0.5 wt%) at temperatures below about 125°C, which is consistent with the loss of residual or lattice-included moisture or solvent.

In one embodiment, the crystalline heminapadisylate salt is characterized by the DMS profile in FIG. 14. This DMS profile demonstrates that this form has a reversible sorption/desorption profile with acceptable levels of hygroscopicity. This crystalline form has a small weight gain (about 0.97%) when it exposed to a broad humidity range from 5% RH up to 90% RH, and less than about 0.68% weight gain when exposed to up to 70% RH. This suggests that the crystalline heminapadisylate salt possesses only a minimal risk of hygroscopicity at ambient conditions.

The crystalline heminapadisylate salt has been further characterized by x-ray diffraction analysis of crystal structure, providing the following lattice parameters: unit cell is triclinic with dimensions a = 9.199(1) Å, b = 10.556(1) Å, c = 19.348(3) Å; α = 80.754(8)°, β = 79.286(7)°, γ = 66.111(6)°, space group is *P*1bar; calculated density is 1.337 g/cm^3. The resulting crystal structure confirms that the chemical composition of the compound is that of formula I and that the assymetric unit contains two symmetry independent {2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid molecules, one ~~naphthalenedisulfate~~ naphthalenedisulfonate anion, and approximately half molecule of water leading to the determination that this crystal is a hydrate. Powder x-ray diffraction peaks calculated from the derived atomic positions are in excellent agreement with observed results.

In another embodiment, the crystalline heminapadisylate salt is characterized by the PLM image in FIG. 15.

Mono-oxalate Salt

The crystalline mono-oxalate salt is characterized by a PXRD pattern in which the peak positions are substantially in accordance with those shown in FIG. 17. Those peaks are listed below. Only peaks having a relative peak height (H%) of about 10 % or greater are listed. Sharp diffraction peaks in the region 5-40° in 2θ indicate the presence of crystalline material. Broad halo in the region 15-30° in 2θ corresponds to some of the uncrystallized amorphous content in the material.

2θ	**d (Å)**	**Height[1]**	**H%[2]**	*
6.1	14.4	484	27.9	*
11.0	8.1	662	38.2	*
13.0	6.8	999	57.6	*

and rotate for 24 hours at room temperature. The resulting suspensions were filtered using a 0.45μm filter (PVDF membrane) into a clean vial for HPLC analysis.

Both the hemiedisylate form II and the heminapadisylate form were found to be more soluble than the freebase at pH>3, as detailed in FIG. 16.

X-ray Structure Analysis

A chunk crystal of crystalline heminapadisylate having dimensions of 0.45x0.40x0.15 mm was mounted on a glass fiber. X-ray structure data was obtained using a Nonius Kappa CCD diffractometer using Mo Kα radiation. Data was collected at a temperature of 120±2°K and was analyzed using SHELXS-97 and SHELXL-97 software. The following lattice parameters were derived: unit cell is triclinic with dimensions a = 9.199(1) Å, b = 10.556(1) Å, c = 19.348(3) Å; α = 80.754(8)°, β = 79.286(7)°, γ = 66.111(6)°, space group is *P*1bar; calculated density is 1.337 g/cm^3. Powder x-ray diffraction peaks calculated from the derived atomic positions were in excellent agreement with the observed results obtained using bulk powder sample.

The resulting molecular structure confirms the chemical composition is that of the compound of formula I and that the assymetric unit contains two symmetry independent {2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid molecules, one ~~naphthalenedisulfate~~ naphthalenedisulfonate anion, and water leading to the determination that this crystal is a hydrate. In this particular experiment, approximately half molecule of water was observed.

While the present invention has been described with reference to specific aspects or embodiments thereof, it will be understood by those of ordinary skilled in the art that various changes can be made or equivalents can be substituted without departing from the true spirit and scope of the invention. Additionally, to the extent permitted by applicable patent statutes and regulations, all publications, patents and patent applications cited herein are hereby incorporated by reference in their entirety to the same extent as if each document had been individually incorporated by reference herein.

CLAIMS

What Is Claimed Is:

1. A crystalline hemiedisylate salt of 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid; wherein the crystalline hemiedisylate salt is selected from: (a) form II, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 9.74±0.20, 11.00±0.20, 12.89±0.20, 14.27±0.20, 15.54±0.20, 18.62±0.20, and 23.78±0.20; and form I, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 9.89±0.20, 11.66±0.20, 13.55±0.20, 18.41±0.20, 20.42±0.20, and 22.46±0.20.

2. The crystalline hemiedisylate salt of Claim 1, wherein form II is further characterized by having one or more additional diffraction peaks at 2θ values selected from 17.81±0.20, 18.14±0.20, 21.44±0.20, 22.25±0.20, 23.15±0.20, 24.80±0.20, 25.28±0.20, 26.03±0.20, 26.58±0.20, and 28.01±0.20.

3. The crystalline hemiedisylate salt of Claim 1, wherein form II is characterized by a powder x-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in FIG. 6.

4. The crystalline hemiedisylate salt of Claim 1, wherein form II is characterized by a differential scanning calorimetry thermogram which has a melting point of about 182°C.

5. The crystalline hemiedisylate salt of Claim 1, wherein form II is characterized by a differential scanning calorimetry thermogram substantially in accordance with that shown in FIG. 7.

6. A process for preparing the crystalline hemiedisylate salt form II of Claim 1, comprising:

a) treating 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid with 1,2-ethanedisulfonic acid;

b) optionally heating, stirring or sonicating to complete dissolution; and

c) allowing solids to form and isolating the solids to yield the crystalline

hemiedisylate salt form II.

7. The crystalline hemiedisylate salt of Claim 1, wherein form I is further characterized by having one or more additional diffraction peaks at 2θ values selected from 18.89±0.20, 19.91±0.20, 20.90±0.20, 21.33±0.20, 24.35±0.20, 25.85±0.20, 28.73±0.20, and 30.92±0.20.

8. The crystalline hemiedisylate salt of Claim 1, wherein form I is characterized by a powder x-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in FIG. 1.

9. The crystalline hemiedisylate salt of Claim 1, wherein form I is characterized by a differential scanning calorimetry thermogram which has a melting point of about 158°C.

10. The crystalline hemiedisylate salt of Claim 1, wherein form I is characterized by a differential scanning calorimetry thermogram substantially in accordance with that shown in FIG. 2.

11. A crystalline heminapadisylate salt of 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 4.84±0.20, 9.41±0.20, 10.82±0.20, 17.39±0.20, 24.17±0.20, and 24.65±0.20.

12. The crystalline heminapadisylate salt of Claim 11, characterized by having one or more additional diffraction peaks at 2θ values selected from 14.05±0.20, 18.65±0.20, 19.55±0.20, 20.21±0.20, 21.44±0.20, 23.48±0.20, 25.69±0.20, 26.65±0.20, 28.79±0.20, 29.63±0.20, and 30.52±0.20.

13. The crystalline heminapadisylate salt of Claim 11, characterized by a powder x-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in FIG. 11.

14. The crystalline heminapadisylate salt of Claim 11, characterized by a differential

scanning calorimetry thermogram which has a melting point of about 181°C.

15. The crystalline heminapadisylate salt of Claim 11, characterized by a differential scanning calorimetry thermogram substantially in accordance with that shown in FIG. 12.

16. A process for preparing the crystalline heminapadisylate salt of Claim 11, comprising:

a) treating 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid with napthalene-1,5-disulfonic acid;

b) optionally heating, stirring or sonicating to complete dissolution; and

c) allowing solids to form and isolating the solids to yield the heminapadisylate salt.

17. A crystalline mono-oxalate salt of 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 6.1±0.20, 11.0±0.20, 13.0±0.20, 14.4±0.20, 15.2±0.20, 16.5±0.20, 17.3±0.20, 18.4±0.20, 21.9±0.20, 23.9±0.20, 24.3±0.20, 24.5±0.20, and 26.1±0.20.

18. The crystalline mono-oxalate salt of Claim 17, characterized by having one or more additional diffraction peaks at 2θ values selected from 15.8±0.20, 18.1±0.20, 19.1±0.20, 20.3±0.20, 20.5±0.20, 22.3±0.20, 22.8±0.20, 24.9±0.20, 27.4±0.20, 27.8±0.20, 30.6±0.20, 31.4±0.20, and 36.9±0.20.

19. The crystalline mono-oxalate salt of Claim 17, characterized by a powder x-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in FIG. 17.

20. The crystalline mono-oxalate salt of Claim 17, characterized by a differential scanning calorimetry thermogram which has a melting point of about 115°C.

21. The crystalline mono-oxalate salt of Claim 17, characterized by a differential

scanning calorimetry thermogram substantially in accordance with that shown in FIG. 18.

22. A process for preparing the crystalline mono-oxalate salt of Claim 17, comprising:

a) treating 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid with oxalic acid;

b) optionally heating, stirring or sonicating to complete dissolution; and

c) allowing solids to form and isolating the solids to yield the crystalline mono-oxalate salt.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the crystalline compound of Claim 1, 11, or 17.

24. The pharmaceutical composition of Claim 23, further comprising a secondary therapeutic agent selected from diuretics, β_1 adrenergic receptor blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, AT_1 receptor antagonists, neprilysin inhibitors, non-steroidal anti-inflammatory agents, prostaglandins, anti-lipid agents, anti-diabetic agents, anti-thrombotic agents, renin inhibitors, endothelin receptor antagonists, endothelin converting enzyme inhibitors, aldosterone antagonists, angiotensin-converting enzyme/neprilysin inhibitors, and combinations thereof.

25. A process for purifying 4'-{2-ethoxy-4-ethyl-5-[((*S*)-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid; comprising forming the crystalline compound of Claim 1, 11, or 17.

26. A compound as claimed in Claim 1, 11, or 17, for use in therapy.

27. The compound of Claim 26, for treating hypertension or heart failure.

28. Use of a compound as claimed in Claim 1, 11, or 17 for the manufacture of a medicament.

29. The use of Claim 28, wherein the medicament is for the treatment of hypertension

or heart failure.

CLAIMS

What Is Claimed Is:

1. A crystalline hemiedisylate salt of 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid form II, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 9.74±0.20, 11.00±0.20, 12.89±0.20, 14.27±0.20, 15.54±0.20, 18.62±0.20, and 23.78±0.20.

2. The crystalline hemiedisylate salt of Claim 1, wherein form II is further characterized by having one or more additional diffraction peaks at 2θ values selected from 17.81±0.20, 18.14±0.20, 21.44±0.20, 22.25±0.20, 23.15±0.20, 24.80±0.20, 25.28±0.20, 26.03±0.20, 26.58±0.20, and 28.01±0.20.

3. The crystalline hemiedisylate salt of Claim 1, wherein form II is characterized by a differential scanning calorimetry thermogram which has a melting point of about 182°C.

4. A process for preparing the crystalline hemiedisylate salt form II of Claim 1, comprising:

a) treating 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid with 1,2-ethanedisulfonic acid;

b) optionally heating, stirring or sonicating to complete dissolution; and

c) allowing solids to form and isolating the solids to yield the crystalline hemiedisylate salt form II.

5. A crystalline heminapadisylate salt of 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 4.84±0.20, 9.41±0.20, 10.82±0.20, 17.39±0.20, 24.17±0.20, and 24.65±0.20.

6. The crystalline heminapadisylate salt of Claim 5, characterized by having one or more additional diffraction peaks at 2θ values selected from 14.05±0.20, 18.65±0.20, 19.55±0.20, 20.21±0.20, 21.44±0.20, 23.48±0.20, 25.69±0.20, 26.65±0.20, 28.79±0.20, 29.63±0.20, and 30.52±0.20.

7. The crystalline heminapadisylate salt of Claim 5, characterized by a differential scanning calorimetry thermogram which has a melting point of about 181°C.

8. A process for preparing the crystalline heminapadisylate salt of Claim 5, comprising:

a) treating 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid with napthalene-1,5-disulfonic acid;

b) optionally heating, stirring or sonicating to complete dissolution; and

c) allowing solids to form and isolating the solids to yield the heminapadisylate salt.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the crystalline compound of Claim 1 or 5.

10. The pharmaceutical composition of Claim 9, further comprising a secondary therapeutic agent selected from diuretics, β_1 adrenergic receptor blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, AT_1 receptor antagonists, neprilysin inhibitors, non-steroidal anti-inflammatory agents, prostaglandins, anti-lipid agents, anti-diabetic agents, anti-thrombotic agents, renin inhibitors, endothelin receptor antagonists, endothelin converting enzyme inhibitors, aldosterone antagonists, angiotensin-converting enzyme/neprilysin inhibitors, and combinations thereof.

11. A process for purifying 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid; comprising forming the crystalline compound of Claim 1 or 5.

12. A compound as claimed in Claim 1 or 5, for use in therapy.

13. The compound of Claim 12, for treating hypertension or heart failure.

14. Use of a compound as claimed in Claim 1 or 5 for the manufacture of a medicament.

15. The use of Claim 14, wherein the medicament is for the treatment of hypertension or heart failure.