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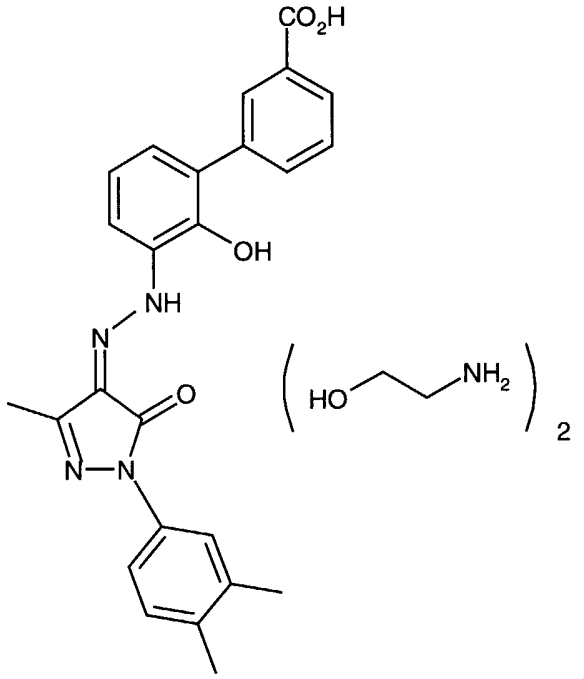
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(54) Title: 3'-[(2Z)-[1-(3,4-DIMETHYLPHENYL)-1,5-DIHYDRO-3-METHYL-5-OXO-4H-PYRAZOL-4-YLIDENE]HYDRAZINO]-2'-HYDROXY-[1,1'-BIPHENYL]-3-CARBOXYLIC ACID BIS-(MONOETHANOLAMINE)

(57) Abstract: An improved thrombopoietin mimetic, the bis-(monoethanolamine) salt of 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid.

3'-[(2Z)-[1-(3,4-DIMETHYLPHENYL)-1,5-DIHYDRO-3-METHYL-5-OXO-4H-PYRAZOL-4-YLIDENE]HYDRAZINO]-2'-HYDROXY-[1,1'-BIPHENYL]-3-CARBOXYLIC ACID bis-(MONOETHANOLAMINE)

This invention relates to an improved thrombopoietin (hereinafter TPO) mimetic, the bis-(monoethanolamine) salt of 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid. The compound is represented by Structure I:



(I)

The compound of this invention is useful as an agonist of the TPO receptor, particularly in enhancing platelet production.

Detailed Description of the Invention

3'-{N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid is a compound which is disclosed and claimed, along with pharmaceutically acceptable salts, hydrates, solvates and esters thereof, as being 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, the entire

disclosure of which is hereby incorporated by reference. International Application No. PCT/US01/16863 does not specifically disclose a salt form for any of the compounds disclosed therein.

It has now surprisingly been found that the bis-(monoethanolamine) salt of 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid has numerous advantages over the free acid. The free acid is poorly soluble in water (approximately 5 micrograms per milliliter). This poor solubility adversely affects the ability of the free acid to be formulated into pharmaceutical dosage forms and reduces the bioavailability of the compound in vivo.

While the free acid is highly useful as an agonist of the TPO receptor, particularly in enhancing platelet production and particularly in the treatment of thrombocytopenia, the bis-(monoethanolamine) salt of 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid has the added advantages of enhanced solubility and bioavailability.

The compound of this invention, 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine) (hereinafter - "Active Ingredient"), is useful as an agonist of the TPO receptor, particularly in enhancing platelet production and particularly in the treatment of thrombocytopenia. The Active Ingredient can be administered in a conventional dosage form prepared by combining the Active Ingredient with a conventional pharmaceutically acceptable carrier or diluent according to techniques readily known to those of skill in the art, such as those described in International Application No. PCT/US01/16863. The route of administration may be oral, parenteral or topical. The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intranasal, intrarectal, intravaginal or intraperitoneal administration. Oral administration is generally preferred.

As used herein the term "monoethanolamine" means "2-aminoethanol".

Doses of the presently invented Active Ingredient in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of total body weight, preferably 0.001 - 50 mg/kg. When treating a human patient in need of a TPO mimetic, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500

mg of Active Ingredient, most preferably from 0.5 to 1,000 mg of Active Ingredient. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient. The above dosages relate to the preferred amount of the Active Ingredient expressed as the free acid.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of the Active Ingredient will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the Active Ingredient given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Generally speaking, the compound of this invention is prepared by dissolving the free acid, 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid, in an appropriate organic solvent, preferably tetrahydrofuran (hereinafter THF) or ethanol/IMS (Industrial Methylated Spirit), filtering the resultant mixture to remove contaminants, then adding this solution to a solution of two or more equivalents of ethanolamine in an organic solvent, preferably a water-miscible solvent, which may contain a measured amount of water, preferably up to 5 volumes of water with respect to the free acid. The compound of this invention is filtered off and dried, for example, dried in vacuo or air dried at an elevated temperature.

Ethanolamine, 99%, was purchased from the Aldrich Chemical Company, Milwaukee, Wisconsin.

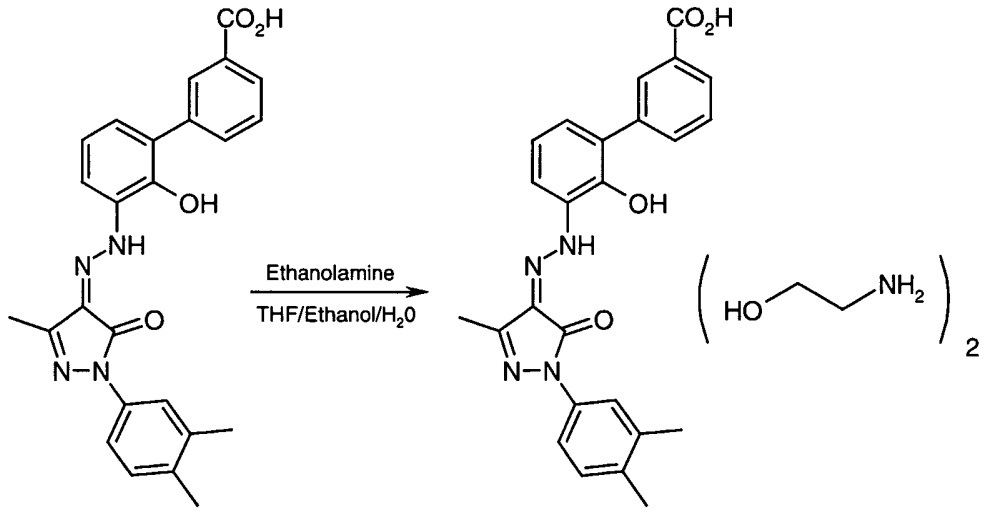
Tetrahydrofuran (THF) and Industrial Methylated Spirit 74 O.P. (IMS) were purchased from BDH Laboratory Supplies, Poole, England.

The following examples further illustrate the present invention. The examples are not intended to limit the scope of the invention as defined hereinabove and as claimed below.

EXAMPLE 1

Preparation of:

3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid-carboxylic acid bis-(monoethanolamine)



3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid, 1 g of crude orange solid, in 16.75 ml of THF was stirred at approximately 30°C. Water (2.0 ml) was added slowly to maintain a temperature greater than 28°C. When the addition was complete, the temperature was returned to 30°C and the solution filtered through a glass fibre pad (2 x Whatman GFC filters) to remove particulate matter. The filter was washed through with THF (2.0 ml) which was added to the filtrate. The filtrate was allowed to cool to room temperature. Ethanolamine (0.324g, 2.35 mol. equiv.) was dissolved in IMS (26ml) and stirred under a nitrogen atmosphere at room temperature. The filtrate containing the free acid was added to the ethanolamine solution over 20 to 30 minutes. The resulting dark red suspension was stirred for 3 hours and the solid isolated by filtration and dried at 50°C in a vacuum oven over night to yield 1.22 g (96 %) of the title compound.

Proton NMR (400 MHz, DMSO-d6 + 20ul TFA, referenced to DMSO-d5 δ2.5):
δ 2.21 (s, 3H), 2.26 (s, 3H), 2.31 (s, 3H), 2.85 (m, 4H), 3.57 (t, 4H), 7.07 (m), 7.14 (s), 7.18 (d, overlapped 3H), 7.61 (t), 7.63 (dd, overlapped 2H), ~7.7 (m, overlapped 2H), 7.79 (d), ~7.8 (br. s, overlapped 2H), 7.96 (d, 2H), 8.13 (s, 1H), 13.8 (br. s, not measurable, superimposed on TFA resonance) and signals for THF 1.76 (m) and 3.60 (overlayed by ethanolamine signal) integrating at 1.05% w/w and for ethanol 1.06 (t) and 3.44 (q) integrating at 1.3% w/w.
IR Data (Nujol mull)

1636, 1506, 1466, 1378, 1348, 1294, 1273, 1255, 1228, 1194, 1127, 1118, 1066, 1015, 767, 747 cm^{-1}.

EXAMPLE 2

Preparation of:
3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine)

3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid, 8 g of crude orange solid, was dissolved at room temperature in THF (240 ml) in a 500 ml round bottom 3-necked flask under a nitrogen atmosphere. Ethanolamine (2.2 ml , 2 molar equivalents) was added via syringe over 5 minutes. The resulting dark red suspension was stirred at room temperature for 1.5 hours and the solid isolated by filtration, washed with THF (16 ml x 2) and dried at 50°C in a vacuum oven over night to yield 10.37 g of the title compound (more than quantitative yield due to residual solvent - approximately 2.4% w/w THF as determined by NMR, otherwise similar to Example 1).

EXAMPLE 3

Preparation of:
3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine)

3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid, 8 g of crude orange solid, was suspended at room temperature in ethanol (800 ml) under a nitrogen atmosphere. Ethanolamine (2.2 ml,- 2 molar equivalents) was added via syringe over 5 minutes. The resulting dark red suspension was stirred at room temperature for 45 hours and the solid isolated by filtration, washed with ethanol (10 ml x 2) and dried at 50°C in a vacuum oven over night to yield 9.83 g (96%

yield) of the title compound. NMR similar to Example 1; ethanol content 1.3% w/w but no THF present.

EXAMPLE 4

Preparation of:
3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine)

3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid (259.0 g) was stirred in THF (4660 ml) at room temperature until completely dissolved. The solution was filtered and the reactor washed with more THF (520 ml) *via* the filter. (Combined filtrate = Solution 1).

Meanwhile, another reactor was set up for atmospheric distillation with overhead stirring. The reactor was charged in turn with IMS 74 O.P. (7770 ml) and then ethanolamine (354 ml). The solution was stirred vigorously and heated until the contents started to distil (BP. 76 - 77°C).

Solution 1 was transferred to the dropping funnel fitted to this reactor. When the contents of the reactor were distilling at a constant rate (ca. 50 ml distillate collected), Solution 1 was added from the dropping funnel at about the same rate or slightly slower than the distillation rate. On completion of the addition the dropping funnel was washed through with IMS (260ml x 2) ensuring that all the free acid was washed into the reaction mixture. The apparatus was rearranged for reflux and the resulting dark red suspension stirred at reflux under nitrogen for 30 minutes. It was allowed to cool slowly (overnight) to room temperature (ca. 20°C) with stirring under nitrogen.

The suspension was filtered and the dark purple solid washed on the filter with IMS (520 ml x 2). It was vacuum dried at room temperature, then dried at 50°C in a vacuum oven over night. Weight yield = 323.9g, 98%. Residual solvents (GCS) THF = <0.05%,ethanol = 0.12%.

The title compound displayed NMR and IR spectra essentially as indicated in Example 1 with only traces of solvent present.

EXAMPLE 5

Relative Solubilities

The solubility of 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid as the free acid (Compound A) and as the bis-(monoethanolamine) salt (Compound B) was determined in three different systems: water, 0.1 HCl and methanol. The data are summarized in Table 1 below.

Table 1

Solvent Solubility at 25 deg	Compound A mg/ml mg/ml	Compound B mg/ml mg/ml
Water	<0.001	14.2
0.1% HCl	<0.001	<0.001
methanol	1.9	6.4

The present invention includes within its scope pharmaceutical compositions comprising 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine), as the active ingredient, in association with a pharmaceutically acceptable carrier or diluent. The compound of this invention can be administered by oral or parenteral routes of administration and can be formulated in dosage forms appropriate for each route of administration including capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert diluent. The oral dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents, glidants and antioxidants. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared for a sustained release.

Preparations according to this invention for parenteral administration include sterile aqueous solutions although nonaqueous suspensions of emulsions can be employed. Such dosage forms may also contain adjuvants such as preserving, wetting, osmotic, buffering, emulsifying and dispersing agents. They may be sterilized by, for example, filtration through a bacteria retaining filter, by incorporating sterilizing agents into the compositions, irradiating the compositions or by heating the compositions.

The following examples further illustrate the pharmaceutical compositions which are a feature of this invention.

EXAMPLE 6

Tablet Composition

Lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine) are blended in the proportions shown in Table 2 below. The blend is then compressed into tablets.

Table 2

INGREDIENT	mg.
3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine)	8.45
microcrystalline cellulose	112
lactose	70
sodium starch glycolate	8
magnesium stearate	2

EXAMPLE 7

Injectable Parenteral Composition

An injectable form for administering 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine) is produced by stirring 5.0 mg. of the compound in 1.0 ml. of normal saline.

While the preferred embodiments of the invention are illustrated by the 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. The compound 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine).

2. A pharmaceutical composition comprising 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid bis-(monoethanolamine) and a pharmaceutically acceptable carrier or diluent.

3. A method of treating thrombocytopenia in a mammal, including a human, in need thereof which comprises administering to such mammal a therapeutically effective amount of a compound as described in claim 1.

4. A method as claimed in claim 3, wherein the mammal is a human.

5. A method of enhancing platelet production in a mammal, including a human, in need thereof which comprises administering to such mammal a therapeutically effective amount of a compound as described in Claim 1.

6. A method as claimed in claim 5, wherein the mammal is a human.

7. The method of claim 3 wherein the compound is administered orally.

8. The method of claim 3 wherein the compound is administered parenterally.

9. A method of agonizing the TPO receptor in a subject which comprises administering an effective amount of a compound as described in claim 1.

10. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable carrier or diluent and an effective amount of a compound as described in claim 1, which process comprises bringing the compound described in claim 1 into association with the pharmaceutically acceptable carrier or diluent.

11. The method of Claim 3 further comprising co-administering a therapeutically effective amount of an agent selected from the group consisting of: a colony stimulating

factor, cytokine, chemokine, interleukin or cytokine receptor agonist or antagonists, soluble receptors, receptor agonists or antagonist antibodies, or small molecules or peptides that act by the same mechanisms of one or more of said agents.

12. The method of Claim 11 wherein the agent is selected from the group consisting of: G-CSF, GM-CSF, TPO, M-CSF, EPO, Gro-beta, IL-11, SCF, FLT3 ligand, LIF, IL-3, IL-6, IL-1, Progenipoietin, NESP, SD-01, IL-8, or IL-5 or a biologically active derivative of any of said agents.

13. A pharmaceutical composition of Claim 2 further comprising co-administering a therapeutically effective amount of an agent selected from the group consisting of: a colony stimulating factor, cytokine, chemokine, interleukin or cytokine receptor agonist.

14. The composition of Claim 13 wherein the agent is selected from the group consisting of: G-CSF, GM-CSF, TPO, M-CSF, EPO, Gro-beta, IL-11, SCF, FLT3 Ligand, LIF, IL-3, IL-6, IL-1, or IL-5 or a biologically active derivative of any of said agents.

15. A method for enhancing platelet production obtained from a donor which comprises administering to such donor a therapeutically effective amount of a compound as described in Claim 1 prior to platelet pheresis, blood donation or platelet donation.

16. A method for enhancing the number of peripheral blood stem cells obtained from a donor which comprises administering to such donor a therapeutically effective amount of a compound as described in Claim 1 prior to leukapheresis.

17. A method of Claim 16 further comprising co-administering a therapeutically effective amount of a hematopoietic-cell mobilizing agent selected from the group consisting of: a colony stimulating factor, cytokine, chemokine, interleukin or cytokine receptor agonist, adhesion molecule antagonists or antibodies.

18. The method of Claim 17 wherein the mobilizing agent is selected from the group consisting of: G-CSF, GM-CSF, TPO, EPO, Gro-beta, IL-8, cytoxan, VLA-4 inhibitors, SCF, FLT3 ligand or a biologically active derivative of G-CSF, GM-CSF, TPO, EPO, Gro-beta or IL-8.

19. An in vitro or ex vivo method for enhancing stimulation of megakaryocyte maturation and/or platelet production which comprises adding an effective amount of a

compound as described in Claim 1 to the culture medium of cells that express the TPO receptor.

20. An in vitro or ex vivo method for enhancing stimulation of megakaryocyte maturation and/or platelet production which comprises adding an effective amount of a compound as described in Claim 1 to the culture medium of stem cells, bone marrow cells, cord-blood cells or peripheral blood cells.

21. A method of claim 20, wherein the megakaryocytes or platelets are returned to the mammal following chemotherapy or radiation therapy.

22. An in vitro or ex vivo method for enhancing the survival and/or proliferation of stem cells, bone marrow cells, cord-blood cells, peripheral blood cells or other types of cells expressing the TPO receptor in culture which comprises culturing said cell in a medium containing an effective amount of a compound as described in Claim 1.

23. A method of claim 22 further comprising co-administration of a therapeutically effective amount of a colony stimulating factor, cytokine, chemokine, interleukin or cytokine receptor agonist.

24. A method of claim 22 wherein the stem cells are returned to the mammal following chemotherapy or radiation therapy.

25. A method of treating of neutropenia in a mammal, including a human, in need thereof which comprises administering to such mammal a therapeutically effective amount of a compound as described in claim 1.

26. An in vitro or ex vivo method for enhancing stimulation of neutrophil production which comprises adding an effective amount of a compound as described in Claim 1 to the culture medium of stem cells, bone marrow cells, cord-blood cells, peripheral blood cells or other types of cells expressing the TPO receptor.

27. A method of claim 26, wherein the neutrophils are returned to the mammal following chemotherapy or radiation therapy.

28. A method of claim 3 wherein said thrombocytopenia is due to myelosuppression caused by chemotherapy or radiation therapy.

29. A method of claim 3 wherein said thrombocytopenia is due to an organ transplant.

30. A method of claim 3 wherein said thrombocytopenia is due to bone marrow, stem cell, or liver transplant.

31. A method of claim 3 wherein said thrombocytopenia is due to idiopathic thrombocytopenia purpura (ITP).

32. A method of claim 3 wherein said thrombocytopenia is due to myelodysplastic syndromes (MDS), aplastic anemia or leukemia.

33. A method of claim 3 wherein said thrombocytopenia is due to viral, fungal, microbial or parasitic infection.

34. A method of claim 3 wherein said thrombocytopenia is due to liver dysfunction.

35. A method of claim 3 wherein said thrombocytopenia is due to surgical procedures.

36. A method of claim 3 wherein said thrombocytopenia is due to treatment with antiviral or antibiotic agents.

37. A process for preparing the compound of claim 1, which process comprises:

i) dissolving 3'-[(2Z)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid in an appropriate organic solvent, to form a solution;

ii) adding two or more equivalents of ethanolamine to the solution; and

iii) isolating the prepared compound.