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 step of: 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 an elevated temperature.

2. The method of Claim 1, further comprising the steps of: cooling said solution to precipitate said maleate salt and filtering said solution after cooling to obtain crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate.

3. The method of Claim 1 or 2, wherein said elevated temperature is from about 40°C to about 60°C.

4. The method of Claim 2 or 3, wherein said cooling continues until the solution reaches a temperature of about 37°C or less.

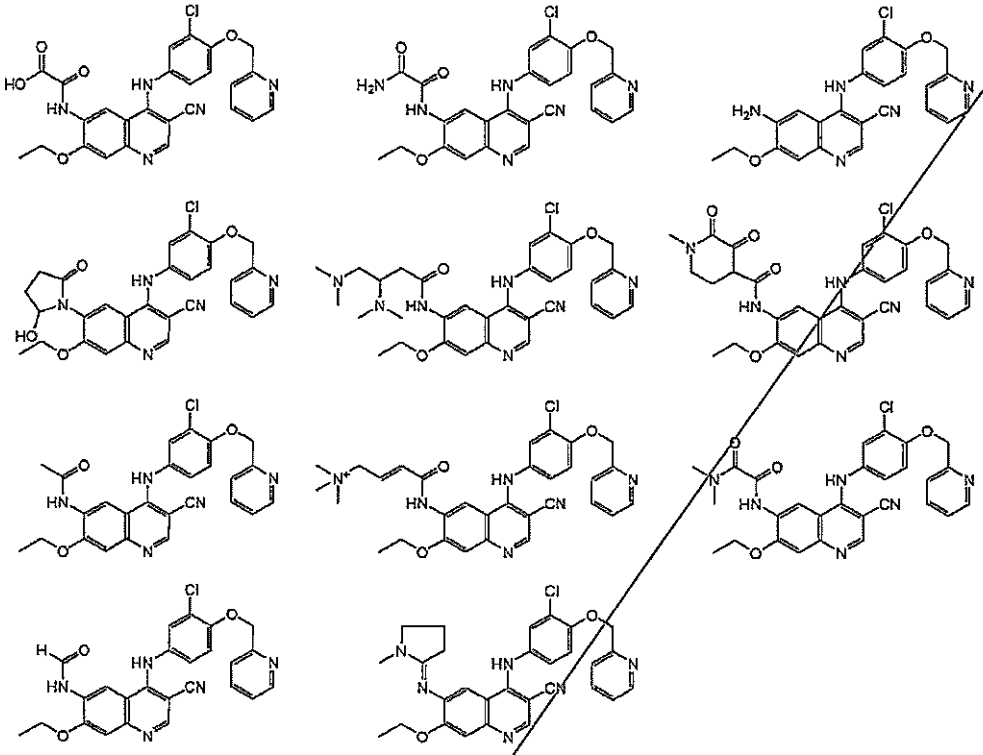
5. The method of Claim 4, wherein said cooling continues until the solution reaches a temperature of about 30°C or less.

6. The method of any one of Claims 1-5, wherein said water-alcohol solution comprises from about 5% to about 20% by volume water and from about 80% to about 95% by volume alcohol.

7. The method of any one of Claims 1-6, wherein said alcohol is n-propanol.

8. The method of Claim 7, wherein said water-alcohol solution comprises about 10% by volume water and about 90% by volume n-propanol.

9. The method of any one of Claims 1-8, wherein said solution further comprises at least one compound selected from the group consisting of:

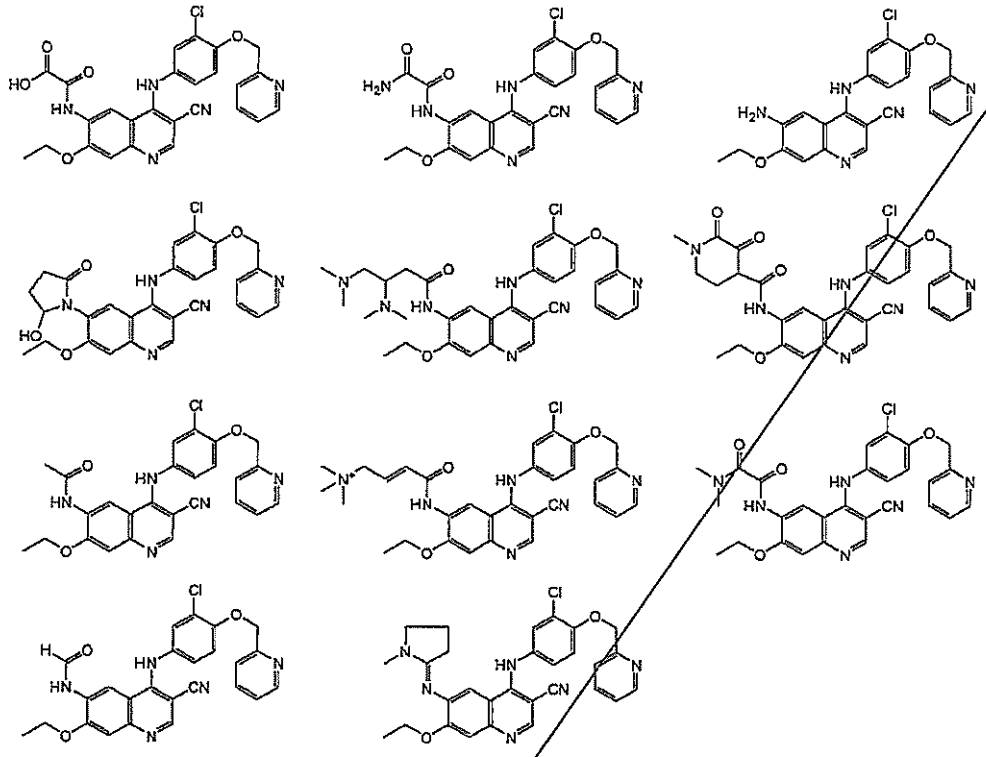


10. The method of any one of Claims 2-9, wherein said crystalline (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate comprises crystals in anhydrous form, monohydrate form, or combinations thereof.

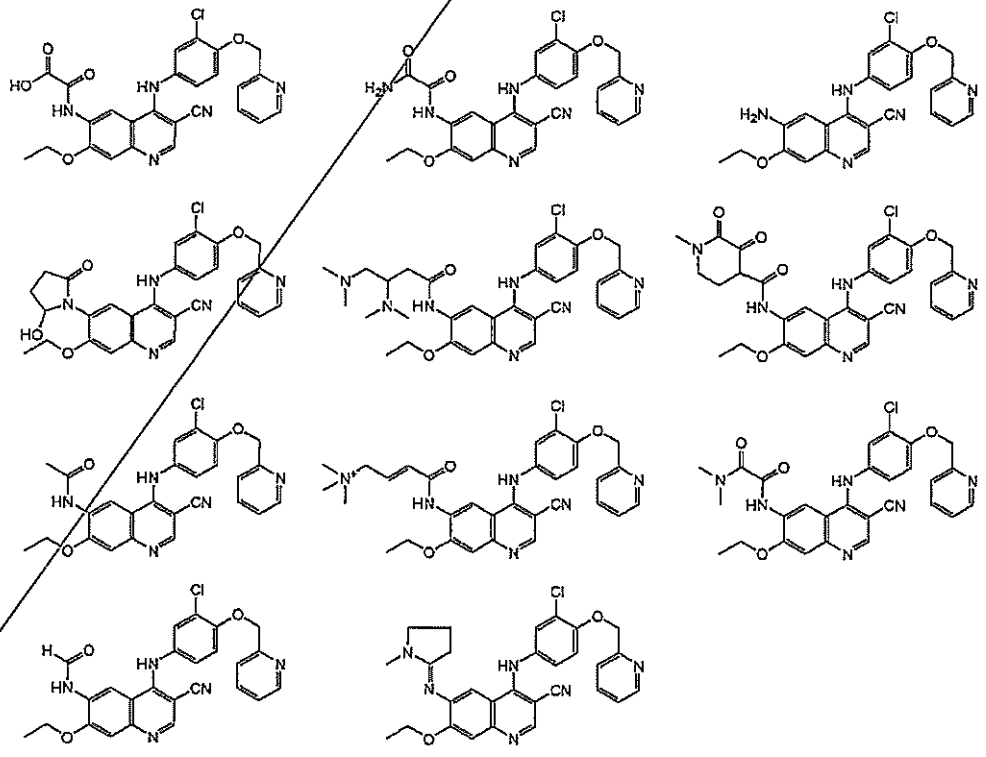
11. A pharmaceutical composition for the inhibition of HER-2 kinase activity comprising, a therapeutically-effective amount of (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition according to Claim 11 wherein said (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate is in a form selected from the group consisting of: an anhydrous form, a monohydrate form, and combinations thereof.

13. The pharmaceutical composition according to Claim 11 or 12 further comprising at least one compound selected from the group consisting of:



14. A compound selected from the group consisting of:



15. A method for preventing, treating, or inhibiting cancer comprising, administering to a subject a therapeutically-effective amount of (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate.

16. The method according to Claim 15 wherein said cancer is selected from at least one of: breast cancer, ovarian cancer, epidermoid tumors, colon cancer, prostate cancer, kidney cancer, bladder cancer, larynx cancer, esophagus cancer, stomach cancer, and lung cancer.

17. A method of preparing (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate monohydrate comprising the steps selected from the group consisting of:

a. dissolving anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate with an organic solvent, adding water, and filtering;

b. dissolving anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate with an organic solvent, adding a solution of a second organic solvent and water, and filtering;

c. dissolving anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate with an organic solvent containing water, and filtering; and

d. reslurrying anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate with an organic solvent containing water for a period of days, and filtering.

18. The method of claim 17, wherein the steps are dissolving anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate with an organic solvent, adding water and filtering.

19. The method of claim 18, wherein the organic solvent is dimethylsulfoxide.

20. The method of Claim 18 or 19 further comprising heating the solution to between about 45°C to about 60°C.

21. The method of claim 17, wherein the steps are dissolving anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate with an organic solvent, adding a solution of a second organic solvent and water and filtering.

22. The method of claim 21, wherein the organic solvent is dimethylsulfoxide, the second organic solvent is selected from the group consisting of tetrahydrofuran, isopropanol, n-propanol, acetone, ethanol, methanol, and acetonitrile, and the amount of water present is about 7.5% to about 15% by weight.

23. The method of claim 17, wherein the steps are dissolving anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate with an organic solvent containing water and filtering.

24. The method of claim 23, wherein the organic solvent is selected from the group consisting of tetrahydrofuran, isopropanol, n-propanol, acetone, ethanol, methanol, and acetonitrile, and the amount of water present is about 7.5% to about 20% by weight.

25. The method of claim 24, wherein the organic solvent is n-propanol and the amount of water present is about 10% to about 15% by weight.

26. The method of claim 17, wherein the steps are: reslurrying anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate with an organic solvent containing water for a period of days, and filtering.

27. The method of claim 26, wherein the organic solvent is tetrahydrofuran and the period of days is about 10-20.

28. A method of preparing anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate comprising drying under vacuum monohydrate (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate at a temperature greater than 30°C for about 12 to about 48 hours.

29. An isolated crystalline form of (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate monohydrate, characterized by X-ray diffraction peaks at the following angles (±0.20°) of 2θ 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.

30. An isolated crystalline form according to Claim 29 having substantially the X-ray diffraction pattern as shown in Fig. 7.

31. An isolated crystalline form of anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, characterized by X-ray diffraction peaks at the following angles (±0.20°) of 2θ in its X-ray diffraction pattern: 6.16, 7.38, 8.75, 10.20, 12.24, 12.61, 14.65, 15.75, 17.33, 18.64, 19.99, 20.66, 21.32, 22.30, 23.18, 24.10, 24.69, 25.49, 26.09, 26.54, 27.52, 28.62, and 29.43.

32. An isolated crystalline form according to Claim 31 having substantially the X-ray diffraction pattern as shown in Fig. 6.

33. An isolated crystalline form of anhydrous (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, characterized by an onset temperature of about 196°C and ending temperature about 204°C, as measured by differential scanning calorimetry.

34. An isolated crystalline form of (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate monohydrate, having a water content of about 2.5 to 2.7%, by weight.

35. An isolated crystalline form of partially hydrated (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide maleate, having a water content of about 1.5% to about 2.3%, by weight.

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.