(54) Title: PROCESS FOR THE PREPARATION OF HIGHLY PURE HYDROXYCHLOROQUINE OR A SALT THEREOF

(57) Abstract:
The present invention is directed at a process for selectively removing compound of formula 1 or a salt thereof from a mixture comprising compound of formula 1 and compound of formula 4: (see formula 1, 4) wherein the process comprises the steps of: (i)
(57) Abrégé(suite)/Abstract(continued):
putting the mixture in solution and treating the solution with a reactant selected from the group consisting of: (see formula (A), (B), (C)) where X is halogen, OH or OCOR'; Hal is halogen; Y is O or S; W is O, N or S; and R, R', and R'' are each independently selected from the group consisting of alkyl, aryl, and aralkyl; to yield protected compounds of formula 5 and diprotected compounds of formula 6, (see formula 5, 6) said protected compounds of formula 5 and diprotected compounds of formula 6 being soluble in the solution; (ii) hydrolysis, in a suitable solvent, of the protected compounds of formula 5 and the diprotected compounds of formula 6 by using a metal hydroxide or metal carbonate, to yield soluble compounds of formula 1 and soluble protected compounds of formula 7; (see formula 7) (iii) adding an acid, preferably sulfuric acid, to form an insoluble salt of compounds of formula 1; (iv) isolating the insoluble salt of compound of formula 1; and optionally, recovering the compound of formula 1 from its salt.
ABSTRACT

The present invention is directed at a process for selectively removing compound of formula 1 or a salt thereof from a mixture comprising compound of formula 1 and compound of formula 4:

wherein the process comprises the steps of:
(i) putting the mixture in solution and treating the solution with a reactant selected from the group consisting of:

\[ R'COX \]  \quad (A);

\[ \text{Hal} \equiv Y \equiv W - R' \]  \quad (B); and

\[ R'' - SO_2 \cdot \text{Hal} \]  \quad (C);

where X is halogen, OH or OCOR';
Hal is halogen;
Y is O or S;
W is O, N or S; and
R, R', and R'' are each independently selected from the group consisting of alkyl, aryl, and aralkyl;
to yield protected compounds of formula 5 and diprotected compounds of formula 6,

\[
\begin{align*}
5 & \quad \text{Cl} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{B} & \quad \text{O} & \quad \text{PG} \\
6 & \quad \text{Cl} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{B} & \quad \text{O} & \quad \text{PG}
\end{align*}
\]

said protected compounds of formula 5 and diprotected compounds of formula 6 being soluble in the solution; (ii) hydrolysis, in a suitable solvent, of the protected compounds of formula 5 and the diprotected compounds of formula 6 by using a metal hydroxide or metal carbonate, to yield soluble compounds of formula 1 and soluble protected compounds of formula 7;

\[
\begin{align*}
7 & \quad \text{Cl} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{B} & \quad \text{N} & \quad \text{PG} & \quad \text{OH}
\end{align*}
\]

(iii) adding an acid, preferably sulfuric acid, to form an insoluble salt of compounds of formula 1; (iv) isolating the insoluble salt of compound of formula 1; and optionally, recovering the compound of formula 1 from its salt.
PROCESS FOR THE PREPARATION OF HIGHLY PURE HYDROXYCHLOROQUINE OR A SALT THEREOF

FIELD OF THE INVENTION

The present invention relates to a process for the manufacture of the antimalarial drug hydroxychloroquine, 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]-ethylamino]ethanol sulfate. In particular, this novel process delivers highly pure hydroxychloroquine or a salt thereof which contains very low but acceptable levels of a particularly difficult to remove impurity (des-ethyl hydroxychloroquine).

BACKGROUND OF THE INVENTION

Hydroxychloroquine (1) has antimalarial and antirheumatic properties and is widely used for the treatment of rheumatoid arthritis sometimes in combination with cyclophosphamide and azathioprine. It has also found uses for the treatment of discoid and systemic lupus erythematosus and is marketed under the trade-name Plaquenil™.

\[
\begin{align*}
\text{Cl} & \\
\text{N} & \\
\text{H} & \\
\text{N} & \\
\text{N} & \\
\text{OH} & \\
\end{align*}
\]

1

Hydroxychloroquine was first disclosed in US 2,546,658 where it was prepared by reacting a mixture of 4,7-dichloroquinoline (2) and \(N'\)-ethyl-\(N'\)-β-hydroxyethyl-1,4-pentadiamine (3) in phenol in the presence of potassium iodide as depicted in Scheme 1. The product was isolated as its diphosphate salt in 35% yield.
Scheme 1

RO 62681 disclosed a process for the purification of hydroxychloroquine by free-basing the salt in water and extracting it into chloroform or dichloromethane. After removal of the solvent by evaporation, the salt was re-formed in ethanol with H₂SO₄.

US 5,314,894 disclosed a process to make (S)-(+-)hydroxychloroquine by refluxing 4,7-dichloroquinoline (2) and (S)-N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine [(S)-3] in N,N-diisopropylethylamine for 48 hours. The free-base was isolated after basic work-up by high vacuum distillation (0.01 Torr; 130°C) in 45.9 % yield.

The drawbacks of the above processes include:

1) Use of toxic and unconventional solvents such as phenol and reagents such as N,N-diisopropylethylamine. Of note is that the use of high-boiling amines cause difficulties since they, like the product, form salts making the purification more challenging.

2) Long reaction times which increases production costs and may lead to impurity formation. Specifically, when 4,7-dichloroquinoline (2) and N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine (3) react at high temperatures (generally over 120°C) for prolonged durations, concomitant production of the des-ethyl by-product 4 occurs. Importantly, the des-ethyl by-product is difficult to remove, even by free-basing and subsequent re-formation of
the salt. All published articles, also, due to the high purity requirements in
the pharmaceutical industry, the allowable limit of 4 is 0.2% by weight.

Thus, an efficient process for the preparation of hydroxychloroquine sulfate
having acceptably low levels of impurity 4 was required. As is, therefore, an
object of the invention to provide a novel process which minimizes the presence
of impurity 4 present with compound 1.

Surprisingly and unexpectedly, it has been found that the des-ethyl-
hydroxychloroquine impurity (4) may be effectively removed by treatment of the
reaction mixture with an amide or amide-like forming agent. The amide or
amide-like form of 4 may be removed from the final product by conventional
processes since, in contrast to hydroxychloroquine, it does not form a salt under
these conditions.

Further, objects will be realized by those persons skilled in the art from the
following summary of the invention and detailed description of embodiments of
the invention.
SUMMARY OF THE INVENTION

According to one aspect of the invention, there is provided a novel process for the preparation of highly pure hydroxychloroquine of formula 1 or a salt thereof, which may be generated from the reaction of 4,7-dichloroquinoline (2) and N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine (3) as depicted in Scheme 1, which process comprises the purifying a mixture containing a compound of formula 1 and an impurity of formula 4 by treatment of solid mixture of formula 1 and 4 with an amide (or an amide-like) forming agent.

According to one aspect of the invention, there is provided a process for selectively removing compound of formula 1 or a salt thereof from a mixture comprising compound of formula 1 and compound of formula 4:

wherein said process comprises the steps of:
(i) putting said mixture in solution and treating said solution with a reactant selected from the group consisting of:

\[ R'\text{-}X \]  \text{ (A),} \\
\[ \text{Hal} = W\text{-}R' \]  \text{ (B), and}
\[ \text{R}''^-\text{SO}_2\cdot\text{Hal} \quad (\text{C}), \]

where

- \( X \) is halogen, OH or OCOR;
- \( \text{Hal} \) is halogen;
- \( Y \) is O or S;
- \( W \) is O, N or S; and
- \( \text{R}, \ \text{R}', \ \text{and} \ \text{R}'' \) are each independently selected from the group consisting of alkyl such as methyl, ethyl, isopropyl, aryl such as phenyl, and aralkyl such as benzyl;

5 to yield protected compounds of formula 5 and diprotected compounds of formula 6,

\[ \text{Cl} \]
\[ \text{N} \]
\[ \text{H} \cdot \text{N} \cdot \text{CH} \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{N} \cdot \text{O} \cdot \text{PG} \]

\[ \text{Cl} \]
\[ \text{N} \]
\[ \text{H} \cdot \text{N} \cdot \text{CH} \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{N} \cdot \text{O} \cdot \text{PG} \]

10 said protected compounds of formula 5 and formula 6 being soluble in said solution;

(ii) hydrolyzing in a suitable solvent the protected compounds of formula 5 and the diprotected compounds of formula 6 by using a metal hydroxide, metal carbonate or metal bicarbonate to yield soluble compounds of formula 1 and soluble protected compounds of formula 7;

\[ \text{Cl} \]
\[ \text{N} \]
\[ \text{H} \cdot \text{N} \cdot \text{CH} \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{N} \cdot \text{PG} \]

\[ \text{OH} \]
(iii) adding a suitable acid, such as sulfuric acid, to form an insoluble salt of compound of formula 1 but which does not form a insoluble salt of compound of formula 7 (or compound of formula 4, if still present);

(iv) isolating the insoluble sulfate salt of compound of formula 1; and

(v) optionally isolating the compound of formula 1.

Preferably the suitable solvent used for the hydrolysis step is selected from the group consisting of C1 to C6 alcohols such as methanol, ethanol, and propanol, C3-C9 alkyl ketones such as acetone and methyl isobutyl ketone and cyclic or acyclic C4 to C8 alkyl ethers such as tetrahydrofuran and methyl tert-butyl ether, and mixtures thereof.

Also preferably, the isolation in step (v) is done by filtration.

Preferably, the reactant used at step (i) is $\text{R}^\text{O}^\text{X}$, wherein $\text{R}$ and $\text{X}$ are as defined above. More preferably, the reactant used at step (i) is a carboxylic acid anhydride or an acyl halide. Even more preferably, the reactant used at step (i) is acetic anhydride.

Also preferably, the reactant used at step (i) is an acyl chloride. More preferably, the reactant used at step (i) is acetyl chloride.

Preferably, the metal hydroxide used in step (ii) is selected from the group consisting of: lithium hydroxide, sodium hydroxide, and potassium hydroxide.

Preferably, the metal carbonate used in step (ii) is potassium carbonate.
The suitable acid may comprise other acids which form an insoluble salt of compound 1 but not of compounds 7 and 4 such as, for example, phosphoric acid.

According to another aspect of the invention, there is provided a novel process for the preparation of highly pure compound of formula 1 or its sulfate salt, substantially free of compound of formula 4 wherein said process comprises the following steps:

(i) reacting 4,7-dichloroquinoline of formula 2 and N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine of formula 3 in the presence of a solvent;

(ii) treating the resulting mixture comprising the compound of formula 1 and the compound of formula 4 with a reactant selected from the group consisting of:

\[ \text{R}^+\text{X} \quad (A), \]

\[ \text{Hal} \quad \text{W} = \text{R}' \quad (B), \text{ and} \]

\[ \text{R}''\rightarrow\text{SO}_2\cdot\text{Hal} \quad (C), \]

where

- X is halogen, OH or OCOR';
- Hal is halogen;
- Y is O or S;
W is O, N or S; and
R, R', and R'' are each independently selected from the
group consisting of: alkyl, aryl, and aralkyl;

to yield protected compounds of formula 5 and diprotected compounds of
formula 6,

\[
\begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{O}_{\text{PG}} \\
\text{5}
\end{array}
\quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{O}_{\text{PG}} \\
\text{6}
\end{array}
\]

said protected compounds of formula 5 and diprotected compounds of
formula 6 being soluble in said solution;

(iii) hydrolysis, in a suitable solvent, of the protected compounds of
formula 5 and the diprotected compounds of formula 6 by using a metal
hydroxide, metal carbonate or metal bicarbonate to yield soluble
compounds of formula 1 and soluble protected compounds of formula 7;

\[
\begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{O}_{\text{PG}} \\
\text{OH} \\
\text{7}
\end{array}
\]

(iv) adding sulfuric acid to form an insoluble salt of compound of formula 1;
(v) isolating the insoluble sulfate salt of compound of formula 1; and
(vi) optionally isolating the compound of formula 1.

Preferably, step (i) is carried out in the presence of an organic solvent which is
subsequently removed at higher temperatures.
Also preferably, there is a work-up after step (ii).

According to another aspect of the invention there is provided a process for carrying out the reaction in such a way which avoids the use of toxic solvent or basic reagent.

In one embodiment of the invention there is provided a process where the compound of formula (1) is the S-enantiomer.

Yet another embodiment of the invention, a pharmaceutical composition comprising hydroxychloroquine in its sulfate salt form produced using the procedures disclosed herein resulting in the minimal presence of impurity compound 4 is produced.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

It is known that the reaction of 4,7-dichloroquinoline (2) and N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine (3) needs to be carried out at high temperature. And it has been found that the reaction can be completed without use of any solvent. However, 4,7-dichloroquinoline (2) is a solid and N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine (3) is in a viscous oil thereby causing difficulties for proper agitation. This is especially problematic if further scale-up to industrial levels is required.

A highly desirable solution was obtained by the addition of a small amount of a common organic solvent thereby causing 2 and 3 to be well-mixed at room temperature. This solvent was then removed at higher temperature allowing the reaction to occur under almost neat conditions. Suitable solvents could be any organic solvent which do not react with the reagents, preferably a low boiling organic solvent, most preferably a C1 to C4 alkyl alcohol such as methanol, ethanol and isopropanol, with the most preferred being isopropanol. The amount
of the organic solvent is the amount required to permit efficient mixing of the 2 and 3, for instance from 0.5 parts to 5 parts relative to 2. This process facilitates scale-up in terms of improved yield, purity and increased safety.

5 Hydroxycchloroquine of formula 1 and des-ethyl hydroxycchloroquine of formula 4, when treated with an acid such as sulfuric acid, can each form a salt. However under appropriate conditions, des-ethyl hydroxycchloroquine of formula 4 can also form an amide or amide-like compounds such as a carbamate when treated with an amide or amide-like group forming agent, while the hydroxycchloroquine of formula 1 does not. Surprisingly, when compound 4 is converted to an amide or amide-like compound (as illustrated by compounds 6) and then hydrolyzed to compounds of formula 7, it does not form a salt when treated with an acid under these conditions, and therefore it is easily removed during the workup procedure.

15 Such amide or amide-like compounds (as illustrated by compounds of formula 6) can be easily formed according to common amino group protection methods such as those described in “Protective Groups in Organic Synthesis” by T. Green and P. Wuts, third edition such as, for example, acetyl amide protection and benzyloxy carbamate protection. Furthermore, amide or amide-like compounds such as carbamates are stable when treated with bases such as metal hydroxides or metal carbonates under normal operating conditions, for instance temperatures less than 50°C.

It is also known that when a hydroxyl group is treated with the above mentioned agents, acetate or acetate-like compounds such as alkyl carbonates can be formed. However, the acetate or the acetate-like compounds are more labile relative to the amide or amide-like compounds. Generally, acetate or alkyl carbonates can be hydrolyzed when treated with metal hydroxide or metal carbonates or metal bicarbonates in organic solvents or aqueous media, or mixtures of organic solvents and water. In mixtures, the ratio of organic solvent
and water can vary greatly so long as the metal hydroxide has sufficient solubility.

As depicted in Scheme 2, after reaction completion between 4,7-dichloroquinoline (2) and N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine (3), the crude hydroxychloroquine product is subjected to basification to remove the HCl generated from the reaction. An amide or amide-like forming agent is then added. The des-ethyl hydroxychloroquine of formula 4 reacts with the amide or amide-like group forming agent to provide a compounds of formula 6, while hydroxychloroquine of formula 1 provides a compounds of formula 5. By treatment with bases such as metal hydroxide or metal carbonate, the compounds of formula 5 can be hydrolyzed to form hydroxychloroquine of formula 1, while the compounds of formula 6 may be hydrolyzed to compounds of formula 7, which are still amide or amide-like compounds. The mixture is then treated with an acid, most preferably sulfuric acid, and only hydroxychloroquine of formula 1 can form a salt under these conditions, thereby permitting facile separation of the des-ethyl impurity. Taken together, the above procedure provides for highly pure hydroxychloroquine sulfate.
Thus, according to an embodiment of the invention there is disclosed a process for purifying compounds of formula 1 or a salt thereof, from a mixture comprising compounds of formula 1 and compounds of formula 4, which may be accomplished by:

1) adding an amide or amide-like group forming agent to the mixture comprising compounds of formula 1 and which may comprise compounds of formula 4;
2) hydrolyzing using a metal hydroxide or metal carbonate;
3) washing with water to remove inorganic salts;
4) adding sulfuric acid to form a sulfate salt of hydroxychloroquine;
5) isolating hydroxychloroquine sulfate by filtration; and
6) optionally isolating/recovering the compound of formula 1.

The reaction of steps 2 and 3 above may occur under neat conditions or, more preferably, in the presence of a small amount of organic solvent, preferably 0.5 to 5 parts relative to compound 2, to allow improved mixing of the reactants. The
organic solvent is then removed during the initial heating of the reaction mixture to a temperature where the reaction mixture will remain homogeneous. The heating is continued thereafter until the completion of the reaction.

The sulfuric acid salt of hydroxychloroquine that may be obtained has a very high purity and with a des-ethyl hydroxychloroquine impurity level at less than 0.2% by weight. The purity of the final compound is determined by any conventional method including HPLC.

Other salts of hydroxychloroquine may also be obtained in a highly pure form by this process by substitution of sulfuric acid in the salt forming step above with another pharmaceutically acceptable acid.

In the event that the purification process of the present invention is not used, then the level of the des-ethyl hydroxychloroquine impurity would be greater than 0.2% and, hence, the material would be unacceptable for use as a pharmaceutical.

According to an embodiment of the process of the invention, the crude product from the synthesis of compound of formula 1 which may contain significant or minor amounts of des-ethyl hydroxychloroquine 4 impurity is reacted with an amide (or amide-like) group forming agent selected from the agents of formula (A), (B) and (C) as shown below:

\[
\begin{align*}
&\text{(A)} \\
&\text{(B)}
\end{align*}
\]
where X is halogen, OH or OCOR';
Hal is halogen;

Y is O or S;

W is O, N or S and;

R, R', and R'' are each independently selected from the group consisting of alkyl, aryl, or aralkyl.

Preferably, R, R', and R'' are independently selected from methyl, ethyl, isopropyl, phenyl or benzyl. The reaction mixture is then subjected to base hydrolysis using a metal hydroxide or metal carbonate to remove the group associated with oxygen as depicted in Scheme 4.

The amide or amide-like group forming agent used in the process of the invention is preferably a compounds of formula (A), more preferably an acid anhydride or an acid halide, most preferably acetic anhydride, acetyl chloride or acetyl bromide. The agent is used in an amount of from about 0.01 eq to about 0.5 eq, relative to 2. This amount used is dependent on the content of the des-ethyl impurity of formula 4 in the hydroxychloroquine.

The reaction between the amide or amide-like forming agent and the des-ethyl hydroxychloroquine impurity is allowed to take place, either neat or in a solvent. The preferred solvents are aprotic organic solvents such as C3-C6 alkyl ketones and C1 to C3 chlorinated hydrocarbons. The most preferred solvent is methyl iso-butyl ketone (MIBK). The temperature for the amide or amide-like forming step ranges from about 5°C to about 40°C, more preferably ranging from about 15°C to about 30°C.
The base used in the hydrolysis step is preferably an alkali hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide, or an alkali carbonate such as potassium carbonate.

After isolation of an insoluble salt of Hydroxychloroquine, most preferably the sulfate salt, the Hydroxychloroquine salt is converted back to the free-base form (Hydroxychloroquine) by standard techniques known in the art such as free-basing. Free basing involves dissolving the salt form of the drug in an organic solvent and adding a base, such as aqueous sodium hydroxide. To recover Hydroxychloroquine in its free-base form, one skilled in the art can either evaporate the solvent to dryness or use a suitable anti-solvent to precipitate out Hydroxychloroquine in crystal form.

The following non-limiting examples further illustrate the manner of carrying out the process according to the present invention.

**Example 1 – Preparation of Hydroxychloroquine in Sulfate form with minimal levels of the impurity compounds of formula 4 and 7.**

To 4,7-dichloroquinoline (1.0 eq. 0.5 moles) was added 4-amino-N-ethyl-(2-hydroxyethyl)pentylamine (1.5 eq. 0.75 mole) followed by isopropanol (2 vol). The mixture was heated, the isopropanol was removed at atmosphere pressure and the mixture was stirred at 120-130°C for 20-24 h. The oil was cooled to 70-80°C whereupon water (2 vol) and MIBK (3 vol) were added. The pH was adjusted to 10-11, the two layers were separated, 0.1 eq of acetic anhydride was added to the organic layer and the mixture was stirred at room temperature overnight. This was followed by the addition of 0.25 eq. LiOH.H₂O, water (0.5 vol) and methanol (0.5 vol). The mixture was stirred at room temperature overnight and then washed once with water. To the organic layer was added methanol (5 vol) followed by H₂SO₄ (1.0 eq. 0.5 moles). The mixture was maintained at 35-45°C for 3-4 hours, cooled to 20-25°C, filtered and washed with
methanol. The crude product was purified in methanol by pulping to obtain an 80% yield of hydroxychloroquine sulfate having a chromatographic purity of greater than 99.5% and a level of impurity (of compound of formula 4) of less than 0.1%.

In a similar experiment but without the purification process according to the present invention, the level of the des-ethyl impurity (compound of formula 4) was greater than 0.2%.

$^1$H NMR (300 MHz): $\delta$ (D$_2$O) = 7.97 (d); 7.77 (d); 7.23 (d); 7.08 (dd); 6.52 (d); 3.84-3.80 (m); 3.65 (t); 3.09-3.00 (m); 1.62-1.53 (m); 1.16 (d); 1.05 (t).

Example 2 – Conversion of Hydroxychloroquine sulfate to Hydroxychloroquine (1)

A flask was charged with Hydroxychloroquine sulfate salt (200.0 g), water (1000 mL) and methyl isobutyl ketone (MIBK) (800 mL). The mixture was stirred until a clear solution was obtained. The solution was then cooled to 0-5°C and 5N Sodium Hydroxide was added until pH = 10.5 - 11.0. This mixture was stirred at room temperature for 0.5 – 1 h. The two layers were then separated and the organic layer washed once with 5% aqueous NaCl (200 mL). To the organic layer was added charcoal (20.0 g). The mixture was stirred at room temperature and then filtered. The residue was washed with methanol (200 mL) and the filtrate contained Hydroxychloroquine free base (1). The filtrate was evaporated to dryness, yielding Hydroxychloroquine free base.

A person of ordinary skill in the art will understand that many changes can be made to the embodiment of the invention without departing from the scope and spirit of the invention. It is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.
CLAIMS

1. A process for selectively removing compound of formula 1 or a sulfate salt thereof from a mixture comprising compound of formula 1 and compound of formula 4:

![Chemical Structures]

wherein said process comprises the steps of:

(i) putting said mixture in solution and treating said solution with a reactant selected from the group consisting of:

\[ R' - X \]  (A);

\[ \text{Hal} - Y - W - R' \]  (B); and

\[ R'' - \text{SO}_2 \cdot \text{Hal} \]  (C);

where

- X is halogen, OH or OCOR';
- Hal is halogen;
- Y is O or S;
- W is O, N or S; and
- R, R', and R'' are each independently selected from the group consisting of alkyl, aryl, and aralkyl;
to yield protected compounds of formula 5 and diprotected compounds of formula 6,

\[ \text{Cl-N} \quad \text{Cl-N} \]
\[ \text{H-N} \quad \text{H-N} \]
\[ \text{H-N} \quad \text{H-N} \]
\[ \text{O-PG} \quad \text{O-PG} \]

said protected compounds of formula 5 and diprotected compounds of formula 6 being soluble in said solution;

(ii) hydrolysis, in a suitable solvent, of the protected compounds of formula 5 and the diprotected compounds of formula 6 by using a metal hydroxide or metal carbonate to yield soluble compounds of formula 1 and soluble protected compounds of formula 7;

\[ \text{Cl-N} \]
\[ \text{H-N} \]
\[ \text{H-N} \]
\[ \text{O-PG} \]
\[ \text{N-PG} \]
\[ \text{CH} \]

(iii) adding sulfuric acid to form an insoluble sulfate salt of compound of formula 1;

(iv) isolating the insoluble sulfate salt of compound of formula 1; and

(v) optionally, recovering the compound of formula 1 from its sulfate salt.

2. Process according to claim 1 wherein the suitable solvent for hydrolysis is selected from the group consisting of C1 to C6 alcohol, C3-C9 alkyl ketone and cyclic or acyclic C4 to C8 alkyl ether and mixtures thereof.
3. Process according to claim 2, wherein the C1 to C6 alcohol is selected from the group consisting of methanol, ethanol, and propanol.

4. Process according to claim 2, wherein the C3-C9 alkyl ketone is selected from the group consisting of acetone and methyl isobutyl ketone.

5. Process according to claim 2, wherein the cyclic or acyclic C4 to C8 alkyl ether is selected from the group consisting of tetrahydrofuran and methyl tert-butyl ether.

6. Process according to any one of claims 1 or 5 wherein the isolation in step (iv) is done by filtration.

7. Process according to any one of claims 1 to 6 wherein R, R', R'' are independently selected from the group consisting of: methyl, ethyl, isopropyl, phenyl and benzyl.

8. The process according to any one of claims 1 to 7 wherein the reactant used at step (i) is \( \text{R} \text{CO} \text{X} \), wherein R and X are as defined in claim 1.

9. The process according to claim 8 wherein the reactant used at step (i) is a carboxylic acid anhydride or an acyl halide.

10. The process according to claim 9 wherein the reactant used at step (i) is acetic anhydride.

11. The process according to claim 1 wherein the reactant used at step (i) is an acyl chloride.
12. The process according to claim 1 wherein the reactant used at step (i) is acetyl chloride.

13. The process according to claim 1 wherein the metal hydroxide used in step (ii) is lithium hydroxide.

14. The process according to claim 1 wherein the metal hydroxide used in step (ii) is sodium hydroxide.

15. The process according to claim 1 wherein the metal hydroxide used in step (ii) is potassium hydroxide.

16. The process according to claim 1 wherein the metal carbonate used in step (ii) is potassium carbonate.

17. Process according to any one of claims 1 to 16 wherein the compound of formula 1 is recovered from its sulfate salt.

18. A process for the preparation of highly pure compound of formula 1 or its sulfate salt, substantially free of compound of formula 4 wherein said process comprises the following steps:

(i) reacting 4,7-dichloroquinoline of formula 2 and \( N'-\text{ethyl}-N'-\beta\)-hydroxyethyl-1,4-pentadiamine of formula 3 in the presence of a solvent;
(ii) treating the resulting mixture comprising the compound of formula 1 and the compound of formula 4 with a reactant selected from the group consisting of:

\[ \text{R'} \text{X} \]  (A),

\[ \text{Hal} \text{W-R'} \]  (B), and

\[ \text{R''-SO}_2\text{Hal} \]  (C),

wherein X is halogen, OH or OCOR';

Hal is halogen;

Y is O or S;

W is O, N or S; and

R, R', and R'' are each independently selected from the group consisting of alkyl, aryl, and aralkyl;

to yield protected compounds of formula 5 and diprotected compounds of formula 6,

\[ \text{Cl}_{\text{5}} \text{N}_{\text{5}} \text{H}_{\text{5}} \text{N}_{\text{5}} \text{O}_{\text{PG}} \]  (5)

\[ \text{Cl}_{\text{6}} \text{N}_{\text{6}} \text{H}_{\text{6}} \text{N}_{\text{6}} \text{O}_{\text{PG}} \]  (6)

said protected compounds of formula 5 and diprotected compounds of formula 6 being soluble in said solution;
(iii) hydrolysis, in a suitable solvent, of the protected compounds of formula 5 and the diprotected compounds of formula 6 by using a metal hydroxide or metal carbonate to yield compounds of formula 1 and protected compounds of formula 7; and

(iv) adding sulfuric acid to form an insoluble sulfate salt of compound of formula 1;

(v) isolating the insoluble sulfate salt of compound of formula 1; and

(vi) optionally, recovering the compound of formula 1 from its sulfate salt.

19. Process according to claim 18, wherein step (i) is carried out in the presence of an organic solvent which is subsequently removed at higher temperatures.

20. Process according to any one of claims 18 and 19 wherein there is a work-up after step (ii).

21. Process according to claim 18 wherein the suitable solvent for step (i) is selected from the group consisting of methanol, ethanol and isopropanol.

22. Process according to any one of claims 18 to 21 wherein the isolation in step (v) is done by filtration.
23. Process according to any one of claims 19 to 22, wherein the isolation of the sulfate salt of the compound of formula 1 is done by filtration.

24. Process according to claim 18 wherein the compound of formula 1 is recovered from its sulfate salt.

25. A process for selectively removing compound of formula 1 or a salt thereof from a mixture comprising compound of formula 1 and compound of formula 4:

wherein said process comprises the steps of:

(i) putting said mixture in solution and treating said solution with a reactant selected from the group consisting of:

\[ R^\prime \text{yn-}SO_2\cdot\text{Hal} \quad \text{(C)}; \]

where

- X is halogen, OH or OCOR';
- Hal is halogen;
- Y is O or S;
W is O, N or S; and

R, R', and R'' are each independently selected from the group consisting of alkyl, aryl, and aralkyl;

to yield protected compounds of formula 5 and diprotected compounds of formula 6,

\[
\begin{align*}
5 & \quad \text{Cl-} \quad \text{N} \\
& \quad \text{H} \\
& \quad \text{N-} \quad \text{N-} \quad \text{O-} \quad \text{PG} \\
\hline
6 & \quad \text{Cl-} \quad \text{N} \\
& \quad \text{H} \\
& \quad \text{N-} \quad \text{N-} \quad \text{O-} \quad \text{PG}
\end{align*}
\]

said protected compounds of formula 5 and diprotected compounds of formula 6 being soluble in said solution;

(ii) hydrolysis, in a suitable solvent, of the protected compounds of formula 5 and the diprotected compounds of formula 6 by using a metal hydroxide or metal carbonate or to yield soluble compounds of formula 1 and soluble protected compounds of formula 7;

\[
\begin{align*}
7 & \quad \text{Cl-} \quad \text{N} \\
& \quad \text{OH} \\
& \quad \text{N-} \quad \text{N-} \quad \text{PG}
\end{align*}
\]

(iii) adding an acid to form an insoluble salt of compound of formula 1, but which acid does not form an insoluble salt of compound of formula 7 and, if still present, compound of formula 4;

(iv) isolating the insoluble salt of compound of formula 1; and
(v) optionally, recovering the compound of formula 1 from its salt.

26. Process according to claim 25 wherein the suitable solvent for hydrolysis is selected from the group consisting of C1 to C6 alcohol, C3-C9 alkyl ketone and cyclic or acyclic C4 to C8 alkyl ether and mixtures thereof.

27. Process according to claim 26, wherein the C1 to C6 alcohol is selected from the group consisting of methanol, ethanol, and propanol.

28. Process according to claim 26, wherein the C3-C9 alkyl ketone is selected from the group consisting of acetone and methyl isobutyl ketone.

29. Process according to claim 26, wherein the cyclic or acyclic C4 to C8 alkyl ether is selected from the group consisting of tetrahydrofuran and methyl tert-butyl ether.

30. Process according to any one of claims 25 to 29 wherein the isolation in step (iv) is done by filtration.

31. Process according to any one of claims 25 to 30 wherein R, R', R* are independently selected from the group consisting of: methyl, ethyl, isopropyl, phenyl and benzyl.

32. The process according to any one of claims 25 to 31 wherein the reactant used at step (i) is \( \text{R}_1\text{O} \text{X} \), wherein R and X are as defined in claim 1.

33. The process according to claim 32 wherein the reactant used at step (i) is a carboxylic acid anhydride or an acyl halide.
34. The process according to claim 33 wherein the reactant used at step (i) is acetic anhydride.

35. The process according to claim 25 wherein the reactant used at step (i) is an acyl chloride.

36. The process according to claim 25 wherein the reactant used at step (i) is acetyl chloride.

37. The process according to claim 25 wherein the metal hydroxide used in step (ii) is lithium hydroxide.

38. The process according to claim 25 wherein the metal hydroxide used in step (ii) is sodium hydroxide.

39. The process according to claim 25 wherein the metal hydroxide used in step (ii) is potassium hydroxide.

40. The process according to claim 25 wherein the metal carbonate used in step (ii) is potassium carbonate.

41. Process according to claims 25 to 40 wherein the acid used is sulfuric acid.

42. Process according to claims 25 to 40 wherein the acid used is phosphoric acid.

43. Process according to claim 25 to 41 wherein the compound of formula 1 is obtained from its sulfate salt.
44. A process for the preparation of highly pure compound of formula 1 or a salt thereof, substantially free of compound of formula 4 wherein said process comprises the following steps:

(i) reacting 4,7-dichloroquinoline of formula 2 and N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine of formula 3 in the presence of a solvent;

(ii) treating the resulting mixture comprising the compound of formula 1 and the compound of formula 4 with a reactant selected from the group consisting of:

\[
\begin{align*}
&\text{R'} \quad \text{X} \\
&\text{Hal} \quad \text{Y} \quad \text{W} \quad \text{R'} \\
&\text{R''} \quad \text{-SO}_2 \cdot \text{Hal}
\end{align*}
\]

wherein \( X \) is halogen, OH or OCOR';
Hal is halogen;
Y is O or S;
W is O, N or S; and
R, R', and R'' are each independently selected from the group consisting of alkyl, aryl, and aralkyl;
to yield protected compounds of formula 5 and diprotected compounds of formula 6,

\[
\begin{align*}
 \text{Cl} & \quad \text{N} & \quad \text{H} & \quad \text{O} \\
\text{5} & \quad \text{N} & \quad \text{H} & \quad \text{O} \\
\text{PG} & \quad \text{PG} & \quad \text{PG} & \quad \text{PG}
\end{align*}
\]

said protected compounds of formula 5 and diprotected compounds of formula 6 being soluble in said solution;

(iii) hydrolysis, in a suitable solvent, of the protected compounds of formula 5 and the diprotected compounds of formula 6 by using a metal hydroxide or metal carbonate to yield compounds of formula 1 and protected compounds of formula 7; and

\[
\begin{align*}
 \text{Cl} & \quad \text{N} & \quad \text{H} & \quad \text{OH} \\
\text{7} & \quad \text{N} & \quad \text{H} & \quad \text{N}
\end{align*}
\]

(iv) adding an acid to form an insoluble salt of compound of formula 1, but which acid does not form an insoluble salt of compound of formula 7 and, if still present, compound of formula 4;

(v) isolating the insoluble salt of compound of formula 1; and

(vi) optionally, recovering the compound of formula 1 from its salt.
45. Process according to claim 44, wherein step (i) is carried out in the presence of an organic solvent which is subsequently removed at higher temperatures.

46. Process according to any one of claims 44 and 45 wherein there is a work-up after step (ii).

47. Process according to claim 44 wherein the suitable solvent for step (i) is selected from the group consisting of methanol, ethanol and isopropanol.

48. Process according to any one of claims 44 to 47 wherein the isolation in step (v) is done by filtration.

49. Process according to any one of claims 44 to 48, wherein the acid used in step (iv) is sulfuric acid and the salt formed is the sulfate salt of the compound of formula 1.

50. Process according to any one of claims 25, 44 and 49, wherein the compound of formula 1 is recovered from the salt of the compound of formula 1.