

METHOD OF SYNTHESIS OF FERROQUINE BY CONVERGENT REDUCTIVE AMINATION

The present invention relates to a new method of synthesis of ferroquine
5 particularly useful for the treatment and/or prevention of malaria.

Malaria is one of the primary infectious causes of mortality in the world and affects annually more than 500 million people, among whom 3 million die each year.

Four types of parasites of the genus *Plasmodium*, carried by Anopheles
10 mosquitoes, spread malaria. *Plasmodium falciparum*, widespread in Africa, is the most virulent parasite among them and is responsible for the deadly forms of the disease.

Among the active principles against *Plasmodium falciparum*, chloroquine is an antimalarial of the family of the 4-aminoquinolines, widely used, but for which resistances have developed since the 1960s. Artemisinin then made its appearance and proves
15 effective against forms of plasmodia resistant to chloroquine. However, since 2006, the WHO noted the risk of resistance of the parasite to this molecule. It was in this same year 2006 that a new molecule, ferroquine (SSR97193), was discovered, displaying efficacy against the strains of *Plasmodium falciparum* resistant to chloroquine described in Malaria Journal 2006, 5:11 and Malaria Journal 2007, 6: 81.

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Ferroquine is an organometallic complex of iron. In particular, it is a derivative of 4-aminoquinoline coupled to a ferrocene nucleus.

Ferroquine, also called ferrocene-chloroquine or ferrochloroquine, corresponds to 7-chloro-4-[(2-N,N-dimethyl-aminomethyl)ferrocenylmethylamino]quinoline. It can be in
25 the form of free base, but also in the form of salt, of hydrate or of solvate (these last being defined as associations or combinations of ferroquine with, respectively, one or more molecules of water or of solvent). Advantageously, ferroquine is used in the form of free base.

Ferroquine of formula (F) in the form of free base and its principal metabolite (Fm)
30 are represented below in **scheme 1**.

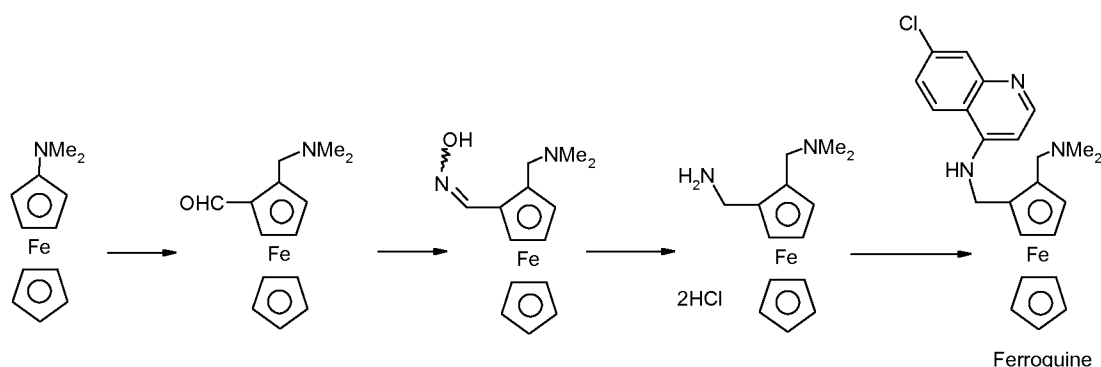
Ferroquine is described in patent WO 96/35698, as well as in scientific articles such as J. Med. Chem., 1997, 40, 3715-3718, Antimicrob. Agents Chemother., 1998, 42, 540-544, J. Org. Chem., 1999, 589, 59-65 and J. Organometallic Chem., 2004, 689, 4678-4682.

Scheme 1

The known method for the manufacture of ferroquine, partially represented in

5 **scheme 2** below, consists in synthesizing firstly 1-[(dimethylamino)methyl]-2-formyl-ferrocene from (dimethylamino)methyl-ferrocene with a yield of about 85%, then in preparing the corresponding intermediate oxime, and finally in carrying out reduction of this oxime which leads to obtaining 1-(aminomethyl)-2-[(dimethylamino)methyl]-ferrocene which can be isolated in the form of dihydrochloride. The yield of synthesis of the

10 dihydrochloride 1-(aminomethyl)-2-[(dimethylamino)methyl]-ferrocene relative to 1-[(dimethylamino)methyl]-2-formyl-ferrocene is 55-65%.

Scheme 2

15 This latter reaction sequence comprises firstly the condensation reaction of 1-[(dimethylamino)methyl]-2-formyl-ferrocene with the reagent hydroxylamine to lead to production of the corresponding oxime. Then, reduction of the oxime function to amine by the metal hydride LiAlH_4 is carried out in rigorously anhydrous medium in order to form after hydrolysis 1-(aminomethyl)-2-[(dimethylamino)methyl]-ferrocene, isolated in the form

20 of dihydrochloride. The latter hereinafter is also called dihydrochloride of diamino

ferrocene which is a salt of 1-(aminomethyl)-2-[(dimethylamino)methyl]-ferrocene, itself hereinafter called diamino ferrocene or diamino ferrocene in the form of free base.

Once diamino ferrocene in the form of free base, or its salt of
5 dihydrochloride SSR244090A is obtained, the latter can be reacted in the presence of (i)
a base, such as for example soda or triethylamine and (ii) of 4,7-dichloroquinoline in
order to synthesize ferroquine by aromatic nucleophilic substitution. This stage of the
synthesis of ferroquine, known and described, is transposable to diamine ferrocene in the
form of free base. The ferroquine thus obtained can then undergo a purification in order
10 to obtain pure ferroquine.

However, there are many drawbacks connected with this method. In fact, the risks
associated with the use of reagents such as hydroxylamine (unstable and explosive) and
 LiAlH_4 (inflammable and very reactive in damp conditions), as well as the use of an
15 intermediate such as the oxime SSR244089, (thermally unstable) do not allow envisaging
the production of ferroquine in adequate conditions of hygiene and safety from an
industrial standpoint.

Moreover, the use of particularly expensive reagents, such as for example LiAlH_4 ,
20 and the low productivity of this method (large number of stages, dilutions) contribute
significantly to the cost of manufacture of Ferroquine. Now, with the aim of permitting
access to ferroquine for the greatest number in poor countries, which moreover have the
greatest need for it, it is essential to minimize the cost of manufacture of an active
principle such as this in order to reduce significantly the cost price of antimalarial
25 treatment.

The applicant has now found a new method of synthesis of ferroquine of formula
(F) or of its metabolite of formula (Fm) making it possible to form said ferroquine or said
metabolite directly from aldehyde-amino ferrocene of formula (III), in which R represents
30 a hydrogen atom or a methyl group (Me), and from 7-chloroquinolin-4-amine.

The method according to the invention therefore consists in coupling the
aldehyde-amino ferrocene of formula (III) with 7-chloroquinolin-4-amine according to a
reaction of reductive amination, called convergent, represented in scheme 3.

Scheme 3

The reaction of reductive amination therefore takes place in a single stage but in
5 several steps:

- Firstly, 7-chloroquinolin-4-amine reacts with the carbonyl function of aldehyde-amino ferrocene of formula (III), to form an imine function (which can be protonated to iminium if the reaction mixture is acid) according to a reaction of condensation, with liberation of a molecule of water;
- 10 • Secondly, the imine function of the imino ferrocene intermediate of formula (II), or if applicable of the iminium, is then reduced by a hydride donor.
- Thirdly, the reaction mixture is hydrolyzed in the presence of an aqueous solution of ammonia or else of citric acid, in order to destroy the excess hydride employed and permit isolation of ferroquine (F) or of its metabolite (Fm).

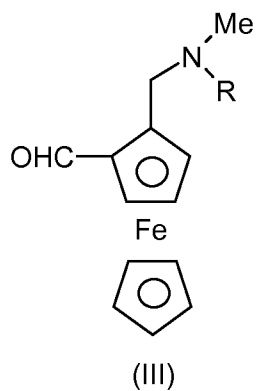
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The imino ferrocene intermediate of formula (II) or the corresponding iminium, not shown, does not to be isolated in contrast to the oxime-amino ferrocene (SSR244089) of the prior art represented above. The reaction of convergent reductive amination according to the present invention can therefore be carried out as a so-called *one pot*
20 process. Moreover, the imino ferrocene intermediate of formula (II) not being stable in conditions of analysis by liquid phase chromatography, its formation can be followed qualitatively by thin-layer chromatography or *in situ* by Infrared analysis.

Rev 1 The invention therefore relates to a method of synthesis of ferroquine of formula (F) or of its metabolite of formula (Fm):

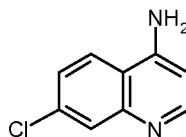
comprising a reaction of reductive amination, in which reaction:

(i) the aldehyde-amino ferrocene of formula (III),

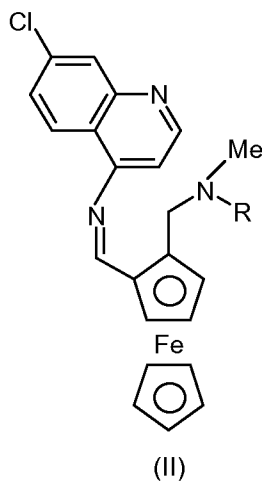


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in which R represents a hydrogen atom or a methyl group, is condensed with 7-chloroquinolin-4-amine



(ii) the product of condensation thus obtained of formula (II),



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is reduced,

with R representing a hydrogen atom or a methyl group,
(iii) the reaction mixture is hydrolyzed.

After hydrolysis, the ferroquine of formula (F) and its metabolite of formula (Fm) are isolated.

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Rev 2 According to the present invention, said compounds 7-chloroquinolin-4-amine and aldehyde-amino ferrocene of formula (III) are advantageously present in stoichiometric proportion.

- 10 Rev 3 The reaction of reductive amination according to the invention takes place in the presence of at least one reaction solvent suitable both for said stage of condensation and for said stage of reduction. This reaction solvent is selected from the protic and aprotic solvents, such as for example ethanol, isopropanol, toluene, THF, dichloromethane and mixtures thereof. The protic solvents are particularly advantageous.
- 15 We may thus mention ethanol and/or isopropanol, advantageously isopropanol, as reaction solvent permitting particularly advantageous yields of reductive amination to be obtained.

The stage of condensation

- 20 Rev 4 The stage of condensation of 7-chloroquinolin-4-amine with the aldehyde-amino ferrocene of formula (III) takes place in the presence of:
- at least one Lewis acid, or
 - at least one Brønsted base or a Brønsted acid.

- This stage can preferably take place under azeotropic distillation of the reaction
- 25 solvent of said stage of condensation or in the presence of at least one drying agent.

- The stage of condensation of 7-chloroquinolin-4-amine with aldehyde-amino ferrocene of formula (III) can take place in the presence of at least one Lewis acid such as $\text{Ti}(\text{OiPr})_4$, TiCl_4 , FeCl_3 , ZnCl_2 , AlCl_3 and BF_3 . The Lewis acid BF_3 can be in the form of a
- 30 complex such as for example $\text{BF}_3 \cdot \text{OEt}_2$ and $\text{BF}_3 \cdot \text{S}(\text{Me})_2$.

Rev 5 Thus, in the method according to the invention, the Lewis acid is selected from $\text{Ti}(\text{OiPr})_4$, TiCl_4 , FeCl_3 , ZnCl_2 , AlCl_3 , BF_3 , $\text{BF}_3 \cdot \text{OEt}_2$ and $\text{BF}_3 \cdot \text{S}(\text{Me})_2$.

Rev 6 According to a particularly advantageous embodiment, the Lewis acid is $\text{Ti}(\text{OiPr})_4$.

- 35 Rev 7 The Lewis acid can be used in stoichiometric amount or in excess.

Rev 8 Advantageously, the Lewis acid is used in an amount between 1 and 2 equivalents, even more advantageously the Lewis acid is present at the level of 1 equivalent.

According to a particularly advantageous embodiment of the stage of
5 condensation in the presence of the Lewis acid $\text{Ti}(\text{OiPr})_4$, 7-chloroquinolin-4-amine, the aldehyde-amino ferrocene of formula (III) and said Lewis acid are present at a level of 1 equivalent each. In this case, the reaction solvent is preferably isopropanol.

Rev 9 The stage of condensation of 7-chloroquinolin-4-amine with aldehyde-amino ferrocene of formula (III) can take place in the presence of at least one Brønsted acid or a
10 Brønsted base selected from acetic acid, trifluoroacetic acid, methanesulfonic acid, para-toluenesulfonic acid, H_2SO_4 , H_3PO_4 , HNO_3 , piperidine and proline.

Rev 10 Advantageously it is para-toluenesulfonic acid or piperidine, even more advantageously it is para-toluenesulfonic acid.

According to an embodiment particularly relating to the stage of condensation in
15 the presence of a Brønsted acid, advantageously para-toluenesulfonic acid, said stage of condensation takes place under azeotropic distillation of the reaction solvent. In this case, the reaction solvent is preferably toluene.

Since the stage of condensation of an equivalent of 7-chloroquinolin-4-amine with
20 an equivalent of aldehyde-amino ferrocene of formula (III) is accompanied by the liberation of an equivalent of water, it is conceivable to trap the water thus formed by means of a drying agent or to evacuate this water from the reaction mixture by carrying out an azeotropic distillation with a suitable reaction solvent such as for example the protic and aprotic solvents enumerated above. This azeotropic distillation can be effected,
25 for example by means of a Dean-Stark, during said stage of condensation, with the aim of displacing the equilibrium toward formation of the imino ferrocene intermediate (II), or iminium if applicable. Said azeotropic distillation can optionally take place at reduced pressure, for example, at a pressure in the range from 100 to 300 mbar.

The stage of condensation of 7-chloroquinolin-4-amine with the aldehyde-amino
30 ferrocene of formula (III) can therefore take place in the presence of at least one drying agent or Rev 11 can take place under azeotropic distillation of the reaction solvent from said reaction of condensation.

Rev 12 As drying agent mention may be made of alumina, a molecular sieve $3\text{\AA}$, MgSO_4 and Na_2SO_4 .

35 Rev 13 Advantageously, it is a molecular sieve $3\text{\AA}$.

The stage of reduction

The stage of reduction of the intermediate obtained at the end of the stage of condensation between 7-chloroquinolin-4-amine with the aldehyde-amino ferrocene of formula (III), Rev 14 is carried out in the presence of at least one hydride donor.

5 The hydride donors known in the state of the art, particularly advantageous for said reaction of reduction, are hydrogen in the presence of a catalyst (transition metal, optionally in the form of complex) and metal hydrides. The metal hydrides are selected from borohydrides of sodium, of potassium, of lithium or of zinc and are optionally coupled to at least one additive selected from LiCl, CaCl₂, MgCl₂, ZnCl₂ and NEt₃. Said
10 borohydrides of sodium, of potassium, of lithium or of zinc are selected from NaBH(OAc)₃, NaBH₃CN, NaBH₄, KBH₄, LiBH₄ and Zn(BH₄)₂ coupled or not to said additive.

NaBH₄, KBH₄ and LiBH₄, coupled or not to said additive prove particularly advantageous for carrying out the reaction of reduction of the imino ferrocene
15 intermediate of formula (II), if necessary of the corresponding iminium, not shown.

Hydrolysis

Rev 24 The stage of hydrolysis takes place in the presence of an aqueous solution of ammonia or of citric acid.

20 When Ti(OiPr)₄ is used as Lewis acid during the stage of condensation, hydrolysis of the reaction mixture in the presence of an aqueous solution of citric acid is a particularly advantageous embodiment since it permits removing the titanium salts at the level of the aqueous phases and thus permits avoiding very difficult filtration of these salts.

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Rev 19 According to one embodiment of the method of the invention, the stage of condensation takes place in the presence of toluene as reaction solvent, optionally under azeotropic distillation, for example by means of a Dean-Stark. In this embodiment, the stage of reduction preferably takes place in the presence of NaBH₄. Rev 19

30 Rev 20 According to one embodiment of the method of the invention, the stage of condensation takes place in the presence of molecular sieve 3Å as drying agent. In this embodiment, the stage of reduction preferably takes place in the presence of NaBH₄.

Rev 21 According to one embodiment of the method of the invention concerning the stage of condensation in the presence of a Brønsted acid, advantageously para-toluenesulfonic
35 acid, said stage of condensation takes place under azeotropic distillation of the reaction solvent. This solvent is advantageously toluene. In this embodiment, the reaction of reduction preferably takes place in the presence of NaBH₄.

According to one embodiment of the method of the invention concerning the stage of condensation in the presence of toluene as reaction solvent, said stage of condensation takes place under azeotropic distillation. In this embodiment, the stage of reduction preferably takes place in the presence of NaBH_4 .

- 5 According to one embodiment of the method of the invention concerning the stage of condensation in the presence of a Lewis acid, advantageously titanium tetra-isopropylate, Rev 22 the reaction solvent is preferably isopropanol.

According to one embodiment of the method of the invention, the stage of condensation takes place in the presence of 1 to 2 equivalents of $\text{Ti}(\text{OiPr})_4$ in ethanol
10 and/or isopropanol as reaction solvent. In this embodiment, the stage of reduction preferably takes place in the presence of LiBH_4 and/or of NaBH_4 and/or of KBH_4 and the stage of hydrolysis preferably takes place in the presence of an aqueous solution of citric acid.

Rev 23 According to one embodiment, the stage of condensation takes place in
15 the presence of 1 equivalent of $\text{Ti}(\text{OiPr})_4$ in ethanol and/or isopropanol as reaction solvent and the stage of reduction preferably takes place in the presence of LiBH_4 and/or of KBH_4 .

At the end of this reaction of reductive amination, ferroquine (F) or its metabolite
20 (Fm) is formed in the form of free base or of salt, for example of salt of dihydrochloride.

Ferroquine in the crude form can be isolated and purified according to techniques known by a person skilled in the art. The isolation of crude ferroquine at the end of the method of synthesis according to the invention, can be done by crystallization in a
25 suitable solvent. Acetone, toluene, isopropanol or methyl ethyl ketone may be mentioned. Advantageously, it is acetone or toluene, even more advantageously it is toluene.

The method of synthesis according to the invention has the advantage relative to the prior art of being shorter if we consider the number of reaction stages and having
30 better performance in terms of yield and productivity. Accordingly, it makes it possible to lower the final cost price of ferroquine through (i) the use of inexpensive reagents, (ii) a reduction in the number of reaction stages relative to the route of synthesis currently used and represented in scheme 1 above and (iii) obtaining particularly advantageous reaction yields: the isolated yield of crude ferroquine is about 70-75 mol% relative to the starting
35 aldehyde-amino ferrocene of formula (III).

Moreover, it offers the advantage of being safer with the absence of reagents or intermediates that may prove dangerous to handle.

The invention will now be described in more detail.

The following procedures and examples describe the preparation of intermediates of ferroquine and of ferroquine according to the invention. These procedures and
5 examples are not limiting and their only purpose is to illustrate the present invention.

In the procedures and examples below:

- The NMR (nuclear magnetic resonance) spectra are obtained with a Fourier transform spectrometer (BRUKER), at a temperature of 300°K (exchangeable protons not recorded);

- 10 - s = singlet,
 - d = doublet,
 - m = multiplet,
 - br = broad signal,
 - t = triplet,
15 - q = quadruplet,
 - DMSO-d₆ = deuterated dimethylsulfoxide,
 - CDCl₃ = deuterated chloroform;

The NMR spectra confirm the structures of the compounds obtained according to examples below.

20

In the examples given below, the following abbreviations are used:

MTBE: Tert-Butyl-Methyl-Ether

LiBH₄: lithium borohydride

NaBH₄: sodium borohydride

25 KBH₄: potassium borohydride

Ti(OiPr)₄: tetraisopropoxy-titanium

DMF: N,N-dimethylformamide

4,7-DCQ: 7-chloroquinolin-4-amine

MeOH: methanol

30 EtOH: ethanol

MEK: methyl ethyl ketone

tBuLi: t-butyllithium

DCM: dichloromethane

RT: room temperature

35 pTSA: para-toluenesulfonic acid

MP: melting point in °C

The mixtures of solvents are quantified in volume ratios, ml signifying milliliter.

In the following procedures, the starting compounds and the reagents, when their method of preparation is not described, are commercially available or are described in the literature, or else can be prepared according to methods described or known by a person skilled in the art.

PREPARATIONS

1. Preparation of the compounds of formula (III)

Preparation of 1-[(dimethylamino)methyl]-2-formyl-ferrocene.

10 Charge an inertized reactor with 39.6 g of 1-[(dimethylamino)methyl]-ferrocene and 360 ml of MTBE. Distil about 160 ml of MTBE (4V) at atmospheric pressure. Cool the solution to -10°C and slowly add 98.2 ml of a solution of t-BuLi in heptane (titer 16%). Stir the reaction mixture at -10°C for 2 hours and then at 0°C, slowly add 25.2 ml of DMF. Continue stirring the reaction mixture at 20°C for 2 hours then at 5°C, slowly add 135 ml
15 of 1.5N aqueous HCl. Continue stirring the reaction mixture at 5°C for 30 min, then at 20°C for 30 min. Leave the reaction mixture to settle and withdraw the aqueous phase then the MTBE phase. Counter-extract the aqueous phase with 125 ml of MTBE. Filter the combined MTBE phases on activated charcoal then concentrate to 120 ml under vacuum. Add 80 ml of isopropanol then distil 420 ml of solvent to constant volume, under
20 vacuum, by regular addition of isopropanol. At the end of distillation, dilute the reaction mixture to 280 ml with isopropanol. 39.9 g of the expected compound is obtained in solution in isopropanol.

2. Preparation of 7-chloroquinolin-4-amine

2.1 Preparation of 7-chloroquinolin-4-amine.

25 Stir a mixture of 100 g of 4,7-DCQ and 1 liter of 5% solution of ammonia in methanol at 160°C for at least 15 hours. After complete conversion of the 4,7-DCQ, concentrate the reaction mixture to 300 ml then slowly add 400 ml of a dilute aqueous solution (3.2%) of soda. Filter the suspension on a Büchner and rinse the cake with
30 100 ml of a water / MeOH mixture (70/30, v/v), then with 100 ml of water. Dry the beige solid in a stove at 100°C under vacuum. 85.5 g of the expected compound is obtained.
MP = 187°C (with decomposition).

2.2 Purification of 7-chloroquinolin-4-amine.

35 Heat a mixture of 85 g of the compound obtained in the preceding stage and 550 ml of toluene under reflux until complete dissolution then cooled slowly to 20°C. Filter the suspension on a Büchner. Rinse the cake with 85 ml of toluene then dry in a stove at

100°C under vacuum. 76.8 g of the expected product is obtained.

EXAMPLES

The following procedures and examples describe the preparation of crude
5 ferroquine from 7-chloroquinolin-4-amine and of 1-[(dimethylamino)methyl]-2-formyl-ferrocene (example 1 to 6) as well as the purification of said crude ferroquine (example 7).

Example 1:

10 Heat a mixture of 0.5 g of the compound from preparation 2.2, 0.76 g of the compound from preparation 1, 25 mg of ApTS and 5 ml of toluene under reflux and remove the water by azeotropic distillation for 16 h. Concentrate the reaction mixture under vacuum and take up in 10 ml of absolute EtOH. Add 0.21 g of NaBH₄ and stir the reaction mixture for 16 h. Concentrate the reaction mixture under vacuum then take up in
15 40 ml DCM and a mixture of 20 ml of water and 2 ml of ammonia 25%. Leave the mixture to settle then extract the aqueous phase 4 times in 20 ml of DCM. Combine and concentrate the organic phases under vacuum, and crystallize the residue in 20 ml of acetone. Filter the solid cold on a Büchner, rinse with 2 times 5 ml of cold acetone then dry in a stove under vacuum. 0.37 g of the expected compound is obtained. A second
20 crystallization stream is recovered from the mother liquor and the wash liquor, from which crystallization stream 0.11 g of the expected compound is obtained.

MP = 197°C.

¹H-NMR (DMSO-d₆, 500 MHz): 2.15 (s, CH₃, 6H), 2.92 (d, NCH₂, 1H), 3.82 (d, NCH₂, 1H), 4.05 (t, CH, 1H), 4.17 (s, CH, 5H), 4.19 (dd, CH, 1H), 4.28 (dd, NCH₂, 1H), 4.31 (dd,
25 CH, 1H), 4.38 (dd, NCH₂, 1H), 6.67 (d, CH, 1H) 7.48 (dd, CH, 1H), 7.75 (dd, NH, 1H), 7.78 (d, CH, 1H), 7.85 (d, CH, 1H), 8.42 (d, CH, 1H).

Example 2:

Put 3.3 g of the compound from preparation 2.2, 5 g of the compound from
30 preparation 1 and 50 ml of isopropanol in a flask. Add 10.9 ml of Ti(OiPr)₄. Stir the reaction mixture at RT for 24h. Cool the reaction mixture to 0°C and add 0.4 g of LiBH₄ in portions at 0°C. Stir the reaction mixture allowing the temperature to rise to RT for 16h, then dilute with 50 ml of DCM. Pour this solution onto 40 ml of an aqueous solution of ammonia at 12.5%. After 30 minutes of stirring, filter the suspension on Clarcel[®]. Then
35 rinse the cake with 6 times 20 ml of DCM. Wash the organic phase with 30 ml of 1N soda then concentrate under vacuum to 40 ml. Effect a change of solvent DCM/acetone by distillation at constant volume. Cool the suspension under reflux of the ketone at 5°C.

Filter the solid on a Büchner, rinse with 2 times 9 ml of cold acetone and dry in a stove under vacuum. 4.2 g of the expected compound is obtained.

Example 3:

- 5 Put 13.4 g of the compound from preparation 2.2 and 152.2 g of the compound from preparation 1 at 13.5% in isopropanol in a reactor. Add 42.8 g of $\text{Ti}(\text{OiPr})_4$. Stir the reaction mixture at 25°C for at least 20h. Then put 5.7 g of finely divided NaBH_4 and 60 ml of isopropanol in a second reactor and cool to 0°C. Slowly pour the solution of imine intermediate onto this suspension of NaBH_4 at 0°C. Stir the reaction mixture at
- 10 25°C for at least 20 h, concentrate under vacuum then dilute with 150 ml of DCM. Cool the solution obtained to 0°C then hydrolyze at 0°C with 60 ml of an aqueous solution of ammonia at 25%. Return the suspension to 20°C then filter on Clartex. Rinse the cake with 5 times 20 ml of DCM. Concentrate the organic phase under vacuum to 200 ml. Effect a change of solvent DCM/acetone by distillation at constant volume. Cool the
- 15 suspension under reflux of the ketone at 5°C. Filter the solid on a Büchner, rinse with 2 times 20 ml of cold acetone and dry in a stove under vacuum. 23.1 g of the expected compound is obtained.

Example 4:

- 20 Put 13.2 g of the compound from preparation 2.2 and 125 g of a 16% solution of the compound from preparation 1 in isopropanol in a reactor. Add 42.0 g of $\text{Ti}(\text{OiPr})_4$. Stir the reaction mixture at 25°C for at least 20 hours. Put 8.0 g of KBH_4 and 60 ml of isopropanol in a second reactor and cool to 0°C. Slowly pour the solution of imine intermediate onto this suspension of KBH_4 at 0°C. Stir the reaction mixture at 25°C for at
- 25 least 20 h, concentrate under vacuum then dilute with 130 ml of DCM. Cool the solution obtained to 0°C then hydrolyze at 0°C with 60 ml of an aqueous solution of ammonia at 25%. Allow the temperature of the suspension to rise to 20°C then filter on textile fiber; rinse the cake with 5 times 20 ml of DCM. Concentrate the organic phase under vacuum to 100 ml. Effect a change of solvent DCM/acetone by distillation at constant volume.
- 30 Cool the suspension under reflux of the ketone at 5°C. Filter the solid on a Büchner, rinse with 2 times 20 ml of cold acetone and dry in a stove under vacuum. 23.1 g of the expected compound is obtained.

Example 5:

- 35 Put 26.3 g of the compound from preparation 2.2 and 227 g of a solution of the compound from preparation 1 at 17.4% in isopropanol in a reactor. Add 83.8 g of $\text{Ti}(\text{OiPr})_4$. Stir the reaction mixture at 40°C for at least 5 hours.

Put 15.9 g of KBH_4 and 120 ml of isopropanol in a second reactor and cool to 0°C . Slowly pour the solution of imine intermediate onto this suspension of KBH_4 at 0°C . Then stir the reaction mixture at 25°C for at least 20 h, then heat at 50°C for at least 3 h. Hydrolyze the reaction mixture at 20°C by slowly adding 500 g of an aqueous solution of citric acid at 11.3%, then 75 g of an aqueous solution of ammonia at 20%. Add 400 ml of toluene, stir the reaction mixture at 50°C for 30 min. Leave the organic phase to settle at 50°C , wash at 50°C with 3 times 120 ml of water then filter on activated charcoal. Concentrate the organic phase under vacuum to 400 ml, then distil under vacuum to constant volume by adding 1 liter of toluene. Heat the toluene phase at 90°C until completely dissolved then cool to 5°C . Filter the solid on a Büchner, rinse with 40 ml of cold MEK and dry in a stove under vacuum. 47.5 g of the expected compound is obtained.

Example 6:

Put 26.3 g of the compound from preparation 2.2 and 217 g of a solution of the compound from preparation 1 at 18.4% in isopropanol in a reactor. Add 41.9 g of $\text{Ti}(\text{OiPr})_4$. Stir the reaction mixture at 40°C for at least 8 h. Put 15.9 g of KBH_4 and 120 ml of isopropanol in a second reactor and cool to 0°C . Slowly pour the solution of imine intermediate onto this suspension of KBH_4 at 0°C . Stir the reaction mixture at 20°C for at least 20 h, then heat at 50°C for at least 3 h. Hydrolyze the reaction mixture at 20°C by slowly adding 320 g of an aqueous solution of citric acid at 13.2%, then 56 g of an aqueous solution of ammonia at 20%. Add 400 ml of toluene, then stir the reaction mixture at 50°C for 30 min. Leave the organic phase to settle at 50°C , wash at 50°C with 3 times 120 ml of water then filter on activated charcoal. Concentrate the organic phase under vacuum to 400 ml, then distil under vacuum to constant volume by adding 1 liter of toluene. Heat the toluene phase at 90°C until completely dissolved then cool to 5°C . Filter the solid on a Büchner, rinse with 2 times 40 ml of cold MEK and dry in a stove under vacuum. 50.7 g of the expected compound is obtained.

Example 7:

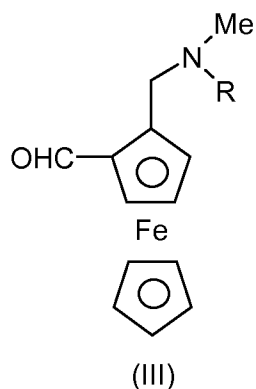
Put 24.0 g of crude ferroquine and 345 ml of MEK in a reactor and heat to 78°C . Cool the solution to 67°C and initiate by adding 0.24 g of ferroquine in suspension in 1.2 ml MEK. Stir the mixture for 1 hour at 67°C then cool to 10°C . Filter the suspension at 10°C on a Büchner then wash the cake with 48 ml of MEK. Dry the solid in a stove under vacuum. 20.2 g of the expected compound is obtained.

CLAIMS

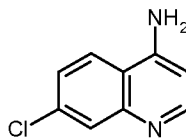
1. A method of synthesis of ferroquine of formula (F) or of its metabolite of
 5 formula (Fm):

comprising a reaction of reductive amination, in which reaction:

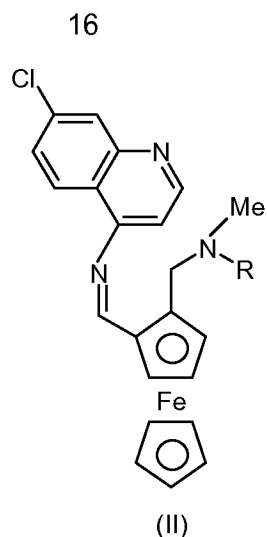
(i) the aldehyde-amino ferrocene of formula (III),



in which R represents a hydrogen atom or a methyl group, is condensed with 7-chloroquinolin-4-amine



(ii) the product of condensation thus obtained of formula (II),



is reduced,

with R representing a hydrogen atom or a methyl group,

(iii) the reaction mixture is hydrolyzed prior to isolation of the ferroquine of formula (F) or of its metabolite of formula (Fm).

2. The method as claimed in claim 1, wherein said compounds 7-chloroquinolin-4-amine and aldehyde-amino ferrocene of formula (III) are in stoichiometric proportion.

3. The method as claimed in either one of claims 1 and 2, characterized in that the reaction of reductive amination takes place in the presence of at least one reaction solvent selected from ethanol, isopropanol, toluene, THF, dichloromethane and mixtures thereof.

4. The method as claimed in any one of claims 1 to 3, characterized in that the stage of condensation of 7-chloroquinolin-4-amine with aldehyde-amino ferrocene of formula (III) takes place in the presence of:

- at least one Lewis acid, or
- at least one base or a Brønsted acid.

5. The method as claimed in any one of claims 1 to 4, characterized in that the stage of condensation of 7-chloroquinolin-4-amine with aldehyde-amino ferrocene of formula (III) takes place under azeotropic distillation of the reaction solvent of said stage of condensation or in the presence of at least one drying agent.

6. The method as claimed in claim 4, characterized in that the Lewis acid is

selected from $\text{Ti}(\text{OiPr})_4$, TiCl_4 , FeCl_3 , ZnCl_2 , AlCl_3 , BF_3 , $\text{BF}_3\cdot\text{OEt}_2$ and $\text{BF}_3\cdot\text{S}(\text{Me})_2$.

- 5 7. The method as claimed in claim 6, characterized in that the Lewis acid is $\text{Ti}(\text{OiPr})_4$.
8. The method as claimed in any one of claims 4 to 7, characterized in that the Lewis acid is used in stoichiometric amount or in excess.
- 10 9. The method as claimed in any one of claims 4 to 8, characterized in that the Lewis acid is used in an amount between 1 and 2 equivalents.
- 15 10. The method as claimed in claim 4, characterized in that the stage of condensation takes place in the presence of at least one Brønsted acid or a Brønsted base selected from acetic acid, trifluoroacetic acid, methanesulfonic acid, para-toluenesulfonic acid, H_2SO_4 , H_3PO_4 , HNO_3 , piperidine and proline.
- 20 11. The method as claimed in claim 10, characterized in that the stage of condensation takes place in the presence of para-toluenesulfonic acid or of piperidine.
12. The method as claimed in claim 5, characterized in that the drying agent is selected from alumina, molecular sieve 3Å, MgSO_4 and Na_2SO_4 .
- 25 13. The method as claimed in any one of claims 1 to 12, characterized in that the stage of reduction takes place in the presence of at least one hydride donor selected from hydrogen in the presence of a catalyst and metal hydrides.
- 30 14. The method as claimed in claim 13, characterized in that the metal hydrides are selected from the borohydrides of sodium, of potassium, of lithium or of zinc, coupled or not to at least one additive selected from LiCl , CaCl_2 , MgCl_2 , ZnCl_2 and NEt_3 .
- 35 15. The method as claimed in either of claims 13 and 14, characterized in that the borohydrides of sodium, of potassium, of lithium or of zinc are selected from $\text{NaBH}(\text{OAc})_3$, NaBH_3CN , NaBH_4 , KBH_4 , LiBH_4 and $\text{Zn}(\text{BH}_4)_2$, coupled or not to said additive.

- 5
16. The method as claimed in claim 15, characterized in that the reduction reaction takes place in the presence of NaBH_4 , KBH_4 and LiBH_4 , coupled or not to said additive.
17. The method as claimed in any one of claims 1 to 5 and characterized in that the stage of condensation takes place in the presence of para-toluenesulfonic acid, under azeotropic distillation of the reaction solvent.
- 10 18. The method as claimed in claim 17, characterized in that the stage of condensation takes place in the presence of toluene.
19. The method as claimed in either one of claims 17 and 18 characterized in that the stage of reduction takes place in the presence of NaBH_4 .
- 15 20. The method as claimed in any one of claims 1 to 5 characterized in that the stage of condensation takes place in the presence of titanium tetra-isopropylate and of isopropanol as reaction solvent.
- 20 21. The method as claimed in any one of claims 1 to 5, characterized in that the stage of condensation takes place in the presence of 1 equivalent of $\text{Ti}(\text{OiPr})_4$ in ethanol and/or isopropanol as reaction solvent and the stage of reduction takes place in the presence of LiBH_4 and/or of KBH_4 .
- 25 22. The method as claimed in any one of claims 1 to 5, characterized in that the stage of hydrolysis takes place in the presence of an aqueous solution of citric acid.

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07F17/02

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/35698 A1 (UNIV LILLE SCIENCES TECH [FR]; BROCARD JACQUES [FR]; LEBIBI JACQUES [G] 14 November 1996 (1996-11-14) cited in the application Synthèse 2; page 10 Synthèse 3; page 11 -----	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 July 2011

Date of mailing of the international search report

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