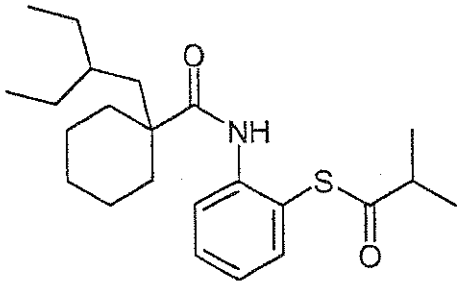
Novel process

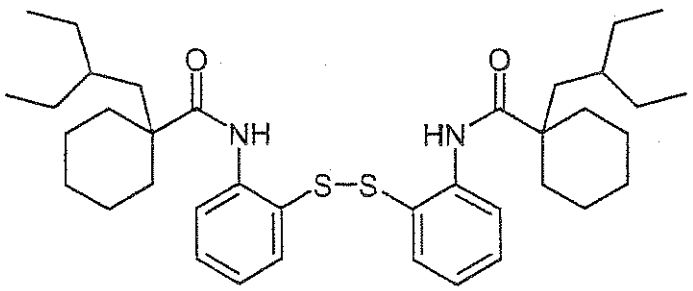
The present invention relates to a process for the preparation of S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl] 2-methylthiopropionate which is a useful pharmaceutically active compound.

In a first aspect, the present ~~invention~~disclosure provides a process for the preparation of compound of formula (I):



(I)

which comprises reacting a compound of formula (II)



(II)

with isobutyric anhydride and a reducing agent. The reducing agent may be ~~such as~~ a phosphine, phosphinite, phosphonite or phosphite.

Preferably the reducing agent is triisopropylphosphite, triphenylphosphine or tributylphosphine, more preferably triphenylphosphine or tributylphosphine, most preferably triphenylphosphine.

Preferably the reductive acylation is carried out in the presence of at least 0.1(mol/L) of the reducing agent as described before.

In another embodiment of the disclosure~~invention~~, the excess of phosphine, phosphite, phosphinite or phosphinite may be oxidized by an oxidizing agent,such as Oxone® (known as potassium peroxomonosulfate or potassium monopersulfate triple salt) or hydrogen peroxide. Most preferably the oxidizing agent is hydrogen peroxide.

In a preferred embodiment, the acylation is followed by the removal of the respective phosphine oxide, phosphate, phosphinate or phosphonate with water/alcohol extraction from organic solvent.

In a second aspect, the compound of Formula (I) when prepared according to the process as defined above .

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"(C_{1-8})alkyl" refers to a branched or straight hydrocarbon chain containing from 1 to 8 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and t-butyl, pentyl, hexyl, heptyl or octyl. (C_{1-6})alkyl is preferred.

"(C_{1-6})alkoxy" means a moiety of the formula –OR^a, wherein R^a is an (C_{1-6})alkyl moiety as defined herein. Examples of alkoxy moieties include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

"alcohol" refers to a an (C_{1-8})alkyl as defined above substituted by an hydroxy group. Examples of alcohols include, but are not limited to, methanol, ethanol, isopropanol, propanol and butanol. Methanol is preferred.

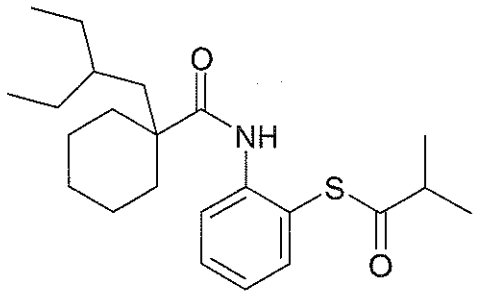
"(C_{3-8})cycloalkyl" refers to a single saturated carbocyclic ring containing from 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

"phenyl(C_{1-3})alkyl" refers to the group R^{8ac}-R^{8ad}-, wherein R^{ac} and R^{ad} are , respectively, "optionally substituted phenyl" and "(C_{1-3})alkyl" as defined above.

"phosphine" refers to a compound of formula PR_3, wherein each "R" may be the same or different and is independently selected from (C_{1-6})alkyl, (C_{3-6})cycloalkyl, phenyl or phenyl(C_{1-3})alkyl as defined above. Representative examples include, but are not limited to,

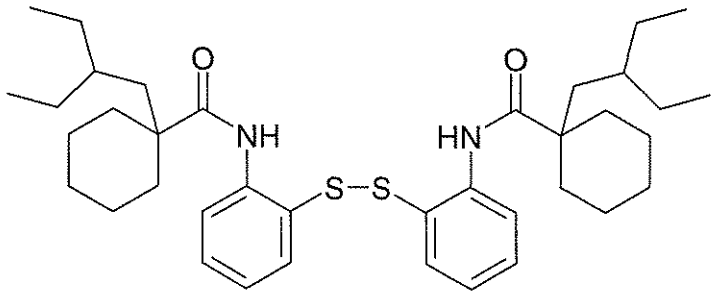
Claims

1. A process for the preparation of the compound of formula (I):



(I)

which comprises reacting a compound of formula (II~~I~~)



(II~~I~~)

with isobutyric anhydride and a reducing agent.

2. The process according to claim 1, wherein the acylation is carried out with at least 0.10M of a reducing agent.

3. The process according to either claim 1 or 2, wherein the said reducing agent is a phosphine, phosphinite, phosphonite or phosphite.

4. A process according to ~~any one of~~ claims ~~1 to~~ 3, which further comprises the oxidation of the excess of the reducing agent with an oxidizing agent.

5. The process according to claim 4, wherein the oxidizing agent is Oxone® known as potassium peroxomonosulfate or potassium monopersulfate triple salt, or hydrogen peroxide~~,~~.

6. The process according to claim 4, wherein the oxidizing agent is ~~most preferably the oxidizing agent is~~ hydrogen peroxide.

~~6~~7. The process according to any one of claims 1 to ~~6~~5, wherein the said reducing agent is a phosphine.

~~7~~8. The process according to any one of claims 1 to ~~7~~6, wherein the said reducing agent is triphenyl phosphine.

~~8~~9. The process according to any one of claims 1 to ~~6~~7 which further comprises the extraction of phosphine oxide, phosphinate, phosphonate or phosphate from compound of formula (I) in the presence of an organic solvent with water/alcohol mixtures.

~~9~~10. The process according to either claim ~~7~~6 or ~~7~~8, which further comprises the extraction of phosphine oxide~~,~~ from compound of formula (I) in the presence of an organic solvent with water/alcohol mixtures.

11. The process according to either claim 7 or 8, which further comprises the extraction of ~~more preferably~~ triphenyl phosphine oxide from compound of formula (I) in the presence of an organic solvent with water/alcohol mixtures.

12. The compound of Formula (I) when prepared according to the process of any one of claims 1 to 11.

~~10. The process according to any of claims 1 to 9 which further comprises crystallizing compound of formula (I) from a water miscible solvent as solvent and water as antisolvent.~~

~~11. The process according to 10 wherein the water miscible solvent is acetone, ethanol, isopropanol, propanol or mixtures thereof, most preferably ethanol.~~

~~12. The process according to any of claims 1 to 9 which further comprises a crystallization from an non polar solvent, preferably hexane, cyclohexane, heptane, pentane, most preferably from heptane.~~

~~13. The process according to any one of claims 1 to 9, which further comprises the following steps:~~

~~a) forming a solution of compound of formula (I) in acetone, ethanol, isopropanol or propanol at a temperature of 40°C to 70°C;~~

~~b) cooling the solution until supersaturation, preferably to room temperature;~~

~~c) adding seed crystals of compound of formula (I);~~

~~d) optionally aging the suspension, preferably for at least 10 min, most preferably for 60 minutes;~~

~~e) adding water while stirring until the desired solvent/water ratio is obtained, more preferably ethanol:water is 7:3 (m/m);~~

~~f) optionally further stirring the crystallization mixture;~~

g) cooling the crystallization mixture to a temperature below 0°C, more preferably between 0°C and -20°C, most preferably to -10°C, to effect the crystallization and precipitation of compound of formula (I) from the solution thereof,

h) separating the crystalline compound of formula (I) from the liquid component of the mixture, preferably the crystalline compound of formula (I) is filtered out.

14. A process for preparing the crystalline S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl] 2-methylthiopropionate, compound of formula (I) which comprises:

a) forming a solution of compound of formula (I) in acetone, ethanol, isopropanol or propanol at a temperature of 40°C to 70°C;

b) cooling the solution until supersaturation, preferably to room temperature;

c) adding seed crystals of compound of formula (I);

d) optionally aging the suspension, preferably for at least 10 min, most preferably for 60 minutes;

e) adding water while stirring until the desired solvent/water ratio is obtained, more preferably ethanol:water is 7:3 (m/m);

f) optionally further stirring the crystallization mixture;

g) cooling the crystallization mixture to a temperature below 0°C, more preferably between 0°C and -20°C, most preferably to -10°C, to effect the crystallization and precipitation of compound of formula (I) from the solution thereof,

h) separating the crystalline compound of formula (I) from the liquid component of the mixture, preferably the crystalline compound of formula (I) is filtered out.

15. S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl] 2-methylthiopropionate crystalline form prepared by a process comprising the steps of :

a) forming a solution of compound of formula (I) in acetone, ethanol, isopropanol or propanol at a temperature of 40°C to 70°C;

b) cooling the solution until supersaturation, preferably to room temperature;

c) adding seed crystals of compound of formula (I);

d) optionally aging the suspension, preferably for at least 10 min, most preferably for 60 minutes;

e) adding water while stirring until the desired solvent/water ratio is obtained, more preferably ethanol:water is 7:3 (m/m);

f) optionally further stirring the crystallization mixture;

g) cooling the crystallization mixture to a temperature below 0°C, more preferably between 0°C and -20°C, most preferably to -10°C, to effect the crystallization and precipitation oof compound of formula (I) from the solution thereof,

h) separating the crystalline compound of formula (I) from the liquid component of the mixture, preferably the crystalline compound of formula (I) is filtered out.

16. The invention as hereinbefore described.