

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 April 2007 (19.04.2007)

PCT

(10) International Publication Number
WO 2007/044982 A2

(51) International Patent Classification:
A61K 31/655 (2006.01)

(21) International Application Number:
PCT/US2006/040494

(22) International Filing Date: 13 October 2006 (13.10.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/726,249 13 October 2005 (13.10.2005) US

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

AT, AU, AZ, BA, BB, BG, 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, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, 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, 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: METHODS FOR THE PRESERVATION OF PLATELET EFFICACY DURING STORAGE

(57) Abstract: Invented is a method for the preservation of human platelet lifespan and/or efficacy during storage which comprises the addition of an effective amount of a non-peptide TPO receptor agonists to a storage solution containing human platelets.



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METHODS FOR THE PRESERVATION OF PLATELET EFFICACY
DURING STORAGE

FIELD OF THE INVENTION

5 This invention relates to non-peptide thrombopoietin (TPO) receptor agonists and their use in the preservation of human platelet lifespan and/or efficacy during storage.

BACKGROUND OF THE INVENTION

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 During storage, platelets undergo a gradual decrease in their efficacy upon tranfusion, as a result of two related processes: loss of cell viability and loss of cell function. These two processes are interconnected: loss of viability leads to loss of function, though loss of function may occur independently of changes in cell viability. Efforts to improve platelet viability and/or platelet function during storage is on going. The loss of cellular viability is associated with a rise in the LDH and lactate content in the storage bag, a drop in the pH, and a wide range of other metabolic phenomena. Characteristic morphologic alterations also occur that are associated with a deterioration of basic metabolic parameters. Efforts to reverse this loss of viability have included the introduction of more effective storage bags that allow better gas exchange and storage at 22 to 24° C. Although inextricably linked to the loss of cellular viability, the loss of cell function has been associated with a decrease in reactivity to weak platelet agonists.

 Thrombopoietin (TPO) has been shown to be the main humoral regulator in situations involving thrombocytopenia. See, e.g., Metcalf Nature 369:519-520 (1994). TPO has been shown in several studies to increase platelet counts, increase platelet size, and increase isotope incorporation into platelets of recipient animals. Because platelets (thrombocytes) are necessary for blood clotting and when their numbers are very low a patient is at risk of death from catastrophic hemorrhage, TPO is considered to have potential useful applications in both the diagnosis and the treatment of various hematological disorders, for example, diseases primarily due to platelet defects. In addition, studies have provided a basis for the projection of efficacy of TPO therapy in the treatment of thrombocytopenia, and particularly thrombocytopenia resulting from chemotherapy, radiation therapy, or bone marrow transplantation as treatment for cancer or

lymphoma. See e.g., McDonald (1992) Am. J. Ped. Hematology/Oncology 14: 8-21 (1992).

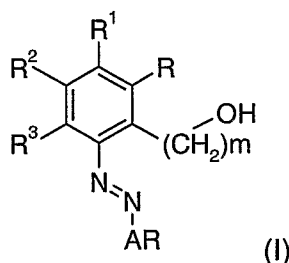
The slow recovery of platelet levels in patients suffering from thrombocytopenia is a serious problem, and has lead to the search for small molecule non-peptide TPO receptor agonists that are able to accelerate platelet regeneration. (e.g. see, International Application No. PCT/US01/16863, having an International filing date of May 24, 2001; International Publication Number WO 01/89457 and an International Publication date of November 29, 2001).

The present invention relates to a novel use of a known class of compounds, non-peptide TPO receptor agonists. The present invention concerns methods for the preservation of human platelet lifespan and/or efficacy during storage.

SUMMARY OF THE INVENTION

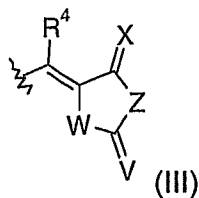
This invention relates to methods for the preservation of human platelet life span and/or efficacy during storage which comprises the addition of an effective amount of a non-peptide TPO receptor agonists to a storage solution containing human platelets.

Included among the non-peptide TPO receptor agonists of the invention are compounds of Formula (I):



wherein:

R, R¹, R² and R³ are each independently selected from hydrogen, C₁-₆alkyl, -(CH₂)_pOR⁴, -C(O)OR⁴, formyl, nitro, cyano, halogen, aryl, substituted aryl, substituted alkyl, -S(O)_nR⁴, cycloalkyl, -NR⁵R⁶, protected -OH, -CONR⁵R⁶, phosphonic acid, sulfonic acid, phosphinic acid, -SO₂NR⁵R⁶, and a heterocyclic methylene substituent as represented by Formula (III),



where,

p is 0-6,

n is 0-2,

- 5 V, W, X and Z are each independently selected from O, S and NR¹⁶,
 where R¹⁶ is selected from: hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl,
 substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl,
 R⁴ is selected from: hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted
 alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and
 10 R⁵ and R⁶ are each independently selected from hydrogen, alkyl,
 substituted alkyl, C₃₋₆cycloalkyl, and aryl,
 or R⁵ and R⁶ taken together with the nitrogen to which they are attached
 represent a 5 to 6 member saturated ring containing up to one other
 heteroatom selected from oxygen and nitrogen;

15

m is 0-6; and

- AR is a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon
 atoms and optionally containing one or more heteroatoms, provided that
 20 when the number of carbon atoms is 3 the aromatic ring contains at least
 two heteroatoms and when the number of carbon atoms is 4 the aromatic
 ring contains at least one heteroatom, and optionally substituted with one
 or more substituents selected from the group consisting of: alkyl,
 substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo,
 25 hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano,
 halogen, -C(O)OR⁴, -C(O)NR¹⁰R¹¹, -S(O)₂NR¹⁰R¹¹, -S(O)_nR⁴ and
 protected -OH,
 where n is 0-2,
 R⁴ is hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted
 30 cycloalkyl and substituted C₁-C₁₂aryl, and
 R¹⁰ and R¹¹ are independently hydrogen, cycloalkyl, C₁-C₁₂aryl,
 substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted
 with one or more substituents selected from the group consisting of:

alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^4$, $-S(O)_nR^4$, $-C(O)NR^4R^4$, $-S(O)_2NR^4R^4$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected $-OH$, or R^{10} and R^{11} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where R^4 is as described above and n is 0-2;

and/or pharmaceutically acceptable salts, hydrates, solvates and esters thereof;

provided that at least one of R , R^1 , R^2 and R^3 is a substituted aryl group or a heterocyclic methylene substituent as represented in Formula (III).

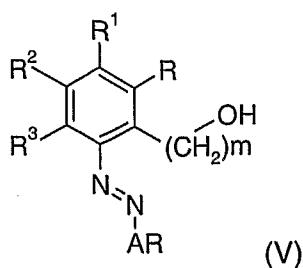
This invention relates to methods for the preservation of human platelet lifespan and/or efficacy during storage which comprises the addition of an effective amount of a non-peptide TPO receptor agonists of Formula (I) to a storage solution containing human platelets.

Also included in the present invention are methods for the preservation of human platelet lifespan and/or efficacy during storage which comprises the co-addition of non-peptide TPO receptor agonists with further active ingredients to a storage solution containing human platelets.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to methods for the preservation of human platelet lifespan and/or efficacy during storage which comprises the addition of an effective amount of a non-peptide TPO receptor agonists, including compounds of Formula (I) as described above, to a storage solution containing human platelets.

Included among the compounds that are useful in the present invention are those having Formula (V):



wherein:

5 R, R¹, R² and R³ are each independently selected from hydrogen, C₁-
6alkyl, C₁-6alkoxy, -(CH₂)_pOR⁴, -C(O)OR⁴, formyl, nitro, cyano, halogen,
aryl, substituted aryl, substituted alkyl, -S(O)_nR⁴, cycloalkyl, -NR⁵R⁶,
protected -OH, -CONR⁵R⁶, phosphonic acid, sulfonic acid, phosphinic
acid and -SO₂NR⁵R⁶,

where,
10 p is 0-6,
n is 0-2,

R⁴ is selected from: hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted
alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and
R⁵ and R⁶ are each independently selected from hydrogen, alkyl,
15 substituted alkyl, C₃-6cycloalkyl, and aryl,
or R⁵ and R⁶ taken together with the nitrogen to which they are attached
represent a 5 to 6 member saturated ring containing up to one other
heteroatom selected from oxygen and nitrogen;

20 m is 0-6; and

AR is a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon
atoms and optionally containing one or more heteroatoms, provided that
when the number of carbon atoms is 3 the aromatic ring contains at least
25 two heteroatoms and when the number of carbon atoms is 4 the aromatic
ring contains at least one heteroatom, and optionally substituted with one
or more substituents selected from the group consisting of: alkyl,
substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo,
hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano,
30 halogen, -C(O)OR⁴, -C(O)NR¹⁰R¹¹, -S(O)₂NR¹⁰R¹¹, -S(O)_nR⁴ and
protected -OH,
where n is 0-2,

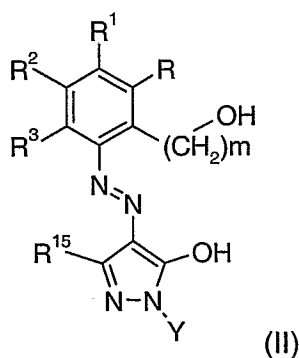
R^4 is hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl; and

R^{10} and R^{11} are independently hydrogen, cycloalkyl, C_1 - C_{12} aryl, substituted cycloalkyl, substituted C_1 - C_{12} aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^4$, $-S(O)_nR^4$, $-C(O)NR^4R^4$, $-S(O)_2NR^4R^4$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected $-OH$, or R^{10} and R^{11} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where R^4 is as described above and n is 0-2;

and/or pharmaceutically acceptable salts, hydrates, solvates and esters thereof;

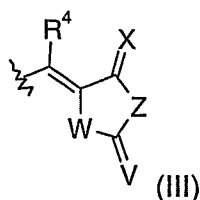
provided that at least one of R , R^1 , R^2 and R^3 is a substituted aryl group.

Included among the compounds that are useful in the present invention are those having Formula (II):



wherein:

R , R^1 , R^2 and R^3 are each independently selected from hydrogen, C_1 - C_6 alkyl, $-(CH_2)_pOR^4$, $-C(O)OR^4$, formyl, nitro, cyano, halogen, aryl, substituted aryl, substituted alkyl, $-S(O)_nR^4$, cycloalkyl, $-NR^5R^6$, protected $-OH$, $-CONR^5R^6$, phosphonic acid, sulfonic acid, phosphinic acid, $-SO_2NR^5R^6$, and a heterocyclic methylene substituent as represented by Formula (III),



where

p is 0-6,

n is 0-2,

5 V, W, X and Z are each independently selected from O, S, and NR¹⁶,
 where R¹⁶ is selected from: hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl,
 substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl,
 R⁴ is hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted
 cycloalkyl and substituted C₁-C₁₂aryl, and
 10 R⁵ and R⁶ are each independently selected from hydrogen, alkyl,
 substituted alkyl, C₃₋₆cycloalkyl, and aryl,
 or R⁵ and R⁶ taken together with the nitrogen to which they are attached
 represent a 5 to 6 member saturated ring containing up to one other
 heteroatom selected from oxygen and nitrogen;

15

R¹⁵ is selected from the group consisting of alkyl, C₁-C₁₂aryl, hydroxy,
 alkoxy, substituted alkyl, substituted C₁-C₁₂aryl and halogen;

m is 0-6; and

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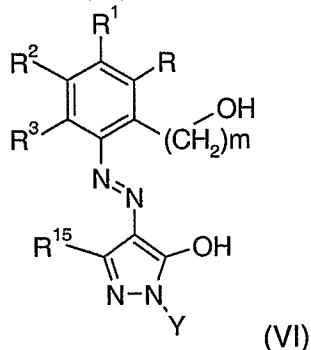
Y is selected from alkyl, substituted alkyl and a cyclic or polycyclic aromatic
 ring containing from 3 to 14 carbon atoms and optionally containing from
 one to three heteroatoms, provided that when the number of carbon
 atoms is 3 the aromatic ring contains at least two heteroatoms and when
 25 the number of carbon atoms is 4 the aromatic ring contains at least one
 heteroatom, and optionally substituted with one or more substituents
 selected from the group consisting of: alkyl, substituted alkyl, C₁-C₁₂aryl,
 substituted cycloalkyl, substituted C₁-C₁₂aryl, hydroxy, aryloxy, alkoxy,
 cycloalkyl, nitro, cyano, halogen and protected -OH;

30

and/or pharmaceutically acceptable salts, hydrates, solvates and esters
 thereof;

provided that at least one of R, R¹, R² and R³ is a substituted aryl group or a heterocyclic methylene substituent as represented in Formula (III).

Included among compounds of Formula (II) that are useful in the current invention are those having Formula (VI):



wherein:

R, R¹, R² and R³ are each independently selected from hydrogen, C₁-6alkyl, C₁-6alkoxy, -(CH₂)_pOR⁴, -C(O)OR⁴, formyl, nitro, cyano, halogen, aryl, substituted aryl, substituted alkyl, -S(O)_nR⁴, cycloalkyl, -NR⁵R⁶, protected -OH, -CONR⁵R⁶, phosphonic acid, sulfonic acid, phosphinic acid and -SO₂NR⁵R⁶,

where

p is 0-6,

n is 0-2,

R⁴ is hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and

R⁵ and R⁶ are each independently selected from hydrogen, alkyl, substituted alkyl, C₃-6cycloalkyl, and aryl,

or R⁵ and R⁶ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen;

R¹⁵ is selected from the group consisting of alkyl, C₁-C₁₂aryl, hydroxy, alkoxy, substituted alkyl, substituted C₁-C₁₂aryl and halogen;

m is 0-6; and

Y is selected from alkyl, substituted alkyl and a cyclic or polycyclic aromatic ring containing from 3 to 14 carbon atoms and optionally containing from one to three heteroatoms, provided that when the number of carbon

atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, hydroxy, aryloxy, alkoxy, cycloalkyl, nitro, cyano, halogen and protected -OH;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof;

provided that at least one of R, R¹, R² and R³ is a substituted aryl group.

Included among the compounds useful in the present invention are those having Formula (VI) in which,

either:

R is a substituted aryl; and R¹ is hydrogen;

or:

R is hydrogen; and R¹ is a substituted aryl;

and in either case:

R² and R³ are each independently selected from hydrogen, C₁-6alkyl, C₁-6alkoxy, nitro, cyano, halogen, aryl, substituted aryl, substituted alkyl, cycloalkyl, phosphonic acid, phosphinic acid and sulfonic acid;

R¹⁵ is selected from the group consisting of alkyl, substituted alkyl, C₁-C₁₂aryl, alkoxy and halogen;

m is 0-4; and

Y is selected from, phenyl, pyridinyl and pyrimidinyl, where the phenyl, pyridinyl and pyrimidinyl are optionally substituted with from one to three substituents selected from the group consisting of: alkyl, substituted alkyl, C₁-C₁₂aryl, substituted C₁-C₁₂aryl, alkoxy and halogen; and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the compounds useful in the present invention are those having Formula (VI) in which,

R is a substituted C₁-C₁₂aryl;

and

R¹ is hydrogen;
 R² and R³ are each independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, nitro, cyano, halogen, substituted alkyl and cycloalkyl;
 R¹⁵ is selected from the group consisting of alkyl, substituted alkyl, C₁₋₁₂aryl, alkoxy and halogen;
 m is 0-2; and
 Y is selected from,
 phenyl, pyridinyl and pyrimidinyl, where the phenyl, pyridinyl and pyrimidinyl are optionally substituted with from one to three substituents
 selected from the group consisting of: alkyl, substituted alkyl, C_{1-C12}aryl, substituted C_{1-C12}aryl, alkoxy and halogen;
 and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the compounds useful in the present invention are those having Formula (VI) in which,
 R is a substituted phenyl or pyridinyl ring; and
 R¹ is hydrogen;
 R² and R³ are each independently selected from hydrogen, C₁₋₆alkyl, substituted alkyl and halogen;
 R¹⁵ is selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, C_{1-C12}aryl and halogen;
 m is 0; and
 Y is selected from,
 phenyl, pyridinyl and pyrimidinyl, where the phenyl, pyridinyl and pyrimidinyl is optionally substituted with from one to three substituents
 selected from the group consisting of: alkyl, substituted alkyl, C_{1-C12}aryl, substituted C_{1-C12}aryl, alkoxy and halogen;
 and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the compounds useful in the present invention are:
 4'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-3'-hydroxybiphenyl-4-carboxylic acid;
 4'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-3'-hydroxybiphenyl-3-carboxylic acid;

- 3'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(4-tert-Butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 5 2-Aza-3'-{N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-5'-chloro-2'-hydroxybiphenyl-3-carboxylic acid;
- 2-Aza-3'-{N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3-Aza-3'-{N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-5-carboxylic acid;
- 10 2-Aza-5'-chloro-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 2-Aza-3'-{N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-5'-methylbiphenyl-3-carboxylic acid;
- 15 2-Aza-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-5'-methylbiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(4-tert-Butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-5'-methylbiphenyl-3-carboxylic acid;
- 3-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-(tetrazol-5-yl)biphenyl;
- 20 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-5'-fluoro-2'-hydroxybiphenyl-3-carboxylic acid;
- 7-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxyphenylquinolin-4[1H]-one-3-carboxylic acid;
- 25 7-{N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxyphenylquinolin-4[1H]-one-3-carboxylic acid;
- 3-Aza-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-5-carboxylic acid;
- 3-Aza-3'-{N'-[1-(3-methyl-4-(1-methylethyl)phenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-5-carboxylic acid;
- 30 3-Aza-3'-{N'-[1-(4-tertbutylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-5-carboxylic acid;
- 5'-Chloro-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 35 3'-{N'-[1-(3,4-Dimethylphenyl)-3,5-dioxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

- 3'-{N'-[1-(2-Ethoxy-2-oxoethyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-4'-(tetrazol-5-yl)biphenyl;
5 3'-{N'-[1-[2-(N-tert-butyl)amino-2-oxoethyl]-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[3-Chloro-1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
5-chloro-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-4'-(tetrazol-5-yl)biphenyl;
10 3'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3,5-dicarboxylic acid;
3-Aza-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-5'-methylbiphenyl-5-carboxylic acid;
15 3'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-4-carboxylic acid;
3'-{N'-[1-(3,4-Dimethylphenyl)-3-methoxy-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(4-methoxyphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
20 (3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-biphenyl)-1,1,1,-trifluoromethanesulfonamide;
3'-{N'-[1-(3,4-Dichlorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
25 3'-{N'-[3-methyl-5-oxo-1-(3-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
8'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}quinolin-4[1H]-one-3-carboxylic acid;
3'-{N'-[3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
30 3'-{N'-[3-methyl-5-oxo-1-(4-N-methylcarboxamidophenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
N-[1-(3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-yl)methanoyl]methanesulfonamide;
35 3'-{N'-[3-methyl-5-oxo-1-phenyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

- 3'-{N'-[3-methyl-1-(4-methylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-
2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(4-chlorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-
2'-hydroxybiphenyl-3-carboxylic acid;
5 3'-{N'-[1-(4-fluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-
2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[3-methyl-5-oxo-1-(4-trifluoromethoxyphenyl)-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(3,4-dimethylphenyl)-3-ethoxy-5-oxo-1,5-dihydropyrazol-4-
10 ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(3,4-dimethylphenyl)-3-(1-methylethoxy)-5-oxo-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[3-tert-butyl-1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
15 3'-{N'-[3-methyl-1-(4-methyl-2,3,5,6-tetrafluorophenyl)-5-oxo-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(4-fluoro-3-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(3,4-dimethylphenyl)-3-phenyl-5-oxo-1,5-dihydropyrazol-4-
20 ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-phenyl-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
3-{N'-[1-(3,4-dimethylphenyl)-3-methoxy-5-oxo-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
25 3-{N'-[1-(3,4-dimethylphenyl)-3-ethoxy-5-oxo-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
3-{N'-[1-(3,4-dimethylphenyl)-3-(1-methylethoxy)-5-oxo-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
3-{N'-[1-(4-fluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-
30 hydroxy-3'-tetrazol-5-ylbiphenyl;
3-{N'-[1-(4-fluoro-3-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
3-{N'-[3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
35 3'-{N'-[1-(3,4-dimethylphenyl)-3-(pyridin-4-yl-5-oxo-1,5-dihydropyrazol-4-
ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

- 3-{N'-[1-(3,4-dimethylphenyl)-3-pyridin-4-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
3-{N'-[1-(3,4-dimethylphenyl)-3-pyridin-2-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
5 3'-{N'-[1-(3,4-dimethylphenyl)-3-(pyridin-2-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3-{N'-[1-(3-fluoro-4-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
3'-{N'-[1-(3-fluoro-4-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
10 3'-{N'-[3-methyl-5-oxo-1-(4-trifluoromethylpyrimidin-2-yl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-N-tert-butoxycarbonylamino-3-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl;
15 3'-amino-3-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl;
3-{N'-[1-(3-fluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
3'-{N'-[1-(3-fluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
20 3-{N'-[3-methyl-5-oxo-1-(2,3,4,5,6-pentafluorophenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
3'-{N'-[3-methyl-5-oxo-1-(2,3,4,5,6-pentafluorophenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
25 3'-{N'-[1-(3,4-difluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(3,4-dimethylphenyl)-3-methoxymethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3-{N'-[1-(3,4-dimethylphenyl)-3-methoxymethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
30 3-{N'-[1-(3,4-difluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-trifluoromethyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
35 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-6-fluoro-2'-hydroxybiphenyl-3-carboxylic acid;

- 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-propyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 3-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-propyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
 5 3'-{N'-[1-(3,4-dimethylphenyl)-3-(1-methyl-1H-pyrrol-3-yl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 3-{N'-[1-(3,4-dimethylphenyl)-3-(1-methyl-1H-pyrrol-3-yl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
 3'-{N'-[1-(3,4-dimethylphenyl)-3-furan-2-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 10 3-{N'-[1-(3,4-dimethylphenyl)-3-furan-2-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
 N-(2'-hydroxy-3'-{N'-[3-methyl-5-oxo-1-(4-trifluoromethyl-phenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}biphenyl-3-yl)-1,1,1-trifluoromethanesulfonamide;
 15 N-(2'-hydroxy-3'-{N'-[1-(3-fluoro-4-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}biphenyl-3-yl)-1,1,1-trifluoromethanesulfonamide;
 N-(2'-hydroxy-3'-{N'-[1-(4-fluoro-3-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}biphenyl-3-yl)-1,1,1-trifluoromethanesulfonamide;
 N-(2'-hydroxy-3'-{N'-[1-(3,4-difluorophenyl)-3-methyl-5-oxo-1,5-dihydro-pyrazol-4-ylidene]hydrazino}biphenyl-3-yl)-1,1,1-trifluoromethanesulfonamide;
 20 N-(3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-yl)guanidine;
 3'-{N'-[1-(3,4-dimethylphenyl)-3-ethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 25 3-{N'-[1-(3,4-dimethylphenyl)-3-ethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-thien-2-yl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 3'-{N'-[3-cyclopropyl-1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 30 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-thiazol-2-yl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 35 3'-{N'-[1-(3,4-dimethylphenyl)-3-(1-methylethyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

- 3'-{N'-[3-(benzyloxymethyl)-1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[3-ethyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 5 3'-{N'-[5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-3-hydroxymethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[3-benzyloxymethyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 10 3'-{N'-[1-(3,4-dimethylphenyl)-3-methylsulfanylmethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-thiophen-3-yl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 15 3'-{N'-[5-oxo-1-(4-trifluoromethylphenyl)-3-thiophen-3-yl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[5-oxo-1-(4-trifluoromethylphenyl)-3-methylsulfanylmethyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- N-(3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-pyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-yl)methanesulfonamide;
- 20 3'-{N'-[1-benzo[1,3]dioxol-5-yl-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,5-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 25 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-4'-hydroxybiphenyl-4-carboxylic acid;
- 3'-{N'-[1-(3-chloro-4-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-4'-hydroxybiphenyl-3-carboxylic acid;
- 30 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-phosphonic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3,4-dicarboxylic acid;
- 35 2',6-dihydroxy-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}biphenyl-3-carboxylic acid;

4-aza-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-5-carboxylic acid;
 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 5 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-sulfonic acid; and
 5-(3'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-ylmethylene)thiazolidine-2,4-dione;
 and/or pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

10

Included among the non-peptide TPO receptor agonists of the invention are the non-peptide compounds described in:

WO 02/59099;
 WO 02/59100;
 15 EP 1 207 155;
 EP 1 253 142A1;
 WO 01/92211 A1;
 WO 01/53267-A1;
 EP 1 104 674- A1; and
 20 WO 01/07423-A1.

Included among the compounds of the above listed applications that are useful in the present invention are:

N-[4-(5-bromo-2-thienyl)-1,3-thiazol-2-yl]-4-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzamide;
 25 N-[4-(3,4-dimethylphenyl)-1,3-thiazol-2-yl]-4-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzamide;
 N-[4-[4-(1,1-dimethylethyl)phenyl]-1,3-thiazol-2-yl]-4-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzamide;
 30 N-[4-(3,4-dichlorophenyl)-1,3-thiazol-2-yl]-4-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzamide; and
 (2E)-3-[4-({[4-(3,4-dichlorophenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]-2-methyl-2-propenoic acid;
 and/or pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

35

Included among the non-peptide TPO receptor agonists of the invention are the non-peptide compounds described in:

WO 99/11262.

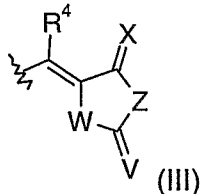
Non-peptide TPO receptor agonists are included in the methods of the invention.

- 5 By the term "protected hydroxy" or "protected -OH" as used herein, is meant the alcoholic or carboxylic-OH groups which can be protected by conventional blocking groups in the art such as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York. Compounds containing protected hydroxy groups may also be useful as
 10 intermediates in the preparation of the pharmaceutically active compounds of the invention.

- By the term "aryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 1 to 14 carbon atoms and optionally containing from one to five heteroatoms, provided that when the number
 15 of carbon atoms is 1 the aromatic ring contains at least four heteroatoms, when the number of carbon atoms is 2 the aromatic ring contains at least three heteroatoms, when the number of carbons is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom.

- 20 By the term "C₁-C₁₂aryl" as used herein, unless otherwise defined, is meant phenyl, naphthalene, 3,4-methylenedioxyphenyl, pyridine, biphenyl, quinoline, pyrimidine, quinazoline, thiophene, furan, pyrrole, pyrazole, imidazole and tetrazole.

- When referring to compounds of Formula (I) and (II), the term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety
 25 has one or more substituents selected from the group consisting of: -CO₂R²⁰, aryl, -C(O)NHS(O)₂R²⁰, -NHS(O)₂R²⁰, hydroxyalkyl, alkoxy, -C(O)NR²¹R²², acyloxy, alkyl, amino, N-acylamino, hydroxy, -(CH₂)_gC(O)OR⁸, -S(O)_nR⁸, nitro, tetrazole, cyano, oxo, halogen, trifluoromethyl, protected -OH and a heterocyclic methylene
 30 substituent as represented by Formula (III),



, where g is 0-6; R⁸ is hydrogen or alkyl; R²⁰ is selected from hydrogen, C₁-C₄alkyl, aryl and trifluoromethyl; R²¹ and R²² are independently selected from hydrogen, C₁-C₄alkyl, aryl and trifluoromethyl; V, W, X and Z are each

independently selected from O, S, and NR¹⁶, where R¹⁶ is selected from: hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl; and n is 0-2.

When referring to compounds of Formula (V) and (VI), the term
5 "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one or more substituents selected from the group consisting of: -CO₂R²⁰, aryl, -C(O)NHS(O)₂R²⁰, -NHS(O)₂R²⁰, hydroxyalkyl, alkoxy, -C(O)NR²¹R²², acyloxy, alkyl, amino, N-acylamino, hydroxy, -(CH₂)_gC(O)OR⁸,
10 -S(O)_nR⁸, nitro, tetrazole, cyano, oxo, halogen, trifluoromethyl and protected -OH, where g is 0-6, R⁸ is hydrogen or alkyl, R²⁰ is selected from hydrogen, C₁-C₄alkyl, aryl and trifluoromethyl, and R²¹ and R²² are independently selected from hydrogen, C₁-C₄alkyl, aryl and trifluoromethyl, and n is 0-2.

By the term "alkoxy" as used herein is meant -Oalkyl where alkyl is as described herein including -OCH₃ and -OC(CH₃)₂CH₃.

15 The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic C₃-C₁₂.

Examples of cycloalkyl and substituted cycloalkyl substituents as used herein include: cyclohexyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, propyl 4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl, cyclopropyl and
20 cyclopentyl.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: -OC(O)CH₃, -OC(O)CH(CH₃)₂ and -OC(O)(CH₂)₃CH₃.

By the term "N-acylamino" as used herein is meant -N(H)C(O)alkyl, where
25 alkyl is as described herein. Examples of N-acylamino substituents as used herein include: -N(H)C(O)CH₃, -N(H)C(O)CH(CH₃)₂ and -N(H)C(O)(CH₂)₃CH₃.

By the term "aryloxy" as used herein is meant -Oaryl where aryl is phenyl, naphthyl, 3,4-methylenedioxyphenyl, pyridyl or biphenyl optionally substituted with one or more substituents selected from the group consisting of: alkyl, hydroxyalkyl,
30 alkoxy, trifluoromethyl, acyloxy, amino, N-acylamino, hydroxy, -(CH₂)_gC(O)OR⁸, -S(O)_nR⁸, nitro, cyano, halogen and protected -OH, where g is 0-6, R⁸ is hydrogen or alkyl, and n is 0-2. Examples of aryloxy substituents as used herein include: phenoxy, 4-fluorophenyloxy and biphenyloxy.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or
35 sulfur.

By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein is meant a linear or branched, saturated or unsaturated hydrocarbon chain, and unless otherwise defined, the carbon chain will contain from 1 to 12 carbon atoms. Examples of alkyl substituents as used herein include: -CH₃, -CH₂-CH₃,
5 -CH₂-CH₂-CH₃, -CH(CH₃)₂, -C(CH₃)₃, -(CH₂)₃-CH₃, -CH₂-CH(CH₃)₂,
-CH(CH₃)-CH₂-CH₃, -CH=CH₂, and -C≡C-CH₃.

By the phrase "preservation of human platelet lifespan and/or efficacy" and derivatives thereof as used herein, unless otherwise defined, is meant that human
10 platelets from a storage solution that contains a non-peptide TPO receptor agonist, upon transfusion, will demonstrate viability and function of normal human platelets to a greater extent and/or for longer duration of time than platelets from a storage solution that does not contain a non-peptide TPO receptor agonist.

By the phrase "effective amount" and derivatives thereof as used herein,
15 unless otherwise defined, is meant an amount of non-peptide TPO receptor agonist that, upon addition to a storage solution containing human platelets, increases the lifespan and/or efficacy of the platelets upon transfusion to a measurable extent, in comparison to platelets from a storage solution that did not contain a non-peptide TPO receptor agonist.

By the phrase "storage solution" and derivatives thereof as used herein, unless otherwise defined, is meant standard blood bank conditions for maintaining human platelets, including preservatives, buffers and maintenance temperature, and excluding non-peptide TPO receptor agonist as defined herein.

By the phrase "non-peptide" as used herein is meant a chemical compound,
25 or a protein or peptide not comprised primarily of natural amino acids. Suitably, the "non-peptide" is a small molecule chemical compound having a molecular weight under 1,500 daltons, suitably under 1,000 daltons.

By the term "primarily" as used above is meant about 60% by weight of naturally occurring amino acid residue.

30 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

The compounds of Formulas I and II are disclosed and claimed, along with pharmaceutically acceptable salts, hydrates, solvates and esters thereof, as being
35 useful as an agonist of the TPO receptor, particularly in enhancing platelet production and particularly in the treatment of thrombocytopenia, in International Application No. PCT/US01/16863, having an International filing date of May 24,

2001; International Publication Number WO 01/89457 and an International Publication date of November 29, 2001. Compounds of Formulas I and II and pharmaceutically acceptable salts, hydrates, solvates and esters thereof, are prepared as described in International Application No. PCT/US01/16863. The bis-
5 (monoethanolamine) salt of a compound described in International Application No. PCT/US01/16863, is described in International Application No. PCT/US03/16255, having an International filing date of May 21, 2003; International Publication Number WO 03/098992 and an International Publication date of December 4, 2003.

10 By the term "co-addition" and derivatives thereof as used herein is meant administration of a non-peptide TPO receptor agonist, as described herein, and a further active ingredient or ingredients, known to preserve human platelet lifespan and/or efficacy when added to a storage solution containing human platelets.

Examples of a further active ingredient or ingredients for use in combination
15 with non-peptide TPO receptor agonists according to the present invention include but are not limited to: cytokines or chemokines such as: SCF, FLT3 ligand, and functional equivalents of such, and other molecules identified as preserving platelet efficacy when added to a storage solution containing human platelets.

The non-peptide TPO receptor agonist compounds of the present invention
20 have utility in preserving human platelet lifespan and/or efficacy during storage.

The non-peptide TPO receptor agonist of this invention interact differently at the TPO receptor than does TPO. One result of this differing interaction is that the non-peptide TPO receptor agonist of this invention are useful in combination with TPO.

25 One skilled in the art can readily determine by known methods if a compound is a non-peptide TPO receptor agonist and thus included within the scope of the current invention. By way of example, the following assays can be employed:

Luciferase Assay

30 Compounds are tested for potency as agonists of the TPO receptor in a Luciferase assay such as described in Lamb, et al., Nucleic Acids Research 23: 3283-3289 (1995) and Seidel, et al., Proc. Natl. Acad. Sci., USA 92: 3041-3045 (1995) by substituting a TPO-responsive BaF3 cell line (Vigon et al. Proc. Natl. Acad. Sci. USA 1992, 89, 5640-5644) for the HepG2 cells utilized therein. The
35 murine BaF3 cells express TPO receptors and closely match the pattern of STAT (signal transducers and activators of transcription) activation observed in primary murine and human bone marrow cells.

Proliferation Assay

Compounds are tested in an in vitro proliferation assay using the human UT7TPO cell line. UT7TPO cells are a human megakaryoblastic cell line that express Tpo-R, whose survival and growth is dependent on the presence of TPO
5 (Komatsu et al. Blood 1996, 87,4552).

Differentiation Assay

Compounds are tested for their ability in stimulating the maturation of megakaryocytes from human bone marrow cells. In this assay, purified human CD34+ progenitor cells are incubated in liquid culture with test compounds for 10
10 days and the number of cells expressing the transmembrane glycoprotein CD41 (gpIIb), a megakaryocytic marker, is then measured by flow cytometry (see Cwirla, S. E. et al Science, 1997, 276, 1696).

The ability of non-peptide TPO receptor agonists to preserve human platelet
15 lifespan and/or efficacy during storage is demonstrated according to known procedures such as described in: Kaufman, Transfusion; 2005; Vol. 45: 1407-1412; Xia et al., Transfusion; 2000; Vol 40: 976-987; and Valeri et al., Transfusion; 2004; Vol. 44: pp 865-870.

20 The present invention therefore provides methods for the preservation of human platelet lifespan and/or efficacy during storage which comprises the addition of an effective amount of a non-peptide TPO receptor agonists to a storage solution containing human platelets.

Optimal amounts of non-peptide TPO receptor agonists to be utilized
25 according to this invention may be readily determined by those skilled in the art.

No unacceptable toxicological effects are expected when compounds of the invention are utilized in accordance with the present invention.

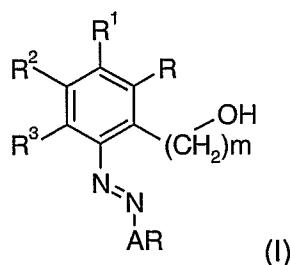
In addition, the non-peptide TPO receptor agonists compounds of the present invention can be co-administered with further active ingredients, such as
30 other compounds known to preserve human platelet efficacy during storage.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent.

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

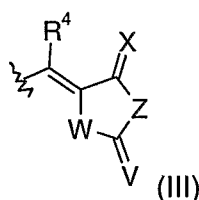
What is claimed is:

1. A method for preserving human platelet lifespan and/or efficacy during storage which comprises the addition of an effective amount of a non-peptide TPO receptor agonists to a storage solution containing human platelets.
2. The method of claim 1 wherein the TPO receptor agonist is a compound having the following Formula (I):



wherein:

R, R¹, R² and R³ are each independently selected from hydrogen, C₁-₆alkyl, -(CH₂)_pOR⁴, -C(O)OR⁴, formyl, nitro, cyano, halogen, aryl, substituted aryl, substituted alkyl, -S(O)_nR⁴, cycloalkyl, -NR⁵R⁶, protected -OH, -CONR⁵R⁶, phosphonic acid, sulfonic acid, phosphinic acid, -SO₂NR⁵R⁶, and a heterocyclic methylene substituent as represented by Formula (III),



where,

p is 0-6,

n is 0-2,

V, W, X and Z are each independently selected from O, S and NR¹⁶, where R¹⁶ is selected from: hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, R⁴ is selected from: hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and

5 R⁵ and R⁶ are each independently selected from hydrogen, alkyl, substituted alkyl, C₃₋₆cycloalkyl, and aryl, or R⁵ and R⁶ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen;

m is 0-6; and

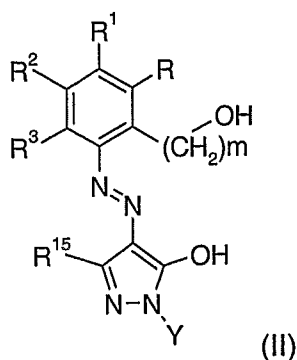
10 AR is a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, 15 substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR⁴, -C(O)NR¹⁰R¹¹, -S(O)₂NR¹⁰R¹¹, -S(O)_nR⁴ and protected -OH,

20 where n is 0-2, R⁴ is hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and R¹⁰ and R¹¹ are independently hydrogen, cycloalkyl, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: 25 alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR⁴, -S(O)_nR⁴, -C(O)NR⁴R⁴, -S(O)₂NR⁴R⁴, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH, or R¹⁰ and R¹¹ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one 30 other heteroatom selected from oxygen and nitrogen, where R⁴ is as described above and n is 0-2;

and/or a pharmaceutically acceptable salt, hydrate, solvate or ester thereof;

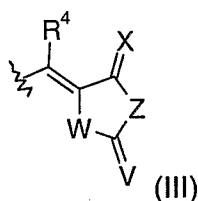
35 provided that at least one of R, R¹, R² and R³ is a substituted aryl group or a heterocyclic methylene substituent as represented in Formula (III).

3. The method of claim 1 wherein the compound is represented by the following Formula (II)



5 wherein:

R, R¹, R² and R³ are each independently selected from hydrogen, C₁-6alkyl, -(CH₂)_pOR⁴, -C(O)OR⁴, formyl, nitro, cyano, halogen, aryl, substituted aryl, substituted alkyl, -S(O)_nR⁴, cycloalkyl, -NR⁵R⁶, protected -OH, -CONR⁵R⁶, phosphonic acid, sulfonic acid, phosphinic acid, -SO₂NR⁵R⁶, and a heterocyclic methylene substituent as represented by Formula (III),



where

p is 0-6,

n is 0-2,

V, W, X and Z are each independently selected from O, S, and NR¹⁶,

where R¹⁶ is selected from: hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl,

R⁴ is hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and

R⁵ and R⁶ are each independently selected from hydrogen, alkyl, substituted alkyl, C₃-6cycloalkyl, and aryl,

or R⁵ and R⁶ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen;

R¹⁵ is selected from the group consisting of alkyl, C₁-C₁₂aryl, hydroxy, alkoxy, substituted alkyl, substituted C₁-C₁₂aryl and halogen;

m is 0-6; and

5

Y is selected from alkyl, substituted alkyl and a cyclic or polycyclic aromatic ring containing from 3 to 14 carbon atoms and optionally containing from one to three heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, hydroxy, aryloxy, alkoxy, cycloalkyl, nitro, cyano, halogen and protected -OH;

10

15

and/or a pharmaceutically acceptable salt, hydrate, solvate or ester thereof;

provided that at least one of R, R¹, R² and R³ is a substituted aryl group or a heterocyclic methylene substituent as represented in Formula (III).

20

4. The method of claim 2 wherein the compound is selected from:

4'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-3'-hydroxybiphenyl-4-carboxylic acid;

25

4'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-3'-hydroxybiphenyl-3-carboxylic acid;

3'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

30

3'-{N'-[1-(4-tert-Butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

2-Aza-3'-{N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-5'-chloro-2'-hydroxybiphenyl-3-carboxylic acid;

2-Aza-3'-{N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

35

3-Aza-3'-{N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-5-carboxylic acid;

- 2-Aza-5'-chloro-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 2-Aza-3'-{N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-5'-methylbiphenyl-3-carboxylic acid;
- 5 2-Aza-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-5'-methylbiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(4-tert-Butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-5'-methylbiphenyl-3-carboxylic acid;
- 3-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 10 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-5'-fluoro-2'-hydroxybiphenyl-3-carboxylic acid;
- 7-({N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxyphenyl)quinolin-4[1H]-one-3-carboxylic acid;
- 15 7-({N'-[1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxyphenyl)quinolin-4[1H]-one-3-carboxylic acid;
- 3-Aza-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-5-carboxylic acid;
- 3-Aza-3'-(N'-[1-{3-methyl-[4-(1-methylethyl)phenyl]-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino)-2'-hydroxybiphenyl-5-carboxylic acid;
- 20 3-Aza-3'-{N'-[1-(4-tertbutylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-5-carboxylic acid;
- 5'-Chloro-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 25 3'-{N'-[1-(3,4-Dimethylphenyl)-3,5-dioxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(2-Ethoxy-2-oxoethyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-4'-(tetrazol-5-yl)biphenyl;
- 30 3'-(N'-{1-[2-(N-tert-butyl)amino-2-oxoethyl]-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino)-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[3-Chloro-1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 35 5-chloro-3-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-4'-(tetrazol-5-yl)biphenyl;

- 3'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3,5-dicarboxylic acid;
3-Aza-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-5'-methylbiphenyl-5-carboxylic acid;
5 3'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-4-carboxylic acid;
3'-{N'-[1-(3,4-Dimethylphenyl)-3-methoxy-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(4-methoxyphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
10 (3-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-biphenyl)-1,1,1,-trifluoromethanesulfonamide;
3'-{N'-[1-(3,4-Dichlorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
15 3'-{N'-[3-methyl-5-oxo-1-(3-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
8-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}quinolin-4[1H]-one-3-carboxylic acid;
3'-{N'-[3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
20 3'-{N'-[3-methyl-5-oxo-1-(4-N-methylcarboxamidophenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
N-[1-(3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-yl)methanoyl]methanesulfonamide;
25 3'-{N'-[3-methyl-5-oxo-1-phenyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[3-methyl-1-(4-methylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(4-chlorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
30 2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[1-(4-fluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
3'-{N'-[3-methyl-5-oxo-1-(4-trifluoromethoxyphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
35 3'-{N'-[1-(3,4-dimethylphenyl)-3-ethoxy-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

- 3'-{N'-[1-(3,4-dimethylphenyl)-3-(1-methylethoxy)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[3-tert-butyl-1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 5 3'-{N'-[3-methyl-1-(4-methyl-2,3,5,6-tetrafluorophenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(4-fluoro-3-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-3-phenyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 10 3-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-phenyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 3-{N'-[1-(3,4-dimethylphenyl)-3-methoxy-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 15 3-{N'-[1-(3,4-dimethylphenyl)-3-ethoxy-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 3-{N'-[1-(3,4-dimethylphenyl)-3-(1-methylethoxy)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 3-{N'-[1-(4-fluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 20 hydroxy-3'-tetrazol-5-ylbiphenyl;
- 3-{N'-[1-(4-fluoro-3-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 3-{N'-[3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 25 3'-{N'-[1-(3,4-dimethylphenyl)-3-(pyridin-4-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3-{N'-[1-(3,4-dimethylphenyl)-3-pyridin-4-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 3-{N'-[1-(3,4-dimethylphenyl)-3-pyridin-2-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 30 3'-{N'-[1-(3,4-dimethylphenyl)-3-(pyridin-2-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3-{N'-[1-(3-fluoro-4-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 35 3'-{N'-[1-(3-fluoro-4-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

- 3'-{N'-[3-methyl-5-oxo-1-(4-trifluoromethylpyrimidin-2-yl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-N-tert-butoxycarbonylamino-3-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl;
- 5 3'-amino-3-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl;
- 3-{N'-[1-(3-fluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 3'-{N'-[1-(3-fluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 10 3-{N'-[3-methyl-5-oxo-1-(2,3,4,5,6-pentafluorophenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 3'-{N'-[3-methyl-5-oxo-1-(2,3,4,5,6-pentafluorophenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 15 3'-{N'-[1-(3,4-difluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-3-methoxymethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3-{N'-[1-(3,4-dimethylphenyl)-3-methoxymethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 20 3-{N'-[1-(3,4-difluorophenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-trifluoromethyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 25 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-6-fluoro-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-propyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-propyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 30 3'-{N'-[1-(3,4-dimethylphenyl)-3-(1-methyl-1H-pyrrol-3-yl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3-{N'-[1-(3,4-dimethylphenyl)-3-(1-methyl-1H-pyrrol-3-yl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;
- 35 3'-{N'-[1-(3,4-dimethylphenyl)-3-furan-2-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

- 3-{N'-[1-(3,4-dimethylphenyl)-3-furan-2-yl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
 N-(2'-hydroxy-3'-{N'-[3-methyl-5-oxo-1-(4-trifluoromethyl-phenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}biphenyl-3-yl)-1,1,1-trifluoromethanesulfonamide;
 5 N-(2'-hydroxy-3'-{N'-[1-(3-fluoro-4-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}biphenyl-3-yl)-1,1,1-trifluoromethanesulfonamide;
 N-(2'-hydroxy-3'-{N'-[1-(4-fluoro-3-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}biphenyl-3-yl)-1,1,1-trifluoromethanesulfonamide;
 N-(2'-hydroxy-3'-{N'-[1-(3,4-difluorophenyl)-3-methyl-5-oxo-1,5-dihydro-pyrazol-4-ylidene]hydrazino}biphenyl-3-yl)-1,1,1-trifluoromethanesulfonamide;
 10 N-(3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-yl)guanidine;
 3'-{N'-[1-(3,4-dimethylphenyl)-3-ethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 15 3-{N'-[1-(3,4-dimethylphenyl)-3-ethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2-hydroxy-3'-tetrazol-5-ylbiphenyl;
 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-thien-2-yl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 3'-{N'-[3-cyclopropyl-1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 20 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-thiazol-2-yl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 25 3'-{N'-[1-(3,4-dimethylphenyl)-3-(1-methylethyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 3'-{N'-[3-(benzyloxymethyl)-1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 3'-{N'-[3-ethyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 30 3'-{N'-[5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 3'-{N'-[1-(3,4-dimethylphenyl)-3-hydroxymethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
 35 3'-{N'-[3-benzyloxymethyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;

- 3'-{N'-[1-(3,4-dimethylphenyl)-3-methylsulfanylmethyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-3-thiophen-3-yl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 5 3'-{N'-[5-oxo-1-(4-trifluoromethylphenyl)-3-thiophen-3-yl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[5-oxo-1-(4-trifluoromethylphenyl)-3-methylsulfanylmethyl-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- N-(3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-pyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-yl)methanesulfonamide;
- 10 3'-[N'-(1-benzo[1,3]dioxol-5-yl-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)hydrazino]-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,5-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 15 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-4'-hydroxybiphenyl-4-carboxylic acid;
- 3'-{N'-[1-(3-chloro-4-methylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-4'-hydroxybiphenyl-3-carboxylic acid;
- 20 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-phosphonic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3,4-dicarboxylic acid;
- 25 2',6-dihydroxy-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}biphenyl-3-carboxylic acid;
- 4-aza-3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-5-carboxylic acid;
- 3'-{N'-[1-(3,4-dimethylphenyl)-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid;
- 30 3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-sulfonic acid; and
- 5-(3'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-ylmethylene)thiazolidine-2,4-dione;
- 35 and/or a pharmaceutically acceptable salt, hydrate, solvate or ester thereof.

5. The method of claim 4 wherein the compound is selected from:

3'-{N'-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid; and
3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxy-3'-tetrazol-5-ylbiphenyl;

5 and/or a pharmaceutically acceptable salt, hydrate, solvate or ester thereof.

6. A method of claim 1 further comprising co-addition of an effective amount of a further active ingredient known to preserve platelet lifespan and/or efficacy during storage.

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7. The method of Claim 6 wherein the further active ingredient for co-addition is selected from the group consisting of: SCF, FLT3 ligand, or a functional equivalent of either of said further active ingredients.

15 8. The method of Claim 1 further comprising co-addition of an effective amount of a further active ingredient selected from the group consisting of: a colony stimulating factor, cytokine, chemokine, interleukin or cytokine receptor agonist or antagonist, or a functional equivalent of any of said further active ingredients.

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9. The method of Claim 8 wherein the further active ingredient is selected from the group consisting of: G-CSF, GM-CSF, TPO, EPO, Gro-beta, IL-8, cytoxin, VLA-4 inhibitors, SCF, FLT3 ligand, G-CSF, GM-CSF, TPO, EPO, Gro-beta or IL-8, or a functional equivalent of any of said further active ingredients.

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