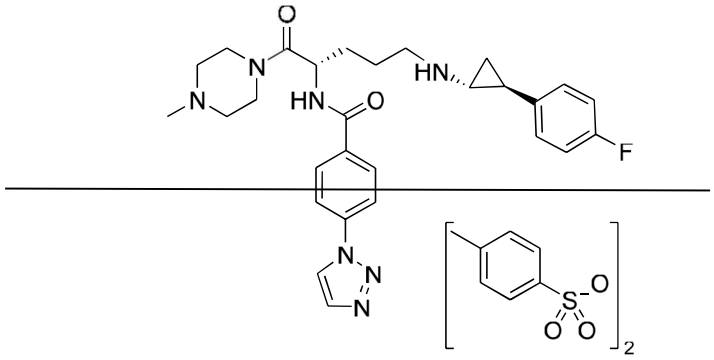
CLAIMS

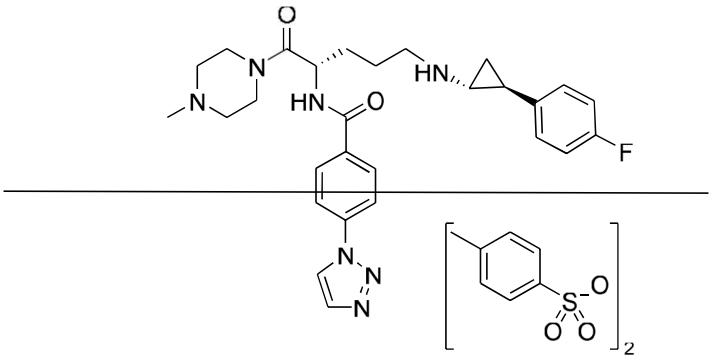
What is claimed is:

1. ~~A method of treating a myeloproliferative neoplasm, comprising administering to a subject in need thereof an amount of *N* [(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)-cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt~~



~~("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.~~

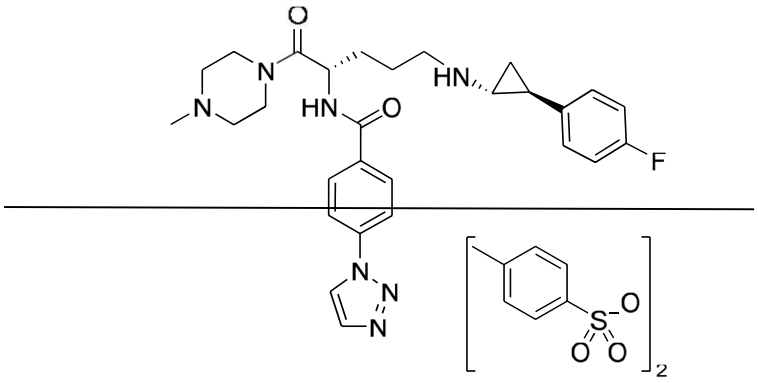
2. ~~A method for reducing the concentration of one or more protein growth factors secreted by bone marrow cells that activate one or more cell types that secrete reticulin and collagen in a subject in need thereof, the method comprising administering an amount of *N* [(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)-cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-~~



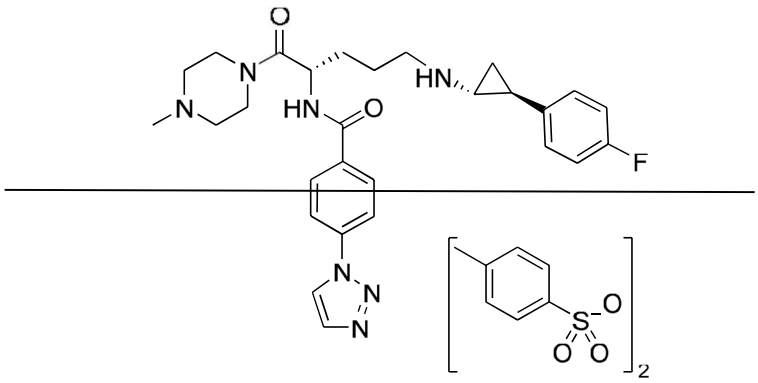
~~tosylate salt~~

~~("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.~~

3. The method as recited in claim 2, wherein the one or more protein growth factors is/are chosen from a platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor beta 1 and platelet factor 4 (aka CXCL4).
4. The method as recited in claim 2 or claim 3, wherein the bone marrow cells that activate one or more cell types that secrete reticulin and collagen are megakaryocytes.
5. The method as recited in any of claims 2-4, wherein the one or more cell types that secrete reticulin and collagen is chosen from stromal cells and/or bone marrow resident fibroblasts and/or myofibroblasts.
6. A method for reducing the concentration of one or more protein growth factors secreted by bone marrow cells that impair the function of bone marrow osteoclasts to reduce the amount of bone marrow osteosclerosis in a subject in need thereof, the method comprising administering an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

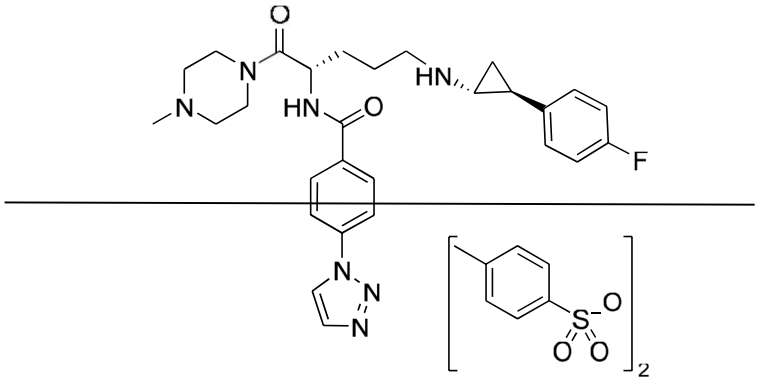


("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.
7. The method as recited in claim 6, wherein the bone marrow cells that that impair the function of bone marrow osteoclasts to reduce the amount of bone marrow osteosclerosis in the subject are megakaryocytes.
8. A method for reducing bone marrow cellularity to age-adjusted normocellularity with fewer than 5% blast cells in a subject in need thereof, the method comprising administering an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



(“Compound 1”) sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

9. A method for maintaining the bone marrow blast count or reducing the bone marrow blast count to <5% in a subject in need thereof, the method comprising administering an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

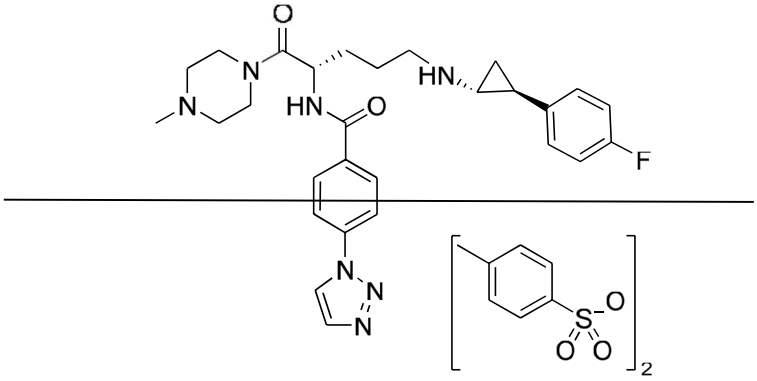


(“Compound 1”) sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

10. A method for suppressing proliferation of malignant myeloid cells in a subject in need thereof, comprising administering to the subject an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

(“Compound 1”) sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

11. A method for reducing the malignant cell burden measured by the mutant allele frequency of myeloid cells in a subject in need thereof, the method comprising administering a therapeutically effective and non-deleterious amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

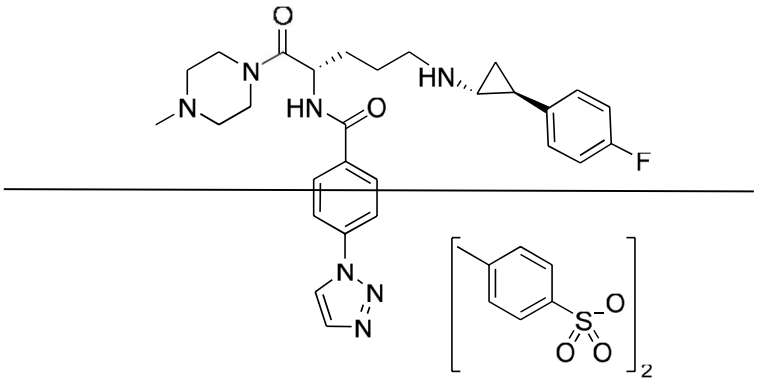


("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

12. A method for eliminating malignant myeloid cells in a subject in need thereof, the method comprising administering a therapeutically effective and non-deleterious amount *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

13. A method for reducing reticulin and collagen bone marrow fibrosis in a subject in need thereof, comprising administering to the subject an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



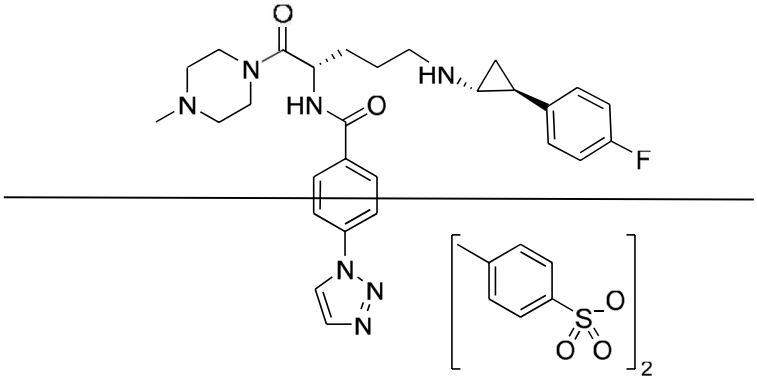
("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

14. A method for reducing plasma levels of one or more inflammatory cytokines in a subject in need thereof, comprising administering to the subject an amount of *N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

15. The method as recited in claim 14, wherein the one or more inflammatory cytokines is one or more cytokines chosen from IFN γ, TNFα, IL-1β, IL-6, IL-8, CXCL4, and CXCL10, S100A9, and RANTES.

16. A method for reducing mutant allele burden in a subject in need thereof, comprising administering to the subject an amount of *N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

17. The method as recited in claim 16, wherein said mutant allele is an allele of one or more genes chosen from Janus Kinase 2 (*JAK2*), myeloproliferative leukemia virus oncogene *(MPL)* and calreticulin (*CALR*).

18. A method for reducing a pathologically elevated red blood cell mass in a subject in need thereof, the method comprising administering to the subject an amount of *N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)-cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

19. The method as recited in claim 18, wherein said subject has polycythemia vera.

20. The method as recited in claim 18, wherein the elevated blood cell mass is measured as hematocrit or blood hemoglobin.

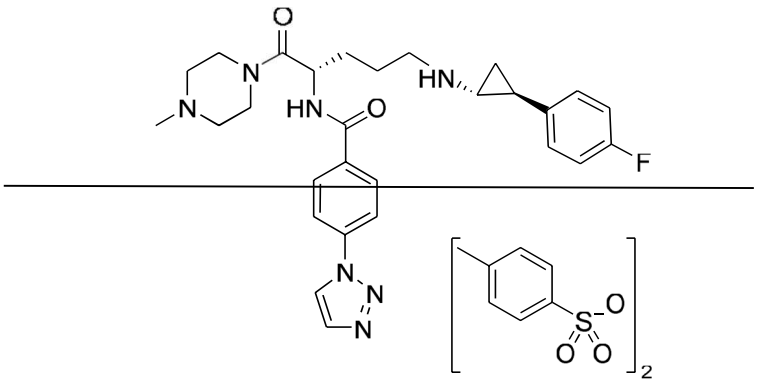
21. The method as recited in claim 20, wherein measured blood hemoglobin has a value greater than 16.5 g/dL for a male subject or greater than 16.0 g/dL for a female subject.

22. The method as recited in claim 20, wherein measured hematocrit is greater than 49% for a male subject or greater than 48% for a female subject.

23. The method as recited in claim 18, wherein the elevated blood cell mass is measured by isotopic red cell mass measurement.

24. The method as recited in claim 23, wherein the increased red cell mass is greater than 25% above mean normal predicted value.

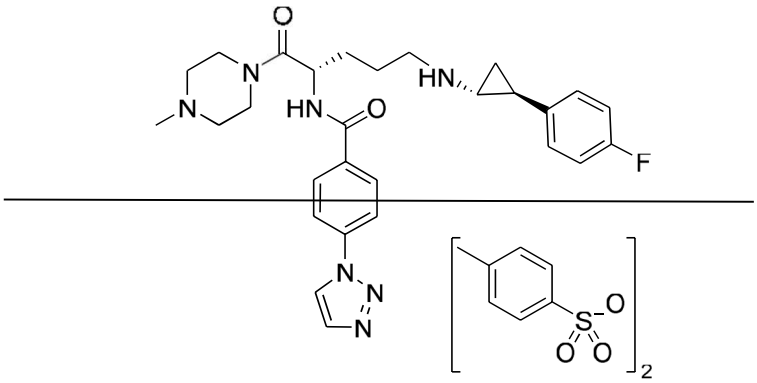
25. A method for reducing the mass of malignant myeloid cells in a subject in a subject in need thereof, comprising administering to the subject an amount of *N* [(2*S*) 5 {[(1*R*, 2*S*) 2 (4 fluorophenyl) cyclopropyl]amino} 1 (4 methylpiperazin 1 yl) 1 oxopentan 2 yl] 4 (1H 1,2,3 triazol 1 yl)benzamide, bis tosylate salt



("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

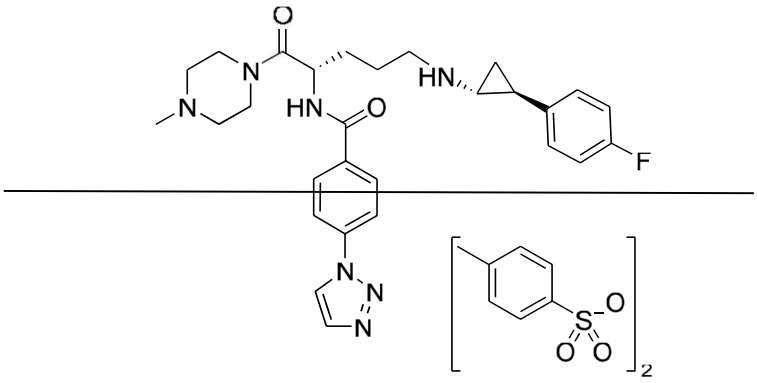
26. The method as recited in claim 25, wherein the cells are neutrophils.

27. A method for reducing abnormal spleen size or volume in a subject in need thereof, the method comprising administering to the subject an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

28. A method for reducing the amount of extramedullary hematopoiesis in a subject in need thereof, the method comprising administering to the subject an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

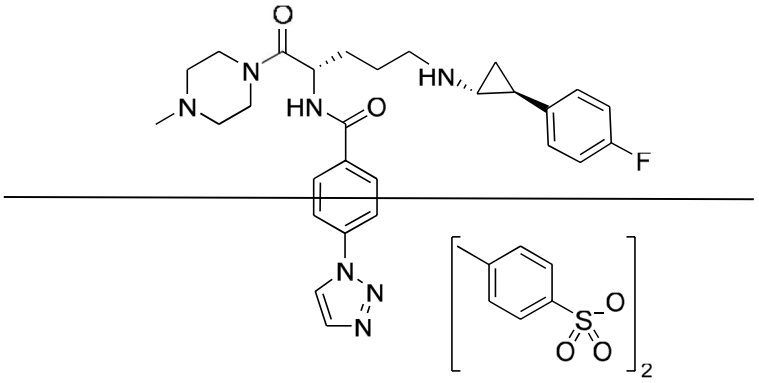


("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

29. The method as recited in claim 28, wherein the amount of extramedullary hematopoiesis is measured by splenomegaly.

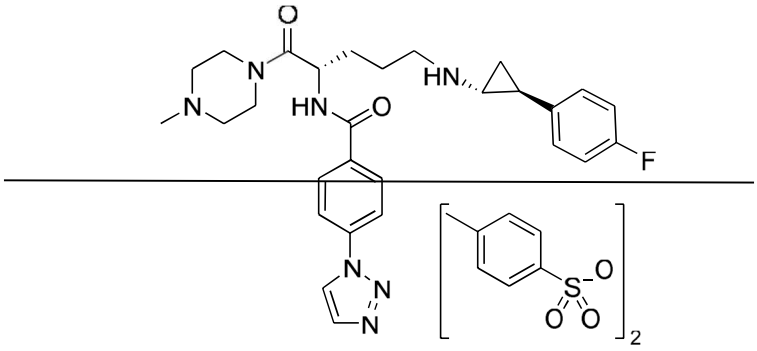
30. The method as recited in claim 29, wherein splenomegaly in said subject is reduced by at least 35 %.

31. A method for reducing the frequency of thrombosis and hemorrhage in a subject in need thereof, the method comprising administering an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

32. A method for reducing the constitutional symptoms of myelofibrosis measured by a subject-reported survey in a subject having myelofibrosis, the method comprising administering to the subject an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1") sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

33. The method as recited in claim 32, wherein said constitutional symptoms comprise one or more symptoms chosen from fatigue, early satiety, abdominal discomfort, inactivity,

problems with concentration, numbness and/or tingling in the hands and feet, night sweats, pruritis, bone pain, fever greater than 100° F, and unintentional weight loss.

34. The method as recited in claim 32 or 33, wherein said subject-reported survey is the Myeloproliferative Neoplasm Assessment Form Total Symptom Score (MPN-SAF:TSS).

35. The method as recited in claim 34, wherein one or more symptoms is reduced by at least 50% in its ranking on the MPN-SAF:TSS score.

36. The method as recited in any of claims 1-35, wherein the subject in need has a myeloproliferative neoplasm.

37. The method as recited in claim 36, wherein the myeloproliferative neoplasm is myelofibrosis (MF).

38. The method as recited in claim 37, wherein the myelofibrosis is chosen from primary myelofibrosis (PMF), post-PV myelofibrosis (PPV-MF), and post-ET myelofibrosis (PET-MF).

39. The method as recited in claim 38, wherein the myelofibrosis is primary myelofibrosis (PMF).

40. The method as recited in claim 36, wherein the myeloproliferative neoplasm is polycythemia vera (PV).

41. The method as recited in claim 36, wherein the myeloproliferative neoplasm is essential thrombocythemia (ET).

42. The method as recited in any of claims 1-41, wherein said subject has, or the subject's malignant myeloid cells have, a mutation in one or more genes chosen from Janus Kinase 2 (*JAK2*), myeloproliferative leukemia virus oncogene *(MPL)* and calreticulin (*CALR*).

43. The method as recited claim 42, further comprising the step of determining whether said subject has mutations in one or more genes chosen from Janus Kinase 2 (*JAK2*), myeloproliferative leukemia virus oncogene *(MPL)* and calreticulin (*CALR*).

44. The method as recited in any one of claims 1-43, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 75 x 10^9 platelets/L.

45. The method as recited in any one of claims 1-44, wherein the amount of Compound 1 is about 0.5 mg/kg/d to about 1.5 mg/kg/d.

46. The method as recited in claim 45, wherein the amount of Compound 1 is about 0.7 mg/kg/d to about 1.2 mg/kg/d.

47. The method as recited in any one of claims 1-44, wherein the amount of Compound 1 is

about 40 mg to about 100 mg per day.

48. The method as recited in claim 47, wherein the amount of Compound 1 is about 50 mg to about 85 mg per day.

49. The method as recited in any one of claims 1-44, wherein the subject is administered a starting dose of 0.5 mg/kg/d Compound 1, then, after one week:

if platelet count is ≥ 90 x 10^9 platelets/L and the % platelet reduction is < 50% from previous visit, the subject's dose is adjusted to add 0.2 mg/kg/d Compound 1 to the daily dose;

if platelet count is ≥ 90 x 10^9 platelets/L and the % platelet reduction is ≥ 50% from previous visit, the subject's dose is adjusted to add 0.1 mg/kg/d Compound 1 to the daily dose;

if platelet count is between 40 x 10^9 platelets/L and 89 x 10^9 platelets/L, the daily dose of Compound 1 is maintained;

if platelet count is between 25 x 10^9 platelets/L and 39 x 10^9 platelets/L, the subject's dose is adjusted to decrease the current mg/kg daily dose of Compound 1 by 25%;

if platelet count is < 25 x 10^9 platelets/L, withhold dosing until platelets return to > 50 x 10^9 platelets/L, then the subject's dose is adjusted to administer Compound 1 at 50% of the dose that was administered when platelet count fell below 25 x 10^9 platelets/L; and optionally, approximately weekly throughout the course of therapy, repeating the platelet count assessment and dose adjustment steps until the subject's platelet count is about 50 x 10^9 to about 100 x 10^9 platelets/L.

50. A method of treating a myeloproliferative neoplasm and achieving a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L in a subject, comprising:

administering a starting dose of 0.5 mg/kg/d Compound 1;

after about one week, assessing the subject's platelet count;

if platelet count is ≥ 90 x 10^9 platelets/L and the % platelet reduction is < 50% from previous visit, add 0.2 mg/kg/d Compound 1 to the daily dose;

if platelet count is ≥ 90 x 10^9 platelets/L and the % platelet reduction is ≥ 50% from previous visit, add 0.1 mg/kg/d Compound 1 to the daily dose;

if platelet count is between 40 x 10^9 platelets/L and 89 x 10^9 platelets/L, maintain the current daily dose of Compound 1;

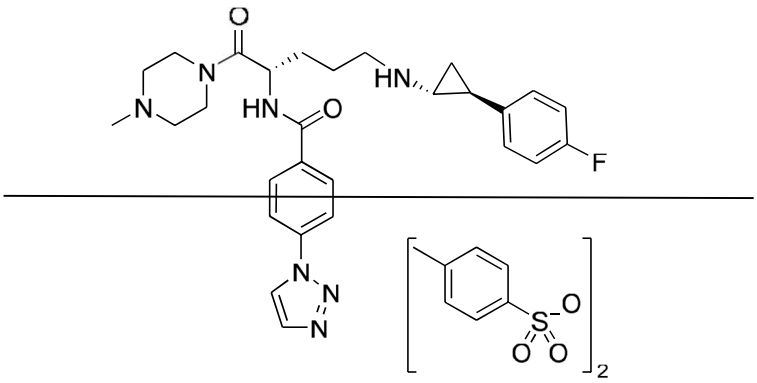
if platelet count is between 25 x 10^9 platelets/L and 39 x 10^9 platelets/L, decrease the current mg/kg daily dose of Compound 1 by 25%;

if platelet count is < 25 x 10^9 platelets/L, withhold dosing until platelets return to > 50 x 10^9 platelets/L, then administer Compound 1 at 50% of the dose that was administered when platelet count fell below 25 x 10^9 platelets/L; and

optionally, repeating the platelet count assessment and dose adjustment steps approximately weekly until the subject's platelet count is about 50 x 10^9 to about 100 x 10^9 platelets/L.

51. A method of treating a myeloproliferative neoplasm in a subject in need thereof wherein the subject has a mutant allele, said method comprising:

administering to the subject an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1").

52. The method as recited in claim 51,wherein said mutant allele is an allele of one or more genes chosen from Janus Kinase 2 (*JAK2*), such as *JAK*^{V617F}, myeloproliferative leukemia virus oncogene (*MPL*), such as *MPL*^{W515K}, and calreticulin (*CALR*), such as *CALR*^{52b_del}, *CALR*^{K385NCX}, or *CALR*^{KKRK374X}.

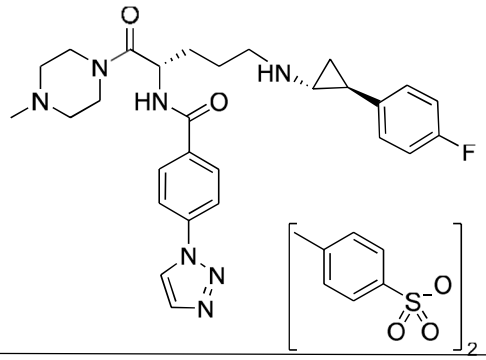
53. The method as recited in claim 51,wherein said mutant allele is an allele of one or more genes chosen from chosen from *DNMT3A, IDH1/2, TET2, ASXLI, EZH2, TP53, NF1, NRAS, KRAS, SF3B1, U2AF1, SRSF2 ,RUNX1, CBL, ZBTB33, PRPF8, CNTN5, FREM2, MAP1B,* and*GPR183.*

54. The method as recited in claim 53, wherein said mutant allele is one or more of ASXL1^{HHCHREAA630X}, ASXL1^{-642X}, ASXL1^{Q780*}, ASXL1^{R693}, ASXL1^{-884X*}, ASXL1^{-642X}, ASXL1^{QLL695HX}, and ASXL1^{Q768*}.

55. The method as recited in claim 51, wherein said mutant allele is an allele of the gene Biorientation Of Chromosomes In Cell Division 1 Like 1 (*BOD1L1*).

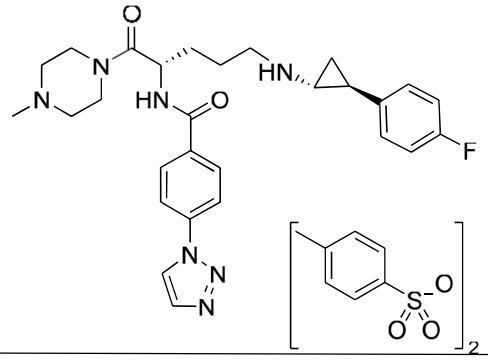
56. The method as recited in claim 55, wherein the mutant allele is one or more of BOD1L1^{S1623C}, BOD1L1^{E1612K}, BOD1L1^{K1136N}, BOD1L1^{R1074W}, BOD1L1^{Y812C}, BOD1L1^{E289K}, and BOD1L1^{R508S}.

1. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1- yl)benzamide, bis-tosylate salt



("Compound 1") in the manufacture of a medicament for treating a myeloproliferative neoplasm in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

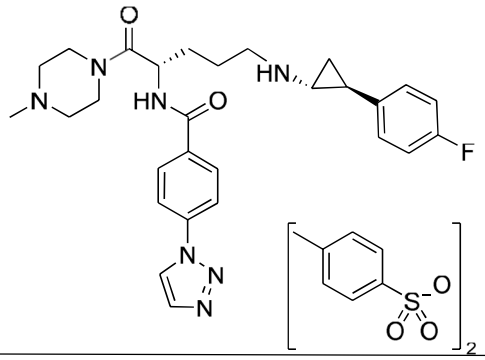
2. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)- 1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



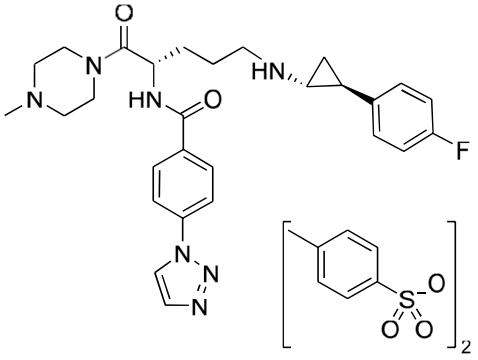
("Compound 1") in the manufacture of a medicament for reducing the concentration of one or more protein growth factors secreted by bone marrow cells that activate one or more cell types that secrete reticulin and collagen in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

3. The use as recited in claim 2, wherein the one or more protein growth factors is/are chosen from a platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor beta 1 and platelet factor 4 (aka CXCL4).

4. The use as recited in claim 2 or claim 3, wherein the bone marrow cells that activate one or more cell types that secrete reticulin and collagen are megakaryocytes.
5. The use as recited in any of claims 2-4, wherein the one or more cell types that secrete reticulin and collagen is chosen from stromal cells and/or bone marrow-resident fibroblasts and/or myofibroblasts.
6. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1- yl)benzamide, bis-tosylate salt

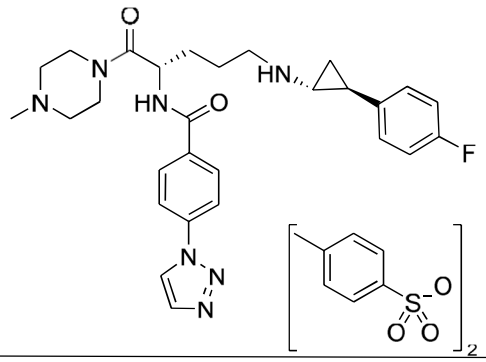


("Compound 1") in the manufacture of a medicament for reducing the concentration of one or more protein growth factors secreted by bone marrow cells that impair the function of bone marrow osteoclasts to reduce the amount of bone marrow osteosclerosis in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.
7. The use as recited in claim 6, wherein the bone marrow cells that that impair the function of bone marrow osteoclasts to reduce the amount of bone marrow osteosclerosis in the subject are megakaryocytes.
8. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}- 1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



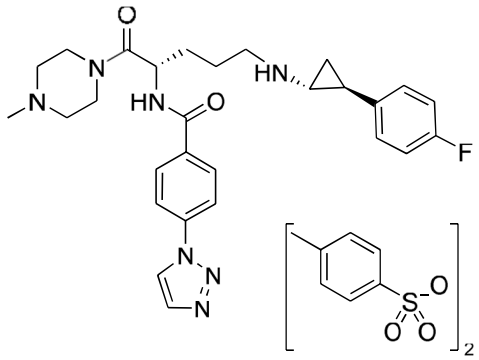
("Compound 1") in the manufacture of a medicament for reducing bone marrow cellularity to age-adjusted normocellularity with fewer than 5% blast cells in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

9. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



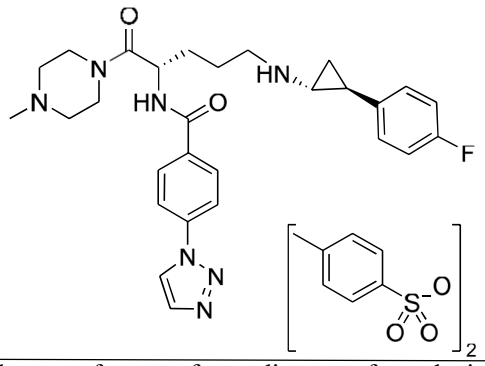
("Compound 1") in the manufacture of a medicament for maintaining the bone marrow blast count or reducing the bone marrow blast count to <5% in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

10. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4- fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H- 1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



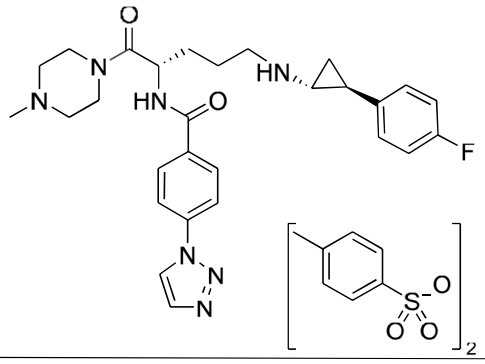
("Compound 1") in the manufacture of a medicament for suppressing proliferation of malignant myeloid cells in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

11. Use of a therapeutically effective and non-deleterious amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4- fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H- 1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



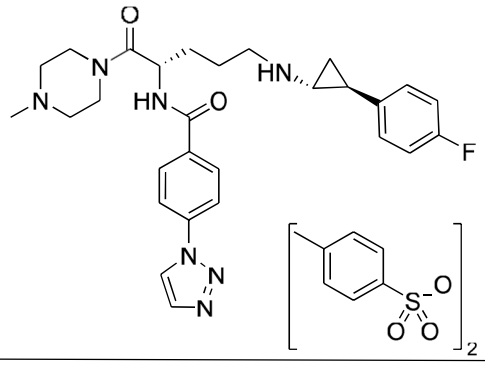
("Compound 1") in the manufacture of a medicament for reducing the malignant cell burden measured by the mutant allele frequency of myeloid cells in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

12. Use of a therapeutically effective and non-deleterious amount *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1- oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



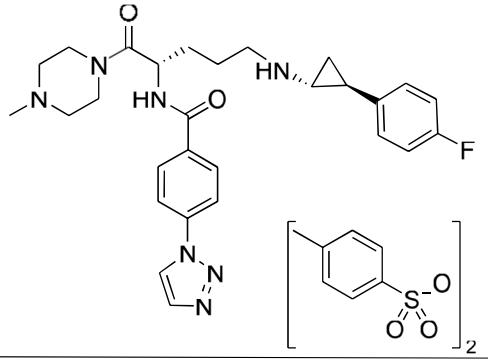
("Compound 1") in the manufacture of a medicament for eliminating malignant myeloid cells in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

13. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4- fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H- 1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1") in the manufacture of a medicament for reducing reticulin and collagen bone marrow fibrosis in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

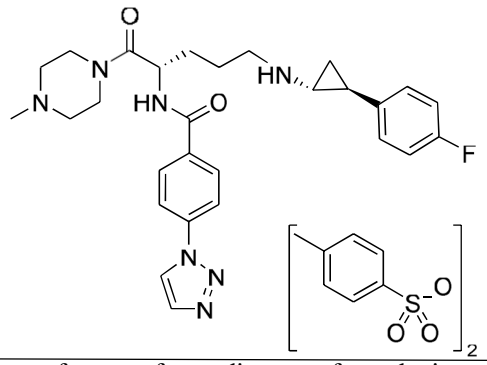
14. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2- yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1") in the manufacture of a medicament for reducing plasma levels of one or more inflammatory cytokines in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

15. The use as recited in claim 14, wherein the one or more inflammatory cytokines is one or more cytokines chosen from IFN-γ, TNFα, IL-1β, IL-6, IL-8, CXCL4, and CXCL10, S100A9, and RANTES.

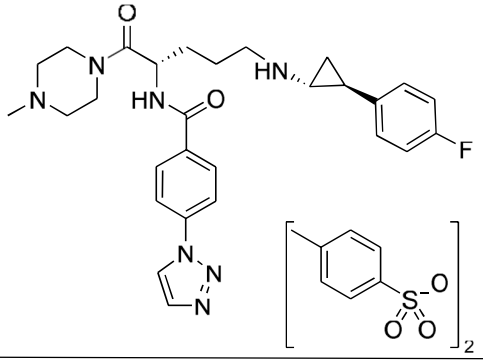
16. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1- yl)benzamide, bis-tosylate salt



("Compound 1") in the manufacture of a medicament for reducing mutant allele burden in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

17. The use as recited in claim 16, wherein said mutant allele is an allele of one or more genes chosen from Janus Kinase 2 (*JAK2)*, myeloproliferative leukemia virus oncogene *(MPL)* and calreticulin (*CALR*).

18. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1- oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1") in a manufacture of a medicament for reducing a pathologically elevated red blood cell mass in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

19. The use as recited in claim 18, wherein said subject has polycythemia vera.

20. The use as recited in claim 18, wherein the elevated blood cell mass is measured as hematocrit or blood hemoglobin.

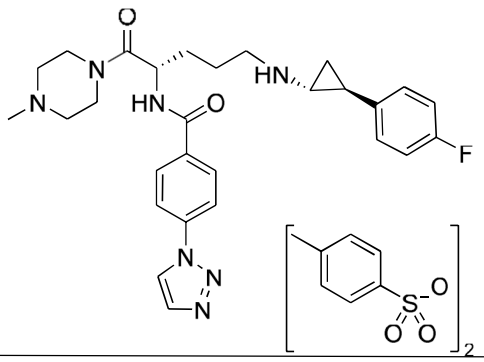
21. The use as recited in claim 20, wherein measured blood hemoglobin has a value greater than 16.5 g/dL for a male subject or greater than 16.0 g/dL for a female subject.

22. The use as recited in claim 20, wherein measured hematocrit is greater than 49% for a male subject or greater than 48% for a female subject.

23. The use as recited in claim 18, wherein the elevated blood cell mass is measured by isotopic red cell mass measurement.

24. The use as recited in claim 23, wherein the increased red cell mass is greater than 25% above mean normal predicted value.

25. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)- 2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4- (1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

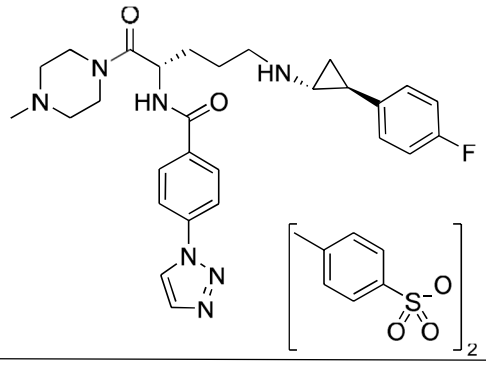


("Compound 1") in the manufacture of a medicament for reducing the mass of malignant

myeloid cells in a subject in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

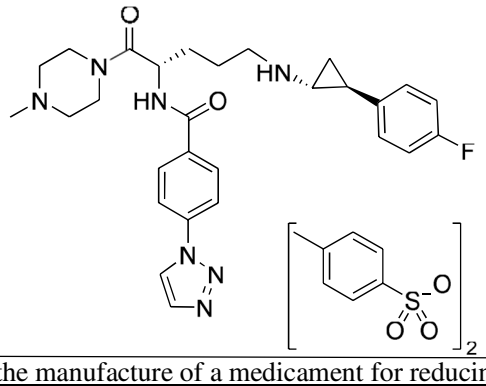
26. The use as recited in claim 25, wherein the cells are neutrophils.

27. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4- fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H- 1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1") in the manufacture of a medicament for reducing abnormal spleen size or volume in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

28. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1- oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt

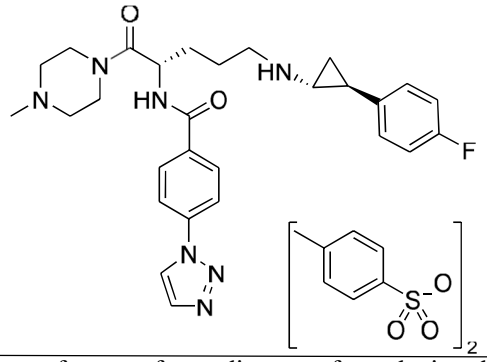


("Compound 1") in the manufacture of a medicament for reducing the amount of extramedullary hematopoiesis in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

29. The use as recited in claim 28, wherein the amount of extramedullary hematopoiesis is measured by splenomegaly.

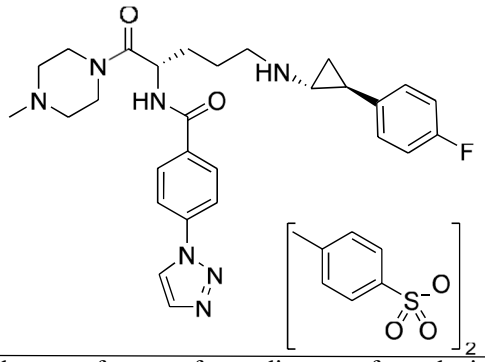
30. The use as recited in claim 29, wherein splenomegaly in said subject is reduced by at least 35 %.

31. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4- fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H- 1,2,3-triazol-1-yl)benzamide, bis-tosylate salt



("Compound 1") in the manufacture of a medicament for reducing the frequency of thrombosis and hemorrhage in a subject in need thereof, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

32. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1- yl)benzamide, bis-tosylate salt



("Compound 1") in the manufacture of a medicament for reducing the constitutional symptoms of myelofibrosis measured by a subject-reported survey in a subject having myelofibrosis, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L.

33. The use as recited in claim 32, wherein said constitutional symptoms comprise one or more symptoms chosen from fatigue, early satiety, abdominal discomfort, inactivity, problems with concentration, numbness and/or tingling in the hands and feet, night sweats, pruritis, bone pain, fever greater than 100° F, and unintentional weight loss.

34. The use as recited in claim 32 or 33, wherein said subject-reported survey is the Myeloproliferative Neoplasm Assessment Form Total Symptom Score (MPN-SAF:TSS).

35. The use as recited in claim 34, wherein one or more symptoms is reduced by at least 50% in its ranking on the MPN-SAF:TSS score.

36. The use as recited in any of claims 1-35, wherein the subject in need has a myeloproliferative neoplasm.

37. The use as recited in claim 36, wherein the myeloproliferative neoplasm is myelofibrosis (MF).

38. The use as recited in claim 37, wherein the myelofibrosis is chosen from primary myelofibrosis (PMF), post-PV myelofibrosis (PPV-MF), and post-ET myelofibrosis (PET-MF).

39. The use as recited in claim 38, wherein the myelofibrosis is primary myelofibrosis (PMF).

40. The use as recited in claim 36, wherein the myeloproliferative neoplasm is polycythemia vera (PV).

41. The use as recited in claim 36, wherein the myeloproliferative neoplasm is essential thrombocythemia (ET).

42. The use as recited in any of claims 1-41, wherein said subject has, or the subject's malignant myeloid cells have, a mutation in one or more genes chosen from Janus Kinase 2 (*JAK2)*, myeloproliferative leukemia virus oncogene *(MPL)* and calreticulin (*CALR*).

43. The use as recited claim 42, further comprising the step of determining whether said subject has mutations in one or more genes chosen from Janus Kinase 2 (*JAK2)*, myeloproliferative leukemia virus oncogene *(MPL)* and calreticulin (*CALR*).

44. The use as recited in any one of claims 1-43, wherein the amount of Compound 1 is sufficient to maintain in the subject a platelet count of about 50 x 10^9 to about 75 x 10^9 platelets/L.

45. The use as recited in any one of claims 1-44, wherein the amount of Compound 1 is about 0.5 mg/kg/d to about 1.5 mg/kg/d.

46. The use as recited in claim 45, wherein the amount of Compound 1 is about 0.7 mg/kg/d to about 1.2 mg/kg/d.

47. The use as recited in any one of claims 1-44, wherein the amount of Compound 1 is about 40 mg to about 100 mg per day.

48. The use as recited in claim 47, wherein the amount of Compound 1 is about 50 mg to about 85 mg per day.

49. The use as recited in any one of claims 1-44, wherein the subject is administered a starting dose of 0.5 mg/kg/d Compound 1, then, after one week:

if platelet count is $\geq$ 90 x 10^9 platelets/L and the % platelet reduction is < 50% from previous visit, the subject's dose is adjusted to add 0.2 mg/kg/d Compound 1 to the daily dose;

if platelet count is $\geq$ 90 x 10^9 platelets/L and the % platelet reduction is $\geq$ 50% from previous visit, the subject's dose is adjusted to add 0.1 mg/kg/d Compound 1 to the daily dose;

if platelet count is between 40 x 10^9 platelets/L and 89 x 10^9 platelets/L, the daily dose of Compound 1 is maintained;

if platelet count is between 25 x 10^9 platelets/L and 39 x 10^9 platelets/L, the subject's dose is adjusted to decrease the current mg/kg daily dose of Compound 1 by 25%;

if platelet count is < 25 x 10^9 platelets/L, withhold dosing until platelets return to > 50 x 10^9 platelets/L, then the subject's dose is adjusted to administer Compound 1 at 50% of the dose that was administered when platelet count fell below 25 x 10^9 platelets/L; and

optionally, approximately weekly throughout the course of therapy, repeating the platelet count assessment and dose adjustment steps until the subject's platelet count is about 50 x 10^9 to about 100 x 10^9 platelets/L.

50. Use of Compound 1 in the manufacture of a medicament for treating a myeloproliferative neoplasm and achieving a platelet count of about 50 x 10^9 to about 100 x 10^9 platelets/L in a subject, wherein a starting dose of 0.5 mg/kg/d Compound 1 is to be administered; after about one week, the subject's platelet count is to be assessed;

if platelet count is ≥ 90 x 10^9 platelets/L and the % platelet reduction is < 50% from previous visit, 0.2 mg/kg/d Compound 1 is to be added to the daily dose;

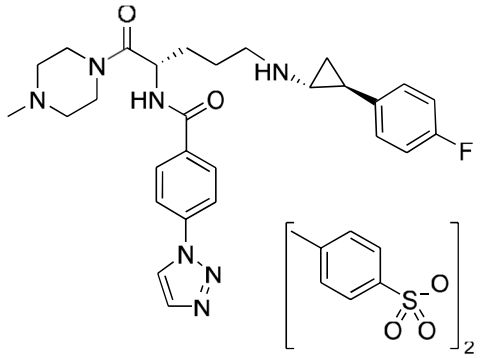
if platelet count is ≥ 90 x 10^9 platelets/L and the % platelet reduction is ≥ 50% from previous visit, 0.1 mg/kg/d Compound 1 is to be added to the daily dose;

if platelet count is between 40 x 10^9 platelets/L and 89 x 10^9 platelets/L, the current daily dose of Compound 1 is to be maintained;

if platelet count is between 25 x 10^9 platelets/L and 39 x 10^9 platelets/L, the current mg/kg daily dose of Compound 1 is to be decreased by 25%; if platelet count is < 25 x 10^9 platelets/L, dosing is to be withheld until platelets return to > 50 x 10^9 platelets/L, then Compound 1 is to be administered at 50% of the dose that was administered when platelet count fell below 25 x 10^9 platelets/L; and

optionally, the platelet count assessment and dose adjustment steps are to be repeated approximately weekly until the subject's platelet count is about 50 x 10^9 to about 100 x 10^9 platelets/L.

51. Use of an amount of *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1- yl)benzamide, bis-tosylate salt



("Compound 1") in the manufacture of a medicament for treating myeloproliferative neoplasm in a subject in need thereof wherein the subject has a mutant allele.

52. The use as recited in claim 51,wherein said mutant allele is an allele of one or more genes chosen from Janus Kinase 2 (*JAK2*), such as JAK^{V617F}, myeloproliferative leukemia virus oncogene *(MPL*), such as MPL^{W515K}, and calreticulin (*CALR*), such as $CALR^{52b_del}$, $CALR^{K385NCX}$, or $CALR^{KKRK374X}$.

53. The use as recited in claim 51,wherein said mutant allele is an allele of one or more genes chosen from chosen from *DNMT3A, IDH1/2, TET2, ASXLI, EZH2*, *TP53, NF1, NRAS, KRAS, SF3B1, U2AF1, SRSF2 ,RUNX1, CBL, ZBTB33, PRPF8, CNTN5, FREM2, MAP1B,* and*GPR183.*

54. The use as recited in claim 53, wherein said mutant allele is one or more of $ASXL1^{HHCHREAA630X}$, $ASXL1^{-642X}$, $ASXL1^{Q780*}$, $ASXL1^{R693}$, $ASXL1^{-884X*}$, $ASXL1^{-642X}$, $ASXL1^{QLL695HX}$, and $ASXL1^{Q768*}$.

55. The use as recited in claim 51, wherein said mutant allele is an allele of the gene Biorientation Of Chromosomes In Cell Division 1 Like 1 (*BOD1L1*).

56. The use as recited in claim 55, wherein the mutant allele is one or more of $BOD1L1^{S1623C}$, $BOD1L1^{E1612K}$, $BOD1L1^{K1136N}$, $BOD1L1^{R1074W}$, $BOD1L1^{Y812C}$, $BOD1L1^{E289K}$, and $BOD1L1^{R508S}$.