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Process for the preparation of 2-[[4-[(7-Chloro-4-quinolyl)amino] pentyl]ethylamino]ethanol sulphate

MSN Laboratories Private Limited, R&D Center; Srinivasan Thirumalai Rajan; Sajja Eswaraiah; Sagyam Rajeshwar Reddy;Shaik mahammad Rafee; K Sreenath Reddy; B Ajay kumar

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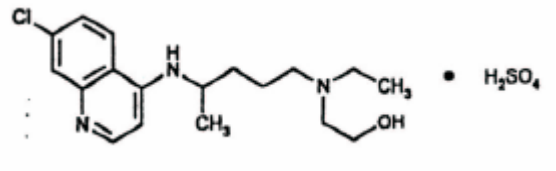
A process for the preparation of 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl] ethylamino]ethanol sulfate of compound of Formula-I, which is represented by the following structural formula.

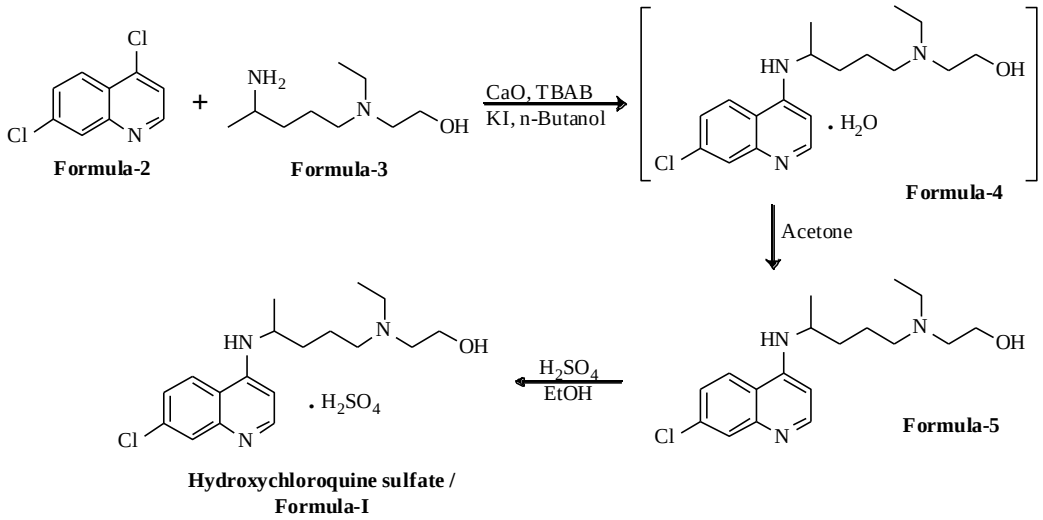


Formula-I

Hydroxychloroquine is chemically known as 2-[[4-[(7-Chloro-4-uinolyl) amino]pentyl]ethylamino]ethanol and it was disclosed in US2546658.

US2546658 discloses process for the preparation of hydroxychloroquine, which involves reacting 4,7-dichloroquinoline with N'-Ethyl-N'-β-hydroxyethyl-l,4-pentadiamine in the presence of potassium iodide (KI) and phenol.

The present disclosure provides an improved process for the preparation of Hydroxychloroquine, Hydroxychloroquine sulphate and its crystalline forms. The said improved process is schematically as mentioned below.



The compound of Formula-2 and Formula-3 used in the present invention are prepared by any of the processes known in prior art.

The following examples specifies the conditions of the process for the preparation of Hydroxychloroquine sulphate.

Example-1: Preparation of Hydroxychloroquine hydrate

Calcium oxide (14.15 g), Potassium iodide (4 g), Tetrabutylammonium bromide (10 g) and 2-((4-aminopentyl)(ethyl)amino)ethanol (114.4 g) were added to the mixture of 4,7-dichloro quinolone (100 g) in n-Butanol (200 ml) at 25-30°C and stirred for 15 minutes. Heated the mixture to 125-130°C and stirred for 70 hrs. Cooled the mixture to 80-85°C and distilled-out the n-butanol at the same temperature. Cooled the mixture to 50-55°C and water (200 ml) was added. Mixture further cooled to 25-30°C and adjusted the mixture pH between 5.0 – 6.0 by using hydrochloric acid. Cooled the mixture to 10-15°C and stirred for 60 minutes. Filtered the precipitated solid and washed with water (100 ml). Dichloromethane (800 ml) was added to the obtained filtrate at 25-30°C. Adjusted the mixture pH between 8.4 – 9.0 by using sodium hydroxide solution and stirred for 20 minutes at 25-30°C. Separated the organic layer from aqueous layer. Distilled-out the organic layer to get residue. Residue co-distilled in acetone (50 ml) and cooled to 25-30°C. Seeding material of Hydroxychloroquine hydrate (500 mg) was added to the residue at 25-30°C and stirred for 10 minutes. Water (800 ml) was added to the residue and stirred for 10 hrs. Filtered the precipitated solid and washed with water.

Yield: 190 g

The PXRD pattern of the obtained compound is as illustrated in figure-1

Example-2: Preparation of Hydroxychloroquine

Calcium oxide (14.15 g), Potassium iodide (4 g), Tetrabutylammonium bromide (10 g) and 2-((4-aminopentyl)(ethyl)amino)ethanol (114.4 g) were added to the mixture of 4,7-dichloro quinolone (100 g) in n-Butanol (200 ml) at 25-30°C and stirred for 15 minutes. Heated the mixture to 125-130°C and stirred for 70 hrs. Cooled the mixture to 80-85°C and distilled-out the n-butanol at the same temperature. Cooled the mixture to 50-55°C and water (200 ml) was added. Mixture further cooled to 25-30°C and adjusted the mixture pH between 5.0 – 6.0 by using hydrochloric acid. Cooled the mixture to 10-15°C and stirred for 60 minutes. Filtered the precipitated solid and washed with water (100 ml). Dichloromethane (800 ml) was added to the obtained filtrate at 25-30°C. Adjusted the mixture pH between 8.4 – 9.0 by using sodium hydroxide solution and stirred for 20 minutes at 25-30°C. Separated the organic layer from aqueous layer. Distilled-out the organic layer to get residue. Residue

co-distilled in acetone (50 ml) and cooled to 25-30°C. Seeding material of Hydroxychloroquine hydrate (500 mg) was added to the residue at 25-30°C and stirred for 10 minutes. Water (800 ml) was added to the residue and stirred for 10 hrs. Filtered the precipitated solid and washed with water. Dichloromethane (1000 ml) was added to the obtained solid at 25-30°C and stirred for 30 minutes. Separate the organic layer and distilled-out the same. Acetone (450 ml) was added to the obtained residue. Heated the mixture to 50-55°C and stirred for 15 minutes. Treated the mixture with carbon. Mixture cooled to 25-30°C. Seeding material of hydroxychloroquine (500 mg) was added to the mixture at 25-30°C and stirred for 3 hrs. Mixture cooled to 5-10°C and stirred for 2 hrs. Filtered the precipitated solid and washed with acetone. Dried to obtain title compound.

Yield: 94 g

M.R: 92.5-93°C; HPLC purity**:** 99.82%

The PXRD pattern of the obtained compound is as illustrated in figure-2

Example-3: Preparation of Hydroxychloroquine sulphate

Ethanol (700 ml) was added to the hydroxychloroquine (100 g) at 25-30°C and stirred for 10 minutes. Heated the mixture to 45-48°C. Sulphuric acid solution (15.46 ml) was added to the mixture at 45-48°C and stirred for 6 hrs. Cooled the mixture to 25-30°C and stirred for 3 hrs. Filtered the precipitated solid and washed with ethanol. Dried to obtain title compound.

Yield: 110 g

M.R: ~240°C

The PXRD pattern of the obtained compound is as illustrated in figure-3

The following drawings shows the PXRD pattern of above examples:

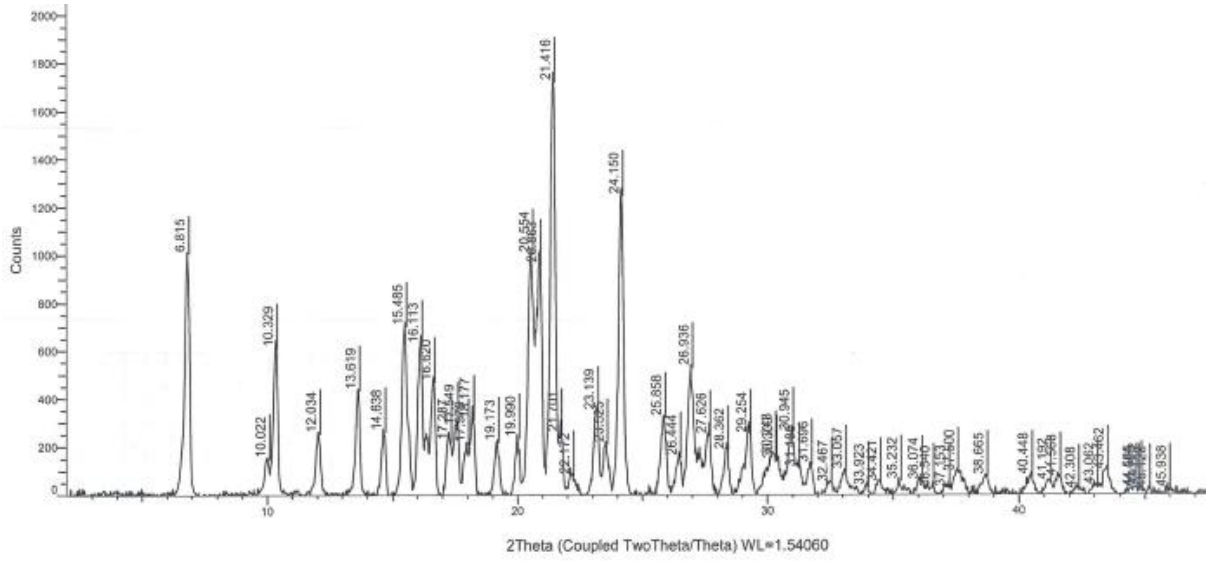


Figure-1

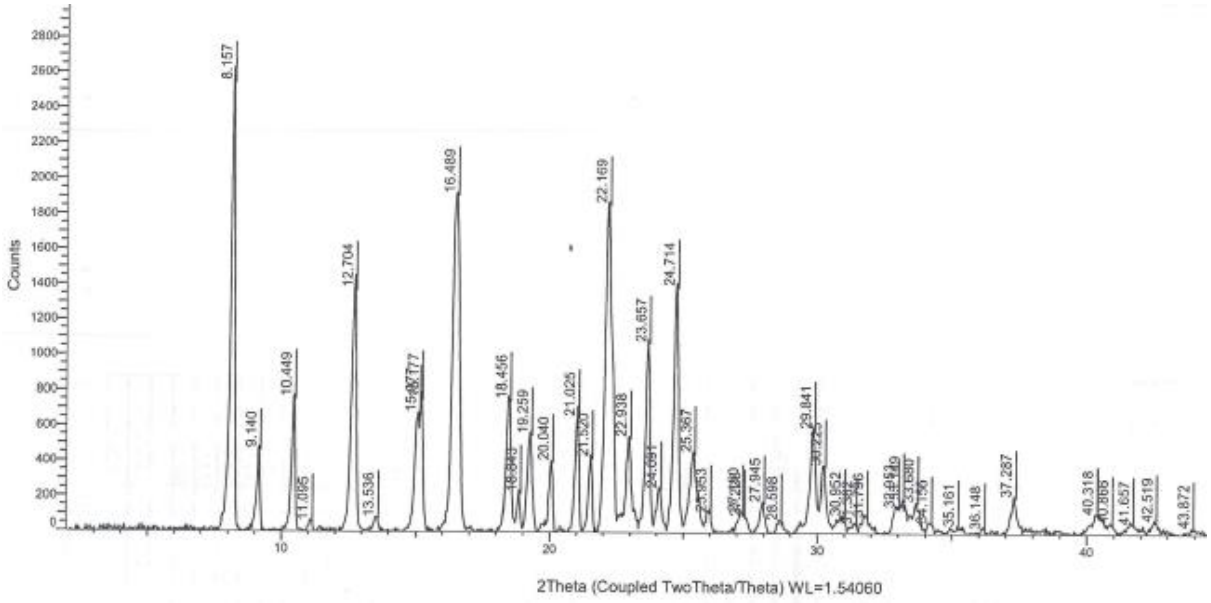


Figure-2

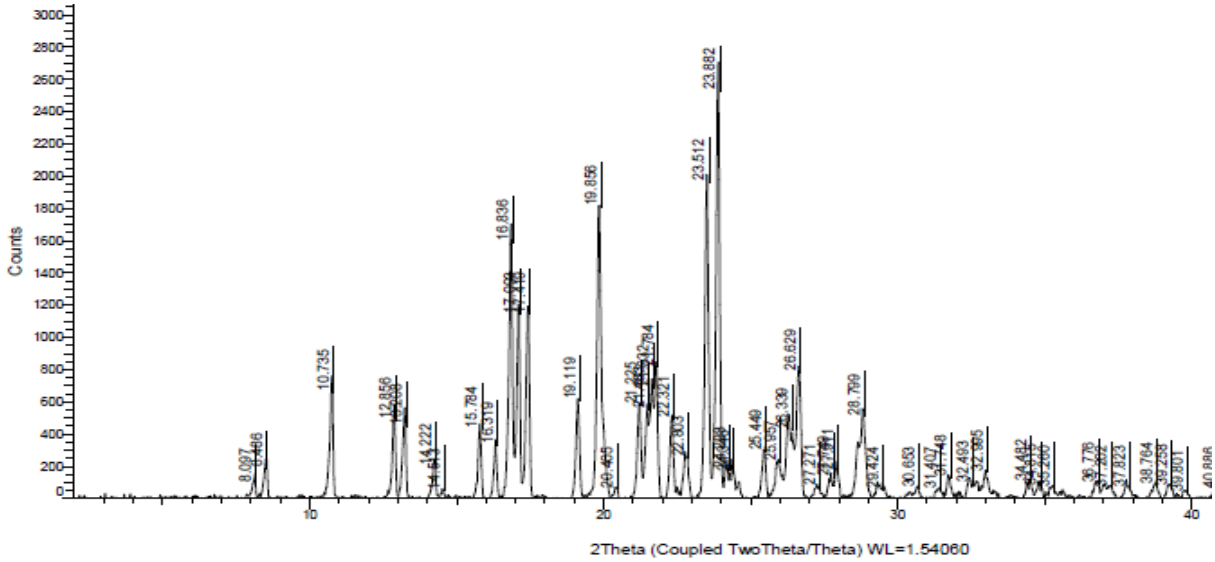


Figure-3

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