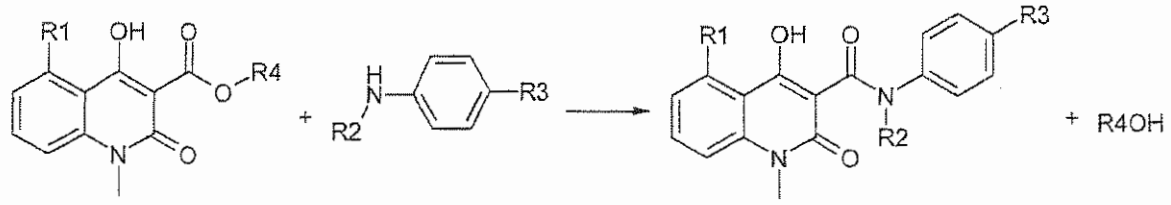
Usually formation of amides from esters and anilines requires very high reaction temperatures that also cause extensive byproduct formation. The above-mentioned reaction is enabled at moderate temperatures by the ability of **4** to unimolecularly form the ketene intermediate **5** instead of a tetrahedral intermediate. The method, which is described e.g. in US patent No. 6,875,869, comprises charging the reactor with an appropriate ester and an aniline derivative in an aliphatic solvent such as n-heptane or n-octane. The equilibrium is driven towards the desired product by distilling off the solvent and any formed alcohol. After complete reaction the mixture is cooled and the precipitated raw product is isolated by filtration.

Unlike most other reactions where esters are transformed into thermodynamically more stable amides this particular reaction needs a very efficient removal of formed alcohol in order to give a high yield.

The method described above has been used for GMP (Good Manufacturing Practice) manufacturing of paquinimod, laquinimod and tasquinimod.

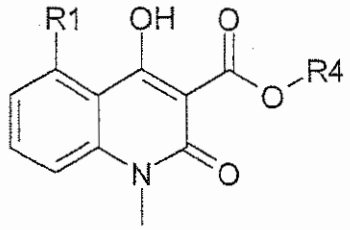
Summary ~~of the invention~~

As noted herein above, in the reaction described in Org. Process. Res&Dev. **2007**, *11*, 674-680 for preparing an N-alkyl-N-phenyl-quinoline-3-carboxamide, the main impurity in the isolated raw product is the alkyl ester, used as the starting material in the final condensation step. This condensation may be represented by to the following general reaction scheme:



(II) (III) (I) (IV)

In the reaction as represented herein above, the remaining ester (II) may be easily removed from the product by recrystallisation, if small amounts of the ester are present. On the other hand, the present inventors have discovered that if larger amounts of remaining ester are present in the raw product, only one recrystallisation may not be enough for achieving a pure product. It is therefore important to drive the equilibrium as far as possible to the product side, by removal of the alcohol (IV) that is formed as a byproduct in the reaction.



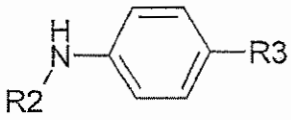
(II)

wherein

R1 is ethyl, chloro or methoxy; and

R4 is C1-C4 alkyl;

with a compound of formula (III)



(III)

wherein

R2 is ethyl and R3 is H; or

R2 is methyl and R3 is trifluoromethyl;

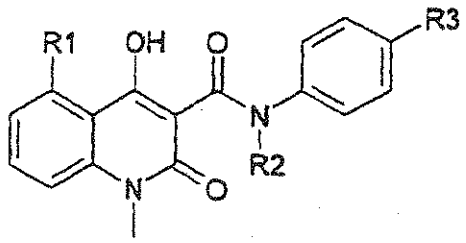
in a refluxing mixture containing an aliphatic solvent or a mixture of aliphatic solvents, said aliphatic solvent(s) having a boiling point in the range of 68-191 °C;

(ii) condensing vapors of the refluxing mixture;

(iii) treating the condensed vapors with an alcohol scavenging agent or a mixture of alcohol scavenging agents; and

(iv) returning the condensed vapors back to the reaction mixture.

In an aspect, there is provided a method for preparing a compound of formula (I)



(I)

wherein

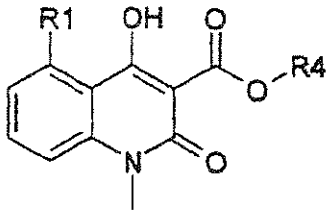
R1 is ethyl, R2 is ethyl and R3 is H; or

R1 is chloro, R2 is ethyl and R3 is H; or

R1 is methoxy, R2 is methyl and R3 is trifluoromethyl;

by

(i) reacting a compound of formula (II)



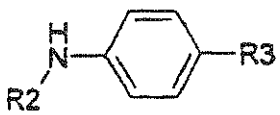
(II)

wherein

R1 is ethyl, chloro or methoxy; and

R4 is C1-C4 alkyl;

with a compound of formula (III)



(III)

wherein

R2 is ethyl and R3 is H; or

R2 is methyl and R3 is trifluoromethyl;

in a refluxing mixture containing an aliphatic solvent or a mixture of aliphatic solvents, said aliphatic solvent(s) having a boiling point in the range of 68-191 °C;

(ii) condensing vapors of the refluxing mixture;

(iii) treating the condensed vapors with an alcohol scavenging agent selected from molecular sieves or with an alcohol scavenging agent which is a mixture of molecular sieves; and

(iv) returning the condensed vapors back to the reaction mixture.

The present inventors have found that by the method as defined herein, a higher reaction yield may be obtained in a shorter reaction time, compared to the prior art methods. This in turn results in reduced energy consumption which, in addition to a reduced solvent consumption during the reaction, is very advantageous from an economic and environmental point of view. Even more importantly, by the method of the present disclosure~~invention~~, a reaction product of a higher purity is obtainable. Very advantageously, a reaction product at a higher yield and improved

purity is obtained in a shorter reaction time and at a lower solvent and energy consumption than according to the prior art methods, in particular when performing the reaction on a large scale.

Other benefits of the present disclosure~~invention~~ are that the use of an alcohol scavenging agent enables a higher distillation rate without reducing the reaction volume, thus a shorter reaction time is obtained; the solvent consumption is decreased to a minimum, by recycling the solvent; there is no need for careful monitoring of the distillation rate and there is an almost complete conversion of the ester, resulting in higher purity of the isolated product.

Brief description of the drawings

Figure 1 represents the modified Soxhlet-apparatus used in the experiments for the evaluation of scavenging agents; and

Figure 2 represents an equipment set-up in pilot plant for production of Paquinimod.

Detailed Description of the Invention

The alcohol scavenging agent

In the method of the present invention, the distillate is treated with an alcohol scavenging agent before being recycled back to the reaction mixture. The alcohol scavenging agent may be selected e.g. from molecular sieves, silica gel, and calcium chloride dihydrate or a mixture of any of these.

The present inventors have tested numerous alcohol scavenging agents in combination with different solvents and have found that molecular sieves are particularly useful for the manufacturing of compounds of formula (I) as defined herein.

Molecular sieves are crystalline metal alumina silicates having a three dimensional interconnecting network of silica and alumina tetrahedra. Molecular sieves are capable of adsorbing various polar compounds into the cavities formed by the network. Different qualities of molecular sieves exist, such as the powder forms of the 3A, 4A, 5A and 13X sieves, which may be purchased e.g. from Sigma-Aldrich Co.

In one preferable embodiment, the alcohol scavenging agent is selected from molecular sieves or is a mixture of molecular sieves. For example, the alcohol scavenging agent may be select-