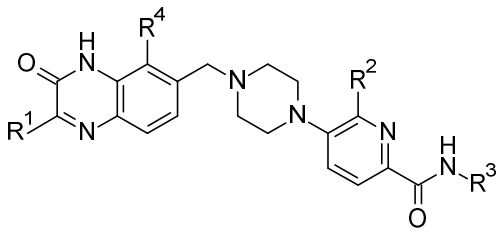
Claims:

1) A poly(ADP-ribose) polymerase (PARP) inhibitor for use in treating a brain tumour or a neuroblastoma in a patient in need thereof,

wherein the brain tumour or neuroblastoma comprises an alpha thalassemia/mental retardation syndrome X-linked (ATRX) deficient phenotype,

wherein the PARP inhibitor is a compound of Formula I



(I)

wherein:

R^1 is independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} fluoroalkyl, and C_{1-4} alkyloxy;

R^2 is independently selected from H, halo, C_{1-4} alkyl, and C_{1-4} fluoroalkyl; and

R^3 is H or C_{1-4} alkyl;

R^4 is halo or C_{1-4} alkyl,

or a pharmaceutically acceptable salt thereof.

2) The PARP inhibitor for use of claim 1, wherein the brain tumour or neuroblastoma further comprises an isocitrate dehydrogenase 1 and/or 2 (IDH1 and/or IDH2) deficient phenotype.

3) The PARP inhibitor for use of claim 1, wherein the brain tumour or neuroblastoma does not comprise an IDH1 deficient phenotype.

4) The PARP inhibitor for use of any one of claims 1 to 3, wherein the brain tumour or neuroblastoma comprises O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.

5) The PARP inhibitor for use of any one of the preceding claims, wherein the patient is diagnosed as having the brain tumour or neuroblastoma comprising the ATRX deficient phenotype prior to the PARP inhibitor is to be administered.

6) The PARP inhibitor for use of claim 5, wherein the patient is diagnosed by determining whether the brain tumour or neuroblastoma further comprises the IDH1 or IDH2 deficient phenotype and/or MGMT promoter methylation.

7) The PARP inhibitor for use of claim 5 or claim 6, wherein the patient is diagnosed by assaying cells obtained from the brain tumour or neuroblastoma from the patient.

8) The PARP inhibitor for use of any one of the preceding claims, wherein the PARP inhibitor is to be administered to the patient in combination with

i) an alkylating chemotherapeutic agent; and/or

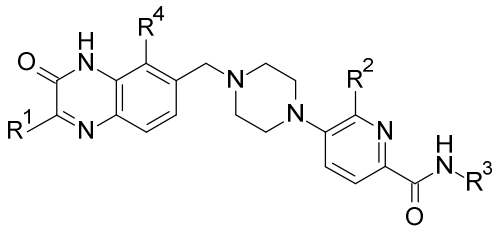
ii) ionizing radiation.

9) A poly(ADP-ribose) polymerase (PARP) inhibitor for use in treating a brain tumour or a neuroblastoma in a patient in need thereof, wherein the PARP inhibitor is to be further administered with

i) an alkylating chemotherapeutic agent; and/or

ii) ionizing radiation administered at a dose of 10 Gy or above,

wherein the PARP inhibitor is a compound of Formula I



(I)

wherein:

R^1 is independently selected from H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} fluoroalkyl, and C_{1-4} alkyloxy;

R^2 is independently selected from H, halo, C_{1-4} alkyl, and C_{1-4} fluoroalkyl; and

R^3 is H or C_{1-4} alkyl;

R^4 is halo or C_{1-4} alkyl,

or a pharmaceutically acceptable salt thereof.

10) The PARP inhibitor for use of claim 9, wherein the brain tumour or neuroblastoma comprises:

(i) an alpha thalassemia/mental retardation syndrome X-linked (ATRX) deficient phenotype;

(ii) an isocitrate dehydrogenase 1 or 2 (IDH1 or IDH2) deficient phenotype; and/or

(iii) O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.

11) The PARP inhibitor for use of any one of claims 8 to 10, wherein the alkylating chemotherapeutic agent is temozolomide (TMZ) or dianhydrogalactitol (VAL-083).

12) The PARP inhibitor for use of claim 11, wherein TMZ is to be administered at:

(i) a dose of less than 200 mg/m^2, a dose of less than 150 mg/m^2, a dose of less than 125 mg/m^2, or less than 100 mg/m^2;

(ii) a dose of between 50 and 150 mg/m^2, a dose of between 75 and 150 mg/m^2, or a dose of between 50 mg/m^2 and 125 mg/m^2.

13) The PARP inhibitor for use of claim 11, wherein VAL-083 is to be administered at:

(i) a dose of less than 50 mg/m^2, a dose of less than 40 mg/m^2, a dose of less than 30 mg/m^2, or less than 20 mg/m^2;

(ii) a dose of between 10 and 50 mg/m^2, a dose of between 10 and 40 mg/m^2, or a dose of between 10 mg/m^2 and 30 mg/m^2.

14) The PARP inhibitor for use of any one of claims 8 to 13, wherein the ionizing radiation is to be administered at:

(i) a dose of less than 60 Gy, less than 55 Gy, less than 50 Gy, less than 45 Gy, or less than 40 Gy; or

(ii) a dose of between 20 Gy and 60 Gy, between 20 Gy and 55 Gy, between 20 Gy and 50 Gy, between 20 and 45 Gy, or between 20 and 40 Gy, between 30 Gy and 60 Gy, between 30 Gy and 55 Gy, between 30 Gy and 50 Gy, between 30 Gy and 45 Gy, between 30 Gy and 40 Gy

optionally wherein the dose of ionizing radiation is to be administered as fractionated radiotherapy.

15) The PARP inhibitor for use of any one of claims 8 to 14, wherein the PARP inhibitor synergistically potentiates the activity of the alkylating chemotherapeutic agent and/or radiotherapeutic agent.

16) The PARP inhibitor for use of any one of the claims 8 to 15, wherein the PARP inhibitor treats the brain tumour or neuroblastoma independent of any effect on the glioma induced by administration of the chemotherapeutic or radiotherapeutic agents.

17) The PARP inhibitor for use according to any one of claims 1 to 16 wherein R^1 is selected from any one of methyl, ethyl, isopropyl, cyclopropyl, 1,1-difluoroethyl, 1-fluoroethyl, trifluoromethyl, difluoromethyl, and methoxy.

18) The PARP inhibitor for use according to claim 17 wherein R^1 is methyl or ethyl.

19) The PARP inhibitor for use according to any one of claims 1 to 18 wherein R^2 is selected from any one of H, chloro, fluoro, methyl, and difluoromethyl.

20) The PARP inhibitor for use according to claim 19 wherein R^2 is fluoro or methyl.

21) The PARP inhibitor for use according to any one of claims 1 to 20 wherein R^3 is methyl or ethyl.

22) The PARP inhibitor for use according to any one of claims 1 to 21 wherein R^4 is selected from any one of chloro, fluoro and methyl.

23) The PARP inhibitor for use according to claim 22 wherein R^4 is fluoro.

24) The PARP inhibitor for use according to any one of claims 1 to 16 wherein R^1 is C_{1-4} alkyl, R^2 is halo, R^3 is C_{1-4} alkyl, R^4 is halo or C_{1-4} alkyl, or a pharmaceutically acceptable salt thereof.

25) The PARP inhibitor for use according any one of claims 1 to 16 wherein the PARP inhibitor is selected from:

5-[4-[(2,5-dimethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-fluoro-N-methyl-pyridine-2-carboxamide,

5-[4-[(2,5-dimethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

6-chloro-5-[4-[(2,5-dimethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(2,5-dimethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

5-[4-[(2,5-dimethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-fluoro-pyridine-2-carboxamide,

5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-methyl-pyridine-2-carboxamide,

5-[4-[(2,5-dimethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-methyl-pyridine-2-carboxamide,

6-chloro-5-[4-[(5-chloro-2-ethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide**,**

5-[4-[(5-chloro-2-ethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-fluoro-N-methyl-pyridine-2-carboxamide,

5-[4-[(5-chloro-2-ethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(5-chloro-2-ethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

6-fluoro-5-[4-[[5-fluoro-2-[(1S and 1R)-1-fluoroethyl]-3-oxo-4H-quinoxalin-6-yl]methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[[5-fluoro-2-[(1S and 1R)-1-fluoroethyl]-3-oxo-4H-quinoxalin-6-yl]methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

5-[4-[(5-chloro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(5-chloro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-fluoro-N-methyl-pyridine-2-carboxamide,

5-[4-[(5-chloro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

5-[4-[[2-(1,1-difluoroethyl)-5-fluoro-3-oxo-4H-quinoxalin-6-yl]methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

6-fluoro-5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

6-(difluoromethyl)-5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

6-fluoro-5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]pyridine-2-carboxamide,

5-[4-[(2-ethyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

6-(difluoromethyl)-5-[4-[(2-ethyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(2-ethyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]pyridine-2-carboxamide,

5-[4-[(2-ethyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-methyl-pyridine-2-carboxamide,

5-[4-[(2-ethyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-fluoro-N-methyl-pyridine-2-carboxamide,

6-chloro-5-[4-[(2-ethyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(2-ethyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

6-chloro-5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

6-chloro-5-[4-[(5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

6-fluoro-5-[4-[(5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[[2-(difluoromethyl)-5-fluoro-3-oxo-4H-quinoxalin-6-yl]methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

5-[4-[(5-fluoro-2-methoxy-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

6-fluoro-5-[4-[(5-fluoro-2-methoxy-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(5-fluoro-2-methoxy-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

6-chloro-5-[4-[(5-fluoro-2-methoxy-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(2-ethyl-5-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

5-[4-[(2-ethyl-5-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-fluoro-N-methyl-pyridine-2-carboxamide,

5-[4-[(2-ethyl-5-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

N-ethyl-6-fluoro-5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]pyridine-2-carboxamide,

N-ethyl-5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-methyl-pyridine-2-carboxamide,

5-[4-[[5-fluoro-3-oxo-2-(trifluoromethyl)-4H-quinoxalin-6-yl]methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

6-fluoro-5-[4-[[5-fluoro-3-oxo-2-(trifluoromethyl)-4H-quinoxalin-6-yl]methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

6-chloro-5-[4-[[5-fluoro-3-oxo-2-(trifluoromethyl)-4H-quinoxalin-6-yl]methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[[5-fluoro-3-oxo-2-(trifluoromethyl)-4H-quinoxalin-6-yl]methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

6-fluoro-5-[4-[(5-fluoro-2-isopropyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(5-fluoro-2-isopropyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

5-[4-[(5-fluoro-2-isopropyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(2-cyclopropyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-6-fluoro-N-methyl-pyridine-2-carboxamide,

5-[4-[(2-cyclopropyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

5-[4-[(2-cyclopropyl-5-fluoro-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

5-[4-[(2-methoxy-5-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N,6-dimethyl-pyridine-2-carboxamide,

6-fluoro-5-[4-[(2-methoxy-5-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

6-(difluoromethyl)-5-[4-[(2-methoxy-5-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide, and

6-(difluoromethyl)-5-[4-[(2,5-dimethyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide,

or a pharmaceutically acceptable salt thereof.

26) The PARP inhibitor for use according to any one of claims 1 to 16 wherein the PARP inhibitor is:

6-fluoro-5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide, or a pharmaceutically acceptable salt thereof.

27) The PARP inhibitor for use according to any one of claims 1 to 16 wherein the PARP inhibitor is:

6-fluoro-5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methyl-pyridine-2-carboxamide.

28) The PARP inhibitor for use according to any one of the claims 1 to 27, wherein the brain tumour is a glioma or an ependymoma.

29) The PARP inhibitor for use according to claim 28, wherein the brain tumour is a glioma.

30) The PARP inhibitor for use according to claim 29, wherein the glioma is a paediatric glioma.

31) The PARP inhibitor for use according to claim 29 or claim 30, wherein the glioma is a high grade glioma, optionally selected from the list consisting of: an oligodendroglioma, an anaplastic astrocytoma, a glioblastoma, and a diffuse midline glioma.

32) The PARP inhibitor for use according to any one of claims 29 to 31, wherein the glioma is a H3K27M mutant glioma.

33) The PARP inhibitor for use according to any one of the claims 1 to 27, wherein the brain tumour or neuroblastoma is characterised as having a high level of genomic instability.