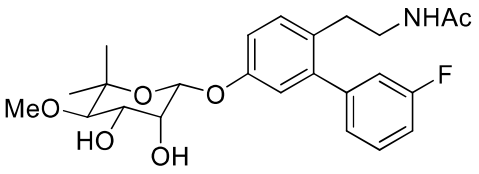


4a



4b

[0005] The published synthesis of **4** (also known as KU-596), while indicating an HPLC purity of 95.6%, does not indicate anomeric purity of the amorphous solid, as evidenced by the fact that only the noviose 2-position lacks definitive assignment of stereochemistry. (Kusuma (2012).

SUMMARY

[0006] The present disclosure is premised upon the surprising discovery that co-crystal forms of novologue **4a** and L-proline or D-proline are realized in high yield, purity, and anomeric purity. The inventive forms moreover demonstrate significant improvements in bioavailability, relative to the known amorphous form **4**.

[0006a] In one aspect, the present disclosure refers to a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline (1:2), characterized by an X-ray powder diffractogram comprising the following peaks: 14.76, 16.86, 19.00, and 21.05 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

[0006b] In another aspect, the present disclosure refers to a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline (1:2), characterized by an X-ray powder diffractogram comprising the following peaks: 9.20, 16.19, 18.45, and 24.51 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

[0006c] In yet another aspect, the present disclosure refers to a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline acetone solvate (1:1:1), characterized by an X-ray powder diffractogram comprising the following peaks: 14.64, 17.53, 18.91, and 21.33 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

[0006d] In a further aspect, the present disclosure refers to a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide, L-proline, methyl ethyl ketone, and pyrazine in a molar ratio of about 1:1.2:0.6:0.1, characterized by an X-ray powder diffractogram comprising the following peaks: 10.42, 14.62, 19.28, and 21.14 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

[0006e] In another aspect, the present disclosure refers to a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and D-proline (1:1), characterized by an X-ray powder diffractogram comprising the following peaks: 11.77, 14.52, 19.54, and 21.23 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-$K_{\alpha 1}$ radiation at a wavelength of 1.5405929 Å.

[0006f] In yet another aspect, the present disclosure refers to a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline (1:1), characterized by an X-ray powder diffractogram comprising the following peaks: 8.52, 16.33, 19.50, and 21.22 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-$K_{\alpha 1}$ radiation at a wavelength of 1.5405929 Å.

[0006g] In a further aspect, the present disclosure refers to a pharmaceutical composition comprising a co-crystal disclosed herein and a pharmaceutically acceptable solid carrier.

[0006h] In another aspect, the present disclosure refers to a co-crystal disclosed herein for use in inhibiting heat shock protein 90 (Hsp90) in a subject.

[0006i] In yet another aspect, the present disclosure refers to a use of a co-crystal disclosed herein, in the manufacture of a medicament for inhibiting heat shock protein 90 (Hsp90) in a subject.

[0006j] In a further aspect, the present disclosure refers to a method of increasing the concentration of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4a**) relative to N-(2-(5-(((2*S*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4b**) in a starting composition comprising **4a** and **4b**, comprising contacting the starting composition with proline in a solvent, and subjecting the

starting composition, proline, and solvent to crystallization conditions, whereby a co-crystal of **4a** and proline is produced, wherein the bulk co-crystal exhibits a concentration of **4a** that is higher than in the starting composition comprising **4a** and **4b**.

[0006k] In another aspect, the present disclosure refers to a co-crystal disclosed herein for use in treating or preventing a neurodegenerative disorder in a subject suffering therefrom.

[0006l] In yet another aspect, the present disclosure refers to a co-crystal disclosed herein for use in preventing or reducing the likelihood of diabetic peripheral neuropathy from developing in a subject who suffers from Type 1 or Type 2 diabetes.

[0006m] In a further aspect, the present disclosure refers to a use of a co-crystal disclosed herein, in the manufacture of a medicament for treating or preventing a neurodegenerative disorder in a subject suffering therefrom.

[0006n] In another aspect, the present disclosure refers to a use of a co-crystal disclosed herein, in the manufacture of a medicament for preventing or reducing the likelihood of diabetic peripheral neuropathy from developing in a subject who suffers from Type 1 or Type 2 diabetes.

[0007] Thus, one example of the present disclosure is a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline (1:2). The co-crystal is characterized by an X-ray powder diffractogram comprising the following peaks: 14.76, 16.86, 19.00, and 21.05 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å. This co-crystal is referred to herein as "Form B."

[0008] Another example is a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline (1:2). The co-crystal is characterized by an X-ray powder diffractogram comprising the following peaks: 9.20, 16.19, 18.45, and 24.51 º2θ ±0.2 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å. This co-crystal is referred to herein as "Form D."

[0009] Additionally, an example is a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-

yl)ethyl)-acetamide and L-proline that is present as an acetone solvate (1:1:1). This co-crystal is characterized by an X-ray powder diffractogram comprising the following peaks: 14.64, 17.53,

18.91, and 21.33 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å. This co-crystal is referred to herein as "Form C."

[0010] In a further example, the present disclosure is drawn to a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline as a solvate of methyl ethyl ketone and pyrazine in a molar ratio of about 1:1.2:0.6:0.1, respectively. The co-crystal is characterized by an X-ray powder diffractogram comprising the following peaks: 10.42, 14.62, 19.28, and 21.14 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å. This co-crystal is referred to herein as "Form G."

[0011] The present disclosure also provides a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and D-proline (1:1), characterized by an X-ray powder diffractogram comprising the following peaks: 11.77, 14.52, 19.54, and 21.23 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-$K_{\alpha 1}$ radiation at a wavelength of 1.5405929 Å.

[0012] The present disclosure further provides a co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline (1:1), characterized by an X-ray powder diffractogram comprising the following peaks: 8.52, 16.33, 19.50, and 21.22 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-$K_{\alpha 1}$ radiation at a wavelength of 1.5405929 Å.

[0013] In accordance with another example, the present disclosure is drawn to a pharmaceutical composition that comprises any one of the co-crystal forms described herein. The composition further comprises a pharmaceutically acceptable solid carrier. In some examples, the composition further comprises one or more additional co-crystal forms.

[0014] Another example of the present disclosure is a method for inhibiting heat shock protein 90 (Hsp90) in a subject. The method comprises administering to the subject a therapeutically effective amount of a co-crystal described herein.

[0015] The present disclosure also is embodied in a method for treating or preventing a neurodegenerative disorder in a subject suffering therefrom. The method comprises

administering to the subject a therapeutically effective amount of a co-crystal described herein. In some examples, the neurodegenerative disorder is diabetic peripheral neuropathy (DPN).

[0016] Alternatively, according to other examples, the present disclosure provides a method for preventing or reducing the likelihood of diabetic peripheral neuropathy from developing in a subject who suffers from Type 1 or Type 2 diabetes. The method comprises administering to the subject a therapeutically effective amount of a co-crystal described herein.

[0017] In accordance with another example, the present disclosure provides a process for making the Form B co-crystal. The process comprises the step of heating to a first temperature a combination of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4a**) and L-proline in about a 1:1 to about a 1:2 molar ratio in a C_{1-6}-alkyl alcohol to yield a solution. The solution is then cooled to a second temperature no higher than about 30 ºC to thereby yield a slurry of the co-crystal, and the slurry is then stirred at the second temperature for a duration of about 72 hours or less.

[0018] Another example is a process of making the Form D co-crystal. The process comprises heating to a first temperature a combination of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4a**) and L-proline in about a 1:1 molar ratio in EtOH or acetonitrile, then cooling the solution to a second temperature no higher than about 30 ºC to thereby yield a suspension of the co-crystal. The suspension is then stirred at the second temperature for a duration of about 72 hours or less.

[0019] The present disclosure is embodied in yet another process drawn to making the Form C co-crystal. The process comprises (a) optionally refluxing equimolar amounts of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4a**) and L-proline in EtOH to yield a solution, and cooling the solution to a temperature no higher than about 30 ºC to thereby yield a solid product. The product of step (a), or otherwise a combination of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4a**) and L-proline in about a 1:1 molar ratio, is then stirred in acetone at a temperature no higher than about 30 °C for a duration of about 72 hours or less to thereby yield the co-crystal.

[0020] In accordance with another example, the present disclosure provides a process for making the Form G co-crystal. The process comprises combining N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4a**), L-proline, and pyrazine in molar ratios of about 1:1:20, respectively, in a mixed solvent of methyl ethyl ketone (MEK) and MeOH to yield a solution, and then stirring the solution to thereby yield the co-crystal.

[0021] The present disclosure additionally provides a process for making the co-crystal of **4a**/D-proline as described herein, comprising heating to a first temperature a combination of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4a**) and D-proline in about a 1:1 molar ratio in a C_{1-6}-alkyl alcohol to yield a solution; and cooling the solution to a second temperature no higher than about 30 °C to thereby yield a suspension of the co-crystal.

[0022] In an additional example, the present disclosure provides a method of increasing the concentration of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4a**) relative to N-(2-(5-(((2*S*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4b**) in a composition comprising **4a** and **4b**. The method comprises contacting the composition with proline in a solvent, and subjecting the composition, proline, and solvent to crystallization conditions, whereby a co-crystal of **4a** and proline is produced. The bulk co-crystal exhibits a concentration of **4a** that is higher than in the composition comprising **4a** and **4b**.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Figure 1 presents an X-ray powder diffraction (XRPD) pattern of Form B.

[0024] Figure 2 is a differential scanning calorimetry (DSC) curve of Form B.

[0025] Figure 3 is a thermal gravimetric analysis (TGA) curve of Form B.

[0026] Figure 4 is a dynamic vapor sorption (DVS) curve of Form B.

[0027] Figure 5 is an infrared (IR) spectrum of Form B.

[0028] Figure 6 is a Raman spectrum of Form B.

WE CLAIM:

1. A co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline (1:2), characterized by an X-ray powder diffractogram comprising the following peaks: 14.76, 16.86, 19.00, and 21.05 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

2. The co-crystal according to claim 1, wherein the X-ray powder diffractogram further comprises peaks at 12.14, 17.51, 18.89, and 19.41 º2θ ±0.20 º2θ.

3. The co-crystal according to claim 1 or 2, wherein the X-ray powder diffractogram is substantially as shown in Figure 1.

4. The co-crystal according to any one of claims 1 - 3, characterized by a differential scanning calorimetry (DSC) thermogram comprising an exotherm at about 211 ºC.

5. The co-crystal according to claim 4, wherein the DSC thermogram is substantially as shown in Figure 2.

6. A co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline (1:2), characterized by an X-ray powder diffractogram comprising the following peaks: 9.20, 16.19, 18.45, and 24.51 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

7. The co-crystal according to claim 6, wherein the X-ray powder diffractogram further comprises peaks at 11.83, 17.16, 20.15, and 25.34 º2θ ±0.2 º2θ.

8. The co-crystal according to claim 6 or 7, wherein the X-ray powder diffractogram is substantially as shown in Figure 14.

9. The co-crystal according to any one of claims 6 - 8, characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm having an onset temperature of about 211.2 ºC.

10. The co-crystal according to claim 9, wherein the DSC thermogram is substantially as shown in Figure 15.

11. A co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline acetone solvate (1:1:1), characterized by an X-ray powder diffractogram comprising the following peaks: 14.64, 17.53, 18.91, and 21.33 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

12. The co-crystal according to claim 11, wherein the X-ray powder diffractogram further comprises peaks at 12.10, 15.14, 18.26, and 19.56 º2θ ±0.2 º2θ.

13. The co-crystal according to claim 11 or 12, wherein the X-ray powder diffractogram is substantially as shown in Figure 10.

14. The co-crystal according to any one of claims 11 - 13, characterized by a thermogravimetric analysis (TGA) thermogram comprising weight loss steps that conclude at about 150 ºC and about 220 ºC.

15. The co-crystal according to claim 14, wherein the TGA thermogram is substantially as shown in Figure 11.

16. A co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide, L-proline, methyl ethyl ketone, and pyrazine in a molar ratio of about 1:1.2:0.6:0.1, characterized by an X-ray powder diffractogram comprising the following peaks: 10.42, 14.62, 19.28, and 21.14 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54178 Å.

17. The co-crystal according to claim 16, wherein the X-ray powder diffractogram further comprises peaks at 11.85, 14.93, 17.40, and 19.28 º2θ ±0.2 º2θ.

18. The co-crystal according to claim 16 or 17, wherein the X-ray powder diffractogram is substantially as shown in Figure 17.

19. The co-crystal according to any one of claims 16 - 18, characterized by unit cell dimensions as follows: a = 10.975 Å, b = 10.310 Å, c = 15.704 Å, α = 90º, β = 108.56º, and γ = 90º.

20. A co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and D-proline (1:1), characterized by an X-ray powder diffractogram comprising the following peaks: 11.77, 14.52, 19.54, and 21.23 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-$K_{\alpha 1}$ radiation at a wavelength of 1.5405929 Å.

21. The co-crystal according to claim 20, wherein the X-ray powder diffractogram further comprises peaks at 8.45, 13.18, 16.95, and 19.12 º2θ ±0.2 º2θ.

22. The co-crystal according to claim 20 or 21, wherein the X-ray powder diffractogram is substantially as shown in Figure 18.

23. The co-crystal according to any one of claims 20 – 22 characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 130 ºC.

24. The co-crystal according to claim 23, wherein the DSC thermogram is substantially as shown in Figure 19.

25. A co-crystal of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide and L-proline (1:1), characterized by an X-ray powder diffractogram comprising the following peaks: 8.52, 16.33,

19.50, and 21.22 º2θ ±0.20 º2θ as determined on a diffractometer using Cu-$K_{\alpha 1}$ radiation at a wavelength of 1.5405929 Å.

26. The co-crystal according to claim 25, wherein the X-ray powder diffractogram further comprises peaks at 9.19, 13.22, 14.75, and 17.57 º2θ ±0.2 º2θ.

27. The co-crystal according to claim 25 or 26, wherein the X-ray powder diffractogram is substantially as shown in Figure 23.

28. The co-crystal according to any one of claims 25 - 27, characterized by unit cell dimensions as follows: a = 10.126 Å, b = 11.021 Å, c = 30.259 Å, α = 90º, β = 90º, and γ = 90º.

29. The co-crystal according to any one of claims 25 - 27, characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 145 ºC.

30. The co-crystal according to claim 29, wherein the DSC thermogram is substantially as shown in Figure 24.

31. A pharmaceutical composition comprising a co-crystal according to any one of claims 1 - 30 and a pharmaceutically acceptable solid carrier.

32. A co-crystal according to any one of claims 1 - 30 for use in inhibiting heat shock protein 90 (Hsp90) in a subject.

33. Use of a co-crystal according to any one of claims 1 - 30, in the manufacture of a medicament for inhibiting heat shock protein 90 (Hsp90) in a subject.

34. A method of increasing the concentration of N-(2-(5-(((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4a**) relative to N-(2-(5-(((2*S*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetra-hydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)-acetamide (**4b**) in a starting composition comprising **4a** and **4b**, comprising contacting the starting composition with proline in a solvent, and subjecting the starting composition, proline, and solvent to crystallization conditions, whereby a co-crystal of **4a** and proline is produced, wherein the bulk co-crystal exhibits a concentration of **4a** that is higher than in the starting composition comprising **4a** and **4b**.

35. The method according to claim 34, wherein the proline is L-proline.

36. The method according to claim 34, wherein the proline is D-proline.

37. The method according to any one of claims 34 to 36, wherein the method further comprises heating the starting composition, proline, and solvent.

38. The method according to any one of claims 34 to 37, wherein the concentration of **4a** is determined by HPLC.

39. The method according to any one of claims 34 to 38, wherein the concentration of **4a** in the bulk co-crystal of **4a** and proline is about 3 to about 20% (w/w) higher than in the starting composition.

40. The method according to any one of claims 34 to 39, wherein the concentration of **4a** in the bulk co-crystal of **4a** and proline is about 5 to about 15% (w/w) higher than in the starting composition.

41. The method according to any one of claims 34 to 40, wherein the concentration of **4a** in the bulk co-crystal of **4a** and proline increases by about 5%, about 10%, or about 15% (w/w).

42. A co-crystal according to any one of claims 1 - 30 for use in treating or preventing a neurodegenerative disorder in a subject suffering therefrom.

43. A co-crystal according to any one of claims 1 - 30 for use in preventing or reducing the likelihood of diabetic peripheral neuropathy from developing in a subject who suffers from Type 1 or Type 2 diabetes.

44. Use of a co-crystal according to any one of claims 1 - 30, in the manufacture of a medicament for treating or preventing a neurodegenerative disorder in a subject suffering therefrom.

45. The use according to claim 44, wherein the neurodegenerative disorder is diabetic peripheral neuropathy.

46. Use of a co-crystal according to any one of claims 1 - 30, in the manufacture of a medicament for preventing or reducing the likelihood of diabetic peripheral neuropathy from developing in a subject who suffers from Type 1 or Type 2 diabetes.