Tutor

Dr. Jose Maria Gutiérrez González
Departament d'Enginyeria Química i Química Analítica

Grau en Enginyeria Química

Treball Final de Grau

Design of a batch plant for quinoline derivatives manufacture

Josep Sastre Galmés

January 2019

UNIVERSITAT DE BARCELONA

If you are going through hell, keep going.

Winston Churchill

Agrair al Dr. Jose Maria Gutiérrez pel seguiment del projecte i la disposició per ajudar.

Gràcies, com no podria ser, a la meva família per donar-me l'oportunitat d'estudiar i pel suport durant tota la vida. Als amics, per ser-hi quan es necessiten.

Per últim, gràcies als Enginyers de futur per amenitzar l'estància a la península i per facilitar l'aprenentatge durant aquests anys.

CONTENTS

SUMMARY

Quinoline is a heterocyclic compound with derivatives having a wide range of applications in the pharmaceutical industry. Traditionally, quinolines have been synthesized from anilines. Batch plants are used due to their flexibility in the production of different chemicals. Moreover, demand of the market does not justify the need of a continuous supply of quinolines, so it will be produced in batches to control which quinoline derivative is needed.

The main objective of this project is to design a batch plant to produce various quinoline derivatives departing from a laboratory recipe to synthesize a single derivative. Design has been done based on one derivative, but others could be introduced thanks to the flexibility of both quinoline and process. Quinoline traditional synthesis are similar, departing from a simple aniline. Manufacture process from the patents are flexible because more than one derivative can be produced from a similar reaction path.

A study on quinoline derivatives manufacture patents has been conducted to find a suitable process that can be scaled up. Once an appropriate recipe has been found, it has been introduced in Aspen Batch Process Developer® and brought from laboratory to an industrial scale. In order to get to this industrial scale, quinoline derivative production has been raised from 29 g to 70 kg and new equipment units of the process have been selected analysing their size utilization and occupancy time.

To implement campaign schedule, total amount of quinoline derivative has been fixed to 2000 kg. Batch number and its size have been studied to find the combination with a shorter total time.

Optimal campaign has been found to be 21 batches of 97.32 kg to produce 2000 kg of quinoline derivative in 22.5 days.

Keywords: Batch process, quinoline, scheduling, Aspen

RESUM

La quinolina és un compost heterocíclic amb derivats que tenen varies aplicacions a l'àmbit de la indústria farmacèutica. Tradicionalment, aquests derivats s'han sintetitzat a partir d'anilines. S'utilitzaran plantes en discontinu degut a la seva flexibilitat per produir diferents substàncies. A més, la demanda de mercat no justifica la necessitat de tenir un subministrament continu d'un cert derivat, per tant es durà a terme a una planta amb lots per a poder controlar quin compost es necessita.

L'objectiu principal és dissenyar una planta en discontinu per a la producció de diferent derivats de la quinolina a partir d'una recepta de laboratori. El disseny s'ha fet a partir d'un derivat concret, però es podria ampliar a diversos degut a la flexibilitat de la síntesis de la quinolina i la del propi procés. Les síntesis tradicionals de quinolines utilitzen anilines com a reactant comú, i en el cas del propi procés seleccionat, es podrien produir diverses quinolines amb unes reaccions similars.

S'han estudiat les patents de la producció de quinolines per trobar una recepta base pel projecte que es pugui escalar. Una vegada ha estat escollit, s'ha introduït a l'Aspen Batch Process Developer® per escalar el procés d'escala laboratori fins a industrial. Per arribar a aquesta nova escala, la producció del derivat de la quinolina ha augmentat de 29 g a 70 kg. Els equips s'han canviat tenint en compte paràmetres com el percentatge de volum utilitzat i el temps total d'utilització.

Per implementar el calendari de la campanya, s'ha fixat la producció total del derivat de la quinolina a 2000 kg, trobant el número de lots i els kilograms per lot que redueixen el temps total.

La combinació òptima s'ha trobat a 21 lots de 97.32 kg per produir 2000 kg del derivat de la quinolina en 22.5 dies.

Paraules clau: Processos en discontinu, quinolina, scheduling, Aspen

1. INTRODUCTION

Quinolines are important substances due to their pharmaceutical applications. Synthesis of different quinolines are sometimes similar, so it can be possible to design a plant to manufacture various quinoline compounds.

Manufacture of quinoline derivatives are optimally made in a batch plant because pharmaceutical industry requires less production and more flexibility than other industrial areas.

Given the objective of this work, the design of a batch plant for the manufacture of quinolines, in this chapter, the main characteristics of the quinolines are described, in a first section, and, in a second section, the main peculiarities of batch plants are introduced in order to take them into account in the design of the manufacturing process for quinolines

1.1. QUINOLINE

1.1.1. Chemical definition

Quinoline is a heterocyclic aromatic organic compound with the chemical formula C_9H_7N and a molecular weight of 129.16 g/mol. Quinoline is the preferred IUPAC name but it can also be named 1-Benzopyridine or 1-Azanaphtalene. It has the following structural formula:

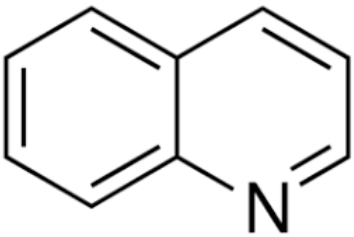


Figure 1. Molecular structure of quinoline

It is a colourless hygroscopic liquid with a characteristic odour that turns brown on exposure to light. This substance has a density of 1.095 kg/m^3, with a boiling point of 238ºC and melting point of -15ºC at atmospheric pressure. (1)

Quinoline is soluble in hot water and most organic compounds. Due to this solubility in water, it has a significant potential for mobility in the environment, which could result into water contamination. A way to avoid this contamination would be degradating quinoline with certain fit microorganisms such as Rhodococcus species, isolated from soil and paper mill sludge. (2)

Short term inhalation of quinoline vapours irritates the eyes, nose, and throat and might cause headaches, dizziness and nausea. It is moderately toxic by skin contact. Quinoline can be found in alcoholic beverages, various plants from Mentha species and in crude oil within the virgin diesel fraction. Nevertheless, its fraction is insignificant.

It was first extracted from coal tar (by-product of the production of coke and coal gas from coal) by Friedlieb Ferdinand Runge in 1834. (3)

1.1.2. Properties and uses

Basic quinoline does not have any remarkable direct application, it is mainly used to produce its derivatives, that will be called just quinolines along this project.

Quinolines have a wide range of biological and pharmacological activity.(4) Principal application of these derivatives has found to be in the treatment of solid **tumours**, especially quinoline-3-carboxylic acid derivatives and amido-anilinoquinolines. (5)

Bisquinolines, compounds with two quinoline groups, possess a degree of **antimalarial** activity against both chloroquine-resistant and chloroquine-sensitive parasites. Other quinoline compounds have also been found to be successful in malaria treatment. (6)

4-substituted-7-trifluoromethylquinolines have a good **analgesic activity** related to their nitric oxide releasing properties.(7) 2-(Furan-2-yl)-4-phenoxy-quinoline derivatives are inhibitors of lysozyme and β-glucuronidase release, working as **anti-inflammatory**. (8)

Phenoxy substituted quinolines have been synthesized with a fair amount of **anti-bacterial** activity.(9) 7-chloro-quinoline derivatives have been found to be effective against multi-drug resistant tuberculosis. (10)

Certain tetrahydroquinolines present **antifungal** activities, especially against *Candida albicans* and *Fusarium oxysporum*.(11) Anilidoquinoline derivatives have activity against encephalitis **virus** (12) and desfluoroquinolines are used in HIV treatment.(13)

2,4-arylquinolines are used against nematode *Haemonchus contortus*, a parasitic worm. It maintains its activity in strains of *H. contortus* resistant to other treatments such as levamisole, ivermectin or thiabendazole. (14)

Aside from its applications in the pharmacological industry, one quinoline derivative is used as a dye. Quinoline Yellow (Sodium 2(1,3-dioxoindan-2-yl)quinolinedisulfonate)(15) is a greenish yellow additive designated in Europe as E104. It is usually added to food such as juices or sorbets and in cosmetics, principally hair products and perfume. This colorant is banned for certain uses in the United States because it is believed to have caused dermatitis in some cases. (16)

1.1.3. Synthesis

As it was said before, quinoline was first extracted from coal tar, the principal líquid product resulting from the carbonization of coal. However, due to their low fraction it will have to be produced synthetically.

Quinolines have been synthesized from anilines since the late 1800s via named reactions. In the next figure, going clockwise from top:

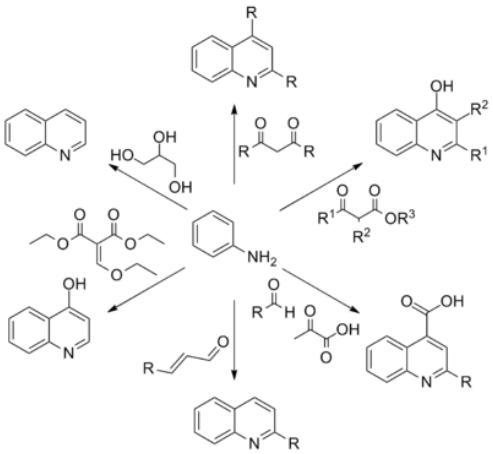


Figure 2. Quinoline named synthesis (retrieved from Project Osprey).

- Combes synthesis, condensation of unsubstituted anilines with β-diketones, forming the final quinoline after an acid-catalyzed ring closure of an intermediate.
- Conrad-Limpach synthesis, is similar to Combes synthesis, but condensating anilines with β-ketoesters to synthesize 4-hydroxyquinolines.
- Doebner reaction, which reacts an aniline with an aldehyde and pyruvic acid to form quinoline-4-carboxylic acids.
- Doebner-Miller reaction, where quinoline derivatives are obtained from α,β-unsaturated carbonyl compounds catalyzed by Lewis acids such as tin tetrachloride.
- Gould-Jacobs reaction is a series of reactions started with the subtitution of an aniline with ethyl ethoxymethylenemalonate.
- Skraup synthesis, which heats aniline with glycerol and nitrobenzene in presence of sulfuric acid.

As it can be seen, these different quinolines can be synthesized departing from a simple anilines. This flexibility is useful for a plant to manufacture different quinolines, because there would be a common reactant.

Another named reaction is Friedländer Synthesis, which reacts 2-aminobenzaldehydes with ketones, producing an intermediate after an amino-ketone condensation. This intermediate goes through a base or acid-catalyzed cyclocondensation to produce a quinoline derivative

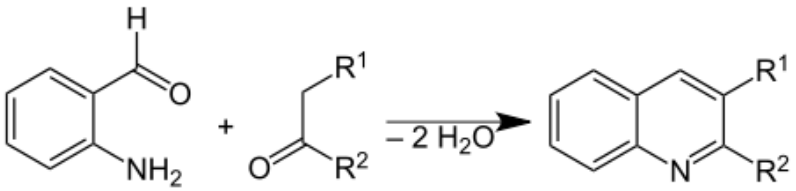


Figure 3. Friedländer synthesis

These methods can be very effective but often produce a large number of by-products, require longer reaction times or involve the use of environmentally incompatible reagents. There

are other methods using alternative reaction media such as supercritical fluids, ionic liquids, polyethylene glycol or solvent-free methods. However, even if these reactions are chemically possible they would be hard to reproduce in an industrial scale. There has also been some microwave-assisted and ultrasound-promoted experiments done from that named reactions with the same problems. For example, 6-hydroxyquinoline has been synthesized from glycerol via improved microwave-assisted modified Skraup reaction. (17)

Other synthesis have been studied in organic chemistry, but they are pretty specific, with low yield and purity so bringing them to industrial scale would not be that useful. (18)

Nevertheless, certain quinolines may be synthesized with its own reaction path without using anilines. For example, they can be manufactured using simpler quinolines or from a totally different compound. This is the case if only patented production is looked at. Currently, none of these synthesis have been published in an industrial scale, but they are definitely done due to its pharmaceutical activity.

1.2. BATCH PLANTS

Like nearly all pharmaceutical products, manufacture of quinoline derivatives will be a batch process due to the low amount but high purity of the product needed. Batch process produce a fixed amount of product (batch), repeated over again and again with new feedstock until target total amount is reached.

Batch plants have a lower initial capital investment than continuous and more flexibility in both production process and scale. Specifically, in this project more than one substance could be produced depending on market request, which is unpredictable. It is practical to produce quinolines in a batch plant due to its flexibility, with various compound synthesis sharing tasks to be carried out.

Batch process are often defined in a recipe style or process step procedure, a list of physicochemical operations (tasks) including their duration, generally developed at laboratory scale.

When a basic route or recipe at laboratory scale is selected, the process at industrial scale can be developed and designed by scaling up starting from laboratory scale to a larger kilo lab, to a pilot plant and eventually into industrial manufacturing.

Batch process design implicates the assigning of process tasks to the available equipment or equipment to be designed. In order to optimize the production, it is required to know the occupancy time of an equipment, the time that tasks taking place in this equipment needs to be completed. The sum of the occupancy times of all the equipment needed for the process is the batch time, the time needed for producing a batch since first task is started until last task is finished.

A campaign is defined as the sum of batches to produce a certain amount of a product in a concrete time. Campaign time would be the time that it takes to produce all this fixed amount the product, from the first batch until the last one.

Batch plants can be operated in overlapping or non-overlapping mode. In overlapping mode, a new batch is started when occupancy time of each equipment permits it, although the previous batch has not yet finished. Non-overlapping mode would mean that a batch would not be loaded until the previous one has ended.

Overlapping mode is usually used, given that if several batches are processed simultaneously the idle time of the equipment, the time that each equipment remains unoccupied, is reduced.

Using overlapping mode, process cycle time is defined by maximum occupancy time of all equipment units in a process. The equipment unit with maximum occupancy time is the time-limiting one, representing a bottleneck given that another batch cannot be processed until this equipment has not been emptied from the previous one. The cycle time defines the number of batches that can be produced by time unit.

Schedule is usually represented in a Gantt chart, where operation times for every equipment are shown. It is useful to visualize together the various times discussed: batch time, cycle time and campaign time.

Both overlapped and non-overlapped Gantt charts will be shown beneath, but as it was told earlier only the overlapped campaign will be studied in the final chosen process.

.

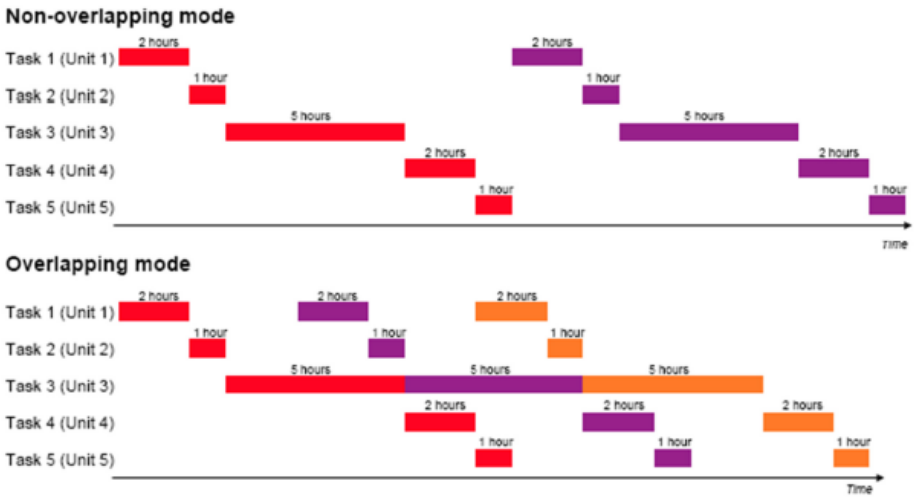


Figure 4. Gantt chart comparation

As it can be visualized, using overlapping mode idle time is minimized, translating into a higher production. In this example, Unit 3 would be the one defining cycle time, batches would have to be calculated so that second batch enters this unit right when the first one exits.

The volume of the different equipment units limits the amount to be processed in each unit, and the volume of one equipment unit would limit the batch size. It would be the equipment which capacity utilization is 100% because does not fit a greater batch, representing a volume bottleneck.

Other resources limiting the production capacity may be workforce, availability of raw material and utilities and size of storage tanks.

All in all, it seems that campaign optimization is done analysing both cycle time and capacity utilization, but this analysis should not be done separately because they are dependent variables. When increasing batch size, cycle time and operating times might also be increased. For complex processes there are mathematical algorithms including not only discussed parameters (batch size, available equipments…) but others such as materials of vessels and maximum operating temperature. [19]

2. OBJECTIVES

2. OBJECTIVES

As stated in the introduction, quinoline compounds have plenty of uses in the pharmaceutical industry. Some of them have a similar synthesis, therefore manufacture of various derivatives could be done in one single plant.

The main objective of this project is to design a batch plant for the manufacture of different quinolines derivatives scheduling production depending on market demand.

Design will be firstly made on a particular quinoline, which then could be changed to include others. To achieve this goal, the following tasks will be proceeded:

- Selection of a recipe through a study of quinoline manufacture patents, a research on quinoline recipes will be conducted in order to select the most suitable.
- Design the process using Aspen Batch Process Developer®: Once the recipe is chosen, it will be incorporated in the simulation software and scaled to industrial scale. Selection of equipment units will be carried out from available equipment in Aspen® catalogue.
- Defining scheduling of the plant, minimizing campaign time for a determined production. Occupation times will be checked in case they can be lowered.

3. PROCESS SELECTION

3. PROCESS SELECTION

Synthesis of quinolines have been studied in the organic chemistry field over the last decades due to their pharmaceutical properties. However, only a few of them have been turned into an accepted patent with a recipe. Moreover, there is not available information about industrial manufacture of quinoline derivatives. A study on quinoline derivatives manufacture patents will be conducted to find a suitable recipe to start the process.

Firstly, patent ***US6875869B2*** [20] will be studied. This patent synthesizes a quinoline-3-carboxamide derivative **C** by reacting a quinoline-3-carboxylic acid ester derivative **A** with an aniline derivative **B**, giving methanol as a byproduct.

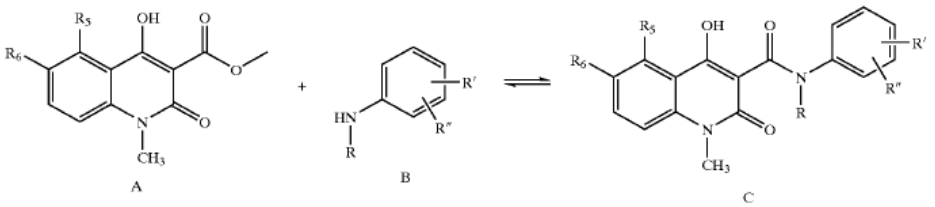


Figure 5. Patent 1 reaction

As it can be seen, different quinolines can be obtained depending on which radicals the reactant has. Not every radical is possible, the patent describes the ones that are. This process path would go along with the idea of a multiproduct batch plant because with a change of a reactant a new product would be obtained.

Different solvents for the reaction are studied, principally heptane, toluene and xylene. It is found that using heptane a higher mass fraction of the final product is obtained compared to toluene (99.4% to 94%).

The patent also points out the synthesis of a concrete quinoline-3-carboxylic ester derivative (1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester), which then could be reacted with an aniline to create the final product of the patent.

This synthesis can be studied because it is a complete recipe that could be scaled. Incomplete recipes that do not point out every mass of product or reaction time could not be scaled that clearly, for example reaction time would have to be estimated and kinetics of these reactions have not been widely studied.

Second researched patent is ***US6335449B1*** [21], which synthesizes a different quinoline (3) via the nitrile compound (1), obtained reacting the aldehyde compound (2) with diethyl cyanomethylphosphonate.

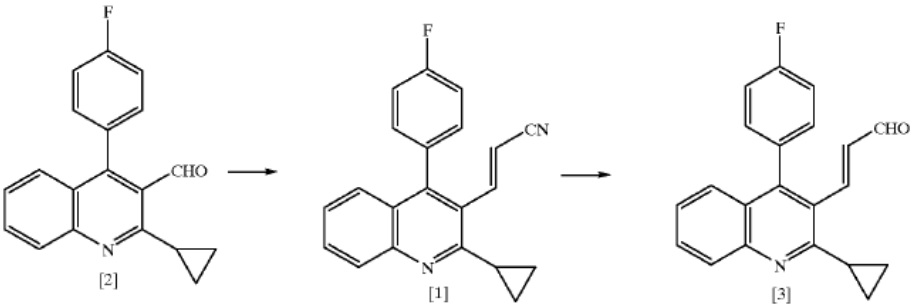


Figure 6. Patent 2 reaction

The product of this patent is used as an intermediate of cholesterol reducing agents.
Essentially, inhibiting the rate-controlling enzyme (HMG-CoA reductase or statin) of the mevalonate pathway, a metabolic pathway that produces cholesterol. Drugs with a lipid-lowering activity are usually just called statins due to this enzyme, including a wide amount currently available in the market.

Compound (3) has been synthesized by converting aldehyde compound (2) into a α,β-unsaturated carboxylic acid, reducing it into an alcohol compound and oxidating to the desired product. Direct reduction of the α,β-unsaturated carboxylic acid is possible, improving production efficiency but reducing control of the process. Therefore, this patent arises as an answer to a better process to manufacture this final product.

It gives a recipe to synthesize both the nitrile compound (1) and the final product through a series of physicochemical transformations, so it could also be designed in Aspen Batch Process Developer®.

Third studied patent, ***US5972841A*** [22], produces quinoline-3-carboxamides reacting quinoline-3-carboxylate with a substituted amine.

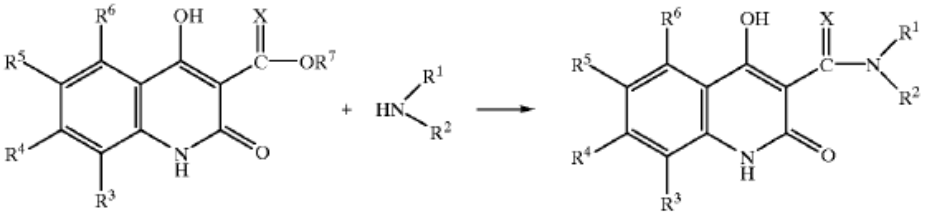


Figure 7. Patent 3 reaction

Like the first invention, various quinolines could be manufactured with this patent. Every possible radical of the reactants are described in the patent. This reaction is optimal in the 100-180ºC range, with an inert organic solvent such as benzene, toluene, various ethers and alcohols or a mixture of these substances. Atmospheric pressure in usually used but depending on the amine it may be advantageous to carry out the reaction in a higher pressure with an autoclave.

It is claimed that two of that compounds, applied postemergence at a rate of 3 kg/ha have a high herbicidal action.

Recipes given are just for the manufacture of quinoline-carboxamides departing from quinoline-carboxylates, with insufficient physicochemical transformations to carry out a lengthy thesis.

With the right radicals, this third patent (quinoline-3-carboxamide derivative) actually uses the same primary reactant as the first patent (quinoline-3-carboxylic acid derivative) but reacting it with a substituted amine instead of an aniline derivative.

Comparing all these patents, the first and the third one would allow a production of a variety of quinolines but the second just one. As explained before, the goal of this project is to design a batch plant to manufacture different quinoline derivatives, so these two processes could serve a base to produce some of them. However, the third patent does not contain a recipe to synthesize the quinoline-3-carboxamide, so it would not be possible to scale

Furthermore, the first patent is made by Active Biotech®, a biotechnological company that already uses these quinoline-3-carboxamide derivatives in experimental drugs such as Tasquinomod®, investigated for the treatment of solid tumors, especially prostate cancer. Laquinomod® is also a quinoline-3-carboxamide used as an oral treatment for multiple sclerosis.

The second patent is exploited by Nissan Chemical®, who have been commercializing Pitavastatin®. Basically, it is a derivative of the final product of that patent with the same function, lowering cholesterol production.

The third one, made by BASF, is said to have some herbicide activity. Nevertheless, it has not been translated into a real application. Moreover, from all the combination of radicals, only two of them have that mentioned herbicidal action.

Except these three patents, there has not been a lot of information about quinoline production, as it was said most of the literature is about the chemical possibility to synthetize very specific quinoline derivatives with certain conditions that would not be easy to replicate in an industrial level.

All in all, it seems the first patent could be more useful for the purpose of a multiproduct plant thanks to its flexibility to produce various quinolines and its already quantifiable utilization as a pharmaceutical drug.

In order to visualize and compare these experimental drugs with the first patent, chemical structure of Tasquinimod® is shown below:

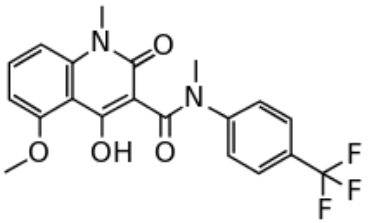


Figure 8. Molecular structure of Tasquinimod®

Being a quinoline-3-carboxylic acid derivative, it could be produced from the first recipe using reactants with the needed radicals. As explained before, patent *US6875869B2* contains the recipe for the production of a certain quinoline 3-carboxylic ester derivative (1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester)

The recipe, extracted from Example 1 of the discussed patent, will be copied beneath:

"2-Amino-6-chlorobenzoic acid (30 g) was suspended in 1,4-dioxane (225 ml) and ethyl chloroformate (75 ml) was added. The mixture was heated at reflux for 1 hour, then cooled back to 50ºC and acetyl chloride (75 ml) was added. The mixture was stirred for 10 hours, after which the precipitated product was filtered off and washed with toluene. Drying yields 6-chloroisatoic anhydride (33 g, 97% yield). 6-chloroisatoic anhydride (30 gram) was dissolved in dimethylacetamide (300 ml) and cooled to 5ºC over a nitrogen atmosphere. Sodium hydride (5.8 g, 70%) was added portionwise, followed by addition of methyl iodide (11.5 ml). The reaction mixture was stirred at room temperature for 18 hours. Sodium hydride (5.8 g, 70%) was added followed by addition of dimethyl malonate (20 ml) and the mixture was heated to 85ºC. After 3 hours at 85ºC, the mixture was cooled and diluted with cold water (2.4 litre). The product was precipitated by addition of HCl (aq.) until pH=1.5-2. Filtration of the precipitated product and recrystallisation from methanol gave the title compound (29g, 70% yield)."

Reaction path is not described in the patent, but it has been predicted from the substances added in the process. Also, the patent points out that 5-chloroisatoic anhydride is produced, but it has

been verified that chemically 6-chloroisatoic anhydride must be produced, synthesis of 5-chloroisatoic is not possible from these reactants.

Reactions occurring in the selected process will be explained below:

Firstly, 2-amino-6-chlorobenzoic acid is dissolved with 1,4-dioxane and ethyl-chloroformate is added. Reaction 1 is produced, obtaining 6-chloro isatoic anhydride.

6-chloro isatoic anhydride is dissolved in dimethylacetamide, after adding sodium hydride and methyl iodide, reaction 2 occurs producing an isatoic derivative with a hydroxyl group.

Dimethyl malonate and sodium hydride are incorporated into the mix, reacting by reaction 3. The product obtained is already the quinoline 3-carboxylic ester derivative.

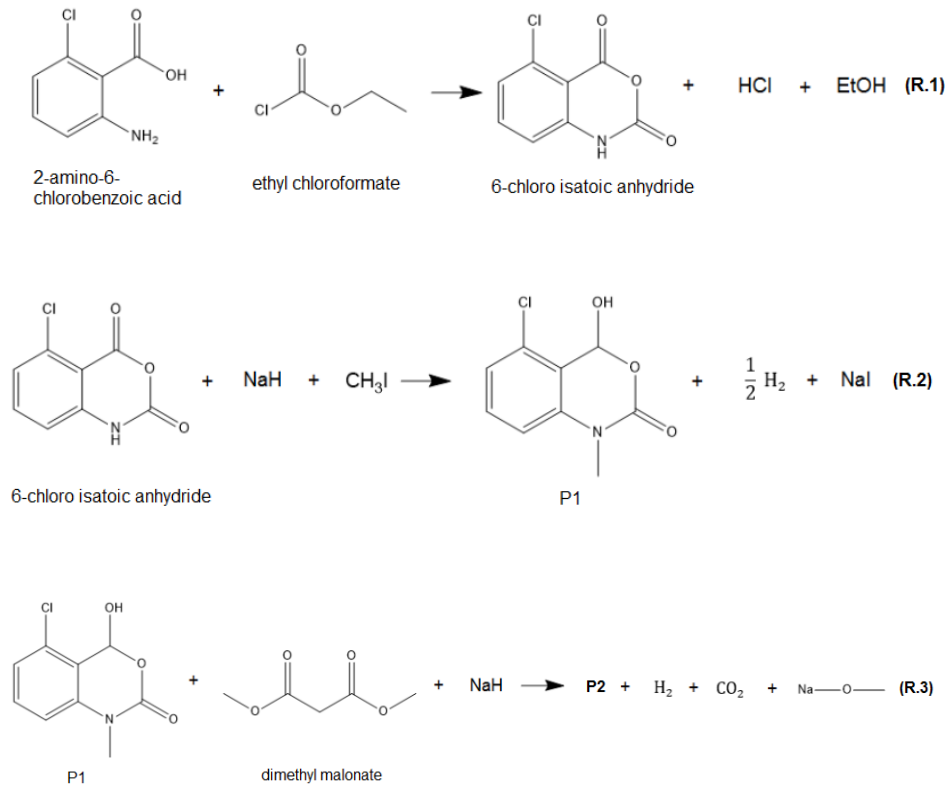


Figure 9. Reactions of the recipe.

Where P2 is the desired product, 1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester.

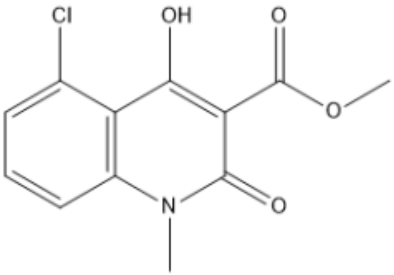


Figure 10. Molecular structure of the final product

This chapter, a scalable process has been selected prioritizing the aim of this project: to design a batch plant for the manufacture of various quinolines departing from a laboratory recipe.

4. PRELIMINARY PROCESS DESIGN

4. PRELIMINARY PROCESS DESIGN

The aim of this first process design is to scale the recipe from laboratory to industrial scale, choosing new equipment bearing in mind their

Recipe of the patent will be introduced in Aspen Batch Process Developer®, where different discontinuous tasks can be introduced with certain parameters. For example, "React" task demands reaction time and selecting the desired pre-introduced reaction, but other parameters can be introduced if needed.

If task time is not known, predetermined time is used but it will be approximated when production scale is obtained. For example, charging and filtering predetermined time used by Aspen® is 15 min.

The recipe is obviously in a laboratory scale, so laboratory equipment such as 500ml Erlenmeyer Flask, 250ml Filter Flask or 5L Tank are used. It can be divided into production of 6-chloroisotoic anhydride, production of the quinoline carboxylic ester derivative and its purification.

Eventually, when recipe is scaled, other appropriate equipment will be selected. The whole recipe already introduced in Aspen Batch Process Developer® is shown beneath:

1. 6-chloroisotoic anhydride production

1.1 Charge Erlenmeyer Flask, 500 ml with 30 g of 2-Amino-6-chlorobenzoic acid. Charge Erlenmeyer Flask, 500 ml with 225 ml of 1,4-dioxane. Charge Erlenmeyer Flask, 500 ml with 75 ml of ethyl chloroformate.

1.2 Mix the contents of unit Erlenmeyer Flask, 500 ml.

1.3 Heat unit Erlenmeyer Flask, 500 ml to reflux through condenser. The time required to bring the batch to boiling is 30 min. The age time is 1h. The outlet temperature of the condenser is 65ºC. The condenser pressure is 0.99 atm

1.4 Cool unit Erlenmeyer Flask, 500 ml to 50ºC

1.5 Mix the contents of unit Erlenmeyer Flask, 500 ml. React in unit Erlenmeyer Flask 500 ml via R1. Reaction occurs over 10 h.

1.6 Filter the batch from unit Erlenmeyer Flask, 500 ml in Filter Flask, 250 ml.

1.7 Dry the batch in unit Filter Flask, 250 ml.

1.8 Transfer contents of unit Filter Flask, 250 ml to Erlenmeyer Flask, 1000 ml. Transfer 89% of vessel contents

2. Quinoline ester production

2.1 Charge Erlenmeyer Flask, 1000 ml with 300 ml of dimethylacetamide.

2.2 Cool unit Erlenmeyer Flask, 1000 ml to 5ºC

2.3 Charge Erlenmeyer Flask, 1000 ml with 5.8 g of sodium hydride and 11.5 ml of methyl iodide

2.4 Heat Erlenmeyer Flask, 1000 ml to 23ºC

2.5 React in unit Erlenmeyer Flask, 1000 ml via R2. Reaction occurs over 18 h.

2.6 Charge Erlenmeyer Flask, 1000 ml with 5.8 g of sodium hydride and 25 ml of dimethyl malonate.

2.7 Heat unit Erlenmeyer Flask, 1000 ml to 85ºC.

2.8 React in unit Erlenmeyer Flask, 1000 ml via R3. Reaction occurs over 3 h.

2.9 Transfer contents of unit Erlenmeyer Flask, 1000 ml to Lab Tank, 5 L.

2.10 Charge Lab Tank, 5L with 2.4 L of water. Maintain the temperature at 10ºC

2.11 Adjust pH in unit Lab Tank, 5L. The final pH is 1.7.

2.12 Crystallize the batch in unit Lab Tank.

2.13 Filter the batch from unit Lab Tank, 5 L in Filter Flask, 125 ml.

2.14 Transfer contents of unit Filter Flask, 125 ml to Erlenmeyer Flask 1000 ml.

2.15 Charge Erlenmeyer Flask, 1000 ml with 800 ml of methanol.

2.16 Dissolve all solids in Erlenmeyer Flask, 1000 ml.

2.17 Transfer contents of unit Erlenmeyer Flask, 1000 ml to Crystallizing Dish.

2.18 Crystallize the batch in unit Crystallizing Dish.

2.19 Filter the batch from unit Crystallizing Dish in unit Filter Flask, 125 ml.

Using this recipe, 29 g of 1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester are obtained, with a 70% yield. Before the first crystallization, approximately 300 ml of HCl (aq.) 0.1M are added to get a pH value of 1.7. Hydrochloric acid concentration will be increased in the last scale in order to reduce the amount of acid needed to get to that value.

The whole process is represented in the next figure, a diagram containing all the equipment required to produce the quinoline-3-carboxylic acid methyl ester derivative, and it will be explained below.

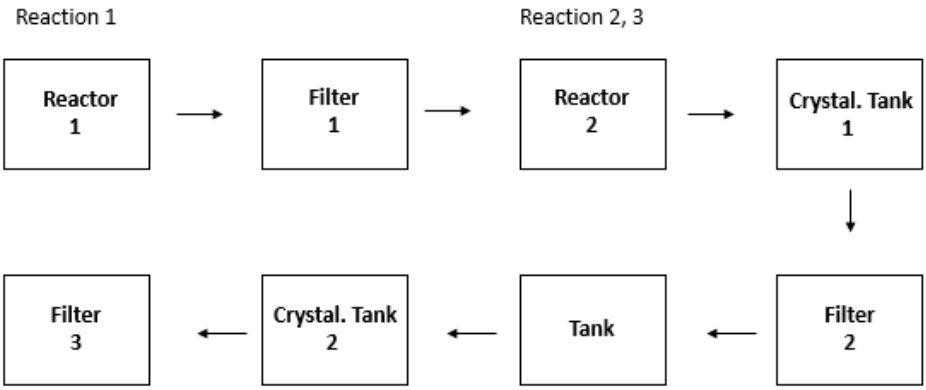


Figure 11. Equipment diagram of the process.

Reactor 1 is where reactants of the first reaction (2-amino-6-chlorobenzoic acid and ethyl chloroformate), its solvents (1,4-dioxane) and the reaction itself occurs. Filter 1 separates the desired product of the first reaction, 6-chloro isatoic anhydride, from excess reactant, the solvent used, and the other products (hydrogen chloride and ethanol).

This filtered product is transferred to Reactor 2, where it will be mixed with dimethylacetamide (solvent) and the other reactants of the second reaction (sodium hydride and methyl iodide) to carry the second reaction out. The third reaction also occurs in Reactor 2, so its respective reactants (sodium hydride and dimethyl malonate) are added.

When the third reaction is completed, contents of Reactor 2 are transferred to the crystallizing-filtering cycle, where the final product (1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester) is purified. Patent does not specify how many equipment is used in the crystallizing-filtering cycle, so it was initially thought to have two tanks between last two filters. One of them (Tank) is basically just to add methanol, which could just be added directly to Crystallization Tank 2. Nevertheless, actual scale up simulation would not be affected if this Tank is initially considered and then taken off, because both tanks will always have the same volume.

Once the laboratory recipe is introduced in Aspen Batch Process Developer®, the process is scaled up to a bigger amount of product. First of all, scale-up is actually non-linear: when a process is increased in size, surface area to mass proportion changes. Because of this, some properties of the system change in a non-linear way. Among others, reaction kinetics, thermodynamics, fluid dynamics or agitation. However, a rigorous computational fluids dynamics analysis would be a completely different project, so scale-up will be assumed to be an equal increase in every chemical substance to then analyse the optimal equipment for the selected amount of product.

In this case, production of quinoline derivative is increased from 29 g to 70 kg per batch. This number is an arbitrary amount, just to have the process in a greater scale, close to the final manufacture. It could have been scaled up first to a smaller amount, but this way, with a quantity similar to manufacture scale, task times such as heating or cooling of the reactor and crystallization will be able to be considered constant.

Process has been scaled from the production of quinoline-3 ester derivative, but it could be done from any other substance or even applying a common scale factor in all the equipment.

The problem of applying the same scale factor to all equipment is that not every equipment volume can be obtained. Most equipment producers can build personalized mechanical device at an increased cost, but in this project only traditional capacities from their catalogue will be used. Because of this, scale will be done from the final product.

In order to optimize the cost of the equipment, size utilization among Aspen equipment catalogue will be looked at, aiming for an 85-90%. Higher size utilization is not recommended, and lower would mean that a great part of the volume of the equipment is wasted. Nevertheless, in some cases an optimal equipment is not found so a lower size utilization will have to be used.

Aspen catalogue consists of basic equipment without brand and others with brands. Basic equipment is going to be used, but in case properties of any equipment are needed, equipment of the producers will be appealed. For example, reactor V201, with 1000 L of maximum capacity is used. If parameters such as heating area are needed, data sheets of De Dietrich or Pfaulder 1000 L reactors will be checked. This data will be important to approximate heating or cooling time of the reactor.

Last filter, which separates the final product (P2) and methanol has not been taken into account, but it will be considered in the last simulation involving campaign.

Considering capacity utilization, these are the optimal equipment units to produce 70 kg of the quinoline-3- carboxylic acid ester derivative:

Unit	Name	Capacity [L]
Reactor 1	R13	680
Filter 1	Filter P100	100
Reactor 2	V201	1000
Cryst. 1	RE-350	6000
Filter 2	FilterPot	150
Tank	Tank SET	2000
Cryst. 2	C-2000	2000

Table 1. Equipment units used in the 70 kg scale

Volume of R13 may seem unnatural if it is taken from a catalogue, but that capacity is actually 150 imperial or UK galloons. Using these reactors does not have any problem itself, but it would be cheaper to bring them from nearer, supposing these producers are based in the UK. Anyway, all equipment will have standard volumes when manufacture scale is obtained.

Capacity of RE-350 might look excessive compared the other volumes, but it makes sense because of all the water and HCl that are added to proceed to the first crystallization.

As it was said, Tank SET and C-2000 will definitely have an equal volume because they are carrying the same. Tasks of Tank SET are just the addition of methanol and its respective transferring from the previous to the next equipment unit, so if this tank is taken off once the manufacture scale is obtained, global time would not change that much. The next equipment units would not be affected in any way.

Occupancy time is the time a task is taking place in the equipment, basically the sum of task times. It is not constant along the scaling-up process because of transferring and filtering tasks, which will be considered constant because there is not that much change between 70 kg and final scalation. “Fixed” tasks, such as reactions or crystallization will be considered constant because, like it was said before, it is not possible to obtain enough kinetical and thermodynamic data. Heating or cooling time of the jacketed reactor would also change because heating area of the heat exchanger varies with volume, but all of these variables will be considered later on, when manufacture scale is studied.

In the next graph size utilization for a production of 70 kg of 1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester is shown:

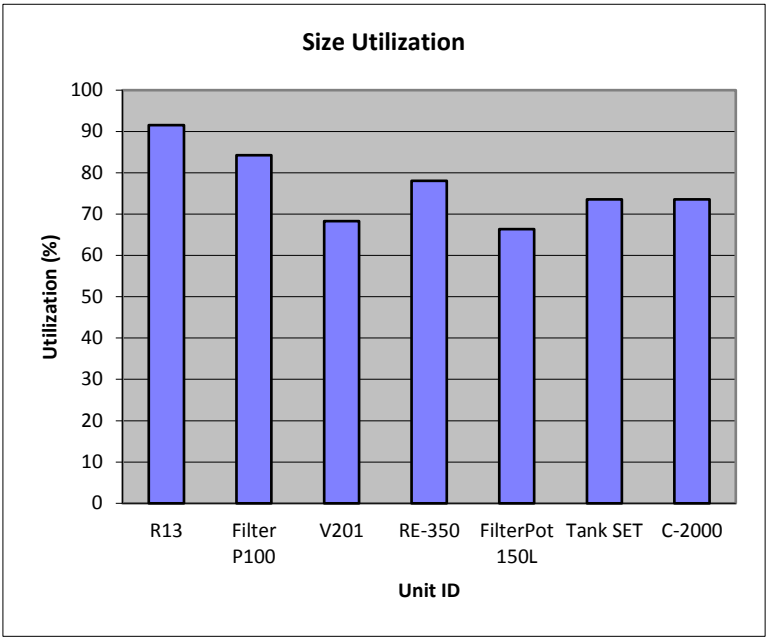


Figure 12. Size utilization graphic

These equipment units would be the optimal ones among Aspen Batch Process Developer® catalogue for the production of 70 kg of selected quinoline ester derivative. However, in the final campaign there could be another optimal batch quantity which could translate into another equipment used.

Reactor 2 (V201) and FilterPot (Filter 2) have been the equipment units with a lower size utilization. In the case of filters, it might be expected because there is not a wide variety like reactors. On the other hand, V201, knowing that it is the main reactor where the final quinoline is produced, would be important to have a higher size utilization because it is basically the amount of quinoline that would exit the system. Nevertheless, these size utilizations do not suppose a problem because equipment will be changed and better optimized in the final manufacture scale up.

Another important parameter of the equipment units that will be important later on is occupancy time, the sum of tasks taking place in one equipment unit. During transferring or filtering, two equipment units are occupied at the same time for the same operation. As it was told in the introduction, when setting up the final schedule it will be important to know the bottleneck equipment, which is the one with a higher occupation time. In this first initial scalation, next occupancy times are obtained:

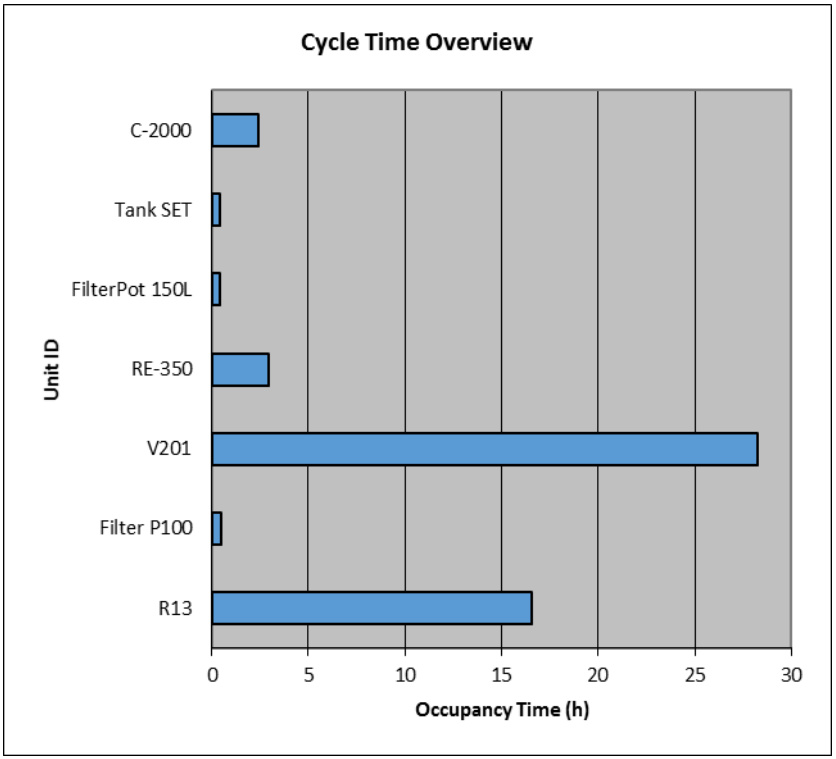


Figure 13. Occupancy time graphic.

As it can be seen, V201 is the equipment containing tasks that take the most time among all the equipment units. It makes sense, given that it is the reactor where reaction 2, the one with a higher duration, and reaction 3 occurs. This total occupancy time will be the cycle time, affecting total campaign time because delimits the time to start another batch.

Like it was explained, these occupancy times are not actually constant along the scaling up because when increasing the volume of the batch, transferring and filtering time should change. Moreover, different equipment means new heat transfer area, with a different cooling or heating time. Still, in this graphic, none of these task times have been approximated. This occupancy times could be described as basic times taken from the patent, with Aspen® filling unknown times with a predetermined time. Nevertheless, this predetermined time is not a random number but their general approximation for a certain task. In the next chapter these times will be approximated using available data.

Even if some of that tasks are not constant, the task that takes more time (reaction) will be considered constant, so at the end batch time will always be similar.

Essentially, this analysis to find suitable equipment to produce 70 kg of 1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester has been done by trying to have the highest size utilization possible among all the equipment units.

5. FINAL PROCESS DESIGN AND PRODUCTION SCHEDULING

5. FINAL PROCESS DESIGN AND PRODUCTION SCHEDULING

Before starting with production schedule, it is important to check the occupation time of every equipment. When the laboratory recipe was introduced in Aspen Batch Process Developer®, if any task time was not known predetermined time was used. Essentially, every task time was known except charge, heating/cooling and crystallization.

New charge times were approximated using average industrial pumping flow in case of liquid substances, and solids were thought to be an operator inserting them directly to the equipment from an industrial sack. Predetermined time of charge task was 15 min in every case, so it has been changed.

Heating or cooling time of the jacketed reactor was calculated using the design equation of the heat exchanger and calculating heat transfer rate via mass flow rate of the fluid, heat capacity and temperature change. The heat capacity of the contents of the reactor and the overall heat transfer of the heat exchanger cannot be found, but its value can be approximated. Heating area of the jacketed reactor can be found on the catalogue of De Dietrich reactors, where other data such as main dimensions on nozzles on vessel can be retrieved. (23)

At the end, these actualized occupancy times should not change that much, because most of them are from reaction times, which will be considered constant when changing equipment. As it was said, scale-up is actually non-linear because of reaction kinetics, thermodynamics and fluid dynamics but these conditions cannot be quantified easily so in this project reaction times will be maintained at the recipe times.

New occupancy times, calculated as it has been discussed, are shown below:

Unit	Occupancy time (h)
Reactor 1	15,58
Filter 1	1,42
Reactor 2	28,92
Crys. Tank 1	3,33
Filter 2	0,58
Tank	0,75
Crys. Tank 2	2,67
Filter 3	0,33
Total	53,58

Table 2. Updated occupancy times.

As it was expected, these times are actually similar to the ones obtained in the base, unchecked 70 kg scale, which would be the same as in the laboratory scale. It seems that batch time, the sum of the occupancy time of all the equipment units, would always be similar to this one, 2.23 days.

After scaling the basic recipe and checking the occupancy times of the equipment, it is time to prepare the campaign: an aggregate of batches to satisfy a certain production in a specific time. Target amount of quinoline ester derivative has been fixed to 2000 kg. To optimize production schedule, time horizon (total campaign time) has been lowered until the process is physically possible.

Batch amount will be changed, so it might imply a change of equipment. However, it is intended not to increase that quantity heavily, since new equipment units with more volume would mean a greater initial inversion to purchase them.

Departing from initial 70 kg production, it is found that it can be increased to 71.74 kg per batch without any equipment changed, except the last filter which was not considered in the first scale up. It is expected, given that 70 kg was just an arbitrary amount to get to a bigger scale. That equipment was the optimal one for the fixed production that was given (70 kg) but it does not necessarily mean that this amount was the maximum. Maximum kilograms of product per

batch for a combination of equipment is reached when any of these equipment units has a 100% size utilization.

This 71.74 kg production is the base case, which will be optimized using the optimization tool of Aspen Batch Process Developer®

.

Aspen campaign scheduling optimizer checks the general process, suggesting other equipment in order to lower total campaign time. Case 1 optimization increases production of quinoline ester derivative to 91.94 kg per batch. This rise is due to a change on the first reactor (from R13, 682 L to V201B, 1000 L) and all the filters. Case 2 changes the first crystallization tank from RE-350, 6000 L to RE-100, 10000 L. This shift leads to a 97.32 kg per batch of final product.

	Base Case		Case 1		Case 2	
Operation	**Equipment**	**Capacity (L)**	**Equipment**	**Capacity (L)**	**Equipment**	**Capacity (L)**
R.1	R13	682	V201B	1.000	V201B	1.000
Filter	Filter P100	100	F201	1.000	F201	1.000
R.2 and R.3	V201	1.000	V201	1.000	V201	1.000
Crystal. 1	RE-350	6.000	RE-350	6.000	RE-100	10.000
Filter	FilterPot 150L	150	FI-100	1.000	FI-100	1.000
Tank	Tank SET	2.000	Tank SET	2.000	Tank SET	2.000
Crystal. 2	C-2000	2.000	C-2000	2.000	C-2000	2.000
Filter	FI-400	4.000	FilterPot 150L	150	FilterPot 150L	150

Table 3. Comparation of equipment in every case

First optimization can be explained looking at the size utilization of the previous chapter. R13 was the equipment unit with a higher size utilization, so it seems reasonable that it will have to be changed if batch size is increased because it was the volume bottleneck. The size utilization of this reactor was initially 90%, so this base case compared to the initial 70 kg scale increases batch time until R13 has a 100% size utilization. This rise between the production of 70 kg and 71.74 kg will increase the size utilization of all the other equipment units.

FI-400 was the last filter added, knowing that the global process would be optimized, the volume was highly overestimated just in case. This volume decrease was already expected.

That increase in the first and the second filter capacities can be explained due to the poor catalogue of filters found in Aspen. After the 150 L filter, the next one is this 1000 L filter used. If this project had to be turned into a real plant, new filters between 150 and 1000 L would have to be designed or searched at the corresponding catalogue from the producer.

Size utilization is being maximized in every simulation. A table with the size utilization of some equipment units of Case 1 and Case 2 will be shown beneath:

	Case 1			Case 2		
Unit	Name	Volume [L]	% Size Util.	Name	Volume [L]	% Size Util.
Reactor 1	V201B	1000	79.98	V201B	1000	84.66
Reactor 2	V201	1000	87.67	V201	1000	92.81
Crys. Tank 1	RE-350	6000	100	RE-100	10000	63.51
Tank	Tank SET	2000	94.47	Tank SET	2000	100
Crys. Tank 2	C-2000	2000	94.47	C-2000	2000	100

Table 4. Comparation of size utilization.

With this comparation of size utilization in Case 1 and Case 2, recommendation of Aspen Batch Process Developer® campaign optimization tool can be totally understood. An equipment unit has already a full utilization, so it will have to be changed to a bigger equipment unit. Once this change is done, the next equipment unit with the highest size utilization percent is increased to the limit, 100%. This procedure could be kept, each time suggesting bigger equipment.

Next table displays, for every case, its batch time and final number of batches. As it was said before, cycle time is the maximum occupation time of all the equipment units, which is reactor V201 in all cases so that time will be practically constant.

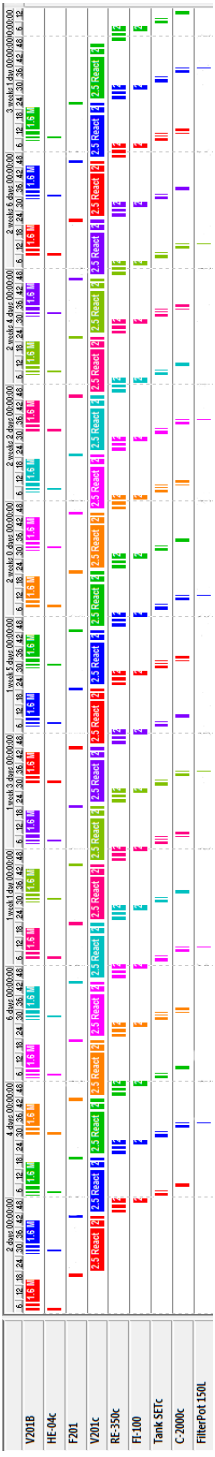
	Base Case	Case 1	Case 2
Batch size (kg)	71,74	91,94	97,32
Batch time (days)	2,25	2,30	2,31
Number of batches	28	22	21
Campaign time (days)	29,40	23,49	22,51

Table 5. Campaign comparation

This batch time difference is, as it was mentioned, due to the extra time taken to transferring and filtering tasks. Aspen automatically calculates new values depending on the new equipment used, which changes batch time, but that new task times are practically equal. There is a tendency to increase this batch time with the batch size, starting from 2.23 days to produce 70 kg and ending in 2.31 days to produce 97.32 kg.

As it can be seen, campaign has been reduced to 21 batches of 97.32 kg of 1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester for a total production of 2000 kg in 22.5 days. Batch size could be increased more, but it would mean a bigger initial investment. A batch size of approximately 100 kg fits with the idea of a batch plant that can produce multiple quinoline derivatives depending on market demand.

Global schedule of the campaign will be represented on a Gantt chart, with every occupation time of the equipment. As it was previously described, batch plants working in overlapping mode are optimized by having the equipment with a higher occupation time always containing substance, introducing the second batch right when the first one is leaving.


V201B
HE-04c
F201
V201c
RE-350c
FI-100
Tank SETc
C-2000c
FilterPot 150L

In this graphic, every batch is designed with one colour, with every sum of task times (occupation time) for every equipment unit.

What was mentioned about the highest occupation time of an equipment unit, which would be the cycle time can be visualized in this graphic. Obviously, Reactor 2 (V201c), where the second and third reactions take place, will be the equipment unit with a higher sum of task times taking place inside.

Comparing different batches, time difference between the same task will always be cycle time, because it is the optimal schedule for a campaign of a batch plant operating in overlapping mode.

First four batches are shown in this schedule chart, but global schedule would go until 21 batches are produced. HE-04c, which has not been mentioned in all the project, is the condenser used to heat reactor V201B. It has not been designed, but it appears in Aspen Batch Process Developer® generated Gantt chart and the optimal one from Aspen equipment list have been chosen.

Emphasizing what was explained last chapter, Tank SETc could be deleted because basically was just added to charge methanol, which could be loaded into the crystallizer C-2000c. General simulation would not be changed remarkably, because these charging and mixing task times are insignificant compared to reacting times.

Once that an optimal campaign schedule for a single quinoline derivative has been obtained, the main objective can be considered. A multiproduct batch plant can be implemented in two ways. On the one hand, a single product campaign, where all batches of one derivative are manufactured before switching to another. On the other hand, with a mixed product campaign, were batches of various quinolines are produced following a certain sequence.

The use of a certain mode will depend on which derivatives the pharmaceutical industry demands, so production schedule of this multiproduct batch plant will be variable and uncertain.

6. CONCLUSIONS

6. CONCLUSIONS

The main objective of the project has been reached: designing a batch plant for the manufacture of 2000 kg of a certain quinoline derivative. As it was told previously, depending on demand it could be used to manufacture another quinoline due to their similar synthesis. Quinolines have a wide range of applications in the pharmaceutical industry, so a plant to produce more than one derivative depending on market demand could be profitable.

Patent US6875869B2 has been the one that could serve better as a base recipe to accomplish this objective among the studied patents, due to its possibility to produce various quinolines from similar reactions in a single plant.

The manufacture process has been designed departing from a laboratory recipe of the select patent. This design has been done in two steps: a preliminary design selecting initial equipment in a 70 kg scale and a final design checking every task time that has been changed during the scale up.

A campaign has been developed to produce 2000 kg of 1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester in the shortest possible time. This total campaign time is lowered analysing occupancy time and size utilization of every equipment unit.

This campaign has been optimized to 21 batches of 97.32 kg to produce the desired product in 22.5 days.

REFERENCES AND NOTES

1 Pubchem quinoline description, https://pubchem.ncbi.nlm.nih.gov/compound/quinoline (accesed October, 2018)
2 O'Loughlin, et al. (1996), Isolation, characterization, and substrate utilization of a quinoline-degrading bacterium.
3 Chisholm, Hugh, ed (1911) Encyclopædia Britannica, Volume 22. Quinoline section.
4 Akranth Marella, et al. (2012), Quinoline: A versatile heterocyclic.
5 Scott D.A, et al. (2009), Identification of 3-amido-4-anilinoquinolines as a potent and selective inhibitor of CSF-1R kinase.
6 Raynes, K. et al. (1996), Novel bisquinoline antimalarials: synthesis, antimalarial activity and inhibition of haem polymerisation.
7 Abadi A.H. et al. (2005), Synthesis of novel 4-substituted-7-trifluoromethylquinoline derivatives with nitric oxide releasing properties and their evaluation as analgesic and anti-inflammatory agents.
8 Chen, Y. et al. (2006), Synthesis, cytotoxicity and anti-inflammatory evaluation of 2-(furan-2-yl)-4-(phenoxy)-quinoline derivatives.
9 Ma, X. et al. (2009), Synthesis in vitro, antitrypansomal and antibacterial activity of phenoxy, phenylthiol or benzyloxy substituted quinolines.
10 Souza, M.V.N.D. et al. (2009), Synthesis and in vitro antitubercular activity of a series of quinoline derivatives
11 Gholap, A.R. et al. (2007), Synthesis and evaluation of antifungal properties of a series of the novel 2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile and its analogues.
12 Ghosh, J. et al. (2008), Therapeutic effect of a novel anilidoquinoline, 2-(2-methyl-quinoline-4ylamino)-N-(2-chlorophenyl)-acetamide, in Japanese encephalitis: correlation with in vitro neuroprotection.
13 Massari, S. et al. (2009), Studies on anti-HIV quinolones: new insights on the C-6 position.
14 Rossiter, S. et al. (2005), Synthesis and anthelmintic properties of arylquinolines with activity against drug-resistant nematodes.
15 World Health Organization article, http://www.fao.org/3/a-bq698e.pdf (accessed November, 2018)
16 Quinoline yellow data sheet, http://datasheets.scbt.com/sc-215774.pdf (accessed October, 2018)
17 Shraddha M. Prajapati et al. (2014) Recent advances in the synthesis of quinolines: a review
18 Synthesis of quinolines recompilation. https://www.organic-chemistry.org/synthesis/heterocycles/benzo-fused/quinolines.shtm (accessed October 2018)
19 Korovessi, E., (2006), Batch process, CRC/Taylor & Francis
20 Jansson, K. (2004), Process for the manufacture of quinoline derivatives, US6875869B2
21 Ohara, Y. (2000), Process for the preparation of quinoline derivative and intermediate therefore US6335449B1
22 Von Deyn, W. (2000), Quinoline-3-carboxamides, their manufacture and use, US5972841A
23 De Dietrich data sheets. https://www.denwel.cz/editor/filestore/File/Leaflets/De%20Dietrich/140528%20DD%20Katalog.pdf (accessed December 2018)

ACRONYMS

aq: Aqueous solution

atm: Standard atmosphere

C-2000: Crystallizer

C_9H_7N: Quinoline

CH_3I: Methyl iodide

CO_2: Carbon dioxide

E104: Sodium 2(1,3-dioxoindan-2-yl)quinolinedisulfonate

EtOH: Ethanol

F201: Filter

FI-100: Filter

FI-400: Filter

g: Gram

H. contortus: *Haemonchus contortus*

h: Hours

H_2: Hydrogen

H_2O: Water

ha: Hectare

HCl: Hydrogen chloride/hydrochloric acid

HIV: Human immundodeficiency virus

HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A

kg: Kilogram

m^3: Cubic meter

min: Minutes

ml: Mililiter

NaH: Sodium hydride

NaI: Sodium iodide

ºC: Celsius

P1: 1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2H-benzo[d][1,3]oxazin-2-one

P100: Filter

P2: 1,2-Dihydro-4-hydroxy-6-chloro-1-methyl-2-oxo quinoline-3-carboxylic acid methyl ester

R13: Reactor

RE-350: Reactor

UK: United Kingdom

V201: Reactor

APPENDICES

APPENDIX 1: QUINOLINE DERIVATIVES MANUFACTURE PATENTS

Patent 1

US 20040034227A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0034227 A1**

Jansson (43) **Pub. Date: Feb. 19, 2004**

(54) **PROCESS FOR THE MANUFACTURE OF QUINOLINE DERIVATIVES**

(75) Inventor: **Karl Jansson**, Dalby (SE)

Correspondence Address:
BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, DC 20001 (US)

(73) Assignee: **ACTIVE BIOTECH AB**, Lund (SE)

(21) Appl. No.: **10/459,718**

(22) Filed: **Jun. 12, 2003**

Related U.S. Application Data

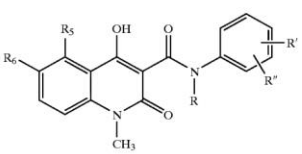
(60) Provisional application No. 60/387,580, filed on Jun. 12, 2002.

Publication Classification

(51) **Int. Cl.**[7] **C07D 215/36**
(52) **U.S. Cl.** **546/155**

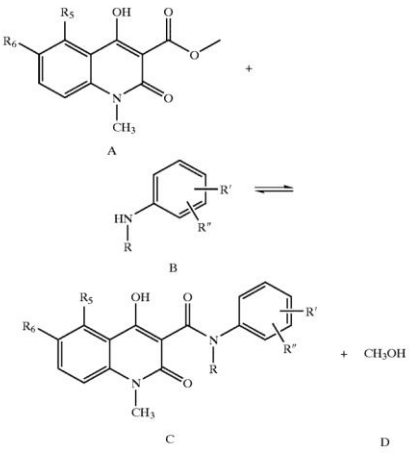
(57) **ABSTRACT**

A process for the preparation of the compounds of general formula (I)



(I)

wherein R is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl and allyl; R_5 is selected from the methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, methylthio, ethylthio, n-propylthio, methylsulphinyl, ethylsulphinyl, fluoro, chloro, bromo, trifluoromethyl, and OCH_xF_y; wherein x=0–2, y=1–3 with the proviso that x+y=3; R_6 is hydrogen; or R_5 and R_6 taken together are methylenedioxy; R' is selected from methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, and OCH_xF_y, wherein x=0–2, y=1–3 with the proviso that x+y=3; R" is selected form hydrogen, fluoro and chloro, with the proviso that R" is selected from fluoro and chloro only when R' is selected from fluoro and chloro; by reacting a quinoline-3-carboxylic acid ester derivative of formula A with an aniline derivative of formula B



in a solvent selected from straight or branched alkanes and cycloalkanes or mixtures thereof with a boiling point between 80 and 200° C.

US 2004/0034227 A1 Feb. 19, 2004

PROCESS FOR THE MANUFACTURE OF QUINOLINE DERIVATIVES

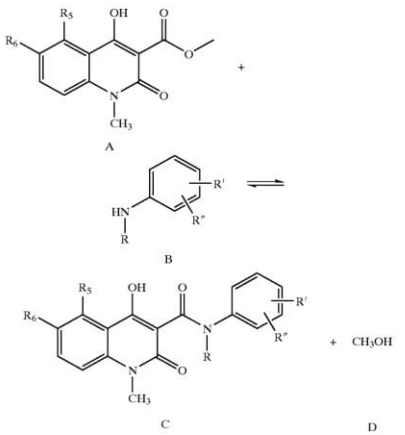
FIELD OF THE INVENTION

[0001] The present invention relates to a process for the manufacturing of quinoline derivatives. More particularly, the present invention relates to an improved and simplified process for the manufacture of quinoline-3-carboxamide derivatives.

BACKGROUND OF THE INVENTION

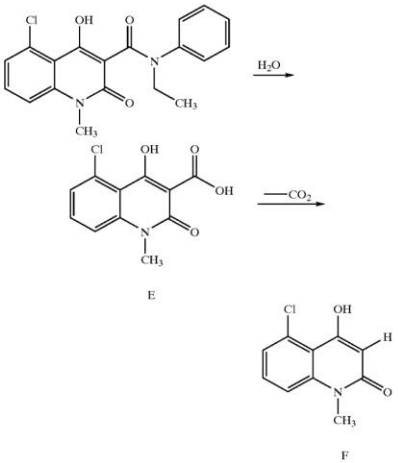
[0002] In U.S. Pat. No. 4,738,971 some derivatives of N-aryl-1,2-dihydro-4-substituted-1-alkyl-2-oxo-quinoline-3-carboxamide are claimed as enhancers of cell-mediated immunity. Said patent discloses four methods for the preparation of the compounds. According to the method closest to that of the present invention, the compounds are prepared by reacting a carboxylic acid or a reactive derivative thereof with an amine or reactive derivative thereof in the presence of pyridine or quinoline as an inert solvent. U.S. Pat. No. 5,912,349 discloses an improved process to produce one of these compounds, roquinimex (Merck Index 12th Ed., No. 8418; Linomide®, LS2616, N-phenyl-N-methyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-quinoline3-carboxamide). In said patent a reaction between N-methylisatoic anhydride and N-methyl-N-phenyl-α-carbomethoxyacetamide gives the desired compound. U.S. Pat. Nos. 6,077,851, 6,133,285 and 6,121,287 disclose the preparation of quinoline-3-carboxamide derivatives. The derivatives may be prepared by various known methods, for example, by reaction of a quinoline-3-carboxylic acid ester derivative with an aniline in a suitable solvent such as toluene, xylene and the like. In the examples disclosed, wherein toluene is used as a solvent, the yields are ≦80%.

[0003] The prior art reaction disclosed below



[0004] showing the N-acylation reaction conducted with a quinoline-3carboxylic acid ester derivative has now been found to be an equilibrium reaction where the equilibrium point unexpectedly lies far to the left. An illustrative example is provided by heating a quinoline-3carboxamide derivative (compound C), for example, wherein R_5=chloro and R_6=H, R=ethyl and R'=R"=hydrogen, in a sealed vessel at 100° C. with one equivalent of methanol in toluene as a solvent. An almost complete transformation into the corresponding methyl ester (compound A) results after less than 30 minutes.

[0005] The chemical stability of the desired product is such that degradation occurs under the reaction conditions.



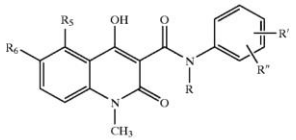
[0006] Degradation of a quinoline-3-carboxamide derivative.

[0007] An illustrative example is provided above. The degradation product (compound F) is the decarboxylated quinoline-3-carboxylic acid (compound E). Compound E is formed from the reaction between the quinoline-3-carboxamide derivative and water. It is unavoidable that small amounts of water exist in a reaction mixture. Small amounts of water are always present in the starting materials and in the solvent and water can also enter the reaction mixture during the reaction. When using, for example, toluene, the desired product is dissolved and prone to reaction with water. The quinoline-3-carboxylic acid that is formed in the reaction between the quinoline-3-carboxamide derivative and water undergoes a decarboxylation reaction to yield the decarboxylated product (compound F). The quinoline-3-carboxylic acid is not present in the crude product in a detectable amount. The quinoline-3-carboxylic acid ester (compound A) also undergoes a similar reaction with water but at a much slower rate.

DESCRIPTION OF THE INVENTION

[0008] A primary objective of the present invention is to provide an improved process for the manufacturing of quinoline-3-carboxamide derivatives which by virtue of their pharmacological profile, with high activity and low side-effects, are considered to be of value in the treatment of disease resulting from pathologic inflammation and autoimmunity and the treatment of a plurality of malignant tumours. More particularly, the present invention relates to a greatly simplified process for the manufacture of a quinoline-3-carboxamide derivative from an aniline by a N-acylation reaction conducted with a quinoline-3-carboxylic acid ester derivative in order to improve yield and chemical purity of the desired product.

[0009] It has now surprisingly been found that the compounds of general formula **(I)**



(I)

[0010] wherein

[0011] R is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl and allyl;

[0012] R_5 is selected from methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, methylthio, ethylthio, n-propylthio, methylsulphinyl, ethylsulphinyl, fluoro, chloro, bromo, trifluoromethyl, and OCH_xF_y;

[0013] wherein

[0014] x=0–2,

[0015] y=1–3 with the proviso that

[0016] x+y=3;

[0017] R_6 is hydrogen; or

[0018] R_5 and R_6 taken together are methylenedioxy;

[0019] R' is selected from methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, and OCH_xF_y,

[0020] wherein

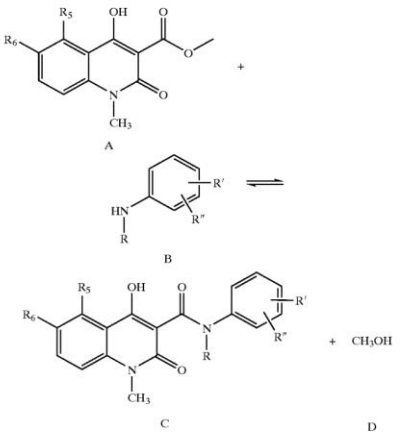
[0021] x=0–2,

[0022] y=1–3 with the proviso that

[0023] x+y=3;

[0024] R" is selected from hydrogen, fluoro and chloro, with the proviso that R" is selected from fluoro and chloro only when R' is selected from fluoro and chloro;

[0025] by the claimed process comprising reacting a quinoline-3-carboxylic acid ester derivative of formula A with an aniline derivative of formula B



[0026] in a solvent selected from straight or branched alkanes and cycloalkanes or mixtures thereof with a boiling point between 80 and 200° C. are manufactured in a greatly improved and simplified way.

[0027] According to a preferred embodiment the solvent is n-heptane, n-octane or mixtures thereof

[0028] In a further preferred embodiment the solvent is cis,trans-decahydronaphthalene (Decalin®).

[0029] The process according to the invention is especially preferred for the preparation of N-ethyl-phenyl-5-chloro-1.2-dihydro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxamide using n-heptane as a solvent; for the preparation of N-methyl-N-(4-trifluoromethyl-phenyl)-1,2-dihydro-4-hydroxy-5-methoxy-1-methyl-2oxo-quinoline-3carboxamide using a mixture of n-heptane and n-octane as a solvent; for the preparation of N-ethyl-N-phenyl-1,2-dihydro-5-thyl-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxamide using cis, trans-decahydronaphthalene as a solvent.

[0030] In relation to the use of toluene, xylene and the like as solvents, it has now surprisingly and unexpectedly been found that yield and impurity profile of the desired products can be very much improved. By using a solvent wherein the desired product is in effect insoluble even at reflux temperature, combined with removal of the alcohol formed, the yield of the desired product is almost 100% with a very low level of impurities in the desired product. Precipitation of the desired product increases the reaction rate even further, and prevents the degradation, i-e., by avoiding the reaction of the desired product with water. Solvents improving the process are straight- or branch-chained alkanes and cycloalkanes or mixtures thereof with a boiling point between 80 and 200° C. Reduced pressure may be used to remove the alcohol formed.

EXAMPLES

[0031] Without further elaboration, it is believed that one skilled in the art, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be considered as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever.

Example 1

[0032] 1,2-Dihydro-4-hydroxy-5-chloro-1-methyl-2-oxo-quinoline-3-carboxylic acid methyl ester

[0033] 2-Amino-6-chlorobenzoic acid (30 g) was suspended in 1,4-dioxane (225 ml) and ethyl chloroformate (75 ml) was added. The mixture was heated at reflux for 1 hour, then cooled to 50° C. and acetyl chloride (75 ml) was added. The mixture was stirred for 10 hours, after which the precipitated product was filtered off and washed with toluene. Drying in vacuum yields 5-chloroisatoic anhydride (33 g, 97% yield). 5-Chloroisatoic anhydride (30 gram) was dissolved in dimethylacetamide (300 ml), and cooled to 5° C. over a nitrogen atmosphere. Sodium hydride (5.8 g, 70%) was added portionwise, followed by addition of methyl iodide (11.5 ml). The reaction mixture was stirred at room temperature for 18 hours and the evacuated (40 mbar) for 1 hour in order to remove excess methyl iodide. Sodium hydride (5.8 g, 70%) was added followed by addition of dimethyl malonate (20 ml), and the mixture was heated to 85° C. After 3 hours at 85° C., the mixture was cooled and diluted with cold water (2.4 litre). The product was precipitated by addition of 5 M HCl (aq) until pH=1.5-2. Filtration of the precipitated product and recrystallisation from methanol gave the title compound (29 g, 70% yield).

[0034] In essentially the same manner the ethyl ester is obtained from the corresponding starting materials.

Example 2

[0035] N-Ethyl-N-phenyl-5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxamide

[0036] 5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylic acid methyl ester (3.0 g), N-ethylaniline (2 eq 2-2.88 ml), and heptaue (60 ml) were heated and the volatiles, mainly heptane and formed methanol, (32 ml) distilled off during 6 hours and 35 minutes. After cooling to room temperature the crystalline suspension was filtered and the crystals were washed with heptane and dried in vacuum to yield the crude title compound (3.94 g, 98%) as white to off-white crystals.

Example 3

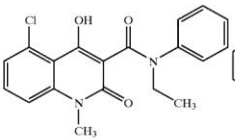
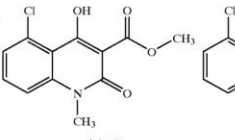
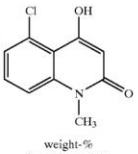
[0037] N-Ethyl-N-phenyl-5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxamide (reaction in toluene not part of the invention)

[0038] 5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylic acid methyl ester (3.0 g), N-ethylaniline (2 eq. 2.88 ml), and toluene (60 ml) were heated and the volatiles, mainly toluene and formed methanol, (32 ml) were distilled off during 6 hours and 35 minutes. After cooling to room temperature and precipitation of the product with heptane (40 ml), the crystals were filtered and washed with heptane and dried in vacuum to yield the crude title compound (3.58 g. 90% yield) as off-white crystals.

[0039] The crude products were analysed using HPLC and reference compounds, see table 1. Only two by-products were detected in the crude products. Peaks with area-% below 0.02% are not included.

TABLE 1

Content of desired product and by-products in tho crude products

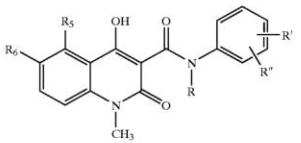
	 weight-% in crude product	 weight-% in crude product	 weight-% in crude product
Heptane as solvent	99.4	0.02	0.03
Toluene as solvent	94.0	4.55	0.54

[0040] The increased reaction rate in heptane is apparent More untransformed ester remained in the crude product when using toluene as compared to heptane as a solvent. The rate difference may be even bigger than indicated in Table 1 since reaction in toluene occurs at a higher temperature than the corresponding reaction in heptane (toluene has bp 110-112° C. and heptane has bp 98° C.) The ester is more soluble in alkanes than the product, a fact that influences the equilibrium positively and favours formation of product.

[0041] The yield of crude product when using toluene wags lower (90%) than when using heptane (98%). This can be attributed to the higher solubility of product and ester in toluene than in heptane. The actual yield when using heptane is close to 100% The decarboxylated quinoline carboxylic acid (toluene 0.54%, and heptane 0.03%, see Table 1) is the result of reaction between water and the desired product.

We claim:

1. A process for the preparation of the compounds of general formula (I)



(I)

wherein

R is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl and allyl;

R_5 is selected from methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, methylthio, ethylthio, n-propylthio, methylsulphinyl, ethylsulphinyl, fluoro, chloro, bromo, trifluoromethyl, and OCH_xF_y;

wherein

x=0−2,

y=1−3 with the proviso that

x+y=3;

R_6 is hydrogen; or

R_5 and R_6 taken together are methylenedioxy;

R' is selected from methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, and OCH_xF_y,

wherein

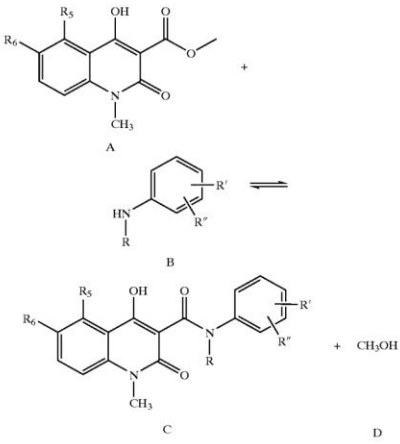
x=0−2,

y=1−3 with the proviso that

x+y=3;

R" is selected from hydrogen,fluoro and chloro, with the proviso that R" is selected from flouro and chloro only when R' is selected from flouro and chloro;

by reacting a quinoline-3-carboxylic acid ester derivative of formula A with an aniline derivative of formula B



A B C D

in a solvent selected from straight or branched alkanes and cycloalkanes or mixtures thereof with a boiling point between 80 and 200° C.

2. The process according to claim 1 wherein the solvent is n-heptane, n-octane or mixtures thereof.

3. The process according to claim 1 wherein the solvent is cis,trans-decahydronaphthalene (Decalin®).

4. The process according to claim 1 for the preparation of N-ethyl-N-phenyl-5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-quinoline-3carboxamide using n-heptane as a solvent.

5. The process according to claim 1 for the preparation of N-methyl-N-(4-trifluoromethyl-phenyl)-1,2-dihydro-4-hydroxy-5-methoxy-1-methyl-2-oxo-quinoline-3-carboxamide using a mixture of n-heptane and n-octane as a solvent.

6. The process according to claim 1 for the preparation of N-ethyl-N-phenyl-1,2-dihydro-5-ethyl-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxamide using cis,trans-decahydro-naphtaalene (Decalin®) as a solvent.

* * * * *

US006335449B1

(12) **United States Patent**
Ohara et al.

(10) **Patent No.: US 6,335,449 B1**
(45) **Date of Patent: Jan. 1, 2002**

(54) **PROCESS FOR THE PREPARATION OF QUINOLINE DERIVATIVE AND INTERMEDIATE THEREFOR**

(75) Inventors: **Yoshio Ohara**; **Mikio Suzuki**; **Yoshinobu Yanagawa**; **Yasutaka Takada**, all of Chiba (JP)

(73) Assignee: **Nissan Chemical Industries, Ltd.**, Tokyo (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/764,994**

(22) PCT Filed: **Jul. 22, 1999**

(86) PCT No.: **PCT/JP99/03923**

§ 371 Date: **Jan. 23, 2001**

§ 102(e) Date: **Jan. 23, 2001**

(87) PCT Pub. No.: **WO00/05213**

PCT Pub. Date: **Feb. 3, 2000**

(30) **Foreign Application Priority Data**

Jul. 23, 1998 (JP) 10-207911

(51) **Int. Cl.**[7] **C07D 215/04**; C07D 215/12; C07D 215/18

(52) **U.S. Cl.** **546/173**; 546/174; 546/176; 546/180

(58) **Field of Search** 546/173, 174, 546/176, 180

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,011,930	A	4/1991	Fujikawa et al.
5,102,888	A	4/1992	Fujikawa et al.
5,185,328	A	2/1993	Fukikawa et al.
5,284,953	A	2/1994	Ohara et al.
5,473,075	A	12/1995	Ohara et al.
5,514,804	A	5/1996	Ohara et al.
5,854,259	A	12/1998	Fujikawa et al.
5,856,336	A	1/1999	Fujikawa et al.
5,872,130	A	2/1999	Fujikawa et al.
5,939,552	A	8/1999	Ikeda et al.
6,162,798	A	12/2000	Saito et al.

FOREIGN PATENT DOCUMENTS

DE	3905908	* 9/1990
JP	01279866	* 11/1989
JP	06329540	* 11/1994

OTHER PUBLICATIONS

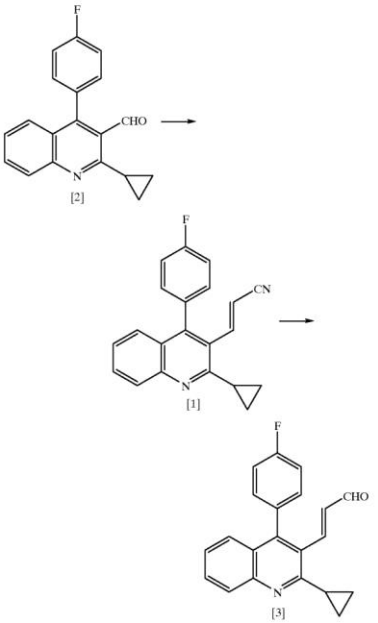
U.S. application No. 09/436,789, filed Nov. 8, 1999, pending.*
U.S. application No. 09/743,810, filed Jan. 22, 2001, pending.*
U.S. application No. 09/764,994, filed Jan. 23, 2001, pending.*

* cited by examiner

Primary Examiner—D. Margaret Seaman
(74) *Attorney, Agent, or Firm*—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

(57) **ABSTRACT**

The present invention relates a process for producing the quinoline derivative (3) via the nitrile compound (1) obtained by reacting the aldehyde compound represented by formula (2) with diethyl cyanomethylphosphonate and its intermediate (1).



2 Claims, No Drawings

US 6,335,449 B1

1

PROCESS FOR THE PREPARATION OF QUINOLINE DERIVATIVE AND INTERMEDIATE THEREFOR

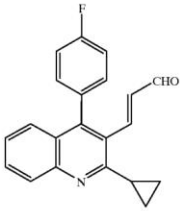
INTERMEDIATE

This application is a 371 of PCT/GP99/03923, filed Jul. 22, 1999.

TECHNICAL FIELD

The present invention relates to a process for producing the quinoline derivative represented by formula (3) which can be a useful intermediate of cholesterol reducing agents (HMG-CoA reductase inhibitors)

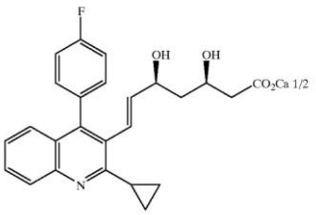
[3]



BACKGROUND ART

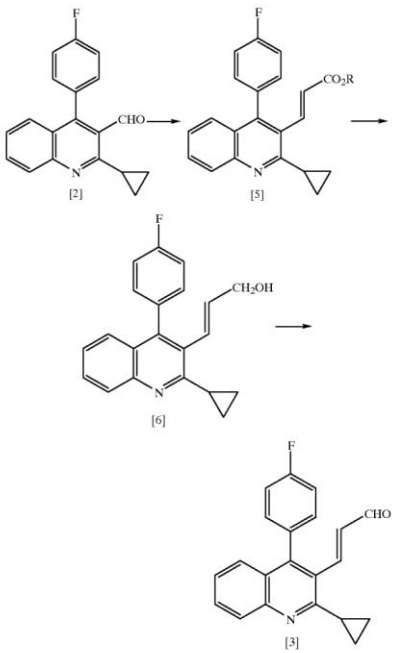
The quinoline compound represented by formula (4) is disclosed in JP-A-1-279866, EP-A-304063 and U.S. Pat. No. 5,011,930 as a useful cholesterol reducing agent (HMG-CoA reductase inhibitor).

[4]



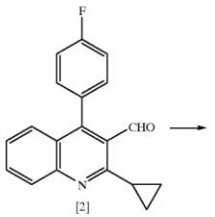
The quinoline compound represented by formula (4) is obtained in the above-mentioned patents as shown below by converting the aldehyde compound (2) into the α,β-unsaturated carboxylic acid ester compound (5) followed by reduction into the alcohol compound (6) and oxidation into the desired quinoline compound (3). Though direct reduction of the α,β-unsaturated carboxylic acid ester compound into the desired quinoline compound (3) would improve production efficiency, the problem is the difficulty of its control.

2

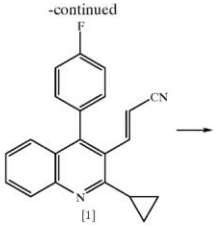


DISCLOSURE OF THE INVENTION

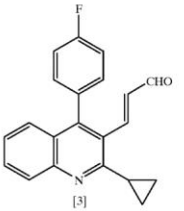
As a result of their extensive research to solve the above-mentioned problem, the present inventors found one-step preparation of the desired quinoline compound (3) via the nitrile compound (1) obtained by reacting the aldehyde compound represented by formula (2) with diethyl cyanomethylphosphonate.



-continued



[1]



[3]

Namely, the present invention relates to a process for producing the quinoline derivative (3) via the nitrile compound (1) obtained by reacting the aldehyde compound represented by formula (2) with diethyl cyanomethylphosphonate and its intermediate (1).

One-step preparation of the desired quinoline compound (3) can be attained via the nitrile compound (formula (1)) obtained by reacting the aldehyde compound represented by formula (2) with diethyl cyanomethylphosphonate.

BEST MODE FOR CARRYING OUT THE INVENTION

Now, the process of the present invention will be described.

Preparation of Nitrile Compound (1)

As the solvent used in the reaction, an aromatic hydrocarbon such as toluene or xylene, an ethereal solvent such as tetrahydrofuran or dioxane or a halogenated solvent such as dichloroethane or o-dichlorobenzene may be mentioned.

From 0.5 to 5 times as many moles, preferably from 0.9 to 1.5 times as many moles, of diethyl cyanomethylphosphonate is used.

A base such as sodium hydride, sodium hydroxide, potassium hydride, sodium methoxide, sodium ethoxide, potassium t-butoxide or potassium carbonate may be used in an amount of from 0.5 to 10 times as many moles, depending on the solvent and the type of the base. A phase transfer catalyst such as Aliquat 336 may be used optionally, for example, when toluene as the solvent is combined with (aqueous) sodium hydroxide as the base.

The reaction temperature is within the range of from −20 to 80° C., preferably within the range of from 20 to 40° C.

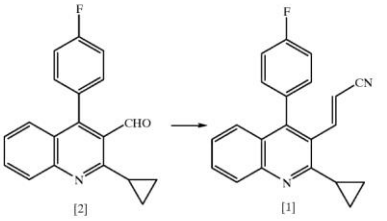
Preparation of Quinoline Derivative (3)

Use of diisobutylaluminum hydride as a reducing agent and an aromatic hydrocarbon such as toluene or xylene as the solvent in the reaction gives good results. Diisobutylaluminum hydride is used in an amount of from 0.5 to 5 times as many moles, preferably from 0.9 to 1.5 times as many moles, and the reaction temperature is within the range of from −50 to 50° C., preferably within the range of from −30 to 5° C. Reduction with Raney nickel in formic acid as the solvent is also available.

EXAMPLE

Now, the present invention will be described in further details with reference to Examples. However, the present invention is by no means restricted to these specific Examples.

Preparation of Nitrile Compound (1)



[2] [1]

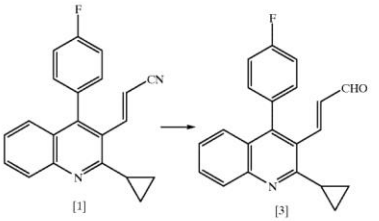
To a solution of 199 g (683 mmol) of 2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-carboaldehyde in 960 g of toluene, 136 g (765 mmol, 1.1 eq) of diethyl cyanomethylphosphonate and 5.5 g (13.6 mmol, 0.02 eq) of Aliquat 336 were added.

400 g of 20% aqueous sodium hydroxide was added dropwise over 0.5–1 hour with stirring while the inner temperature was maintained at 25–35° C., and the reaction solution was stirred at the same temperature for 1 hour.

After completion of the reaction, 200 g of water was added, and the mixture was stirred for 30 minutes and allowed to separate. The resulting organic layer was washed with 400 ml of 10% aqueous sodium hydroxide, combined with 400 ml of saturated aqueous sodium chloride, adjusted to pH 7 with IN aqueous hydrochloric acid and allowed to separate. After addition of 50 g of sodium sulfate, the resulting organic layer was stirred for 1 hour, then stirred for another 30 minutes together with 5 g of activated carbon and 20 g of silica gel and filtered through a celite-layered funnel.

The solvent was distilled off the filtrate under reduced pressure until the residual amount became about 400 g, and the precipitated crystals were melted in situ by heating and refluxed together with 580 g of hexane under heating for 30 minutes, then cooled to 5° C. and stirred at the same temperature for 2 hours. The precipitated crystals were collected by filtration, washed with toluene-hexane (1:5, w/w) and with hexane and dried to give 189 g of 3-{2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl}prop-2-enenitrite in a 88% yield. m.p. 176–178° C.

Preparation of Quinoline Derivative (3)



A solution of 181 g (576 mmol) of 3-{2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl}prop-2-enenitrite in 1812 ml of toluene was cooled to an inner temperature of −10° C. 650 ml of a 1.02 M toluene solution of diisobutylaluminum hydride (663 mmol, 1.15 eq) was added dropwise over 1 hour while the inner temperature was maintained at from −10 to −5° C., and the mixture was stirred at the same temperature for 1 hour.

After the reaction, 30.5 g of ethanol was added dropwise while the temperature was maintained at from −10 to −5° C., and the mixture was stirred at the same temperature for 30 minutes. 155 ml of 1 N hydrochloric acid was added dropwise while the temperature was maintained at 10° C. or below, and the mixture was stirred at the same temperature for 1 hour. Further, 9.06 ml of 35% hydrochloric acid was added dropwise while the temperature was maintained at the same temperature, and the mixture was stirred at an inner temperature of 25–30° C., and the resulting mixture was filtered through a celite-layered funnel.

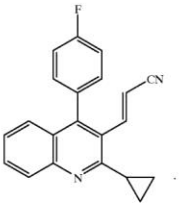
After addition of 725 ml of 1 N hydrochloric acid, the filtrate was stirred for 30 minutes and allowed to separate. The organic layer was washed with 360 ml of 1 N hydrochloric acid and with 545 ml of saturated aqueous sodium chloride. All the aqueous layers were combined and extracted with 725 ml of ethyl acetate again, and the extract was washed with 360 ml of saturated aqueous sodium chloride and combined with the above-mentioned organic layer. After addition of 1090 ml of water, the mixture was adjusted to pH 7 with saturated aqueous sodium hydrogen carbonate and washed with 1090 ml of water and 1090 ml of saturated aqueous sodium chloride.

The solvent was distilled away from the resulting solution under reduced pressure, and 360 g of cyclohexane and 720 g of n-hexane were added. The mixture was refluxed under heating for 30 minutes, then cooled to 0–5° C. and stirred at the same temperature for 2 hours. The precipitated crystals were collected by filtration, washed with cyclohexane-n-hexane (1:2, w/w) and n-hexane and dried to give 170 g of 3-(2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl)prop-2-enal in a 93% yield. m.p.: 146–147° C.

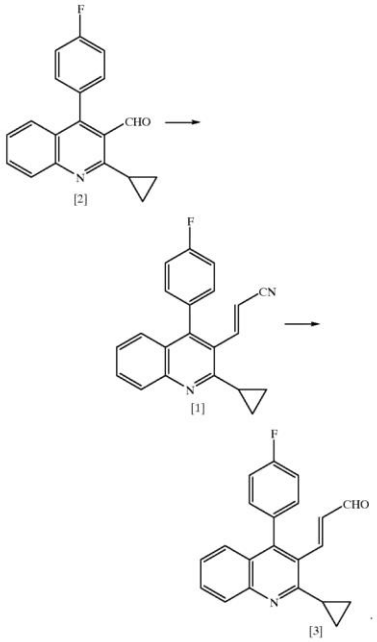
What is claimed is:

1. A nitrile compound represented by formula (1)

[1]



2. A process for producing the quinoline derivative (3) via the nitrile compound (1) obtained by reacting the aldehyde compound represented by formula (2) with diethyl cyanomethylphosphonate



* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,335,449 B1
DATED : January 1, 2002
INVENTOR(S) : Yoshio Ohara et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,
Line 51, "with IN aqueous" should read -- with 1N aqueous --.
Line 67, "enenitrite" should read -- enenitrile --.

Signed and Sealed this

Third Day of December, 2002

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US005972841A

United States Patent [19]

von Deyn et al.

[11] **Patent Number: 5,972,841**

[45] **Date of Patent: Oct. 26, 1999**

[54] **QUINOLINE-3-CARBOXAMIDES, THEIR MANUFACTURE AND USE**

[75] Inventors: **Wolfgang von Deyn**, Neustadt; **Hans Theobald**, Limburgerhof; **Christoph Nuebling**, Hassloch; **Uwe Kardorff**, Mannheim; **Helmut Walter**, Obrigheim; **Karl-Otto Westphalen**, Speyer; **Thomas Kappe**, Graz; **Matthias Gerber**, Mutterstadt, all of Germany

[73] Assignee: **BASF Aktiengesellschaft**, Ludwigshafen, Germany

[21] Appl. No.: **08/988,765**

[22] Filed: **Dec. 11, 1997**

Related U.S. Application Data

[62] Division of application No. 08/794,572, Feb. 3, 1997, Pat. No. 5,798,451, which is a continuation of application No. 08/542,136, Oct. 12, 1995, abandoned, which is a continuation of application No. 08/241,390, May 11, 1994, abandoned, which is a continuation of application No. 07/981,356, Nov. 25, 1992, abandoned.

[30] **Foreign Application Priority Data**

Nov. 26, 1991 [DE] Germany 41 38 820

[51] **Int. Cl.**^{6} **A01N 43/42**

[52] **U.S. Cl.** **504/247**

[58] **Field of Search** 504/147, 149, 504/247; 546/155

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,960,868	6/1976	Ferrini et al.	546/155
4,107,310	8/1978	Allais et al.	546/155
4,959,363	9/1990	Wentland	546/155

FOREIGN PATENT DOCUMENTS

152966	6/1990	Japan	546/155

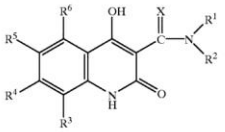
OTHER PUBLICATIONS

Suzuki et al Chem Abstr vol. 116 Entry 235457g (1990).

Primary Examiner—John M. Ford
Attorney, Agent, or Firm—Keil & Weinkauf

[57] **ABSTRACT**

Quinoline-3-carboxamides I



(I)

where

R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, and the organic radicals may be substituted or unsubstituted;

R^2 is hydrogen, hydroxyl, alkoxy, alkenyloxy, dialkylamino, alkyl, alkenyl, alkynyl, cycloalkyl, and the organic radicals may be substituted or unsubstituted;

or

R^1, R^2 together denote an alkylene chain of 4 to 7 members and which may be interrupted by oxygen, sulfur or N-methyl;

R^3–R^6 are hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkylthio, haloalkylthio, halogen, cyano or nitro;

X is oxygen or sulfur;

with the proviso that R^2 is not hydrogen, C_1–C_3-alkyl, n-butyl, 3-methylbutyl, cyclohexyl, hexyl, heptyl, octyl, 2-chlorobenzyl, 3-(dimethylamino)propyl, 3-(diethylamino) propyl, 2-morpholinoethyl or 2-(3,4-dimethoxyphenyl)ethyl when R^1 and R^3 to R^6 are hydrogen and X is oxygen, and that R^2 is not benzyl when R^1 is methyl, R^3 to R^6 are hydrogen and X is oxygen, and that R^1 and R^2 do not jointly denote morpholino when R^3 to R^6 are hydrogen and X is oxygen.

1 Claim, No Drawings

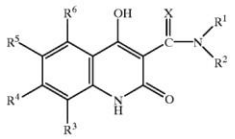
5,972,841

QUINOLINE-3-CARBOXAMIDES, THEIR MANUFACTURE AND USE

This is a Divisional of prior application Ser. No. 08/794,572, filed Feb. 3, 1997, now U.S. Pat. No. 5,798,451 which is an FWC of 08/542,136, Oct. 12, 1995 abandoned; which is an FWC of 08/241,390, May 11, 1994 abandoned; which is an FWC of 07/981,356, Nov. 25, 1992 abandoned.

The present invention relates to quinoline-3-carboxamides of the formula I

(I)



where the substituents have the following meanings:

R^1 hydrogen, C_1–C_{25}-alkyl, C_3–C_{25}-alkenyl, C_3–C_{25}-alkynl or C_3–C_8-cycloalkyl, where these groups may carry from one to five halogen atoms and/or from one to three of the following radicals: cyano, C_3–C_8-cycloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy, C_1–C_4-alkylthio, C_1–C_4-haloalkylthio, di-C_1–C_4-alkylamino, phenyl, phenylthio, phenoxy, and the phenyl radicals in turn may bear from one to three of the following groups: C_1–C_4-alkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkyl, C_1–C_4-haloalkoxy, halogen, cyano or nitro;

R^2 hydrogen, hydroxyl, C_1–C_8-alkoxy, C_3–C_8-alkenyloxy, di-C_1–C_4-alkylamino, C_1–C_{25}-alkyl, C_3–C_{25}-alkenyl, C_3–C_{25}-alkynyl or C_3–C_8-cycloalkyl, where these groups may carry from one to five halogen atoms and/or from one to three of the following radicals: cyano, C_3–C_8-cycloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy, C_1–C_4-alkylthio, C_1–C_4-haloalkylthio, di-C_1–C_4-alkylamino, phenyl, phenylthio, phenoxy, and the phenyl radicals in turn may bear from one to three of the following groups: C_1–C_4-alkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkyl, C_1–C_4-haloalkoxy, halogen, cyano or nitro;

R^2 further denotes substituted C_1–C_8-alkoxy, C_3–C_8-alkenyloxy, di-C_1–C_4-alkylamino, C_1–C_{25}-alkyl, C_3–C_{25}-alkenyl, C_3–C_{25}-alkynyl or C_3–C_8-cycloalkyl, where these groups are substituted by from one to five halogen atoms and/or by one or two 5- to 6-membered heterocyclic, aliphatic or aromatic radicals containing from one to three heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and which radicals may bear one or two of the following substituents: halogen, C_1–C_3-alkyl or C_1–C_3-alkoxy;

or

R^1, R^2 together denote an alkylene chain of 4 to 7 members and which may be interrupted by oxygen, sulfur or N-methyl;

R^3–R^6 hydrogen, C_1–C_4-alkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkyl, C_1–C_4-haloalkoxy, C_1–C_4-alkylthio, C_1–C_4-haloalkylthio, halogen, cyano or nitro;

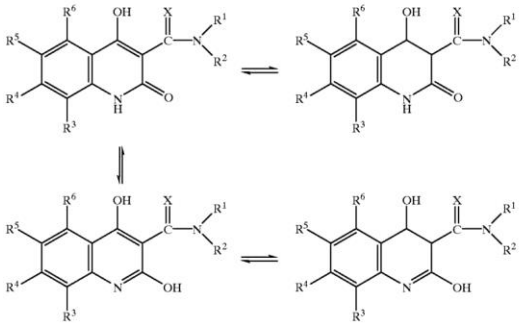
X oxygen or sulfur

or environmentally tolerated salts thereof;

with the proviso that R^2 is not hydrogen, C_1–C_3-alkyl, n-butyl, 3-methylbutyl, cyclohexyl, hexyl, heptyl, octyl, 2-chlorobenzyl, 3-(dimethylamino)propyl, 3-(diethylamino) propyl, 2-morpholinoethyl or 2-(3,4-dimethoxyphenyl)ethyl when R^1 and R^3 to R^6 are hydrogen and X is oxygen, and with the proviso that R^2 is not benzyl when R^1 is methyl, R^3 to R^6 are hydrogen and X is oxygen, and further with the proviso that R^1 and R^2 do not together denote morpholino when R^3 to R^6 are hydrogen and X is oxygen.

The invention further relates to herbicidal agents containing compounds I as active ingredients, and the herbicidal use of quinoline-3-carboxamides of the formula I, including the compounds disclaimed in the disclaimer.

The compounds of the formula I may be present in the following tautomeric forms, which are also encompassed by the invention:



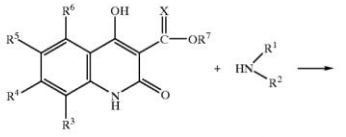
4-Hydroxycarbostyryls having anti-inflammatory and anti-allergic properties are known from Chemical Abstracts, Vol. 113, No. 211864z.

Quinoline-3-carboxamides having anticoagulant (Khim.-Farm. Zh., 24(4), 31 (Russ), 1990) and antibacterial (Chemical Abstracts 70, Nr. 67681x) properties, and derivatives acting as local anesthetics (Farm. Zh. (Kiev) (2), 78,1991), are also known.

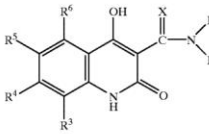
The object of the present invention was to provide novel, herbicidally effective quinoline-3-carboxamides and methods of preparing them.

This object was achieved by the quinoline-3-carboxamides I, methods of preparing them and herbicidal agents containing the compounds I. Salts of the compounds I are also encompassed by the invention.

The quinoline-3-carboxamides I are obtained for example by reacting a quinoline-3-carboxylate of the formula IIa in conventional manner (Khim.-Farm. Zh., Vol. 24, issue 4, pp. 31 and 32 (Russ.)= pp. 257–259 (Engl.), 1990), in the presence or absence of an organic solvent, with a substituted amine of the formula III:



(IIa) (III)



(I)

R^7 in formula IIa is a low-molecular-weight alkyl group, preferably C_1–C_4-alkyl such as methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl.

The reaction is generally carried out at from 20° C. to 250° C., preferably 100° C. to 180° C., in an inert organic solvent.

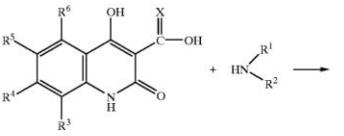
Examples of suitable solvents or diluents are aliphatic, alicyclic and aromatic hydrocarbons, such as pentane, hexane, cyclohexane, benzene, toluene, and xylenes; ethers such as diethyl and di-n-butyl ether, methyl tert.-butyl ether, dimethoxyethane, ethylene glycol dimethyl ether, tetrahydrofuran and dioxane; alcohols such as methanol, ethanol, propanol and butanol; and aprotic dipolar solvents such as dimethylformamide, dimethyl sulfoxide and pyridine.

Mixtures of these substances may also be used as solvents and diluents.

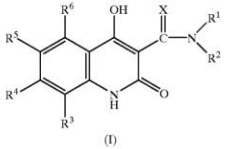
The starting materials are generally reacted with each other in stoichiometric amounts. It may be advantageous, for instance to increase the yield, to use one of the starting materials, preferably the amine, in an excess of 0.1 to 10 mole equivalents.

The reaction is generally carried out at atmospheric pressure. However, it may be advantageous, depending on the type of amine employed, to carry out the reaction at superatmospheric pressure, especially autogenously increased pressure, in an autoclave.

The compounds I may also be obtained from quinoline-3-carboxylic acids IIb by first converting IIb in conventional manner into the halide or another active form of the carboxylic acid function, and then amidating this derivative with an amine III.



(IIb) (III)



(I)

Examples of active forms of the carboxylic acids are, in addition to the halides (especially chlorides and bromides), imidazolides. Generally, the halides are preferred.

They are obtained by reacting the carboxylic acids IIb with a halogenating agent such as phosgene, thionyl chloride, phosphorus oxychloride, and phosphorus tri- and -pentachloride.

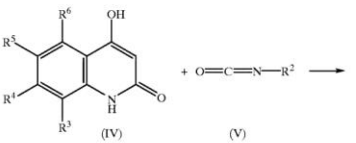
The subsequent amidation is carried out at from (−20) to 80° C., preferably from 0 to 30° C., in an inert organic solvent.

Suitable solvents for this reaction are, in particular, hydrocarbons such as benzene and toluene, halohydrocarbons such as dichloromethane, and ethers such as diethyl ether and tert-butyl methyl ether.

As hydrogen halide is formed on the amidation of acid halides, it is advantageous for increasing the yield to use the amine III in an excess, or to add an acid-binding agent such as triethylamine.

The quinoline-3-carboxamides I may advantageously be prepared from the carboxylic acids IIb in a single stage: the carboxylic acid IIb is reacted with an amine III in conventional manner (WO 90 15052) in the presence of a dehydrating agent, e.g., propanephosphonic anhydride or dicyclohexylcarbodiimide, at from 0 to 50° C., preferably 5 to 25° C., in an inert solvent such as dichloromethane, tetrahydrofuran, toluene or ethyl acetate.

Compounds of the formula I in which X is oxygen and R^1 is hydrogen may also be obtained in conventional manner (J. Org. Chem. Vol. 44, pp. 4877 et seq. (1979)) by reacting a 2,4-dihydroxyquinoline IV with an isocyanate of the formula V.



(IV) (V)