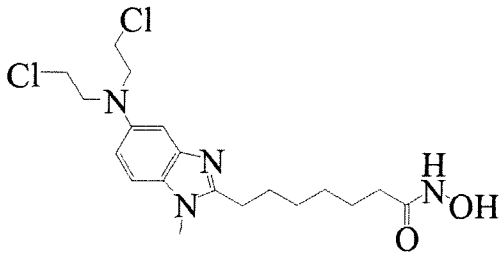
Claims

1. A combination comprising a glucocorticoid and a compound of formula I or a pharmaceutically acceptable salt thereof:



I

2. The combination according to claim 1, wherein the pharmaceutically acceptable salt of the compound of formula I is the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate or acetate.

3. The combination according to claim 1 or claim 2, wherein the glucocorticoid is selected from the group consisting of dexamethasone, fluocinolone acetonide and prednisone.

4. The combination according to claim 1 or claim 2, wherein the glucocorticoid is dexamethasone.

5. The combination according to any one of claims 1 to 4, further comprising a proteasome inhibitor .

6. The combination according to claim 5, wherein the proteasome inhibitor is selected from the group consisting of bortezomib, carfilzomib, marizomib, delanzomib (CEP-18770), oprozomib (ONX 0912), ixazomib (MLN-9708) and LU-102 or a pharmaceutically acceptable salt thereof.

7. The combination according to claim 5, wherein the proteasome inhibitor is selected from bortezomib, carfilzomib and LU-102.

8. The combination according to any one of claims 1 to 7, further comprising one or more additional pharmaceutically active agents.

9. The combination according to any one of claims 1 to 8, wherein the compound of formula I or a pharmaceutically acceptable salt thereof, the glucocorticoid and, if present, the proteasome inhibitor are adapted for administration concurrently, sequentially or separately.

10. The combination according to claim 9, wherein the compound of formula I or a pharmaceutically acceptable salt thereof, the glucocorticoid and, if present, the proteasome inhibitor are adapted for administration concurrently.

11. The combination according to any one of claims 1 to 10, wherein the molar ratio of glucocorticoid to compound of formula I or a pharmaceutically acceptable salt thereof in said combination is from 1:500 to 500:1.

12. The combination according to claim 11, wherein the molar ratio of glucocorticoid to compound of formula I or a pharmaceutically acceptable salt thereof in said combination is from 1:500 to 1:100.

13. The combination according to claim 11, wherein the molar ratio of glucocorticoid to compound of formula I or a pharmaceutically acceptable salt thereof in said combination is from 1:300 to 1:100.

14. The combination according to claim 11, wherein the molar ratio of glucocorticoid to compound of formula I or a pharmaceutically acceptable salt thereof in said combination is from 1:250 to 1:150.

15. The combination according to claim 11 comprising the compound of formula I or the acetate salt thereof and dexamethasone, wherein the molar ratio of the dexamethasone to the compound of formula I or the acetate salt thereof in said combination is from 1:250 to 1:150.

16. The combination according to any one of claims 1 to 15, wherein the glucocorticoid and the compound of formula I or a pharmaceutically acceptable salt thereof is a synergistic combination.

17. The combination according to any one of claims 1 to 16, further comprising a proteasome inhibitor wherein the molar ratio of proteasome inhibitor to the compound of formula

I or a pharmaceutically acceptable salt thereof to the glucocorticoid in said combination is from 1:1000:10 to 1000:1:20.

18. The combination according to claim 17, wherein the molar ratio of proteasome inhibitor to the compound of formula I or a pharmaceutically acceptable salt thereof to the glucocorticoid used in said combination is from 1:1000:10 to 1:100:2.

19. The combination according to claim 17, wherein the molar ratio of proteasome inhibitor to the compound of formula I or a pharmaceutically acceptable salt thereof to the glucocorticoid used in said combination is from 1:700:4 to 1:400:3.

20. The combination according to claim 17 comprising a proteasome inhibitor selected from bortezomib and carfilzomib, the compound of formula I or the acetate salt thereof and dexamethasone, wherein the molar ratio of the proteasome inhibitor selected from bortezomib and carfilzomib to the compound of formula I or the acetate salt thereof to dexamethasone in said combination is from 1:700:4 to 1:400:3.

21. The combination according to claim 17 comprising a proteasome inhibitor selected from LU-102, the compound of formula I or the acetate salt thereof and dexamethasone, wherein the molar ratio of LU-102 to the compound of formula I or the acetate salt thereof to dexamethasone in said combination is from 1:3:4 to 1:0.5:3.

22. The combination according to any one of claims 17 to 21 comprising a compound of formula I or a pharmaceutically acceptable salt thereof, a glucocorticoid and a proteasome inhibitor, wherein the compound of formula I or the pharmaceutically acceptable salt thereof, the glucocorticoid and the proteasome inhibitor are a synergistic combination.

23. A pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier and a combination according to any one of claims 1 to 22.

24. A kit comprising a combination according to any one of claims 1 to 22, and optionally, instructions for treating a patient.

25. The combination according to any one of claims 1 to 22, composition according to claim 23 or kit according to claim 24, for use in the treatment of cancer.

26. The combination, composition or kit for use according to claim 25, wherein said cancer is selected from a hematologic cancer and breast cancer.

27. The combination, composition or kit for use according to claim 26, wherein said hematologic cancer is selected from multiple myeloma, lymphoma and leukemia.

28. The combination, composition or kit for use according to claim 27, wherein said multiple myeloma is selected multiple myeloma is selected from active myeloma, plasmacytoma, light chain myeloma and non-secretory myeloma.

29. The combination, composition or kit for use according to claim 27, wherein said lymphoma is selected from Hodgkin lymphoma and non-Hodgkin lymphoma.

30. The combination, composition or kit for use according to claim 27, wherein said leukemia is selected from acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia and T-cell acute lymphoblastic leukemia.

31. The combination, composition or kit for use according to claim 26, wherein said breast cancer is selected from claudin-low tumors, basal-like tumors, human epidermal growth factor receptor 2 (HER2) positive tumors, luminal A tumors and luminal B tumors.

32. The combination, composition or kit for use according to claim 26, wherein said breast cancer is a triple-negative breast cancer.

33. The combination, composition or kit for use according to any one of claims 25 to 32, wherein in said treatment the glucocorticoid, the compound of formula I or a pharmaceutically acceptable salt thereof and, if present, the proteasome inhibitor are administered concurrently, sequentially or separately.

34. The combination, composition or kit for use according to claim 33, wherein in said treatment the glucocorticoid, the compound of formula I or a pharmaceutically acceptable salt thereof and, if present, the proteasome inhibitor are administered concurrently.

35. The combination, composition or kit for use according to any one of claims 25 to 34, wherein in said treatment the compound of formula I or a pharmaceutically acceptable salt

thereof is administered to the patient in need thereof at a dosage range of 10 to 100 mg/kg body weight patient.

36. The combination, composition or kit for use according to claim 35 wherein in said treatment the compound of formula I or a pharmaceutically acceptable salt thereof is administered to the patient in need thereof at a dosage range of 40 to 80 mg/kg body weight patient.

37. The combination, composition or kit for use according to any one of claims 25 to 36, wherein in said treatment the glucocorticoid is administered at a dosage range of from 0.1 to 1 mg/kg body weight patient.

38. The combination, composition or kit for use according to claim 37 wherein in said treatment the glucocorticoid is administered at a dosage range of from 0.3 to 0.5 mg/kg body weight patient.

39. The combination, composition or kit for use according to any one of claims claim 25 to 38, wherein the proteasome inhibitor, if present, is administered to the patient at a dosage range of 0.01 to 0.3 mg/kg body weight patient.

40. The combination, composition or kit for use according to claim 39, wherein the proteasome inhibitor is administered to the patient at a dosage range of 0.05 to 0.15 mg/kg body weight patient.

41. A method of treating cancer in a patient in need thereof comprising administering to said patient a combination according to any one of claims 1 to 22, a composition according to claim 23 or a kit according to claim 24.

42. The method according to claim 41, wherein said cancer is selected from a hematologic cancer and breast cancer.

43. The method according to claim 42, wherein said hematologic cancer is selected from multiple myeloma, lymphoma and leukemia.

44. The method according to claim 43, wherein said multiple myeloma is selected from active myeloma, plasmacytoma, light chain myeloma and non-secretory myeloma.

45. The method according to claim 43, wherein said lymphoma is selected from Hodgkin lymphoma and non-Hodgkin lymphoma.

46. The method according to claim 43, wherein said leukemia is selected from acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia and T-cell acute lymphoblastic leukemia.

47. The method according to claim 42, wherein said breast cancer is selected from claudin-low tumors, basal-like tumors, human epidermal growth factor receptor 2 (HER2) positive tumors, luminal A tumors and luminal B tumors.

48. The method according to claim 42, wherein said breast cancer is selected from a triple negative breast cancer.

49. The method according to any one of claims 41 to 48, wherein in said method the glucocorticoid, the compound of formula I or a pharmaceutically acceptable salt thereof and, if present, the proteasome inhibitor are administered concurrently, sequentially or separately.

50. The method according to claim 49, wherein in said method the glucocorticoid, the compound of formula I or a pharmaceutically acceptable salt thereof and, if present, the proteasome inhibitor are administered concurrently.

51. The method according to any one of claims 41 to 50, wherein the compound of formula I or a pharmaceutically acceptable salt thereof is administered to the patient in need thereof at a dosage range of 10 to 100 mg/kg body weight patient.

52. The method according to claim 51, wherein the compound of formula I or a pharmaceutically acceptable salt thereof is administered to the patient in need thereof at a dosage range of 40 to 80 mg/kg body weight patient.

53. The method according to any one of claims 41 to 52, wherein the glucocorticoid is administered at a dosage range of from 0.1 to 1.0 mg/kg body weight patient.

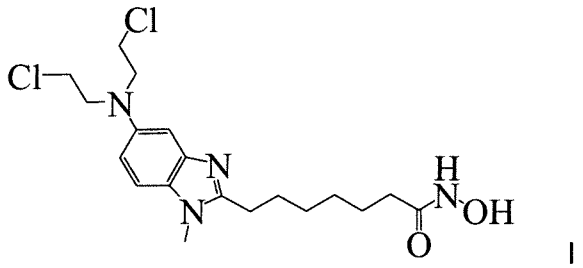
54. The method according to claim 53, wherein the glucocorticoid is administered at a dosage range of from 0.3 to 0.5 mg/kg body weight patient.

55. The method according to any one of claims 41 to 54, wherein the proteasome inhibitor, if present, is administered to the patient at a dosage range of 0.01 to 0.3 mg/kg body weight patient.

56. The method according to claim 55, wherein the proteasome inhibitor is administered to the patient at a dosage range of 0.05 to 0.15 mg/kg body weight patient.

Claims

1. A combination comprising a glucocorticoid and a compound of formula I or a pharmaceutically acceptable salt thereof:



I

2. The combination according to claim 1, wherein the pharmaceutically acceptable salt of the compound of formula I is the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate or acetate.

3. The combination according to claim 1 or claim 2, wherein the glucocorticoid is selected from the group consisting of dexamethasone, fluocinolone acetonide and prednisone.

4. The combination according to claim 1 or claim 2, wherein the glucocorticoid is dexamethasone.

5. The combination according to any one of claims 1 to 4, further comprising a proteasome inhibitor .

6. The combination according to claim 5, wherein the proteasome inhibitor is selected from the group consisting of bortezomib, carfilzomib, marizomib, delanzomib (CEP-18770), oprozomib (ONX 0912), ixazomib (MLN-9708) and LU-102 or a pharmaceutically acceptable salt thereof.

7. The combination according to claim 5, wherein the proteasome inhibitor is selected from bortezomib, carfilzomib and LU-102.

8. The combination according to any one of claims 1 to 7, further comprising one or more additional pharmaceutically active agents.

9. The combination according to any one of claims 1 to 8, wherein the compound of formula I or a pharmaceutically acceptable salt thereof, the glucocorticoid and, if present, the proteasome inhibitor are adapted for administration concurrently, sequentially or separately.

10. The combination according to claim 9, wherein the compound of formula I or a pharmaceutically acceptable salt thereof, the glucocorticoid and, if present, the proteasome inhibitor are adapted for administration concurrently.

11. The combination according to any one of claims 1 to 10, wherein the molar ratio of glucocorticoid to compound of formula I or a pharmaceutically acceptable salt thereof in said combination is from 1:500 to 500:1.

12. The combination according to claim 11, wherein the molar ratio of glucocorticoid to compound of formula I or a pharmaceutically acceptable salt thereof in said combination is from 1:500 to 1:100.

13. The combination according to claim 11, wherein the molar ratio of glucocorticoid to compound of formula I or a pharmaceutically acceptable salt thereof in said combination is from 1:300 to 1:100.

14. The combination according to claim 11, wherein the molar ratio of glucocorticoid to compound of formula I or a pharmaceutically acceptable salt thereof in said combination is from 1:250 to 1:150.

15. The combination according to claim 11 comprising the compound of formula I or the acetate salt thereof and dexamethasone, wherein the molar ratio of the dexamethasone to the compound of formula I or the acetate salt thereof in said combination is from 1:250 to 1:150.

16. The combination according to any one of claims 1 to 15, wherein the glucocorticoid and the compound of formula I or a pharmaceutically acceptable salt thereof is a synergistic combination.

17. The combination according to any one of claims 1 to 16, further comprising a proteasome inhibitor wherein the molar ratio of proteasome inhibitor to the compound of formula I or a pharmaceutically acceptable salt thereof to the glucocorticoid in said combination is from 1:1000:10 to 1000:1:20.

18. The combination according to claim 17, wherein the molar ratio of proteasome inhibitor to the compound of formula I or a pharmaceutically acceptable salt thereof to the glucocorticoid used in said combination is from 1:1000:10 to 1:100:2.

19. The combination according to claim 17, wherein the molar ratio of proteasome inhibitor to the compound of formula I or a pharmaceutically acceptable salt thereof to the glucocorticoid used in said combination is from 1:700:4 to 1:400:3.

20. The combination according to claim 17 comprising a proteasome inhibitor selected from bortezomib and carfilzomib, the compound of formula I or the acetate salt thereof and dexamethasone, wherein the molar ratio of the proteasome inhibitor selected from bortezomib and carfilzomib to the compound of formula I or the acetate salt thereof to dexamethasone in said combination is from 1:700:4 to 1:400:3.

21. The combination according to claim 17 comprising a proteasome inhibitor selected from LU-102, the compound of formula I or the acetate salt thereof and dexamethasone, wherein the molar ratio of LU-102 to the compound of formula I or the acetate salt thereof to dexamethasone in said combination is from 1:3:4 to 1:0.5:3.

22. The combination according to any one of claims 17 to 21 comprising a compound of formula I or a pharmaceutically acceptable salt thereof, a glucocorticoid and a proteasome inhibitor, wherein the compound of formula I or the pharmaceutically acceptable salt thereof, the glucocorticoid and the proteasome inhibitor are a synergistic combination.

23. A pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier and a combination according to any one of claims 1 to 22.

24. A kit comprising a combination according to any one of claims 1 to 22, and optionally, instructions for treating a patient.

25. The combination according to any one of claims 1 to 22, composition according to claim 23 or kit according to claim 24, for use in the treatment of cancer.

26. The combination, composition or kit, for use according to claim 25, wherein said cancer is selected from a hematologic cancer and breast cancer.

27. The combination, composition or kit, for use according to claim 26, wherein said hematologic cancer is selected from multiple myeloma, lymphoma and leukemia.

28. The combination, composition or kit, for use according to claim 27, wherein said multiple myeloma is selected multiple myeloma is selected from active myeloma, plasmacytoma, light chain myeloma and non-secretory myeloma.

29. The combination, composition or kit, for use according to claim 27, wherein said lymphoma is selected from Hodgkin lymphoma and non-Hodgkin lymphoma.

30. The combination, composition or kit, for use according to claim 27, wherein said leukemia is selected from acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia and T-cell acute lymphoblastic leukemia.

31. The use of the combination according to any one of claims 1 to 22, composition according to claim 23 or kit according to claim 24 in the manufacture of a medicament for the treatment of cancer.

32 The use of a combination, composition, or kit according to claim 31, wherein said cancer is selected from a hematologic cancer and breast cancer.

33. The use of a combination, composition, or kit according to claim 32, wherein said hematologic cancer is selected from multiple myeloma, lymphoma and leukemia.

34. The use of a combination, composition, or kit according to claim 33, wherein said multiple myeloma is selected multiple myeloma is selected from active myeloma, plasmacytoma, light chain myeloma and non-secretory myeloma.

35. The use of a combination, composition, or kit according to claim 33, wherein said lymphoma is selected from Hodgkin lymphoma and non-Hodgkin lymphoma.

36. The use of a combination, composition, or kit according to claim 33, wherein said leukemia is selected from acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia and T-cell acute lymphoblastic leukemia.

37. The use of a combination, composition, or kit according to claim 32, wherein said breast cancer is selected from claudin-low tumors, basal-like tumors, human epidermal growth factor receptor 2 (HER2) positive tumors, luminal A tumors and luminal B tumors.

38. The use of a combination, composition, or kit according to claim 32, wherein said breast cancer is a triple-negative breast cancer.

39. The use of a combination, composition, or kit according to any one of claims 31 to 38, wherein in said treatment the glucocorticoid, the compound of formula I or a pharmaceutically acceptable salt thereof and, if present, the proteasome inhibitor are administered concurrently, sequentially or separately.

40. The use of a combination, composition, or kit according to claim 39, wherein in said treatment the glucocorticoid, the compound of formula I or a pharmaceutically acceptable salt thereof and, if present, the proteasome inhibitor are administered concurrently.

41. The use of a combination, composition, or kit according to any one of claims 31 to 40, wherein in said treatment the compound of formula I or a pharmaceutically acceptable salt thereof is administered to the patient in need thereof at a dosage range of 10 to 100 mg/kg body weight patient.

42. The use of a combination, composition, or kit according to claim 41 wherein in said treatment the compound of formula I or a pharmaceutically acceptable salt thereof is administered to the patient in need thereof at a dosage range of 40 to 80 mg/kg body weight patient.

43. The use of a combination, composition, or kit according to any one of claims 31 to 42, wherein in said treatment the glucocorticoid is administered at a dosage range of from 0.1 to 1 mg/kg body weight patient.

44. The use of a combination, composition, or kit according to claim 43 wherein in said treatment the glucocorticoid is administered at a dosage range of from 0.3 to 0.5 mg/kg body weight patient.

45. The use of a combination, composition, or kit according to any one of claims 31 to 44, wherein the proteasome inhibitor, if present, is administered to the patient at a dosage range of 0.01 to 0.3 mg/kg body weight patient.

46. The use of a combination, composition, or kit according to claim 45, wherein the proteasome inhibitor is administered to the patient at a dosage range of 0.05 to 0.15 mg/kg body weight patient.

47. A method of treating cancer in a patient in need thereof comprising administering to said patient a combination according to any one of claims 1 to 22, a composition according to claim 23 or kit according to claim 24.