Claims

1. A process for the preparation of 7-chloro-4-(piperazin-1-yl)-quinoline, which comprises the following steps:
   a. reacting 4,7-dichloroquinoline with anhydrous piperazine in a polar protic solvent for a time of between 6 and 10 hours at reflux temperature;
   b. filtrating the suspension obtained from step a;
   c. removing the solvent under reduced pressure and washing the oil thus obtained until crystallization occurs;
   d. washing the crystals obtained from step c.
2. A process according to claim 1 in which the number of equivalents of piperazine is less than 3 times the amount of 4,7-dichloroquinoline.
3. A process according to claim 2, in which the number of equivalents of piperazine is 2.5 times the amount of 4,7-dichloroquinoline.
4. A process according to any one of claims 1 to 3, in which the polar protic solvent of step a is MeOH.
5. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline obtainable by the process of any one of claims 1 to 4.
6. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline according to claim 5 which has a X-ray powder diffraction pattern with at least five specific peaks at about 2-theta = 6.95°, 20.40°, 25.80°, 10.30° and 13.70° wherein said values may be plus or minus 0.1° 2-theta and have an intensity of at least 30%.
7. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline according to claim 6, which X-ray powder diffraction pattern further shows the following peaks at about 2-theta = 12.35°, 25.25°, 29.05°, 22.85°, 17.9°, 24.6°, 28.5° and 28.85° wherein said values may be plus or minus 0.1° 2-theta.
8. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline obtainable by the process of any one of claims 1 to 4, which process further includes the following steps:
   a. dissolving the crystals obtained from step d as claimed in claim 1 in hot hexane;
   b. allowing the solution from step a to cool back to RT to enable crystallization;
   c. filtrating the crystals obtained from step b.

9. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline according to claim 8, which X-ray powder diffraction pattern further shows the following peaks at about 2-theta = 23.6°, 23.95°, 20.4°, 23.2°, 24.45°, 18.3°, 18.6°, 24.7°, and 22.2° wherein said values may be plus or minus 0.1° 2-theta and have an intensity of at least 30%.

10. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline according to claim 9, which X-ray powder diffraction pattern further shows the following peaks at about 2-theta = 25.75°, 22.5°, 26.3°, 14.75°, 15.25°, 27.6°, 28.55°, 31.1°,and 28.05° wherein said values may be plus or minus 0.1° 2-theta.

11. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline obtainable by the process of any one of claims 1 to 4, which process further includes the following steps:

a. dissolving the crystals obtained from step d as claimed in claim 1 in dichloromethane;

b. concentrating the solution from step a under reduced pressure.

12. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline according to claim 11, which X-ray powder diffraction pattern shows the following peaks at about 2-theta = 18.1°, 19.8°, 16.45°, 17.85°, 23.1°, 24.65°, 20.35°, and 27.65° wherein said values may be plus or minus 0.1° 2-theta and have an intensity of at least 30%.

13. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline according to claim 12, which X-ray powder diffraction pattern further shows the following peaks at about 2-theta = 8.05°, 13.5°, 8.25°, 24.25°, 12.05°, and 24.05 wherein said values may be plus or minus 0.1° 2-theta.

14. A crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline according to claim 7, 9 or 12, having substantially the same X-ray diffraction pattern as the one depicted in Figure 2, Figure 3, or Figure 4 respectively.

15. Use of the crystalline polymorph of 7-chloro-4-(piperazin-1-yl)-quinoline according to claim 14 in the synthesis of piperaquine or one of its pharmaceutically acceptable salts.

The invention claimed is:

1. A process for the preparation of crystalline polymorph type B of 7-chloro-4-(piperazin-1-yl)-quinoline, the process comprising:

a) reacting 4,7-dichloroquinoline with anhydrous piperazine in a polar protic solvent for a time of between 6 and 10 hours at reflux temperature to give a suspension;

b) filtrating the suspension obtained from a);

c) removing the solvent under reduced pressure and washing the oil thus obtained until crystallization occurs; and

d) washing the crystals obtained from c), to give the crystalline polymorph type B of 7-chloro-4-(piperazin-1-yl)-quinoline which has a X-ray powder diffraction pattern with at least five specific peaks at about 2-theta=6.95° , 20.40° , 25.80° , 10.30° and 13.70° wherein said values may be plus or minus 0.1° 2-theta and have an intensity of at least 30%, wherein the number of equivalents of anhydrous piperazine is less than 3 times the amount of 4,7-dichloroquinoline, and the crystalline polymorph type B of 7-chloro-4-(piperazin-1-yl)-quinoline has a purity equal to or higher than 99%.

2. The process according to claim 1, in which the number of equivalents of piperazine is 2.5 times the amount of 4,7-dichloroquinoline.

3. The process according to claim 1, in which the polar protic solvent of a) is MeOH.

4. A crystalline polymorph of type B of 7-chloro-4-(piperazin-1-yl)-quinoline which has a X-ray powder diffraction pattern with at least five specific peaks at about 2-theta=6.95° , 20.40° , 25.80° , 10.30° and 13.70° wherein said values may be plus or minus 0.1° 2-theta and have an intensity of at least 30%, and further shows the following peaks at about 2-theta=12.35° , 25.25° , 29.05° , 22.85° , 17.9° , 24.6° , 28.5° and 28.85° wherein said values may be plus or minus 0.1° 2-theta.

5. The process of claim 1 further comprising:

a) dissolving the crystals obtained from d) of claim 1 in hot hexane to give a solution;

b) allowing the solution from a) to cool back to room temperature to enable crystallization; and

c) filtrating the crystals obtained from b) to give a crystalline polymorph of type C of 7-chloro-4-(piperazin-1-yl)-quinoline which has a X-ray powder diffraction pattern with at least nine specific peaks at about 2-theta=23.6° , 23.95° , 20.4° , 23.2° , 24.45° , 18.3° , 18.6° , 24.7° , and 22.2° wherein said values may be plus or minus 0.1° 2-theta and have an intensity of at least 30%.

6. A crystalline polymorph of type C of 7-chloro-4-(piperazin-1-yl)-quinoline which has a X-ray powder diffraction pattern with at least nine specific peaks at about 2-theta=23.6° , 23.95° , 20.4° , 23.2° , 24.45° , 18.3° , 18.6° , 24.7° , and 22.2° wherein said values may be plus or minus 0.1° 2-theta and have an intensity of at least 30%, and that further shows the following peaks at about 2-theta=25.75° , 22.5° , 26.3° , 14.75° , 15.25° , 27.6° , 28.55° , 31.1° , and 28.05° wherein said values

may be plus or minus 0.1° 2-theta.

7. The process of claim 1 further comprising:

a) dissolving the crystals obtained from d) of claim 1 in dichloromethane to give a solution; and

b) concentrating the solution from a) under reduced pressure to give a crystalline polymorph of type D of 7-chloro-4-(piperazin-1-yl)-quinoline which has a X-ray powder diffraction pattern with at least eight specific peaks at about 2-theta=18.1° , 19.8° , 16.45° , 17.85° , 23.1° , 24.65° , 20.35° , and 27.65° wherein said values may be plus or minus 0.1° 2-theta and have an intensity of at least 30%.

8. A crystalline polymorph of type D of 7-chloro-4-(piperazin-1-yl)-quinoline which has a X-ray powder diffraction pattern with at least eight specific peaks at about 2-theta=18.1° , 19.8° , 16.45° , 17.85° , 23.1° , 24.65° , 20.35° , and 27.65° wherein said values may be plus or minus 0.1° 2-theta and have an intensity of at least 30%, and that further shows the following peaks at about 2-theta=8.05° , 13.5° , 8.25° , 24.25° , 12.05° , and 24.05° wherein said values may be plus or minus 0.1° 2-theta.