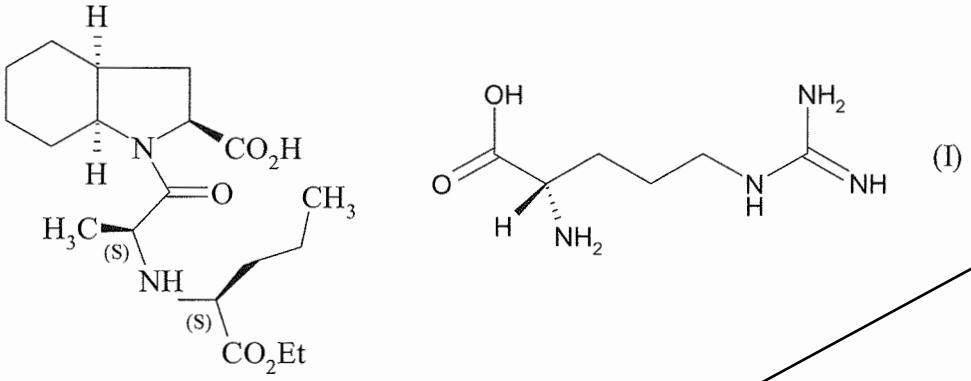
CLAIMS

1. Process for the preparation of perindopril L-arginine salt of formula (I):



by means of reaction between perindopril and L-arginine in a solvent system selected from:

a binary mixture of acetonitrile and dimethyl sulphoxide,

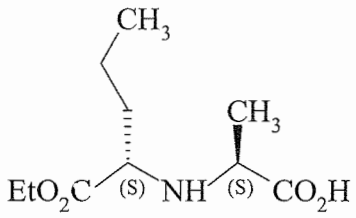
a binary mixture of ethyl acetate and dimethyl sulphoxide,

a ternary mixture of acetonitrile, dimethyl sulphoxide and toluene,

at a temperature from 10 to 100°C,

followed by isolation by means of filtration of the L-arginine salt thereby obtained.

2. Process for the preparation of perindopril L-arginine salt according to claim 1, wherein the perindopril is obtained by reaction of N-[1-(S)-ethoxycarbonyl-butyl]-(S)-alanine of formula (II):

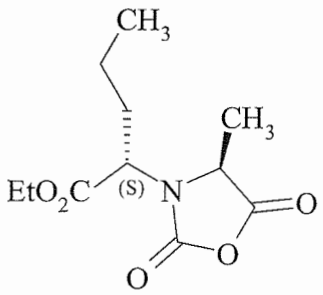


with an activation agent of formula $X_2C=O$ wherein X represents a leaving group,

in an organic solvent or a system of organic solvents,

at a temperature from –20 to 80°C,

followed by reaction of the intermediate compound of formula (III) thereby obtained:



(III)

with (2S, 3aS, 7aS)-2-carboxyperhydroindole,
at a temperature from 0 to 80°C,

and then the perindopril thereby obtained is reacted with L-arginine in accordance with the process of claim 1.

3. Process for the preparation of perindopril L-arginine salt according to claim 2, wherein the activation agent is N,N'-carbonyldiimidazole, phosgene, triphosgene, (1,1'-carbonyldi(1,2,4-triazole) or di(N-succinimidyl) carbonate.

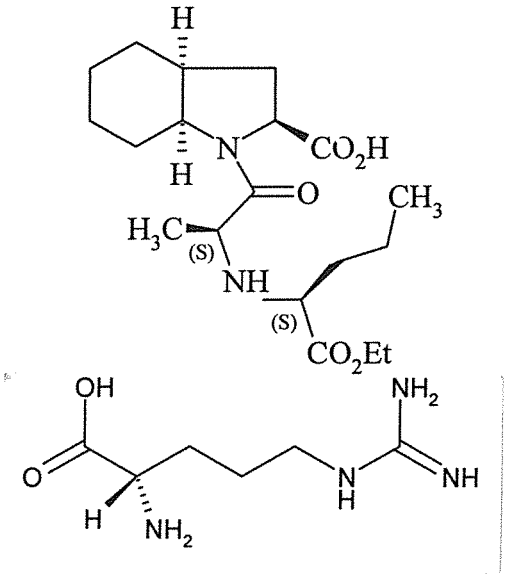
4. Process for the preparation of perindopril L-arginine salt according to claim 3, wherein the activation agent is N,N'-carbonyldiimidazole and the amount of N,N'-carbonyldiimidazole is between 0.8 and 1.2 moles, inclusive, per mole of N-[1-(S)-ethoxycarbonyl-butyl]-(S)-alanine.

5. Process for the preparation of perindopril L-arginine salt according to any one of claims 2 to 4, wherein the amount of (2S, 3aS, 7aS)-2-carboxyperhydroindole is between 0.8 and 1.2 moles, inclusive, per mole of N-[1-(S)-ethoxycarbonyl-butyl]-(S)-alanine.

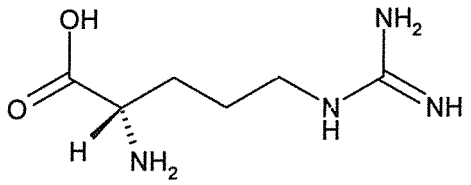
6. Process for the preparation of perindopril L-arginine salt according to claim 1, wherein the perindopril is obtained by desaltification of perindopril tert-butylamine by the action of an acid, and then the perindopril thereby obtained is reacted with L-arginine in accordance with the process of claim 1.

The invention claimed is:

1. A process for the preparation of perindopril L-arginine salt of formula (I):



(I)



(I)

by means of reaction between perindopril and L-arginine in a solvent system selected fr the group consisting of:

a binary mixture of acetonitrile and dimethyl sulphoxide,

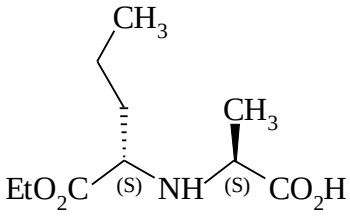
a binary mixture of ethyl acetate and dimethyl sulphoxide, and

a ternary mixture of acetonitrile, dimethyl sulphoxide and toluene,

at a temperature from 10 to 100°C,

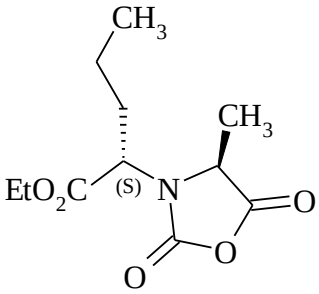
followed by isolation by means of filtration of the L-arginine salt thereby obtained.

2. The process accordingly to claim 1, wherein the perindopril is obtained by reaction of N-[1-(S)-ethoxycarbonyl-butyl]-(S)-alanine of formula (II):



(II)

with an activation agent of formula $X_2C=O$ wherein X represents a leaving group,
in an organic solvent or a system of organic solvents,
at a temperature from –20 to 80°C,
followed by reaction of the intermediate compound of formula (III) thereby obtained:



(III)

with (2S, 3aS, 7aS)-2-carboxyperhydroindole,
at a temperature from 0 to 80°C,

3. The process according to claim 2, wherein the activation agent is carbonyldiimidazole, phosgene, triphosgene, (1,1'-carbonyldi(1,2,4-triazole) or di(N-succinimidyl) carbonate.

4. The process according to claim 3, wherein the activation agent is carbonyldiimidazole and the amount of N,N'-carbonyldiimidazole is between 0.8 and 1.2 moles, inclusive, per mole of N-[1-(S)-ethoxycarbonyl-butyl]-(S)-alanine.

5. The process according to claim 2, wherein the amount of (2S, 3aS, 7aS)-2-carboxyperhydroindole is between 0.8 and 1.2 moles, inclusive, per mole of N-[1-(S)-ethoxycarbonyl-butyl]-(S)-alanine.

6. The process according to claim 3, wherein the amount of (2S, 3aS, 7aS)-2-carboxyperhydroindole is between 0.8 and 1.2 moles, inclusive, per mole of N-[1-(S)-ethoxycarbonyl-butyl]-(S)-alanine.

7. The process accordingly to claim 4, wherein the amount of (2S, 3aS, 7aS)-2-carboxyperhydroindole is between 0.8 and 1.2 moles, inclusive, per mole of N-[1-(S)-ethoxycarbonyl-butyl]-(S)-alanine.

8. The process accordingly to claim 1, wherein the perindopril is obtained desaltification of perindopril tort-butylamine by the action of an acid.