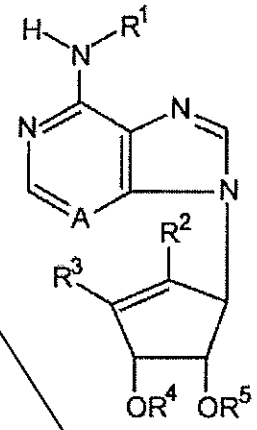
Claims

What is claimed is:

1. The use of a compound of the general formula (I)



wherein in formula (I)

A is C or N,

R^1, R^4 and R^5 are independently selected from the group consisting of H and aliphatic, cycloaliphatic, aromatic, arylaliphatic, and arylcycloaliphatic hydrocarbyl groups, comprising 0 - 3 heteroatoms selected from the group N, O, S, and Si,

wherein R^4 and R^5 may optionally be linked so as to define an aliphatic hydrocarbyl bridge,

R^2 is selected from the group consisting of H and a halogen, and

R^3 is H, or an aliphatic or arylaliphatic hydrocarbyl group comprising 1 - 8 main chain carbon atoms and 0 - 3 heteroatoms selected from the group N, O, S, Si, and halogen,

in the manufacture of a medicament for inducing apoptosis in a tumour cell and/or modulating pluripotency and/or self-renewing characteristics of a stem/progenitor cell.

2. The use of claim 1, wherein inducing apoptosis in a tumour cell, and/or modulating pluripotency and/or self-renewing characteristics of a stem/progenitor cell, is a therapy for the treatment or prevention of cancer.

3. The use of claim 2, wherein modulating pluripotency and/or self-renewing characteristics of a stem/progenitor cell is a therapy for the treatment or prevention of teratoma.

4. The use of claims 2 or 3, wherein said therapy is an epigenetic therapy.

5. The use of claim 4, wherein inducing apoptosis in a tumour cell and/or modulating pluripotency and/or self-renewing characteristics of a stem/progenitor cell comprises an inhibition of histone methylation.

6. The use of claim 5, wherein said inhibition of histone methylation comprises an inhibition of methylation of lysine 27 on histone 3.

7. The use of claims 5 or 6, wherein said inhibition of histone methylation comprises depleting in the respective cell a polycomb repressive complex.

8. The method of claim 7, wherein said polycomb repressive complex is at least one of polycomb repressive complex 2, polycomb repressive complex 3, and polycomb repressive complex 4.

9. The use of claims 7 or 8, wherein depleting said polycomb repressive complex causes the release of a complex between said polycomb repressive complex and a tumour suppressor gene.

10. The use of claim 9, wherein inducing apoptosis is achieved by means of reactivating a tumour suppressor gene.

11. The use of claim 10, wherein said tumour suppressor gene is FBX032.

12. The use of any one of claims 1 - 11, wherein said tumour cell is a breast cancer cell.

13. The use of any one of claims 1 - 12, wherein said tumour cell is obtained from a mammal.

14. The use of claim 13, wherein the mammal is selected from the group consisting of a rat, a mouse, a cow, a pig and a human.

15. The use of claims 13 or 14, comprising contacting said tumour cell with a predetermined quantity of a compound of the general formula (I).

16. The use of any one of claims 1 - 15, wherein said tumour cell is cultured.

17. The use of claim 16, wherein said tumour cell is a cell selected from the group of cell lines consisting of MCF-7, MB-468, SK-BR-3, and T47D.

18. The use of claim 15, comprising the use of at least two different predetermined quantities of a compound of the general formula (I) and at least a first and a second tumour cell, wherein the first tumour cell is contacted with the lower of the two predetermined quantities and the second tumour cell is contacted with the higher of the two predetermined quantities.

19. The use of claim 18, wherein the first tumour cell and the second tumour cell are obtained from the same patient.

20. The use any one of claims 1 - 19, further comprising determining apoptosis in said tumour cell.

21. The use of any one of claims 18 - 20 for predicting a patient's individual response to a compound of the general formula (I).

22. The use of any one of claims 1 - 8, wherein the stem/progenitor cell is an embryonic stem cell.

23. The use of any one of claims 1 - 22, wherein said compound is 3-deazaneplanocin.

24. A pharmaceutical composition, comprising

(a) a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, and

(b) a carrier or diluent,

for inducing apoptosis in a tumour cell and/or modulating pluripotency and/or self-renewing characteristics of a stem/progenitor cell.

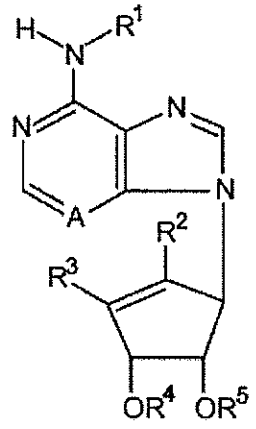
25. The pharmaceutical composition of claim 24, further comprising a DNA methyltransferase inhibitor, a DNA demethylating agent, and/or a histone-deacetylase inhibitor.

26. The pharmaceutical composition of claim 25, wherein said DNA methyltransferase inhibitor is selected from the group consisting of 5-azacytidine, decitabine (5-aza-2'-deoxycytidine), 5-fluoro-2'-deoxycytidine, 5,6-dihydro-5-azacytidine, and zebularine.

27. The pharmaceutical composition of claims 25 or 26, wherein said DNA demethylating agent is selected from the group consisting of hydralazine, procainamide, procaine, (–)-epigallocatechin-3-gallate (EGCG), psammaplin A, the oligodeoxynucleotide MB98, and 2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(1H-indol-3-yl)propionic acid (MG98).

28. The pharmaceutical composition of any one of claims 25 to 27, wherein said histone-deacetylase inhibitor is selected from the group consisting of butyrate, phenylbutyrate, valproic acid, m-carboxycinnamic acid bishydroxamic acid (CBHA), oxamflatin, PDX-101, MS-275, depsipeptide, pyroxamide, scriptaid, suberoylanilide hydroxyamic acid (SAHA), trichostatin (TSA), NVP-LAQ824, LBH589, apicidin, CHAP, trapoxin, N-acetyldinaline, and MS-275.

29. A method of inducing apoptosis in a tumour cell, said method comprising administering to said tumour cell a compound of the general formula (I)



wherein in formula (I)

A is C or N,

R^1, R^4 and R^5 are independently selected from the group consisting of H and aliphatic, cycloaliphatic, aromatic, arylaliphatic, and arylcycloaliphatic hydrocarbyl groups, comprising 0 - 3 heteroatoms selected from the group N, O, S, and Si,

wherein R^4 and R^5 may optionally be linked so as to define an aliphatic hydrocarbyl bridge,

R^2 is selected from the group consisting of H and halogen, and

R^3 is H, or an aliphatic or arylaliphatic hydrocarbyl group comprising 1 - 8 main chain carbon atoms and 0 - 3 heteroatoms selected from the group N, O, S, Si, and halogen.

30. The method of claim 29, wherein said tumour cell is cultured.

31. The method of claim 29, wherein said tumour cell is a breast cancer cell.

32. The method of claim 21, wherein said cell is a cell selected from the group of cell lines consisting of MCF-7, MB-468, SK-BR-3, and T47D.

33. The method of claim 29, further comprising determining apoptosis in said tumour cell.

34. The method of claim 29, wherein said tumour cell is obtained from a mammal.

35. The method of claim 29, wherein said tumour cell is comprised in a mammal.

36. The method of claim 34, wherein the mammal is selected from the group consisting of a rat, a mouse, a cow, a pig and a human.

37. The method of claim 29, comprising contacting said tumour cell with a predetermined quantity of a compound of the general formula (I).

38. The method of claim 29, comprising the use of at least two different predetermined quantities of a compound of the general formula (I) and at least a first and a second tumour cell, wherein the first tumour cell is contacted with the lower of the two predetermined quantities and the second tumour cell is contacted with the higher of the two predetermined quantities.

39. The method of claim 38, wherein the first tumour cell and the second tumour cell are obtained from the same patient.

40. The method of claim 39, wherein said method is a method for predicting a patient's individual response to a compound of the general formula (I).

41. The method of claim 29, wherein said method is an in epigenetic method.

42. The method of claim 41, wherein inducing apoptosis in a tumour cell comprises an inhibition of histone methylation.

43. The method of claim 42, wherein said inhibition of histone methylation comprises an inhibition of methylation of lysine 27 on histone 3.

44. The method of claim 42, wherein said inhibition of histone methylation comprises depleting in the respective cell a polycomb repressive complex.

45. The method of claim 44, further comprising measuring the levels of at least one component of at least one polycomb repressive complex.

46. The method of claim 45, further comprising comparing the result of the measurement of levels of said at least one component of at least one polycomb repressive complex with that of a control measurement.

47. The method of claim 44, wherein depleting said polycomb repressive complex releases a complex between said polycomb repressive complex and a tumour suppressor gene.

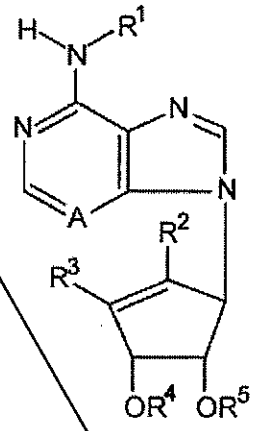
48. The method of claim 47, wherein apoptosis is achieved by means of reactivating a tumour suppressor gene.

49. The method of claim 48, wherein said tumour suppressor gene is FBX032.

50. The method of claim 49, further comprising measuring the expression of FBX032 in the respective cell.

51. The method of claim 50, further comprising comparing the result of the measurement of FBX032 expression with that of a control measurement.

52. A method of modulating pluripotency and/or self-renewing characteristics of a stem/progenitor cell, said method comprising administering to said stem/progenitor cell a compound of the general formula (I)



wherein

A is C or N,

R^1, R^4 and R^5 are independently selected from the group consisting of H and aliphatic, cycloaliphatic, aromatic, arylaliphatic, and arylcycloaliphatic hydrocarbyl groups, comprising 0 - 3 heteroatoms selected from the group N, O, S, and Si,

wherein R^4 and R^5 may optionally be linked so as to define an aliphatic hydrocarbyl bridge,

R^2 is selected from the group consisting of H and halogen, and

R^3 is H, or an aliphatic or arylaliphatic hydrocarbyl group comprising 1 - 8 main chain carbon atoms and 0 - 3 heteroatoms selected from the group N, O, S, Si, and halogen,.

53. The method of claim 52, wherein the stem/progenitor cell is an embryonic stem cell.

54. The method of claim 52, wherein the stem/progenitor cell is a cell of a teratoma.

55. The method of claim 52, wherein said stem/progenitor cell is cultured.

56. The method of claim 52, wherein said stem/progenitor cell is obtained from a mammal.

57. The method of claim 52, wherein said stem/progenitor cell is comprised in a mammal.

58. The method of claim57, wherein the mammal is selected from the group consisting of a rat, a mouse, a cow, a macaque and a human.

59. The method of claim 52, wherein said method is an in epigenetic method.

60. The method of claim 59, wherein modulating pluripotency and/or self-renewing characteristics of a stem/progenitor cell comprises an inhibition of histone methylation.

61. The method of claim 60, comprising inhibiting methylation of lysine 27 on histone 3.

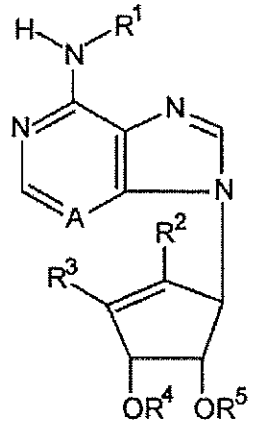
62. The method of claim 60, wherein said inhibition of histone methylation comprises depleting in said cell a polycomb repressive complex.

63. The method of claim 62, further comprising measuring the levels of at least one component of at least one polycomb repressive complex.

64. The method of claim 63, further comprising comparing the result of the measurement of levels of said at least one component of at least one polycomb repressive complex with that of a control measurement.

65. The method of claim62, wherein said polycomb repressive complex is at least one of polycomb repressive complex 2, polycomb repressive complex 3, and polycomb repressive complex 4.

66. A method for modulating gene expression in a cell that expresses the components of a polycomb repressive complex,
said method comprising administering to said cell a compound of the general formula (I)



wherein in formula (I)

A is C or N,

R^1, R^4 and R^5 are independently selected from the group consisting of H and aliphatic, cycloaliphatic, aromatic, arylaliphatic, and arylcycloaliphatic hydrocarbyl groups, comprising 0 - 3 heteroatoms selected from the group N, O, S, and Si,

wherein R^4 and R^5 may optionally be linked so as to define an aliphatic hydrocarbyl bridge,

R^2 is selected from the group consisting of H and halogen and

R^3 is H, or an aliphatic or arylaliphatic hydrocarbyl group comprising 1 - 8 main chain carbon atoms and 0 - 3 heteroatoms selected from the group N, O, S, Si, and halogen.

67. The method of claim 66, wherein said polycomb repressive complex is at least one of polycomb repressive complex 2, polycomb repressive complex 3, and polycomb repressive complex 4.

68. The method of claims 66 or 67, wherein the cell is a stem/progenitor cell or a primordial germ cell.

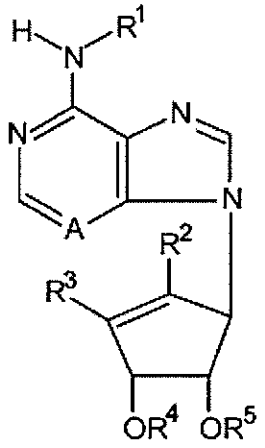
69. The method of claim 68, wherein the stem cell is an embryonic stem cell.

70. The method of any one of claims 66 - 69, wherein the cell is a recombinant cell comprising a target gene under the control of the promoter of the FBX032 gene.

71. The method of any one of claims 66 to 70, wherein the target gene, the expression of which is modulated, is any one of a reporter gene, a drug resistance gene, an apoptosis gene (so-called 'death' gene), or any other gene with desirable expression in a respective cell.

Claims

1. Compound of the general formula (I)



wherein in formula (I)

A is C or N,

R^1, R^4 and R^5 are independently selected from the group consisting of H and aliphatic, cycloaliphatic, aromatic, arylaliphatic, and arylcycloaliphatic hydrocarbyl groups, comprising 0 - 3 heteroatoms selected from the group N, O, S, and Si,

wherein R^4 and R^5 may optionally be linked so as to define an aliphatic hydrocarbyl bridge,

R^2 is selected from the group consisting of H and a halogen, and

R^3 is H, or an aliphatic or arylaliphatic hydrocarbyl group comprising 1 - 8 main chain carbon atoms and 0 - 3 heteroatoms selected from the group N, O, S, Si, and halogen,

for use in a method for treating or preventing cancer by inducing apoptosis in a tumour cell, wherein the tumour cell is selected from the group consisting of a breast cancer cell and a colorectal cancer cell.

2. The compound for use according to claim 1, wherein said tumour cell is a breast cancer cell.

3. A pharmaceutical composition, comprising

(a) a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, and

(b) a carrier or diluent,

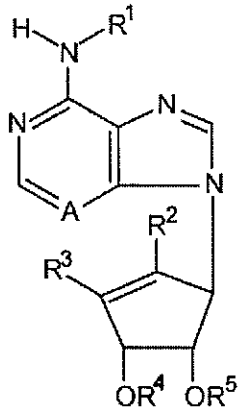
for use in a method for treating or preventing cancer by inducing apoptosis in a tumour cell, wherein the tumour cell is selected from the group consisting of a breast cancer cell and a colorectal cancer cell.

4. The pharmaceutical composition for use according to claim 3, further comprising a DNA methyltransferase inhibitor, a DNA demethylating agent, and/or a histone-deacetylase inhibitor, wherein said DNA methyltransferase inhibitor is selected from the group consisting of 5-azacytidine, decitabine (5-aza-2'-deoxycytidine), 5-fluoro-2'-deoxycytidine, 5,6-dihydro-5-azacytidine, and zebularine,

said DNA demethylating agent is selected from the group consisting of hydralazine, procainamide, procaine, (–)-epigallocatechin-3-gallate (EGCG), psammaplin A, the oligodeoxynucleotide MB98, and 2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(1H-indol-3-yl)propionic acid (MG98), and

said histone-deacetylase inhibitor is selected from the group consisting of butyrate, phenylbutyrate, valproic acid, m-carboxycinnamic acid bishydroxamic acid (CBHA), oxamflatin, PDX-101, MS-275, depsipeptide, pyroxamide, scriptaid, suberoylanilide hydroxyamic acid (SAHA), trichostatin (TSA), NVP-LAQ824, LBH589, apicidin, CHAP, trapoxin, N-acetyldinaline, and MS-275.

5. A method of inducing apoptosis in a cultured tumour cell by inhibiting histone methylation, the method comprising contacting the tumour cell with a predetermined quantity of a compound of the general formula (I),



wherein in formula (I)

A is C or N,

R^1, R^4 and R^5 are independently selected from the group consisting of H and aliphatic, cycloaliphatic, aromatic, arylaliphatic, and arylcycloaliphatic hydrocarbyl groups, comprising 0 - 3 heteroatoms selected from the group N, O, S, and Si,

wherein R^4 and R^5 may optionally be linked so as to define an aliphatic hydrocarbyl bridge,

R^2 is selected from the group consisting of H and a halogen, and

R^3 is H, or an aliphatic or arylaliphatic hydrocarbyl group comprising 1 - 8 main chain carbon atoms and 0 - 3 heteroatoms selected from the group N, O, S, Si, and halogen,

wherein the tumour cell is selected from the group consisting of a breast cancer cell and a colorectal cancer cell.

6. The method of claim 5, wherein said tumour cell is a breast cancer cell.

7. The method of claim 5 or 6, wherein said inhibition of histone methylation comprises depleting in the respective cell a polycomb repressive complex.

8. The method of claim 7, wherein depleting said polycomb repressive complex releases a complex between said polycomb repressive complex and the tumour suppressor gene FBX032, such that the tumour suppressor gene FBX032 is reactivated thereby inducing apoptosis in the respective cell.

9. The method of claims 5 to 8, wherein the tumour cell is obtained from a mammal.

10. The method of claim 5, comprising the use of at least two different predetermined quantities of a compound of the general formula (I) and at least a first and a second tumour cell, wherein the first tumour cell is contacted with the lower of the two predetermined quantities and the second tumour cell is contacted with the higher of the two predetermined quantities.

11. The method of claim 10, wherein the first tumour cell and the second tumour cell are obtained from the same patient.

12. The method any one of claims 5 - 11, further comprising determining apoptosis in said tumour cell.

13. The method of any one of claims 10 -- 12 for predicting a patient's individual response to a compound of the general formula (I).