CLAIMS

1. A method for treating anemia, comprising administering to a patient having anemia an effective amount of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof, wherein a daily dose comprises about 150 mg, about 300 mg, about 450 mg, about 600 mg, or about 750 mg of the compound.

2. The method of claim 1, wherein the compound is a pharmaceutically acceptable salt of {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid.

3. The method of claim 1, wherein the compound is a solvate of {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid.

4. The method of claim 1, wherein the compound is a hydrate of {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid.

5. The method of claim 1, wherein the compound is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid.

6. The method of any one of claims 1 to 5 wherein the daily dose comprises about 150 mg, about 300 mg, about 450 mg, or about 600 mg of the compound.

7. The method of claim 1, wherein the anemia is anemia secondary to chronic kidney disease.

8. The method of claim 3, wherein the chronic kidney disease is stage 3, 4, or 5 chronic kidney disease.

9. The method of claim 3 or 8, wherein the chronic kidney disease is pre-dialysis chronic kidney disease.

10. The method of any one of the preceding claims, wherein the daily dose is (i) administered continuously, or (ii) is administered indefinitely, or (iii) is administered orally, once daily, or (iv) is administered orally, as a divided dose administered twice daily.

11. The method of any one of the preceding claims, wherein the patient has not been previously treated for anemia.

12. The method of any one of the preceding claims, wherein the patient is refractory to treatment with recombinant erythropoietin.

13. The method of any one of the preceding claims, wherein the patient has been previously treated for anemia.

14. The method of any one of the preceding claims, wherein hemoglobin levels of the patient

a. are maintained at a level of at least about 9.0 g/dL and at or below about 13.0 g/dL; or

b. are maintained at a level of at least about 10.0 g/dL and at or below about 13.0 g/dL; or

c. are maintained at a level of at least about 11.0 g/dL and at or below about 13.0 g/dL; or

d. are increased by at least about 1.2 g/dL relative to a baseline hemoglobin level.

15. The method of claim 14 wherein the hemoglobin levels are tested at least about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or about 8 weeks after the initial administering of the compound.

16. The method of any one of the preceding claims, wherein the method does not comprise administering an iron supplement.

17. The method of any one of the preceding claims, wherein the compound is optionally administered in combination with another medicament.

18. The method of claim 17, wherein the other medicament is an iron supplement.

19. The method of claim 18, wherein the iron supplement is administered at least two hours following administration of the compound.

20. The method of claim 18 or 19, wherein the iron supplement is administered in an amount such that ferritin is maintained at a level of between about 50 ng/mL and about 300 ng/mL.

21. The method of claim 18 or 19, wherein the iron supplement is administered orally at a daily dose about 50 mg of elemental iron.

22. The method of any one of claims 18 to 21, wherein the iron supplement is administered (i) on an as needed basis; (ii) continuously; and/or (iii) indefinitely.

23. The method of claim 17, wherein the other medicament is an erythropoiesis stimulating agent (ESA) that is an erythropoietin mimetic.

24. The method of claim 23, wherein the other medicament is an rhEPO product.

25. The method of claim 24, wherein the rhEPO product is selected from epoetin alfa, epoetin beta, darbepoetin, and peginesatide.

26. The method of any one of claims 23 to 25, wherein the ESA is administered (i) as a rescue therapy; (ii) continuously; and/or (iii) indefinitely.

27. The method of any one of the preceding claims, wherein the compound is administered once a day at the same time of the day.

28. The method of claim 27, wherein the time of day is in the morning or early afternoon.

29. A method for treating anemia, comprising administering to a patient having anemia a daily dose of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof, wherein the daily dose is about 450 mg.

30. The method of claim 29, wherein the daily dose is increased by about 150 mg such that the daily dose of the compound is about 600 mg.

31. The method of claim 29, wherein the daily dose is decreased by about 150 mg, such that the daily dose of the compound is about 300 mg.

32. The method of claim 29, wherein the daily dose is decreased by about 300 mg, such that the daily dose of the compound is about 150 mg.

33. A method of treating anemia, comprising

a. administering to a patient having anemia an initial daily dose of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof;

b. taking a first measurement of the hemoglobin level in the patient and subsequently taking a second measurement of the hemoglobin level in the patient, wherein

i. if the hemoglobin level in the patient at the second measurement is less than about 10.0 g/dL and the level of hemoglobin has decreased by less than about 0.5 g/dL as compared to the level at the first measurement; or

ii. if the hemoglobin level in the patient at the second measurement is less than about 10.0 g/dL and the level of hemoglobin has changed by up to about 0.4 g/dL as compared to the level at the first measurement; or

iii. if the hemoglobin level in the patient at the second measurement is between about 10.0 and about 10.9 g/dL and the level of hemoglobin has decreased by less than about 0.5 g/dL as compared to the level at the first measurement; then

c. administering an adjusted daily dose of the compound that is greater than the initial daily dose.

34. The method of claim 33, wherein the adjusted daily dose of the compound is about 150 mg greater than the initial daily dose.

35. A method of treating anemia, comprising

a. administering to a patient having anemia an initial daily dose of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl] amino} acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof;

b. taking a first measurement of the hemoglobin level in the patient and subsequently taking a second measurement of the hemoglobin level in the patient, wherein

i. if the hemoglobin level in the patient at the second measurement is less than about 10.0 g/dL and the level of hemoglobin has increased by greater than about 1.5 g/dL as compared to the level at the first measurement; or

ii. if the hemoglobin level in the patient at the second measurement is between about 10.0 and about 10.9 g/dL and the level of hemoglobin has increased by greater than about 1.5 g/dL as compared to the level at the first measurement; or

iii. if the hemoglobin level in the patient at the second measurement is between about 11.0 and about 12.2 g/dL and the level of hemoglobin has increased by between about 1.0 and about 1.4 g/dL as compared to the level at the first measurement; or

iv. if the hemoglobin level in the patient at the second measurement is between about 12.3 and about 12.9 g/dL and the level of hemoglobin has decreased by up to about 0.4 g/dL or increased by up to about 0.4 g/dL as compared to the at the first measurement; or

v. if the hemoglobin level in the patient at the second measurement is between about 12.3 and about 12.9 g/dL and the level of hemoglobin has increased by about 0.5 to about 0.9 g/dL as compared to the level at the first measurement; then

c. administering an adjusted daily dose of the compound that is less than the initial daily dose.

36. The method of claim 35, wherein the adjusted daily dose of the compound is about 150 mg less than the initial daily dose.

37. A method of treating anemia, comprising

a. administering to a patient having anemia an initial daily dose of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof;

b. taking a first measurement of the hemoglobin level in the patient and subsequently taking a second measurement of the hemoglobin level in the patient, wherein

i. if the hemoglobin level in the patient at the second measurement is between about 11.0 and about 12.2 g/dL and the level of hemoglobin has increased by greater than about 1.5 g/dL as compared to the level at the first measurement; or

ii. if the hemoglobin level in the patient at the second measurement is between about 12.3 and about 12.9 g/dL and the level of hemoglobin has increased by between about 1.0 and about 1.4 g/dL as compared to the level at the first measurement; or

iii. if the hemoglobin level in the patient at the second measurement is between about 12.3 and about 12.9 g/dL and the level of hemoglobin has increased by greater than about 1.5 g/dL as compared to the level at the first measurement; then

c. administering an adjusted daily dose of the compound that is less than the initial daily dose.

38. The method of claim 37, wherein the adjusted daily dose of the compound is about 300 mg less than the initial daily dose.

39. The method of any one of claims 33 to 38, wherein the initial dose is 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, or 450 mg.

40. The method of any one of claims 33 to 38, wherein the maximum daily dose is at most 750 mg.

41. The method of any one of claims 33 to 38, wherein the minimum daily dose is 150 mg and the maximum daily dose is at most 750 mg.

42. The method of any one of claims 33 to 38, wherein the period between the first and second measurement is 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks.

43. The method of any one of claims 33 to 42, wherein the first measurement is taken prior to the commencement of the treatment.

44. The method of any one of claims 33 to 42, wherein the first measurement is taken immediately after commencement of the treatment or within at most 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 1 week, or 2 weeks thereof.

45. The method of any one of claims 33 to 36, wherein the anemia is anemia secondary to chronic kidney disease.

46. The method of claim 45, wherein the chronic kidney disease is stage 3, 4, or 5 chronic kidney disease.

47. The method of claim 45 or 46, wherein the chronic kidney disease is pre-dialysis chronic kidney disease.

48. The method of any one of claims 33 to 47, wherein the daily dose is administered (i) continuously; (ii) indefinitely; (iii) orally, once daily; and/or (iv) orally, as a divided dose administered twice daily.

49. The method of any one of claims 33 to 48, wherein the patient has not been previously treated for anemia.

50. The method of any one of claims 33 to 48, wherein the patient is refractory to treatment with recombinant erythropoietin.

51. The method of any one of claims 33 to 50, wherein the compound is optionally administered in combination with another medicament.

52. The method of claim 51, wherein the other medicament is an iron supplement.

53. The method of claim 52, wherein the iron supplement is administered at least two hours following administration of the compound.

54. The method of claim 51 to 53, wherein the iron supplement is administered in an amount such that ferritin is maintained at a level of between about 50 ng/mL and about 300 ng/mL.

55. The method of claim 51 to 53, wherein the iron supplement is administered orally at a daily dose about 50 mg of elemental iron.

56. The method of claim 51 to 53, wherein the iron supplement is administered (i) continuously; and/or (ii) indefinitely.

57. The method of any one of claims 33 to 50, wherein the method does not comprise administration of an iron supplement.

58. The method of claim 51, wherein the other medicament is an erythropoiesis stimulating agent (ESA) that is an erythropoietin mimetic.

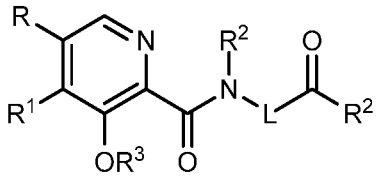
59. The method of claim 58, wherein the other medicament is an rhEPO product.

60. The method of claim 5959, wherein the rhEPO product is epoetin alfa.

61. The method of any one of claim 58 to claim 60, wherein the ESA is administered as a rescue therapy.

62. The method of any one of claim 58 to claim 60, wherein the ESA is administered continuously and/or indefinitely.

63. A method for treating anemia in a subject, wherein the method comprises administering to the subject a pharmaceutically effective amount of a compound of Formula **(I)**:



Formula **(I)**

wherein

R and R^1 are each independently:

(i) hydrogen
(ii) substituted or unsubstituted phenyl; or
(iii) substituted or unsubstituted heteroaryl;
said substitution selected from:

(i) C_1-C_4 alkyl;
(ii) C_3-C_4 cycloalkyl;
(iii) C_1-C_4 alkoxy;
(iv) C_3-C_4 cycloalkoxy;
(v) C_1-C_4 haloalkyl;
(vi) C_3-C4 halocycloalkyl;
(vii) halogen;
(viii) cyano;
(ix) $NHC(O)R^4$;
(x) $C(O)NR^{5a}R^{5b}$; and
(xi) heteroaryl; or
(xii) two substituents are taken together to form a fused ring having from 5 to 7 atoms;

R^4 is a C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{5a} and R^{5b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl;
(iii) C_3-C_4 cycloalkyl; or
(iv) R^{5a} and R^{5b} are taken together to form a ring having from 3 to 7 atoms;

R^2 is selected from:

(i) OR^6
(ii) $NR^{7a}R^{7b}$; and

R^6 is selected from hydrogen and C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{7a} and R^{7b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl or C_3-C_4 cycloalkyl; or
(iii) R^{7a} and R^{7b} are taken together to form a ring having from 3 to 7 atoms;

R^3 is selected from hydrogen, methyl, and ethyl;

L is a linking unit having a structure $-[C(R^{8a}R^{8b})]_n-$

R^{8a} and R^{8b} are each independently selected from hydrogen, methyl and ethyl;

n is an integer from 1 to 3; and

R^9 is selected from hydrogen and methyl; and

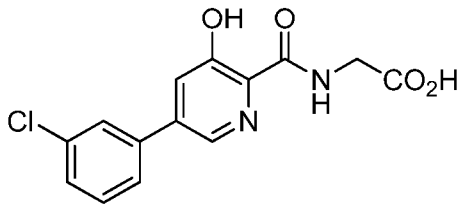
wherein the pharmaceutically effective amount is suitable to increase overall levels of erythropoietin in a diurnal pattern.

64. The method of claim 63, wherein the compound is administered once daily.

65. The method of claim 63, wherein the trough levels of erythropoietin are elevated compared to trough levels of erythropoietin in the subject immediately prior to the administering step by at most 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20%.

66. The method of claim 63, wherein the administering step is performed in the afternoon.

67. The method of claim 63, wherein the compound of Formula (I) is Compound **1** having the structure:



Compound **1**

68. The method of claim 63, wherein the pharmaceutically effective amount is 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, or 450 mg.

69. The method of any one of claim 63 to claim 68, wherein the anemia is anemia secondary to or associated with chronic kidney disease; anemia associated with or resulting from chemotherapy; or anemia associated with AIDS.

70. A method of treating a disease or condition related to diminished endogenous production of erythropoietin (EPO), comprising administering to a patient having a disease or condition related to diminished endogenous production of EPO a sufficient number of successive doses of a HIF prolyl hydroxylase inhibitor or a HIF-alpha stabilizer so as to raise the total iron binding capacity (TIBC) relative to a baseline TIBC in a patient, without significantly increasing the serum iron level relative to a baseline serum iron level.

71. The method of claim 70, wherein the cardiovascular side-effects and risk of thromboembolic events associated with increased serum iron levels are minimized.

72. The method of claim 70 or 71, wherein the transferrin saturation (TSAT) decreases relative to a baseline TSAT.

73. The method of any one of claims 70 to 72, wherein the serum iron level decreases relative to a baseline serum iron level.

74. The method of any one of claims 70 to 73, wherein the TIBC increases by at least about 10 μg/dL, 20 μg/dL, 30 μg/dL, 40 μg/dL, 50 μg/dL, or at least about 60 μg/dL relative to a baseline TIBC.

75. The method of claim 74, wherein the TIBC increase occurs over about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, or about 6 weeks relative to a baseline TIBC.

76. The method of any one of claims 70 to 75, wherein the serum iron level increases by less than about 20 μg/dL, less than about 15 μg/dL, less than about 10 μg/dL, or less than about 5 μg/dL relative to a baseline serum iron level.

77. The method of any one of claims 70 to 76, wherein the disease or condition is anemia.

78. The method of claim 77, wherein the anemia is anemia secondary to chronic kidney disease (CKD).

79. The method of claim 78, wherein the chronic kidney disease is stage 3, 4, or 5 chronic kidney disease.

80. The method of claim 78, wherein the chronic kidney disease is pre-dialysis chronic kidney disease.

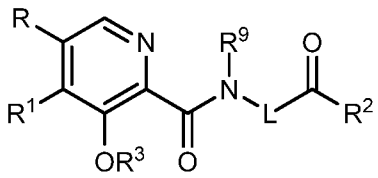
81. The method of any one of claims 70 to 80, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is administered once daily.

82. The method of any one of claims 70 to 81, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is administered orally.

83. The method of any one of claims 70 to 82, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a heterocyclic carboxamide.

84. The method of claim 83, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is selected from a pyridine carboxamide, a quinoline carboxamide, and an isoquinoline carboxamide.

85. The method of any one of claims 70 to 82, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a compound having a structure of Formula **(I)**



Formula **(I)**

or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

R and R^1 are each independently:

(i) hydrogen
(ii) substituted or unsubstituted phenyl; or
(iii) substituted or unsubstituted heteroaryl;
said substitution selected from:

(i) C_1-C_4 alkyl;
(ii) C_3-C_4 cycloalkyl;
(iii) C_1-C_4 alkoxy;
(iv) C_3-C_4 cycloalkoxy;
(v) C_1-C_4 haloalkyl;
(vi) C_3-C4 halocycloalkyl;
(vii) halogen;
(viii) cyano;
(ix) $NHC(O)R^4$;
(x) $C(O)NR^{5a}R^{5b}$; and
(xi) heteroaryl; or
(xii) two substituents are taken together to form a fused ring having from 5 to 7 atoms;

R^4 is a C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{5a} and R^{5b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl;
(iii) C_3-C_4 cycloalkyl; or
(iv) R^{5a} and R^{5b} are taken together to form a ring having from 3 to 7 atoms;

R^2 is selected from:

(i) OR^6
(ii) $NR^{7a}R^{7b}$; and

R^6 is selected from hydrogen and C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{7a} and R^{7b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl or C_3-C_4 cycloalkyl; or
(iii) R^{7a} and R^{7b} are taken together to form a ring having from 3 to 7 atoms;

R^3 is selected from hydrogen, methyl, and ethyl;

L is a linking unit having a structure $-[C(R^{8a}R^{8b})]_n-$

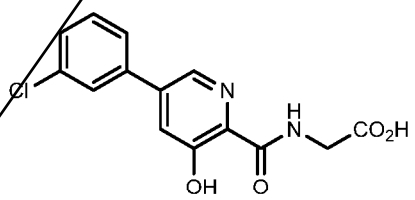
R^{8a} and R^{8b} are each independently selected from hydrogen, methyl and ethyl;

n is an integer from 1 to 3; and

R^9 is selected from hydrogen and methyl.

86. The method of claim 85, wherein R and R^1 are not both hydrogen.

87. The method of claim 85, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is Compound **1** having a structure



Compound **1**

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

88. A method of treating a disease or condition selected from non-severe anemia secondary to chronic kidney disease, non-severe anemia secondary to congestive heart failure, and idiopathic anemia of aging, comprising administering a sufficient number of successive doses of a HIF prolyl hydroxylase inhibitor or a HIF-alpha stabilizer to a patient having non-severe anemia secondary to chronic kidney disease, non-severe anemia secondary to congestive

heart failure, or idiopathic anemia of aging so as to raise the patient's serum hemoglobin levels relative to a baseline serum hemoglobin level, without significantly decreasing hepcidin levels in the patient relative to a baseline hepcidin expression level.

89. The method of claim 88, wherein the patient's serum hemoglobin level is raised by between about 0.1 and about 1.0 g/dL over a period of one week or over a period of two weeks or over a period of three weeks or over a period of four weeks or over a period of five weeks or over a period of six weeks relative to the baseline hemoglobin level.

90. The method of claim 89, wherein the patient's serum hemoglobin level is raised:

a. by about 0.1 g/dL over a period of one week or over a period of two weeks relative to the baseline hemoglobin level; or

b. by about 0.5 g/dL over a period of three weeks relative to the baseline hemoglobin level; or

c. by about 0.6 g/dL over a period of four weeks or over a period of five weeks or over a period of six weeks relative to the baseline hemoglobin level.

91. The method of any one of claims 88 to 90, wherein hepcidin protein expression decreases less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% relative to the baseline hepcidin expression level.

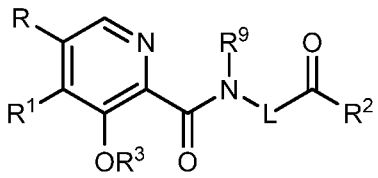
92. The method of any one of claims 88 to 91, wherein the disease or condition is non-severe anemia secondary to chronic kidney disease, non-severe congestive heart failure, or idiopathic anemia of aging.

93. The method of any one of claims 88 to 92, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is administered once daily and/or orally.

94. The method of any one of claims 88 to 93, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a heterocyclic carboxamide.

95. The method of claim 94, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is selected from a pyridine carboxamide, a quinoline carboxamide, and an isoquinoline carboxamide.

96. The method of any one of claims 88 to 95, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a compound having a structure of Formula **(I)**



Formula **(I)**

or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

R and R^1 are each independently:

(i) hydrogen
(ii) substituted or unsubstituted phenyl; or
(iii) substituted or unsubstituted heteroaryl;
said substitution selected from:

(i) C_1-C_4 alkyl;
(ii) C_3-C_4 cycloalkyl;
(iii) C_1-C_4 alkoxy;
(iv) C_3-C_4 cycloalkoxy;
(v) C_1-C_4 haloalkyl;
(vi) C_3-C4 halocycloalkyl;
(vii) halogen;
(viii) cyano;
(ix) $NHC(O)R^4$;
(x) $C(O)NR^{5a}R^{5b}$; and
(xi) heteroaryl; or
(xii) two substituents are taken together to form a fused ring having from 5 to 7 atoms;

R^4 is a C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{5a} and R^{5b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl;
(iii) C_3-C_4 cycloalkyl; or
(iv) R^{5a} and R^{5b} are taken together to form a ring having from 3 to 7 atoms;

R^2 is selected from:

(i) OR^6
(ii) $NR^{7a}R^{7b}$; and

R^6 is selected from hydrogen and C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{7a} and R^{7b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl or C_3-C_4 cycloalkyl; or
(iii) R^{7a} and R^{7b} are taken together to form a ring having from 3 to 7 atoms;

R^3 is selected from hydrogen, methyl, and ethyl;

L is a linking unit having a structure $-[C(R^{8a}R^{8b})]_n-$

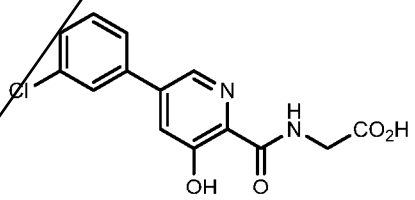
R^{8a} and R^{8b} are each independently selected from hydrogen, methyl and ethyl;

n is an integer from 1 to 3; and

R^9 is selected from hydrogen and methyl.

97. The method of claim 96, wherein R and R^1 are not both hydrogen.

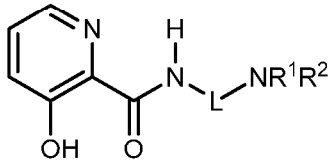
98. The method of claim 96, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a compound having a structure



Compound **1**

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

99. A method for treating anemia, comprising administering to a patient having anemia an effective amount of a compound having the formula:



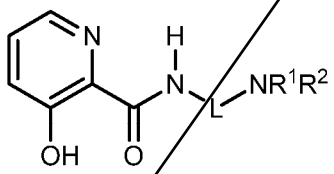
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

100. A method for treating or preventing a disease or disorder ameliorated by inhibiting HIF prolyl hydroxylase, comprising administering to a patient having a disease or disorder ameliorated by inhibiting HIF prolyl hydroxylase an effective amount of a compound having the formula:



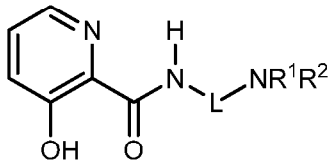
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

101. A method for treating or preventing a disease or disorder ameliorated by stabilizing HIF-alpha, comprising administering to a patient having a disease or disorder ameliorated by stabilizing HIF-alpha an effective amount of a compound having the formula:



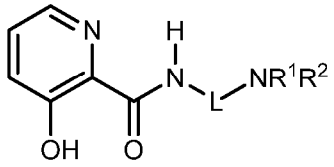
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

102. A method for treating or preventing a disease or condition related to diminished endogenous erythropoietic production, comprising administering to a patient having a disease or disorder related to diminished endogenous erythropoietic production an effective amount a compound having the formula:



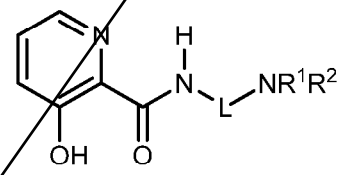
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

103. A method for increasing endogenous EPO production in a human cell, comprising contacting said human cell with a compound having the formula:



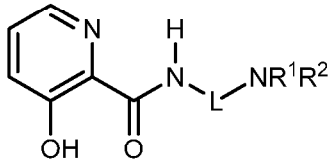
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

104. A method for inducing an endogenous EPO response in a human cell, comprising contacting said human cell with a compound having Formula **(V)**:



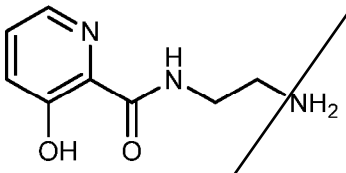
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

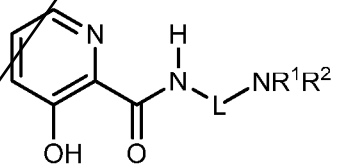
105. The method of any one of claims 99 to 104, wherein the compound is Compound **13** having the structure



Compound **13**

or a pharmaceutically acceptable salt or tautomer thereof.

106. A pharmaceutical composition comprising a compound having Formula **(V)**:



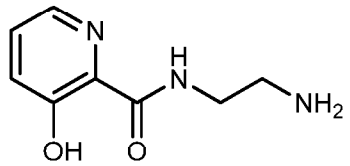
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

107. The pharmaceutical composition of claim 106, wherein the compound is Compound **13** having the structure



Compound **13**

or a pharmaceutically acceptable salt or tautomer thereof.

108. The pharmaceutical composition of claim 106 or claim 107, suitable for oral administration.

What is claimed is:

1. Use of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof for manufacturing a medicament for treating anemia in a patient having anemia, wherein medicament is manufactured to adminster a daily dose comprises about 150 mg, about 300 mg, about 450 mg, about 600 mg, or about 750 mg of the compound.

2. The use of claim 1, wherein the compound is a pharmaceutically acceptable salt of {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid.

3. The use of claim 1, wherein the compound is a solvate of {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid.

4. The use of claim 1, wherein the compound is a hydrate of {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid.

5. The use of claim 1, wherein the compound is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid.

6. The use of any one of claims 1 to 5 wherein the daily dose comprises about 150 mg, about 300 mg, about 450 mg, or about 600 mg of the compound.

7. The use of claim 1, wherein the anemia is anemia secondary to chronic kidney disease.

8. The use of claim 3, wherein the chronic kidney disease is stage 3, 4, or 5 chronic kidney disease.

9. The use of claim 3 or 8, wherein the chronic kidney disease is pre-dialysis chronic kidney disease.

10. The use of any one of the preceding claims, wherein the daily dose is (i) administered continuously, or (ii) is administered indefinitely, or (iii) is administered orally, once daily, or (iv) is administered orally, as a divided dose administered twice daily.

11. The use of any one of the preceding claims, wherein the patient has not been previously treated for anemia.

12. The use of any one of the preceding claims, wherein the patient is refractory to treatment with recombinant erythropoietin.

13. The use of any one of the preceding claims, wherein the patient has been previously treated for anemia.

14. The use of any one of the preceding claims, wherein hemoglobin levels of the patient

a. are maintained at a level of at least about 9.0 g/dL and at or below about 13.0 g/dL; or

b. are maintained at a level of at least about 10.0 g/dL and at or below about 13.0 g/dL; or

c. are maintained at a level of at least about 11.0 g/dL and at or below about 13.0 g/dL; or

d. are increased by at least about 1.2 g/dL relative to a baseline hemoglobin level.

15. The use of claim 14 wherein the hemoglobin levels are tested at least about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or about 8 weeks after the initial administering of the medicament.

16. The use of any one of the preceding claims, wherein the medicament does not comprise an iron supplement.

17. The use of any one of the preceding claims, wherein the medicament is optionally administered in combination with another medicament.

18. The use of claim 17, wherein the other medicament is an iron supplement.

19. The use of claim 18, wherein the iron supplement is administered at least two hours following administration of the medicament.

20. The use of claim 18 or 19, wherein the iron supplement is administered in an amount such that ferritin is maintained at a level of between about 50 ng/mL and about 300 ng/mL.

21. The use of claim 18 or 19, wherein the iron supplement is administered orally at a daily dose about 50 mg of elemental iron.

22. The use of any one of claims 18 to 21, wherein the iron supplement is administered (i) on an as needed basis; (ii) continuously; and/or (iii) indefinitely.

23. The use of claim 17, wherein the other medicament is an erythropoiesis stimulating agent (ESA) that is an erythropoietin mimetic.

24. The use of claim 23, wherein the other medicament is an rhEPO product.

25. The use of claim 24, wherein the rhEPO product is selected from epoetin alfa, epoetin beta, darbepoetin, and peginesatide.

26. The use of any one of claims 23 to 25, wherein the ESA is administered (i) as a rescue therapy; (ii) continuously; and/or (iii) indefinitely.

27. The use of any one of the preceding claims, wherein the medicament is administered once a day at the same time of the day.

28. The use of claim 27, wherein the time of day is in the morning or early afternoon.

29. Use of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof for manufacturing a medicament for treating anemia in a patient having anemia, wherein the medicament is manufactured to be administered at a daily dose of about 450 mg.

30. The use of claim 29, wherein the daily dose is increased by about 150 mg such that the daily dose of the compound is about 600 mg.

31. The use of claim 29, wherein the daily dose is decreased by about 150 mg, such that the daily dose of the compound is about 300 mg.

32. The use of claim 29, wherein the daily dose is decreased by about 300 mg, such that the daily dose of the compound is about 150 mg.

33. Use of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof for manufacturing a medicament for treating anemia in a patient having anemia, wherein the medicament is manufactured to

a. administer to a patient having anemia an initial daily dose of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof;

b. taking a first measurement of the hemoglobin level in the patient and subsequently taking a second measurement of the hemoglobin level in the patient, wherein

i. if the hemoglobin level in the patient at the second measurement is less than about 10.0 g/dL and the level of hemoglobin has decreased by less than about 0.5 g/dL as compared to the level at the first measurement; or

ii. if the hemoglobin level in the patient at the second measurement is less than about 10.0 g/dL and the level of hemoglobin has changed by up to about 0.4 g/dL as compared to the level at the first measurement; or

iii. if the hemoglobin level in the patient at the second measurement is between about 10.0 and about 10.9 g/dL and the level of hemoglobin has decreased by less than about 0.5 g/dL as compared to the level at the first measurement; then

c. administer an adjusted daily dose of the compound that is greater than the initial daily dose.

34. The use of claim 33, wherein the adjusted daily dose of the compound is about 150 mg greater than the initial daily dose.

35. Use of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof for manufacturing a medicament for treating anemia in a patient having anemia, wherein the medicament is manufactured to

a. administer to a patient having anemia an initial daily dose of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl] amino} acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof;

b. taking a first measurement of the hemoglobin level in the patient and subsequently taking a second measurement of the hemoglobin level in the patient, wherein

i. if the hemoglobin level in the patient at the second measurement is less than about 10.0 g/dL and the level of hemoglobin has increased by greater than about 1.5 g/dL as compared to the level at the first measurement; or

ii. if the hemoglobin level in the patient at the second measurement is between about 10.0 and about 10.9 g/dL and the level of hemoglobin has increased by greater than about 1.5 g/dL as compared to the level at the first measurement; or

iii. if the hemoglobin level in the patient at the second measurement is between about 11.0 and about 12.2 g/dL and the level of hemoglobin has increased by between about 1.0 and about 1.4 g/dL as compared to the level at the first measurement; or

iv. if the hemoglobin level in the patient at the second measurement is between about 12.3 and about 12.9 g/dL and the level of hemoglobin has decreased by up to about 0.4 g/dL or increased by up to about 0.4 g/dL as compared to the at the first measurement; or

v. if the hemoglobin level in the patient at the second measurement is between about 12.3 and about 12.9 g/dL and the level of hemoglobin has increased by about 0.5 to about 0.9 g/dL as compared to the level at the first measurement; then

c. administer an adjusted daily dose of the compound that is less than the initial daily dose.

36. The use of claim 35, wherein the adjusted daily dose of the compound is about 150 mg less than the initial daily dose.

37. Use of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof for manufacturing a medicament for treating anemia in a patient having anemia, wherein the medicament is manufactured to

a. administer to a patient having anemia an initial daily dose of a compound which is {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt, solvate, or hydrate thereof;

b. taking a first measurement of the hemoglobin level in the patient and subsequently taking a second measurement of the hemoglobin level in the patient, wherein

i. if the hemoglobin level in the patient at the second measurement is between about 11.0 and about 12.2 g/dL and the level of hemoglobin has increased by greater than about 1.5 g/dL as compared to the level at the first measurement; or

ii. if the hemoglobin level in the patient at the second measurement is between about 12.3 and about 12.9 g/dL and the level of hemoglobin has increased by between about 1.0 and about 1.4 g/dL as compared to the level at the first measurement; or

iii. if the hemoglobin level in the patient at the second measurement is between about 12.3 and about 12.9 g/dL and the level of hemoglobin has increased by greater than about 1.5 g/dL as compared to the level at the first measurement; then

c. administer an adjusted daily dose of the compound that is less than the initial daily dose.

38. The use of claim 37, wherein the adjusted daily dose of the compound is about 300 mg less than the initial daily dose.

39. The use of any one of claims 33 to 38, wherein the initial dose is 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, or 450 mg.

40. The use of any one of claims 33 to 38, wherein the maximum daily dose is at most 750 mg.

41. The use of any one of claims 33 to 38, wherein the minimum daily dose is 150 mg and the maximum daily dose is at most 750 mg.

42. The use of any one of claims 33 to 38, wherein the period between the first and second measurement is 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks.

43. The use of any one of claims 33 to 42, wherein the first measurement is taken prior to the commencement of the treatment.

44. The use of any one of claims 33 to 42, wherein the first measurement is taken immediately after commencement of the treatment or within at most 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 1 week, or 2 weeks thereof.

45. The use of any one of claims 33 to 36, wherein the anemia is anemia secondary to chronic kidney disease.

46. The use of claim 45, wherein the chronic kidney disease is stage 3, 4, or 5 chronic kidney disease.

47. The use of claim 45 or 46, wherein the chronic kidney disease is pre-dialysis chronic kidney disease.

48. The use of any one of claims 33 to 47, wherein the daily dose is administered (i) continuously; (ii) indefinitely; (iii) orally, once daily; and/or (iv) orally, as a divided dose administered twice daily.

49. The use of any one of claims 33 to 48, wherein the patient has not been previously treated for anemia.

50. The use of any one of claims 33 to 48, wherein the patient is refractory to treatment with recombinant erythropoietin.

51. The use of any one of claims 33 to 50, wherein the medicament is optionally administered in combination with another medicament.

52. The use of claim 51, wherein the other medicament is an iron supplement.

53. The use of claim 52, wherein the iron supplement is administered at least two hours following administration of the compound.

54. The use of claim 51 to 53, wherein the iron supplement is administered in an amount such that ferritin is maintained at a level of between about 50 ng/mL and about 300 ng/mL.

55. The use of claim 51 to 53, wherein the iron supplement is administered orally at a daily dose about 50 mg of elemental iron.

56. The use of claim 51 to 53, wherein the iron supplement is administered (i) continuously; and/or (ii) indefinitely.

57. The use of any one of claims 33 to 50, wherein the medicament does not comprise an iron supplement.

58. The use of claim 51, wherein the other medicament is an erythropoiesis stimulating agent (ESA) that is an erythropoietin mimetic.

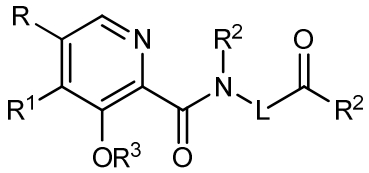
59. The use of claim 58, wherein the other medicament is an rhEPO product.

60. The use of claim 5959, wherein the rhEPO product is epoetin alfa.

61. The use of any one of claim 58 to claim 60, wherein the ESA is administered as a rescue therapy.

62. The use of any one of claim 58 to claim 60, wherein the ESA is administered continuously and/or indefinitely.

63. Use of a pharmaceutically effective amount of a compound of Formula **(I)** for manufacturing a medicament for treating anemia in a subject:



Formula **(I)**

wherein

R and R^1 are each independently:

(i) hydrogen
(ii) substituted or unsubstituted phenyl; or
(iii) substituted or unsubstituted heteroaryl;
said substitution selected from:

(i) C_1-C_4 alkyl;
(ii) C_3-C_4 cycloalkyl;
(iii) C_1-C_4 alkoxy;
(iv) C_3-C_4 cycloalkoxy;
(v) C_1-C_4 haloalkyl;
(vi) C_3-C4 halocycloalkyl;
(vii) halogen;
(viii) cyano;
(ix) $NHC(O)R^4$;
(x) $C(O)NR^{5a}R^{5b}$; and
(xi) heteroaryl; or
(xii) two substituents are taken together to form a fused ring having from 5 to 7 atoms;

R^4 is a C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{5a} and R^{5b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl;
(iii) C_3-C_4 cycloalkyl; or
(iv) R^{5a} and R^{5b} are taken together to form a ring having from 3 to 7 atoms;

R^2 is selected from:

(i) OR^6
(ii) $NR^{7a}R^{7b}$; and

R^6 is selected from hydrogen and C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{7a} and R^{7b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl or C_3-C_4 cycloalkyl; or
(iii) R^{7a} and R^{7b} are taken together to form a ring having from 3 to 7 atoms;

R^3 is selected from hydrogen, methyl, and ethyl;

L is a linking unit having a structure $-[C(R^{8a}R^{8b})]_n-$

R^{8a} and R^{8b} are each independently selected from hydrogen, methyl and ethyl;

n is an integer from 1 to 3; and

R^9 is selected from hydrogen and methyl; and

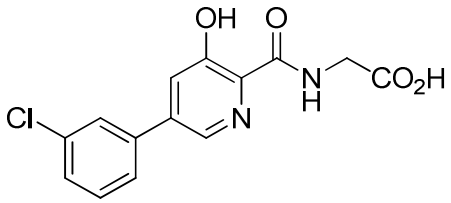
wherein the pharmaceutically effective amount is suitable to increase overall levels of erythropoietin in a diurnal pattern.

64. The use of claim 63, wherein the medicament is administered once daily.

65. The use of claim 63, wherein the trough levels of erythropoietin are elevated compared to trough levels of erythropoietin in the subject immediately prior to the administering step by at most 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20%.

66. The use of claim 63, wherein the administering step is performed in the afternoon.

67. The use of claim 63, wherein the compound of Formula (I) is Compound **1** having the structure:



Compound **1**

68. The use of claim 63, wherein the pharmaceutically effective amount is 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, or 450 mg.

69. The use of any one of claim 63 to claim 68, wherein the anemia is anemia secondary to or associated with chronic kidney disease; anemia associated with or resulting from chemotherapy; or anemia associated with AIDS.

70. Use of a HIF prolyl hydroxylase inhibitor or a HIF-alpha stabilizer for manufacturing a medicament for treating a disease or condition related to diminished

endogenous production of erythropoietin (EPO) in a patient having a disease or condition related to diminished endogenous production of EPO, wherein the medicament is manufacture to administer a sufficient number of successive doses of the HIF prolyl hydroxylase inhibitor or the HIF-alpha stabilizer so as to raise the total iron binding capacity (TIBC) relative to a baseline TIBC in the patient, without significantly increasing the serum iron level relative to a baseline serum iron level.

71. The use of claim 70, wherein the cardiovascular side-effects and risk of thromboembolic events associated with increased serum iron levels are minimized.

72. The use of claim 70 or 71, wherein the transferrin saturation (TSAT) decreases relative to a baseline TSAT.

73. The use of any one of claims 70 to 72, wherein the serum iron level decreases relative to a baseline serum iron level.

74. The use of any one of claims 70 to 73, wherein the TIBC increases by at least about 10 µg/dL, 20 µg/dL, 30 µg/dL, 40 µg/dL, 50 µg/dL, or at least about 60 µg/dL relative to a baseline TIBC.

75. The use of claim 74, wherein the TIBC increase occurs over about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, or about 6 weeks relative to a baseline TIBC.

76. The use of any one of claims 70 to 75, wherein the serum iron level increases by less than about 20 µg/dL, less than about 15 µg/dL, less than about 10 µg/dL, or less than about 5 µg/dL relative to a baseline serum iron level.

77. The use of any one of claims 70 to 76, wherein the disease or condition is anemia.

78. The use of claim 77, wherein the anemia is anemia secondary to chronic kidney disease (CKD).

79. The use of claim 78, wherein the chronic kidney disease is stage 3, 4, or 5 chronic kidney disease.

80. The use of claim 78, wherein the chronic kidney disease is pre-dialysis chronic kidney disease.

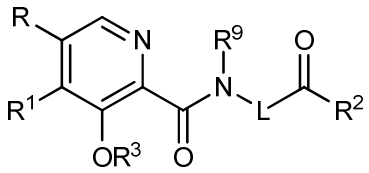
81. The use of any one of claims 70 to 80, wherein the medicament is administered once daily.

82. The use of any one of claims 70 to 81, wherein the medicament is administered orally.

83. The use of any one of claims 70 to 82, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a heterocyclic carboxamide.

84. The use of claim 83, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is selected from a pyridine carboxamide, a quinoline carboxamide, and an isoquinoline carboxamide.

85. The use of any one of claims 70 to 82, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a compound having a structure of Formula **(I)**



Formula **(I)**

or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

R and R^1 are each independently:

(i) hydrogen
(ii) substituted or unsubstituted phenyl; or
(iii) substituted or unsubstituted heteroaryl;
said substitution selected from:

(i) C_1-C_4 alkyl;
(ii) C_3-C_4 cycloalkyl;
(iii) C_1-C_4 alkoxy;
(iv) C_3-C_4 cycloalkoxy;
(v) C_1-C_4 haloalkyl;
(vi) C_3-C4 halocycloalkyl;
(vii) halogen;
(viii) cyano;
(ix) $NHC(O)R^4$;
(x) $C(O)NR^{5a}R^{5b}$; and
(xi) heteroaryl; or
(xii) two substituents are taken together to form a fused ring having from 5 to 7 atoms;

R^4 is a C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{5a} and R^{5b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl;
(iii) C_3-C_4 cycloalkyl; or
(iv) R^{5a} and R^{5b} are taken together to form a ring having from 3 to 7 atoms;

R^2 is selected from:

(i) OR^6
(ii) $NR^{7a}R^{7b}$; and

R^6 is selected from hydrogen and C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{7a} and R^{7b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl or C_3-C_4 cycloalkyl; or
(iii) R^{7a} and R^{7b} are taken together to form a ring having from 3 to 7 atoms;

R^3 is selected from hydrogen, methyl, and ethyl;

L is a linking unit having a structure $-[C(R^{8a}R^{8b})]_n-$

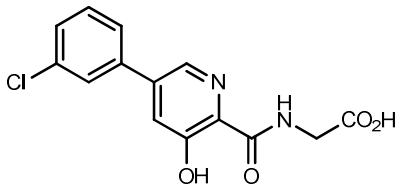
R^{8a} and R^{8b} are each independently selected from hydrogen, methyl and ethyl;

n is an integer from 1 to 3; and

R^9 is selected from hydrogen and methyl.

86. The use of claim 85, wherein R and R^1 are not both hydrogen.

87. The use of claim 85, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is Compound **1** having a structure



Compound **1**

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

88. Use of a HIF prolyl hydroxylase inhibitor or a HIF-alpha stabilizer for manufacturing a medicament for treating a disease or condition selected from non-severe anemia secondary to chronic kidney disease, non-severe anemia secondary to congestive heart failure, and idiopathic anemia of aging in a patient having non-severe anemia secondary to chronic kidney disease, non-severe anemia secondary to congestive heart failure, or idiopathic anemia of aging, wherein the medicament is manufacture to administer a sufficient number of successive doses of the HIF prolyl hydroxylase inhibitor or the HIF-alpha stabilizer so as to raise the patient's serum hemoglobin levels relative to a baseline serum hemoglobin level, without significantly decreasing hepcidin levels in the patient relative to a baseline hepcidin expression level.

89. The use of claim 88, wherein the patient's serum hemoglobin level is raised by between about 0.1 and about 1.0 g/dL over a period of one week or over a period of two weeks or over a period of three weeks or over a period of four weeks or over a period of five weeks or over a period of six weeks relative to the baseline hemoglobin level.

90. The use of claim 89, wherein the patient's serum hemoglobin level is raised:

a. by about 0.1 g/dL over a period of one week or over a period of two weeks relative to the baseline hemoglobin level; or

b. by about 0.5 g/dL over a period of three weeks relative to the baseline hemoglobin level; or

c. by about 0.6 g/dL over a period of four weeks or over a period of five weeks or over a period of six weeks relative to the baseline hemoglobin level.

91. The use of any one of claims 88 to 90, wherein hepcidin protein expression decreases less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% relative to the baseline hepcidin expression level.

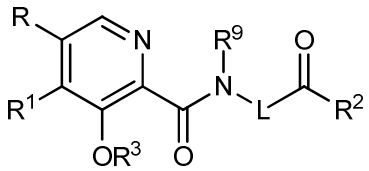
92. The use of any one of claims 88 to 91, wherein the disease or condition is non-severe anemia secondary to chronic kidney disease, non-severe congestive heart failure, or idiopathic anemia of aging.

93. The use of any one of claims 88 to 92, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is administered once daily and/or orally.

94. The use of any one of claims 88 to 93, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a heterocyclic carboxamide.

95. The use of claim 94, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is selected from a pyridine carboxamide, a quinoline carboxamide, and an isoquinoline carboxamide.

96. The use of any one of claims 88 to 95, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a compound having a structure of Formula **(I)**



Formula **(I)**

or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

R and R^1 are each independently:

(i) hydrogen
(ii) substituted or unsubstituted phenyl; or
(iii) substituted or unsubstituted heteroaryl;
said substitution selected from:

(i) C_1-C_4 alkyl;
(ii) C_3-C_4 cycloalkyl;
(iii) C_1-C_4 alkoxy;
(iv) C_3-C_4 cycloalkoxy;
(v) C_1-C_4 haloalkyl;
(vi) C_3-C4 halocycloalkyl;
(vii) halogen;
(viii) cyano;
(ix) $NHC(O)R^4$;
(x) $C(O)NR^{5a}R^{5b}$; and
(xi) heteroaryl; or
(xii) two substituents are taken together to form a fused ring having from 5 to 7 atoms;

R^4 is a C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{5a} and R^{5b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl;
(iii) C_3-C_4 cycloalkyl; or
(iv) R^{5a} and R^{5b} are taken together to form a ring having from 3 to 7 atoms;

R^2 is selected from:

(i) OR^6
(ii) $NR^{7a}R^{7b}$; and

R^6 is selected from hydrogen and C_1-C_4 alkyl or C_3-C_4 cycloalkyl;

R^{7a} and R^{7b} are each independently selected from:

(i) hydrogen;
(ii) C_1-C_4 alkyl or C_3-C_4 cycloalkyl; or
(iii) R^{7a} and R^{7b} are taken together to form a ring having from 3 to 7 atoms;

R^3 is selected from hydrogen, methyl, and ethyl;

L is a linking unit having a structure $-[C(R^{8a}R^{8b})]_n-$

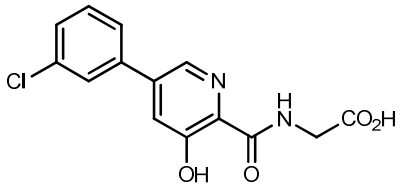
R^{8a} and R^{8b} are each independently selected from hydrogen, methyl and ethyl;

n is an integer from 1 to 3; and

R^9 is selected from hydrogen and methyl.

97. The use of claim 96, wherein R and R^1 are not both hydrogen.

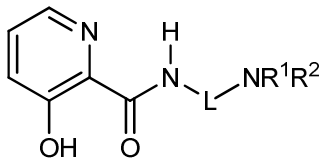
98. The use of claim 96, wherein the HIF prolyl hydroxylase inhibitor or HIF-alpha stabilizer is a compound having a structure



Compound **1**

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

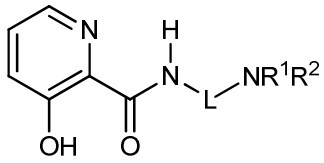
99. Use of a compound having the formula (V) or a pharmaceutically acceptable salt or tautomer thereof for manufacturing a medicament for treating anemiain a patient having anemia:



Formula **(V)**

wherein L is $C_{1\text{-}6}$ alkyl; and
wherein R^1 and R^2 are independently H or $C_{1\text{-}6}$ alkyl.

100. Use of a compound having the formula (V) or a pharmaceutically acceptable salt or tautomer thereof for manufacturing a medicament for treating or preventing a disease or disorder ameliorated by inhibiting HIF prolyl hydroxylasein a patient having a disease or disorder ameliorated by inhibiting HIF prolyl hydroxylase:

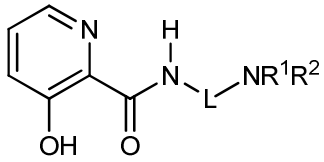


Formula **(V)**

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

101. Use of a compound having the formula (V) or a pharmaceutically acceptable salt or tautomer thereof for manufacturing a medicament for treating or preventing a disease or disorder ameliorated by stabilizing HIF-alphain a patient having a disease or disorder ameliorated by stabilizing HIF-alpha:

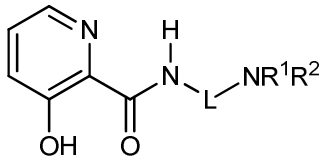


Formula **(V)**

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

102. Use of a compound having the formula (V) or a pharmaceutically acceptable salt or tautomer thereof for manufacturing a medicament for treating or preventing a disease or condition related to diminished endogenous erythropoietic productionin a patient having a disease or disorder related to diminished endogenous erythropoietic production:

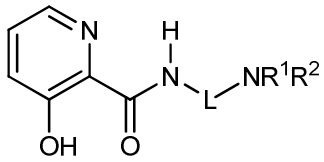


Formula **(V)**

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

103. A method for increasing endogenous EPO production in a human cell, comprising contacting said human cell with a compound having the formula:



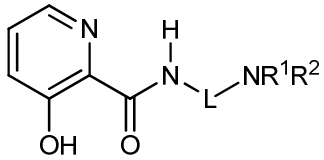
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

104. A method for inducing an endogenous EPO response in a human cell, comprising contacting said human cell with a compound having Formula **(V)**:



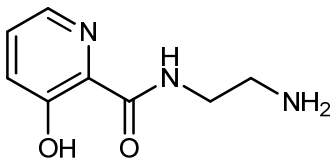
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

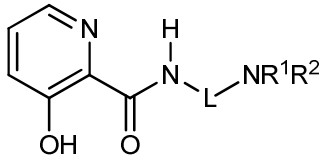
105. The method of any one of claims 99 to 104, wherein the compound is Compound **13** having the structure



Compound **13**

or a pharmaceutically acceptable salt or tautomer thereof.

106. A pharmaceutical composition comprising a compound having Formula **(V)**:



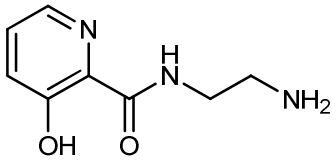
Formula **(V)**

or a pharmaceutically acceptable salt or tautomer thereof,

wherein L is C_{1-6} alkyl; and

wherein R^1 and R^2 are independently H or C_{1-6} alkyl.

107. The pharmaceutical composition of claim 106, wherein the compound is Compound **13** having the structure



Compound **13**

or a pharmaceutically acceptable salt or tautomer thereof.

108. The pharmaceutical composition of claim 106 or claim 107, suitable for oral administration.

109. A single unit dosage form comprising about 150 mg, about 300 mg, about 450 mg, or about 600 mg of {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

110. The dosage form of claim 109, further comprising one or more excipients.

111. The dosage form of claim 109 or claim 110, wherein the dosage form is suitable for oral administration.

112. The dosage form of claim 111, wherein the dosage form is in form of a tablet.

113. The dosage form of any one of claims 109-112, wherein the dosage form is formulated as a lactose-free composition.

114. The dosage form of any one of claims 109-113, wherein the dosage form is formulated as an anhydrous pharmaceutical composition.

115. The dosage form of any one of claims 109-114, further comprising a stabilizer.

116. The dosage form of any one of claims 109-115, further comprising a binder, a filler, a disintegrant, or a lubricant.

117. The dosage form of any one of claims 109-116 wherein the dosage form is suitable for daily use.

118. A single unit dosage form comprising about 150 mg of {[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, wherein the dosage form is in form of a tablet.