

5

CLAIMS

10

15

20

25

30

35

40

1. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate.
2. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in claim 1 characterised by a PXRD pattern measured using Cu K-alpha radiation comprising at least 3 characterising peaks selected from about 5.8, 10.5, 10.7, 11.5 and 17.5 degrees 2-theta (+/- 0.2 degrees 2-theta).
3. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in claim 2 characterised by a PXRD pattern measured using Cu K-alpha radiation comprising characterising peaks at about 5.8, 10.5 and 10.7 degrees 2-theta (+/- 0.2 degrees 2-theta).
4. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in claim 2 characterised by a PXRD pattern measured using Cu K-alpha radiation comprising characterising peaks at about 5.8, 11.5 and 17.5 degrees 2-theta (+/- 0.2 degrees 2-theta).
5. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in claim 3 characterised by a PXRD pattern measured using Cu K-alpha radiation comprising characterising peaks at about 5.8, 10.5, 10.7 and 17.5 degrees 2-theta (+/- 0.2 degrees 2-theta).
6. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in claim 2 characterised by a PXRD pattern measured using Cu K-alpha radiation comprising characterising peaks at about 5.8, 10.5, 10.7, 11.5 and 17.5 degrees 2-theta (+/- 0.2 degrees 2-theta).

- 5 7. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
monophosphate hydrate as claimed in claim 6 characterised by a PXRD pattern measured
using Cu K-alpha radiation comprising characterising peaks at about 5.8, 8.9, 10.5, 10.7,
11.5 and 17.5 degrees 2-theta (+/- 0.2 degrees 2-theta).
- 10 8. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
monophosphate hydrate as claimed in claim 1 or 2 characterised by a PXRD pattern
measured using Cu K-alpha radiation essentially the same as shown in Figure 1.
- 15 9. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
monophosphate hydrate as claimed in claim 1 or 2 characterised by a PXRD pattern
measured using Cu K-alpha radiation having a PXRD peak listing essentially the same as
20 in Table 1.
10. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
monophosphate hydrate as claimed in any one of claims 1 to 9 characterised by a ¹³C-
25 ssNMR spectrum comprising characterising peaks at about 123.5 and 149.3ppm ± 0.2
ppm.
11. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
30 monophosphate hydrate as claimed in claim 10 characterised by a ¹³C-ssNMR spectrum
comprising characterising peaks at about 40.1, 123.5 and 149.3ppm ± 0.2 ppm.
12. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
35 monophosphate hydrate as claimed in claim 11 characterised by a ¹³C-ssNMR spectrum
comprising characterising peaks at about 40.1, 121.3, 123.5 and 149.3ppm ± 0.2 ppm.
13. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
40 monophosphate hydrate as claimed in claim 12 characterised by a ¹³C-ssNMR spectrum
comprising characterising peaks at about 40.1, 121.3, 123.5, 149.3 and 151.3 ppm ± 0.2
ppm.

- 5
14. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in any one of claims 1 to 9 characterised by a ^{13}C -ssNMR spectrum essentially the same as shown in Figure 2.
- 10
15. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in any one of claims 1 to 9 characterised by a ^{13}C -ssNMR spectrum peak listing essentially the same as in Table 2.
- 15
16. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in any one of claims 1 to 15 characterised by a ^{19}F -ssNMR spectrum comprising a characterising peak at about $-129.6\text{ppm} \pm 0.2\text{ ppm}$.
- 20
17. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in claim 16 characterised by a ^{19}F -ssNMR spectrum comprising characterising peaks at about -129.6 and $-128.4\text{ppm} \pm 0.2\text{ ppm}$.
- 25
18. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in any one of claims 1 to 15 characterised by a ^{19}F -ssNMR spectrum essentially the same as shown in Figure 3.
- 30
19. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in any one of claims 1 to 15 characterised by a ^{19}F -ssNMR spectrum peak listing essentially the same as in Table 3.
- 35
20. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in any one of claims 1 to 19 characterised by a FT Raman spectrum comprising characterising peaks at about 702 and $1630\text{cm}^{-1} \pm 2\text{ cm}^{-1}$.
- 40
21. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol

- 5 monophosphate hydrate as claimed in claim 20 characterised by a FT Raman spectrum comprising characterising peaks at about 702, 1604 and 1630cm⁻¹ ±2 cm⁻¹.
22. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
- 10 monophosphate hydrate as claimed in any one of claims 1 to 19 characterised by a FT Raman spectrum essentially the same as shown in Figure 4.
23. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
- 15 monophosphate hydrate as claimed in any one of claims 1 to 19 characterised by a FT Raman spectrum peak listing essentially the same as in Table 4.
24. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
- 20 monophosphate hydrate as claimed in any one of claims 1 to 23 in substantially pure form.
25. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
- 25 monophosphate hydrate as claimed in claim 24 wherein “substantially pure” means the presence of equal or above 90%, equal or above 95%, equal or above 98%, or equal or above 99% weight/weight of crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as compared to any other physical form of (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol or a pharmaceutically acceptable salt or solvate thereof.
- 30
26. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
- 35 monophosphate hydrate as claimed in any one of claims 1 to 25 wherein about 1.0 to about 1.4 molar equivalents of water per mole of (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate are present.
- 40
27. A pharmaceutical composition comprising crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-

pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in
5 any one of claims 1 to 26 and a pharmaceutically acceptable carrier or excipient.

28. Crystalline (1S,2S,3S,5R)-34(6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-
yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-Acyclopentane-1,2-diol
monophosphate hydrate as claimed in any one of claims 1 to 26, or a composition thereof
10 as claimed in claim 27, for use as a medicament.

29. Crystalline (1S,2S,3S,5R)-34(6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-
yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-Acyclopentane-1,2-diol
monophosphate hydrate as claimed in any one of claims 1 to 26, or a composition thereof
15 as claimed in claim 27, for use in the treatment of abnormal cell growth in a mammal.

30. Crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-
yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol
monophosphate hydrate for use as claimed in claim 29 where the abnormal cell growth is
20 cancer.

31. ~~A method of treatment of abnormal cell growth in a mammal comprising administering to
the mammal a therapeutically effective amount of crystalline (1S,2S,3S,5R)-3-((6-
25 (difluoromethyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1,2-diol monophosphate hydrate as claimed in
any one of claims 1 to 26, or a composition thereof as claimed in claim 27. Use of crystalline
(1S,2S,3S,5R)-3-((6- (difluoromethyl)-5-fluoro-1 ,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-
pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-1 ,2-diol monophosphate hydrate as claimed in any one of
claims 1 to 26, or a composition thereof as claimed in claim 27 in the manufacture of a medicament
30 for the treatment of abnormal cell growth in a mammal, wherein a therapeutically effective amount of
the medicament is to be administered to the mammal.~~

32. ~~A method as claimed in claim 31 where the abnormal cell growth is cancer. The use as claimed in
claim 31, wherein the abnormal cell growth is cancer.~~

33. A combination of crystalline (1S,2S,3S,5R)-3-((6-(difluoromethyl)-5-fluoro-1,2,3,4-
tetrahydroisoquinolin-8-yl)oxy)-5-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentane-
1,2-diol monophosphate hydrate as claimed in any one of claims 1 to 26, or a composition
thereof as claimed in claim 27, with another anti-cancer agent.