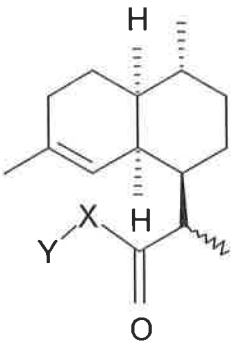
CLAIMS

1. A process for preparing artemisinin, comprising the steps of:

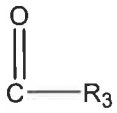
- preparing a mixture comprising (i) a dihydroartemisinic acid derivative of formula (I)



(I)

wherein

- X is O
- Y is formula (II)



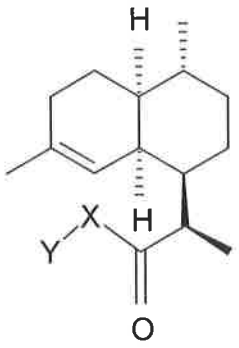
(II)

- R_1 is hydrogen; a C_1-C_{12} alkyl group which is linear or branched or a C_3-C_{10} cycloalkyl group, said alkyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; a trifluoromethyl group; a cycloalkylalkyl group where cycloalkyl and alkyl are as defined above; a C_2-C_{12} alkenyl group which is linear or branched, said alkenyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; a C_5-C_{14} aryl or heteroaryl group, said aryl or heteroaryl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; an arylalkyl group where aryl and alkyl are as defined above; or a heteroarylalkyl group where heteroaryl and alkyl are as defined above;
- R_3 is OR_1, where R_1 is as defined above;

(ii) at least one organic solvent and (iii) a photosensitizer,

- subjecting said mixture to photooxidation by means of a light source, and
- recovering the artemisinin thus obtained.

2. The process of claim 1, wherein the dihydroartemisinic acid derivative has the formula (Ia)



(Ia)

in which X and Y are as defined in claim 1.

3. The process according to claim 1 or 2, wherein the at least one organic solvent is selected from the group consisting of alcohols, chlorinated solvents, ketones, sulfoxides, nitriles, N,N-disubstituted amines, esters, nitrogenated heterocycles, ethers, alkanes, aromatic solvents, and mixtures thereof.

4. The process according to claim 1 or 2, wherein the at least one organic solvent is dichloromethane.

5. The process according to claim 1 or 2, wherein the organic solvent comprises a polar solvent and the polar solvent is used in a ratio of about 4 to 20 volumes with respect to the dihydroartemisinic acid derivative of formula (I) or (Ia).

6. The process according to claim 1 or 2, wherein the photosensitizer is selected from Rose bengal, tetraphenylporphyrin, tetraphenylporphyrin derivatives, tetramethylthionine chloride (methylene blue) and toluidine blue.

7. The process according to claim 1 or 2, wherein the photosensitizer is used in a molar ratio of about 0.000001 to 1 equivalent with respect to the dihydroartemisinic acid derivative of formula (I) or (Ia).

8. The process according to claim 1 or 2, wherein the mixture comprises an acid catalyst.

9. The process according to claim 8, wherein the acid catalyst is present in an amount of 0.5 equivalent per equivalent of compound of formula (I) or (Ia).

10. The process according to claim 8, wherein the acid catalyst is a protic acid.

11. The process according to claim 8, wherein the acid catalyst is trifluoroacetic acid.

12. The process according to claim 1 or 2, wherein it comprises the steps of:

- preparing a mixture comprising (i) a dihydroartemisinic acid derivative of formula (I) or (Ia) as defined in claim 1 or 2, (ii) at least one organic solvent, and (iii) a photosensitizer at ambient temperature,
- cooling the reaction mixture to a temperature in the range of about -78°C to ambient temperature with air or oxygen bubbling into it,
- adding a catalytic amount of an acid catalyst,
- switching the light source on,
- maintaining the reaction mixture at the same temperature for 3 h to 24 h,
- warming up the reaction mixture to a temperature in the range of about 5 to 15°C for 2 to 4 hours, and then to a higher temperature in the range of about 15 to 25°C for 1 to 3 hours,
- stopping the reaction,

- maintaining the reaction mixture at a temperature in the range of about 15°C to 25°C for 1 to 3 hours, and

- recovering the artemisinin thus obtained.

13. The process according to claim 12, wherein the acid catalyst is chosen from protic acids or Lewis acids.

14. The process according to claim 12, wherein:

- the first cooling step is carried out at a temperature between -5°C and -20°C;

- during the warming up step, the reaction mixture is warmed up to 10°C for 2h, and then to ambient temperature for 1 hour, or

- after stopping the reaction, the reaction mixture is maintained at ambient temperature for 2h.

15. The process according to claim 12, further comprising further purifying the recovered artemisinin.

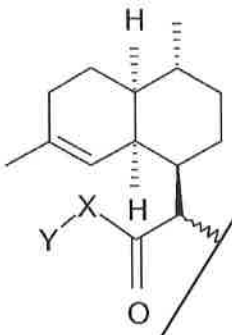
16. The process according to claim 1 or 2, wherein the artemisinin is recovered by precipitation and isolation in an alkane/alcohol mixture.

17. The process according to claim 16, wherein the alkane is selected from n-heptane, n-hexane, cyclohexane, n-pentane, and CMC; and the alcohol is selected from ethanol and isopropanol.

CLAIMS

1. A process for preparing artemisinin, comprising the steps of:

- preparing a mixture comprising (i) a dihydroartemisinic acid derivative of formula (I)



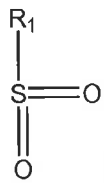
(I)

wherein

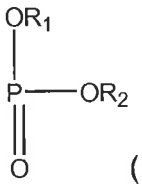
- X is O, S, NH or NO
- Y is a group selected from formulae (II), (III) and (IV)



(II)



(III)



(IV)

or, when, X is O, Y can represent OR_4

- R_1 and R_2, independently from each other, are hydrogen; a C_1-C_{12} alkyl group which is linear or branched or a C_3-C_{10} cycloalkyl group, said alkyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; a trifluoromethyl group; a cycloalkylalkyl group where cycloalkyl and alkyl are as defined above; a C_2-C_{12} alkenyl group which is linear or branched, said alkenyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-

C_6 alkyl group and a halogen; a C_5-C_{14} aryl or heteroaryl group, said aryl or heteroaryl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; an arylalkyl group where aryl and alkyl are as defined above; or a heteroarylalkyl group where heteroaryl and alkyl are as defined above;

- R_3 is R_1, OR_1, NHR_1 or NR_1R_2, where R_1 and R_2 are as defined above;

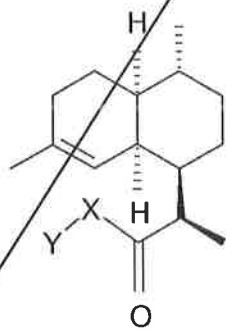
- R_4 is identical to R_1, except that R_4 cannot represent hydrogen or else R_4 represents a silyl group;

(ii) at least one organic solvent and (iii) a photosensitizer,

- subjecting said mixture to photooxidation by means of a light source, and

- recovering the artemisinin thus obtained.

2. The process of claim 1, characterized in that the dihydroartemisinic acid derivative has the formula (Ia)



(Ia)

in which X and Y are as defined in claim 1.

3. The process according to claim 1 or 2, characterized in that the at least one organic solvent is selected from the group consisting of alcohols, chlorinated solvents, ketones, sulfoxides, nitriles, N,N-disubstituted amines, esters, nitrogenated heterocycles, ethers, alkanes, aromatic solvents, and mixtrues thereof.

4. The process according to any one of claims 1 to 3, characterized in that the at least one organic solvent is dichloromethane.

5. The process according to any one of claims 1 to 4, characterized in that the polar solvent is used in a ratio of about 4 to 20 volumes with respect to the dihydroartemisinic acid derivative of formula (I) or (Ia).

6. The process according to any one of claims 1 to 5, characterized in that the photosensitizer is selected from Rose bengal, tetraphenylporphyrin, tetraphenylporphyrin derivatives, tetramethylthionine chloride (methylene blue) and toluidine blue.

7. The process according to any one of claims 1 to 6, characterized in that the photosensitizer is used in a molar ratio of about 0.000001 to 1 equivalent with respect to the dihydroartemisinic acid derivative of formula (I) or (Ia).

8. The process according to any one of claims 1 to 7, characterized in that the mixture comprises an acid catalyst.

9. The process according to any one of claims 1 to 8, characterized in that the acid catalyst is present in an amount of 0.5 equivalent per equivalent of compound of formula (I) or (Ia).

10. The process according to any one of claims 1 to 9, characterized in that the acid catalyst is a protic acid.

11. The process according to any one of claims 1 to 9, characterized in that the acid catalyst is trifluoroacetic acid.

12. The process according to any one of claims 1 to 11, characterized in that it comprises the steps of:

- preparing a mixture comprising (i) a dihydroartemisinic acid derivative of formula (I) or (Ia) as defined in claim 1 or 2, (ii) at least one organic solvent, and (iii) a photosensitizer at ambient temperature,
- cooling the reaction mixture to a temperature in the range of about -78°C to ambient temperature with air or oxygen bubbling into it,
- adding a catalytic amount of an acid catalyst,
- switching the light source on,

- maintaining the reaction mixture at the same temperature for 3 h to 24 h,

- warming up the reaction mixture to a temperature in the range of about 5 to 15°C for 2 to 4 hours, and then to a higher temperature in the range of about 15 to 25°C for 1 to 3 hours,

- stopping the reaction by means such as sequentially, in either sequence, or concurrently switching the light source off and stopping the air or oxygen bubbling, followed by adding a quencher at ambient temperatures,

- maintaining the reaction mixture at a temperature in the range of about 15°C to 25°C for 1 to 3 hours, and

- recovering the artemisinin thus obtained.

13. The process according to claim 12, characterized in that the acid catalyst is chosen amongst protic acids and/or Lewis acids, such as amongst protic acids, such as trifluoroacetic acid.

14. The process according to any one of claims 12 to 13, characterized in that:

- the first cooling step is carried out at a temperature between -5°C and -20°C, for example -10°C;

- during the warming up step, the reaction mixture is warmed up to 10°C for 2h, and then to ambient temperature, such as 20°C for 1 hour, and/or

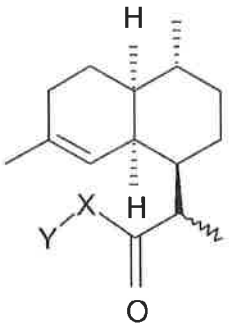
- after stopping the reaction, the reaction mixture is maintained at ambient temperature, such as 20°C for 2h.

15. The process according to any one of claims 12 to 14, characterized in that it comprises an additional purification step of the recovered artemisinin.

16. The process according to any one of claims 1 to 14 characterized in that the artemisinin is recovered by precipitation and isolation in an alkane/alchohol mixture.

17. The process according to claim 16, wherein the alkane is selected from n-heptane, n-hexane, cyclohexane, n-pentane, and CMC; and the alcohol is selected from ethanol and isopropanol.

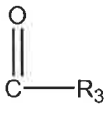
18. Compounds of formula (I)



(I)

wherein

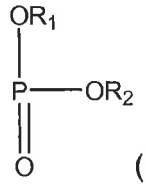
- X is O, S, NH or NO
- Y is a group selected from formulae (II), (III) and (IV)



(II)



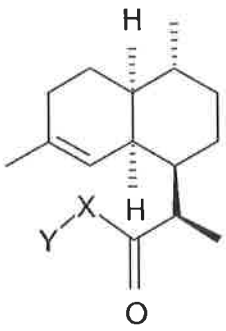
(III)



(IV)

- R_1 and R_2, independently from each other, are hydrogen; a C_1-C_{12} alkyl group which is linear or branched or a C_3-C_{10} cycloalkyl group, said alkyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; a trifluoromethyl group; a cycloalkylalkyl group where cycloalkyl and alkyl are as defined above; a C_2-C_{12} alkenyl group which is linear or branched, said alkenyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; a C_5-C_{14} aryl or heteroaryl group, said aryl or heteroaryl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; an arylalkyl group where aryl and alkyl are as defined above; or a heteroarylalkyl group where heteroaryl and alkyl are as defined above; and
- R_3 is R_1, OR_1, NHR_1 or NR_1R_2, where R_1 and R_2 are as defined above.

19. A compound of formula (I) according to claim 18, which is the diastereoisomer of formula (Ia)



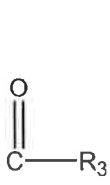
(Ia)

wherein X and Y are as defined in claim 16.

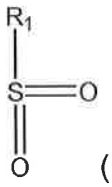
20. A compound of formula (I) or (Ia) according to claims 18 or 19, wherein X is O.

21. A compound of formula (I) or (Ia) according to any one of claims 18 to 20, wherein

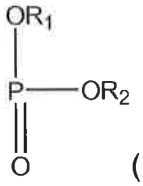
- X is O;
- Y is a group selected from formulae (II), (III) or (IV)



(II)



(III)



(IV)

- R_1 and R_2, independently from each other, are hydrogen; a C_1-C_{12} alkyl group which is linear or branched or a C_3-C_{10} cycloalkyl group, said alkyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; a C_2-C_{12} alkenyl group which is linear or branched, said alkenyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; a trifluoromethyl group; or a C_5-C_{14} aryl or heteroaryl group, said aryl or heteroaryl group being unsubstituted or substituted by one or more

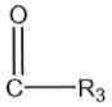
substituent(s) selected from a C_1-C_6 alkyl group and a halogen; and

- R_3 is R_1, OR_1 or NR_1R_2, where R_1 and R_2 are as defined above.

22. A compound of formula (I) or (Ia) according to any one of claims 18 to 21, wherein

- X is O;

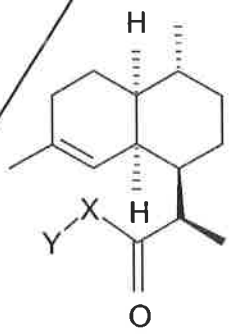
- Y represents a group of formula (II)



(II)

where R_3 is OR_1 and R_1 is a C_1-C_{12} alkyl group which is linear or branched or a C_3-C_{10} cycloalkyl group, said alkyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen, or a C_6-C_{14} aryl or heteroaryl group, said aryl or heteroaryl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen.

23. The use of a compound of formula (I) or (Ia)

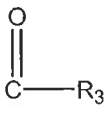


(Ia)

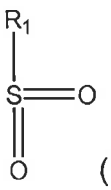
wherein

- X is O, S, NH or NO

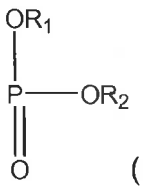
- Y is a group selected from formulae (II), (III) or (IV)



(II)



(III)



(IV)

- R_1 and R_2, independently from each other, are hydrogen; a C_1-C_{12} alkyl group which is linear or branched or a C_3-C_{10} cycloalkyl group, said alkyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; a trifluoromethyl group; a cycloalkylalkyl group where cycloalkyl and alkyl are as defined above; a C_2-C_{12} alkenyl group which is linear or branched, said alkenyl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; a C_5-C_{14} aryl or heteroaryl group, said aryl or heteroaryl group being unsubstituted or substituted by one or more substituent(s) selected from a C_1-C_6 alkyl group and a halogen; an arylalkyl group where aryl and alkyl are as defined above; or a heteroarylalkyl group where heteroaryl and alkyl are as defined above; and

- R_3 is R_1, OR_1, NHR_1 or NR_1R_2, where R_1 and R_2 are as defined above, for preparing artemisinin.