CLAIMS

1. 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one as crystalline Form A.

2. The compound of claim 1 having the following characteristic peaks in a powder XRD:

Peak	2θ° (± 0.1°) (λ=1.5418Å)
1	12.0
2	17.8
3	21.1
4	22.3
5	29.2

3. The compound of claim 1 having the following characteristic peaks in a powder XRD:

Peak	2θ° (± 0.1°) (λ=1.5418Å)
1	12.0
2	17.8
3	21.1
4	22.3
5	29.2
6	10.5
7	14.0
8	21.7
9	24.3
10	26.1

4. The compound of any one of claims 1 to 3, which begins melting at 210.1°C ±1°C when heated from 25°C to 325°C at 10°C per minute in DSC.

5. A method of obtaining 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one (compound A) as crystalline Form A comprising the steps of:

(i) crystallising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one from a solvent;

(ii) if the original solvent is not ethanol, treating the crystalline compound A with ethanol;

(iii) treating the crystalline compound A with water to remove trapped ethanol;
(iv) drying the resulting product.

6. A method of obtaining 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one (compound A) as crystalline Form A comprising the steps of:
(i) crystallising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one from a solvent;
(ii) if the original solvent used in the synthesis of compound A in the crystalline form is not a mixture of water and a C_{1-2} alcohol, heating the compound with a mixture of water and a C_{1-2} alcohol;
(iii) distilling the mixture at ambient pressure; and
(iv) drying the resulting product.

7. A method of obtaining 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one (compound A) as crystalline Form A comprising the steps of:
(i) suspending compound A in a mixture of water and a C_{1-2} alcohol as the solvent;
(ii) heating the suspension to reflux;
(iii) cooling the solution and seeding with compound A as Form A;
(iv) drying the resulting product.

8. A method of synthesising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one from 4-[4-fluoro-3-(piperazine-1-carbonyl)-benzyl]-2H-phthalazin-1-one comprising the step of:

(i) adding a pre-mixed solution of triethylamine and cyclopropane carbonyl chloride, in an organic solvent in a controlled manner, to 4-[4-fluoro-3-(piperazine-1-carbonyl)-benzyl]-2H-phthalazin-1-one in the same organic solvent with the temperature of the solution being controlled to be below 20°C.

9. A method of synthesising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one from 2-fluoro-5-(4-oxo-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid comprising reacting 2-fluoro-5-(4-oxo-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid with 1-(cyclopropylcarbonyl)piperazine or a mineral acid salt thereof in the presence of an amide coupling agent.

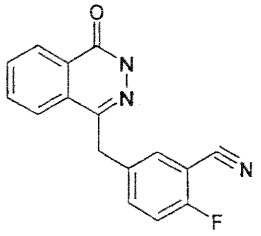
10. A method synthesising 2-fluoro-5-(4-oxo-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid, comprising the step of:

(a) synthesising diethyl (3-oxo-1,3-dihydro-2-benzofuran-1-yl)phosphonate from 2-carboxybenzaldehyde;

(b) synthesising 2-fluoro-5-[(E/Z)-(3-oxo-2-benzofuran-1(*3H*)-ylidene)methyl]benzonitrile from diethyl (3-oxo-1,3-dihydro-2-benzofuran-1-yl)phosphonate.

11. The method of claim 10, further comprising the step of:

(c) synthesising 2-fluoro-5-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]benzonitrile (ED):

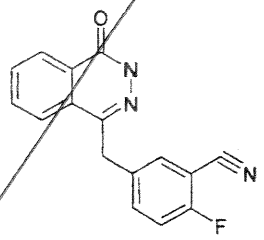


ED

from compound E by reaction with hydrazine hydrate; and

(d) synthesising compound D from compound ED by reaction with sodium hydroxide.

12. 2-Fluoro-5-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]benzonitrile (ED):



ED

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier or diluent.

14. A compound according to any one of claims 1 to 4 for use in a method of treatment of the human or animal body.

15. A compound according to any one of claims 1 to 4 for the use in a method of inhibiting PARP in the treatment of the human or animal body.

16. The use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for inhibiting the activity of PARP.

17. The use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for the treatment of: vascular disease; septic shock; ischaemic injury; neurotoxicity; haemorraghic shock; viral infection; or diseases ameliorated by the inhibition of the activity of PARP.

18. The use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for use as an adjunct in cancer therapy or for potentiating tumour cells for treatment with ionizing radiation or chemotherapeutic agents.

19. Use of a compound according to claims 1 to 4 in the manufacture of a medicament for use in the treatment of cancer in an individual, wherein said cancer is deficient in HR dependent DNA DSB repair pathway.

20. Use according to claim 19, wherein said cancer comprises one or more cancer cells having a reduced or abrogated ability to repair DNA DSB by HR relative to normal cells.

21. Use according to claim 20, wherein said cancer cells have a BRCA1 or BRCA2 deficient phenotype.

22. Use according to claim 21, wherein said cancer cells are deficient in BRCA1 or BRCA2.

23. Use according to any one of claims 19 to 22, wherein said individual is heterozygous for a mutation in a gene encoding a component of the HR dependent DNA DSB repair pathway.

24. Use according to claim 23, wherein said individual is heterozygous for a mutation in BRCA1 and/or BRCA2.

25. Use according to any one of the claims 19 to 24, wherein said cancer is breast, ovary, pancreas or prostate cancer.

26. Use according to any one of claims 19 to 25, wherein said treatment further comprises administration of ionising radiation or a chemotherapeutic agent.

CLAIMS

1. A method of synthesising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one from 2-carboxybenzaldehyde, comprising the steps of:

(a) synthesising diethyl (3-oxo-1,3-dihydro-2-benzofuran-1-yl)phosphonate from 2-carboxybenzaldehyde;

(b) synthesising 2-fluoro-5-[(E/Z)-(3-oxo-2-benzofuran-1(*3H*)-ylidene)methyl]benzonitrile (from diethyl (3-oxo-1,3-dihydro-2-benzofuran-1-yl)phosphonate;

(c) synthesising 2-fluoro-5-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]benzonitrile from 2-fluoro-5-[(E/Z)-(3-oxo-2-benzofuran-1(*3H*)-ylidene)methyl]benzonitrile by reaction with hydrazine hydrate;

(d) synthesising 2-fluoro-5-(4-oxo-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid from 2-fluoro-5-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]benzonitrile by reaction with sodium hydroxide;

(e) reacting 2-fluoro-5-(4-oxo-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid with 1-(cyclopropylcarbonyl)piperazine or a mineral acid salt thereof in the presence of an amide coupling agent.

2. A method according to claim 1, wherein diethyl (3-oxo-1,3-dihydro-2-benzofuran-1-yl)phosphonate is not isolated in the synthesis.

3. A method according to either claim 1 or claim 2, wherein step (a) occurs in 2-methyltetrahydrofuran.

4. A method according to claim 3, where in step (a), 2-carboxybenzaldehyde is reacted with the sodium salt of diethyl phosphite, which is formed *in situ* by adding diethyl phosphite to a cooled solution of sodium t-amylate in 2-methyltetrahydrofuran.

5. A method according to claim 4, where in step (a), the reaction with the sodium salt of diethyl phosphite is followed by reaction with methanesulphonic acid.

6. A method according to any one of claims 1 to 5, wherein step (b) is carried out in 2-methyltetrahydrofuran, with the addition of triethylamine.

7. A method according to any one of claims 1 to 6, where in step (c) 1.1 and 1.3 equivalents of hydrazine hydrate in tetrahydrofuran are used, followed by neutralisation of the excess hydrazine hydrate using acetic acid.

8. A method according to any one of claims 1 to 7, wherein step (e) is carried out in the presence of a base.

9. A method according to claim 8, wherein the base is diisopropylethylamine.

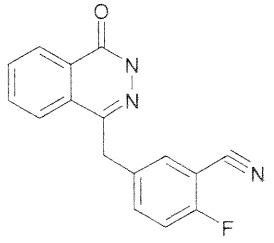
10. A method according to any one of claims 1 to 9, where in step (e) the mineral acid salt is the hydrochloride salt.

11. A method according to any one of claims 1 to 10, where in step (e) the amide coupling agent is 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

12. A method according to any one of claims 1 to 11, wherein step (e) is carried out in acetonitrile.

13. A method according to claim 9, where in step (e) the amide coupling agent is 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, which is added to the solution of 1-(cyclopropylcarbonyl)piperazine, or its mineral acid salt, diisopropylethylamine and 2-fluoro-5-(4-oxo-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid, and the temperature of the resulting solution is maintained at 25°C or below.

14. 2-Fluoro-5-[(4-oxo-3,4-dihydrophthalazin-1-yl)methyl]benzonitrile (ED):



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