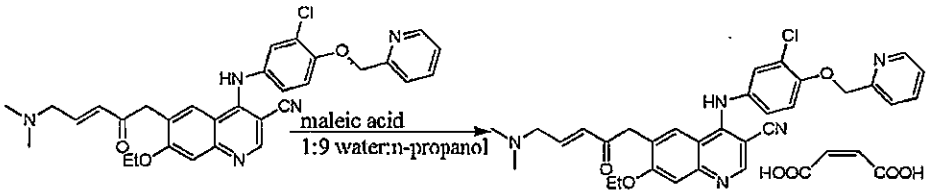
SCHEME 1



The reaction of the free base and maleic acid occurs at an elevated temperature of from about 40 °C to about 60 °C, preferably between about 40°C to about 50°C. The ratio of water:n-propanol may vary, for example between about 1:10 to about 1:5, and the optimal ratio of water:n-propanol is about 1:9. The water-alcohol solution may comprise from about 5% to about 20% by volume water and from about 80% to about 95% by volume alcohol. The alcohol may be n-propanol. In one embodiment, the water-alcohol solution comprises about 10% by volume water and about 90% by volume n-propanol. The volume of the solvent solution may be between about 8 to about 25 volumes, including about 10 to about 12 volumes. About 1.0-1.2 equivalents of maleic acid is used per equivalent of the free base, preferably about 1.03 equivalents of maleic acid per equivalent of the free base.

The resulting solution of the maleate salt may be clarified by filtration prior to cooling. The cooling step may be continued until the solution reaches a temperature of about 45°C or less, including a temperature of about 39°C or less, and more preferably to about 30°C or less. In one embodiment, the solution is filtered after cooling to about room temperature, preferably from about 23°C to about 25 °C. Typically, the maleate salt begins to crystallize out of solution once the temperature reaches 37°C or below. The solution may be allowed to sit for at least 12 hours, preferably about 12 to about 15 hours at room temperature, and is then filtered and washed to recover the crystalline maleate salt product. The resulting filter cake may be washed with the same or a different water-alcohol solution to obtain the product. The product may be dried to obtain crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate. At this point, the maleate salt product recovered and isolated is typically in the form of the monohydrate form of the maleate salt.

The product may be dried under vacuum with heating to make the anhydrous form of the maleate salt (Form I) at about 70 to about 95% yield, preferably about 80 to about 95% yield. This product is usually better than about 98% pure, and often about 99% pure. Typically, the drying process is performed over about 12 to about 48 hours to get complete conversion of the ~~anhydrous form of the maleate salt to the monohydrate form of the maleate salt (Form II).~~ monohydrate form of the maleate salt (Form II) to the anhydrous form of the maleate salt.

CLAIMS:

1. A method for preparing (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide as a maleate salt comprising the steps of:

i) mixing (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide and maleic acid in a water-alcohol solution at a temperature in the range of between about 50 °C to about 60 °C;

ii) cooling said solution to a temperature of about 40 °C and maintaining the cooled solution at about 40 °C for about 12 hours to precipitate the maleate salt;

iii) further cooling the cooled solution to room temperature (about 25 °C) over about 4 hours and maintaining the further cooled solution at room temperature (about 25 °C) for about 2 hours;

iv) filtering the maintained, further cooled solution to obtain crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate.

2. The method of claim 1, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate comprises (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II.

3. The method of claim 2, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II is characterized by X-ray diffraction peaks at the following angles (±0.20°) of 2Theta in its X-ray diffraction pattern: 6.53, 8.43, 10.16, 12.19, 12.47, 13.01, 15.17, 16.76, 17.95, 19.86, 21.11, 21.88, 23.22, 23.78, 25.69, 26.17, 27.06, 27.58, 28.26, 28.73, and 29.77.

4. The method of claim 3, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II, has a water content of about 2.5 to 2.7%, by weight.

5. A method of formulating neratinib as a maleate salt, according to the method of claim 1, the resulting salt being capable of increased oral absorption.

6. The method of claim 5, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate comprises (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II.

7. The method of claim 6, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II is characterized by X-ray diffraction peaks at the following angles (±0.20°) of 2Theta in its X-ray diffraction pattern:

6.53, 8.43, 10.16, 12.19, 12.47, 13.01, 15.17, 16.76, 17.95, 19.86, 21.11, 21.88, 23.22, 23.78, 25.69, 26.17, 27.06, 27.58, 28.26, 28.73, and 29.77.

8. The method of claim 7, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II, has a water content of about 2.5 to 2.7%, by weight.

9. The use of neratinib as a maleate salt in the manufacture of a medicament for treating or reducing emesis associated with neratinib therapy, wherein the neratinib maleate salt is prepared according to the method of claim 1.

10. The use of claim 9, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate comprises (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II.

11. The use of claim 10, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II is characterized by X-ray diffraction peaks at the following angles (±0.20°) of 2Theta in its X-ray diffraction pattern: 6.53, 8.43, 10.16, 12.19, 12.47, 13.01, 15.17, 16.76, 17.95, 19.86, 21.11, 21.88, 23.22, 23.78, 25.69, 26.17, 27.06, 27.58, 28.26, 28.73, and 29.77.

12. The use of claim 11, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II, has a water content of about 2.5 to 2.7%, by weight.

13. The use of neratinib as a maleate salt in the manufacture of a medicament for treating or reducing diarrhea associated with neratinib therapy, wherein the neratinib maleate salt is prepared according to the method of claim 1.

14. The use of claim 13, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate comprises (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II.

15. The use of claim 14, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II is characterized by X-ray diffraction peaks at the following angles (±0.20°) of 2Theta in its X-ray diffraction pattern: 6.53, 8.43, 10.16, 12.19, 12.47, 13.01, 15.17, 16.76, 17.95, 19.86, 21.11, 21.88, 23.22, 23.78, 25.69, 26.17, 27.06, 27.58, 28.26, 28.73, and 29.77.

16. The use of claim 15, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II, has a water content of about 2.5 to 2.7%, by weight.

17. The use of neratinib as a maleate salt in the manufacture of a medicament for treating cancer, wherein the neratinib maleate salt is prepared according to the method of claim 1.

18. The use of claim 17, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate comprises (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II.

19. The use of claim 18, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II is characterized by X-ray diffraction peaks at the following angles (±0.20°) of 2Theta in its X-ray diffraction pattern: 6.53, 8.43, 10.16, 12.19, 12.47, 13.01, 15.17, 16.76, 17.95, 19.86, 21.11, 21.88, 23.22, 23.78, 25.69, 26.17, 27.06, 27.58, 28.26, 28.73, and 29.77.

20. The use of claim 19, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II, has a water content of about 2.5 to 2.7%, by weight.

21. The use of claim 17, wherein the cancer comprises one or more of breast cancer, ovarian cancer, epidermoid tumors, colon cancer, prostate cancer, kidney cancer, bladder cancer, larynx cancer, esophagus cancer, stomach cancer, or lung cancer.

22. The use of claim 21, wherein the cancer comprises breast cancer.

23. The use of claim 21, wherein the cancer comprises ovarian cancer.

24. The use of claim 21, wherein the cancer comprises lung cancer.

25. The use of claim 21, wherein the cancer comprises colon cancer.

26. The use of claim 21, wherein the cancer comprises stomach cancer.

27. The use of claim 21, wherein the cancer comprises epidermoid cancer.

28. The use of claim 21, wherein the cancer comprises esophagus cancer.

CLAIMS:

1. A method for preparing crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate monohydrate (Form II) comprising the steps of:

i) heating (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide free base and maleic acid to 50-60 °C in a water:n-propanol solution, and maintaining the mixture at 50-60 °C for a minimum of 15 min. until a solution is obtained;

ii) cooling said solution over at least one hour to 40 °C and maintaining the cooled solution at 40 °C for 12 hours;

iii) further cooling the cooled solution to room temperature of 25 °C over a minimum of 4 hours and maintaining the further cooled solution at room temperature 25 °C for at least 2 hours; and

iv) filtering the mixture obtained in step iii) to obtain the crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate monohydrate (Form II);

wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II is:

a) characterized by X-ray diffraction peaks at the following angles (±0.20°) of 2Theta in its X-ray diffraction pattern: 6.53, 8.43, 10.16, 12.19, 12.47, 13.01, 15.17, 16.76, 17.95, 19.86, 21.11, 21.88, 23.22, 23.78, 25.69, 26.17, 27.06, 27.58, 28.26, 28.73, and 29.77; and

b) further characterized by a DSC-plot with two thermal events at 109.63°C and 203.81°C.

2. The method of claim 1, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II has substantially the X-ray diffraction pattern as shown in Fig. 7.

3. The method of claim 1, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-buten-

amide maleate, monohydrate, Form II, has a water content of 2.5 to 2.7%, by weight.

4. A use of neratinib as a maleate salt, monohydrate, Form II, in the manufacture of a medicament for increasing oral absorption of neratinib, relative to oral absorption of neratinib as a free base, wherein the neratinib maleate salt, monohydrate, Form II, is prepared according to the method of claim 1.

5. The use of claim 4, wherein the neratinib maleate salt, monohydrate, Form II, formulation, produces at least a two-fold greater AUC (area under concentration), relative to neratinib in a free base formulation.

6. The use of claim 4, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinyl-methoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II, has a water content of 2.5 to 2.7%, by weight.

7. The use of neratinib as a maleate salt, monohydrate, Form II, in the manufacture of a medicament for treating or reducing emesis associated with neratinib therapy, wherein the neratinib maleate salt, monohydrate, Form II, is prepared according to the method of claim 1.

8. The use of claim 7, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinyl-methoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, monohydrate, Form II, has a water content of 2.5 to 2.7%, by weight.

9. The use of neratinib as a maleate salt, monohydrate, Form II, in the manufacture of a medicament for treating or reducing diarrhea associated with neratinib therapy, wherein the neratinib maleate salt, monohydrate, Form II, is prepared according to the method of claim 1.

10. The use of claim 9, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-buten-amide maleate, monohydrate, Form II, has a water content of 2.5 to 2.7%, by weight.

11. The use of neratinib as a maleate salt, monohydrate, Form II, in the manufacture of a medicament for treating cancer, wherein the neratinib maleate salt, monohydrate, Form II, is prepared according to the method of claim 1.

12. The use of claim 11, wherein the obtained crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-buten-amide maleate, monohydrate, Form II, has a water content of 2.5 to 2.7%, by weight.

13. The use of claim 11, wherein the cancer comprises one or more of breast cancer, ovarian cancer, epidermoid tumors, colon cancer, prostate cancer, kidney cancer, bladder cancer, larynx cancer, esophagus cancer, stomach cancer, or lung cancer.

14. The use of claim 13, wherein the cancer comprises breast cancer.

15. The use of claim 13, wherein the cancer comprises ovarian cancer.

16. The use of claim 13, wherein the cancer comprises lung cancer.

17. The use of claim 13, wherein the cancer comprises colon cancer.

18. The use of claim 13, wherein the cancer comprises stomach cancer.

19. The use of claim 13, wherein the cancer comprises epidermoid cancer.

20. The use of claim 13, wherein the cancer comprises esophagus cancer.