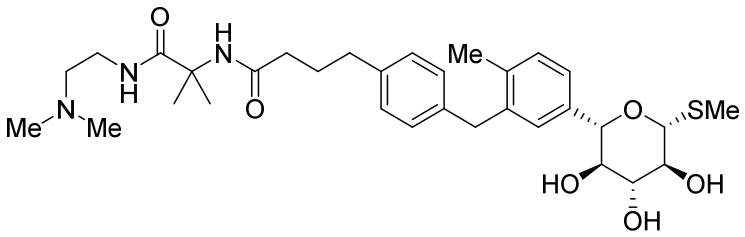
Compounds may exist in one or more salts, crystalline forms, or co-crystals, but their existence and characteristics cannot be predicted with any certainty. Different forms may have different physical properties such as, for example, melting temperatures, heats of fusion, solubilities, dissolution rates, and/or vibrational spectra as a result of the arrangement or conformation of the molecules or ions in the crystal lattice. The differences in physical properties exhibited by polymorphs may affect pharmaceutical parameters, such as storage stability, compressibility, density (important in formulation and product manufacturing), and dissolution rate (an important factor in bioavailability). Differences in stability can result from changes in chemical reactivity (*e.g.*, differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph), mechanical changes (*e.g.*, tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph), or both (*e.g.*, tablets of one polymorph are more susceptible to breakdown at high humidity). In addition, the physical properties of a crystalline form may be important in processing; for example, one polymorph might be more likely to form solvates or might be difficult to filter and wash free of impurities (*e.g.*, particle shape and size distribution might be different between polymorphs). Polymorphs may be characterized by a variety of methods known in the art, including X-ray powder diffraction, and melting point.

No standard procedure exists for the preparation of all possible solid forms of a compound, and the chemical and physical properties of a form (*e.g.*, stability, flowability) that affect its use as a pharmaceutical cannot be predicted with any certainty. Yet these characteristics play a critical role in pharmaceutical formulation. For example, capsules of the anti-retroviral drug ritonavir were withdrawn from the market in the late 1990s after it was discovered that the manufactured polymorphic form of the drug converted to a more thermodynamically stable, but less therapeutically effective form, within the capsules. *See, e.g.*, S. L. Morisette *et al.*, *Proc. Natl. Acad. Sci. USA*. 100 (5): 2180–84. For reasons such as this, regulatory authorities (*e.g.*, the U.S. Food and Drug Administration) may require the identification of solid (*e.g.*, polymorphic) forms of a new drug substance before approving products containing it. A. Goho, *Science News* 166(8):122-123 (2004).

3. SUMMARY

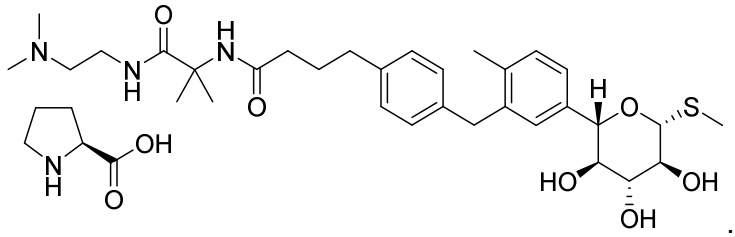
This disclosure is directed to solid forms of *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide:



and pharmaceutically acceptable salts, solvates, and co-crystals thereof.

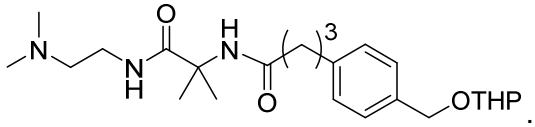
Particular solid forms include amino acid co-crystals of *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide. A particular amino acid is *L*-proline.

In one aspect, the present disclosure refers to a crystalline form of *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide *L*-proline:



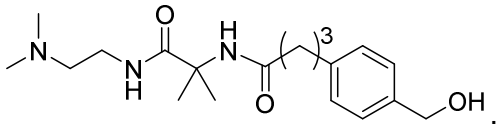
.

In another aspect, the present disclosure refers to a compound, which compound is *N*-(1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)butanamide:



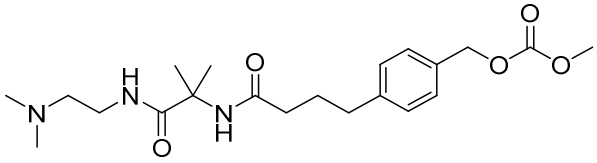
.

In another aspect, the present disclosure refers to a compound, which compound is *N*-(1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)-4–(4–(hydroxymethyl)phenyl)butanamide:



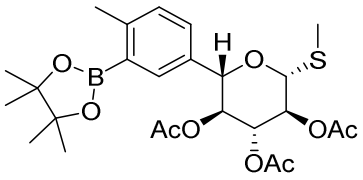
.

In another aspect, the present disclosure refers to a compound, which compound is 4-(4-((1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-4-oxobutyl)benzyl methyl carbonate:



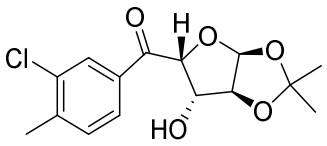
.

In another aspect, the present disclosure refers to a compound, which compound is (2S,3S,4R,5S,6R)-2-(4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate:



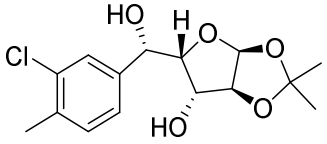
.

In another aspect, the present disclosure refers to a compound, which compound is (3-chloro-4-methylphenyl)((3αS,5R,6S,6αS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methanone:



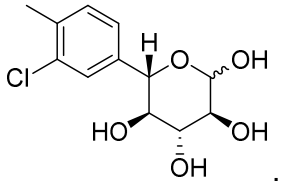
.

In another aspect, the present disclosure refers to a compound, which compound is (3aS,5S,6R,6aS)-5-((S)-(3-chloro-4-methylphenyl)(hydroxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol:



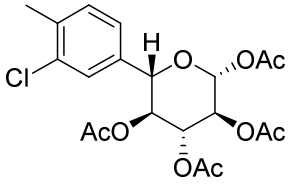
.

In another aspect, the present disclosure refers to a compound, which compound is (3S,4R,5R,6S)-6-(3-chloro-4-methylphenyl)tetrahydro-2H-pyran-2,3,4,5-tetraol:



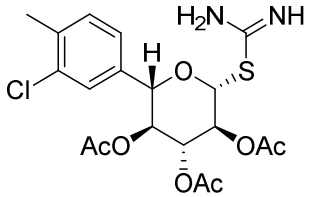
.

In another aspect, the present disclosure refers to a compound, which compound is (2R,3S,4R,5S,6S)-6-(3-chloro-4-methylphenyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate:



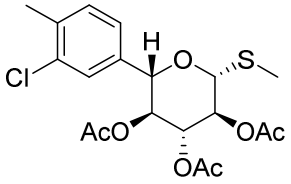
.

In another aspect, the present disclosure refers to a compound, which compound is (2R,3S,4R,5S,6S)-2-(carbamimidoylthio)-6-(3-chloro-4-methylphenyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate:

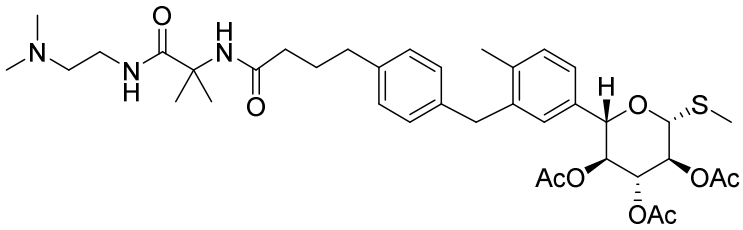


.

In another aspect, the present disclosure refers to a compound, which compound is (2S,3S,4R,5S,6R)-2-(3-chloro-4-methylphenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate:



In another aspect, the present disclosure refers to a compound, which compound is (2S,3S,4R,5S,6R)-2-(3-(4-(4-((1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-4-oxobutyl)benzyl)-4-methylphenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate:

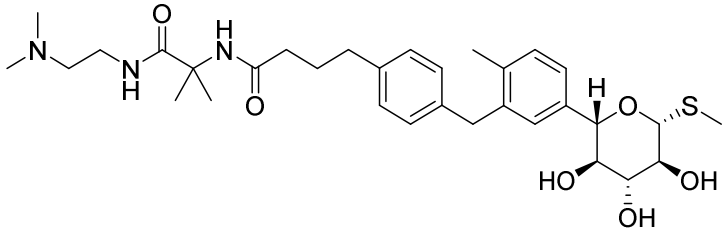


This disclosure is also directed to pharmaceutical compositions comprising the solid forms described herein.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising pharmaceutically acceptable excipients and crystalline form of *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide *L*-proline.

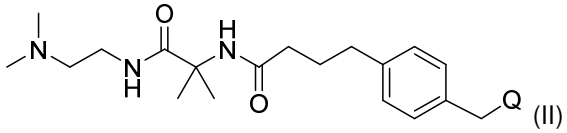
This disclosure is also directed to processes for the manufacture of *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide and pharmaceutically acceptable salts, solvates, and co-crystals thereof.

In another aspect, the present disclosure refers to a process for preparing *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide:

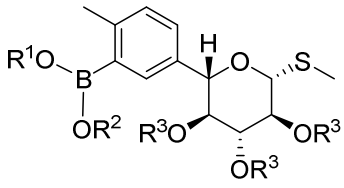


or a pharmaceutically acceptable salt, solvate or co-crystal thereof, which process comprises:

(i) providing a mixture by contacting a compound of formula (II) with a compound of formula (III) in the presence of a palladium catalyst and a base:



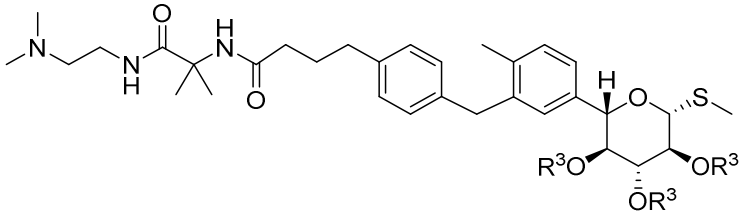
(II)



(III)

wherein **Q** is a leaving group; **R1** and **R2** are $C_{1\text{-}5}$ alkyl, or **R1** and **R2** are joined and together with the atoms to which they are attached from a cyclic boronate; and each **R3** is a protecting group;

(ii) isolating from the mixture a compound of formula (IV):



(IV)

and

(iii) deprotecting the compound of formula (IV).

This disclosure is also directed to methods of treating, managing, and preventing various diseases and conditions, which comprise the use of the solid forms described herein. Particular methods include the use of a solid form of *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2S,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide for treating, preventing, or managing a metabolic disease or disorder. Others include the use of a solid form of *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide for the manufacture of a medicament for use in treating, preventing or managing a metabolic disease or disorder.

In another aspect, the present disclosure refers to use of crystalline *N*-(1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide *L*-proline in the manufacture of a medicament for treating, preventing, or managing a metabolic disease or disorder.

4. BRIEF DESCRIPTION OF THE FIGURES

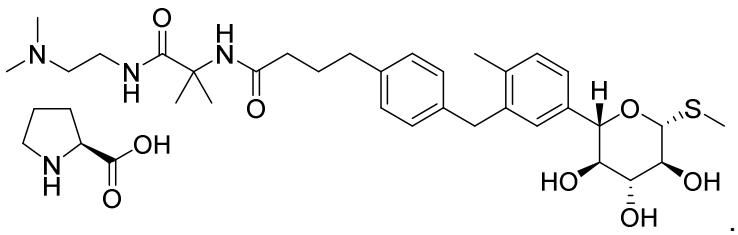
Figure 1 is an X-ray powder diffraction (XRPD) pattern of what is referred to herein as Form II of *N*-(1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2H-pyran-2-yl)benzyl)phenyl)butanamide *L*-proline. The diffractogram was obtained at room temperature using a Bruker D8 system using copper Kα radiation (40 kV/40 mA), a range of 2-50 degrees 2θ, a step time of 37 s, and a LynxEye detector with a 3 degree window.

Figure 2 is an XRPD pattern of what is referred to herein as Form III of *N*-(1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2H-pyran-2-yl)benzyl)phenyl)butanamide *L*-proline.

CLAIMS

What is claimed is:

1. A crystalline form of *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide *L*-proline:



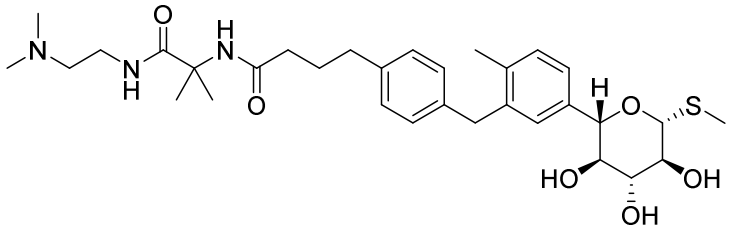
2. The crystalline form of claim 1 having a melting point of 147 ± 5.0 °C.

3. The crystalline form of claim 2 having an X-ray powder diffraction pattern comprising peaks at one or more of 4.5, 5.3, 10.5, 12.1, 17.1, 18.8, 19.3, 22.3, 26.1, and 26.2 ± 0.5 degrees 2θ.

4. The crystalline form of claim 1 having a melting point of 150 ± 5.0 °C.

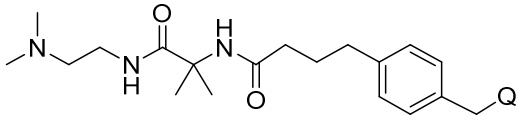
5. The crystalline form of claim 4 having an X-ray powder diffraction pattern comprising peaks at one or more of 4.2, 7.5, 8.3, 10.9, 12.5, 14.7, 16.6, 17.7, 19.8, and 20.6 ± 0.5 degrees 2θ.

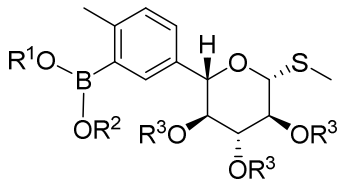
6. A process for preparing *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide:



or a pharmaceutically acceptable salt, solvate or co-crystal thereof, which process comprises:

(i) providing a mixture by contacting a compound of formula (II) with a compound of formula (III) in the presence of a palladium catalyst and a base:

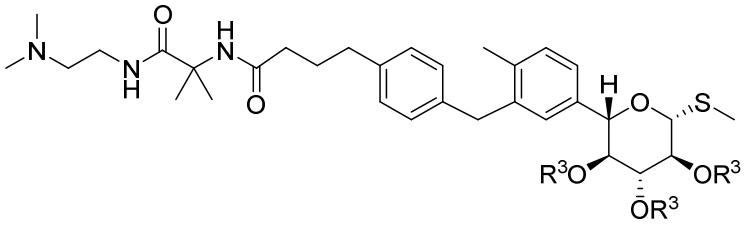

(II)



(III)

wherein **Q** is a leaving group; **R¹** and **R²** are C_{1-5} alkyl, or **R¹** and **R²** are joined and together with the atoms to which they are attached from a cyclic boronate; and each **R³** is a protecting group;

(ii) isolating from the mixture a compound of formula (IV):



(IV)

and

(iii) deprotecting the compound of formula (IV).

7. The process of claim 6, wherein **Q** is halo, a triflate, a phosphate, an acetate, a carbonate, or a nitrogen leaving group.

8. The process of claim 7, wherein **Q** is methyl carbonate.

9. The process of claim 8, wherein each **R³** is an acetyl, benzyl or benzoyl group.

10. The process of claim 9, wherein each **R³** is an acetyl group.

11. The process of any one of claims 6-10, wherein the base is KOAc or K_2CO_3.

12. The process of any one of claims 6-10, wherein the palladium catalyst is preformed or formed in-situ from a palladium pre-catalyst and phosphine ligands.

13. The process of claim 12, wherein the palladium pre-catalyst is $[Pd(allyl)Cl]_2$ or $Pd(OAc)_2$.

14. The process of claim 12, wherein the phosphene ligand is 1,4-bis(diphenylphosphino)pentane, 1,4-bis(diphenylphosphino)butane, 1,1'-bis(diphenylphosphino)ferrocene, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos), or bis[(2-diphenylphosphino)phenyl] ether.

15. The process of claim 14, wherein the base is K_2CO_3 and the palladium catalyst is formed from $[Pd(allyl)Cl]_2$ and 1,4-bis(diphenylphosphino)butane.

16. The process of claim 14, wherein the base is K_2CO_3 and the palladium catalyst is formed from $Pd(OAc)_2$ and 1,1'-bis(diphenylphosphino)ferrocene.

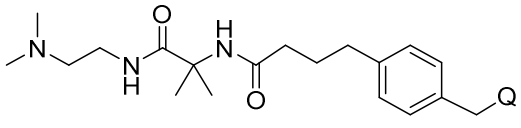
17. The process any one of claims 6-16, wherein **R³** is acetyl.

18. The process of claim 17, wherein the compound of formula (IV) is deprotected by contacting it with a base and an alcohol or water.

19. The process of claim 18, wherein the base is sodium methoxide and the alcohol is ethanol.

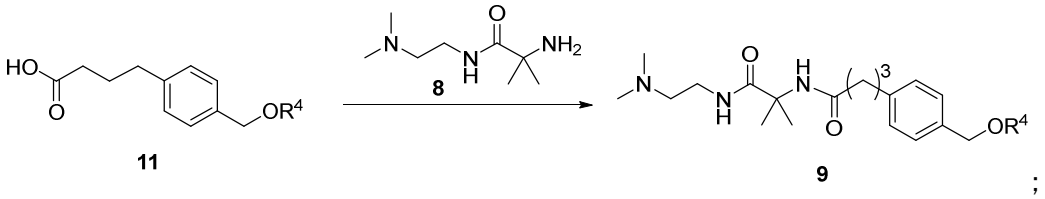
20. The process of claim 19, further comprising contacting the deprotected compound of formula (IV) with *L*-proline under conditions sufficient to obtain *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide *L*-proline cocrystal.

21. The process of any one of claims 6-20, wherein the compound of formula (II)


(II)

is prepared by:

(i) contacting a compound of formula **11** with compound **8** under conditions sufficient to obtain a compound of formula **9**:



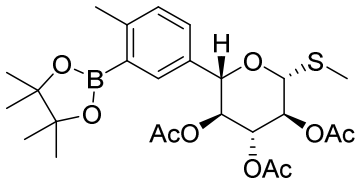
;

wherein **R⁴** is a silyl protecting group or a tetrahyropyranyl group;

(ii) deprotecting the compound of formula **9** to obtain compound **9b**; and

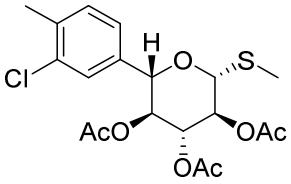
(iii) contacting compound **9b** with Q-Cl or Q-OMe in the presence of a base under conditions sufficient to obtain the compound of formula (II).

22. The process of any one of claims 6-20, wherein the compound of formula (III) is (2*S*,3*S*,4*R*,5*S*,6*R*)-2-(4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6-(methylthio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate:



III .

23. The process of claim 22, wherein the compound of formula (III) is prepared by borylating (2*S*,3*S*,4*R*,5*S*,6*R*)-2-(3-chloro-4-methylphenyl)-6-(methylthio)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate:



.

24. A pharmaceutical composition comprising pharmaceutically acceptable excipients and crystalline form of *N*-(1-((2-(dimethylamino)ethyl)-amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide *L*-proline.

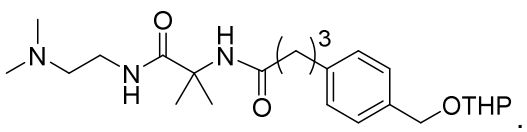
25. The pharmaceutical composition of claim 24, wherein the crystalline form has a melting point of 147 ± 5.0 °C.

26. The pharmaceutical composition of claim 24, wherein the crystalline form has a melting point of 150 ± 5.0 °C.

27. Use of crystalline *N*-(1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(2-methyl-5-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(methylthio)tetrahydro-2*H*-pyran-2-yl)benzyl)phenyl)butanamide *L*-proline in the manufacture of a medicament for treating, preventing, or managing a metabolic disease or disorder.

28. The use according to claim 27, wherein the metabolic disease or disorder is diabetes.

29. A compound, which compound is *N*-(1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)-4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)butanamide:



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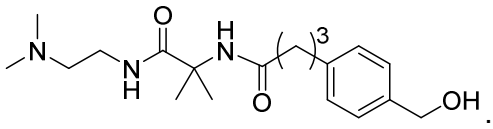
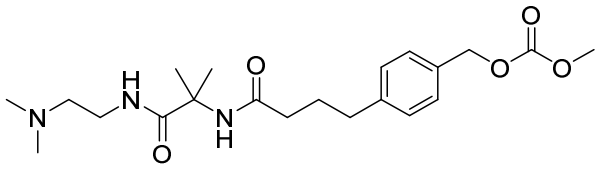
30. The compound of claim 29, which has a melting point of 88 ± 5.0 °C.

31. A compound, which compound is *N*-(1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)-4–(4–(hydroxymethyl)phenyl)butanamide:



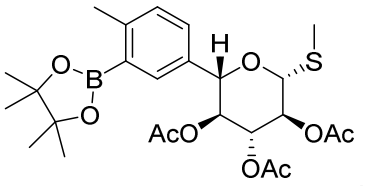
32. The compound of claim 31, which has a melting point of 92 ± 5.0 °C.

33. A compound, which compound is 4-(4-((1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-4-oxobutyl)benzyl methyl carbonate:



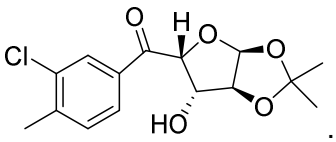
34. The compound of claim 33, which has a melting point of 92 ± 5.0 °C.

35. A compound, which compound is (2S,3S,4R,5S,6R)-2-(4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate:

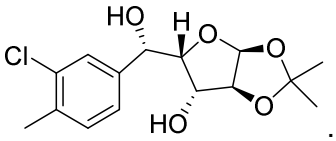


36. The compound of claim 35, which has a melting point of 149 ± 5.0 °C.

37. A compound, which compound is (3-chloro-4-methylphenyl)((3αS,5R,6S,6αS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methanone:

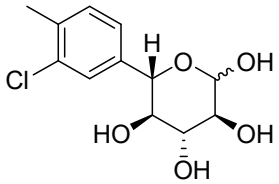


38. A compound, which compound is (3aS,5S,6R,6aS)-5-((S)-(3-chloro-4-methylphenyl)(hydroxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol:



39. The compound of claim 38, which has a melting point of 153 ± 5.0 °C.

40. A compound, which compound is (3S,4R,5R,6S)-6-(3-chloro-4-methylphenyl)tetrahydro-2H-pyran-2,3,4,5-tetraol:



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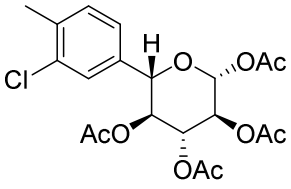
41. A compound, which compound is (2R,3S,4R,5S,6S)-6-(3-chloro-4-methylphenyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate:



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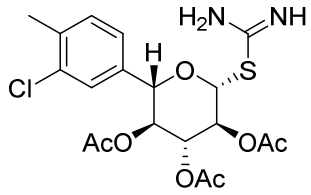
42. The compound of claim 41, which has a melting point of 181 ± 5.0 °C.

43. A compound, which compound is (2R,3S,4R,5S,6S)-2-(carbamimidoylthio)-6-(3-chloro-4-methylphenyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate:



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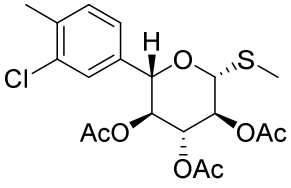
44. A compound, which compound is (2S,3S,4R,5S,6R)-2-(3-chloro-4-methylphenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate:



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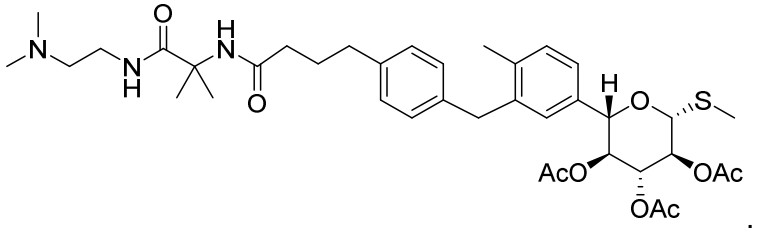
45. The compound of claim 44, which has a melting point of 170 ± 5.0 °C.

46. A compound, which compound is (2S,3S,4R,5S,6R)-2-(3-(4-(4-((1-((2-(dimethylamino)ethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-4-oxobutyl)benzyl)-4-methylphenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate:



47. The compound of claim 46, which has a melting point of 143 ± 5.0 °C.