JM et al., Curr Opin Organ Transplant 2015, PMC4391059. Good review of preclinical and clinical studies.

The subject referred to herein is, for example, a bone marrow donor or an individual with or at risk for depleted or limited blood cell levels. Optionally, the subject is a bone marrow donor prior
10 to bone marrow harvesting or a bone marrow donor after bone marrow harvesting. The subject is optionally a recipient of a bone marrow transplant. The methods described herein are particularly useful in subjects that have limited bone marrow reserve such as elderly subjects or subjects previously exposed to an immune depleting treatment or myeloablative treatment such as chemotherapy, e.g., for treating leukemia or lymphomas. The subject, optionally, has a
15 decreased blood cell level or is at risk for developing a decreased blood cell level as compared to a control blood cell level. As used herein the term control blood cell level refers to an average level of blood cells in a subject prior to or in the substantial absence of an event that changes blood cell levels in the subject. An event that changes blood cell levels in a subject includes, for example, anemia, trauma, chemotherapy, bone marrow transplant and radiation therapy. For
20 example, the subject has anemia or blood loss due to, for example, trauma.

As used herein, the term "hematopoietic stem cells" or "HSCs" is intended to mean cells having both pluripotency which allows them to differentiate into functional mature cells such as granulocytes (e.g., promyelocytes, neutrophils, eosinophils, basophils), erythrocytes (e.g.,
25 reticulocytes, erythrocytes), thrombocytes (e.g., megakaryoblasts, platelet producing megakaryocytes, platelets), and monocytes (e.g., monocytes, macrophages), and the ability to regenerate while maintaining their pluripotency (self-renewal).

HSCs are part of the starting cell population. These cells are optionally obtained from the body
30 or an organ of the body containing cells of hematopoietic origin. Such sources include unfractionated bone marrow, umbilical cord, peripheral blood, liver, thymus, lymph and spleen. All of the aforementioned crude or un-fractionated blood products can be enriched for cells having hematopoietic stem cell characteristics in ways known to those of skill in the art.

As used herein, the term "starting cell population" is meant to identify a cell population comprising stem and/or progenitor cells, such as hematopoietic stem cells (HSCs) and/or hematopoietic progenitor cells, harvested from one of various sources mentioned above, as known in the art.

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The starting cell population may first be subjected to enrichment or purification steps, including negative and/or positive selection of cells based on specific cellular markers in order to provide the starting cell population. Methods for isolating said starting cell population based on specific cellular markers may use fluorescent activated cell sorting (FACS) technology also called flow
10 cytometry or solid or insoluble substrate to which is bound antibodies or ligands that interact with specific cell surface markers. For example, cells may be contacted with a solid substrate (e.g., column of beads, flasks, magnetic particles) containing the antibodies and any unbound cells are removed. When a solid substrate comprising magnetic or paramagnetic beads is used, cells bound to the beads can be readily isolated by a magnetic separator.

15

The starting cell population can be enriched in CD34+ cells meaning a cell population selected based on the presence of the cell surface marker CD34+. CD34+ cells can be detected and counted using for example flow cytometry and fluorescently labeled anti-CD34 antibodies. Moreover, the starting cell population may be used directly for expansion or frozen and stored
20 for use at a later point in time. Methods for enriching blood cell population in CD34+ cells include kits commercialized by Miltenyi Biotec (CD34+ direct isolation kit, Miltenyi Biotec, Bergisch, Gladbach, Germany) or by Baxter (Isolex 3000). The starting cell population may preferably contain at least 50% CD34+ cells, in some embodiments, more than 90% of CD34+ cells.

25

The compounds and further cell expanding agent as used herein may be added to expansion medium immobilized onto a substrate or support used for the culture.

30

The expansion of stem cells may be carried out in natural medium, a semi-synthetic medium or a synthetic medium in terms of composition, and may be a solid medium, a semisolid medium or a liquid medium in terms of shape, and any nutrient medium used for hematopoietic stem cell and/or hematopoietic progenitor cell culture, which is supplemented with the mixtures of cell expanding factors described above. Such medium typically comprises sodium, potassium, calcium, magnesium, phosphorus, chlorine, amino acids, vitamins, cytokines, hormones,

antibiotics, serum, fatty acids, saccharides or the like. In the culture, other chemical components or biological components may be incorporated singly or in combination, as the case requires. Such components to be incorporated in the medium may be fetal calf serum, human serum, horse serum, insulin, transferrin, lactoferrin, cholesterol, ethanolamine, sodium selenite, monothioglycerol, 2-mercaptoethanol, bovine serum albumin, sodium pyruvate, polyethylene glycol, various vitamins, various amino acids, agar, agarose, collagen, methylcellulose, various cytokines, various growth factors or the like. Examples of such basal medium appropriate for a method of expanding HSCs include, without limitation, StemSpan™ Serum-Free Expansion Medium (SFEM) (StemCell Technologies, Vancouver, Canada), StemSpan™ H3000-Defined Medium (StemCell Technologies, Vancouver, Canada), CellGro™, SCGM (CellGenix, Freiburg Germany), StemPro™-34 SFM (Invitrogen), Dulbecco's Modified Eagles's Medium (DMEM), Ham's Nutrient Mixture H12 Mixture F12, McCoy's 5A medium, Eagles's Minimum Essential Medium (EMEM), α MEM medium (alpha Modified Eagles's Minimum Essential Medium), RPMI1640 medium, Isocove's Modified Dulbecco's Medium (IMDM), StemPro34 (Invitrogen), X-VIVO 10 (Cambrex), X-VIVO 15 (Cambrex) and Stemline II (Sigma-Aldrich).

The stem cells and/or progenitor cells can be cultured in a culture vessel generally used for animal cell culture such as a Petri dish, a flask, a plastic bag, a Teflon™ bag, optionally after preliminary coating with an extracellular matrix or a cell adhesion molecule. The material for such a coating may be collagens I to XIX, fibronectin, vitronectin, laminins 1 to 12, nitrogen, tenascin, thrombospondin, von Willebrand factor, osteopontin, fibrinogen, various elastins, various proteoglycans, various cadherins, desmocollin, desmoglein, various integrins, E-selectin, P-selectin, L-selectin, immunoglobulin superfamily, Matrigel, poly-D-lysine, poly-L-lysine, chitin, chitosan, Sepharose, alginic acid gel, hydrogel or a fragment thereof. Such a coating material may be a recombinant material having an artificially modified amino acid sequence. The hematopoietic stem cells and/or hematopoietic progenitor cells may be cultured by using a bioreactor which can mechanically control the medium composition, pH and the like and obtain high density culture (Schwartz R M, Proc. Natl. Acad. Sci. U.S.A., 88:6760, 1991; Koller M R, Bone Marrow Transplant, 21:653, 1998; Koller, M R, Blood, 82: 378, 1993; Astori G, Bone Marrow Transplant, 35: 1101, 2005). These publications and their content are incorporated herein by reference.

A starting cell population, in particular CD34+ enriched cells, may be grown under conditions for HSC expansion, for example between 2 and 21 days and/or until the indicated fold expansion

and the characteristic cell populations are obtained. In one specific embodiment, the cells are grown ex vivo under conditions for HSC expansion not more than 21 days, 12 days, 10 days or 7 days.

- 5 Pharmaceutical compositions may comprise pharmaceutically acceptable carrier(s) and/or excipient(s). Many pharmaceutically acceptable carrier(s) and/or excipient(s) are known in the art. It will be understood by those in the art that a pharmaceutically acceptable carrier and/or excipient must be compatible with the other ingredients of the formulation and tolerated by a subject in need thereof. The proportion of each carrier and/or excipient can be determined by
10 the skilled practitioner in accordance with standard pharmaceutical practice.

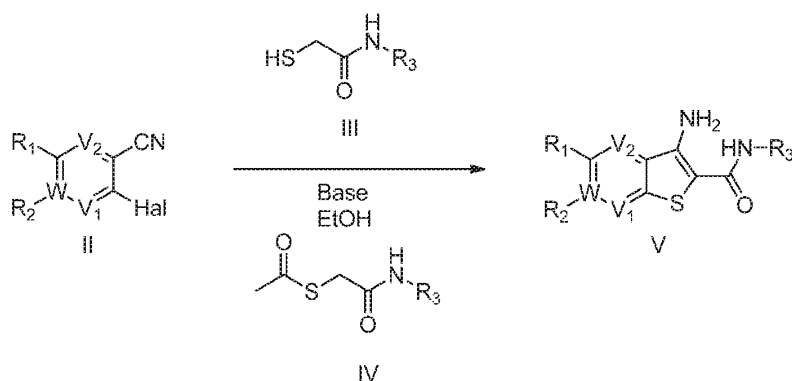
- In order to ensure consistency of administration, in an embodiment of the present disclosure, the pharmaceutical composition is in the form of a discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of
15 bringing into association the active compound with a liquid carrier or solid carrier or both and then, if necessary, shaping the product into the desired formulation.

- The compounds and expanded cells according to the disclosure may be formulated for parenteral administration, e.g. by injection, for example bolus injection or continuous infusion, and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with/without an added preservative. The compositions are formulated in any conventional manner for use in the methods described herein. Administration is via any route known to be effective by one of ordinary skill. For example, the compositions is administered orally, parenterally (e.g., intravenously), by intramuscular injection, by
20 intraperitoneal injection, transdermally, extracorporeally, intranasally or topically.

- The following examples are provided to further illustrate details for the preparation and use of the compounds of the present disclosure. They are not intended to be limitations on the scope of the instant disclosure in any way, and they should not be so construed. Furthermore, the compounds described in the following examples are not to be construed as forming the only
30 genus that is considered as the disclosure, and any combination of the compounds or their moieties may itself form a genus.

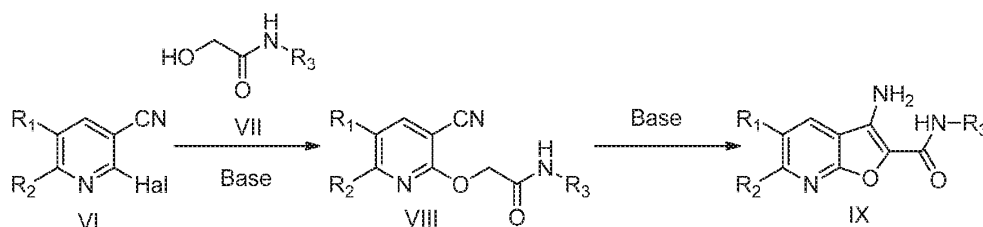
Examples:

Scheme I: General synthesis of compounds of the invention wherein X = S



- 5 The compounds of the general formula V can be prepared by the condensation of compounds II, an ortho halo-pyridinecarbonitrile (V₁ or V₂ or W = N) or a 2-halobenzonitrile (V₁, V₂, W = C, R₂ = H), with 2-mercaptoacetamide derivatives III or IV in the presence of a base in a solvent such as ethanol or DMF.

- 10 Scheme II: General synthesis of compounds of the invention wherein X = O



The compounds of the general formula IX can be prepared by the condensation of compounds VI, an ortho halo-pyridinecarbonitrile (R₂ = H, CH₃ or linked to R₁ via (CH₂)₃₋₅ linkers), with 2-hydroxyacetamide derivatives VII in the presence of a base in a solvent such as ethanol followed by the cyclization of intermediate VIII in the presence of a stronger base.

CHEMISTRY EXPERIMENTAL

Abbreviations or symbols used herein include: **AcOH**: acetic acid; **dba**: dibenzylidene acetone;

- 20 **DMF**: *N,N*-dimethylformamide; **DIPEA**: diisopropylamine; **DMSO**: dimethylsulfoxide; **dppf**: 1,1'-

bis(diphenylphosphino)ferrocene; **EtOAc**: ethyl acetate; **EtOH**: ethanol; **MeOH**: methanol; **Hex**: hexanes; **MS**: mass spectrometry; **NMR**: nuclear magnetic resonance; **THF**: tetrahydrofuran.

EXAMPLES

5

Other features of the present invention will become apparent from the following non-limiting examples which illustrate, by way of examples, the principle of the invention. As it is well known to a person skilled in the art, reactions are performed in an inert atmosphere (nitrogen or argon) where necessary to protect reaction components from air and moisture. Temperature are given in degrees Celsius (°C). The reactants used in the examples below may be obtained either as described herein, or if not described herein, are themselves either commercially available (described as **A0** in table) or may be prepared from commercially available materials by methods known in the art. Flash chromatography is carried out on silica (SiO₂) using a Teledyne Isco Rf instrument. Mass spectra analyses are recorded using electrospray mass spectrometry. NMR are recorded on a 500 MHz Bruker or 400 MHz Varian instruments. Preparative HPLC is performed using an Agilent instrument with one the following conditions:

Column: Phenomenex-Kinetex C18, 21x100mm, 5 µm
Mobile Phase: Solvent A: 5% MeOH, 95% Water + 0.1% Formic acid, Solvent B: 95% MeOH, 5% Water + 0.1% Formic acid
Flow: 20 mL / min, room temperature.
Collection wavelength = 220 and 254 nm

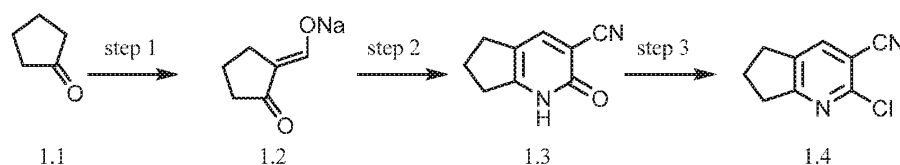
Condition A:

Mobile Phase: From 0 to 3 min: isocratic 30% solvent B, followed by a 12 minutes gradient to 100% solvent B. Last 5 minutes 100% solvent B.

Condition B:

Mobile Phase: From 0 to 2 min: isocratic 30% solvent B, followed by an 8 minutes gradient to 100% solvent B. Last 2 minutes 100% solvent B.

30 Example 1: Preparation of intermediate **1.4** (General procedure A1)



Step 1

EtOH (4.16 mL, 71.3 mmol) is added slowly to an ice-cold suspension of NaH (60% w/w; 2.85 g, 71.3 mmol) in ether (51 mL). Additional EtOH (8.5 mL) is added. A mixture of **1.1** (5.0 g, 59.4 mmol) and ethyl formate (5.02 mL, 62.4 mmol) is next added dropwise (55 min). Additional ether

5 (10 mL) is added and the mixture is stirred at room temperature overnight. Ether (50 mL) is added and the mixture is filtered. The solid is washed with ether (25 mL) then dried under reduced pressure to give sodium salt **1.2**; ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.56 (quin, $J=7.90$ Hz, 2 H), 1.87 (t, $J=7.72$ Hz, 2 H), 2.24 (td, $J=7.30, 0.95$ Hz, 2 H), 8.50, 8.87 (2s, 1 H).

10 Step 2

A solution of 2-cyanoacetamide (4.58 g, 54.4 mmol) in water (27.5 mL) is added to **1.2** (7.30 g, 54.4 mmol) followed by a solution of piperidin-1-ium acetate (1.38 g, 9.53 mmol) (prepared by adding piperidine (0.81 g; 0.94 mL) to AcOH (0.57 g; 0.54 mL) in water (1.4 mL)) in water (1.4 mL). The mixture is heated at reflux for 2 h and let warm to room temperature (overnight). The

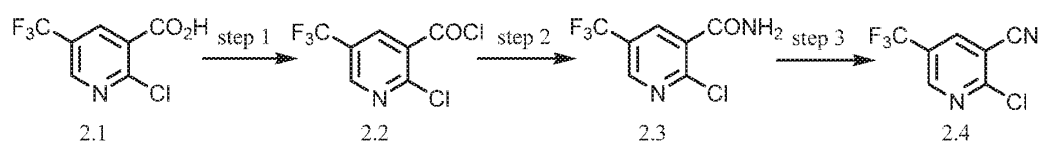
15 pH is adjusted to 5 by addition of AcOH. The resulting suspension is cooled in an ice-bath and is filtered. The solid is washed with water and dried in the air to give pyridone **1.3**; $m/z = 161.1$ (MH^+); ^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.03 (quin, $J=7.57$ Hz, 2 H), 2.64 (t, $J=7.41$ Hz, 2 H), 2.80 (t, $J=7.72$ Hz, 2 H), 8.00 (s, 1 H), 12.62 (br. s., 1 H).

20 Step 3

Pyridone **1.3** (1.0 g, 6.24 mmol) is added to a suspension of PCl_5 (0.390 g, 1.87 mmol) in POCl_3 (1.75 mL, 18.7 mmol) at room temperature. The mixture is heated at reflux for 2.5 h. The cooled mixture is poured into a mixture of ice and water (75 mL). The mixture is basified by addition of solid Na_2CO_3 (pH 7-8). The mixture is extracted with EtOAc (2x). The combined organic layers

25 are washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (10-40% EtOAc:Hex) to afford 2-chloropyridine **1.4**; MS: $m/z = 179.3/181.1$ (MH^+); ^1H NMR (500 MHz, DMSO- d_6) δ ppm 2.11 (quin, $J=7.65$ Hz, 2 H), 2.93 (t, $J=7.57$ Hz, 2 H), 3.00 (t, $J=7.72$ Hz, 2 H), 8.26 (s, 1 H).

30 Example 2: Preparation of intermediate **2.4** (Procedure A2)



Step 1

DMF (10.30 μ l, 0.133 mmol) is added to a suspension of acid 2.1 (0.6 g, 2.66 mmol), (COCl)₂ (0.466 mL, 5.32 mmol) in CH₂Cl₂ (10.6 mL) at room temperature. The mixture is stirred at room temperature for 6 h then is concentrated under reduced pressure to give acyl chloride 2.2.

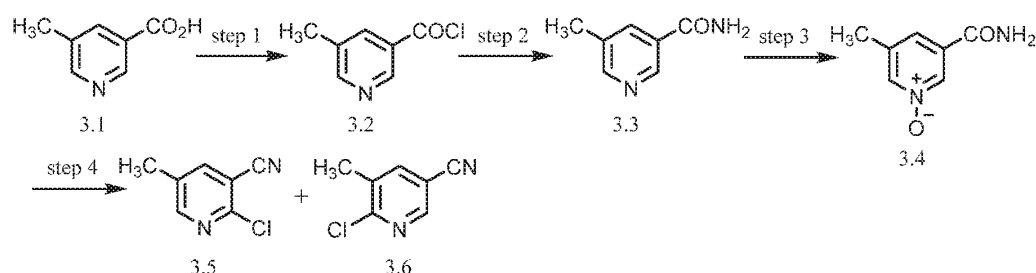
Step 2

A solution of acyl chloride 2.2 (649 mg, 2.66 mmol) in dioxane (1.5 mL) is added to an ice-cold NH₄OH solution (1.60 mL, 23.9 mmol). The mixture is stirred at 0°C for 45 min. The mixture is diluted with water (50 mL) and EtOAc is added (100 mL). The phases are separated. The organic layer is washed with water (2 x), brine (25 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give amide 2.3; MS: m/z = 225.2 (MH⁺); ¹H NMR (500 MHz, DMSO-d₆) δ ppm 7.95 (br. s., 1 H), 8.17 (br. s., 1 H), 8.39 (dd, J=2.52, 0.63 Hz, 1 H), 8.91 (dd, J=2.52, 0.63 Hz, 1 H).

Step 3

(CF₃CO)₂O (0.308 mL, 2.18 mmol) is added quickly to an ice-cold solution/suspension of amide 2.3 (445 mg, 1.98 mmol) in CH₂Cl₂ (14 mL). The mixture is stirred at 0°C for 2 h. Saturated NaHCO₃ solution (15 mL) and CH₂Cl₂ are added and the mixture is stirred at room temperature for 5 min. The phases are separated. The organic layer is washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (10-20% EtOAc:Hex) to yield chloropyridine 2.4; ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.09 (dd, J=2.52, 0.63 Hz, 1 H), 9.16 (dd, J=2.52, 0.63 Hz, 1 H).

Example 3: Preparation of intermediate 3.5 (Procedure A3)



Step 1

(COCl)₂ (1.28 mL, 14.6 mmol) is added to a suspension of acid **3.1** (1.00 g, 7.29 mmol) in CH₂Cl₂ (29 mL) at room temperature. The mixture is stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure to give acyl chloride **3.2**. The compound is used directly in the next reaction.

Step 2

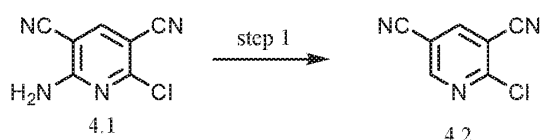
Cold NH₄OH solution (4.86 mL, 72.9 mmol) is added quickly to an ice-cold suspension acyl chloride **3.2** (1.13 g, 7.29 mmol) in a mixture of dioxane (10 mL) and THF (10 mL). The mixture is stirred at 0°C for 45 min. The crude mixture is diluted with water and extracted with EtOAc (3 x). The aqueous layer is saturated with solid NaCl and re-extracted with EtOAc (2 x). The combined organic layers are washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give amide **3.3**; MS: m/z = 137.2 (MH⁺); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.34 (d, *J*=0.63 Hz, 3 H), 7.53 (br. s., 1 H), 7.98 - 8.04 (m, 1 H), 8.08 (br. s., 1 H), 8.54 (dd, *J*=2.21, 0.63 Hz, 1 H), 8.82 (d, *J*=1.58 Hz, 1 H).

Step 3

H₂O₂ (0.90 mL, 7.90 mmol) is added to a cold solution of amide **3.3** (538 mg, 3.95 mmol) in AcOH (4.9 mL). The mixture is stirred at room temperature for 30 min then is heated at 80°C for 4 h. The mixture is cooled in an ice-bath and 20% Na₂SO₃ solution is added until there are no trace of peroxide left as determined with a KI-starch paper. 15 N NH₄OH is next added to basify the mixture. The resulting suspension is warmed to room temperature and is filtered, washing the solid with water. The solid is dried in the air to yield **3.4**; MS: m/z = 153.2 (MH⁺); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.29 (d, *J*=0.63 Hz, 2 H), 7.54 - 7.62 (m, 1 H), 7.72 (br. s., 1 H), 8.15 (br. s., 1 H), 8.24 - 8.29 (m, 1 H), 8.43 (s, 1 H).

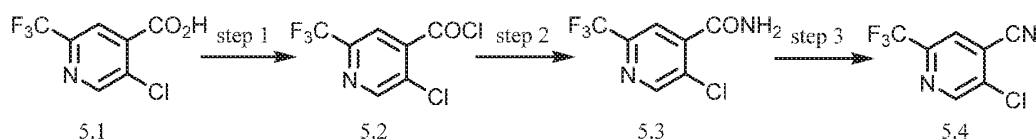
Step 4

Pyridine 1-oxide **3.4** (306 mg, 2.01 mmol) is added to cold (about 5°C) POCl₃ (1.87 mL, 20.11 mmol). The resulting suspension is heated at 60°C for 4 h and at 100°C for 2.5 h. The cooled reaction mixture is poured into a mixture of ice and water (50 mL) and stirred vigorously. Solid Na₂CO₃ is added to obtain a pH of about 7. The mixture is extracted with EtOAc. The organic layer is washed with water and brine, then dried (Na₂SO₄) and concentrated under reduced pressure. The residue is purified by flash chromatography (10-30% EtOAc:Hex) to give first 6-chloro isomer **3.6** and, in second, 2-chloro isomer **3.5**; **3.6**: MS: m/z = 153.1 (MH⁺); ¹H NMR (500 MHz, CDCl₃) δ ppm 2.46 (d, J=0.63 Hz, 3 H), 7.82 (dq, J=2.21, 0.90 Hz, 1 H), 8.54 (dd, J=2.21, 0.63 Hz, 1 H); **3.5**: MS: m/z = 153.3/155.2 (MH⁺); ¹H NMR (500 MHz, CDCl₃) δ ppm 2.40 (t, J=0.60 Hz, 3 H), 7.82 (dq, J=2.20, 0.60 Hz, 1 H), 8.43 (dq, J=2.52, 0.90 Hz, 1 H).

Example 4: Preparation of intermediate **4.2** (Procedure A4)

Step 1

A solution of **4.1** (1.0 g, 5.60 mmol; M. Graffner-Nordberg, J. Med. Chem. 2001, 44, 2391) in DMF (11.2 mL) is added over 10 min to a solution of isoamyl nitrite (1.13 mL, 8.40 mmol) in DMF (4.7 mL) maintained at 70°C. After 1.5 h, the temperature is raised to 85°C and maintained for 18 h. An additional amount of isoamyl nitrite (3.5 mL, 25.99 mmol) is added and the mixture is stirred at 85°C for 4 h. The mixture is cooled to room temperature and is poured into water (200 mL). The mixture is extracted with EtOAc (3x). The combined organic layers are washed with water and brine, then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (0-50% EtOAc:Hex) to give **4.2**; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.28 (d, J=2.21 Hz, 1 H), 8.87 (d, J=2.21 Hz, 1 H).

Example 5: Preparation of intermediate **5.4** (Procedure A5)

Step 1

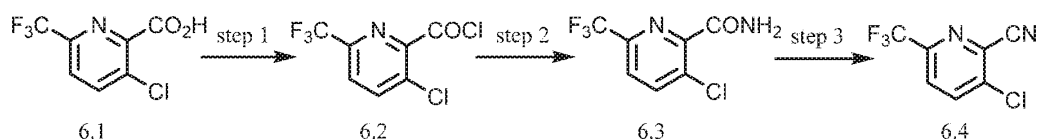
(COCl)₂ (0.49 mL, 5.61 mmol) and DMF (8.7 µl, 0.112 mmol) are added to a suspension of **5.1** (506 mg, 2.24 mmol; Schlosser et al. Tetrahedron 2004, 60, 11869) in CH₂Cl₂ (11.2 mL) at room temperature. The mixture is stirred at room temperature for 3.5 h then is concentrated under reduced pressure to give **5.2**; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.15 (s, 1 H), 8.90 (s, 1 H).

Step 2

A solution of **5.2** (547 mg, 2.24 mmol) in dioxane (1.5 mL) is added dropwise to an ice-cold solution of NH₄OH (15 M) (1.49 mL, 22.43 mmol) in dioxane (1.0 mL). The mixture is stirred at 0°C for 1 h. The reaction mixture is poured into water (125 mL) and the mixture is extracted with EtOAc (2x). The combined organic layers are washed with water and brine, then dried (Na₂SO₄), filtered and concentrated under reduced pressure to give **5.3**; MS: m/z: no molecular peak observed; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.11 (br. s., 1 H), 6.42 (br. s., 1 H), 8.09 (s, 1 H), 8.80 (s, 1 H).

Step 3

(CF₃CO)₂O (0.33 mL, 2.34 mmol) is added dropwise to an ice cold suspension/solution of **5.3** (405 mg, 1.80 mmol) in Et₃N (0.654 mL, 4.69 mmol) and CH₂Cl₂ (12 mL). The reaction mixture is stirred at 0°C for 1.75 h. Saturated NaHCO₃ solution (5 mL) is added and the mixture is stirred vigorously for 5 min. The mixture is diluted with CH₂Cl₂ (60 mL) and saturated NaHCO₃ solution (20 mL). The phases are separated. The organic layer is washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (0-50% EtOAc:Hex) to give **5.4**; MS: m/z = no molecular peak observed; ¹H NMR (500 MHz, CDCl₃) δ ppm 7.94 (s, 1 H), 8.93 (s, 1 H).

Example 6: Preparation of intermediate **6.4** (Procedure A6)

Step 1

(COCl)₂ (1.91 mL, 21.8 mmol) and DMF (0.012 mL, 0.156 mmol) are added to solution of **6.1** (1.35 g, 3.11 mmol; Schlosser et al. Tetrahedron 2004, 60, 11869) in CH₂Cl₂ (18 mL) at room temperature. The mixture is stirred at room temperature for 3 h then is concentrated under reduced pressure. The residue is kept on the high vacuum pump until stable weight to give **6.2**;
5 (500 MHz, CDCl₃) δ ppm 7.85 (d, *J*=8.2 Hz, 1 H), 8.08 (dq, *J*=8.2, 0.06 Hz, 1 H).

Step 2

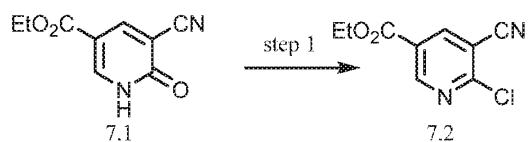
A solution of **6.2** (759 mg, 3.11 mmol) in dioxane (3.1 mL) is added dropwise to an ice-cold solution of NH₄OH (15 M) (2.1 mL, 31.1 mmol). The mixture is stirred at 0°C for 1 h. The mixture
10 is poured into water (125 mL) and extracted with EtOAc (2x). The combined organic layers are washed with water, brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (10-50%EtOAc:Hex) to give **6.3**; MS: *m/z* = 225.1/227.3 (MH⁺); ¹H NMR (500 MHz, CDCl₃) δ ppm 5.68 (br. s., 1 H), 7.55 (br. s., 1 H), 7.77 (d, *J*=8.51 Hz, 1 H), 8.05 (dd, *J*=8.51, 0.63 Hz, 1 H).

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Step 3

(CF₃CO)₂O (0.23 mL, 1.63 mmol) is added dropwise to an ice-cold solution/suspension of **6.3** (281 mg, 1.251 mmol) and Et₃N (0.45 mL, 3.25 mmol) in CH₂Cl₂ (8.3 mL). The mixture is stirred at 0°C for 2 h. Saturated NaHCO₃ solution and CH₂Cl₂ are added and the mixture is stirred at
20 room temperature for 5 min. The phases are separated. The organic layer is washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (10-20%EtOAc:Hex) to give **6.4**; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.87 (d, *J*=8.61 Hz, 1 H), 8.10 (d, *J*=8.61 Hz, 1 H).

25 Example 7: Preparation of intermediate **7.2** (Procedure A7)



Step 1

A mixture of **7.1** (302 mg, 1.57 mmol; V.J. Colandrea, WO2005/058848), SOCl₂ (6.9 mL, 94
30 mmol) and DMF (0.68 mL, 8.79 mmol) is heated at reflux overnight (14 h). The cooled mixture is

concentrated under reduced pressure. The residue is taken in EtOAc (70 mL) and the solution is washed with a 1:1 mixture of saturated NaHCO₃ solution and brine (3x), then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (0-20%EtOAc:Hex) to give **7.2**; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.44 (t, J=7.04 Hz, 3 H), 4.47 (q, J=7.04 Hz, 2 H), 8.58 (d, J=2.35 Hz, 1 H), 9.16 (d, J=2.35 Hz, 1 H).

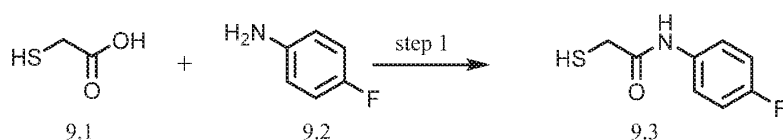
Example 8: Preparation of intermediate **8.2** (Procedure A8)



Step 1

A mixture of **8.1** (1.70 g, 10.51 mmol), Zn(CN)₂ (0.74 g, 6.30 mmol) and Zn (0.031 g, 0.47 mmol) in DMF (10.5 mL) is degassed (B. Van Wageningen, US2003/55085). PdCl₂(dppf)-CH₂Cl₂ adduct (0.189 g, 0.231 mmol) is added and the solution is again degassed then is heated at 125°C for 5 h. The crude mixture is diluted with EtOAc (150 mL) and the mixture is filtered through diatomaceous earth (washing the cake with EtOAc (25 mL)). The filtrate is washed twice with a mixture of water and saturated NaHCO₃ solution (3/1) and with brine, then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (10-100%EtOAc:Hex) to give **8.2**; MS: m/z = 153.1/155.1 (MH⁺); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.60 (s, 3 H), 7.34 (d, J=8.22 Hz, 1 H), 7.73 (d, J=8.61 Hz, 1 H).

Example 9: Preparation of intermediate **9.3** (General procedure B1)

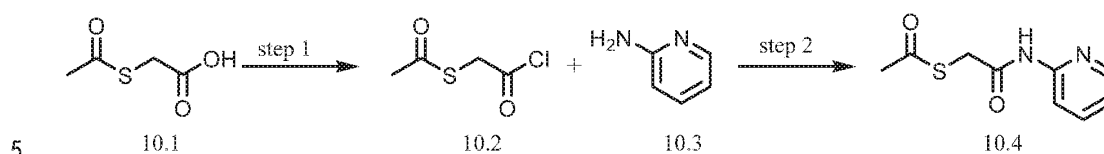


Step 1

A mixture of 2-mercaptoacetic acid **9.1** (0.679 mL, 9.77 mmol) and 4-fluoroaniline **9.2** (0.926 mL, 9.77 mmol) is heated at 130°C for 5 h. The cooled mixture is taken in EtOAc and the solution is washed with 0.5N HCl solution, water and brine, then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (15-40%EtOAc:Hex) to give thiol **9.3**; MS: m/z = 186.1 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm

2.95 (t, $J=5.90$ Hz, 1 H), 3.28 (d, $J=5.87$ Hz, 2 H), 7.15 (t, $J=9.00$ Hz, 2 H), 7.59 (dd, $J=9.39$, 5.48 Hz, 2 H), 10.13 (s, 1 H).

Example 10: Preparation of intermediate **10.4** (General procedure B2)



Step 1

DMF (0.042 mL, 0.54 mmol) is added to an ice-cold solution of acid **10.1** (1.45 g, 10.81 mmol) and (COCl)₂ (1.892 mL, 21.62 mmol) in CH₂Cl₂ (21.6 mL). The mixture is stirred overnight (16 h) at room temperature. The reaction mixture is concentrated under reduced pressure to give intermediate **10.2**; ¹H NMR (500 MHz, CDCl₃) δ ppm 2.44 (s, 3 H), 4.18 (s, 2 H).

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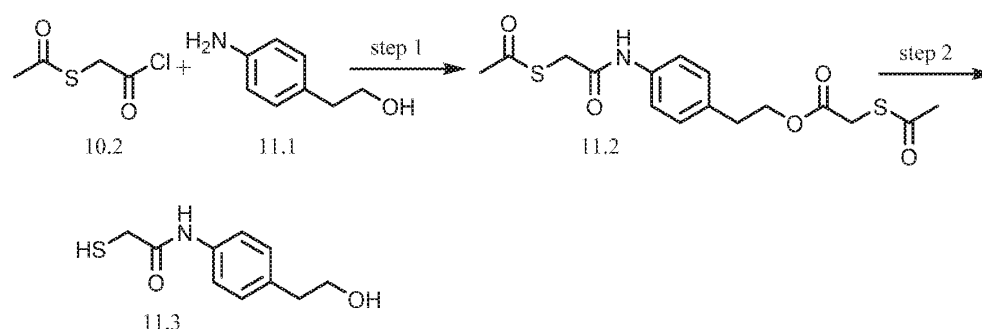
Step 2

DIPEA (0.717 mL, 4.10 mmol) is added dropwise to an ice-cold solution of **10.2** (569 mg, 3.73 mmol) and **10.3** (369 mg, 3.92 mmol) in CH₂Cl₂ (19 mL). The mixture is stirred at 0°C for 1 h and at room temperature for 1 h. The mixture is diluted with CH₂Cl₂ and the solution is washed with water and brine, then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (20-50% EtOAc:Hex) to give intermediate **10.4**; MS: m/z = 211.1 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.37 (s, 3 H), 3.90 (s, 2 H), 7.11 (dd, $J=7.43$, 5.09 Hz, 1 H), 7.78 (ddd, $J=8.20$, 7.40, 1.96 Hz, 1 H), 8.00 (d, $J=8.22$ Hz, 1 H), 8.32 (ddd, $J=4.70$, 2.00, 1.00 Hz, 1 H), 10.71 (s, 1 H).

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Example 11: Preparation of intermediate **11.3** (General procedure B3)

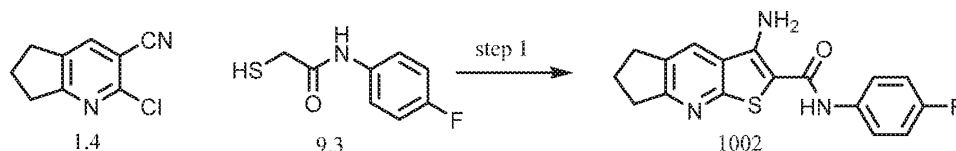


Step 1

A solution of **10.2** (0.848 g, 5.56 mmol) in CH_2Cl_2 (2.8 mL) is added dropwise to an ice-cold suspension of **11.1** (0.381 g, 2.78 mmol) in CH_2Cl_2 (8.4 mL) and pyridine (0.450 mL, 5.56 mmol). The mixture is stirred at 0°C for 1.5 h. Water (5 mL) is added and the mixture is diluted with CH_2Cl_2 . The mixture is washed with 1 N HCl solution, water, saturated NaHCO_3 solution, brine, then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (20-50% EtOAc:Hex) to afford **11.2**; ^1H NMR (500 MHz, CDCl_3) δ ppm 2.39 (s, 3 H), 2.46 (s, 3 H), 2.92 (t, $J=7.09$ Hz, 2 H), 3.66 (s, 2 H), 3.68 (s, 2 H), 4.32 (t, $J=6.94$ Hz, 2 H), 7.18 (d, $J=8.51$ Hz, 2 H), 7.44 (d, $J=8.51$ Hz, 2 H), 8.08 (br. s., 1 H).

Step 2

K_2CO_3 (400 mg, 2.89 mmol) is added to a degassed solution of **11.2** (356 mg, 0.964 mmol) in MeOH (9.6 mL) at room temperature. The mixture is stirred at room temperature overnight (20 h). The mixture is concentrated under reduced pressure. Water (10 mL) is added and the mixture is acidified with 1N HCl solution ($\text{pH} < 2$). The mixture is extracted with EtOAc (2x). The combined organic layers are washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (40-100% EtOAc:Hex) to give **11.3**; MS: m/z 212.1 (MH^+); ^1H NMR (500 MHz, CDCl_3) δ ppm 1.39 (br. s., 1 H), 2.03 (t, $J=9.30$ Hz, 1 H), 2.86 (t, $J=6.46$ Hz, 2 H), 3.41 (d, $J=9.14$ Hz, 2 H), 3.82 - 3.90 (m, 2 H), 7.23 (d, $J=8.20$ Hz, 2 H), 7.50 (d, $J=8.51$ Hz, 2 H), 8.46 (br. s., 1 H).

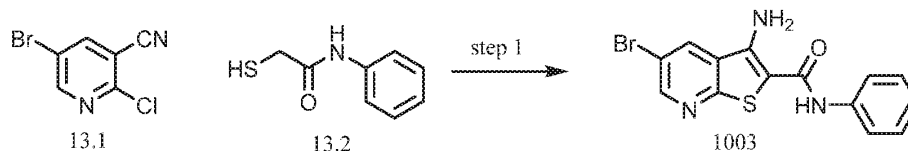
Example 12: Preparation of compound **1002** (General procedure C1)

Step 1

- 25 A mixture of chloropyridine **1.4** (30 mg, 0.168 mmol), thiol **9.3** (34.2 mg, 0.185 mmol) and K_2CO_3 (58.0 mg, 0.420 mmol) in EtOH (1.7 mL) is heated at reflux for 4.5 h. The cooled mixture is diluted with EtOAc and the resulting solution is washed with water and brine, then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is recrystallized in a mixture of MeOH and CHCl_3 to give compound **1002**; MS: m/z = 328.1 (MH^+); ^1H NMR (400

MHz, DMSO- d_6) δ ppm 2.14 (quin, $J=7.53$ Hz, 2 H), 3.00 (t, $J=7.43$ Hz, 2 H), 3.02 (t, $J=7.60$ Hz, 2 H), 7.15 (t, $J=9.00$ Hz, 2 H), 7.29 (br. s, 2 H), 7.69 (dd, $J=9.00, 5.09$ Hz, 2 H), 8.28 (s, 1 H), 9.42 (s, 1 H).

5 Example 13: Preparation of compound **1003** (General procedure C2)

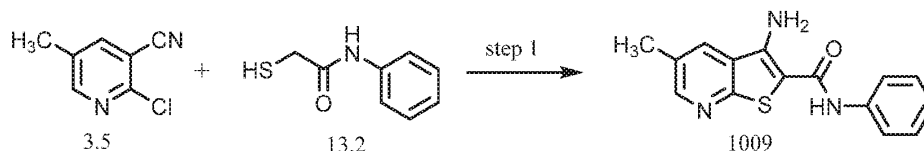


Step 1

A mixture of chloropyridine **13.1** (50 mg, 0.23 mmol), thiol **13.2** (42 mg, 0.25 mmol) and K_2CO_3 (79.5 mg, 0.575 mmol) in EtOH (2.3 mL) is heated at reflux for 5 h. The cooled mixture is diluted with water (15 mL). The resulting suspension is stirred for 15 min then is filtered and the solid is washed with a few drops of MeOH and hexanes to yield compound **1003**; MS: $m/z = 347.9/349.7$ (MH^+); 1H NMR (500 MHz, DMSO- d_6) δ ppm 7.09 (t, $J=7.41$ Hz, 1 H), 7.33 (t, $J=7.88$ Hz, 2 H), 7.37 (s, 1 H), 7.69 (d, $J=7.57$ Hz, 1 H), 8.78 (d, $J=2.21$ Hz, 1 H), 8.84 (d, $J=2.21$ Hz, 1 H), 9.54 (s, 1 H).

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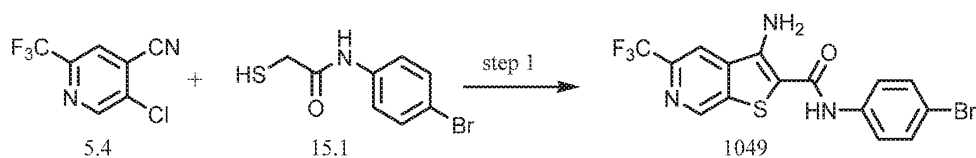
Example 14: Preparation of compound **1009** (General procedure C3)



Step 1

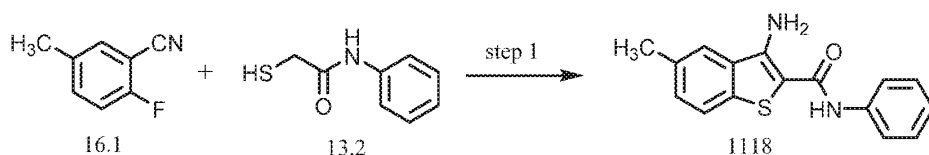
A suspension of **3.5** (40 mg, 0.262 mmol), thiol **13.2** (48.2 mg, 0.288 mmol) and K_2CO_3 (91 mg, 0.655 mmol) in EtOH (2.6 mL) is heated at reflux for 5.5 h. The cooled mixture is diluted with EtOAc and is washed with water and brine (15 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (30-50% EtOAc:Hex) to give compound **1009**; MS: $m/z = 284.3$ (MH^+); 1H NMR (500 MHz, DMSO- d_6) δ ppm 2.43 (s, 3 H), 7.07 (tt, $J=7.37, 1.14$ Hz, 1 H), 7.24 - 7.37 (m, 4 H), 7.69 (dd, $J=8.67, 1.10$ Hz, 2 H), 8.32 (dd, $J=2.05, 0.79$ Hz, 1 H), 8.54 (dd, $J=2.21, 0.63$ Hz, 1 H), 9.40 (s, 1 H).

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Example 15: Preparation of compound **1049** (general procedure C4)

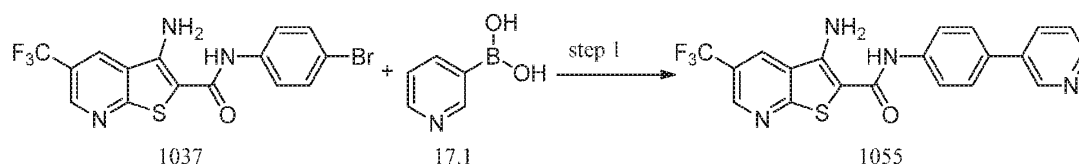
5 Step 1

A mixture of **5.4** (30 mg, 0.145 mmol), thiol **15.1** (41.1 mg, 0.167 mmol) and K_2CO_3 (50.2 mg, 0.363 mmol) in EtOH (1.4 mL) is stirred at room temperature for 10 min then heated at reflux for 3 h. The cooled mixture is diluted with EtOAc (60 mL) and the solution is washed with water and brine, then is dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (10-50%EtOAc:Hex) then further purified by preparative HPLC (method A) to give compound **1049**; MS: $m/z = 415.9/417.9$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.48 (br. s., 2 H), 7.53 (d, $J=8.61$ Hz, 2 H), 7.70 (d, $J=8.61$ Hz, 2 H), 8.73 (s, 1 H), 9.39 (s, 1 H), 9.92 (s, 1 H).

15 Example 16: Preparation of compound **1118** (General procedure C5)

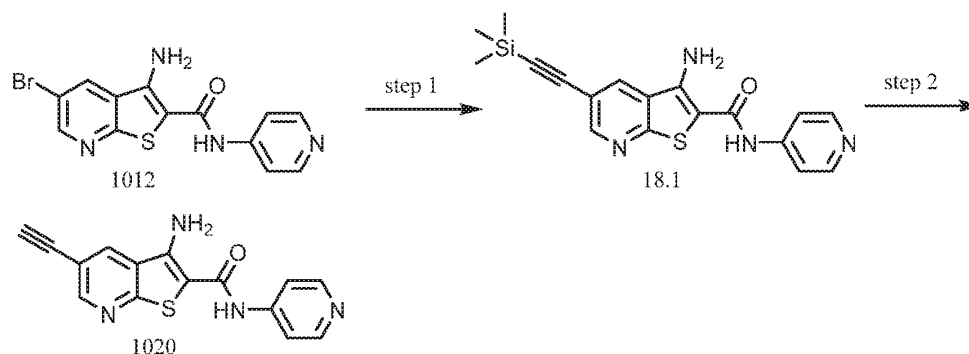
Step 1

A mixture of **16.1** (22 mg, 0.163 mmol), thiol **13.2** (28.6 mg, 0.171 mmol) and K_2CO_3 (56.2 mg, 0.407 mmol) in DMF (0.65 mL) is stirred at room temperature for 7 h. The mixture is diluted with EtOAc (50 mL) and the solution is washed with water and brine, then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (10-20%EtOAc:Hex) to give compound **1118**; MS: $m/z = 283.1$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.44 (s, 3 H), 7.06 (tt, $J=7.40, 1.17$ Hz, 1 H), 7.19 (s, 2 H), 7.31 (dd, $J=8.61, 7.43$ Hz, 1 H), 7.35 (dd, $J=8.22, 1.17$ Hz, 1 H), 7.69 (dd, $J=8.80, 0.98$ Hz, 2 H), 7.76 (d, $J=8.22$ Hz, 1 H), 7.91 (s, 1 H), 9.29 (s, 1 H).

Example 17: Preparation of compound **1055** (General procedure D)

5 Step 1

PdCl₂(dppf)-CH₂Cl₂ adduct (4.91 mg, 6.01 μmol) is added to a degassed (vacuum to argon 3x) partial solution of compound **1037** (50 mg, 0.120 mmol), boronic acid **17.1** (44.3 mg, 0.360 mmol) and K₂CO₃ (49.8 mg, 0.360 mmol) in dioxane (1.15 mL) and water (0.287 mL) at room temperature. The mixture is degassed again and heated at 85°C for 21 h. The cooled mixture is taken in EtOAc (150 mL) and water (30 mL) is added. The separated aqueous layer is extracted with CH₂Cl₂ (3 x). The combined organic layers are washed with brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The solid is recrystallized in a 1:1 mixture of CHCl₃ and MeOH to give compound **1055**; MS: m/z = 415.0 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.39 - 7.47 (m, 2 H), 7.50 (dd, *J*=8.02, 5.28 Hz, 1 H), 7.57 (s, 2 H), 7.78 (dt, *J*=7.04, 2.15 Hz, 1 H), 7.99 - 8.12 (m, 2 H), 8.58 (dd, *J*=4.70, 1.57 Hz, 1 H), 8.87 (d, *J*=1.96 Hz, 1 H), 9.04 (d, *J*=5.87 Hz, 1 H), 9.72 (s, 1 H).

Example 18: Preparation of compound **1020**

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Step 1

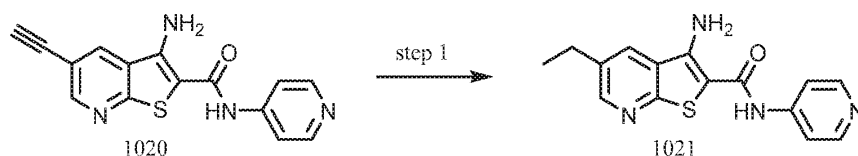
To a mixture of compound **1012** (50 mg, 0.143 mmol), Pd(Ph₃P)₄ (16.5 mg, 0.014 mmol) and CuI (2.73 mg, 0.014 mmol) in THF (0.72 mL) and DMF (0.72 mL) are added sequentially DIPEA

(0.41 mL, 2.86 mmol) and ethynyltrimethylsilane (101 μ L, 0.716 mmol). The mixture is flushed with N_2 and heated at 110 $^{\circ}$ C for 2.5 h. The cooled mixture is diluted with water (15 mL) and extracted with EtOAc (3 x). The aqueous layer is filtered and extracted with EtOAc. The combined organic layers are dried (Na_2SO_4), filtered and concentrated. The residue is purified by flash chromatography (0-100%EtOAc:Hex) to give **18.1**; MS: m/z = 367.2 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 0.22 - 0.32 (m, 9 H), 7.55 (s, 2 H), 7.77 (br. s., 2 H), 8.71 - 8.77 (m, 2 H), 9.84 (s, 1 H).

Step 2

To a solution of **18.1** (50 mg, 0.136 mmol) in MeOH (2 mL) is added K_2CO_3 (37.7 mg, 0.273 mmol). The mixture is stirred at room temperature for 1 h then is concentrated under reduced pressure. The residue dissolved in 10% MeOH in CH_2Cl_2 (50 mL) is diluted with water. The resulting suspension is filtered and the solid dried in the air to give compound **1020**; MS: m/z = 295.2 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 4.50 (s, 1 H), 7.57 (s, 2 H), 7.76 (br. s., 1 H), 8.44 (br. s., 1 H), 8.69 - 8.80 (m, 1 H), 9.84 (br. s., 1 H).

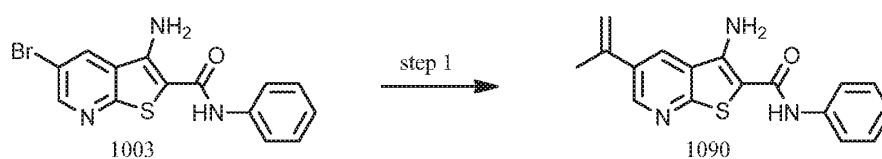
Example 19: Preparation of compound **1021**



Step 1

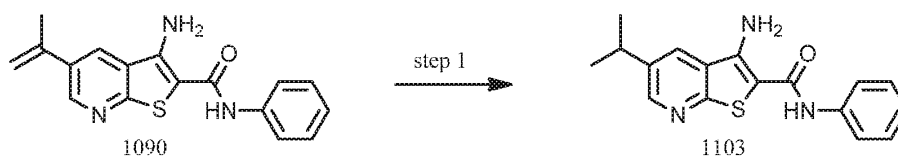
A suspension of **1020** (20 mg, 0.068 mmol) and Pd-C 10% Degussa Type, 50% wet (7.2 mg) in MeOH (5 mL) is stirred under a hydrogen atmosphere for 45 min. The mixture is filtered through a 0.45 μ m filter unit, washed with MeOH (1 mL) and concentrated to afford compound **1021**; MS: m/z = 299.2 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 1.28 (t, $J=7.57$ Hz, 3 H), 2.76 (q, $J=7.57$ Hz, 2 H), 7.52 (s, 2 H), 7.75 - 7.77 (m, 2 H), 8.41 - 8.44 (m, 3 H), 8.59 (d, $J=1.89$ Hz, 1 H), 9.74 (s, 1 H).

Example 20: Preparation of compound **1090**



Step 1

A mixture of **1003** (25.7 mg, 0.074 mmol), prop-1-en-2-ylboronic acid (7.8 μ L, 0.081 mmol) and K_3PO_4 (47.0 mg, 0.221 mmol) in DME-Water (2:1, 3 mL) is purged with a stream of N_2 for 5 min in a sealable vial. To this mixture is added $\text{Pd}(\text{Ph}_3\text{P})_4$ (8.53 mg, 7.38 μ mol), the vial is sealed and the mixture is heated at 90°C under microwave radiations for 4 h. The cooled mixture is diluted with EtOAc and water. The aqueous phase is extracted with EtOAc (3x) and the combined organic layers are washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by preparative HPLC (method B) to afford **1090**; MS: $m/z = 310.0$ (MH^+); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.22 (s, 3 H), 5.27 (s, 1 H), 5.65 (s, 1 H), 7.03 - 7.12 (m, 1 H), 7.33 (t, $J=7.83$ Hz, 2 H), 7.42 (s, 1 H), 7.70 (d, $J=7.43$ Hz, 2 H), 8.66 (d, $J=2.35$ Hz, 1 H), 8.87 (d, $J=2.35$ Hz, 1 H), 9.44 (s, 1 H).

Example 21: Preparation of compound **1103**

Step 1

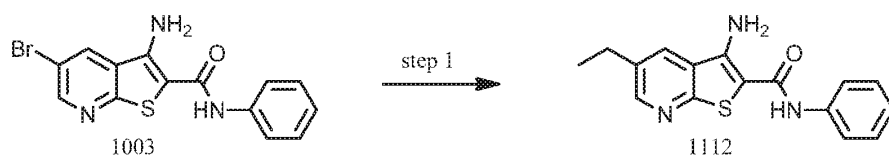
A suspension of compound **1090** (57.3 mg, 0.185 mmol) and Pd-C 10% Degussa Type, 50% wet (20 mg) in MeOH (25 mL) is stirred under a hydrogen atmosphere for 18 h. The mixture is filtered on a pad of diatomaceous earth, washed with MeOH and concentrated under reduced pressure. The residue is purified by preparative HPLC (method B) to afford compound **1103**; MS: $m/z = 312.1$ (MH^+); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.31 (d, $J=6.65$ Hz, 6 H), 3.09 (dt, $J=13.89, 6.75$ Hz, 1 H), 7.03 - 7.11 (m, 1 H), 7.28 - 7.40 (m, 4 H), 7.70 (d, $J=7.83$ Hz, 2 H), 8.44 (d, $J=1.96$ Hz, 1 H), 8.60 (d, $J=1.96$ Hz, 1 H), 9.40 (s, 1 H).

Example 22: Preparation of compound **1111**



Step 1

A suspension of compound **1003** (56.9 mg, 0.163 mmol), allyltributylstannane (60.2 μ L, 0.196 mmol) and K_2CO_3 (45.2 mg, 0.327 mmol) in toluene/water (5/1) (3.3 mL) is purged with a stream of N_2 for 10 min in a sealable vial. To this mixture is added $Pd(Ph_3)_4$ (4.72 mg, 4.09 μ mol) and the vial is sealed and the mixture is heated at $105^\circ C$ for 23 h. The mixture is diluted with EtOAc and water, extracted twice with EtOAc. The combined organic layers are washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Since the reaction is not complete, the residue is resubmitted to the same reaction conditions (15 h heating). The crude material is purified by preparative HPLC (method B) then is filtered through a pad of silica gel (Hex/EtOAc (50/50) with 3% Et_3N). The filtrate is concentrated under reduced pressure to give compound **1111**; MS: $m/z = 310.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 3.53 (d, $J=6.65$ Hz, 2 H), 5.10 - 5.19 (m, 2 H), 5.97 - 6.11 (m, 1 H), 7.04 - 7.11 (m, 1 H), 7.35 (d, $J=6.65$ Hz, 2 H), 7.31 (d, $J=8.22$ Hz, 2 H), 7.65 - 7.73 (m, 2 H), 8.34 (d, $J=1.96$ Hz, 1 H), 8.54 (d, $J=1.96$ Hz, 1 H), 9.42 (s, 1 H).

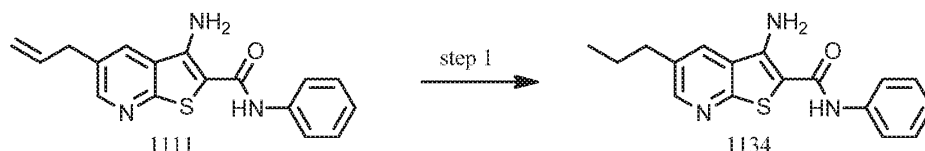
Example 23: Preparation of compound **1112**

Step 1

A suspension of compound **1003** (29.8 mg, 0.086 mmol), triethylborane (34.2 μ L, 0.034 mmol), K_3PO_4 (36.3 mg, 0.171 mmol) and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphine (1.53 mg, 4.28 μ mol) in toluene/water (10/1) (1.57 mL) is purged with a stream of N_2 for 5 min in a sealable vial. To this mixture is added $Pd_2(dba)_3$ (0.980 mg, 1.070 μ mol) and the vial is sealed and the mixture is heated at $105^\circ C$ for 17 h. The cooled mixture is diluted with EtOAc and water and extracted twice with EtOAc. The combined organic layers are washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by

preparative HPLC (method B) to get compound **1112**; MS: $m/z = 298.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.28 (t, $J=7.43$ Hz, 3 H), 2.76 (q, $J=7.70$ Hz, 2 H), 7.07 (t, $J=7.24$ Hz, 1 H), 7.29 - 7.36 (m, 4 H), 7.69 (d, $J=8.22$ Hz, 2 H), 8.38 (s, 1 H), 8.57 (s, 1 H), 9.40 (s, 1 H).

5 Example 24: Preparation of compound **1134**

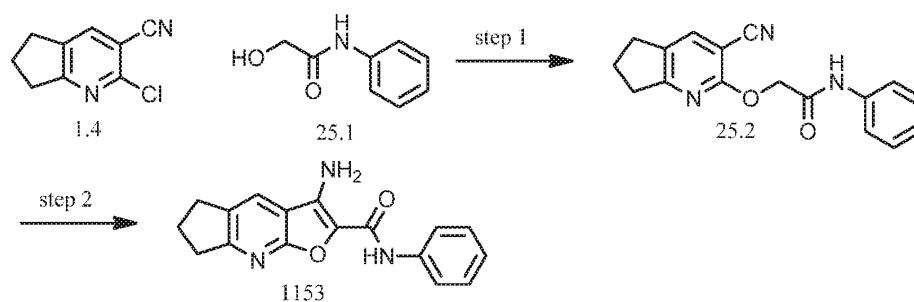


Step 1

A suspension of compound **1111** (30 mg, 0.097 mmol) and Pd-C 10% Degussa Type, 50% wet (10.3 mg) in MeOH (6 mL) is stirred under a hydrogen atmosphere for 18 h. The mixture is filtered (0.45 μm filter unit) and concentrated under reduced pressure. The residue is purified by preparative HPLC (method B) to give compound **1134**; MS: $m/z = 312.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 0.94 (t, $J=7.43$ Hz, 3 H), 1.69 (dq, $J=15.06, 7.24$ Hz, 2 H), 2.67 - 2.74 (m, 2 H), 7.05 - 7.10 (m, 1 H), 7.28 - 7.37 (m, 4 H), 7.67 - 7.73 (m, 2 H), 8.36 (d, $J=1.96$ Hz, 1 H), 8.54 (d, $J=1.96$ Hz, 1 H), 9.40 (s, 1 H).

15

Example 25: Preparation of compound **1153** (General procedure E)



Step 1

A mixture of **1.4** (75 mg, 0.420 mmol), **25.1** (66.6 mg, 0.441 mmol; J.M. Hung et al., Eur. J. Med. Chem. 2014, 86, 420) and Na_2CO_3 (46.7 mg, 0.441 mmol) in EtOH (1.7 mL) is heated at reflux for 18 h. The cooled mixture is partitioned between EtOAc and water. The organic layer is washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (10-30% EtOAc:Hex) to give **25.2**; MS: $m/z = 294.2$

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(MH⁺); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.06 (quin, *J*=7.65 Hz, 2 H), 2.85 (td, *J*=7.49, 3.63 Hz, 4 H), 5.06 (s, 2 H), 7.06 (t, *J*=7.41 Hz, 1 H), 7.31 (t, *J*=8.20 Hz, 2 H), 7.56 (dd, *J*=8.67, 1.10 Hz, 2 H), 8.09 (s, 1 H), 10.16 (s, 1 H).

5 Step 2

t-BuOK (45.4 mg, 0.405 mmol) is added to a solution of **25.2** (95 mg, 0.324 mmol) in THF (3.2 mL) at room temperature. The mixture is heated at reflux for 2 h. The mixture is taken in CH₂Cl₂ and the solution is washed with water and brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (2-15% EtOAc:CH₂Cl₂) to yield compound **1153**; MS: *m/z* = 294.2 (MH⁺); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.14 (quin, *J*=7.57 Hz, 2 H), 2.98 (t, *J*=7.25 Hz, 2 H), 2.99 (t, *J*=7.57 Hz, 2 H), 6.33 (s, 2 H), 7.04 (tt, *J*=7.57, 0.95 Hz, 1 H), 7.30 (dd, *J*=8.51, 7.57 Hz, 2 H), 7.82 (dd, *J*=7.57, 1.26 Hz, 2 H), 8.12 (s, 1 H), 9.84 (s, 1 H).

15 List of MS and NMR Data

Compound **1001**; MS: *m/z* = 310.3; ¹H NMR (500 MHz, DMSO-*d*₆) □ ppm 2.14 (quin, *J*=7.49 Hz, 2 H), 2.90 - 3.06 (m, 4 H), 7.06 (tt, *J*=7.57, 0.95 Hz, 1 H), 7.29 (s, 1 H), 7.31 (dd, *J*=8.51, 7.57 Hz, 2 H), 7.69 (dd, *J*=8.51, 1.30 Hz, 2 H), 8.28 (s, 1 H), 9.35 (s, 1 H).

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Compound **1002**; Described in example 12

Compound **1003**; MS: Described in example 13

25 Compound **1004**; MS: *m/z* = 304.1/306.1 (MH⁺); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.09 (tt, *J*=7.25, 1.26 Hz, 1 H), 7.33 (dd, *J*=8.51, 7.57 Hz, 1 H), 7.37 (s, 2 H), 7.69 (dd, *J*=8.83, 1.26 Hz, 1 H), 8.65 - 8.76 (m, 1 H), 9.54 (s, 1 H).

30 Compound **1005**; MS: *m/z* = 298.2 (MH⁺); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.36 (s, 3 H) 2.55 (s, 3 H) 7.06 (tt, *J*=7.33, 1.18 Hz, 1 H) 7.27 (s, 2 H) 7.31 (dd, *J*=8.51, 7.57 Hz, 2 H) 7.68 (dd, *J*=8.83, 1.26 Hz, 2 H) 8.22 (s, 1 H) 9.34 (s, 1 H)

Compound **1006**; MS: $m/z = 311.3$ (MH^+); 1H NMR (500 MHz, DMSO- d_6) δ ppm 2.14 (quin, $J=7.49$ Hz, 2 H), 3.00 (t, $J=7.25$ Hz, 2 H), 3.02 (t, $J=7.25$ Hz, 2 H), 7.35 (dd, $J=8.51$, 4.73 Hz, 1 H), 7.37 (s, 2 H), 8.09 (ddd, $J=8.35$, 2.52, 1.42 Hz, 1 H), 8.27 (dd, $J=4.73$, 1.58 Hz, 1 H), 8.30 (s, 1 H), 8.87 (d, $J=2.52$ Hz, 1 H), 9.57 (s, 1 H).

5

Compound **1007**; MS: $m/z = 311.1$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.14 (quin, $J=7.53$ Hz, 2 H), 3.00 (t, $J=7.00$ Hz, 2 H), 3.01 (t, $J=6.90$ Hz, 2 H), 7.12 (dd, $J=7.04$, 5.09 Hz, 1 H), 7.36 (s, 2 H), 7.80 (ddd, $J=8.00$, 6.70, 1.56 Hz, 1 H), 8.05 (d, $J=8.61$ Hz, 1 H), 8.31 (s, 1 H), 8.35 (d, $J=3.91$ Hz, 1 H), 9.49 (s, 1 H).

10

Compound **1008**; MS: $m/z = 338.2$ (MH^+); 1H NMR (500 MHz, DMSO- d_6) δ ppm 7.10 (tt, $J=7.41$, 1.26 Hz, 1 H), 7.34 (dd, $J=8.51$, 7.25 Hz, 2 H), 7.52 (s, 2 H), 7.70 (dd, $J=8.67$, 1.10 Hz, 2 H), 8.97 - 9.10 (m, 2 H), 9.61 (s, 1 H).

15 Compound **1009**; Described in example 14

Compound **1010**; MS: $m/z = 288.3$ (MH^+); 1H NMR (500 MHz, DMSO- d_6) δ ppm 7.09 (tt, $J=7.41$, 0.90 Hz, 1 H), 7.33 (s, 2 H), 7.33 (t, $J=7.88$ Hz, 2 H), 7.69 (dd, $J=8.67$, 1.10 Hz, 2 H), 8.46 (dd, $J=9.62$, 2.68 Hz, 1 H), 8.74 (dd, $J=2.84$, 0.95 Hz, 1 H), 9.51 (s, 1 H).

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Compound **1011**; MS: $m/z = 305.2/307.1$ (MH^+); 1H NMR (500 MHz, DMSO- d_6) δ ppm 7.54 (s, 2 H), 7.75 (d, $J=6.31$ Hz, 1 H), 8.44 (d, $J=6.31$ Hz, 1 H), 8.74 (d, $J=2.21$ Hz, 1 H), 8.75 (d, $J=2.52$ Hz, 1 H) 9.86 (s, 1 H).

25 Compound **1012**; MS: $m/z = 349.1/351.1$ (MH^+); 1H NMR (500 MHz, DMSO- d_6) δ ppm 7.54 (s, 2 H), 7.75 (d, $J=6.31$ Hz, 2 H), 8.43 (d, $J=6.31$ Hz, 2 H), 8.80 (d, $J=2.21$ Hz, 1 H), 8.88 (d, $J=2.21$ Hz, 1 H), 9.86 (s, 1 H).30 Compound **1013**; MS: $m/z = 339.2$ (MH^+); 1H NMR (500 MHz, DMSO- d_6) δ ppm 7.69 (s, 2 H), 7.76 (d, $J=6.31$ Hz, 2 H), 8.45 (d, $J=6.31$ Hz, 2 H), 9.06 (dd, $J=2.21$, 0.63 Hz, 1 H), 9.09 (dd, $J=2.21$, 0.63 Hz, 1 H), 9.93 (s, 1 H).

Compound **1014**; MS: m/z = 311.3 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 2.14 (quin, $J=7.57$ Hz, 2 H), 3.00 (t, $J=6.90$ Hz, 2 H), 3.02 (t, $J=7.60$ Hz, 2 H), 7.47 (s, 2 H), 7.75 (d, $J=6.31$ Hz, 2 H), 8.32 (s, 1 H), 8.41 (d, $J=6.31$ Hz, 2 H), 9.69 (s, 1 H).

- 5 Compound **1015**; MS: m/z = 339.2 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.38 (dd, $J=8.04, 4.89$ Hz, 1 H), 7.60 (br. s., 2 H), 8.09 (d, $J=8.20$ Hz, 1 H), 8.30 (d, $J=4.10$ Hz, 1 H), 8.89 (br. s., 1 H), 9.05 (s, 1 H), 9.07 (s, 1 H), 9.82 (s, 1 H).

- 10 Compound **1016**; MS: m/z = 295.3 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.10 (tt, $J=7.60, 0.90$ Hz, 1 H), 7.34 (dd, $J=8.51, 7.25$ Hz, 2 H), 7.47 (s, 2 H), 7.69 (dd, $J=8.51, 1.26$ Hz, 2 H), 8.99 - 9.08 (m, 2 H), 9.63 (s, 1 H).

- 15 Compound **1017**; MS: m/z = 382.1 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 2.70 (t, $J=7.09$ Hz, 2 H), 3.59 (td, $J=7.17, 5.20$ Hz, 2 H), 4.62 (t, $J=5.20$ Hz, 1 H), 7.17 (d, $J=8.51$ Hz, 2 H), 7.50 (s, 2 H), 7.58 (d, $J=8.51$ Hz, 2 H), 9.04 (d, $J=0.95$ Hz, 2 H), 9.55 (s, 1 H).

- Compound **1018**; MS: m/z = 382.2 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 3.28 (s, 3 H), 4.37 (s, 2 H), 7.28 (d, $J=8.83$ Hz, 2 H), 7.53 (s, 2 H), 7.68 (d, $J=8.51$ Hz, 2 H), 8.94 - 9.08 (m, 2 H), 9.63 (s, 1 H).

- 20 Compound **1019**; MS: m/z = 368.2 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 4.47 (d, $J=5.67$ Hz, 2 H), 5.11 (t, $J=5.83$ Hz, 1 H), 7.28 (d, $J=8.51$ Hz, 2 H), 7.51 (s, 2 H), 7.64 (d, $J=8.51$ Hz, 2 H), 8.97 - 9.08 (m, 2 H), 9.58 (s, 1 H).

- 25 Compound **1020** ; Described in example 18

Compound **1021**; Described in example 19

- 30 Compound **1022** MS: m/z = 339.2 (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.15 (td, $J=5.99, 0.95$ Hz, 1 H) 7.59 (s, 2 H) 7.78 - 7.87 (m, 1 H) 8.06 (d, $J=8.20$ Hz, 1 H) 8.38 (dd, $J=4.89, 1.10$ Hz, 1 H) 9.00 - 9.10 (m, 2 H) 9.97 (s, 1 H).

Compound **1023** MS: $m/z = 359.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.25 (d, $J=1.17$ Hz, 3 H) 6.87 (s, 1 H) 7.21 (br. s., 2 H) 8.72 (s, 1 H) 8.83 (d, $J=1.57$ Hz, 1 H).

5 Compound **1024** MS: $m/z = 366.3$ (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 1.19 (t, $J=7.57$ Hz, 3 H) 2.59 (q, $J=7.57$ Hz, 2 H) 7.18 (m, $J=8.83$ Hz, 2 H) 7.50 (s, 2 H) 7.56 - 7.63 (m, 2 H) 9.04 (s, 2 H) 9.55 (s, 1 H).

10 Compound **1025**; MS: $m/z = 338.2$ (MH^+); 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 7.11 (tt, $J=7.30$, 1.30 Hz, 1 H), 7.35 (dd, $J=8.51$, 7.25 Hz, 2 H), 7.43 (s, 2 H), 7.69 (dd, $J=8.67$, 1.10 Hz, 2 H), 8.72 (br. d, $J=0.60$ Hz, 1 H), 9.39 (s, 1 H), 9.80 (s, 1 H).

15 Compound **1026**; MS: $m/z = 339.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.60 (s, 2 H), 7.76 (d, $J=6.26$ Hz, 2 H), 8.46 (d, $J=6.26$ Hz, 2 H), 8.76 (s, 1 H), 9.41 (s, 1 H), 10.13 (br. s., 1 H).

Compound **1027**; MS: $m/z = 338$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 6.97 (s, 2 H), 7.11 (tt, $J=7.40$, 1.20 Hz, 1 H), 7.35 (dd, $J=8.22$, 7.43 Hz, 2 H), 7.70 (dd, $J=8.41$, 0.98 Hz, 2 H), 8.01 (d, $J=8.61$ Hz, 1 H), 8.78 (d, $J=8.61$ Hz, 1 H), 9.73 (s, 1 H).

20 Compound **1028**; MS: $m/z = 339.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.14 (s, 2 H), 7.77 (d, $J=6.26$ Hz, 1 H), 8.03 (d, $J=8.22$ Hz, 1 H), 8.46 (d, $J=6.26$ Hz, 1 H), 8.80 (d, $J=8.22$ Hz, 1 H), 10.07 (br. s., 1 H).

25 Compound **1029**; MS: 394.9 $m/z = (MH^+)$; 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.59 (s, 2 H) 7.80 (dd, $J=8.80$, 2.15 Hz, 1 H) 8.05 (d, $J=8.61$ Hz, 1 H) 8.56 (d, $J=1.96$ Hz, 1 H) 9.06 (d, $J=3.13$ Hz, 2 H) 9.30 (s, 1 H) 9.89 (s, 1 H).

30 Compound **1030**; MS: 414.0 $m/z = (MH^+)$; 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.28 - 7.36 (m, 1 H) 7.39 - 7.48 (m, 2 H) 7.55 (br. s., 2 H) 7.61 - 7.70 (m, 4 H) 7.77 - 7.85 (m, 2 H) 8.99 - 9.09 (m, 2 H) 9.70 (s, 1 H).

Compound **1031**; MS: 444.0 m/z = (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.10 (s, 2 H) 6.75 (dt, *J*=8.22, 1.17 Hz, 1 H) 7.19 - 7.28 (m, 1 H) 7.29 - 7.37 (m, 2 H) 7.37 - 7.44 (m, 2 H) 7.44 - 7.51 (m, 3 H) 7.54 (s, 2 H) 9.05 (d, *J*=3.52 Hz, 2 H) 9.58 (s, 1 H).

- 5 Compound **1032**; MS: 424.0 m/z = (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.19 (t, *J*=7.04 Hz, 2 H) 3.63 (s, 2 H) 4.08 (q, *J*=7.04 Hz, 2 H) 7.22 (m, *J*=8.61 Hz, 2 H) 7.52 (s, 2 H) 7.60 - 7.68 (m, 2 H) 9.04 (s, 2 H) 9.61 (s, 1 H).

- 10 Compound **1033**; MS: 444.0 m/z = (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.76 (s, 3 H) 7.10 (d, *J*=8.61 Hz, 1 H) 7.31 - 7.36 (m, 1 H) 7.40 - 7.45 (m, 2 H) 7.50 (dd, *J*=8.41, 1.37 Hz, 4 H) 7.64 - 7.70 (m, 2 H) 9.03 (s, 2 H) 9.57 (s, 1 H).

- 15 Compound **1034**; MS: m/z = 337.0 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.08 (tt, *J*=7.40, 1.20 Hz, 1 H), 7.33 (t, *J*=7.83 Hz, 2 H), 7.42 (s, 2 H), 7.69 (dd, *J*=8.61, 1.17 Hz, 2 H), 7.79 (dd, *J*=8.61, 1.57 Hz, 1 H), 8.15 (d, *J*=8.61 Hz, 1 H), 8.62 (s, 1 H), 9.52 (s, 1 H).

- 20 Compound **1035**; MS: m/z = 338.0 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.61 (s, 2 H), 7.78 (d, *J*=6.65 Hz, 2 H), 7.82 (dd, *J*=8.61, 1.57 Hz, 1 H), 8.17 (d, *J*=8.61 Hz, 1 H), 8.45 (d, *J*=5.09 Hz, 2 H), 8.67 (s, 1 H), 9.91 (br. s., 1 H).

- Compound **1036**; MS: m/z = 415.9/417.9 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.26 - 7.34 (m, 2 H) 7.60 (s, 2 H) 7.70 (dt, *J*=7.43, 1.96 Hz, 1 H) 8.06 (t, *J*=1.76 Hz, 1 H) 9.02 - 9.09 (m, 2 H) 9.75 (s, 1 H).

- 25 Compound **1037**; MS: m/z = 415.9/417.9 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.50 (d, *J*=8.61 Hz, 2 H) 7.55 (br. s., 2 H) 7.63 - 7.75 (m, 2 H) 9.03 (d, *J*=4.70 Hz, 2 H) 9.71 (s, 1 H).

- 30 Compound **1038**; MS: m/z = 377.0 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.98 (s, 2 H) 7.30 (d, *J*=8.61 Hz, 2 H) 7.53 (s, 2 H) 7.67 - 7.74 (m, 2 H) 8.98 - 9.06 (m, 2 H) 9.67 (s, 1 H).

Compound **1039**; MS: m/z = 391.0 (MH⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.51 (s, 2 H) 7.67 - 7.80 (m, 2 H) 7.82 (d, *J*=6.65 Hz, 1 H) 8.07 (d, *J*=8.22 Hz, 1 H) 8.53 (d, *J*=5.87 Hz, 1 H) 9.04 - 9.10 (m, 2 H) 9.36 (d, *J*=0.78 Hz, 1 H) 10.00 (s, 1 H).

Compound **1040**; MS: m/z = 389.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.48 (s, 2 H)
7.55 (dd, $J=8.41, 4.11$ Hz, 1 H) 7.62 (dd, $J=7.43, 1.17$ Hz, 1 H) 7.78 (dd, $J=8.22, 7.43$ Hz, 1 H)
7.95 (d, $J=8.61$ Hz, 1 H) 8.24 - 8.35 (m, 1 H) 8.92 (dd, $J=4.11, 1.76$ Hz, 1 H) 9.05 (s, 2 H) 10.00
5 (s, 1 H).

Compound **1041**; MS: m/z = 389.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.49 (dd,
 $J=8.22, 4.30$ Hz, 1 H) 7.62 (s, 2 H) 7.97 (d, $J=9.00$ Hz, 1 H) 8.04 (dd, $J=9.00, 2.35$ Hz, 1 H) 8.24
- 8.32 (m, 1 H) 8.40 (d, $J=2.35$ Hz, 1 H) 8.79 (dd, $J=4.11, 1.76$ Hz, 1 H) 9.01 - 9.11 (m, 2 H) 9.94
10 (s, 1 H).

Compound **1042**; MS: m/z = 389.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.58 (td,
 $J=7.53, 1.37$ Hz, 1 H) 7.66 (td, $J=7.53, 1.37$ Hz, 3 H) 7.89 - 8.01 (m, 2 H) 8.70 (d, $J=2.35$ Hz, 1
H) 9.01 - 9.11 (m, 2 H) 9.14 (d, $J=2.74$ Hz, 1 H) 10.07 (s, 1 H).
15

Compound **1043**; MS: m/z = 389.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.40 - 7.69 (m,
3 H) 7.72 - 7.88 (m, 2 H) 7.98 (br. s., 1 H) 8.13 (s, 1 H) 8.82 (br. s., 1 H) 9.04 (br. s., 2 H) 10.14
(br. s., 1 H).

Compound **1044**; MS: m/z = 342.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.39 (t, $J=7.04$
Hz, 3 H), 4.41 (q, $J=7.04$ Hz, 2 H), 7.09 (tt, $J=7.40, 1.20$ Hz, 1 H), 7.33 (dd, $J=8.61, 7.43$ Hz, 2
H), 7.59 (s, 2 H), 7.69 (dd, $J=8.80, 0.98$ Hz, 2 H), 9.14 (d, $J=1.96$ Hz, 1 H), 9.16 (d, $J=1.96$ Hz, 1
H), 9.56 (s, 1 H).
20

Compound **1045**; MS: m/z = 372.0/374.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.39 (d,
 $J=9.00$ Hz, 2 H), 7.56 (s, 1 H), 7.75 (d, $J=9.00$ Hz, 2 H), 9.00 - 9.08 (m, 2 H), 9.74 (s, 1 H).
25

Compound **1046**; MS: m/z = 396.1 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.78 (t, $J=6.85$
Hz, 2 H), 3.25 (s, 3 H), 3.53 (t, $J=6.85$ Hz, 2 H), 7.19 (d, $J=8.22$ Hz, 2 H), 7.50 (s, 2 H), 7.59 (d,
 $J=8.22$ Hz, 2 H), 9.04 (s, 2 H), 9.56 (s, 1 H).
30

Compound **1047**; MS: m/z = 352.1 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.28 (s, 3 H),
7.14 (d, $J=8.61$ Hz, 2 H), 7.50 (s, 2 H), 7.57 (d, $J=8.22$ Hz, 2 H), 9.03 (s, 2 H), 9.54 (s, 1 H).

Compound **1048**; MS: $m/z = 368.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 3.75 (s, 3 H), 6.91 (d, $J=9.00$ Hz, 2 H), 7.47 (s, 2 H), 7.58 (d, $J=9.00$ Hz, 2 H), 9.03 (s, 2 H), 9.51 (s, 1 H).

Compound **1049**; Described in example 15

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Compound **1050**; MS: $m/z = 413.9/415.9$ ($M-H$); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.02 (br. s., 2 H), 7.53 (d, $J=9.00$ Hz, 2 H), 7.71 (d, $J=8.61$ Hz, 2 H), 8.01 (d, $J=8.61$ Hz, 1 H), 8.78 (d, $J=8.61$ Hz, 1 H), 9.85 (s, 1 H).

10 Compound **1051**; MS: $m/z = 372.0/374.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.41 (d, $J=9.00$ Hz, 2 H), 7.47 (s, 2 H), 7.75 (d, $J=9.00$ Hz, 2 H), 8.73 (s, 1 H), 9.39 (s, 1 H), 9.93 (s, 1 H).

15 Compound **1052**; MS: $m/z = 350.0$ ($M-H$); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.28 (s, 3 H), 7.15 (d, $J=8.22$ Hz, 2 H), 7.41 (s, 2 H), 7.57 (d, $J=8.61$ Hz, 2 H), 8.71 (s, 1 H), 9.38 (s, 1 H), 9.73 (s, 1 H).

20 Compound **1053**; MS: $m/z = 369.9/371.9$ ($M-H$); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.01 (s, 2 H), 7.41 (d, $J=9.00$ Hz, 2 H), 7.76 (d, $J=9.00$ Hz, 2 H), 8.01 (d, $J=8.61$ Hz, 1 H), 8.78 (d, $J=8.61$ Hz, 1 H), 9.86 (s, 1 H).

Compound **1054**; MS: $m/z = 350.0$ ($M-H$); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.29 (s, 3 H), 6.94 (s, 2 H), 7.15 (d, $J=8.61$ Hz, 2 H), 7.58 (d, $J=8.61$ Hz, 2 H), 8.00 (d, $J=8.22$ Hz, 1 H), 8.77 (d, $J=8.61$ Hz, 1 H), 9.66 (s, 1 H).

25

Compound **1055**; Described in example 17

Compound **1056**; MS: $m/z = 415.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.40 - 7.54 (m, 2 H) 7.58 (s, 2 H) 7.63 - 7.71 (m, 2 H) 7.82 (dt, $J=7.83, 1.76$ Hz, 1 H) 8.16 (t, $J=1.76$ Hz, 1 H) 8.61 - 8.70 (m, 2 H) 9.00 - 9.09 (m, 2 H) 9.75 (s, 1 H).

30 Compound **1057**; MS: $m/z = 415.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.46 (dd, $J=7.83, 4.70$ Hz, 1 H) 7.56 (br. s., 2 H) 7.72 (m, $J=9.00$ Hz, 2 H) 7.85 (m, $J=8.61$ Hz, 2 H) 8.07 (d, $J=7.83$ Hz, 1 H) 8.53 (d, $J=3.52$ Hz, 1 H) 8.90 (d, $J=1.96$ Hz, 1 H) 9.04 (d, $J=5.09$ Hz, 2 H) 9.74 (s, 1 H).

Compound **1058**; MS: $m/z = 415.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.58 (s, 2 H) 7.66 - 7.74 (m, 2 H) 7.77 - 7.85 (m, 2 H) 7.85 - 7.93 (m, 2 H) 8.56 - 8.62 (m, 2 H) 9.00 - 9.09 (m, 2 H) 9.79 (s, 1 H).

5

Compound **1059**; MS: $m/z = 414.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.34 - 7.39 (m, 2 H) 7.39 - 7.45 (m, 1 H) 7.45 - 7.50 (m, 2 H) 7.56 (s, 2 H) 7.62 - 7.66 (m, 2 H) 7.72 (dt, $J=7.53$, 1.71 Hz, 1 H) 8.04 (t, $J=1.96$ Hz, 1 H) 9.02 - 9.06 (m, 2 H) 9.68 (s, 1 H).

10 Compound **1060**; MS: $m/z = 356.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.10 - 7.21 (m, 2 H) 7.50 (br. s., 2 H) 7.63 - 7.73 (m, 2 H) 9.02 (s, 2 H) 9.66 (br. s., 1 H).

Compound **1061**; MS: $m/z = 406.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.62 (s, 2 H) 7.68 (d, $J=8.61$ Hz, 2 H) 7.94 (d, $J=8.61$ Hz, 2 H) 9.00 - 9.11 (m, 2 H) 9.92 (s, 1 H).

15

Compound **1062**; MS: $m/z = 362.0/364.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.43 (s, 3 H), 7.36 (s, 2 H), 7.50 (d, $J=8.61$ Hz, 2 H), 7.69 (d, $J=9.00$ Hz, 2 H), 8.33 (dd, $J=1.96$, 0.78 Hz, 1 H), 8.54 (d, $J=1.56$ Hz, 1 H), 9.53 (s, 1 H).

20 Compound **1063**; MS: $m/z = 285.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.43 (s, 3 H), 7.50 (s, 2 H), 7.75 (d, $J=6.65$ Hz, 2 H), 8.37 (dd, $J=1.96$, 0.78 Hz, 1 H), 8.42 (d, $J=6.26$ Hz, 2 H), 8.56 (d, $J=1.96$ Hz, 1 H), 9.74 (s, 1 H).

25 Compound **1064**; MS: $m/z = 412.9/414.9$ ($M-H$); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.46 (s, 2 H), 7.51 (d, $J=9.00$ Hz, 2 H), 7.69 (d, $J=9.00$ Hz, 2 H), 7.80 (dd, $J=8.61$, 1.57 Hz, 1 H), 8.16 (d, $J=8.61$ Hz, 1 H), 8.63 (s, 1 H), 9.65 (s, 1 H).

30 Compound **1065**; MS: $m/z = 351.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.28 (s, 3 H), 7.13 (d, $J=8.22$ Hz, 2 H), 7.39 (s, 2 H), 7.56 (d, $J=8.61$ Hz, 2 H), 7.79 (dd, $J=8.61$, 1.57 Hz, 1 H), 8.15 (d, $J=8.61$ Hz, 1 H), 8.61 (s, 1 H), 9.44 (s, 1 H).

Compound **1066**; MS: $m/z = 371.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.38 (d, $J=8.61$ Hz, 2 H), 7.46 (s, 2 H), 7.74 (d, $J=8.61$ Hz, 2 H), 7.80 (dd, $J=8.61$, 1.57 Hz, 1 H), 8.16 (d, $J=8.22$ Hz, 1 H), 8.63 (s, 1 H), 9.65 (s, 1 H).

Compound **1067**; MS: $m/z = 338.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.37 (dd, $J=8.22, 4.70$ Hz, 1 H), 7.50 (s, 2 H), 7.81 (dd, $J=8.41, 1.37$ Hz, 1 H), 8.09 (ddd, $J=8.31, 2.45, 1.37$ Hz, 1 H), 8.17 (d, $J=8.61$ Hz, 1 H), 8.29 (br. d, $J=3.90$ Hz, 1 H), 8.65 (s, 1 H), 8.88 (d, $J=1.96$ Hz, 1 H), 9.73 (s, 1 H).

Compound **1068**; MS: $m/z = 318.1/320.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.43 (s, 3 H), 7.36 (s, 2 H), 7.37 (d, $J=9.00$ Hz, 2 H), 7.74 (d, $J=8.61$ Hz, 2 H), 8.33 (dd, $J=2.15, 0.98$ Hz, 1 H), 8.54 (dd, $J=2.35, 0.78$ Hz, 1 H), 9.53 (s, 1 H).

Compound **1069**; MS: $m/z = 298.1$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.27 (s, 3 H), 2.43 (s, 3 H), 7.12 (d, $J=8.22$ Hz, 2 H), 7.28 (s, 2 H), 7.56 (d, $J=8.22$ Hz, 1 H), 8.31 (dd, $J=1.96, 0.78$ Hz, 1 H), 8.53 (d, $J=1.57$ Hz, 1 H), 9.33 (s, 1 H).

Compound **1070**; MS: $m/z = 353.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.44 (s, 3 H), 7.23 (d, $J=8.22$ Hz, 1 H), 7.57 (s, 2 H), 7.96 (dd, $J=8.41, 2.54$ Hz, 1 H), 8.74 (d, $J=2.35$ Hz, 1 H), 9.02 - 9.09 (m, 2 H), 9.74 (s, 1 H).

Compound **1071**; MS: $m/z = 369.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 3.84 (s, 3 H), 6.83 (dd, $J=8.61, 0.78$ Hz, 1 H), 7.53 (s, 2 H), 7.96 (dd, $J=8.61, 2.74$ Hz, 1 H), 8.39 - 8.45 (m, 1 H), 9.00 - 9.08 (m, 2 H), 9.68 (s, 1 H).

Compound **1072**; MS: $m/z = 284.1$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.63 (s, 3 H), 6.80 (s, 2 H), 7.08 (tt, $J=7.40, 1.20$ Hz, 1 H), 7.33 (dd, $J=8.61, 7.43$ Hz, 2 H), 7.42 (d, $J=8.61$ Hz, 1 H), 7.70 (dd, $J=8.61, 1.17$ Hz, 2 H), 8.30 (d, $J=8.22$ Hz, 1 H), 9.50 (s, 1 H).

Compound **1073**; MS: $m/z = 318.1/320.1$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.63 (s, 3 H), 6.85 (s, 2 H), 7.38 (d, $J=9.00$ Hz, 2 H), 7.43 (d, $J=8.61$ Hz, 1 H), 7.75 (d, $J=8.61$ Hz, 2 H), 8.30 (d, $J=8.22$ Hz, 1 H), 9.64 (s, 1 H).

Compound **1074**; MS: $m/z = 390.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.38 (t, $J=9.00$ Hz, 1 H) 7.58 (s, 2 H) 7.65 (ddd, $J=9.10, 4.40, 2.54$ Hz, 1 H) 7.98 - 8.03 (m, 1 H) 9.01 - 9.06 (m, 2 H) 9.78 (s, 1 H).

Compound **1075**; MS: $m/z = 374.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.39 (dt, $J=10.56, 9.19$ Hz, 1 H) 7.44 - 7.53 (m, 1 H) 7.57 (br. s., 2 H) 7.85 (ddd, $J=13.40, 7.53, 2.54$ Hz, 1 H) 9.03 (d, $J=4.70$ Hz, 2 H) 9.79 (br. s., 1 H).

- 5 Compound **1076**; MS: $m/z = 370.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.22 (d, $J=1.96$ Hz, 3 H) 7.09 (t, $J=9.19$ Hz, 1 H) 7.45 - 7.54 (m, 3 H) 7.60 (dd, $J=7.04, 2.35$ Hz, 1 H) 9.02 (s, 2 H) 9.58 (s, 1 H).

- 10 Compound **1077**; MS: $m/z = 356.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 6.85 - 6.93 (m, 1 H) 7.35 (td, $J=8.12, 6.85$ Hz, 1 H) 7.48 - 7.54 (m, 1 H) 7.58 (s, 2 H) 7.67 (dt, $J=12.03, 2.20$ Hz, 1 H) 9.00 - 9.07 (m, 2 H) 9.76 (s, 1 H).

- 15 Compound **1078**; MS: $m/z = 370.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.18 (s, 3 H) 7.20 (t, $J=8.61$ Hz, 1 H) 7.40 (dd, $J=8.22, 1.96$ Hz, 1 H) 7.54 (br. s., 2 H) 7.60 (dd, $J=12.52, 1.96$ Hz, 1 H) 9.03 (d, $J=4.70$ Hz, 2 H) 9.68 (br. s., 1 H).

Compound **1079**; MS: $m/z = 374.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 6.91 (tt, $J=9.39, 2.35$ Hz, 1 H) 7.47 - 7.56 (m, 2 H) 7.64 (s, 2 H) 9.05 (dd, $J=11.15, 1.76$ Hz, 2 H) 9.89 (s, 1 H).

- 20 Compound **1080**; MS: $m/z = 368.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 3.75 (s, 3 H), 6.92 (d, $J=9.00$ Hz, 2 H), 7.39 (s, 2 H), 7.58 (d, $J=9.00$ Hz, 2 H), 8.70 (s, 1 H), 9.37 (s, 1 H), 9.70 (s, 1 H).

- 25 Compound **1081**; MS: $m/z = 340.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.14 (quin, $J=7.53$ Hz, 2 H), 3.00 (q, $J=7.56$ Hz, 2 H), 3.74 (s, 3 H), 6.89 (d, $J=9.39$ Hz, 2 H), 7.23 (s, 2 H), 7.56 (d, $J=9.00$ Hz, 1 H), 8.26 (s, 1 H), 9.25 (s, 1 H).

- 30 Compound **1082**; MS: $m/z = 344.0/346.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.14 (quin, $J=7.53$ Hz, 2 H), 3.01 (q, $J=7.56$ Hz, 4 H), 7.33 (s, 2 H), 7.36 (d, $J=8.61$ Hz, 2 H), 7.74 (d, $J=9.00$ Hz, 2 H), 8.29 (s, 1 H), 9.48 (s, 1 H).

Compound **1083**; MS: $m/z = 367.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 3.75 (s, 3 H), 6.91 (d, $J=9.00$ Hz, 2 H), 7.37 (s, 2 H), 7.57 (d, $J=9.00$ Hz, 2 H), 7.78 (d, $J=8.61$ Hz, 1 H), 8.14 (d, $J=8.61$ Hz, 1 H), 8.60 (s, 1 H), 9.42 (s, 1 H).

Compound **1084**; MS: $m/z = 422.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.35 (d, $J=8.61$ Hz, 2 H), 7.57 (br. s, 2 H), 7.82 (d, $J=9.00$ Hz, 2 H), 9.02 - 9.09 (m, 2 H), 9.80 (s, 1 H).

- 5 Compound **1085**; MS: $m/z = 368.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 3.75 (s, 3 H), 6.67 (dd, $J=8.22, 2.35$ Hz, 1 H), 7.23 (t, $J=8.22$ Hz, 1 H), 7.32 (dd, $J=9.00, 1.56$ Hz, 1 H), 7.39 (t, $J=2.15$ Hz, 1 H), 7.54 (br. s, 2 H), 9.01 - 9.08 (m, 2 H), 9.57 (s, 1 H).

- 10 Compound **1086**; MS: $m/z = 404.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.16 (d, $J=9.00$ Hz, 2 H), 7.18 (t, $J=73.95$ Hz, 1 H), 7.54 (s, 2 H), 7.73 (d, $J=9.39$ Hz, 2 H), 8.97 - 9.11 (m, 2H), 9.71 (s, 1 H).

- 15 Compound **1087**; MS: $m/z = 402.0/404.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 3.84 (s, 3 H), 7.14 (d, $J=9.00$ Hz, 1 H), 7.54 (s, 2 H), 7.60 (dd, $J=9.00, 2.74$ Hz, 1 H), 7.87 (d, $J=2.35$ Hz, 1 H), 8.99 - 9.09 (m, 2 H), 9.62 (s, 1 H).

Compound **1088**; MS: $m/z = 356.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.19 (t, $J=9.00$ Hz, 2 H), 7.44 (s, 2 H), 7.70 (dd, $J=9.00, 5.09$ Hz, 2 H), 8.72 (s, 1 H), 9.39 (s, 1 H), 9.86 (s, 1 H).

- 20 Compound **1089**; MS: $m/z = 355.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.17 (t, $J=8.80$ Hz, 2 H), 7.42 (s, 2 H), 7.70 (dd, $J=9.39, 5.09$ Hz, 2 H), 7.79 (dd, $J=8.61, 1.57$ Hz, 1 H), 8.15 (d, $J=8.22$ Hz, 1 H), 8.62 (s, 1 H), 9.58 (s, 1 H).

Compound **1090**; Described in example 20

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Compound **1091**; MS: $m/z = 310.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 0.80 (d, $J=5.09$ Hz, 2 H), 1.07 (d, $J=7.83$ Hz, 2 H), 2.06 - 2.13 (m, 1 H), 7.07 (t, $J=7.24$ Hz, 1 H), 7.27 - 7.35 (m, 4 H), 7.69 (d, $J=8.22$ Hz, 2 H), 8.15 (s, 1 H), 8.57 (s, 1 H), 9.39 (s, 1 H).

- 30 Compound **1092**; MS: $m/z = 430.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 6.95 - 7.03 (m, 4 H) 7.07 - 7.14 (m, 1 H) 7.33 - 7.41 (m, 2 H) 7.50 (s, 2 H) 7.65 - 7.72 (m, 2 H) 9.02 (s, 2 H) 9.64 (s, 1 H).

Compound **1093**; MS: m/z = 372.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.12 (dt, $J=9.10, 0.93$ Hz, 1 H) 7.34 (t, $J=8.22$ Hz, 1 H) 7.52 - 7.69 (m, 3 H) 7.90 (t, $J=1.96$ Hz, 1 H) 8.98 - 9.09 (m, 2 H) 9.75 (br. s., 1 H).

- 5 Compound **1094**; MS: m/z = 352.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.29 (s, 3 H) 6.90 (d, $J=7.83$ Hz, 1 H) 7.20 (t, $J=7.83$ Hz, 1 H) 7.43 - 7.57 (m, 4 H) 9.02 (d, $J=0.78$ Hz, 2 H) 9.52 (s, 1 H).

- 10 Compound **1095**; MS: m/z = 407.9 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.57 (d, $J=9.00$ Hz, 1 H) 7.61 (br. s., 2 H) 7.69 (dd, $J=8.80, 2.54$ Hz, 1 H) 8.10 (d, $J=2.35$ Hz, 1 H) 9.00 - 9.08 (m, 2 H) 9.83 (br. s., 1 H).

- 15 Compound **1096**; MS: m/z = 386.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.31 (s, 3 H) 7.34 (d, $J=8.61$ Hz, 1 H) 7.51 - 7.58 (m, 3 H) 7.71 (d, $J=2.35$ Hz, 1 H) 9.03 (d, $J=3.52$ Hz, 2 H) 9.64 (s, 1 H).

- 20 Compound **1097**; MS: m/z = 388.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.12 (dd, $J=8.61, 2.35$ Hz, 1 H) 7.23 (d, $J=8.61$ Hz, 1 H) 7.50 (d, $J=2.35$ Hz, 3 H) 9.02 (d, $J=1.96$ Hz, 2 H) 9.60 (s, 1 H) 10.15 (s, 1 H).

- Compound **1098**; MS: m/z = 382.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 5.99 (s, 2 H) 6.86 (d, $J=8.22$ Hz, 1 H) 7.09 (dd, $J=8.41, 2.15$ Hz, 1 H) 7.31 (d, $J=1.96$ Hz, 1 H) 7.47 (s, 2 H) 9.01 (s, 2 H) 9.51 (s, 1 H).

- 25 Compound **1099**; MS: m/z = 396.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 4.15 - 4.26 (m, 4 H) 6.79 (d, $J=9.00$ Hz, 1 H) 7.11 (dd, $J=8.80, 2.54$ Hz, 1 H) 7.27 (d, $J=2.35$ Hz, 1 H) 7.46 (br. s., 2 H) 9.01 (s, 2 H) 9.44 (s, 1 H).

- 30 Compound **1100**; MS: m/z = 344.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.34 (dd, $J=5.28, 1.37$ Hz, 1 H) 7.45 (dd, $J=5.28, 3.33$ Hz, 1 H) 7.53 (s, 2 H) 7.66 (dd, $J=3.13, 1.57$ Hz, 1 H) 9.02 (d, $J=3.13$ Hz, 2 H) 10.08 (s, 1 H).

Compound **1101**; MS: $m/z = 409.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.78 (s, 3 H) 7.55 (s, 2 H) 7.70 (dd, $J=9.00, 1.96$ Hz, 1 H) 7.94 (d, $J=8.61$ Hz, 1 H) 8.31 (d, $J=1.96$ Hz, 1 H) 9.04 (d, $J=5.87$ Hz, 2 H) 9.78 (s, 1 H).

- 5 Compound **1102**; MS: $m/z = 340.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.76 (s, 2 H) 8.08 (d, $J=5.87$ Hz, 1 H) 8.66 (d, $J=5.48$ Hz, 1 H) 8.91 (s, 1 H) 9.05 (d, $J=1.56$ Hz, 1 H) 9.09 (s, 1 H) 10.54 (s, 1 H).

Compound **1103**; Described in example 21

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Compound **1104**; MS: $m/z = 324.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.76 - 1.92 (m, 4 H) 2.88 (t, $J=6.06$ Hz, 2 H) 2.95 (t, $J=6.46$ Hz, 2 H) 7.03 - 7.09 (m, 1 H) 7.25 - 7.35 (m, 4 H) 7.68 (d, $J=7.43$ Hz, 2 H) 8.18 (s, 1 H) 9.34 (s, 1 H).

- 15 Compound **1105**; MS: $m/z = 354.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.74 - 1.93 (m, 4 H), 2.87 (t, $J=6.06$ Hz, 2 H), 2.95 (t, $J=6.46$ Hz, 2 H), 3.73 (s, 3 H), 6.85 - 6.92 (m, 2 H), 7.24 (s, 2 H), 7.53 - 7.59 (m, 2 H), 8.16 (s, 1 H), 9.24 (s, 1 H).

- 20 Compound **1106**; MS: $m/z = 342.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.76 - 1.92 (m, 4 H), 2.87 (t, $J=6.06$ Hz, 2 H), 2.95 (t, $J=6.46$ Hz, 2 H), 7.11 - 7.18 (m, 2 H), 7.29 (br. s., 2 H), 7.65 - 7.72 (m, 2 H), 8.18 (s, 1 H), 9.41 (br. s., 1 H).

Compound **1107**; MS: $m/z = 340.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.21 (t, $J=4.70$ Hz, 1 H) 7.61 (s, 2 H) 8.68 (d, $J=4.70$ Hz, 2 H) 9.04 (d, $J=5.87$ Hz, 2 H) 10.42 (s, 1 H).

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Compound **1108**; MS: $m/z = 340.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.70 (s, 2 H) 8.37 (d, $J=2.74$ Hz, 1 H) 8.45 (dd, $J=2.74, 1.57$ Hz, 1 H) 9.01 - 9.06 (m, 1 H) 9.08 (d, $J=1.56$ Hz, 1 H) 9.27 (d, $J=1.57$ Hz, 1 H) 10.44 (s, 1 H).

- 30 Compound **1109**; MS: $m/z = 340.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.67 (s, 2 H) 8.89 (s, 1 H) 9.05 (d, $J=1.56$ Hz, 1 H) 9.08 (d, $J=1.57$ Hz, 1 H) 9.10 (s, 2 H) 10.00 (s, 1 H).

Compound **1110**; MS: $m/z = 378.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.44 - 7.52 (m, 3 H) 7.53 - 7.59 (m, 1 H) 8.03 (s, 1 H) 8.06 (s, 1 H) 9.02 (s, 2 H) 9.64 (s, 1 H) 12.99 (s, 1 H).

Compound 1111; Described in example 22

Compound 1112; Described in example 23

- 5 Compound 1113; MS: $m/z = 338.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.66 (br. s., 4 H), 1.85 (d, $J=4.70$ Hz, 2 H), 2.85 - 2.91 (m, 2 H), 3.08 (d, $J=10.96$ Hz, 2 H), 6.99 - 7.13 (m, 1 H), 7.21 - 7.37 (m, 4 H), 7.63 - 7.75 (m, 2 H), 8.19 (s, 1 H), 9.35 (s, 1 H).

- Compound 1114; MS: $m/z = 314.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.43 (s, 3 H),
10 3.74 (br. s, 2 H), 6.90 (d, $J=9.00$ Hz, 2 H), 7.26 (s, 2 H), 7.57 (d, $J=9.00$ Hz, 2 H), 8.30 (dd, $J=2.15, 0.98$ Hz, 1 H), 8.53 (d, $J=1.57$ Hz, 1 H), 9.30 (s, 1 H).

- Compound 1115; MS: $m/z = 302.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.43 (s, 3 H),
15 7.16 (t, $J=8.80$ Hz, 2 H), 7.32 (s, 2 H), 7.70 (dd, $J=9.39, 5.09$ Hz, 2 H), 8.32 (dd, $J=1.96, 0.78$ Hz, 1 H), 8.54 (d, $J=1.57$ Hz, 1 H), 9.47 (s, 1 H).

- Compound 1116; MS: $m/z = 368.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 3.75 (s, 3 H),
20 6.92 (br. s, 2 H), 6.93 (d, $J=9.00$ Hz, 2 H), 7.58 (d, $J=9.00$ Hz, 2 H), 7.99 (d, $J=8.61$ Hz, 1 H), 8.77 (d, $J=8.22$ Hz, 1 H), 9.63 (s, 1 H).

- Compound 1117; MS: $m/z = 356.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 6.98 (s, 2 H),
7.19 (t, $J=8.80$ Hz, 2 H), 7.71 (dd, $J=9.39, 5.09$ Hz, 2 H), 8.01 (d, $J=8.22$ Hz, 1 H), 8.78 (d, $J=8.61$ Hz, 1 H), 9.79 (s, 1 H).

- 25 Compound 1118; Described in example 16

- Compound 1119; MS: $m/z = 313.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.43 (s, 3 H),
3.74 (s, 3 H), 6.89 (d, $J=9.00$ Hz, 2 H), 7.13 (s, 2 H), 7.33 (dd, $J=8.41, 1.37$ Hz, 1 H), 7.56 (d, $J=9.00$ Hz, 2 H), 7.74 (d, $J=8.22$ Hz, 1 H), 7.89 (s, 1 H), 9.19 (s, 1 H).

- 30 Compound 1120; MS: $m/z = 301.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.43 (s, 3 H),
7.15 (t, $J=9.00$ Hz, 2 H), 7.19 (s, 2 H), 7.35 (dd, $J=8.41, 1.37$ Hz, 1 H), 7.69 (dd, $J=9.00, 5.48$ Hz, 2 H), 7.75 (d, $J=8.22$ Hz, 1 H), 7.91 (s, 1 H), 9.37 (s, 1 H).

Compound **1121**; MS: $m/z = 386.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 3.82 (s, 3 H) 7.14 (dd, $J=11.35, 8.61$ Hz, 1 H) 7.25 - 7.33 (m, 1 H) 7.46 - 7.62 (m, 3 H) 9.03 (d, $J=5.09$ Hz, 2 H) 9.61 (s, 1 H).

- 5 Compound **1122**; MS: $m/z = 382.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.30 (t, $J=7.04$ Hz, 3 H) 3.99 (q, $J=6.91$ Hz, 2 H) 6.83 - 6.92 (m, 2 H) 7.45 (s, 2 H) 7.50 - 7.58 (m, 2 H) 9.01 (s, 2 H) 9.48 (s, 1 H).

- 10 Compound **1123**; MS: $m/z = 381.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.23 (br. s., 1 H) 7.58 (s, 2 H) 7.78 (d, $J=9.00$ Hz, 2 H) 7.84 (d, $J=9.00$ Hz, 3 H) 9.04 (d, $J=6.26$ Hz, 2 H) 9.78 (s, 1 H).

- 15 Compound **1124**; MS: $m/z = 395.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.76 (d, $J=4.30$ Hz, 3 H) 7.58 (s, 2 H) 7.79 (s, 4 H) 8.32 (d, $J=4.70$ Hz, 1 H) 9.04 (d, $J=5.87$ Hz, 2 H) 9.77 (s, 1 H).

Compound **1125**; MS: $m/z = 396.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 3.82 (s, 3 H) 7.62 (s, 2 H) 7.85 - 7.96 (m, 4 H) 8.99 - 9.09 (m, 2 H) 9.90 (s, 1 H).

- 20 Compound **1126**; MS: $m/z = 381.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.86 (s, 6 H) 6.69 (d, $J=9.39$ Hz, 2 H) 7.35 - 7.50 (m, 4 H) 8.99 (s, 2 H) 9.36 (s, 1 H).

Compound **1127**; MS: $m/z = 417.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.25 (s, 2 H) 7.62 (s, 2 H) 7.72 - 7.80 (m, 2 H) 7.85 - 7.93 (m, 2 H) 8.99 - 9.10 (m, 2 H) 9.90 (s, 1 H).

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Compound **1128**; MS: $m/z = 357.0$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.58 (s, 2 H) 7.77 (td, $J=8.71, 2.93$ Hz, 1 H) 8.05 (dd, $J=9.19, 4.11$ Hz, 1 H) 8.37 (d, $J=3.13$ Hz, 1 H) 8.99 - 9.08 (m, 2 H) 10.16 (s, 1 H).

- 30 Compound **1129**; MS: $m/z = 314.1$ (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.63 (s, 3 H), 3.75 (s, 3 H), 6.75 (br. s, 2 H), 6.91 (d, $J=9.00$ Hz, 2 H), 7.41 (d, $J=8.61$ Hz, 1 H), 7.57 (d, $J=9.00$ Hz, 2 H), 8.29 (d, $J=8.22$ Hz, 1 H), 9.40 (s, 1 H).

Compound 1130; MS: $m/z = 315.0/317.0$ ($M-H$); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.43 (s, 3 H), 7.23 (s, 2 H), 7.35 (dd, $J=7.83, 1.57$ Hz, 1 H), 7.36 (d, $J=9.00$ Hz, 3 H), 7.76 (d, $J=8.22$ Hz, 1 H), 7.74 (d, $J=9.00$ Hz, 3 H), 7.92 (s, 1 H), 9.43 (s, 1 H).

- 5 Compound 1131; LCMS: $m/z = 297.1$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.27 (s, 3 H), 2.43 (s, 3 H), 7.12 (d, $J=8.22$ Hz, 2 H), 7.16 (s, 2 H), 7.34 (dd, $J=8.22, 0.78$ Hz, 1 H), 7.56 (d, $J=8.22$ Hz, 2 H), 7.75 (d, $J=8.22$ Hz, 1 H), 7.90 (s, 1 H), 9.22 (s, 1 H).

- 10 Compound 1132; MS: $m/z = 361.0/363.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.43 (s, 3 H), 7.24 (s, 2 H), 7.35 (dd, $J=8.22, 1.17$ Hz, 1 H), 7.49 (d, $J=9.00$ Hz, 2 H), 7.69 (d, $J=9.00$ Hz, 2 H), 7.76 (d, $J=8.22$ Hz, 1 H), 7.92 (s, 1 H), 9.43 (s, 1 H).

- 15 Compound 1133; MS: $m/z = 384.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.45 (s, 3 H), 7.24 (m, $J=8.61$ Hz, 2 H), 7.51 (s, 2 H), 7.65 (m, $J=8.61$ Hz, 2 H), 9.02 (d, $J=1.17$ Hz, 2 H), 9.61 (s, 1 H).

Compound 1134; Described in example 24

- 20 Compound 1135; MS: $m/z = 348.2/350.2$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.43 (s, 3 H), 3.83 (s, 3 H), 7.11 (d, $J=9.00$ Hz, 1 H), 7.32 (br. s., 2 H), 7.58 (dd, $J=9.00, 2.35$ Hz, 1 H), 7.87 (d, $J=2.74$ Hz, 1 H), 8.31 (s, 1 H), 8.52 (s, 1 H), 9.42 (br. s., 1 H).

- 25 Compound 1136; MS: $m/z = 401.0/403.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 3.84 (s, 3 H), 7.13 (d, $J=9.00$ Hz, 1 H), 7.43 (s, 2 H), 7.60 (dd, $J=9.00, 2.74$ Hz, 1 H), 7.79 (d, $J=8.61$ Hz, 1 H), 7.86 (d, $J=2.74$ Hz, 1 H), 8.15 (d, $J=8.22$ Hz, 1 H), 8.62 (s, 1 H), 9.53 (s, 1 H).

- 30 Compound 1137; MS: $m/z = 352.2$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.43 (s, 3 H), 7.42 (br. s., 2 H), 7.67 (m, $J=8.61$ Hz, 2 H), 7.94 (m, $J=8.61$ Hz, 2 H), 8.34 (s, 1 H), 8.53 - 8.56 (m, 1 H), 9.74 (br. s., 1 H).

Compound 1138; MS: $m/z = 405.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.54 (s, 2 H), 7.69 (d, $J=9.00$ Hz, 2 H), 7.81 (dd, $J=8.61, 1.57$ Hz, 1 H), 7.96 (d, $J=8.61$ Hz, 2 H), 8.17 (d, $J=8.22$ Hz, 1 H), 8.65 (s, 1 H), 9.86 (s, 1 H).

Compound **1139**; MS: m/z = 318.1 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.41 (s, 3 H) 7.07 - 7.13 (m, 1 H) 7.33 (t, $J=8.02$ Hz, 1 H) 7.38 (s, 2 H) 7.61 - 7.66 (m, 1 H) 7.90 (t, $J=2.15$ Hz, 1 H) 8.33 (d, $J=1.17$ Hz, 1 H) 8.53 (d, $J=1.96$ Hz, 1 H) 9.54 (s, 1 H).

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Compound **1140**; MS: m/z = 298.1 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.28 (s, 3 H) 2.41 (s, 3 H) 6.87 (d, $J=7.43$ Hz, 1 H) 7.18 (t, $J=7.63$ Hz, 1 H) 7.29 (s, 2 H) 7.46 (d, $J=7.43$ Hz, 1 H) 7.53 (s, 1 H) 8.28 - 8.32 (m, 1 H) 8.52 (d, $J=1.57$ Hz, 1 H) 9.30 (s, 1 H).

10 Compound **1141**; MS: m/z = 342.1 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.41 (s, 3 H) 4.16 - 4.24 (m, 4 H) 6.77 (d, $J=9.00$ Hz, 1 H) 7.10 (dd, $J=8.80, 2.54$ Hz, 1 H) 7.20 - 7.31 (m, 3 H) 8.29 (d, $J=1.17$ Hz, 1 H) 8.51 (d, $J=1.96$ Hz, 1 H) 9.23 (s, 1 H).

Compound **1142**; MS: m/z = 328.1 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.30 (t, $J=7.04$ Hz, 3 H) 2.41 (s, 3 H) 3.98 (q, $J=6.78$ Hz, 2 H) 6.82 - 6.90 (m, 2 H) 7.23 (s, 2 H) 7.48 - 7.57 (m, 2 H) 8.25 - 8.31 (m, 1 H) 8.51 (d, $J=1.96$ Hz, 1 H) 9.27 (s, 1 H).

15

Compound **1143**; MS: m/z = 330.1 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.41 (s, 3 H) 2.44 (s, 3 H) 7.18 - 7.26 (m, 2 H) 7.30 (s, 2 H) 7.61 - 7.68 (m, 2 H) 8.30 (d, $J=1.17$ Hz, 1 H) 8.52 (d, $J=1.56$ Hz, 1 H) 9.40 (s, 1 H).

20

Compound **1144**; MS: m/z = 371.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.11 (dt, $J=6.85, 1.08$ Hz, 1 H) 7.34 (t, $J=8.02$ Hz, 1 H) 7.48 (s, 2 H) 7.60 - 7.67 (m, 1 H) 7.79 (dd, $J=8.61, 1.57$ Hz, 1 H) 7.89 (t, $J=2.15$ Hz, 1 H) 8.14 (d, $J=8.61$ Hz, 1 H) 8.62 (s, 1 H) 9.66 (s, 1 H).

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Compound **1145**; MS: m/z = 351.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.28 (s, 3 H) 6.89 (d, $J=7.43$ Hz, 1 H) 7.19 (t, $J=7.63$ Hz, 1 H) 7.40 (s, 2 H) 7.46 (d, $J=8.61$ Hz, 1 H) 7.53 (s, 1 H) 7.77 (dd, $J=8.61, 1.57$ Hz, 1 H) 8.13 (d, $J=8.61$ Hz, 1 H) 8.60 (s, 1 H) 9.42 (s, 1 H).

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Compound **1146**; MS: m/z = 395.0 (MH^+); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 4.15 - 4.26 (m, 4 H) 6.78 (d, $J=8.61$ Hz, 1 H) 7.10 (dd, $J=8.80, 2.54$ Hz, 1 H) 7.26 (d, $J=2.74$ Hz, 1 H) 7.35 (s, 2 H) 7.76 (dd, $J=8.61, 1.57$ Hz, 1 H) 8.12 (d, $J=8.61$ Hz, 1 H) 8.58 (s, 1 H) 9.34 (s, 1 H).

Compound **1147**; MS: $m/z = 381.1$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.30 (t, $J=6.85$ Hz, 3 H) 3.99 (q, $J=6.78$ Hz, 2 H) 6.84 - 6.91 (m, 2 H) 7.34 (s, 2 H) 7.50 - 7.56 (m, 2 H) 7.76 (dd, $J=8.61, 1.57$ Hz, 1 H) 8.12 (d, $J=8.61$ Hz, 1 H) 8.58 (s, 1 H) 9.38 (s, 1 H).

5

Compound **1148**; MS: $m/z = 383.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.45 (s, 3 H) 7.19 - 7.26 (m, 2 H) 7.41 (s, 2 H) 7.60 - 7.69 (m, 2 H) 7.77 (dd, $J=8.61, 1.57$ Hz, 1 H) 8.13 (d, $J=8.22$ Hz, 1 H) 8.60 (s, 1 H) 9.52 (s, 1 H).

10 Compound **1149**; MS: $m/z = 368.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.42 (s, 3 H) 7.31 (d, $J=8.22$ Hz, 2 H) 7.35 (s, 2 H) 7.77 - 7.83 (m, 2 H) 8.32 (d, $J=1.17$ Hz, 1 H) 8.53 (d, $J=1.96$ Hz, 1 H) 9.58 (s, 1 H).

15 Compound **1150**; MS: $m/z = 290.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.41 (s, 3 H) 7.28 - 7.39 (m, 3 H) 7.43 (dd, $J=5.09, 3.52$ Hz, 1 H) 7.64 (dd, $J=3.33, 1.37$ Hz, 1 H) 8.30 (d, $J=1.17$ Hz, 1 H) 8.52 (d, $J=1.96$ Hz, 1 H) 9.88 (s, 1 H).

20 Compound **1151**; MS: $m/z = 421.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.32 (d, $J=8.61$ Hz, 2 H) 7.45 (s, 2 H) 7.75 - 7.84 (m, 3 H) 8.15 (d, $J=8.22$ Hz, 1 H) 8.62 (s, 1 H) 9.70 (s, 1 H).

Compound **1152**; MS: $m/z = 343.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 7.34 (dd, $J=5.09, 1.17$ Hz, 1 H) 7.39 - 7.47 (m, 3 H) 7.65 (dd, $J=3.13, 1.17$ Hz, 1 H) 7.77 (dd, $J=8.41, 1.37$ Hz, 1 H) 8.13 (d, $J=8.22$ Hz, 1 H) 8.60 (s, 1 H) 9.99 (s, 1 H).

25 Compound **1153**; Described in example 25

Compound **1154**; MS: $m/z = 340.0$ (MH^+); 1H NMR (400 MHz, DMSO- d_6) δ ppm 6.56 (s, 2 H), 7.17 (t, $J=8.61$ Hz, 2 H), 7.85 (dd, $J=9.39, 5.09$ Hz, 2 H), 8.88 (d, $J=2.35$ Hz, 1 H), 8.90 (d, $J=1.96$ Hz, 1 H), 10.21 (s, 1 H).

30

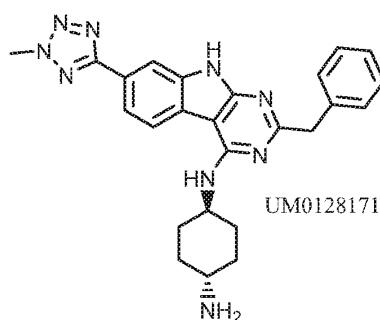
Materials and Methods related to Examples 1 and 2 (Table 1 and 2)

Example 1

CD34+ Activity Assessment

Human CD34+ cord blood (CB) cells were isolated from fresh units using RosetteSep™ CD34 pre-enrichment cocktail followed by CD34 positive selection using EasySep kit™ (StemCell Technologies). The cells were then pre-expanded in bulk, by culturing at 37°C for 6 days in HSC expansion media consisting of StemSpan ACF (StemCell Technologies) supplemented with 100
5 ng/mL Stem Cell Factor (SCF, Shenandoah), 100 ng/mL FMS-like Tyrosine Kinase 3 Ligand (FLT3L, Shenandoah), 50 ng/mL Thrombopoietin (TPO, Shenandoah), 2 mM GlutaMAX™ (Invitrogen), 10 µg/mL low density lipoproteins (LDL, StemCell Technologies), 10 µg/mL Ciprofloxacin and 35nM UM0128171. The culture was monitored daily and supplemented with fresh media as required. Following the pre-expansion, cells were harvested, aliquoted and frozen until use.

10 For each activity assessment, CD34+ pre-expanded cells (approximately 2000 per well in a 384-well plate) were cultured in HSC expansion media, in the presence of 35nM UM0128171. Compounds were serially diluted (1/2) in DMSO (10 dilutions per compound) and added to the cells in order to achieve a 1/1000 final dilution. StemRegenin1 (SR1) and/or Compound 1001
15 were included in all experiments as controls to monitor assay performance. The plate was incubated at 37°C for 7 days in static conditions (i.e. no shaking and no addition of media). Flow cytometry analysis was performed at the end of the 7-day expansion. Cells were stained with PE-labeled anti-human CD45RA (BD Biosciences) and APC-labeled anti-human CD34 (BD Biosciences) and analyzed using Intellicyt IQue cytometer equipped with ForeCyt software.
20 Gates were drawn around the populations of interest to obtain cell numbers and relative proportions. The EC_{1.5} value, which is the concentration at which the compound/vehicle ratio is greater or equal to 1.5, was calculated by plotting the CD34+ cell number against concentrations (log-scale) in a 4-PL curve and fitting the curve using IDBS XLfit (set model 251) in Microsoft Excel. Results are presented in **Tables 1 and 2**.



*Example 2**Inhibition of AhR-Mediated Gene Transcription.*

HEK cells line was transfected with an AhR-responsive firefly luciferase reporter gene X4-4.27 and the stable transfectants generated were again transfected with phRL-CMV (a Renilla luciferase expression vector; Promega) along with pBasi-hU6 Pur DNA (a plasmid carrying the puromycin-resistant gene; TaKaRa, Shiga, Japan), and maintained in the presence of both hygromycin B and puromycin (2 mg/mL). One of the resultant clones was named HEK-XRE 11.1, and used in the reporter gene assays.

HEK-XRE 11.1 cells were plated in 384-well plates at a density of 25,000 cells in 50 uL volume per well. The induction of ARh pathway was done by addition of MeBIO at 0.1 nM concentration. ARh antagonist compounds were then added to seeded cells in serial dilutions (8 dilutions, 1:3, 10 mM down to 5 nM) in duplicate wells. Renilla expression was not used as internal control. On each plate, Compound 1001 and SR1 were added as dose control (8 dilutions, 1:3, 5 mM down to 2.5 nM for SR1 and 2 mM down to 1 nM for compound 1001). Luminescence activity was evaluated after 24 hours culture using Lumi-384-CellTiterGlo-Coming protocol. Dose-response curves were generated using nonlinear regression in Excel. Results are presented in **Tables 1 and 2**.

Materials and Methods related to Examples 3 to 4 (Figures 1 and 2)*Example 3**Assessment of cell composition in vitro*

Human CD34+ cord blood (CB) cells from three cord blood units were isolated as previously described and frozen until use. In a first experiment, two units were pooled upon thawing and CB CD34+ cells were cultured for 7 days in HSC expansion media supplemented with 35 nM UM0128171 (referred to as UM171), 1 µM Compound 1001, a combination of both or DMSO. Cultures were monitored daily and supplemented with fresh media as required. In a second experiment, one unit was thawed and CB CD34+ cells were cultured for 7 days in HSC expansion media supplemented with 0.5 µM Compound 1001 (alone or in combination with 35nM UM171), 0.5 µM Compound 1114 (alone or in combination with 35nM UM171), 0.5 µM SR1 (alone or in combination with 35nM UM171), DMSO or 35 nM UM171.

Phenotype of unexpanded (d0) and expanded (d7) CB cells were analysed using a combination of the following anti-human antibodies: CD34 (BD Biosciences), CD45RA (BD Biosciences or BioLegend), CD201, CD90 and CD117 (from BioLegend), CD86 and FcεR1 (both from eBiosciences). Following staining under reduced light at room temperature for 15-30 minutes,

5 cells were washed and analyzed on a FACSCanto II (BD Biosciences) flow cytometer. Fold expansion was calculated by dividing the number of live total cells obtained following expansion by the number of live total cells seeded for each condition. For each subpopulation of interest, the absolute cell numbers were calculated as follows:

$$(\text{cell percentage of subpopulation of interest} \times \text{live total cell count})/100$$

10

Whereas the total number of cells in culture was increased in all conditions (FIG. 1A, left panel), the use of Compound 1001 in CB cultures increases the number of CD34+ cells (i.e. hematopoietic stem and progenitor cells) compared to other conditions (FIG 1A, middle). The combined use of UM171 and Compound 1001 or Compound 1114 increased the overall

15 percentage of CD34+ cells in cultures (FIG 1A, right panel and FIG 1D). The presence of Compound 1001 or Compound 1114, alone or in combination with UM171, favors the expansion of CD34+CD45RA+ cells (FIGs 1B, 1C and 1D), enriched in short term progenitors (Doulatov, Sergei, *et al.*, *Nature immunology* 11.7 (2010): 585.). On the other hand, the presence of UM171 in culture, alone or in combination with Compound 1001 or Compound 1114, increases

20 the expansion (FIG 1B) and proportions (FIGs 1C and 1D) of CD34+CD45RA- and CD34+CD201+ cells, enriched in long-term progenitors (Majeti, Ravindra, Christopher Y. Park, and Irving L. Weissman. *Cell stem cell* 1.6 (2007): 635-645; Notta, Faiyaz, *et al.* *Science* 333.6039 (2011): 218-221 and Fares, Iman, *et al.* *Blood* (2017): blood-2016.). The combined use of UM171 and Compound 1001 or Compound 1114 also increased the percentage of

25 Dendritic Cells and Mast Cells compared to Compounds used alone (FIG 1D). Therefore, we can induce different proportions of the different types of hematopoietic progenitors or other cellular types depending on the presence of UM171 and Compound 1001 or Compound 1114.

Example 4

30 *Assessment of engraftment and myeloid vs lymphoid lineage contribution in vivo*

NSG (NOD.Cg-Prkdcscid l12rgtm1Wjl/SzJ, The Jackson Laboratory, ME, USA) mice were bred and housed under specific-pathogen-free conditions in sterile ventilated racks at the Institute for Research in Immunology and Cancer. All animal work was in accordance with the Canadian

Council on Animal Care guidelines and approved by the Comité de Déontologie et Expérimentation Animale de l'Université de Montréal.

- Human CD34+ cord blood (CB) cells from two cord blood units were isolated as previously described and frozen until use. Upon thawing, both units were pooled and CB CD34+ cells were cultured for 7 days in HSC expansion media supplemented with 35 nM UM0128171, 1 μ M Compound 1001, a combination of both or DMSO. Cultures were monitored daily and supplemented with fresh media as required.
- Two thousand unexpanded CD34+ CB cells or their progeny present in 7-day cultures were transplanted by tail vein injection into sub-lethally irradiated (250 cGy, <24 hr before transplantation) 8 to 12 week-old female NSG (NODScid *IL2R γ null*, Jackson Laboratory). Human cells in NSG bone marrow (BM) was monitored by flow cytometry 3, 12 and 20 weeks post-transplantation. NSG BM cells were collected by femoral aspiration (weeks 3 and 12) or by flushing the two femurs when animals were sacrificed at week 20. Flow cytometry analysis was performed on freshly collected BM cells. Cells were treated with 1x red blood cell lysis buffer (StemCell Technologies), washed and stained with anti-human CD45 (BioLegend), anti-mouse CD45.1 (eBioscience) and anti-human CD33, anti-human CD19, anti-human CD3 and anti-human CD34 (all from BD Biosciences). Cells then were washed and analyzed using a FACSCanto II (BD Biosciences).

- While CB cells expanded in the presence UM171, alone or in combination with Compound 1001, resulted in higher engraftment at 3 weeks post transplantation, CB cells expanded in the presence of Compound 1001, alone or in combination with UM171, engrafted with higher efficiency in the long term (12 and 20 weeks post transplantation, **FIG 2A**). Furthermore, the contribution of lymphoid lineage was greatly increased in the presence of Compound 1001 (**FIG 2B**).

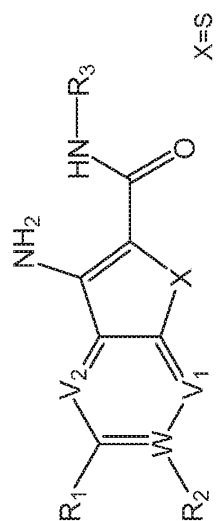


TABLE 1

Cpd#	V ₁	V ₂	W	R ₁	R ₂	R ₃	procedures	EC1.5 (nM)	AHR (nM)
1001	N	CH	C	(CH ₂) ₃		Ph	A1,B1,C1	<100	<50
1002	N	CH	C	(CH ₂) ₃		4-F-Ph	A1,B1,C1	100 – 1000	<50
1003	N	CH	C	Br	H	Ph	A0,B1,C2	100 – 1000	<50
1004	N	CH	C	Cl	H	Ph	A0,B1,C1	100 – 1000	<50
1005	N	CH	C	CH ₃	CH ₃	Ph	A0,B1,C1	100 – 1000	50 – 500
1006	N	CH	C	(CH ₂) ₃		3-pyridinyl	A1,B1,C1	1000 - 5000	50 – 500
1007	N	CH	C	(CH ₂) ₃		2-pyridinyl	A1,B2,C1	100 – 1000	<50
1008	N	CH	C	CF ₃	H	Ph	A2,B1,C1	100 – 1000	>500
1009	N	CH	C	CH ₃	H	Ph	A3,B1,C3	100 – 1000	<50
1010	N	CH	C	F	H	Ph	A0,B1,C3	>5000	50 – 500
1011	N	CH	C	Cl	H	4-pyridinyl	A0,B2,C3	1000 - 5000	<50
1012	N	CH	C	Br	H	4-pyridinyl	A0,B2,C1	100 – 1000	50 – 500
1013	N	CH	C	CF ₃	H	4-pyridinyl	A2,B2,C3	100 – 1000	>500
1014	N	CH	C	(CH ₂) ₃		4-pyridinyl	A1,B2,C1	1000 - 5000	50 – 500

Cpd#	V ₁	V ₂	W	R ₁	R ₂	R ₃	procedures	EC1.5 (nM)	AHR (nM)
1015	N	CH	C	CF ₃	H	3-pyridinyl	A2, B1, C3	100 – 1000	>500
1016	N	CH	C	CN	H	Ph	A4, B1, C1	100 – 1000	>500
1017	N	CH	C	CF ₃	H	4-(CH ₂ CH ₂ OH)-Ph	A2, B3, C1	100 – 1000	50 – 500
1018	N	CH	C	CF ₃	H	4-(CH ₂ OCH ₃)-Ph	A2, B2, C1	1000 – 5000	<50
1019	N	CH	C	CF ₃	H	4-(CH ₂ OH)-Ph	A2, B3, C1	>5000	>500
1020	N	CH	C	CCH	H	4-pyridinyl	Example 18	>5000	50 – 500
1021	N	CH	C	Et	H	4-pyridinyl	Example 19	100 – 1000	50 – 500
1022	N	CH	C	CF ₃	H	2-pyridinyl	A2, B2, C1	100 – 1000	<50
1023	N	CH	C	CF ₃	H	5-CH ₃ -2-thiazolyl	A2, B2, C1	>5000	50 – 500
1024	N	CH	C	CF ₃	H	4-Et-Ph	A2, B2, C1	100 – 1000	<50
1025	CH	CH	N	CF ₃		Ph	A5, B1, C3	100 – 1000	<50
1026	CH	CH	N	CF ₃		4-pyridinyl	A5, B2, C3	1000 – 5000	50 – 500
1027	CH	N	C	CF ₃	H	Ph	A6, B1, C3	>5000	<50
1028	CH	N	C	CF ₃	H	4-pyridinyl	A6, B2, C3	>5000	50 – 500
1029	N	CH	C	CF ₃	H	6-benzothiazolyl	A2, B2, C2	100 – 1000	50 – 500
1030	N	CH	C	CF ₃	H	4-Ph-Ph	A2, B2, C2	>5000	50 – 500
1031	N	CH	C	CF ₃	H	4-BnO-Ph	A2, B2, C2	100 – 1000	50 – 500
1032	N	CH	C	CF ₃	H	4-(CH ₂ CO ₂ Et)-Ph	A2, B2, C1	1000 – 5000	50 – 500
1033	N	CH	C	CF ₃	H	(4-OCH ₃ -3-Ph)-Ph	A2, B2, C4	100 – 1000	50 – 500
1034	CH	CH	C	CF ₃	H	Ph	A0, B1, C3	100 – 1000	<50

Cpd#	V ₁	V ₂	W	R ₁	R ₂	R ₃	procedures	EC1.5 (nM)	AHR (nM)
1035	CH	CH	C	CF ₃	H	4-pyridinyl	A0, B2, C3	100 – 1000	<50
1036	N	CH	C	CF ₃	H	3-Br-Ph	A2, B2, C2	100 – 1000	<50
1037	N	CH	C	CF ₃	H	4-Br-Ph	A2, B2, C2	100 – 1000	<50
1038	N	CH	C	CF ₃	H	4-(CH ₂ CN)-Ph	A2, B2, C4	>5000	<50
1039	N	CH	C	CF ₃	H	5-isoquinolinyl	A2, B2, C2	>5000	50 – 500
1040	N	CH	C	CF ₃	H	5-quinolinyl	A2, B2, C2	>5000	50 – 500
1041	N	CH	C	CF ₃	H	6-quinolinyl	A2, B2, C2	1000 – 5000	50 – 500
1042	N	CH	C	CF ₃	H	3-quinolinyl	A2, B2, C2	1000 – 5000	>500
1043	N	CH	C	CF ₃	H	4-quinolinyl	A2, B2, C2	>5000	>500
1044	N	CH	C	CO ₂ Et	H	Ph	A7, B1, C3	>5000	50 – 500
1045	N	CH	C	CF ₃	H	4-Cl-Ph	A2, B1, C1	<100	<50
1046	N	CH	C	CF ₃	H	4-(CH ₂ CH ₂ OMe)-Ph	A2, B1, C3	>5000	50 – 500
1047	N	CH	C	CF ₃	H	4-CH ₃ -Ph	A2, B1, C1	100 – 1000	<50
1048	N	CH	C	CF ₃	H	4-OCH ₃ -Ph	A2, B1, C1	<100	<50
1049	CH	CH	N	CF ₃		4-Br-Ph	A5, B1, C4	100 – 1000	50 – 500
1050	CH	N	C	CF ₃	H	4-Br-Ph	A6, B1, C4	>5000	50 – 500
1051	CH	CH	N	CF ₃		4-Cl-Ph	A5, B1, C3	1000 – 5000	50 – 500
1052	CH	CH	N	CF ₃		4-CH ₃ -Ph	A5, B1, C3	1000 – 5000	50 – 500
1053	CH	N	C	CF ₃	H	4-Cl-Ph	A6, B1, C3	1000 – 5000	50 – 500
1054	CH	N	C	CF ₃	H	4-CH ₃ -Ph	A6, B1, C3	>5000	50 – 500

Cpd#	V ₁	V ₂	W	R ₁	R ₂	R ₃	procedures	EC1.5 (nM)	AHR (nM)
1055	N	CH	C	CF ₃	H	4-(3-pyridinyl)-Ph	Example 17	>5000	50 – 500
1056	N	CH	C	CF ₃	H	4-(4-pyridinyl)-Ph	D	>5000	50 – 500
1057	N	CH	C	CF ₃	H	3-(3-pyridinyl)-Ph	D	1000 – 5000	<50
1058	N	CH	C	CF ₃	H	3-(4-pyridinyl)-Ph	D	100 – 1000	<50
1059	N	CH	C	CF ₃	H	3-Ph-Ph	D	1000 – 5000	50 – 500
1060	N	CH	C	CF ₃	H	4-F-Ph	A2,B1,C2	<100	<50
1061	N	CH	C	CF ₃	H	4-CF ₃ -Ph	A2,B2,C2	<100	<50
1062	N	CH	C	CH ₃	H	4-Br-Ph	A3,B1,C4	<100	<50
1063	N	CH	C	CH ₃	H	4-pyridinyl	A3,B2,C3	>5000	50 – 500
1064	CH	CH	C	CF ₃	H	4-Br-Ph	A0,B1,C4	100 – 1000	50 – 500
1065	CH	CH	C	CF ₃	H	4-CH ₃ -Ph	A0,B1,C3	100 – 1000	50 – 500
1066	CH	CH	C	CF ₃	H	4-Cl-Ph	A0,B1,C3	100 – 1000	<50
1067	CH	CH	C	CF ₃	H	3-pyridinyl	A0,B1,C3	1000 – 5000	<50
1068	N	CH	C	CH ₃	H	4-Cl-Ph	A3,B1,C1	<100	<50
1069	N	CH	C	CH ₃	H	4-CH ₃ -Ph	A3,B1,C3	100 – 1000	<50
1070	N	CH	C	CF ₃	H	6-CH ₃ -3-pyridinyl	A2,B1,C3	>5000	50 – 500
1071	N	CH	C	CF ₃	H	6-OCH ₃ -3-pyridinyl	A2,B1,C1	100 – 1000	<50
1072	CH	N	C	CH ₃	H	Ph	A8,B1,C3	>5000	50 – 500
1073	CH	N	C	CH ₃	H	4-Cl-Ph	A8,B1,C3	>5000	50 – 500
1074	N	CH	C	CF ₃	H	3-Cl-4-F-Ph	A2,B1,C4	100 – 1000	<50

Cpd#	V ₁	V ₂	W	R ₁	R ₂	R ₃	procedures	EC1.5 (nM)	AHR (nM)
1075	N	CH	C	CF ₃	H	3,4-diF-Ph	A2,B1,C2	100 – 1000	<50
1076	N	CH	C	CF ₃	H	3-CH ₃ -4-F-Ph	A2,B1,C2	100 – 1000	50 – 500
1077	N	CH	C	CF ₃	H	3-F-Ph	A2,B1,C2	100 – 1000	<50
1078	N	CH	C	CF ₃	H	3-F-4-CH ₃ -Ph	A2,B1,C2	1000 – 5000	50 – 500
1079	N	CH	C	CF ₃	H	3,5-diF-Ph	A2,B1,C4	1000 – 5000	50 – 500
1080	CH	CH	N	CF ₃		3-OCH ₃ -Ph	A5,B1,C3	100 – 1000	<50
1081	N	CH	C	(CH ₂) ₃		3-OCH ₃ -Ph	A1,B1,C1	<100	<50
1082	N	CH	C	(CH ₂) ₃		4-Cl-Ph	A1,B1,C1	<100	<50
1083	CH	CH	C	CF ₃	H	4-OCH ₃ -Ph	A0,B1,C3	<100	50 – 500
1084	N	CH	C	CF ₃	H	4-CF ₃ O-Ph	A2,B1,C1	<100	<50
1085	N	CH	C	CF ₃	H	3-OCH ₃ -Ph	A2,B1,C1	100 – 1000	50 – 500
1086	N	CH	C	CF ₃	H	4-OCHF ₂ -Ph	A2,B1,C1	100 – 1000	<50
1087	N	CH	C	CF ₃	H	3-Cl-4-OCH ₃ -Ph	A2,B1,C1	<100	<50
1088	CH	CH	N	CF ₃		4-F-Ph	A5,B1,C3	>5000	<50
1089	CH	CH	C	CF ₃	H	4-F-Ph	A0,B1,C3	100 – 1000	<50
1090	N	CH	C	CH ₂ =CMe	H	Ph	Example 20	>5000	<50
1091	N	CH	C	c-Pr	H	Ph	D	100 – 1000	50 – 500
1092	N	CH	C	CF ₃	H	4-OPh-Ph	A2,B1,C2	100 – 1000	50 – 500
1093	N	CH	C	CF ₃	H	3-Cl-Ph	A2,B1,C2	<100	<50
1094	N	CH	C	CF ₃	H	3-CH ₃ -Ph	A2,B1,C2	<100	<50

Cpd#	V ₁	V ₂	W	R ₁	R ₂	R ₃	procedures	EC1.5 (nM)	AHR (nM)
1095	N	CH	C	CF ₃	H	3,4-diCl-Ph	A2,B1,C2	100 – 1000	50 – 500
1096	N	CH	C	CF ₃	H	3-CH ₃ -4-Cl-Ph	A2,B1,C2	1000 – 5000	50 – 500
1097	N	CH	C	CF ₃	H	3-OH-4-Cl-Ph	A2,B1,C1	1000 – 5000	>500
1098	N	CH	C	CF ₃	H	3,4-(OCH ₂ O)-Ph	A2,B1,C2	<100	50 – 500
1099	N	CH	C	CF ₃	H	3,4-(OCH ₂ CH ₂ O)-Ph	A2,B1,C2	<100	50 – 500
1100	N	CH	C	CF ₃	H	3-thienyl	A2,B2,C2	<100	<50
1101	N	CH	C	CF ₃	H	2-CH ₃ -5-benzothiazolyl	A2,B2,C2	100 – 1000	<50
1102	N	CH	C	CF ₃	H	4-pyrimidinyl	A2,B2,C2	>5000	50 – 500
1103	N	CH	C	i-Pr	H	Ph	Example 21	100 – 1000	<50
1104	N	CH	C	(CH ₂) ₄		Ph	A1,B1,C1	100 – 1000	50 – 500
1105	N	CH	C	(CH ₂) ₄		4-OCH ₃ -Ph	A1,B1,C1	>5000	50 – 500
1106	N	CH	C	(CH ₂) ₄		4-F-Ph	A1,B1,C2	1000 – 5000	50 – 500
1107	N	CH	C	CF ₃	H	2-pyrimidinyl	A2,B2,C4	1000 – 5000	<50
1108	N	CH	C	CF ₃	H	2-pyridazinyl	A2,B2,C4	>5000	<50
1109	N	CH	C	CF ₃	H	5-pyrimidinyl	A2,B2,C4	>5000	>500
1110	N	CH	C	CF ₃	H	5-indazolyl	A2,B2,C4	>5000	50 – 500
1111	N	CH	C	Allyl	H	Ph	Example 22	1000 – 5000	50 – 500
1112	N	CH	C	Et	H	Ph	Example 23	100 – 1000	50 – 500
1113	N	CH	C	(CH ₂) ₅		Ph	A1,B1,C2	1000 – 5000	50 – 500
1114	N	CH	C	CH ₃	H	4-OCH ₃ -Ph	A3,B1,C1	<100	<50

Cpd#	V ₁	V ₂	W	R ₁	R ₂	R ₃	procedures	EC1.5 (nM)	AHR (nM)
1115	N	CH	C	CH ₃	H	4-F-Ph	A3,B1,C1	<100	<50
1116	CH	N	C	CF ₃	H	4-OCH ₃ -Ph	A6,B1,C3	100 – 1000	50 – 500
1117	CH	N	C	CF ₃	H	4-F-Ph	A6,B1,C3	100 – 1000	<50
1118	CH	CH	C	CH ₃	H	Ph	A0,B1,C5	>5000	<50
1119	CH	CH	C	CH ₃	H	4-OCH ₃ -Ph	A0,B1,C5	100 – 1000	50 – 500
1120	CH	CH	C	CH ₃	H	4-F-Ph	A0,B1,C5	<100	<50
1121	N	CH	C	CF ₃	H	3-OCH ₃ -4-F-Ph	A2,B1,C2	100 – 1000	50 – 500
1122	N	CH	C	CF ₃	H	4-OEt-Ph	A2,B1,C4	<100	<50
1123	N	CH	C	CF ₃	H	4-CONH ₂ -Ph	A2,B1,C2	>5000	50 – 500
1124	N	CH	C	CF ₃	H	4-(CONHCH ₃)-Ph	A2,B1,C2	100 – 1000	50 – 500
1125	N	CH	C	CF ₃	H	4-(CO ₂ CH ₃)-Ph	A2,B1,C2	100 – 1000	50 – 500
1126	N	CH	C	CF ₃	H	4-(NMe ₂)-Ph	A2,B1,C2	1000 – 5000	50 – 500
1127	N	CH	C	CF ₃	H	4-(SO ₂ NH ₂)-Ph	A2,B1,C2	>5000	50 – 500
1128	N	CH	C	CF ₃	H	5-F-2-pyridinyl	A2,B1,C2	100 – 1000	-
1129	CH	N	C	CH ₃	H	4-OCH ₃ -Ph	A8,B1,C5	100 – 1000	50 – 500
1130	CH	CH	C	CH ₃	H	4-Cl-Ph	A0,B1,C5	>5000	50 – 500
1131	CH	CH	C	CH ₃	H	4-CH ₃ -Ph	A0,B1,C5	>5000	50 – 500
1132	CH	CH	C	CH ₃	H	4-Br-Ph	A0,B1,C5	>5000	50 – 500
1133	N	CH	C	CF ₃	H	4-SCH ₃ -Ph	A2,B1,C4	<100	<50
1134	N	CH	C	n-Pr	H	Ph	Example 24	>5000	<50

Cpd#	V ₁	V ₂	W	R ₁	R ₂	R ₃	procedures	EC1.5 (nM)	AHR (nM)
1135	N	CH	C	CH ₃	H	3-Cl-4-OCH ₃ -Ph	A3,B2,C2	<100	<50
1136	CH	CH	C	CF ₃	H	3-Cl-4-OCH ₃ -Ph	A0,B2,C1	>5000	<50
1137	N	CH	C	CH ₃	H	4-CF ₃ -Ph	A3,B2,C3	<100	<50
1138	CH	CH	C	CF ₃	H	4-CF ₃ -Ph	A0,B2,C4	>5000	50 – 500
1139	N	CH	C	CH ₃	H	3-Cl-Ph	A3,B1,C2	100 – 1000	<50
1140	N	CH	C	CH ₃	H	3-CH ₃ -Ph	A3,B1,C2	100 – 1000	50 – 500
1141	N	CH	C	CH ₃	H	3,4-(OCH ₂ CH ₂ O)-Ph	A3,B1,C2	100 – 1000	50 – 500
1142	N	CH	C	CH ₃	H	4-OEt-Ph	A3,B1,C2	100 – 1000	<50
1143	N	CH	C	CH ₃	H	4-SCH ₃ -Ph	A3,B1,C2	<100	<50
1144	CH	CH	C	CF ₃	H	3-Cl-Ph	A0,B1,C2	>5000	<50
1145	CH	CH	C	CF ₃	H	3-CH ₃ -Ph	A0,B1,C2	>5000	50 – 500
1146	CH	CH	C	CF ₃	H	3,4-(OCH ₂ CH ₂ O)-Ph	A0,B1,C2	>5000	50 – 500
1147	CH	CH	C	CF ₃	H	4-OEt-Ph	A0,B1,C2	>5000	50 – 500
1148	CH	CH	C	CF ₃	H	4-SCH ₃ -Ph	A0,B1,C2	100 – 1000	50 – 500
1149	N	CH	C	CH ₃	H	4-OCF ₃ -Ph	A3,B1,C2	100 – 1000	<50
1150	N	CH	C	CH ₃	H	3-thienyl	A0,B2,C2	100 – 1000	<50
1151	CH	CH	C	CH ₃	H	4-OCF ₃ -Ph	A3,B1,C2	>5000	50 – 500
1152	CH	CH	C	CF ₃	H	3-thienyl	A0,B2,C3	>5000	<50



TABLE 2

Cpd#	V ₁	V ₂	W	R ₁	R ₂	R ₃	Procedures	EC1.5 nM	AHR
1153	N	CH	C	(CH ₂) ₃		Ph	Example 25	>5000	50 – 500
1154	N	CH	C	CF ₃	H	4-F-Ph	A2,E	100 – 1000	<50

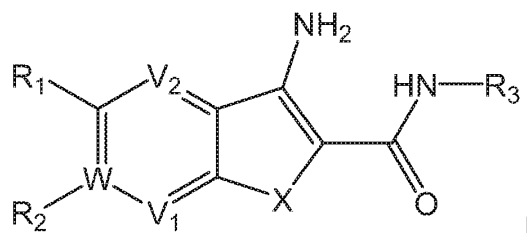
While the present description has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations, including such departures from the present disclosure as come within known or customary practice within the art to and as may be
5 applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

All references cited herein are incorporated by reference in their entirety.

CLAIMS:

1. A method for expanding stem cells and/or progenitor cells, said method comprising contacting a starting cell population with a compound of formula I

5



or a pharmaceutically acceptable salt thereof, wherein

X is O or S;

V1 is N or CH;

10 V2 is N or CH;

W is N or C;

wherein not more than one of said V1, V2 and W is N;

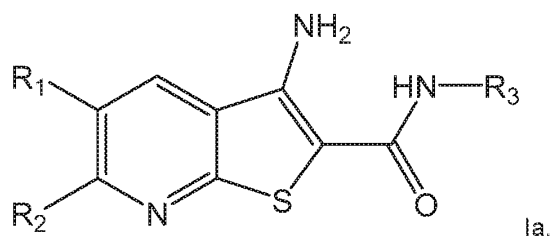
R₁ is halo, alkyl, fluoroalkyl, cycloalkyl, alkynyl, alkenyl, cyano, or COOR_a, wherein R_a is an alkyl;

15 R₂ is H, or alkyl and R₂ is absent when W is N;

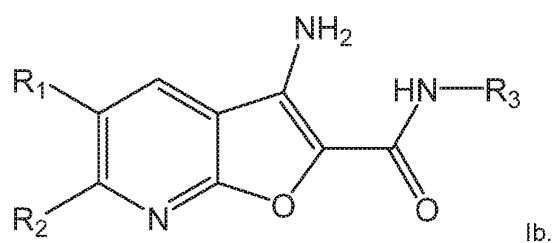
or R₁ and R₂ are attached together with the aromatic ring atoms to form a carbocyclic ring;

R₃ is an optionally substituted phenyl, an optionally substituted 5- or 6-membered heteroaryl, or an optionally substituted fused bicyclic heteroaryl.

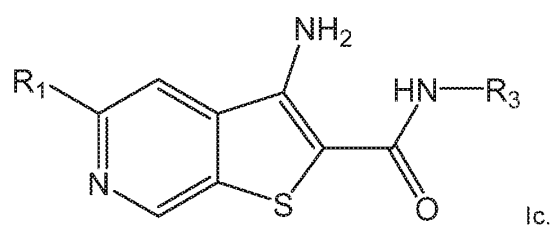
20 2. The method as defined in claim 1, wherein said compound is a compound of formula Ia



3. The method as defined in claim 1, wherein said compound is a compound of formula Ib

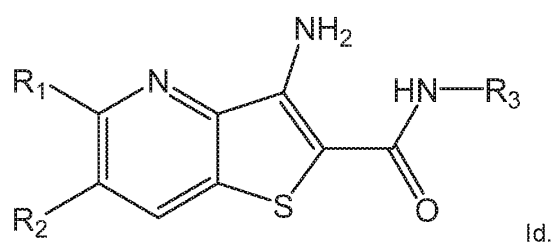


4. The method as defined in claim 1, wherein said compound is a compound of formula Ic

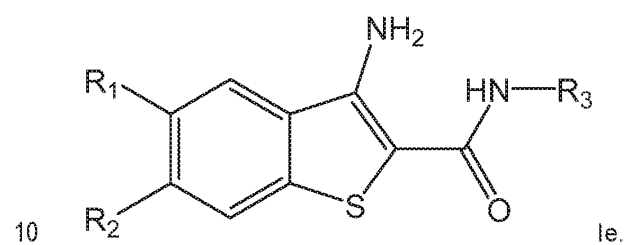


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5. The method as defined in claim 1, wherein said compound is a compound of formula Id

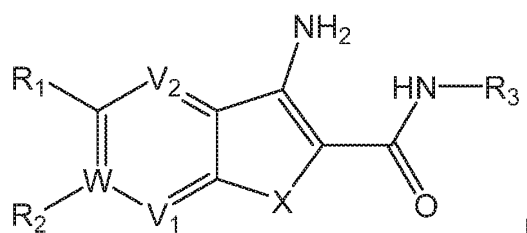


6. The method as defined in claim 1, wherein said compound is a compound of formula Ie



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7. The method of any one of claims 1 to 6, wherein R_1 is halo, C1-6alkyl, C1-6fluoroalkyl, C3-6cycloalkyl, C2-3alkynyl, C2-3alkenyl, cyano, or COORa wherein Ra is a C1-6alkyl.
8. The method of any one of claims 1 to 7, wherein R_2 is H.
9. The method of any one of claims 1 to 8, wherein R_3 is an optionally mono or
5 disubstituted phenyl at any of positions 3, 4 and 5 of said phenyl.
10. The method of any one of claims 1 to 8, wherein R_3 is an optionally monosubstituted 5- or 6-membered heteroaryl.
11. The method of any one of claims 1 to 10, comprising either i) contacting said starting cell population with a first compound for expanding stem cells and/or progenitor cells and expanding
10 the cells for a first period of time, optionally substantially removing said first compound, adding said compound of formula I or a pharmaceutically acceptable salt thereof and expanding the cells further for a second period of time or ii) contacting said starting cell population with a compound for expanding stem cells and/or progenitor cells and said compound of formula I.
12. A stem cells and/or progenitor cells population as expanded by a method as defined in
15 any one of claims 1 to 11.
13. A method of treating a hematopoietic disorder/malignancy, an autoimmune disease and/or an inherited immunodeficient disease, comprising administering cell population as defined in claim 12 or administering a compound as described in any one of claims 1 to 10.
- 20 14. A compound of formula I



- 25 or a pharmaceutically acceptable salt thereof, wherein

X is O or S;

V1 is N or CH;

V2 is N or CH;

W is N or C;

- 5 wherein not more than one of said V1, V2 and W is N;

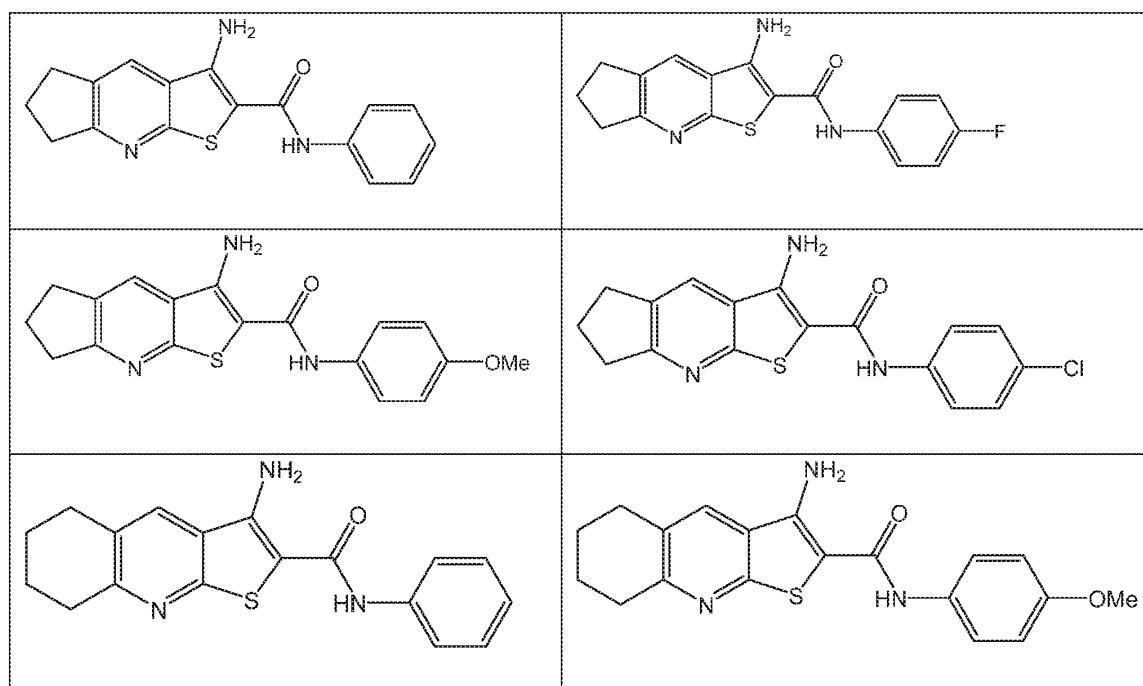
R₁ is halo, alkyl, fluoroalkyl, cycloalkyl, alkynyl, alkenyl, cyano, or COOR_a, wherein R_a is an alkyl;

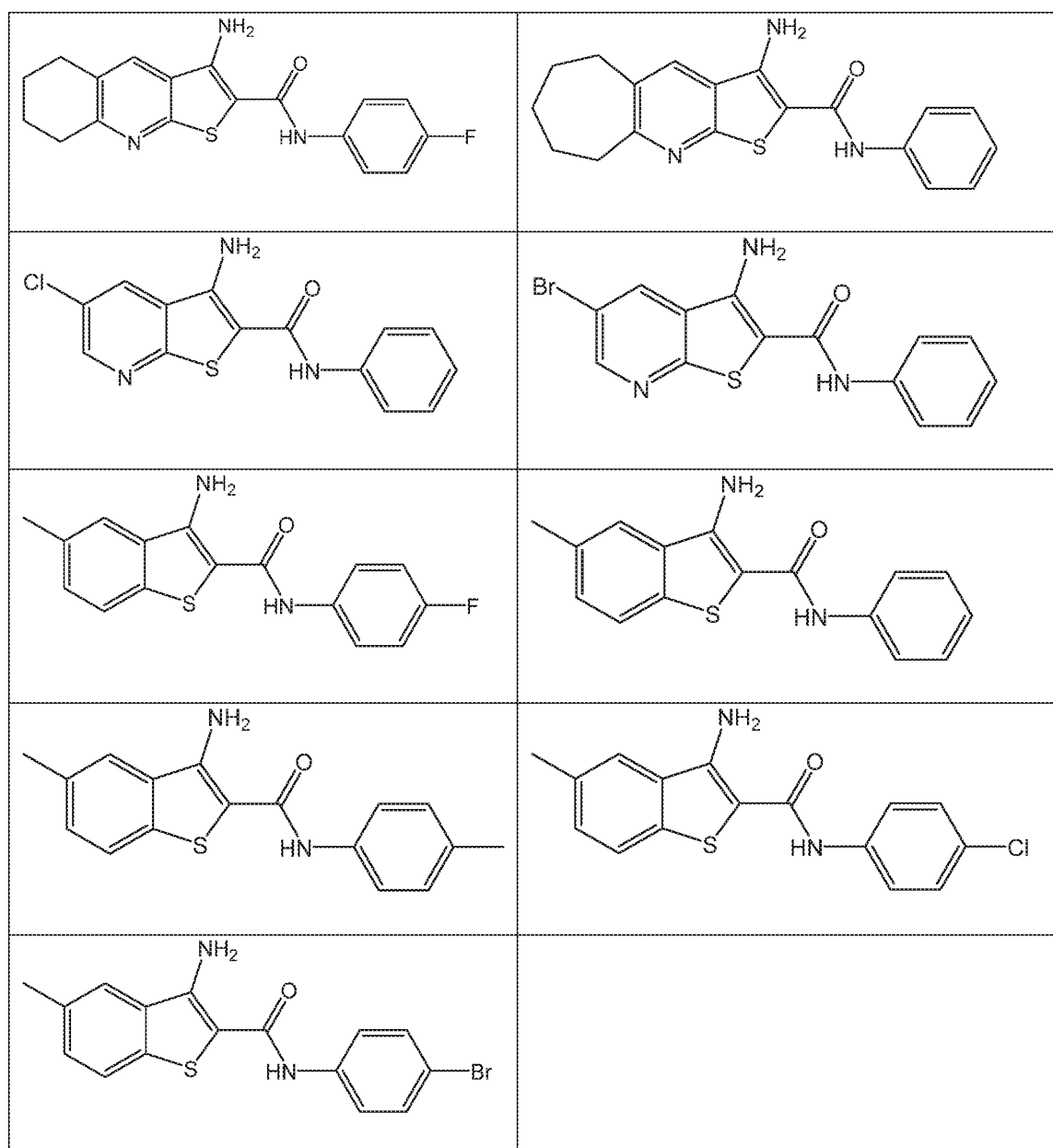
R₂ is H, alkyl or R₂ is absent when W is N;

or R₁ and R₂ are attached together with the aromatic ring atoms to form a carbocyclic ring;

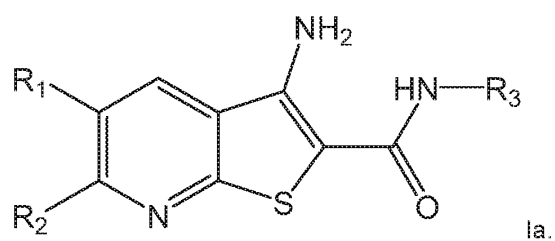
- 10 R₃ is an optionally substituted phenyl, an optionally substituted 5- or 6-membered heteroaryl, or an optionally substituted fused bicyclic heteroaryl;

provided that the compound is other than:

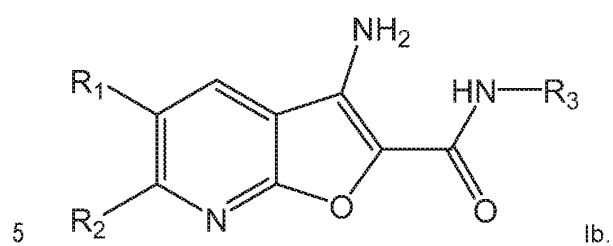




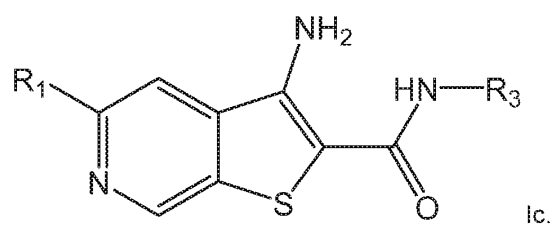
15. The compound as defined in claim 14, wherein said compound is a compound of formula Ia



16. The compound as defined in claim 14, wherein said compound is a compound of formula 1b

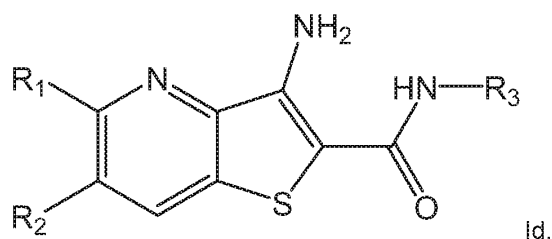


17. The compound as defined in claim 14, wherein said compound is a compound of formula 1c

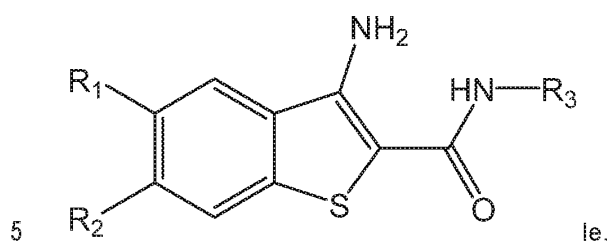


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18. The compound as defined in claim 14, wherein said compound is a compound of formula 1d



19. The compound as defined in claim 14, wherein said compound is a compound of formula
le



20. The compound as defined in any one of claims 14 to 19, wherein R_1 is halo, C1-6alkyl, C1-6fluoroalkyl, C3-6cycloalkyl, C2-3alkynyl, C2-3alkenyl, cyano, or COORa wherein Ra is a C1-6alkyl.

10 21. The compound as defined in any one of claims 14 to 20, wherein R_2 is H.

22. The compound as defined in any one of claims 14 to 21, wherein R_3 is an optionally mono or disubstituted phenyl at any of positions 3, 4 and 5 of said phenyl.

23. The compound as defined in any one of claims 14 to 21, wherein R_3 is an optionally monosubstituted 5- or 6-membered heteroaryl.

15 24. The compound as defined in claim 14, wherein said compound is selected from Tables 1 and 2 as described herein.

25. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable carrier.
- 5 26. A pharmaceutical composition comprising stem cells and/or progenitor cells as defined in claim 12 or as expanded by the method as defined in any one of claims 1 to 13, and optionally a pharmaceutically acceptable carrier.