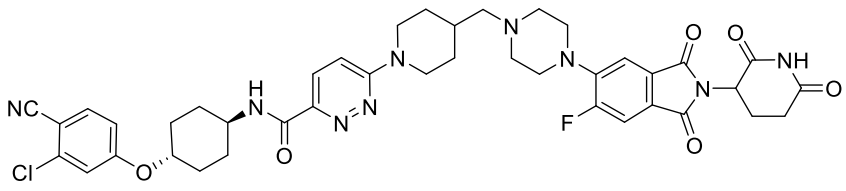
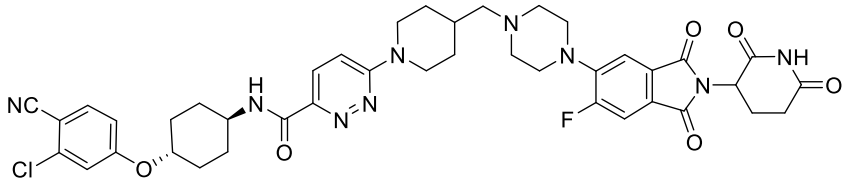
yl}methyl)piperidin-1-yl]pyridazine-3-carboxamide, referred to herein as Compound A, and processes for manufacturing Compound A:



(Compound A).

[0012a] In an aspect of the present disclosure, there is provided a

crystalline form of Compound A



(Compound A)

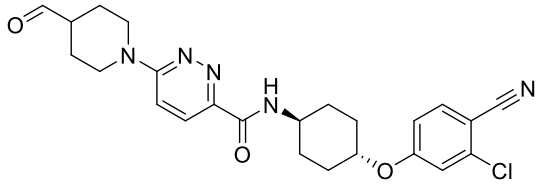
having a powder x-ray diffraction pattern comprising peaks at 7.6° ± 0.2° 2θ, 11.5° ± 0.2° 2θ, and 17.6° ± 0.2° 2θ, wherein said powder x-ray diffraction pattern is obtained using Cu Kα radiation at an x-ray wavelength of 1.5406 Å.

[0012b] In another aspect of the present disclosure, there is provided a crystalline form of Compound A having a powder x-ray diffraction pattern as shown in FIG. 3A.

[0012c] In a further aspect of the present disclosure, there is provided a crystalline form of Compound A having a powder x-ray diffraction pattern comprising peaks at 11.0° ± 0.2° 2θ, 16.1° ± 0.2° 2θ, and 17.9° ± 0.2° 2θ, wherein said powder x-ray diffraction pattern is obtained using Cu Kα radiation at an x-ray wavelength of 1.5406 Å.

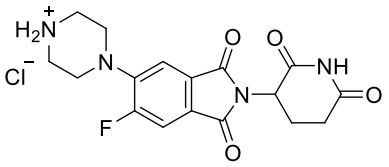
[0012d] In another aspect of the present disclosure, there is provided a crystalline form of Compound A having a powder x-ray diffraction pattern as shown in FIG. 3C.

[0012e] In a further aspect of the present disclosure, there is provided a process for manufacturing Compound A, wherein the process comprises the reductive amination of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-formylpiperidin-1-yl)pyridazine-3-carboxamide (**Intermediate 3**) with 2-(2,6-dioxopiperidin-3-yl)-5-fluoro-6-(piperazin-1-yl)isoindoline-1,3-dione hydrochloride (**Intermediate 5**) and a reducing agent to provide Compound A:

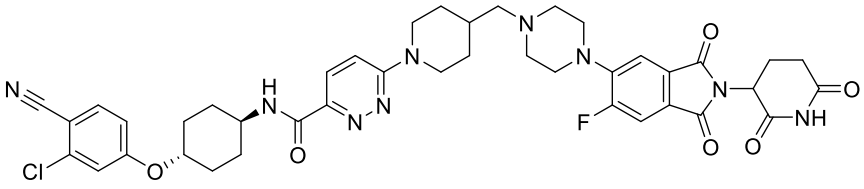


Intermediate 3

+



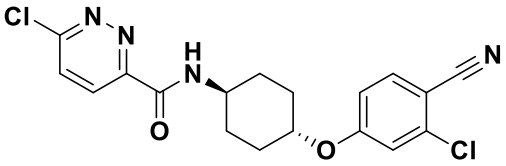
Intermediate 5



Compound A

.

[0012f] In another aspect of the present disclosure, there is provided a compound which is: 6-chloro-N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)pyridazine-3-carboxamide,

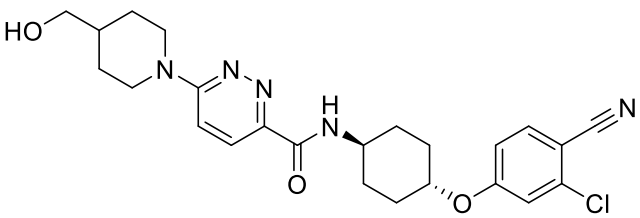


Intermediate 4

.

[0012g] In a further aspect of the present disclosure, there is provided an ultrapure form of Compound A having a purity greater than about 98%.

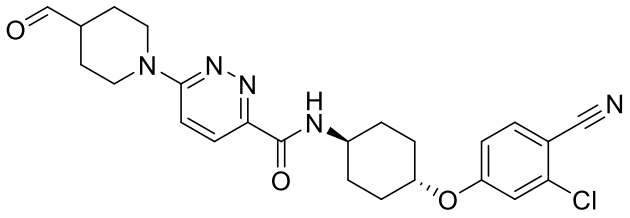
[0012h] In another aspect of the present disclosure, there is provided an ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of impurity **Intermediate 2**:



Intermediate 2

.

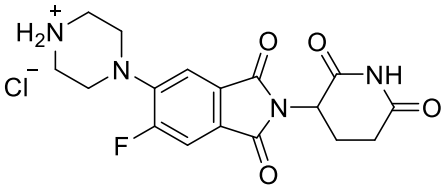
[0012i] In a further aspect of the present disclosure, there is provided an ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of impurity **Intermediate 3**:



Intermediate 3

.

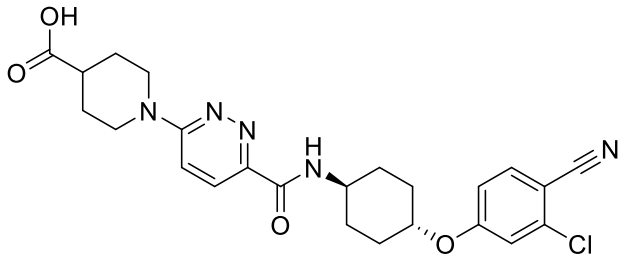
[0012j] In another aspect of the present disclosure, there is provided an ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of impurity **Intermediate 5**:



Intermediate 5

.

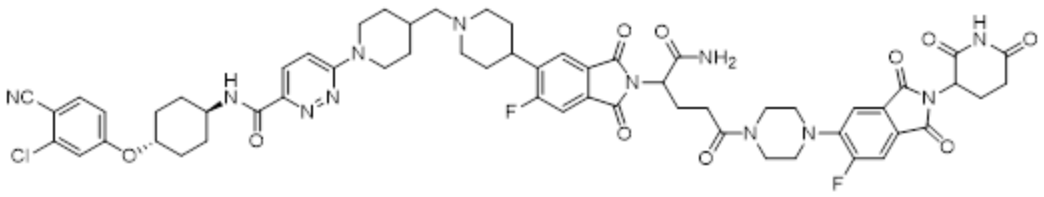
[0012k] In a further aspect of the present disclosure, there is provided an ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of **Impurity 1**:



Impurity 1

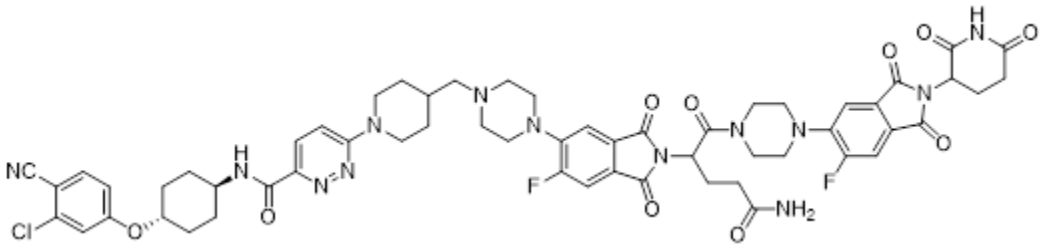
.

[0012l] In another aspect of the present disclosure, there is provided an ultrapure form of Compound A having a purity greater than about 95%, and comprising less than about 1% of **Impurity 2**:



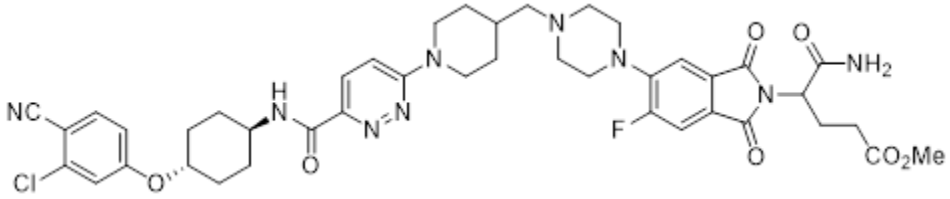
Impurity 2.

[0012m] In a further aspect of the present disclosure, there is provided an ultrapure form of Compound A having a purity greater than about 95%, and comprising less than about 1% of **Impurity 3**:



Impurity 3.

[0012n] In another aspect of the present disclosure, there is provided an ultrapure form of Compound A having a purity greater than about 95%, and comprising less than about 1% of **Impurity 4**:



Impurity 4.

[0012o] In a further aspect of the present disclosure, there is provided an ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of at least two of the following impurities: Intermediate 2, Intermediate 3, Intermediate 5, Impurity 1, Impurity 2, Impurity 3, and Impurity 4.

[0012p] In another aspect of the present disclosure, there is provided a process for manufacturing the amorphous form of Compound A disclosed herein, wherein the process comprises the following steps:

(D1) dissolving crystalline Compound A in solvent to afford a solution of Compound A;

(D2) introducing the Compound A solution from step (1) into a spray dryer;

(D3) spraying the Compound A solution from the spray dryer to form the amorphous form of the Compound A; and

(D4) Removing the residual solvent from the amorphous form of Compound A.

[0012q] In a further aspect of the present disclosure, there is provided an oral dosage form comprising one or more pharmaceutically acceptable excipients and Compound A disclosed herein, wherein the oral dosage form is selected from the group consisting of a tablet, a sachet, or a capsule.

[0012r] In another aspect of the present disclosure, there is provided a method of manufacturing the oral dosage form disclosed herein comprising the following steps:

(E1) blending a form of Compound A with at least one pharmaceutically acceptable excipient to create a powder;

(E2) delumping the powder from step (E1), adding at least one pharmaceutically acceptable excipient, and blending to create a first blend;

(E3) granulating the blend from step (E2) and passing the resultant powder through a screen to produce a plurality of granules;

(E4) adding at least one pharmaceutically acceptable excipient to plurality of granules from step (E3) and blending to produce a second blend; and

(E5) compressing the second blend from step (E4) into one or more tablets.

[0012s] In a further aspect of the present disclosure, there is provided a use of an oral dosage form disclosed herein, in the manufacture of a medicament for treating prostate cancer in a subject.

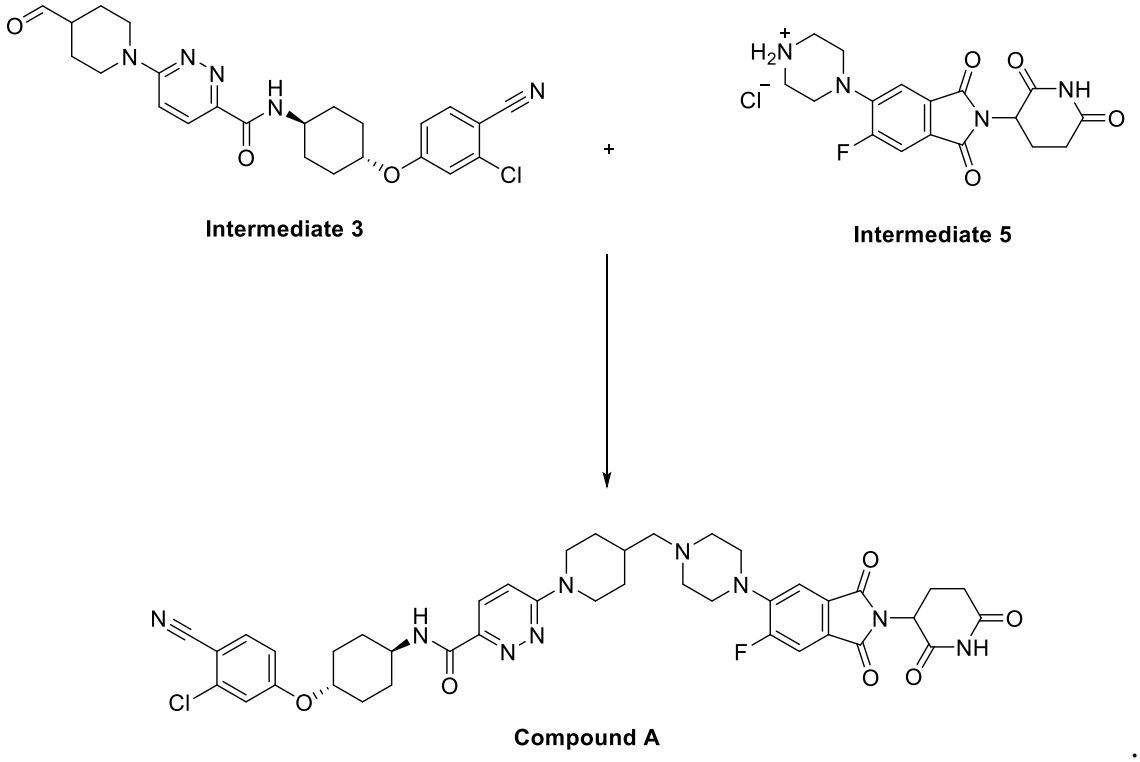
[0012t] In another aspect of the present disclosure, there is provided an oral dosage form disclosed herein, for use in therapy.

[0013] In one example, this application pertains to a method of treating prostate cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Compound A. In one example, the method further comprises the administration of an additional anti-cancer agent.

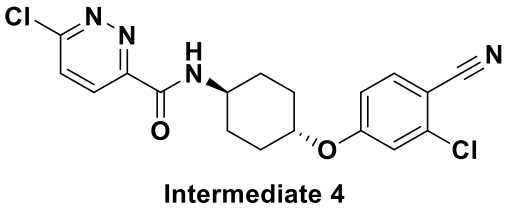
[0014] In one example, this disclosure provides a crystalline form of Compound A having a powder x-ray diffraction pattern comprising peaks at 7.6° ± 0.2° 2θ, 11.5° ± 0.2° 2θ, and 17.6° ± 0.2° 2θ, wherein said powder x-ray diffraction pattern is obtained using Cu Kα radiation at an x-ray wavelength of 1.5406 Å. This crystalline form is designated as "Form 2."

[0015] In another example, this disclosure provides a crystalline form of Compound A having a powder x-ray diffraction pattern comprising peaks at 11.0° ± 0.2° 2θ, 16.1° ± 0.2° 2θ, and 17.9° ± 0.2° 2θ, wherein said powder x-ray diffraction pattern is obtained using Cu Kα radiation at an x-ray wavelength of 1.5406 Å. This crystalline form is designated as "Form 4."

[0016] In another example, this disclosure provides processes for manufacturing Compound A, wherein the process comprises the reductive amination of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-formylpiperidin-1-yl)pyridazine-3-carboxamide (**Intermediate 3**) with 2-(2,6-dioxopiperidin-3-yl)-5-fluoro-6-(piperazin-1-yl)isoindoline-1,3-dione hydrochloride (**Intermediate 5**) and a reducing agent to provide Compound A:



[0017] In another example, this disclosure provides an intermediate useful for the synthesis of Compound A which is 6-chloro-N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)pyridazine-3-carboxamide (**Intermediate 4**),



[0018] In another example, this disclosure provides an ultrapure form of Compound A having a purity greater than about 95 wt% .

[0019] In another example, this disclosure provides processes for manufacturing an amorphous form of Compound A wherein the process comprises the following steps:

(1) dissolving crystalline Compound A in a solvent to afford a solution of Compound A;

(2) introducing the solution of Compound A from step (1) into a spray dryer to create the amorphous form of Compound A; and

(3) Drying the amorphous form of Compound A to remove residual solvent.

[0020] Alternative methods of preparing amorphous forms of Compound A may include lyophilization, hot-melt extrusion, milling, or high-shear mixing.

[0021] In another example, this disclosure provides an oral dosage form comprising one or more pharmaceutically acceptable excipients and Compound A, wherein the oral dosage form is selected from the group consisting of a tablet, a sachet, or a capsule.

[0022] In a preferred example, the oral dosage form comprises one or more pharmaceutically acceptable excipients and an ultrapure form of Compound A.

[0023] In another example, this disclosure provides processes of manufacturing a tablet Compound A comprising the following steps:

(1) blending a form of Compound A with at least one pharmaceutically acceptable excipient to create a powder;

(2) delumping the powder from step (1), adding at least one pharmaceutically acceptable excipient, and blending to create a first blend;

(3) granulating the blend from step (2) and passing the resultant powder through a screen to produce a plurality of granules;

(4) adding at least one pharmaceutically excipient to the at least one granule from step (3) and blending to produce a second blend; and

(5) compressing the second blend from step (4) into one or more tablets.

[0024] In another example, this disclosure provides methods of treating cancer in a subject comprising administering to a subject in need of such treatment one or more unit dosage forms (e.g., tablets) of the present disclosure. In one example, the method further comprises the administration of an additional anti-cancer agent.

[0025] The preceding general areas of utility are given by way of example only and are not intended to limit the scope of the present disclosure or appended claims. Additional objects and advantages associated with the compositions, methods, and processes of the present disclosure will be appreciated by one of ordinary skill in the art in light of the instant claims, description, and examples. For example, the various examples and examples of the present disclosure may be utilized in numerous combinations, all of which are expressly contemplated by the present description. These additional advantages, objects, and examples are expressly included within the scope of the present disclosure. The publications and other materials used herein to illuminate the background

of the present disclosure, and in particular cases, to provide additional details respecting the practice, are incorporated by reference.

[0026] Where applicable or not specifically disclaimed, any one of the examples described herein are contemplated to be able to combine with any other one or more examples, even though the examples are described under different examples of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] FIG. 1 is a Differential Scanning Calorimetry plot for Compound A.

[0028] FIG. 2 is a dynamic vapor solution (DVS) isotherm plot of Compound A obtained on a laboratory batch of Compound A having the same powder x-ray diffraction pattern as in FIG. 3A.

[0029] FIG. 3A is a powder X-ray diffraction pattern of Form 2 of Compound A and FIG. 3B is a table that includes the peak listings of the diffraction pattern in FIG. 3A.

[0030] FIG. 3C is a powder X-ray diffraction pattern of Form 4 of Compound A and FIG. 3D is a table that includes the peak listings of the diffraction pattern in FIG. 3C.

[0031] FIG. 4 is a ^{1}H NMR Spectrum of Compound A in deuterated dimethylsulfoxide (DMSO-d_6).

[0032] FIG. 5 is a ^{13}C NMR Spectrum of Compound A in deuterated dimethylsulfoxide (DMSO-d_6).

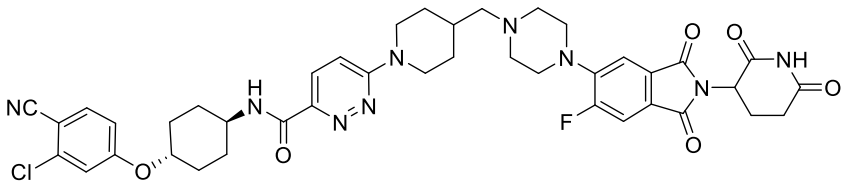
[0033] FIG. 6 is a high resolution mass spectrum of Compound A. High resolution mass spectrometry (MS) analyses of Compound A were conducted with flow injection analysis using positive ion electrospray [high-resolution electrospray ionization mass spectrometry (HR-ESI)] on a Thermo Orbitrap MS in Fourier Transform mode.

[0034] FIG. 7 shows the major peaks resulting from MS/MS fragmentation of the 812.308 parent ion from the high resolution mass spectrum of Compound A and FIG. 8A and FIG. 8B are an ion map and corresponding table showing the further fragmentation of the observed MS/MS ions (MS^3).

[0035] FIG. 9 is an infrared spectrum of Compound A obtained on a Bomem MB-102 FTIR spectrometer equipped with a DuraSamplIR diamond ATR probe. Key features which lend further support to the structure for Compound A are bands at 2225 cm^{-1}, representing a nitrile stretch vibration, and five peaks between 1774 and 1594, which represent four imide carbonyl vibrations and an amide carbonyl stretch vibration.

CLAIMS

1. A crystalline form of Compound A



(Compound A)

having a powder x-ray diffraction pattern comprising peaks at 7.6° ± 0.2° 2θ, 11.5° ± 0.2° 2θ, and 17.6° ± 0.2° 2θ, wherein said powder x-ray diffraction pattern is obtained using Cu Kα radiation at an x-ray wavelength of 1.5406 Å.

2. The crystalline form of Compound A of claim 1, further comprising a peak at 18.5° ± 0.2° 2θ.

3. The crystalline form of Compound A of claim 1 or 2, further comprising a peak at 21.4° ± 0.2° 2θ.

4. The crystalline form of Compound A of any one of claims 1-3, further comprising a peak at 3.1° ± 0.2° 2θ.

5. A crystalline form of Compound A having a powder x-ray diffraction pattern as shown in FIG. 3A.

6. A crystalline form of Compound A having a powder x-ray diffraction pattern comprising peaks at 11.0° ± 0.2° 2θ, 16.1° ± 0.2° 2θ, and 17.9° ± 0.2° 2θ, wherein said powder x-ray diffraction pattern is obtained using Cu Kα radiation at an x-ray wavelength of 1.5406 Å.

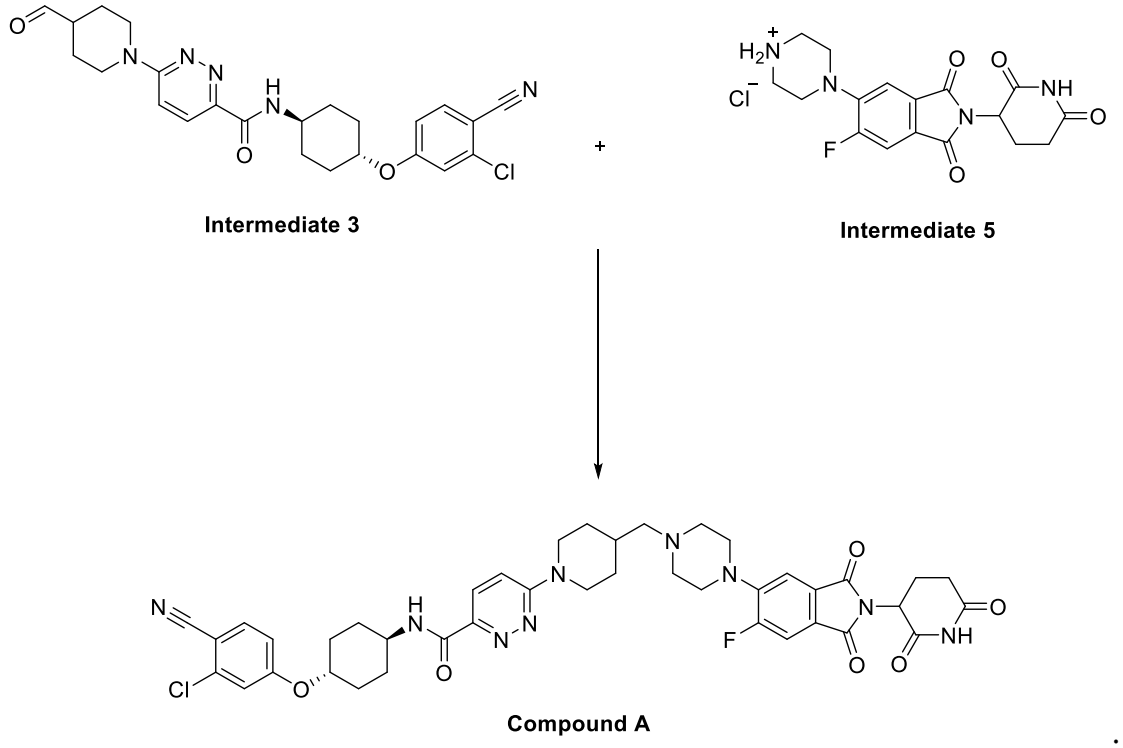
7. The crystalline form of Compound A of claim 6, further comprising a peak at 11.3° ± 0.2° 2θ.

8. The crystalline form of Compound A of claim 6 or 7, further comprising a peak at 17.2° ± 0.2° 2θ.

9. The crystalline form of Compound A of any one of claims 6-8, further comprising a peak at 7.9° ± 0.2° 2θ.

10. A crystalline form of Compound A having a powder x-ray diffraction pattern as shown in FIG. 3C.

11. A process for manufacturing Compound A, wherein the process comprises the reductive amination of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-formylpiperidin-1-yl)pyridazine-3-carboxamide (**Intermediate 3**) with 2-(2,6-dioxopiperidin-3-yl)-5-fluoro-6-(piperazin-1-yl)isoindoline-1,3-dione hydrochloride (**Intermediate 5**) and a reducing agent to provide Compound A:



12. The process of claim 11, further comprising a step for the purification of Compound A.

13. The process of claim 12, wherein the purification of Compound A comprises:

(A1) dissolving Compound A in about a mixture of dichloromethane and methanol;

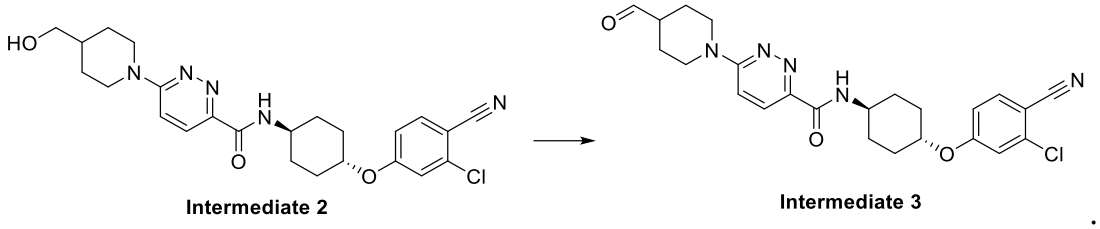
(A2) filtering the solution comprising Compound A;

(A3) distillatively exchanging the solvent of the solution comprising Compound A with ethanol;

(A4) crystallizing Compound A from the ethanol solution; and

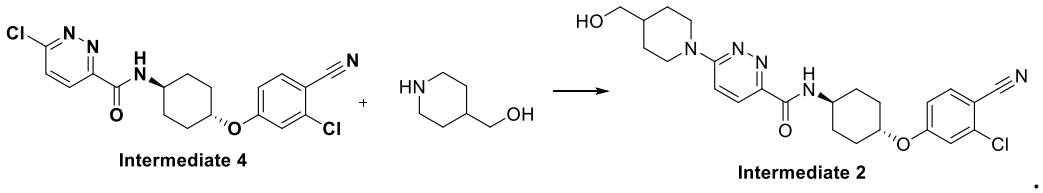
(A5) drying the purified crystalline solid form of Compound A.

14. The process of any one of claims 11-13, further comprising the oxidation of N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(hydroxymethyl)piperidin-1-yl)pyridazine-3-carboxamide (**Intermediate 2**) to form N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-formylpiperidin-1-yl)pyridazine-3-carboxamide (**Intermediate 3**):



15. The process of claim 14 further comprising the step of purifying Intermediate 3 by recrystallization.

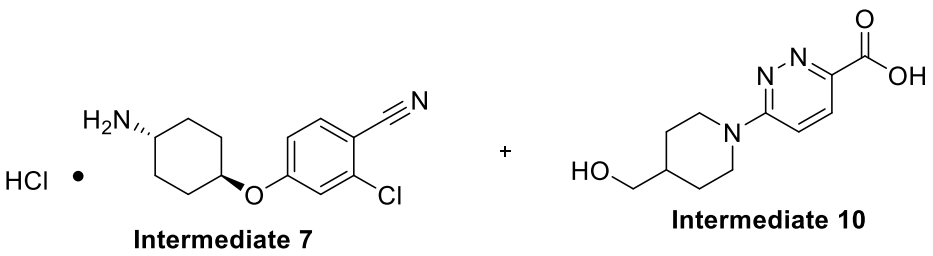
16. The process of any one of claims 11-15, further comprising a nucleophilic aromatic substitution reaction of 6-chloro-N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)pyridazine-3-carboxamide (**Intermediate 4)** and piperidin-4-yl methanol in the presence of a base to provide N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-(hydroxymethyl)piperidin-1-yl)pyridazine-3-carboxamide (**Intermediate 2**):

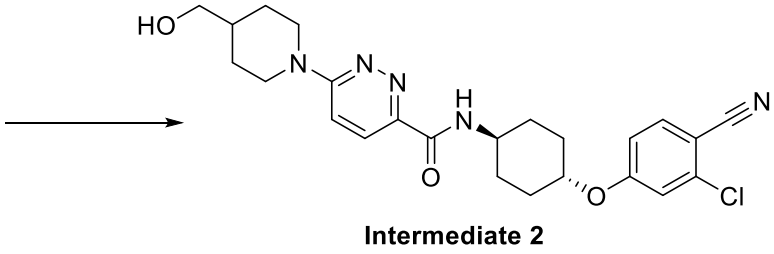


17. The process of claim 16, further comprising the step of purifying Intermediate 2 by recrystallization in an organic solvent.

18. The process of any one of claims 11-17, further comprising an amide coupling of 4-(((1r,4r)-4-aminocyclohexyl)oxy)-2-chlorobenzonitrile hydrochloride (**Intermediate 7**) and 6-(4-(hydroxymethyl)piperidin-1-yl)pyridazine-3-carboxylic acid (**Intermediate 10**), facilitated by a coupling agent, to provide N-((1r,4r)-4-(3-chloro-4-

cyanophenoxy)cyclohexyl)-6-(4-(hydroxymethyl)piperidin-1-yl)pyridazine-3-carboxamide (**Intermediate 2**):





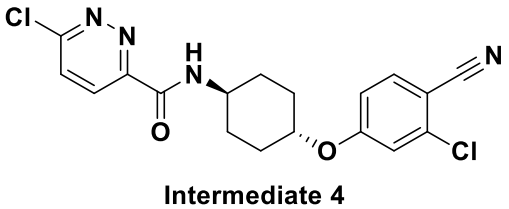
.

19. The process of claim 18, further comprising the step of purifying Intermediate 2 by recrystallization in an organic solvent.

20. The process of any one of claims 11-19, wherein the purified form of Compound A has a crystalline form with a powder x-ray diffraction pattern comprising peaks at 7.6° ± 0.2° 2θ, 11.5° ± 0.2° 2θ, and 17.6° ± 0.2° 2θ, wherein said powder x-ray diffraction pattern is obtained using Cu Kα radiation at an x-ray wavelength of 1.5406 Å.

21. A compound which is:

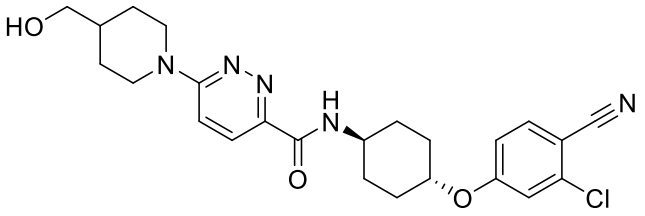
6-chloro-N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)pyridazine-3-carboxamide,



.

22. An ultrapure form of Compound A having a purity greater than about 98%.

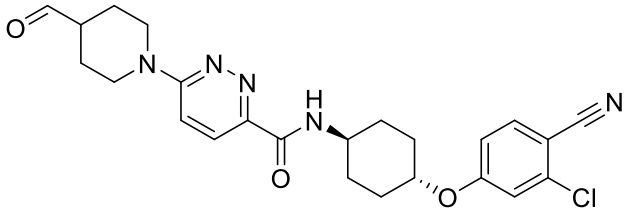
23. An ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of impurity **Intermediate 2**:



Intermediate 2

24. The ultrapure form of Compound A of claim 23, comprising less than about 0.5% of impurity **Intermediate 2**.

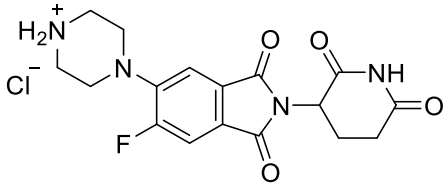
25. An ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of impurity **Intermediate 3**:



Intermediate 3

26. The ultrapure form of Compound A of claim 25, comprising less than about 0.5% of impurity **Intermediate 3**.

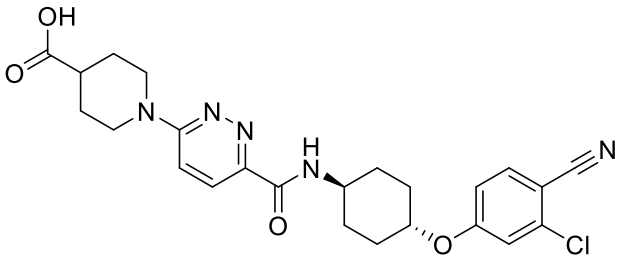
27. An ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of impurity **Intermediate 5**:



Intermediate 5

28. The ultrapure form of Compound A of claim 27, comprising less than about 0.5% of impurity **Intermediate 5**.

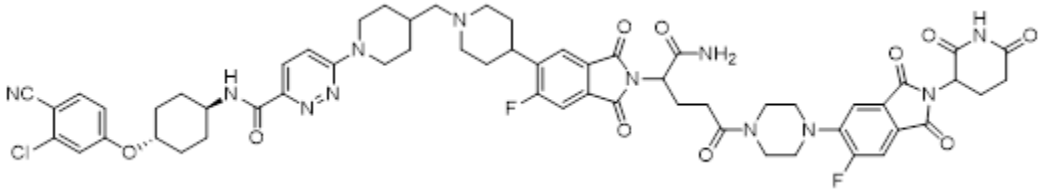
29. An ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of **Impurity 1**:



Impurity 1

30. The ultrapure form of Compound A of claim 29, comprising less than about 0.5% of **Impurity 1**.

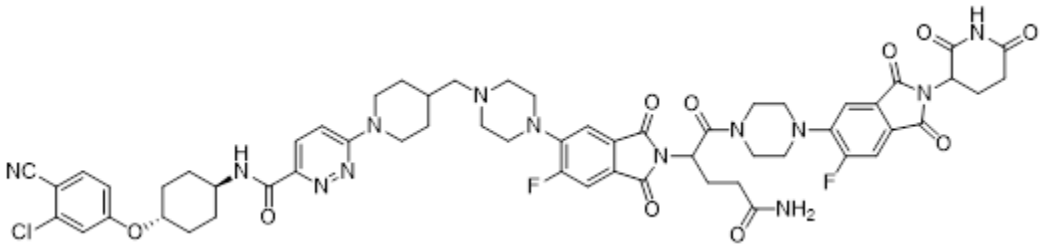
31. An ultrapure form of Compound A having a purity greater than about 95%, and comprising less than about 1% of **Impurity 2**:



Impurity 2.

32. The ultrapure form of Compound A of claim 31, comprising less than about 0.5% of **Impurity 2**.

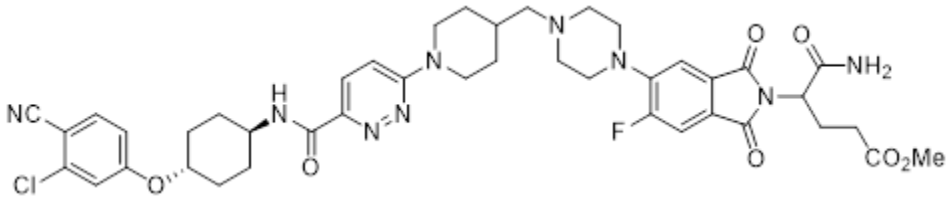
33. An ultrapure form of Compound A having a purity greater than about 95%, and comprising less than about 1% of **Impurity 3**:



Impurity 3.

34. The ultrapure form of Compound A of claim 33, comprising less than about 0.5% of **Impurity 3**.

35. An ultrapure form of Compound A having a purity greater than about 95%, and comprising less than about 1% of **Impurity 4**:



Impurity 4.

36. The ultrapure form of Compound A of claim 35, comprising less than about 0.5% of **Impurity 4**.

37. The ultrapure form of Compound A of any one of claims 22-36, wherein the purity of Compound A is determined by HPLC.

38. The ultrapure form of Compound A of any one of claims 23-37, wherein the amount of the Intermediate or Impurity is determined by HPLC.

39. The ultrapure form of Compound A of any one of claims 22-38, wherein the purity of Compound A is greater than about 99%, about 99.5%, or about 99.9%.

40. An ultrapure form of Compound A having a purity greater than about 98%, and comprising less than about 1% of at least two of the following impurities: Intermediate 2, Intermediate 3, Intermediate 5, Impurity 1, Impurity 2, Impurity 3, and Impurity 4.

41. The ultrapure form of Compound A of claim 40, wherein the purity of Compound A is greater than about 99%.

42. The ultrapure form of Compound A of any one of claims 22-38, comprising less than about 0.9%, about 0.8%, about 0.7%, about 0.6%, or about 0.5% of at least two of the following impurities: Intermediate 2, Intermediate 3, Intermediate 5, Impurity 1, Impurity 2, Impurity 3, and Impurity 4.

43. The ultrapure form of Compound A of any one of claims 22-38, wherein the Compound A has a purity of about 99.9%.

44. The ultrapure form of Compound A of any one of claims 22-43, wherein Compound A is in amorphous form.

45. The ultrapure form of Compound A of any one of claims 22-44, further characterized by a $D_V(50)$ particle size of about 5 to about 20 μm.

46. A process for manufacturing the amorphous form of Compound A of any one of claims 22-45, wherein the process comprises the following steps:

(D1) dissolving crystalline Compound A in solvent to afford a solution of Compound A;

(D2) introducing the Compound A solution from step (1) into a spray dryer;

(D3) spraying the Compound A solution from the spray dryer to form the amorphous form of the Compound A; and

(D4) Removing the residual solvent from the amorphous form of Compound A.

47. The process of claim 46, wherein, the solvent of step (D1) is a mixture of dichloromethane and methanol.

48. The process of claim 47, wherein the solvent of step (D1) is a mixture of about 95:5 (w/w) to about 80:20 (w/w) dichloromethane:methanol.

49. An oral dosage form comprising one or more pharmaceutically acceptable excipients and Compound A of any one of claims 22-45, wherein the oral dosage form is selected from the group consisting of a tablet, a sachet, or a capsule.

50. The oral dosage form of claim 49, wherein the Compound A is the ultrapure form of Compound A of any one of claims 22-45.

51. The oral dosage form of claim 49 or 50, wherein the oral dosage form is a tablet.

52. The oral dosage form of claim 51, wherein the amount of Compound A in the tablet is between about 5 mg and 1000 mg.

53. The oral dosage form of claim 52, wherein the amount of Compound A in the tablet is about 35 mg to about 280 mg.

54. The oral dosage form of claim 53, wherein the amount of Compound A in the tablet is about 35 mg, about 70 mg, about 105 mg, about 140 mg, about 175 mg, about 210 mg, about 245 mg, or about 280 mg.

55. The oral dosage form of claim 53, wherein the amount of Compound A in the tablet is about 100 mg, about 200 mg, about 300 mg, about 400 mg, or about 420 mg.

56. The oral dosage form of any one of claims 51-55, wherein the pharmaceutically acceptable excipients are selected from the group consisting of fillers, disintegrants, glidants, and lubricants, wherein:

the filler is microcrystalline cellulose, silicified microcrystalline cellulose, lactose monohydrate, mannitol, sorbitol, xylitol, hydroxypropyl methylcellulose, hydroxypropyl cellulose, pullulan, fast-dissolving carbohydrates such as Pharmaburst™, or any mixture thereof;

the disintegrant is sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, chitosan, agar, alginic acid, calcium alginate, methyl cellulose, microcrystalline cellulose, powdered cellulose, lower alkylsubstituted hydroxypropyl cellulose, hydroxylpropyl starch, low-substituted hydroxypropylcellulose, polacrilin potassium, starch, pregelatinized starch, sodium alginate, magnesium aluminum silicate, polacrilin potassium, povidone, or any mixture thereof;

the glidant is silicon dioxide, colloidal silicon dioxide, calcium silicate, magnesium silicate, magnesium trisilicate, talc, starch, or any mixture thereof; and

the lubricant is magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl behenate, glyceryl palmitostearate, hexagonal boron nitride, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, poloxamer, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, zinc stearate, or any mixture thereof.

57. The oral dosage form of any one of claims 51-55, comprising:

About 1 to about 50% w/w of Compound A;
About 35 to about 60% w/w microcrystalline cellulose;
About 15 to about 50% w/w lactose monohydrate;
About 1 to about 5% w/w croscarmellose sodium;
0 to about 1 % w/w silicon dioxide; and

0 to about 1 % w/w magnesium stearate.

58. The oral dosage form of any one of claims 51-55, comprising:

About 5 % w/w of Compound A;

About 45.5 % w/w microcrystalline cellulose;

About 45.5 % w/w lactose monohydrate;

About 3 % w/w croscarmellose sodium;

About 0.5 % w/w silicon dioxide; and

About 0.5 % w/w magnesium stearate.

59. The oral dosage form of any one of claims 51-55, comprising an intra-granular portion and an extra-granular portion, wherein the intra-granular portion comprises

About 10 to about 40% w/w of Compound A;

About 35 to about 60% w/w microcrystalline cellulose;

About 15 to about 30% w/w lactose monohydrate;

About 1 to about 10% w/w croscarmellose sodium;

0 to about 1 % w/w silicon dioxide; and

0 to about 0.5% w/w magnesium stearate;

and wherein the extra-granular portion comprises

About 1 to about 5% w/w croscarmellose sodium;

0 to about 1 % w/w magnesium stearate; and

0 to about 2 % w/w silicon dioxide.

60. The oral dosage form of any one of claims 51-55, comprising an intra-granular portion and an extra-granular portion, wherein the intra-granular portion comprises:

About 20% w/w of Compound A;

About 48.7% w/w microcrystalline cellulose;

About 24.3% w/w lactose monohydrate;

About 3% w/w croscarmellose sodium;

About 0.5 % w/w silicon dioxide; and

About 0.25% w/w magnesium stearate;

and wherein the extra-granular portion comprises:

About 2% w/w croscarmellose sodium;

About 0.5% w/w magnesium stearate; and

About 0.25 % w/w silicon dioxide.

61. The oral dosage form of any one of claims 51-60, wherein the Compound A is an ultrapure form of Compound A.

62. The oral dosage form of any one of claims 51-60, wherein the Compound A is prepared according to the process of any one of claims 46-48.

63. A method of manufacturing the oral dosage form of any one of claims 51-60 comprising the following steps:

(E1) blending a form of Compound A with at least one pharmaceutically acceptable excipient to create a powder;

(E2) delumping the powder from step (E1), adding at least one pharmaceutically acceptable excipient, and blending to create a first blend;

(E3) granulating the blend from step (E2) and passing the resultant powder through a screen to produce a plurality of granules;

(E4) adding at least one pharmaceutically acceptable excipient to plurality of granules from step (E3) and blending to produce a second blend; and

(E5) compressing the second blend from step (E4) into one or more tablets.

64. The method of claim 63, wherein the form of Compound A in step (E1) is the amorphous form of Compound A.

65. The method of claim 63 or 64, wherein, in step (E1), Compound A is blended with at least one filler, at least one disintegrant, and at least one glidant.

66. The method of claim 65, wherein, in step (E1), Compound A is blended with two fillers, one disintegrant, and one glidant.

67. The method of claim 65, wherein, in step (E1), Compound A is blended with two fillers, one disintegrant, one glidant, and one lubricant.

68. The method of any one of claims 63-67, wherein at least one pharmaceutically acceptable excipient of step (E2) is a lubricant.

69. The method of any one of claims 63-68, wherein the at least one pharmaceutically acceptable excipient of step (E4) comprises at least one lubricant.

70. The method of any one of claims 63-69, wherein at least one glidant, at least one disintegrant, and at least one lubricant are added to the plurality of granules in step (E4).

71. Use of an oral dosage form of any one of claims 49-62, in the manufacture of a medicament for treating prostate cancer in a subject.

72. The use of claim 71, wherein the prostate cancer is metastatic castration resistant prostate cancer.

73. The use of claim 71 or 72, wherein the oral dosage form is a tablet, and wherein one or more tablets are to be administered to the subject once a day, twice a day, three times a day, or four times a day.

74. The use of any one of claims 71-73, wherein the oral dosage form is a tablet, and wherein one or more tablets are to be administered to the subject all at once or subdivided in two, three, four, or more sub-portions.

75. The use of any one of claims 71-74, wherein the subject is in a fed state.

76. The use of any one of claims 71-74, wherein the subject is in a fasted state.

77. The use of any one of claims 71-76, wherein the subject is to take or is to be administered an antacid medication.

78. The use of any one of claims 71-77, wherein the oral dosage form is to be administered to the subject, and wherein an additional anti-cancer agent is to be further administered.

79. An oral dosage form of any one of claims 49-62, for use in therapy.