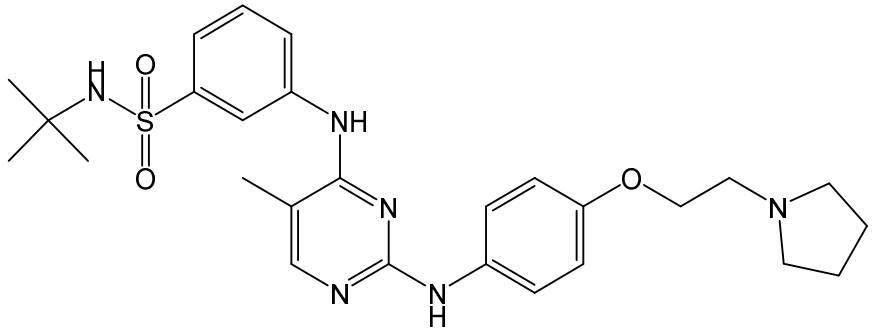
WHAT IS CLAIMED IS:

1. Use of a compound of formula (I):



(I);

or a pharmaceutically acceptable salt and/or a solvate thereof in the manufacture of a medicament for treating a myeloproliferative disorder in a patient in need thereof, wherein an effective amount of the compound is to be administered to the patient, wherein a dual CYP2C19 and CYP3A4 inhibitor is to be concurrently received by the patient.

2. The use of claim 1, wherein the solvate is a hydrate.

3. The use of claim 1 or 2, wherein the pharmaceutically acceptable salt is a hydrochloride salt or a hydrate thereof.

4. The use of any one of claims 1 to 3, wherein the dihydrochloride monohydrate of the compound of formula (I) is to be administered.

5. The use of any one of claims 1 to 4, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a standard dose.

6. The use of any one of claims 1 to 4, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose less than a standard dose.

7. The use of claim 5 or 6, wherein the standard dose is about 400 mg/day.

8. The use of any one of claims 1 to 4, 6, or 7, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose that is about 1/2 of a standard dose.

9. The use of any one of claims 1 to 4 or 6 to 8, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose of about 200 mg/day.

10. The use of any one of claims 1-4, 6, or 7 wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose that is about 1/4 of a standard dose.

11. The use of any one of claims 1 to 4, 6, 7, or 10, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose of about 100 mg/day.

12. The use of any one of claims 1 to 11, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered once daily.

13. The use of any one of claims 1 to 4, 6, or 7, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose that is about 1/8 a standard dose.

14. The use of any one of claims 1 to 4, 6, 7, or 13, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose of about 50 mg/day.

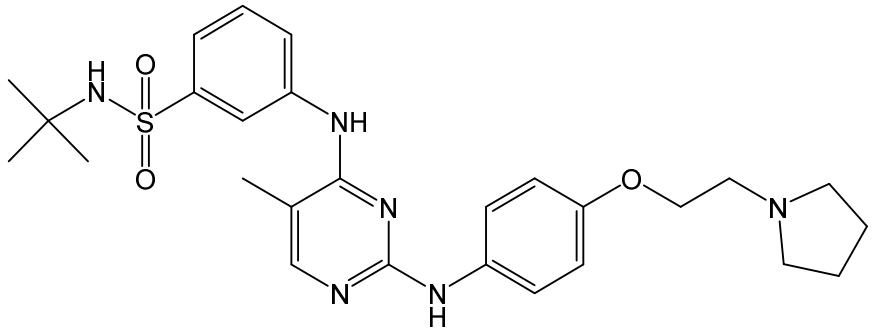
15. The use of any one of claims 1-4, 6, 7, or 13, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered every other day.

16. The use of any one of claims 1 to 4, 6, 7, 13, and 15, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose of about 100 mg every other day.

17. The use of any one of claims 1 to 16, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered orally.

18. Use of

a compound of formula (I):



(I);

or a pharmaceutically acceptable salt and/or a solvate thereof in the manufacture of a medicament for treating a myeloproliferative disorder in a patient receiving a dual CYP2C19 and CYP3A4 inhibitor, wherein

(a) an effective amount of the compound is to be administered to the patient;

(b) the patient is to be monitored for adverse reactions; and

(c) in response to said monitoring, the dose of the compound of formula (I) or the pharmaceutically acceptable salt and/or solvate thereof is to be either maintained or adjusted.

19. The use of claim 18, wherein the dose of the compound of formula (I) or the pharmaceutically acceptable salt and/or solvate thereof is to be maintained.

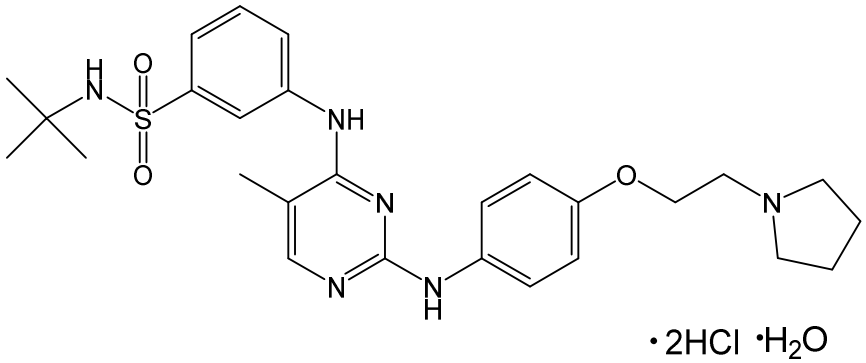
20. The use of claim 18, wherein the dose of the compound of formula (I) or the pharmaceutically acceptable salt and/or solvate thereof is to be adjusted.

21. The use of claim 20, wherein the dose of the compound of formula (I) or the pharmaceutically acceptable salt and/or solvate thereof is to be lowered.

22. The use of any one of claims 1 to 21, wherein the dual CYP2C19 and CYP3A4 inhibitor is selected from itraconazole, fluconazole, fluvoxamine, voriconazole, and combinations thereof.

23. The use of any one of claims 1 to 22, wherein the dual CYP2C19 and CYP3A4 inhibitor is fluconazole.

24. The use of any one of claims 1 to 23, wherein the patient is to be administered a compound of formula (Ia):



(Ia).

25. The use of any one of claims 1 to 24, wherein the myeloproliferative disorder is myelofibrosis.

26. The use of claim 25, wherein the myelofibrosis is primary myelofibrosis.

27. The use of claim 26, wherein the primary myelofibrosis is selected from intermediate risk primary myelofibrosis and high risk primary myelofibrosis.

28. The use of claim 25, wherein the myelofibrosis is secondary myelofibrosis.

29. The use of claim 25, wherein the myelofibrosis is post-essential thrombocythemia myelofibrosis.

30. The use of claim 25, wherein the myelofibrosis is post-polycythemia vera myelofibrosis.

31. The use of any one of claims 1 to 24, wherein the myeloproliferative disorder is acute myeloid leukemia (AML).

32. The use of any one of claims 1 to 24, wherein the myeloproliferative disorder is polycythemia vera.

33. The use of any one of claims 1 to 24, wherein the myeloproliferative disorder is essential thrombocythemia.

34. The use of any one of claims 1 to 33, wherein thiamine or a thiamine equivalent is to be administered to the patient prior to, simultaneously with, or after the compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof.

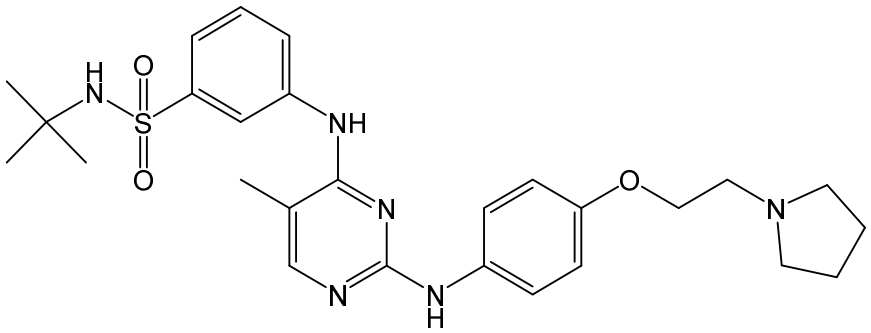
35. The use of claim 34, wherein the thiamine or thiamine equivalent is to be administered orally.

36. The use of claim 35, wherein the thiamine or thiamine equivalent is to be administered intravenously.

37. The use of any one of claims 1 to 36, wherein a 5-HT3 receptor antagonist is to be administered to the patient prior to, simultaneously with, or after the compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof.

38. The use of claim 37, wherein the 5-HT3 receptor antagonist is ondasetron.

39. A method of increasing the safety and/or tolerability of a compound of formula (I):



(I);

or a pharmaceutically acceptable salt and/or a solvate thereof, the method comprising:

(a) monitoring a patient who had been concurrently received a dual CYP2C19 and CYP3A4 inhibitor and has been subsequently administered a dose of the compound of formula (I) or a pharmaceutically acceptable salt and/or a solvate thereof, for adverse reactions; and

(b) in response to said monitoring, determining either to maintain or adjust the dose of the dual CYP2C19 and CYP3A4 inhibitor in the patient to obtain a desired clinical effect.

40. The method of claim 39, wherein the dose of the compound of formula (I) or the pharmaceutically acceptable salt and/or solvate thereof is to be maintained.

41. The method of claim 39, wherein the dose of the compound of formula (I) or the pharmaceutically acceptable salt and/or solvate thereof is to be adjusted.

42. The method of claim 41, wherein the dose of the compound of formula (I) or the pharmaceutically acceptable salt and/or solvate thereof is to be lowered.

43. The method of any one of claims 39 to 42, wherein the solvate is a hydrate.

44. The method of any one of claims 39 to 43, wherein the pharmaceutically acceptable salt is a hydrochloride salt or a hydrate thereof.

45. The method of any one of claims 39 to 44, wherein the dihydrochloride monohydrate of the compound of formula (I) is to be administered.

46. The method of any one of claims 39 to 45, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a standard dose.

47. The method of claim 46, wherein the standard dose is about 400 mg/day.

48. The method of any one of claims 39 to 45 or 47, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose that is about 1/2 of a standard dose.

49. The method of any one of claims 39 to 45, 47, or 48, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose of about 200 mg/day.

50. The method of any one of claims 39 to 45 or 47, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose that is about 1/4 of a standard dose.

51. The method of any one of claims 39 to 45, 47, or 50, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose of about 100 mg/day.

52. The method of any one of claims 39 to 51, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered once daily.

53. The method of any one of claims 39 to 45, or 47, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose that is about 1/8 a standard dose.

54. The method of any one of claims 39 to 45 or 53, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose of about 50 mg/day.

55. The method of any one of claims 39 to 54, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered every other day.

56. The method of any one of claims 39 to 45 or 53, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered at a dose of about 100 mg every other day.

57. The method of any one of claims 39 to 56, wherein an increased dose of the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof is to be administered, if the patient discontinues receiving the dual CYP2C19 and CYP3A4 inhibitor.

58. The method of claim 57, wherein the increased dose is less than the standard dose.

59. The method of claim 57, wherein the increased dose is the standard dose.

60. The method of any one of claims 39 to 59, wherein the safety and/or tolerability is increased relative to that when the standard dose is to be administered to the patient.

61. The method of any one of claims 39 to 60, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof is to be administered, the administration is capable of treating a myeloproliferative disorder in the patient and reducing one or more conditions selected from anemia, thrombocytopenia, gastrointestinal toxicity, hepatic toxicity, amylase elevation, and lipase elevation.

62. The method of any one of claims 39 to 61, wherein the increase in safety and/or tolerability comprises a reduction in toxicity and/or side effects.

63. The method of claim any one of claims 39 to 62, wherein the increased safety and/or tolerability comprises a reduction in one or more conditions selected from anemia, thrombocytopenia, gastrointestinal toxicity, hepatic toxicity, amylase elevation, and lipase elevation.

64. The method of claim 61, wherein the myeloproliferative disorder is myelofibrosis.

65. The method of claim 64, wherein the myelofibrosis is primary myelofibrosis.

66. The method of claim 65, wherein the primary myelofibrosis is selected from intermediate risk primary myelofibrosis and high risk primary myelofibrosis.

67. The method of claim 64, wherein the myelofibrosis is secondary myelofibrosis.

68. The method of claim 64, wherein the myelofibrosis is post-essential thrombocythemia myelofibrosis.

69. The method of claim 64, wherein the myelofibrosis is post-polycythemia vera myelofibrosis.

70. The method of claim 61, wherein the myeloproliferative disorder is acute myeloid leukemia (AML).

71. The method of claim 61, wherein the myeloproliferative disorder is polycythemia vera.

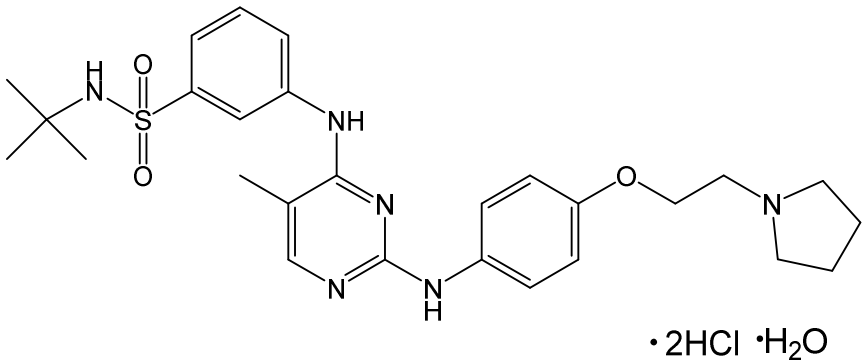
72. The method of claim 61, wherein the myeloproliferative disorder is essential thrombocythemia.

73. The method of any one of claims 39 to 72, wherein the compound of formula (I), or the pharmaceutically acceptable salt and/or solvate thereof, is to be administered orally.

74. The method of any one of claims 39 to 73, wherein the dual CYP2C19 and CYP3A4 inhibitor is selected from itraconazole, fluconazole, fluvoxamine, voriconazole, and combinations thereof.

75. The method of any one of claims 39 to 74, wherein the dual CYP2C19 and CYP3A4 inhibitor is fluconazole.

76. The method of any one of claims 39 to 75, wherein the patient is to be administered a compound of formula (Ia):



(Ia).

77. The method of any one of claims 39 to 76, thiamine or a thiamine equivalent is to be administered to the patient prior to, simultaneously with, or after the compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof.

78. The method of claim 77, wherein the thiamine or thiamine equivalent is to be administered orally.

79. The method of claim 77, wherein the thiamine or thiamine equivalent is to be administered intravenously.

80. The method of any one of claims 39 to 79, a 5-HT3 receptor antagonist is to be administered to the patient prior to, simultaneously with, or after the compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof.

81. The method of claim 80, wherein the 5-HT3 receptor antagonist is ondasetron.