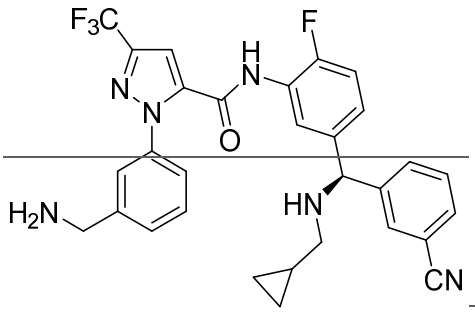
CLAIMS

1. A crystalline salt of Compound I,



I.

2. The crystalline salt of claim 1, wherein the salt is a hydrochloride salt.

3. The crystalline salt of claim 2, wherein the salt is a bis(hydrochloride) salt.

4. The crystalline salt of any one of claims 1-3, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.3, 9.0, and 22.0.

5. The crystalline salt of any one of claims 1-3, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.3, 9.0, and 22.0.

6. The crystalline salt of claim 4 or 5, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.3, 9.0, 19.8, 21.2, 22.0, and 23.3.

7. The crystalline salt of claim 5, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.3, 9.0, 19.8, 21.2, 22.0, and 23.3.

8. The crystalline salt of claim 6 or 7, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.3, 9.0, 14.3, 16.2, 19.8, 21.2, 22.0, 23.3, 24.6, and 30.3.

9. The crystalline salt of claim 7, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.3, 9.0, 14.3, 16.2, 19.8, 21.2, 22.0, 23.3, 24.6, and 30.3.

10. The crystalline salt of any one of claims 1-3, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.28, 8.96, and 22.01.

~~11. The crystalline salt of any one of claims 1-3, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.28, 8.96, and 22.01.~~

~~12. The crystalline salt of claim 10 or 11, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.28, 8.96, 19.79, 21.16, 22.01, and 23.31.~~

~~13. The crystalline salt of claim 11, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.28, 8.96, 19.79, 21.16, 22.01, and 23.31.~~

~~14. The crystalline salt of claim 12 or 13, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.28, 8.96, 14.27, 16.18, 19.79, 21.16, 22.01, 23.31, 24.64, and 30.31.~~

~~15. The crystalline salt of claim 13, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.28, 8.96, 14.27, 16.18, 19.79, 21.16, 22.01, 23.31, 24.64, and 30.31.~~

~~16. The crystalline salt of any one of claims 1-15, having an XRPD pattern substantially similar to that shown in Fig. 1.~~

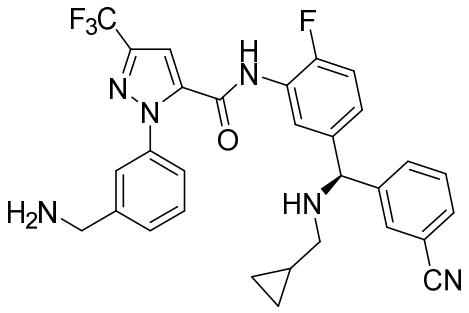
~~17. The crystalline salt of any one of claims 1-16, wherein the crystalline salt is complexed with water in a molar ratio of 1:1 crystalline salt to water.~~

~~18. The crystalline salt of any one of claims 1-16, wherein the crystalline salt is complexed with water in a molar ratio of 1:2 crystalline salt to water.~~

~~19. The crystalline salt of any one of claims 1-16, wherein the crystalline salt is complexed with water in a molar ratio of 1:2.5 crystalline salt to water.~~

~~20. The crystalline salt of any one of claims 1-16, wherein the crystalline salt has a thermogravimetric-infrared spectrum substantially as shown in Fig. 2.~~

~~21~~1. A crystalline salt of Compound I,



I;

wherein the salt is a bis(hydrochloride) salt having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.3, 9.0, and 22.0.

~~22. The crystalline salt of claim 21, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.3, 9.0, and 22.0.~~

~~23~~2. The crystalline salt of claim ~~21~~1, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.3, 9.0, and 22.0.

~~24~~3. The crystalline salt of claim ~~22~~ 1 or ~~23~~2, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.3, 9.0, 19.8, 21.2, 22.0, and 23.3.

~~25~~4. The crystalline salt of claim ~~23~~2, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.3, 9.0, 19.8, 21.2, 22.0, and 23.3.

~~26~~5. The crystalline salt of claim ~~24~~ 3 or ~~25~~4, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.3, 9.0, 14.3, 16.2, 19.8, 21.2, 22.0, 23.3, 24.6, and 30.3.

~~27~~6. The crystalline salt of claim ~~25~~4, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.3, 9.0, 14.3, 16.2, 19.8, 21.2, 22.0, 23.3, 24.6, and 30.3.

~~28~~7. The crystalline salt of claim ~~21~~1, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.28, 8.96, and 22.01.

~~29~~8. The crystalline salt of claim ~~21~~1, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.28, 8.96, and 22.01.

309. The crystalline salt of claim 28 7 or 298, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.28, 8.96, 19.79, 21.16, 22.01, and 23.31.

3110. The crystalline salt of claim 298, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.28, 8.96, 19.79, 21.16, 22.01, and 23.31.

3211. The crystalline salt of claim 30 9 or 3110, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ ± 0.2°) of 5.28, 8.96, 14.27, 16.18, 19.79, 21.16, 22.01, 23.31, 24.64, and 30.31.

3312. The crystalline salt of claim 3110, having characteristic peaks in the X-ray powder diffraction (XRPD) pattern at values of two theta (°2θ) of 5.28, 8.96, 14.27, 16.18, 19.79, 21.16, 22.01, 23.31, 24.64, and 30.31.

3413. The crystalline salt of any one of claims 211-3312, having an XRPD pattern substantially similar to that shown in Fig. 1.

3514. The crystalline salt of any one of claims 211-3413, wherein the crystalline salt is complexed with water in a molar ratio of 1:1 crystalline salt to water.

3615. The crystalline salt of any one of claims 211-3413, wherein the crystalline salt is complexed with water in a molar ratio of 1:2 crystalline salt to water.

3716. The crystalline salt of any one of claims 211-3413, wherein the crystalline salt is complexed with water in a molar ratio of 1:2.5 crystalline salt to water.

3817. The crystalline salt of any one of claims 211-3413, wherein the crystalline salt has a thermogravimetric-infrared spectrum substantially as shown in Fig. 2.

3918. A pharmaceutical composition comprising the crystalline salt of any one of claims 1-3817; and one or more pharmaceutically acceptable carriers.

4019. The pharmaceutical composition of claim 3918, wherein the pharmaceutical composition is formulated for parenteral administration.

4120. The pharmaceutical composition of claim 3918, wherein the pharmaceutical composition is formulated for oral administration.

~~42~~21. The pharmaceutical composition of claim ~~39~~18, wherein the pharmaceutical composition is formulated for the prophylactic or therapeutic treatment of a disease or condition characterized by aberrant plasma kallikrein activity.

~~43~~22. Use of the crystalline salt of any one of claims 1-~~38~~ 17 in the manufacture of a medicament for treating or preventing a disease or condition characterized by aberrant plasma kallikrein activity;

wherein the disease or condition characterized by aberrant plasma kallikrein activity is selected from the group consisting of stroke, inflammation, reperfusion injury, acute myocardial infarction, deep vein thrombosis, post fibrinolytic treatment condition, angina, edema, angioedema, hereditary angioedema, sepsis, arthritis, hemorrhage, blood loss during cardiopulmonary bypass, inflammatory bowel disease, diabetes mellitus, retinopathy, diabetic retinopathy, diabetic macular edema, diabetic macular degeneration, age-related macular edema, age-related macular degeneration, proliferative retinopathy, neuropathy, hypertension, brain edema, increased albumin excretion, macroalbuminuria, and nephropathy.

~~44. The use of claim 43, wherein the disease or condition characterized by aberrant plasma kallikrein activity is selected from the group consisting of stroke, inflammation, reperfusion injury, acute myocardial infarction, deep vein thrombosis, post fibrinolytic treatment condition, angina, edema, angioedema, hereditary angioedema, sepsis, arthritis, hemorrhage, blood loss during cardiopulmonary bypass, inflammatory bowel disease, diabetes mellitus, retinopathy, diabetic retinopathy, diabetic macular edema, diabetic macular degeneration, age-related macular edema, age-related macular degeneration, proliferative retinopathy, neuropathy, hypertension, brain edema, increased albumin excretion, macroalbuminuria, and nephropathy.~~

~~45~~23. The use of claim ~~44~~22, wherein the disease or condition characterized by aberrant plasma kallikrein activity is angioedema.

~~46~~24. The use of claim ~~44~~22, wherein the disease or condition characterized by aberrant plasma kallikrein activity is hereditary angioedema.

~~47~~25. The use of claim ~~44~~22, wherein the disease or condition characterized by aberrant plasma kallikrein activity is stroke.

~~48~~26. The use of claim ~~44~~22, wherein the disease or condition characterized by aberrant plasma kallikrein activity is reperfusion injury.

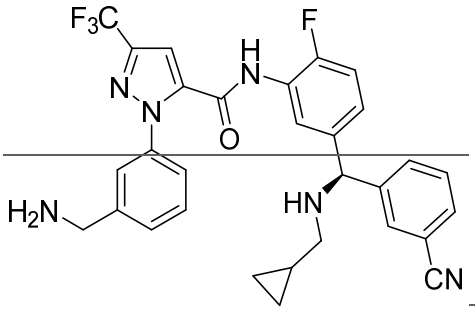
~~49~~27. The use of claim ~~44~~22, wherein the disease or condition characterized by aberrant plasma kallikrein activity is acute myocardial infarction.

~~50~~28. The use of claim ~~44~~22, wherein the disease or condition characterized by aberrant plasma kallikrein activity is hemorrhage.

~~51~~29. The use of claim ~~44~~22, wherein the disease or condition characterized by aberrant plasma kallikrein activity is blood loss during cardiopulmonary bypass.

~~52~~30. The use of claim ~~44~~22, wherein the disease or condition characterized by aberrant plasma kallikrein activity is selected from the group consisting of retinopathy, diabetic retinopathy, diabetic macular edema, diabetic macular degeneration, age-related macular edema, age-related macular degeneration, and proliferative retinopathy.

~~53. A method for preparing a crystalline salt of Compound I:~~



~~I;~~

~~comprising:~~

~~a) providing a freebase mixture of Compound I in a first organic solvent;~~

~~b) combining the freebase mixture with a reagent solution under conditions sufficient to form a mixture comprising a salt of Compound I, wherein the reagent solution comprises an acid and a second organic solvent; and~~

~~c) crystallizing the salt of Compound I from the mixture comprising a salt of Compound I.~~

~~54. The method of claim 53, wherein the crystalline salt is a hydrochloride salt.~~

~~55. The method of claim 54, wherein the crystalline salt is a bis(hydrochloride) salt.~~

~~56. The method of any one of claims 53-55, wherein the first organic solvent comprises a polar aprotic solvent.~~

~~57. The method of claim 56, wherein the polar aprotic solvent is methyl tert-butyl ether.~~

~~58. The method of claim 56 or 57, wherein the first organic solvent further comprises a non-polar solvent.~~

~~59. The method of claim 58, wherein the non-polar solvent is toluene.~~

~~60. The method of any one of claims 53-59, wherein the acid is hydrochloric acid.~~

~~61. The method of any one of claims 53-60, wherein the second organic solvent is a polar protic solvent.~~

~~62. The method of claim 61, wherein the polar protic solvent is methanol.~~

~~63. The method of any one of claims 53-62, wherein the mixture comprising a salt of Compound I is a solution, and the step of crystallizing the salt of Compound I from the mixture comprises bringing the solution to supersaturation to cause the salt of Compound I to precipitate out of solution.~~

~~64. The method of claim 63, wherein the step of bringing the solution to supersaturation comprises slowly adding an anti-solvent, allowing the solution to cool, reducing the volume of the solution, or any combination thereof.~~

~~65. The method of any one of claims 53-62, wherein the mixture comprising a salt of Compound I is a solution, and the step of crystallizing the salt of Compound I from the mixture comprises inducing crystallization.~~

~~66. The method of claim 65, wherein inducing crystallization comprises seeding the solution with crystalline seeds of the salt of Compound I.~~

~~67. The method of any one of claims 53-66, further comprising isolating the crystalline salt.~~

~~68. The method of claim 67, wherein isolating the crystalline salt comprises filtering the crystallized salt from the mixture.~~

~~69. The method of claim 67 or 68, further comprising drying the crystalline salt under reduced pressure.~~

~~70. The method of any one of claims 53-69, wherein the crystalline salt is the crystalline salt of any one of claims 1-38.~~

~~71~~31. The crystalline salt of any one of claims 1-~~38~~ 17 for use in therapy.