

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 November 2007 (29.11.2007)

PCT

(10) International Publication Number
WO 2007/136990 A2

(51) International Patent Classification:

A61K 31/4745 (2006.01)

(21) International Application Number:

PCT/US2007/068419

(22) International Filing Date: 8 May 2007 (08.05.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/747,312

16 May 2006 (16.05.2006)

US

(71) Applicant (for all designated States except US):

SMITHKLINE BEECHAM CORPORATION
[US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FITCH, Duke, M.**
[US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **CHAI, Deping** [CN/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US).

(74) Agents: **KANAGY, James, M.** et al.; Glaxosmithkline, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King Of Prussia, PA 19406-0939 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

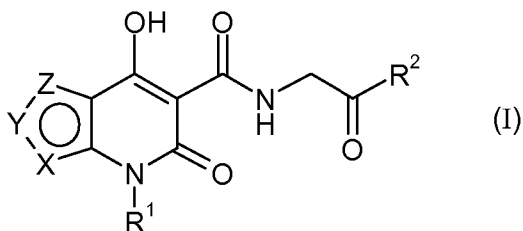
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROLYL HYDROXYLASE INHIBITORS



(57) Abstract: The invention described herein relates to certain bicyclic heteroaromatic N-substituted glycine derivatives of formula (I) which are antagonists of HIF prolyl hydroxylases and are useful for treating diseases benefiting from the inhibition of this enzyme, anemia being one example.

Prolyl Hydroxylase Inhibitors

FIELD OF THE INVENTION

This invention relates to certain bicyclic heteroaromatic N-substituted glycine derivatives that are inhibitors of HIF prolyl hydroxylases, and thus have use in treating diseases benefiting from the inhibition of this enzyme, anemia being one example.

BACKGROUND OF THE INVENTION

Anemia occurs when there is a decrease or abnormality in red blood cells, which leads to reduced oxygen levels in the blood. Anemia occurs often in cancer patients, particularly those receiving chemotherapy. Anemia is often seen in the elderly population, patients with renal disease, and in a wide variety of conditions associated with chronic disease.

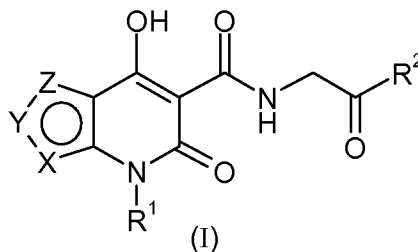
Frequently, the cause of anemia is reduced erythropoietin (Epo) production resulting in prevention of erythropoiesis (maturation of red blood cells). Epo production can be increased by inhibition of prolyl hydroxylases that regulate hypoxia inducible factor (HIF).

One strategy to increase erythropoietin (Epo) production is to stabilize and thus increase the transcriptional activity of the HIF. HIF-alpha subunits (HIF-1alpha, HIF-2alpha, and HIF-3alpha) are rapidly degraded by proteasome under normoxic conditions upon hydroxylation of proline residues by prolyl hydroxylases (EGLN1, 2, 3). Proline hydroxylation allows interaction with the von Hippel Lindau (VHL) protein, a component of an E3 ubiquitin ligase. This leads to ubiquitination of HIF-alpha and subsequent degradation. Under hypoxic conditions, the inhibitory activity of the prolyl hydroxylases is suppressed, HIF-alpha subunits are therefore stabilized, and HIF-responsive genes, including Epo, are transcribed. Thus, inhibition of prolyl hydroxylases results in increased levels of HIF-alpha and thus increased Epo production.

The compounds of this invention provide a means for inhibiting these hydroxylases, increasing Epo production, and thereby treating anemia. Ischemia, stroke, and cytoprotection may also benefit by administering these compounds.

SUMMARY OF THE INVENTION

In the first instance, this invention relates to a compound of formula (I):



wherein:

R^1 is hydrogen, $-NR^3R^4$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_5 - C_8 cycloalkenyl, C_1 - C_{10} alkyl- C_5 - C_8 cycloalkenyl, C_3 - C_8 heterocycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 heterocycloalkyl, aryl, C_1 - C_{10} alkyl-aryl, heteroaryl or

5 C_1 - C_{10} alkyl-heteroaryl;

R^2 is $-NR^6R^7$ or $-OR^8$;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, , C_1 - C_{10} alkyl- C_3 - C_8 heterocycloalkyl, aryl, C_1 - C_{10} alkyl-aryl, heteroaryl, C_1 - C_{10} alkyl-heteroaryl, $-CO(C_1$ - C_4 alkyl),
 10 $-CO(C_3$ - C_6 cycloalkyl), $-CO(C_3$ - C_6 heterocycloalkyl), $-CO(aryl)$, $-CO(heteroaryl)$, $-SO_2(C_1$ - C_4 alkyl); or R^3 and R^4 taken together with the nitrogen to which they are attached form a 5- or 6- or 7-membered saturated ring optionally containing one other heteroatom which is oxygen, nitrogen or sulphur;

each R^5 is independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl,
 15 C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, $-CO(C_1$ - C_4 alkyl), $-CO(aryl)$, $-CO(heteroaryl)$, $-CO(C_3$ - C_6 cycloalkyl), $-CO(C_3$ - C_6 heterocycloalkyl), $-SO_2(C_1$ - C_4 alkyl), C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_6 - C_{14} aryl, C_1 - C_{10} alkyl-aryl, heteroaryl, and C_1 - C_{10} alkyl-heteroaryl;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl and heteroaryl;

20 R^8 is H or a cation, or C_1 - C_{10} alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C_3 - C_6 cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

X, Y, and Z are part of a 5-membered aromatic heterocycle and are independently CR^9 , O, N, NR^{10} , or S, provided that at least one of the atoms X, Y, and Z is O, NR^{10} , or S;

25 each R^9 is independently selected from the group consisting of hydrogen, nitro, cyano, halogen, $-C(O)R^5$, $-C(O)OR^5$, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-S(O)_2R^5$, $-NR^3R^4$, $-CONR^3R^4$, $-N(R^3)C(O)R^5$, $-N(R^3)C(O)OR^5$, $-OC(O)NR^3R^4$, $-N(R^3)C(O)NR^3R^4$, $-P(O)(OR^5)_2$, $-SO_2NR^3R^4$, $-N(R^3)SO_2R^5$, C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl, C_1 - C_{10} alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, aryl and heteroaryl group;

30 each R^{10} is selected from the group consisting of hydrogen, cyano, $-C(O)R^5$, $-NR^3R^4$, $-CONR^3R^4$, $-N(R^3)C(O)R^5$, $-N(R^3)C(O)OR^5$, $-N(R^3)C(O)NR^3R^4$, $-SO_2NR^3R^4$, $-N(R^3)SO_2R^5$, C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl, C_1 - C_{10} alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, aryl and heteroaryl group;

any carbon or heteroatom of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 or R^{10} is unsubstituted or,
 35 where possible, is substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, heteroaryl, halogen, $-OR^5$, $-NR^3R^4$, cyano, nitro, $-C(O)R^5$, $-C(O)OR^5$, $-SR^5$, $-S(O)R^5$,

-S(O)₂R⁵, -NR³R⁴, -CONR³R⁴, -N(R³)C(O)R⁵, -N(R³)C(O)OR⁵, -OC(O)NR³R⁴, -N(R³)C(O)NR³R⁴, -SO₂NR³R⁴, -N(R³)SO₂R⁵, C₁-C₁₀ alkenyl, C₁-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, aryl or heteroaryl group, wherein R³, R⁴, and R⁵ are the same as defined above; or a pharmaceutically acceptable salt or solvate thereof.

5 In a second aspect of the present invention, there is provided a compound of formula (I) or a salt or solvate thereof for use in mammalian therapy, e.g. treating amenia. An example of this therapeutic approach is that of a method for treating anemia caused by increasing the production of erythropoietin (Epo) by inhibiting HIF prolyl hydroxylases comprising administering a compound of formula (I) to a patient in need thereof, neat or admixed with a pharmaceutically acceptable
10 excipient, in an amount sufficient to increase production of Epo.

In a third aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a salt, solvate, or the like thereof, and one or more of pharmaceutically acceptable carriers, diluents and excipients.

In a fourth aspect, there is provided the use of a compound of formula (I) or a salt or
15 solvate thereof in the preparation of a medicament for use in the treatment of a disorder mediated by inhibiting HIF prolyl hydroxylases, such as an anemia, that can be treated by inhibiting HIF prolyl hydroxylases.

DETAILED DESCRIPTION OF THE INVENTION

20 For the avoidance of doubt, unless otherwise indicated, the term “substituted” means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups the selected groups may be the same or different.

The term “independently” means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

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

As used herein the term “alkyl” refers to a straight- or branched-chain hydrocarbon radical having the specified number of carbon atoms, so for example, as used herein, the terms “C₁-C₄ alkyl” and “C₁-C₁₀ alkyl” refers to an alkyl group having at least 1 and up to 4 or 10 carbon
35 atoms respectively. Examples of such branched or straight-chained alkyl groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, n-

butyl, t-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl, and branched analogs of the latter 5 normal alkanes.

When the term "alkenyl" (or "alkenylene") is used it refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and at least 1 and up to 5 carbon-carbon double bonds. Examples include ethenyl (or ethenylene) and propenyl (or propenylene).

When the term "alkynyl" (or "alkynylene") is used it refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and at least 1 and up to 5 carbon-carbon triple bonds. Examples include ethynyl (or ethynylene) and propynyl (or propynylene).

When "cycloalkyl" is used it refers to a non-aromatic, saturated, cyclic hydrocarbon ring containing the specified number of carbon atoms. So, for example, the term "C₃-C₈ cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from three to eight carbon atoms. Exemplary "C₃-C₈ cycloalkyl" groups useful in the present invention include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "C₅-C₈cycloalkenyl" refers to a non-aromatic monocyclic carboxycyclic ring having the specified number of carbon atoms and up to 3 carbon-carbon double bonds. "Cycloalkenyl" includes by way of example cyclopentenyl and cyclohexenyl.

Where "C₃-C₈ heterocycloalkyl" is used, it means a non-aromatic heterocyclic ring containing the specified number of ring atoms being, saturated or having one or more degrees of unsaturation and containing one or more heteroatom substitutions selected from O, S and/or N. Such a ring may be optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, aziridine, thiirane, oxirane, azetidine, oxetane, thietane, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, piperazine, 2,4-piperazinedione, pyrrolidine, imidazolidine, pyrazolidine, morpholine, thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

"Aryl" refers to optionally substituted monocyclic and polycarbocyclic unfused or fused groups having 6 to 14 carbon atoms and having at least one aromatic ring that complies with Hückel's Rule. Examples of aryl groups are phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl and the like.

"Heteroaryl" means an optionally substituted aromatic monocyclic ring or polycarbocyclic fused ring system wherein at least one ring complies with Hückel's Rule, has the specified number of ring atoms, and that ring contains at least one heteroatom selected from N, O, and/or S. Examples of "heteroaryl" groups include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl,

isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, and indazolyl.

The term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

5 The term "solvate" refers to a complex of variable stoichiometry formed by a solute and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation,
10 water, ethanol and acetic acid. Most preferably the solvent used is water.

Herein, the term "pharmaceutically-acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically-acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or
15 free base form with a suitable base or acid, respectively.

In certain embodiments, compounds according to Formula I may contain an acidic functional group, one acidic enough to form salts. Representative salts include pharmaceutically-acceptable metal salts such as sodium, potassium, lithium, calcium, magnesium, aluminum, and zinc salts; carbonates and bicarbonates of a pharmaceutically-acceptable metal cation such as
20 sodium, potassium, lithium, calcium, magnesium, aluminum, and zinc; pharmaceutically-acceptable organic primary, secondary, and tertiary amines including aliphatic amines, aromatic amines, aliphatic diamines, and hydroxy alkylamines such as methylamine, ethylamine, 2-hydroxyethylamine, diethylamine, triethylamine, ethylenediamine, ethanolamine, diethanolamine, and cyclohexylamine.

25 In certain embodiments, compounds according to Formula (I) may contain a basic functional group and are therefore capable of forming pharmaceutically-acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically-acceptable inorganic acids and pharmaceutically-acceptable organic acids. Representative pharmaceutically-acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methylnitrate, sulfate,
30 bisulfate, sulfamate, phosphate, acetate, hydroxyacetate, phenylacetate, propionate, butyrate, isobutyrate, valerate, maleate, hydroxymaleate, acrylate, fumarate, malate, tartrate, citrate, salicylate, *p*-aminosalicylate, glycollate, lactate, heptanoate, phthalate, oxalate, succinate, benzoate, *o*-acetoxybenzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, mandelate, tannate, formate, stearate, ascorbate, palmitate, oleate, pyruvate,
35 pamoate, malonate, laurate, glutarate, glutamate, estolate, methanesulfonate (mesylate),

ethanesulfonate (esylate), 2-hydroxyethanesulfonate, benzenesulfonate (besylate), *p*-aminobenzenesulfonate, *p*-toluenesulfonate (tosylate), and naphthalene-2-sulfonate.

Compounds of particular interest include those wherein:

X is sulphur and Y and Z are CR⁹, or those where Z is sulphur and Y and Z are CR⁹, or
 5 those compounds where X is NR¹⁰, Y is N, and Z is CR⁹;

R¹ is hydrogen, C₁-C₁₀alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₃-C₈cycloalkyl, C₁-C₁₀alkyl-C₃-C₈cycloalkyl, or C₅-C₈cycloalkenyl, C₁-C₁₀alkyl-C₅-C₈cycloalkenyl, aryl, or C₁-C₁₀alkylaryl;

R² is -NR⁶R⁷ or -OR⁸;

R⁵ is independently selected from the group consisting of hydrogen, C₁-C₁₀alkyl,
 10 C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, -CO(C₁-C₄ alkyl), -CO(aryl), -CO(heteroaryl), -SO₂(C₁-C₄ alkyl), C₃-C₈ cycloalkyl, C₃-C₈heterocycloalkyl, C₆-C₁₄ aryl, heteroaryl, and aryl-C₁-C₁₀ alkyl;

R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkyl-C₃-C₈cycloalkyl, C₃-C₈heterocycloalkyl, aryl, -CO(C₁-C₄ alkyl), or C₃-C₈ cycloalkyl-C₁-C₁₀ alkyl; or R⁶ and R⁷ taken together with the nitrogen to which they are attached
 15 form a 5- or 6-membered saturated ring;

R⁸ is H or a cation, or C₁-C₁₀alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C₃-C₆ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

R⁹ is hydrogen, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, C₁-C₁₀ alkyl-C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, C₁-C₁₀ alkyl-C₃-C₆ heterocycloalkyl, aryl, C₁-C₁₀ alkylaryl, or heteroaryl;
 20

R¹⁰ is selected from the group consisting of C₁-C₁₀alkyl, C₁-C₁₀alkenyl, C₁-C₁₀alkynyl, C₃-C₆cycloalkyl, C₃-C₆ heterocycloalkyl, aryl, C₁-C₁₀alkylaryl, heteroaryl or C₁-C₁₀alkylheteroaryl;

any carbon or heteroatom of R¹, R², R⁵, R⁶, R⁷, R⁸, OR⁹ or R¹⁰ is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C₁-C₆ alkyl, aryl,
 25 halogen, -OR⁵, -NR⁶R⁷, -C(O)OR⁵, -OR⁵, -CONR⁶R⁷, -N(R⁶)C(O)R⁵, -N(R⁶)C(O)OR⁵, -OC(O)NR⁶R⁷, -N(R⁶)C(O)NR⁶R⁷, or C₃-C₆ cycloalkyl, wherein R⁵, R⁶, and R⁷ are the same as defined above.

Compounds of further interest are those wherein:

X is sulphur and Y and Z are CR⁹, or those where Z is sulphur and Y and Z are CR⁹, or
 30 those compounds where X is NR¹⁰, Y is N, and Z is CR⁹;

R¹ is hydrogen, C₁-C₁₀alkyl, aryl, C₃-C₈cycloalkyl, C₁-C₁₀alkyl-C₃-C₈cycloalkyl, or C₁-C₁₀alkylaryl;

R² is -NR⁶R⁷ or -OR⁸;

R⁵ is independently selected from the group consisting of hydrogen, C₁-C₁₀alkyl, -CO(C₁-C₄ alkyl), -CO(aryl), -CO(heteroaryl), C₃-C₈ cycloalkyl, C₁-C₁₀alkyl-C₃-C₈ cycloalkyl, C₃-C₈heterocycloalkyl, C₆-C₁₄ aryl, heteroaryl, and aryl-C₁-C₁₀ alkyl;
 35

R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl, $-CO(C_1$ - C_4 alkyl), or C_3 - C_8 cycloalkyl- C_1 - C_{10} alkyl; or R^6 and R^7 taken together with the nitrogen to which they are attached form a 5- or 6-membered saturated ring;

5 R^8 is H or a cation, or C_1 - C_{10} alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C_3 - C_6 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^9 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_6 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 heterocycloalkyl, aryl, C_1 - C_{10} alkylaryl, or heteroaryl group;

10 R^{10} is selected from the group consisting of C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl, C_1 - C_{10} alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, aryl, C_1 - C_{10} alkylaryl, heteroaryl or C_1 - C_{10} alkylheteroaryl; any carbon or heteroatom of R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , OR^9 or R^{10} is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, halogen, $-OR^5$, $-NR^6R^7$, $-C(O)OR^5$, $-OR^5$, $-CONR^6R^7$, wherein R^5 , R^6 , and R^7 are the same as
15 defined above.

Of further interest are those compounds where:

X is sulphur and Y and Z are CR^9 , or those where Z is sulphur and Y and Z are CR^9 , or those compounds where X is NR^{10} , Y is N, and Z is CR^9 ;

R^1 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, or
20 C_1 - C_{10} alkylaryl;

R^2 is $-OR^8$;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl, $-CO(C_1$ - C_4 alkyl), or C_3 - C_8 cycloalkyl- C_1 - C_{10} alkyl; or R^6 and R^7 taken together with the nitrogen to which they are attached
25 form a 5- or 6-membered saturated ring;

R^8 is H or a cation;

R^9 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_6 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 heterocycloalkyl, aryl, C_1 - C_{10} alkylaryl, or heteroaryl group;

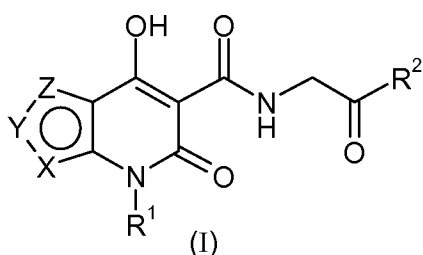
any carbon or heteroatom of R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , OR^9 or R^{10} is unsubstituted or, where
30 possible, is substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, heteroaryl, halogen, cyano, nitro, $-OR^5$, $-NR^6R^7$, $-C(O)OR^5$, $-OR^5$, $-CONR^6R^7$, wherein R^5 , R^6 , and R^7 are the same as defined above.

Specific compounds exemplified herein are:

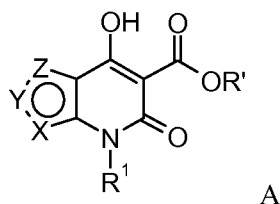
- 1) *N*-[(4-hydroxy-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridin-5-yl)carbonyl]glycine;
- 35 2) *N*-{[4-hydroxy-6-oxo-7-(phenylmethyl)-6,7-dihydrothieno[2,3-*b*]pyridin-5-yl]carbonyl}glycine;

- 3) *N*-[(4-hydroxy-3-methyl-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridin-5-yl)carbonyl]glycine;
 4) *N*-[(7-hydroxy-5-oxo-4,5-dihydrothieno[3,2-*b*]pyridin-6-yl)carbonyl]glycine;
 5) *N*-{[7-hydroxy-5-oxo-4-(phenylmethyl)-4,5-dihydrothieno[3,2-*b*]pyridin-6-yl]carbonyl}glycine; and
 5 6) *N*-[(4-hydroxy-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)carbonyl]glycine.

Processes for preparing the compound of formula (I) are also within the ambit of this invention. To illustrate, process for preparing a compound of formula (I)



wherein R^1 , R^2 , X, Y and Z are the same as defined above for formula (I), the process comprising treating a compound of formula A:



wherein R^1 , X, Y and Z are the same as for those groups in formula (I) and R' is a ester-forming group, with glycine sodium salt or glycine and an appropriate base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium ethoxide or sodium hydride, in an appropriate solvent, such as ethanol or 1,4-dioxane, under either conventional thermal conditions or by microwave irradiation, to form a compound of formula (I) where R^2 is -OH.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope stoichiometric solvates (e.g. hydrates) as well as compounds containing variable amounts of solvent (e.g. water).

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers. The compounds claimed below include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I), or claimed below, as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the claimed

compounds as mixtures with isomers thereof in which one or more chiral centers are inverted. Also, it is understood that any tautomers and mixtures of tautomers of the claimed compounds are included within the scope of the compounds of formula (I) as disclosed herein above or claimed herein below.

5 Where there are different isomeric forms they may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

 While it is possible that, for use in therapy, a compound of formula (I), as well as salts, solvates and the like, may be administered as a neat preparation, i.e. no additional carrier, the more
10 usual practice is to present the active ingredient confectioned with a carrier or diluent. Accordingly, the invention further provides pharmaceutical compositions, which includes a compound of formula (I) and salts, solvates and the like, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of formula (I) and salts, solvates, etc, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being
15 compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula (I), or salts, solvates etc, with one or more pharmaceutically acceptable carriers, diluents or excipients.

 It will be appreciated by those skilled in the art that certain protected derivatives of
20 compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as “prodrugs”. Further, certain compounds of the invention may act as prodrugs of other compounds of the invention. All protected
25 derivatives and prodrugs of compounds of the invention are included within the scope of the invention. Examples of suitable pro-drugs for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in “Design of Prodrugs” by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the
30 art, that certain moieties, known to those skilled in the art as “pro-moieties”, for example as described by H. Bundgaard in “Design of Prodrugs” (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within compounds of the invention. Preferred prodrugs for compounds of the invention include : esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides,
35 carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, more preferably 5 mg to 100 mg of a compound of the formula (I), depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association a compound of formula (I) with the carrier(s) or excipient(s).

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginat, gelatin, or polyvinyl

pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of a compound of formula (I). Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit pharmaceutical compositions for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

Pharmaceutical compositions adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical compositions adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The pharmaceutical compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the pharmaceutical compositions may include other agents conventional in the art having regard to

the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the intended recipient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant prescribing the medication. However, an effective amount of a compound of formula (I) for the treatment of anemia will generally be in the range of 0.1 to 100 mg/kg body weight of recipient per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, etc., may be determined as a proportion of the effective amount of the compound of formula (I) *per se*. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

Definitions:

rt – room temperature,

DMF – dimethylformamide,

THF – tetrahydrofuran,

DBU -1,8-diazabicyclo[5.4.0]undec-7-ene,

TFA – Trifluoroacetic acid.

Chemical Background:

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention as prepared are given in the examples.

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I). Those skilled in the art will recognize if a stereocenter exists in compounds of formula (I). Accordingly, the

present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a compound is desired as a single enantiomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

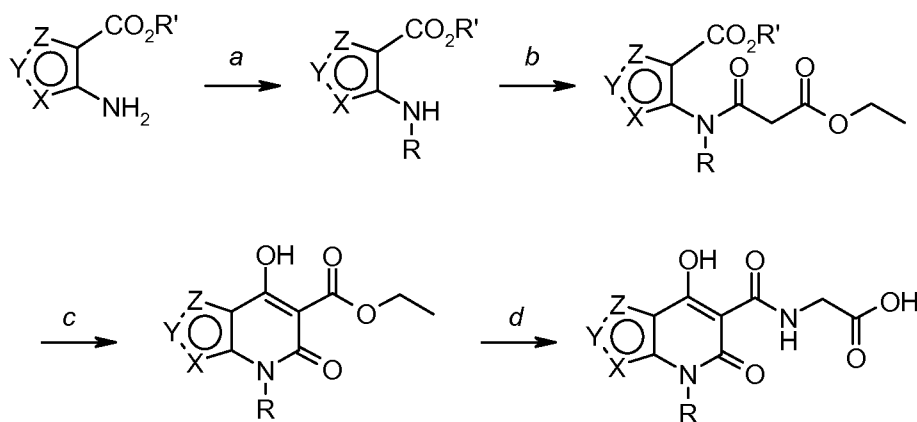
The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic and/or enzymatic processes. An illustrative method for making these starting compounds and intermediates can be found in a WIPO-published patent application, namely:

D. Chai, M. G. Darcy, D. Dhanak, K. J. Duffy, G. A. Erickson, D. M. Fitch, A. T. Gates, V. K. Johnston, R. T. Sarisky, M. J. Sharp, A. N. Shaw, R. Tedesco, K. J. Wiggall, M. N. Zimmerman "Quinolinythiadiazine dioxides as antiviral agents for treating hepatitis C" PCT Int. Appl. (2002), WO 2002098424 A1

See also M. G. Darcy, D. Dhanak, K. J. Duffy, D. M. Fitch, R. T. Sarisky, A. N. Shaw, R. Tedesco, M. N. Zimmerman "Preparation of 1,1-dioxodihydrobenzothiadiazines as antiviral agents" PCT Int. Appl. (2003), WO 2003059356 A2.

Illustrated Methods of preparation

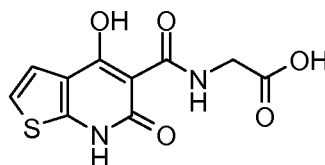
Scheme 1



a) $\text{Na}(\text{OAc})_3\text{BH}$, AcOH, RCHO, CH_2Cl_2 , rt; b) $\text{ClC}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, Et_3N , CH_2Cl_2 ; c) NaOEt or NaH, THF; d) glycine, DBU, EtOH, μwave or glycine sodium salt, EtOH, μwave .

Experimentals

Example 1



N-[(4-Hydroxy-6-oxo-6,7-dihydrothieno[2,3-b]pyridin-5-yl)carbonyl]glycine

5 1a) Methyl 2-{[3-(ethyloxy)-3-oxopropanoyl]amino}-3-thiophenecarboxylate

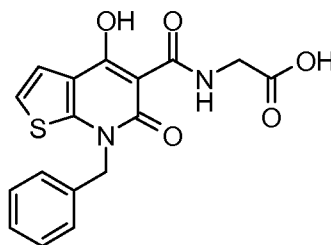
To a solution of methyl 2-amino-3-thiophenecarboxylate (2.00 g, 12.7 mmol) and triethyl amine (3.50 mL, 25.2 mmol) in methylene chloride (20.0 mL) was added ethyl 3-chloro-3-oxopropanoate (1.76 mL, 14.0 mmol) dropwise. The reaction was stirred for 3 h at ambient temperature and quenched with ice water. The mixture was extracted with ethyl acetate. The organic layer was dried over MgSO_4 , filtered, concentrated in vacuo, and purified *via* flash chromatography (0-100% ethyl acetate in hexanes) to afford the title compound as a yellow solid (1.20 g, 34%). ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm 12.1 (s, 1 H) 7.24 (d, $J=5.8$ Hz, 1 H) 6.78 (d, $J=5.8$ Hz, 1 H) 4.33 (q, $J=7.1$ Hz, 2 H) 3.94 (s, 3 H) 3.62 (s, 2 H) 1.34 (t, $J=7.2$ Hz, 3 H). MS(ES+) m/e 272 $[\text{M}+\text{H}]^+$.

15 1b) Ethyl 4-hydroxy-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-5-carboxylate

To a solution of compound from example 1a) (0.150 g, 0.55 mmol) in THF (10.0 mL) was added NaH (0.066 g, 60% dispersion in mineral oil, 1.65 mmol). The reaction was stirred overnight at ambient temperature and quenched with ice water. The mixture was extracted with ethyl acetate. The organic layer was dried over MgSO_4 , filtered, concentrated in vacuo, and purified *via* flash chromatography (0-100% ethyl acetate in hexanes) to afford the title compound as a yellow solid (0.080 g, 65%). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.24 (d, $J=8.0$ Hz, 1 H) 7.20 (d, $J=8.0$ Hz, 1 H) 4.30 (q, $J=7.1$ Hz, 2 H) 1.31 (t, $J=7.1$ Hz, 3 H). MS(ES+) m/e 240 $[\text{M}+\text{H}]^+$.

3c) N-[(4-hydroxy-6-oxo-6,7-dihydrothieno[2,3-b]pyridin-5-yl)carbonyl]glycine

A mixture of the compound from Example 1b) (0.080 g, 0.33 mmol), glycine (0.040 g, 0.53 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.10 mL, 0.70 mmol) in ethanol (3.0 mL) was heated to 180°C for 20 min. in a Biotage Initiator microwave synthesizer (<http://www.biotage.com/DynPage.aspx?id=22001>). The mixture was purified via preparative HPLC (YMC 75 X 30 mm column, 0.1% TFA in water and 0.1% TFA in acetonitrile) to afford the title compound as a yellow solid (0.035 g, 40%). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 12.7 (s, 1 H) 10.4 (t, $J=5.6$ Hz, 1 H) 7.25 (d, $J=5.6$ Hz, 1 H) 7.23 (d, $J=5.6$ Hz, 1 H) 4.10 (d, $J=5.8$ Hz, 2 H). MS(ES+) m/e 269 $[\text{M}+\text{H}]^+$.

Example 2

N-([4-hydroxy-6-oxo-7-(phenylmethyl)-6,7-dihydrothieno[2,3-b]pyridin-5-yl]carbonyl)glycine

5 2a) Methyl 2-[(phenylmethyl)amino]-3-thiophenecarboxylate

To a solution of benzaldehyde (0.85 mL, 8.40 mmol) and methyl 2-amino-3-thiophenecarboxylate (1.20 g, 7.60 mmol) in CH₂Cl₂ (20.0 mL) was added sodium triacetoxyborohydride (2.10 g, 9.90 mmol) and acetic acid (0.42 mL, 7.60 mmol). The mixture was stirred overnight at ambient temperature, quenched with water and extracted with CH₂Cl₂.

10 The organic layer was dried over MgSO₄, filtered, concentrated in vacuo, and purified *via* flash chromatography (0-100% ethyl acetate in hexane) to afford the title compound as a yellow oil (1.20 g, 64%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.83 (s, 1 H) 7.30 - 7.40 (m, 5 H) 7.06 (d, *J*=5.81 Hz, 1 H) 6.19 (dd, *J*=5.81, 1.01 Hz, 1 H) 4.46 (d, *J*=5.81 Hz, 2 H) 3.82 (s, 3 H). MS(ES+) *m/e* 248 [M+H]⁺.

15 2b) Methyl 2-[[3-(ethyloxy)-3-oxopropanoyl](phenylmethyl)amino]-3-thiophenecarboxylate

Following the procedure of Example 1a), except substituting the compound from Example 2a) for methyl 2-amino-3-thiophenecarboxylate, the title compound was obtained as a yellow oil. MS(ES+) *m/e* 362 [M+H]⁺.

20 2c) Ethyl 4-hydroxy-6-oxo-7-(phenylmethyl)-6,7-dihydrothieno[2,3-b]pyridine-5-carboxylate

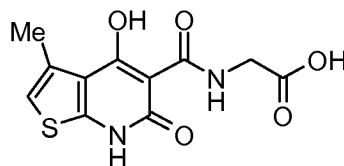
To a solution of the compound from Example 2b) (0.69 g, 2.79 mmol) in THF (10.0 mL) was added NaOEt (2.08 mL, 21% in ethanol, 5.58 mmol). The reaction was stirred at ambient temperature overnight, quenched with ice water and neutralized with 1N HCl. The mixture was extracted with ethyl acetate. The organic layer was dried over MgSO₄, filtered, concentrated in vacuo, and purified *via* flash chromatography (0-100% ethyl acetate in hexane) to afford the title compound as a yellow solid (0.56 g, 61%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.2 (s, 1 H) 7.16 - 7.49 (m, 7 H) 5.26 (s, 2 H) 4.33 (q, *J*=7.1 Hz, 2 H) 1.31 (t, *J*=7.2 Hz, 3 H). MS(ES+) *m/e* 330 [M+H]⁺.

30 2d) N-([4-Hydroxy-6-oxo-7-(phenylmethyl)-6,7-dihydrothieno[2,3-b]pyridin-5-yl]carbonyl)glycine

Following the procedure of Example 1c), except substituting the compound from Example 2c) for the compound from Example 1b), the title compound was obtained as a grey solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 13.0 (s, 1 H) 10.4 (t, $J=5.3$ Hz, 1 H) 6.97 - 7.44 (m, 7 H) 5.36 (s, 2 H) 4.10 (d, $J=5.3$ Hz, 2 H). MS(ES+) m/e 359 $[\text{M}+\text{H}]^+$.

5

Example 3



N-[(4-hydroxy-3-methyl-6-oxo-6,7-dihydrothieno[2,3-b]pyridin-5-yl)carbonyl]glycine

3a) Ethyl 2-{[3-(ethyloxy)-3-oxopropanoyl]amino}-4-methyl-3-thiophenecarboxylate

10

Following the procedure of Example 1a), except substituting ethyl 2-amino-5-methyl-3-thiophenecarboxylate for methyl 2-amino-3-thiophenecarboxylate, the title compound was obtained as a white solid. ^1H NMR (400 MHz, $\text{CHLOROFORM}-d$) δ ppm 6.44 (s, 1 H) 4.43 (q, $J=7.2$ Hz, 2 H) 4.31 (q, $J=7.2$ Hz, 2 H) 3.60 (s, 2 H) 2.40 (s, 3 H) 1.42 (t, $J=7.1$ Hz, 3 H) 1.34 (t, $J=7.2$ Hz, 3 H). MS(ES+) m/e 300 $[\text{M}+\text{H}]^+$.

15

3b) Ethyl 4-hydroxy-3-methyl-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-5-carboxylate

Following the procedure of Example 2c), except substituting the compound from Example 3a) for the compound from Example 2b), the title compound was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 6.71 (s, 1 H) 4.31 (q, $J=7.2$ Hz, 2 H) 2.39 (s, 3 H) 1.29 (t, $J=7.2$ Hz, 3 H). MS(ES+) m/e 254 $[\text{M}+\text{H}]^+$.

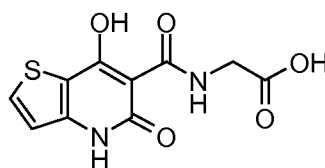
20

3c) N-[(4-Hydroxy-3-methyl-6-oxo-6,7-dihydrothieno[2,3-b]pyridin-5-yl)carbonyl]glycine

Following the procedure of Example 1c), except substituting the compound from Example 3b) for the compound from Example 1b), the title compound was obtained as a grey solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.9 (s, 1 H) 12.7 (s, 1 H) 10.4 (t, $J=5.6$ Hz, 1 H) 6.82 (s, 1 H) 4.10 (d, $J=5.6$ Hz, 2 H) 2.42 (s, 3 H). MS(ES+) m/e 283 $[\text{M}+\text{H}]^+$.

25

Example 4



N-[(7-hydroxy-5-oxo-4,5-dihydrothieno[3,2-b]pyridin-6-yl)carbonyl]glycine

4a) Methyl 3-{[3-(ethyloxy)-3-oxopropanoyl]amino}-2-thiophenecarboxylate

Following the procedure of Example 1a), except substituting methyl 3-amino-2-thiophenecarboxylate for methyl 2-amino-3-thiophenecarboxylate, the title compound was obtained as a yellow oil. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 11.1 (s, 1 H) 8.11 (d, $J=5.6$ Hz, 1 H) 7.46 (d, $J=5.6$ Hz, 1 H) 4.28 (q, $J=7.1$ Hz, 2 H) 3.91 (s, 3 H) 3.53 (s, 2 H) 1.31 (t, $J=7.2$ Hz, 3 H). MS(ES+) m/e 272 $[\text{M}+\text{H}]^+$.

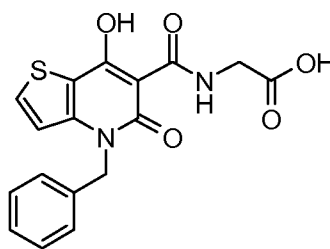
4b) Ethyl 7-hydroxy-5-oxo-4,5-dihydrothieno[3,2-*b*]pyridine-6-carboxylate

Following the procedure of Example 2c), except substituting the compound from Example 4a) for the compound from Example 2b), the title compound was obtained as a yellow solid. MS(ES+) m/e 240 $[\text{M}+\text{H}]^+$.

4c) N-[(7-Hydroxy-5-oxo-4,5-dihydrothieno[3,2-*b*]pyridin-6-yl)carbonyl]glycine

Following the procedure of Example 1c), except substituting the compound from Example 4b) for the compound from Example 1b), the title compound was obtained as a yellow solid. ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.0 (s, 1 H) 12.4 (s, 1 H) 10.5 (t, $J=5.6$ Hz, 1 H) 8.15 (d, $J=5.3$ Hz, 1 H) 7.06 (d, $J=5.1$ Hz, 1 H) 4.11 (d, $J=5.6$ Hz, 2 H). MS(ES+) m/e 269 $[\text{M}+\text{H}]^+$.

Example 5



N-[(7-hydroxy-5-oxo-4-(phenylmethyl)-4,5-dihydrothieno[3,2-*b*]pyridin-6-yl)carbonyl]glycine

5a) Methyl 3-[(phenylmethyl)amino]-2-thiophenecarboxylate

Following the procedure of Example 2a), except substituting methyl 3-amino-2-thiophenecarboxylate for methyl 2-amino-3-thiophenecarboxylate, the title compound was obtained as a yellow solid. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.23 - 7.47 (m, 6 H) 6.59 (d, $J=5.6$ Hz, 1 H) 4.52 (s, 2 H) 3.85 (s, 3 H). MS(ES+) m/e 248 $[\text{M}+\text{H}]^+$.

5b) Methyl 3-[[3-(ethyloxy)-3-oxopropanoyl](phenylmethyl)amino]-2-

thiophenecarboxylate

Following the procedure of Example 1a), except substituting the compound from Example 5a) for methyl 2-amino-3-thiophenecarboxylate, the title compound was obtained as a yellow solid. MS(ES+) m/e 362 $[\text{M}+\text{H}]^+$.

5c) Ethyl 7-hydroxy-5-oxo-4-(phenylmethyl)-4,5-dihydrothieno[3,2-*b*]pyridine-6-

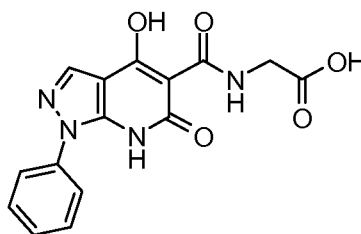
carboxylate

Following the procedure of Example 2c), except substituting the compound from Example 5b) for the compound from Example 2b), the title compound was obtained as a yellow solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.44 (d, *J*=5.3 Hz, 1 H) 7.17 - 7.30 (m, 5 H) 6.67 (d, *J*=5.3 Hz, 1 H) 4.14 (q, *J*=7.3 Hz, 2 H) 3.25 (s, 2 H) 1.25 (t, *J*=7.2 Hz, 3 H). MS(ES+) *m/e* 330 [M+H]⁺.

5d) N-{[7-Hydroxy-5-oxo-4-(phenylmethyl)-4,5-dihydrothieno[3,2-*b*]pyridin-6-yl]carbonyl}glycine

Following the procedure of Example 1c), except substituting the compound from Example 5c) for the compound from Example 1b), the title compound was obtained as a grey solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.9 (s, 1 H) 10.5 (t, *J*=5.6 Hz, 1 H) 8.21 (d, *J*=5.3 Hz, 1 H) 7.41 (d, *J*=5.6 Hz, 1 H) 7.30 - 7.36 (m, 2 H) 7.22 - 7.29 (m, 3 H) 5.47 (s, 2 H) 4.13 (d, *J*=5.6 Hz, 2 H). MS(ES+) *m/e* 359 [M+H]⁺.

Example 6



N-[(4-hydroxy-6-oxo-1-phenyl-6,7-dihydro-1H-pyrazolo[3,4-*b*]pyridin-5-yl)carbonyl]glycine

6a) Ethyl 5-{[3-(ethyloxy)-3-oxopropanoyl]amino}-1-phenyl-1H-pyrazole-4-carboxylate

Following the procedure of Example 1a), except substituting ethyl 5-amino-1-phenyl-1H-pyrazole-4-carboxylate for methyl 2-amino-3-thiophenecarboxylate, the title compound was obtained as a yellow solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.81 (s, 1 H) 8.05 (s, 1 H) 7.36 - 7.58 (m, 5 H) 4.35 (q, *J*=7.2 Hz, 2 H) 4.27 (q, *J*=7.2 Hz, 2 H) 3.38 (s, 2 H) 1.38 (t, *J*=7.2 Hz, 3 H) 1.32 (t, *J*=7.1 Hz, 3 H). MS(ES+) *m/e* 346 [M+H]⁺.

6b) Ethyl 4-hydroxy-6-oxo-1-phenyl-6,7-dihydro-1H-pyrazolo[3,4-*b*]pyridine-5-carboxylate

Following the procedure of Example 2c), except substituting the compound from Example 6a) for the compound from Example 2b), the title compound was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.2 (s, 1 H) 8.22 (d, *J*=7.8 Hz, 2 H) 7.75 (s, 1 H) 7.37 - 7.50 (m, 2 H) 7.20 (t, *J*=7.5 Hz, 1 H) 4.22 (q, *J*=7.1 Hz, 2 H) 1.27 (t, *J*=7.1 Hz, 3 H). MS(ES+) *m/e* 300 [M+H]⁺.

6c) N-[(4-Hydroxy-6-oxo-1-phenyl-6,7-dihydro-1H-pyrazolo[3,4-*b*]pyridin-5-yl)carbonyl]glycine

A mixture of the compound from Example 6b) (0.060 g, 0.20 mmol) and glycine sodium salt (0.039 g, 0.40 mmol) in ethanol (3.0 mL) was heated to 150 °C for 20 minutes in a Biotage Initiator microwave synthesizer. The reaction was quenched with water (10 mL) and neutralized with 1N aqueous HCl. The resulting precipitate was collected and dried in vacuo to afford the title compound as brown solid (0.051 g, 78%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.8 (s, 1 H) 12.5 (s, 1 H) 10.2 (t, *J*=5.6 Hz, 1 H) 8.21 (s, 1 H) 7.65 (d, *J*=6.8 Hz, 2 H) 7.57 (t, *J*=7.6 Hz, 2 H) 7.49 (t, *J*=7.2 Hz, 1 H) 4.10 (d, *J*=5.8 Hz, 2 H). MS(ES+) *m/e* 329 [M+H]⁺.

Biological Background:

The following references set out information about the target enzymes, HIF prolyl hydroxylases, and methods and materials for measuring inhibition of same by small molecules.

M. Hirsilä, P. Koivunen, V. Günzler, K. I. Kivirikko, and J. Myllyharju "Characterization of the Human Prolyl 4-Hydroxylases That Modify the Hypoxia-inducible Factor" *J. Biol. Chem.*, **2003**, 278, 30772-30780.

C. Willam, L. G. Nicholls, P. J. Ratcliffe, C. W. Pugh, P. H. Maxwell "The prolyl hydroxylase enzymes that act as oxygen sensors regulating destruction of hypoxia-inducible factor α" *Advan. Enzyme Regul.*, **2004**, 44, 75-92

M. S. Wiesener, J. S. Jürgensen, C. Rosenberger, C. K. Scholze, J. H. Hörstrup, C. Warnecke, S. Mandriota, I. Bechmann, U. A. Frei, C. W. Pugh, P. J. Ratcliffe, S. Bachmann, P. H. Maxwell, and K.-U. Eckardt "Widespread hypoxia-inducible expression of HIF-2α in distinct cell populations of different organs" *FASEB J.*, **2003**, 17, 271-273.

S. J. Klaus, C. J. Molineaux, T. B. Neff, V. Guenzler-Pukall, I. Lansetmo Parobok, T. W. Seeley, R. C. Stephenson "Use of hypoxia-inducible factor α (HIFα) stabilizers for enhancing erythropoiesis" PCT Int. Appl. (**2004**), WO 2004108121 A1

C. Warnecke, Z. Zaborowska, J. Kurreck, V. A. Erdmann, U. Frei, M. Wiesener, and K.-U. Eckardt "Differentiating the functional role of hypoxia-inducible factor (HIF)-1α and HIF-2α (EPAS-1) by the use of RNA interference: erythropoietin is a HIF-2α target gene in Hep3B and Kelly cells" *FASEB J.*, **2004**, 18, 1462-1464.

For the expression of *EGLN3* see:

R. K. Bruick and S. L. McKnight "A Conserved Family of Prolyl-4-Hydroxylases That Modify HIF" *Science*, **2001**, 294, 1337-1340.

For the expression of HIF2 α -CDD see:

a) P. Jaakkola, D. R. Mole, Y.-M. Tian, M. I. Wilson, J. Gielbert, S. J. Gaskell, A. von Kriegsheim, H. F. Hebestreit, M. Mukherji, C. J. Schofield, P. H. Maxwell, C. W. Pugh, P. J. Ratcliffe "Targeting of HIF- α to the von Hippel-Lindau Ubiquitylation Complex by O₂-Regulated Prolyl Hydroxylation" *Science*, **2001**, 292, 468-472.

b) M. Ivan, K. Kondo, H. Yang, W. Kim, J. Valiando, M. Ohh, A. Salic, J. M. Asara, W. S. Lane, W. G. Kaelin Jr. "HIF α Targeted for VHL-Mediated Destruction by Proline Hydroxylation: Implications for O₂ Sensing" *Science*, **2001**, 292, 464-468.

For the expression of VHL, elongin b and elongin c see:

A. Pause, S. Lee, R. A. Worrell, D. Y. T. Chen, W. H. Burgess, W. M. Linehan, R. D. Klausner "The von Hippel-Lindau tumor-suppressor gene product forms a stable complex with human CUL-2, a member of the Cdc53 family of proteins" *Proc. Natl. Acad. Sci. USA*, **1997**, 94, 2156-2161.

Biological Assay(s)

EGLN3 Assay

Materials:

His-MBP-EGLN3 (6HisMBPAttB1EGLN3(1-239)) was expressed in *E. Coli* and purified from an amylose affinity column. Biotin-VBC [6HisSumoCysVHL(2-213), 6HisSumoElonginB(1-118), and 6HisSumoElonginC(1-112)] and His-GB1-HIF2 α -CDD (6HisGB1tevHIF2A(467-572)) were expressed from *E. Coli*.

Method:

Cy5-labelled HIF2 α CDD, and a biotin-labeled VBC complex were used to determine EGLN3 inhibition. EGLN3 hydroxylation of the Cy5CDD substrate results in its recognition by the biotin-VBC. Addition of a Europium/streptavidin (Eu/SA) chelate results in proximity of Eu to Cy5 in the product, allowing for detection by energy transfer. A ratio of Cy5 to Eu emission (LANCE Ratio) is the ultimate readout, as this normalized parameter has significantly less variance than the Cy5 emission alone.

Then 50nL of inhibitors in DMSO (or DMSO controls) were stamped into a 384-well low volume Corning NBS plate, followed by addition of 2.5 μ L of enzyme [50 mL buffer (50 mM HEPES/50 mM KCl) + 1 mL of a 10 mg/mL BSA in buffer + 6.25 μ L of a 10mg/mL FeCl₂ solution in water + 100 μ L of a 200 mM solution of ascorbic acid in water + 15.63 μ L EGLN3] or control [50 mL buffer + 1 mL of a 10 mg/mL BSA in buffer + 6.25 μ L of a 10mg/mL FeCl₂ solution in water + 100 μ L of a 200 mM solution of ascorbic acid in water]. Following a 3 minutes

incubation, 2.5 μ L of substrate [50mL Buffer + 68.6 μ L biotin-VBC + 70.4 μ L Eu (at 710 μ g/mL stock) + 91.6 μ L Cy5CDD + 50 μ L of a 20 mM solution of 2-oxoglutaric acid in water + 0.3mM CHAPS] was added and incubated for 30 minutes. The plate was loaded into a PerkinElmer Viewlux for imaging. For dose response experiments, normalized data were fit by ABASE/XC50 using the equation $y = a + (b-a)/(1+(10^x/10^c)^d)$, where a is the minimum % activity, b is the maximum % activity, c is the pIC₅₀, and d is the Hill slope.

The IC₅₀ for exemplified compounds in the EGLN3 assay ranged from approximately 1 - 100 nanomolar. This range represents the data accumulated as of the time of the filing of this initial application. Later testing may show variations in IC₅₀ data due to variations in reagents, conditions and variations in the method(s) used from those given herein above. So this range is to be viewed as illustrative, and not a absolute set of numbers.

Measure Epo protein produced by Hep3B cell line using ELISA method.

Hep3B cells obtained from the American Type Culture Collection (ATCC) are seeded at 2x10⁴ cells/well in Dulbecco's Modified Eagle Medium (DMEM) + 10% FBS in 96-well plates. Cells are incubated at 37degC/5% CO2/90% humidity (standard cell culture incubation conditions). After overnight adherence, medium is removed and replaced with DMEM without serum containing test compound or DMSO negative control. Following 48 hours incubation, cell culture medium is collected and assayed by ELISA to quantitate Epo protein.

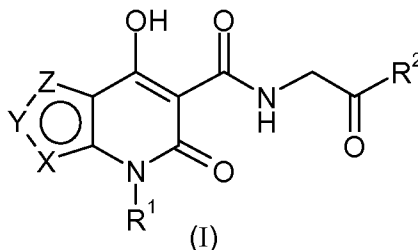
The EC₅₀ for exemplar compounds in the Hep3B ELISA assay ranged from approximately 1 - 20 micromolar using the reagents and under the conditions outlined herein above. This range represents the data accumulated as of the time of the filing of this initial application. Later testing may show variations in EC₅₀ data due to variations in reagents, conditions and variations in the method(s) used from those given herein above. So this range is to be viewed as illustrative, and not a absolute set of numbers.

These compound are believed to be useful in therapy as defined above and to not have unacceptable or untoward effects when used in compliance with a permitted therapeutic regime.

The foregoing examples and assay have been set forth to illustrate the invention, not limit it. What is reserved to the inventors is to be determined by reference to the claims.

What is claimed is:

1. A compound of formula (I):



5

wherein:

R¹ is hydrogen, -NR³R⁴, C₁-C₁₀alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₃-C₈cycloalkyl, C₁-C₁₀alkyl-C₃-C₈cycloalkyl, C₅-C₈cycloalkenyl, C₁-C₁₀alkyl-C₅-C₈cycloalkenyl, C₃-C₈heterocycloalkyl, C₁-C₁₀alkyl-C₃-C₈heterocycloalkyl, aryl, C₁-C₁₀alkyl-aryl, heteroaryl or C₁-C₁₀alkyl-heteroaryl;

10

R² is -NR⁶R⁷ or -OR⁸;

R³ and R⁴ are each independently selected from the group consisting of hydrogen, C₁-C₁₀alkyl, C₃-C₈cycloalkyl, C₁-C₁₀alkyl-C₃-C₈cycloalkyl, C₃-C₈heterocycloalkyl, C₁-C₁₀alkyl-C₃-C₈heterocycloalkyl, aryl, C₁-C₁₀alkyl-aryl, heteroaryl, C₁-C₁₀alkyl-heteroaryl, -CO(C₁-C₄alkyl), -CO(C₃-C₆cycloalkyl), -CO(C₃-C₆heterocycloalkyl), -CO(aryl), -CO(heteroaryl), -SO₂(C₁-C₄alkyl); or R³ and R⁴ taken together with the nitrogen to which they are attached form a 5- or 6- or 7-membered saturated ring optionally containing one other heteroatom which is oxygen, nitrogen or sulphur;

15

each R⁵ is independently selected from the group consisting of hydrogen, C₁-C₁₀alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, -CO(C₁-C₄alkyl), -CO(aryl), -CO(heteroaryl), -CO(C₃-C₆cycloalkyl), -CO(C₃-C₆heterocycloalkyl), -SO₂(C₁-C₄alkyl), C₃-C₈cycloalkyl, C₃-C₈heterocycloalkyl, C₆-C₁₄aryl, C₁-C₁₀alkyl-aryl, heteroaryl, and C₁-C₁₀alkyl-heteroaryl;

20

R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, C₁-C₁₀alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₃-C₈cycloalkyl, C₃-C₈heterocycloalkyl, aryl and heteroaryl;

25

R⁸ is H or a cation, or C₁-C₁₀alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C₃-C₆cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

X, Y, and Z are part of a 5-membered aromatic heterocycle and are independently CR⁹, O, N, NR¹⁰, or S, provided that at least one of the atoms X, Y, and Z is O, NR¹⁰, or S;

30

each R⁹ is independently selected from the group consisting of hydrogen, nitro, cyano, halogen, -C(O)R⁵, -C(O)OR⁵, -OR⁵, -SR⁵, -S(O)R⁵, -S(O)₂R⁵, -NR³R⁴, -CONR³R⁴, -N(R³)C(O)R⁵, -N(R³)C(O)OR⁵, -OC(O)NR³R⁴, -N(R³)C(O)NR³R⁴, -P(O)(OR⁵)₂, -SO₂NR³R⁴, -N(R³)SO₂R⁵,

C₁-C₁₀ alkyl, C₁-C₁₀ alkenyl, C₁-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, aryl and heteroaryl group;

each R¹⁰ is selected from the group consisting of hydrogen, cyano, -C(O)R⁵, -NR³R⁴, -CONR³R⁴, -N(R³)C(O)R⁵, -N(R³)C(O)OR⁵, -N(R³)C(O)NR³R⁴, -SO₂NR³R⁴, -N(R³)SO₂R⁵, C₁-C₁₀ alkyl, C₁-C₁₀ alkenyl, C₁-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, aryl and heteroaryl group;

any carbon or heteroatom of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ or R¹⁰ is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C₁-C₆ alkyl, aryl, heteroaryl, halogen, -OR⁵, -NR³R⁴, cyano, nitro, -C(O)R⁵, -C(O)OR⁵, -SR⁵, -S(O)R⁵, -S(O)₂R⁵, -NR³R⁴, -CONR³R⁴, -N(R³)C(O)R⁵, -N(R³)C(O)OR⁵, -OC(O)NR³R⁴, -N(R³)C(O)NR³R⁴, -SO₂NR³R⁴, -N(R³)SO₂R⁵, C₁-C₁₀ alkenyl, C₁-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, aryl or heteroaryl group, wherein R³, R⁴, and R⁵ are the same as defined above; or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 wherein:

X is sulphur, and Y and Z are CR⁹; or Z is sulphur, and Y and Z are CR⁹; or X is NR¹⁰, Y is N, and Z is CR⁹;

R¹ is hydrogen, C₁-C₁₀alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₃-C₈cycloalkyl, C₁-C₁₀alkyl-C₃-C₈cycloalkyl, or C₅-C₈cycloalkenyl, C₁-C₁₀alkyl-C₅-C₈cycloalkenyl, aryl, or C₁-C₁₀alkylaryl;

R² is -NR⁶R⁷ or -OR⁸;

R⁵ is independently selected from the group consisting of hydrogen, C₁-C₁₀alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, -CO(C₁-C₄ alkyl), -CO(aryl), -CO(heteroaryl), -SO₂(C₁-C₄ alkyl), C₃-C₈ cycloalkyl, C₃-C₈heterocycloalkyl, C₆-C₁₄ aryl, heteroaryl, and aryl-C₁-C₁₀ alkyl;

R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkyl-C₃-C₈cycloalkyl, C₃-C₈heterocycloalkyl, aryl, -CO(C₁-C₄ alkyl), or C₃-C₈ cycloalkyl-C₁-C₁₀ alkyl; or R⁶ and R⁷ taken together with the nitrogen to which they are attached form a 5- or 6-membered saturated ring;

R⁸ is H or a cation, or C₁-C₁₀alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C₃-C₆ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

R⁹ is hydrogen, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, C₁-C₁₀ alkyl-C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, C₁-C₁₀ alkyl-C₃-C₆ heterocycloalkyl, aryl, C₁-C₁₀ alkylaryl, or heteroaryl group;

R¹⁰ is selected from the group consisting of C₁-C₁₀alkyl, C₁-C₁₀alkenyl, C₁-C₁₀alkynyl, C₃-C₆cycloalkyl, C₃-C₆ heterocycloalkyl, aryl, C₁-C₁₀alkylaryl, heteroaryl or C₁-C₁₀alkylheteroaryl group;

any carbon or heteroatom of R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^9 or R^{10} is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, halogen, $-OR^5$, $-NR^6R^7$, $-C(O)OR^5$, $-OR^5$, $-CONR^6R^7$, $-N(R^6)C(O)R^5$, $-N(R^6)C(O)OR^5$, $-OC(O)NR^6R^7$, $-N(R^6)C(O)NR^6R^7$, or C_3 - C_6 cycloalkyl, wherein R^5 , R^6 , and R^7 are the same as

5 defined above; or

a pharmaceutically acceptable salt or solvate thereof.

3. A compound according to claim 2 wherein:

X is sulphur, and Y and Z are CR^9 ;

10 R^1 is hydrogen, C_1 - C_{10} alkyl, aryl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, or C_1 - C_{10} alkylaryl;

R^2 is $-NR^6R^7$ or $-OR^8$;

R^5 is independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, $-CO(C_1$ - C_4 alkyl), $-CO(aryl)$, $-CO(heteroaryl)$, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl,

15 C_3 - C_8 heterocycloalkyl, C_6 - C_{14} aryl, heteroaryl, and aryl- C_1 - C_{10} alkyl;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl, $-CO(C_1$ - C_4 alkyl), or C_3 - C_8 cycloalkyl- C_1 - C_{10} alkyl; or R^6 and R^7 taken together with the nitrogen to which they are attached form a 5- or 6-membered saturated ring;

20 R^8 is H or a cation, or C_1 - C_{10} alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C_3 - C_6 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^9 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_6 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 heterocycloalkyl, aryl, C_1 - C_{10} alkylaryl, or heteroaryl group;

25 any carbon or heteroatom of R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^9 or R^{10} is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, halogen, $-OR^5$, $-NR^6R^7$, $-C(O)OR^5$, $-OR^5$, $-CONR^6R^7$, wherein R^5 , R^6 , and R^7 are the same as defined above;

or a pharmaceutically acceptable salt or solvate thereof.

30

4. A compound according to claim 2 wherein:

Z is sulphur, and X and Y are CR^9 ;

R^1 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, aryl, or C_1 - C_{10} alkylaryl;

35 R^2 is $-NR^6R^7$ or $-OR^8$;

R^5 is independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, $-CO(C_1$ - C_4 alkyl), $-CO(aryl)$, $-CO(heteroaryl)$, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_6 - C_{14} aryl, heteroaryl, and aryl- C_1 - C_{10} alkyl;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl, $-CO(C_1$ - C_4 alkyl), or C_3 - C_8 cycloalkyl- C_1 - C_{10} alkyl; or R^6 and R^7 taken together with the nitrogen to which they are attached form a 5- or 6-membered saturated ring;

R^8 is H or a cation, or C_1 - C_{10} alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C_3 - C_6 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^9 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_6 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 heterocycloalkyl, aryl, C_1 - C_{10} alkylaryl, or heteroaryl group;

any carbon or heteroatom of R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^9 or R^{10} is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, halogen, $-OR^5$, $-NR^6R^7$, $-C(O)OR^5$, $-OR^5$, $-CONR^6R^7$, wherein R^5 , R^6 , and R^7 are the same as defined above;

or a pharmaceutically acceptable salt or solvate thereof.

5. A compound according to claim 2 wherein:

X is NR^{10} , Y is N , and Z is CR^9 ;

R^1 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, aryl, or C_1 - C_{10} alkylaryl;

R^2 is $-NR^6R^7$ or $-OR^8$;

R^5 is independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, $-CO(C_1$ - C_4 alkyl), $-CO(aryl)$, $-CO(heteroaryl)$, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_6 - C_{14} aryl, heteroaryl, and aryl- C_1 - C_{10} alkyl;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl, $-CO(C_1$ - C_4 alkyl), or C_3 - C_8 cycloalkyl- C_1 - C_{10} alkyl; or R^6 and R^7 taken together with the nitrogen to which they are attached form a 5- or 6-membered saturated ring;

R^8 is H or a cation, or C_1 - C_{10} alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C_3 - C_6 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^9 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_6 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 heterocycloalkyl, aryl, C_1 - C_{10} alkylaryl, or heteroaryl group; or

any carbon or heteroatom of $R^1, R^2, R^5, R^6, R^7, R^8, R^9$ or R^{10} is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, halogen, $-OR^5$, $-NR^6R^7$, $-C(O)OR^5$, $-OR^5$, $-CONR^6R^7$, wherein R^5, R^6 , and R^7 are the same as defined above; or

5 a pharmaceutically acceptable salt or solvate thereof

6. A compound according to claim 3 wherein:

X is sulphur and Y and Z are CR^9 ;

R^1 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, or

10 C_1 - C_{10} alkylaryl;

R^2 is $-NR^6R^7$ or $-OR^8$;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl, $-CO(C_1$ - C_4 alkyl), or C_3 - C_8 cycloalkyl- C_1 - C_{10} alkyl; or R^6 and R^7 taken together with the nitrogen to which they are attached

15 form a 5- or 6-membered saturated ring;

R^8 is H or a cation, or C_1 - C_{10} alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C_3 - C_6 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^9 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_6 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 cycloalkyl, C_3 - C_6

20 heterocycloalkyl, C_1 - C_{10} alkyl- C_3 - C_6 heterocycloalkyl, aryl, C_1 - C_{10} alkylaryl, or heteroaryl group; or

any carbon or heteroatom of $R^1, R^2, R^5, R^6, R^7, R^8, R^9$ or R^{10} is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, halogen, $-OR^5$, $-NR^6R^7$, $-C(O)OR^5$, $-OR^5$, $-CONR^6R^7$, wherein R^5, R^6 , and R^7 are the same as

25 defined above;

or a pharmaceutically acceptable salt or solvate thereof.

7. A compound according to claim 4 wherein

Z is sulphur, and Y and Z are CR^9 ;

30 R^1 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, or C_1 - C_{10} alkylaryl;

R^2 is $-NR^6R^7$ or $-OR^8$;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl, $-CO(C_1$ - C_4 alkyl), or C_3 - C_8

35 cycloalkyl- C_1 - C_{10} alkyl; or R^6 and R^7 taken together with the nitrogen to which they are attached form a 5- or 6-membered saturated ring;

R⁸ is H or a cation, or C₁-C₁₀alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C₃-C₆ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R⁹ is hydrogen, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, C₁-C₁₀ alkyl-C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, C₁-C₁₀ alkyl-C₃-C₆ heterocycloalkyl, aryl, C₁-C₁₀ alkylaryl, or heteroaryl group;

or
any carbon or heteroatom of R¹, R², R⁵, R⁶, R⁷, R⁸, R⁹ or R¹⁰ is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C₁-C₆ alkyl, aryl, halogen, -OR⁵, -NR⁶R⁷, -C(O)OR⁵, -OR⁵, -CONR⁶R⁷, wherein R⁵, R⁶, and R⁷ are the same as defined above;

or a pharmaceutically acceptable salt or solvate thereof.

8. A compound according to claim 5 wherein

X is NR¹⁰, Y is N, and Z is CR⁹;

R¹ is hydrogen, C₁-C₁₀alkyl, C₃-C₈cycloalkyl, C₁-C₁₀alkyl-C₃-C₈cycloalkyl, or C₁-C₁₀alkylaryl;

R² is -NR⁶R⁷ or -OR⁸;

R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkyl-C₃-C₈cycloalkyl, C₃-C₈heterocycloalkyl, aryl, -CO(C₁-C₄ alkyl), or C₃-C₈ cycloalkyl-C₁-C₁₀ alkyl; or R⁶ and R⁷ taken together with the nitrogen to which they are attached form a 5- or 6-membered saturated ring;

R⁸ is H or a cation, or C₁-C₁₀alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C₃-C₆ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R⁹ is hydrogen, C₁-C₁₀ alkyl, C₃-C₆ cycloalkyl, C₁-C₁₀ alkyl-C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, C₁-C₁₀ alkyl-C₃-C₆ heterocycloalkyl, aryl, C₁-C₁₀ alkylaryl, or heteroaryl group;

or
any carbon or heteroatom of R¹, R², R⁵, R⁶, R⁷, R⁸, R⁹ or R¹⁰ is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C₁-C₆ alkyl, aryl, halogen, -OR⁵, -NR⁶R⁷, -C(O)OR⁵, -OR⁵, -CONR⁶R⁷, wherein R⁵, R⁶, and R⁷ are the same as defined above;

or a pharmaceutically acceptable salt or solvate thereof.

9. A compound according to claim 1 which is:

N-[(4-hydroxy-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridin-5-yl)carbonyl]glycine;

N-{[4-hydroxy-6-oxo-7-(phenylmethyl)-6,7-dihydrothieno[2,3-*b*]pyridin-5-yl]carbonyl}glycine;

N-[(4-hydroxy-3-methyl-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridin-5-yl)carbonyl]glycine;

N-[(7-hydroxy-5-oxo-4,5-dihydrothieno[3,2-*b*]pyridin-6-yl)carbonyl]glycine;

5 *N*-{[7-hydroxy-5-oxo-4-(phenylmethyl)-4,5-dihydrothieno[3,2-*b*]pyridin-6-yl]carbonyl}glycine; and

N-[(4-hydroxy-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)carbonyl]glycine;

or a pharmaceutically acceptable salt or solvate thereof.

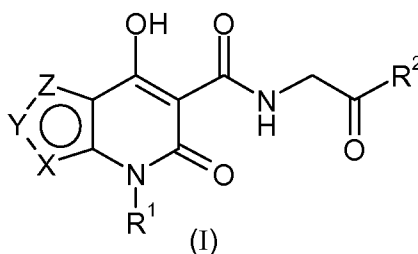
10

10. A method for treating anemia in a mammal, which method comprises administering an effective amount of a compound of formula (I) or a salt or solvate thereof according to claim 1 to a mammalian suffering from anemia which can be treated by inhibiting HIF prolyl hydroxylases.

15 11. A pharmaceutical composition comprising a compound of formula (I) or a salt, solvate, according to claim 1 and one or more of pharmaceutically acceptable carriers, diluents and excipients.

12. A process for preparing a compound of formula (I)

20



wherein:

25 R^1 is hydrogen, $-NR^3R^4$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_5 - C_8 cycloalkenyl, C_1 - C_{10} alkyl- C_5 - C_8 cycloalkenyl, C_3 - C_8 heterocycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 heterocycloalkyl, aryl, C_1 - C_{10} alkyl-aryl, heteroaryl or C_1 - C_{10} alkyl-heteroaryl;

R^2 is $-NR^6R^7$ or $-OR^8$;

30 R^3 and R^4 are each independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_1 - C_{10} alkyl- C_3 - C_8 heterocycloalkyl, aryl, C_1 - C_{10} alkyl-aryl, heteroaryl, C_1 - C_{10} alkyl-heteroaryl, $-CO(C_1$ - C_4 alkyl), $-CO(C_3$ - C_6 cycloalkyl), $-CO(C_3$ - C_6 heterocycloalkyl), $-CO(aryl)$, $-CO(heteroaryl)$, $-SO_2(C_1$ - C_4

alkyl); or R³ and R⁴ taken together with the nitrogen to which they are attached form a 5- or 6- or 7-membered saturated ring optionally containing one other heteroatom selected from oxygen, nitrogen and sulphur;

R⁶ and R⁷ are each independently selected from the group consisting of hydrogen, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₃-C₈ heterocycloalkyl, aryl and heteroaryl;

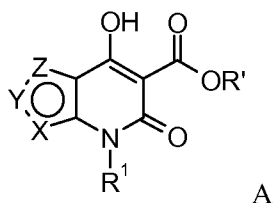
R⁸ is H or a cation, or C₁-C₁₀alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C₃-C₆ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

X, Y, and Z are part of a 5-membered aromatic heterocycle and are independently selected from CR⁹, O, N, NR¹⁰, and S, provided that at least one of the atoms X, Y, and Z is O, NR¹⁰, or S;

each R⁹ is independently selected from the group consisting of hydrogen, nitro, cyano, halogen, -C(O)R⁵, -C(O)OR⁵, -OR⁵, -SR⁵, -S(O)R⁵, -S(O)₂R⁵, -NR³R⁴, -CONR³R⁴, -N(R³)C(O)R⁵, -N(R³)C(O)OR⁵, -OC(O)NR³R⁴, -N(R³)C(O)NR³R⁴, -P(O)(OR⁵)₂, -SO₂NR³R⁴, -N(R³)SO₂R⁵ and a C₁-C₁₀ alkyl, C₁-C₁₀ alkenyl, C₁-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, aryl and heteroaryl group;

each R¹⁰ is selected from the group consisting of hydrogen, cyano, -C(O)R⁵, -NR³R⁴, -CONR³R⁴, -N(R³)C(O)R⁵, -N(R³)C(O)OR⁵, -N(R³)C(O)NR³R⁴, -SO₂NR³R⁴, -N(R³)SO₂R⁵ and a C₁-C₁₀ alkyl, C₁-C₁₀ alkenyl, C₁-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, aryl and heteroaryl group,

each R⁵ is independently selected from the group consisting of hydrogen, C₁-C₁₀alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, -CO(C₁-C₄ alkyl), -CO(aryl), -CO(heteroaryl), -CO(C₃-C₆ cycloalkyl), -CO(C₃-C₆ heterocycloalkyl), -SO₂(C₁-C₄ alkyl), C₃-C₈ cycloalkyl, C₃-C₈heterocycloalkyl, C₆-C₁₄ aryl, C₁-C₁₀alkyl-aryl, heteroaryl, and C₁-C₁₀alkyl-heteroaryl; where any carbon or heteroatom of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ or R¹⁰ is unsubstituted or, where possible, is substituted with one or more substituents independently selected from C₁-C₆ alkyl, aryl, heteroaryl, halogen, -OR⁵, -NR³R⁴, cyano, nitro, -C(O)R⁵, -C(O)OR⁵, -SR⁵, -S(O)R⁵, -S(O)₂R⁵, -NR³R⁴, -CONR³R⁴, -N(R³)C(O)R⁵, -N(R³)C(O)OR⁵, -OC(O)NR³R⁴, -N(R³)C(O)NR³R⁴, -SO₂NR³R⁴, -N(R³)SO₂R⁵, C₁-C₁₀ alkenyl, C₁-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, aryl or heteroaryl group, wherein R³, R⁴, and R⁵ are the same as defined above; comprising treating a compound of formula A:



wherein R^1 , X, Y and Z are the same as for those groups in formula (I) and R' is a ester-forming group, with glycine sodium salt or glycine and an appropriate base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium ethoxide or sodium hydride, in an appropriate solvent, such as ethanol or 1,4-dioxane, under either conventional thermal conditions or by microwave irradiation, to form a compound of formula (I) where R^2 is -OH.

5