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(54) **Title**: PROCESS FOR THE PREPARATION OF AROMATIC THIOL DERIVATIVES BY HYDROGENATION OF DISULFIDES

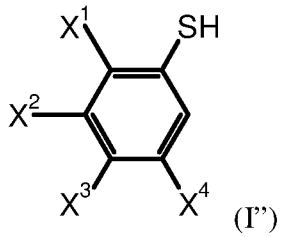
(57) **Abstract**: The application relates to the preparation of thiophenols by reacting the corresponding disulfide with hydrogen in the presence of a heterogeneous transition metal hydrogenation catalyst. If the reaction is carried out in the presence of an acylating agent such as a carboxylic acid anhydride or halide, an acylated thiophenol is obtained. The pharmaceutically active compound S - [2 - [1 - (2 - ethylbutyl) cyclohexylcarbonylamino] -phenyl] 2 -methylthiopropionate is produced via said process.

PROCESS FOR THE PREPARATION OF AROMATIC THIOL DERIVATIVES BY HYDROGENATION OF DISULFIDES

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.

S-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl] amino) phenyl] 2- methylpropanethioate has been shown to be an inhibitor of CETP activity in humans (de Grooth et al., Circulation, 105, 2159-2165 (2002)) and rabbits (Shinkai et al., J. Med. Chem., 43, 3566-3572 (2000); Kobayashi et al., Atherosclerosis, 162, 131-135 (2002); and Okamoto et al., Nature, 406 (13), 203-207 (2000)). S-[2-([[1-(2- ethylbutyl) cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate has been shown to increase plasma HDL cholesterol in humans (de Grooth et al., supra) and in rabbits (Shinkai et al., supra ; Kobayashi et al., supra ; Okamoto et al., supra). Moreover, S-[2-([[1-(2- ethylbutyl) cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate has been shown to decrease LDL cholesterol in humans (de Grooth et al. , supra) and rabbits (Okamoto et al., supra). Additionally, S-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2- methylpropanethioate inhibits the progression of atherosclerosis in rabbits (Okamoto et al., supra).

In a first embodiment, the invention provides a process for the preparation of a compound of formula (I"):



(I")

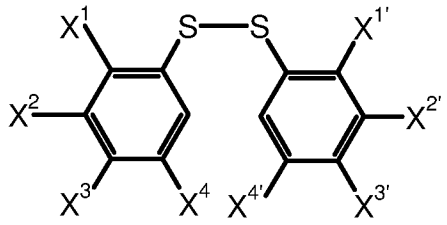
wherein X^1, X^2, X^3 and X^4 are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$; or

two adjacent substituents (i.e. X^1 and X^2 or X^2 and X^3 or X^3 and X^4) together with the carbon atoms to which they are attached form a four, five or six membered cycloalkyl ring that optionally includes an additional heteroatom selected from O, NH and S wherein the heresaid four, five or six membered cycloalkyl ring is optionally substituted with one to three substituents independently selected from with (C_1- C_8)alkyl or aryl;

R^a, R^b, R^c and R^d are independently (C_1- C_8)alkyl, (C_3- C_8)cycloalkyl, aryl or heteroaryl;

each R^e are independently hydrogen, (C_1- C_8)alkyl or aryl;

which comprises reacting a compound of formula (II"):



(II")

wherein $X^{1'}$, $X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$; or

two adjacent substituents (i.e. $X^{1'}$ and $X^{2'}$ or $X^{2'}$ and $X^{3'}$ or $X^{3'}$ and $X^{4'}$) together with the carbon atoms to which they are attached form a four, five or six membered cycloalkyl ring that optionally includes an additional heteroatom selected from O, NH and S wherein the heresaid four, five or six membered cycloalkyl ring is optionally substituted one to three substituents independently selected from with (C_1- C_8)alkyl or aryl; and

R^a, R^b, R^c, R^d, R^e, X^1, X^2, X^3 and X^4 are as defined above,

with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

Common reduction disulfide processes result inter alia to the similar disadvantages. They use reducing agents in stoichiometric amounts leading to safety issues, large amount of waste and/or laborious work-up. Although these disadvantages on lab scale may not be seen of great importance, when going on large production scale they are looked at carefully due their factorial impact.

The S-S disulfide bonds (and the S-H bonds formed during the hydrogenation) are considered as catalyst poisons, due to the strong chemisorptions of sulfur-containing molecules on metal surfaces (Houben-Weyl, Methoden der Organischen Chemie, Band IV/1c, published 1980, page 486; or F. Zymalkowski, Katalytische Hydrierungen im Organisch-Chemischen Laboratorium, F. Enke Verlag Stuttgart, published 1965, page37).

Therefore, it was surprisingly found that the reduction of a disulfide bond according to the present invention is selective with a high throughput.

The present invention does not require a pretreatment of the catalyst, in particular, there is no need of sulfide pretreatment of the catalysts.

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

The term "halo" or "halide" means fluoro, chloro, bromo or iodo, in particular chloro or bromo.

"(C_1- C_8)alkyl" refers to a branched or straight hydrocarbon chain of one to eight carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, ethyl-butyl, pentyl, hexyl, heptyl and octyl.

"(C_1- C_8)alkoxy" means a moiety of the formula –OR^{ab}, wherein R^{ab} is an (C_1- C_8)alkyl moiety as defined herein. Examples of alkoxy moieties include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

"(C_3- C_8)cycloalkyl" refers to a single saturated carbocyclic ring of thee to eight ring carbons, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Cycloalkyl may optionally be substituted with one or more substituents, preferably one, two or three, substituents. Preferably, cycloalkyl substituent is selected from the group consisting of (C_1- C_8)alkyl, hydroxy, (C_1- C_8)alkoxy, halo(C_1- C_8)alkyl, halo(C_1- C_8)alkoxy, halo, amino, mono- and di(C_1- C_8)alkylamino, hetero(C_1- C_8)alkyl, acyl, aryl and heteroaryl.

"Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon moiety which is optionally substituted with one or more, preferably one, two or three, substituents, each of which is preferably selected from the group consisting of (C_1- C_8)alkyl, hydroxy, (C_1- C_8)alkoxy, amino, mono- and di(C_1- C_8)alkylamino, carboxy, (C_1- C_8)alkylsulfonyl, -SO_2-aryl, -SO_3H, -SO_3-(C_1- C_8)alkyl or -SO_2-NR^{ac}_2, wherein each R^{ac} is independently hydrogen or (C_1- C_8)alkyl. More specifically the term aryl includes, but is not limited to, phenyl, 1-naphthyl, 2-naphthyl, and the like, each of which can be substituted or unsubstituted.

"Heteroaryl" means a monovalent monocyclic or bicyclic moiety of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S (preferably N or O), the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl moiety will be on an aromatic ring. The heteroaryl ring is optionally substituted independently with one or more substituents, preferably one, two or three substituents, each of which is independently selected from (C_1-

C_8)alkyl, halo(C_1- C_8)alkyl, hydroxy, (C_1- C_8)alkoxy, halo, nitro and cyano. More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidinyl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, tetrahydroquinolinyl, isoquinolyl, benzimidazolyl, benzisoxazolyl or benzothienyl, imidazo[1,2-a]-pyridinyl, imidazo[2,1-b]thiazolyl, and the derivatives thereof.

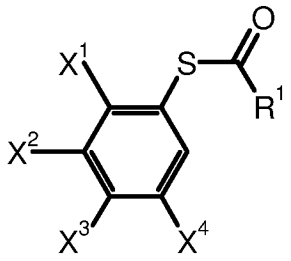
"Heterogeneous transition metal hydrogenation catalyst" refers to a transition metal hydrogenation catalyst which acts in different phase than the substrate. Especially the transition metal hydrogenation catalyst is in the solid phase. In particular while the transition metal hydrogenation catalyst is in the solid phase the reactants are in the liquid phase. The transition metal hydrogenation catalyst contains a transition metal which forms one or more stable ions which have incompletely filled *d* orbitals (i.e. Pd, Pt, Rh, Au, Ni, Co, Ru, Ir) in particular noble metal, such as Pd, Pt, Rh or Au. In these catalysts the transition metal is in particular "supported", which means that the catalyst is dispersed on a second material that enhances the effectiveness. The "support" can be merely a surface on which the metal is spread to increase the surface area. The supports are porous materials with a high surface area, most commonly alumina or various kinds of carbon. Further examples of supports include, but are not limited to, silicon dioxide, titanium dioxide, calcium carbonate, barium sulfate, diatomaceous earth and clay. The metal itself can also act as a support, if no other support is present. More specifically the term "heterogeneous transition metal hydrogenation catalyst" includes but is not limited to, a Raney catalyst (e.g. Ra-Ni, Ra-Co,) Pd/C, $Pd(OH)_2$/C, Au/TiO_2, Rh/C, Ru/Al_2O_3, Ir/$CaCO_3$, or Pt/C. In a particular embodiment, the "heterogeneous transition metal hydrogenation catalyst" are not pre-treated with sulphide.

"area%" for a substance A refers to the (area of substance A)/(sum of areas of all peaks)x100, area as obtained from HPLC or GC analysis.

In particular, the chemical groups whose definitions are given above are those specifically exemplified in the examples.

Unless otherwise stated all percentages are given in weight percent of the total weight of the compound of formula (I).

In a second embodiment, the invention provides a process for the preparation of a compound of formula (I'''):



(I''')

wherein X^1, X^2, X^3 and X^4 are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$; or

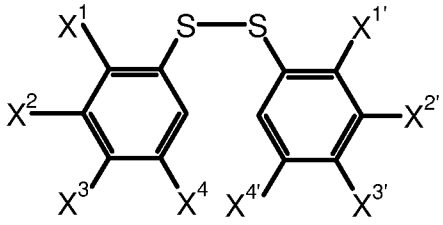
two adjacent substituents (i.e. X^1 and X^2 or X^2 and X^3 or X^3 and X^4) together with the carbon atoms to which they are attached form a four, five or six membered cycloalkyl ring that optionally includes an additional heteroatom selected from O, NH and S wherein the heresaid four, five or six membered cycloalkyl ring is optionally substituted one to three substituents independently selected from with (C_1- C_8)alkyl or aryl;

R^1 is (C_1-C_8)alkyl or aryl;

R^a, R^b, R^c and R^d are independently (C_1- C_8)alkyl, (C_3- C_8)cycloalkyl, aryl or heteroaryl;

each R^e are independently hydrogen, (C_1- C_8)alkyl or aryl;

which comprises reacting a compound of formula (II''):



(II'')

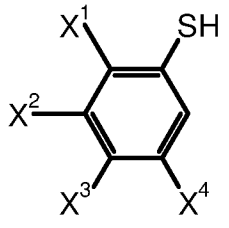
wherein $X^{1'}$, $X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$; or

two adjacent substituents (i.e. $X^{1'}$ and $X^{2'}$ or $X^{2'}$ and $X^{3'}$ or $X^{3'}$ and $X^{4'}$) together with the carbon atoms to which they are attached form a four, five or six membered cycloalkyl ring that optionally includes an additional heteroatom selected from O, NH and S wherein the heresaid four, five or six membered cycloalkyl ring is optionally substituted one to three substituents independently selected from with (C_1- C_8)alkyl or aryl; and

R^a, R^b, R^c, R^d, R^e, X^1, X^2, X^3 and X^4 are as defined above,

with H_2 in the presence of an acylating agent such as an anhydride derivative [($(C_1$-$C_8)$alkyl)C(=O)]$_2$O or [aryl(C=O)]$_2$O or a halide derivative ($(C_1$-$C_8)$alkyl)C(=O)halide or aryl(C=O)halide and a heterogeneous transition metal hydrogenation catalyst.

In another embodiment, the present invention provides a process for the preparation of a compound of formula (I"):



(I")

wherein

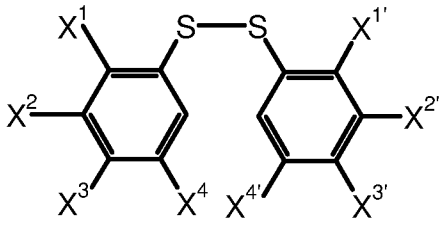
X^1 is -NH-C(=O)R^d, wherein R^d is (C_3- C_8)cycloalkyl substituted by (C_1- C_8)alkyl, in particular R^d is (2-Ethyl-butyl)-cyclohexyl;

X^2, X^3 and X^4 are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –NR^e_2, in particular X^2, X^3 and X^4 are each independently hydrogen or (C_1- C_8)alkyl;

R^a, R^b, R^c and R^d are independently (C_1- C_8)alkyl, (C_3- C_8)cycloalkyl, aryl or heteroaryl;

each R^e are independently hydrogen, (C_1- C_8)alkyl or aryl;

which comprises reacting a compound of formula (II"):



(II")

wherein $X^{1'}$ is -NH-C(=O)R^d or -N$R^{e'}_2$;

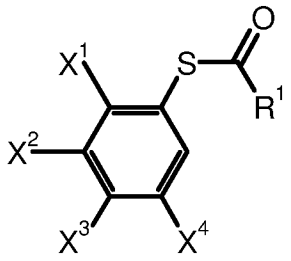
R^d is (C_3- C_8)cycloalkyl substituted by (C_1- C_8)alkyl, in particular R^d is (2-Ethyl-butyl)-cyclohexyl;

$R^{e'}$ are hydrogen;

$X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –NR^e_2, in particular $X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen or (C_1- C_8)alkyl; and

R^a, R^b, R^c, R^d, R^e, X^1, X^2, X^3 and X^4 are as defined above, with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

In another embodiment, the present invention provides a process for the preparation of a compound of formula (I"'):



(I"')

wherein

X^1 is -NH-C(=O)R^d , wherein R^d is (C_3- C_8)cycloalkyl substituted by (C_1- C_8)alkyl, in particular R^d is (2-Ethyl-butyl)-cyclohexyl;

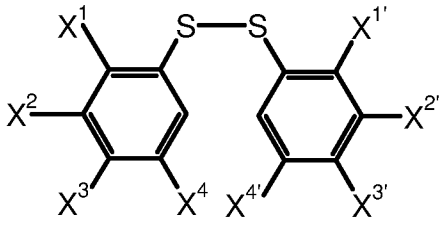
X^2, X^3 and X^4 are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$, in particular X^2, X^3 and X^4 are each independently hydrogen or (C_1- C_8)alkyl;

R^a, R^b, R^c and R^d are independently (C_1- C_8)alkyl, (C_3- C_8)cycloalkyl, aryl or heteroaryl;

each R^e are independently hydrogen, (C_1- C_8)alkyl or aryl;

R^1 is (C_1-C_8)alkyl or aryl;

which comprises reacting a compound of formula (II"):



(II")

wherein $X^{1'}$ is -NH-C(=O)R^d or -$NR^{e'}{}_2$;

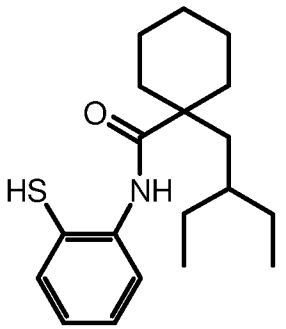
R^d is (C_3- C_8)cycloalkyl substituted by (C_1- C_8)alkyl, in particular R^d is (2-Ethyl-butyl)-cyclohexyl;

$R^{e'}$ are hydrogen;

$X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$, in particular $X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen or (C_1- C_8)alkyl; and

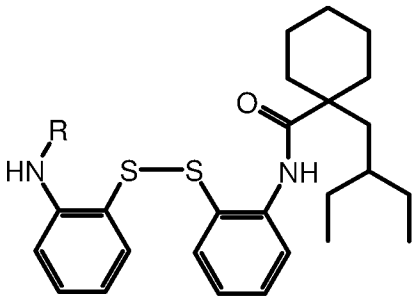
R^a, R^b, R^c, R^d, R^e, X^1, X^2, X^3 and X^4 are as defined above, with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

In a further embodiment the present invention provides a process for the preparation of compound of formula (I'):

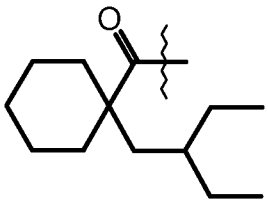


(I')

which comprises reacting a compound of formula (II'):



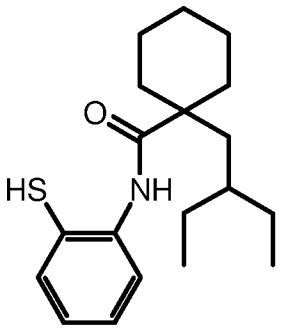
(II')



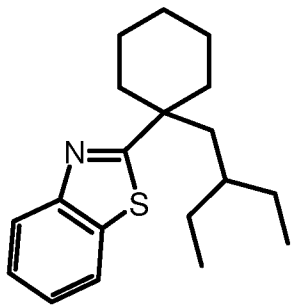
wherein R is H or

with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

In a further embodiment the present invention provides a process for the preparation of compounds of formula (I') and Formula(X):

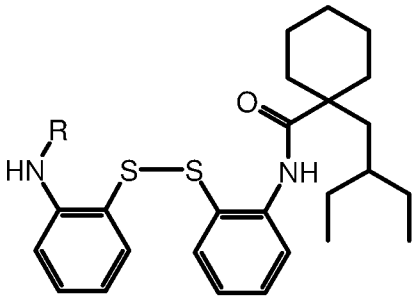


(I')

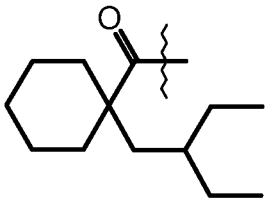


(X)

which comprises reacting a compound of formula (II'):



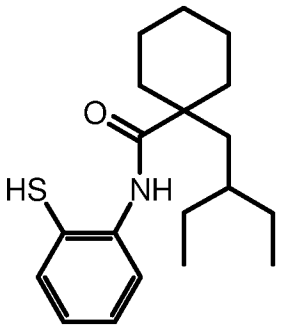
(II')



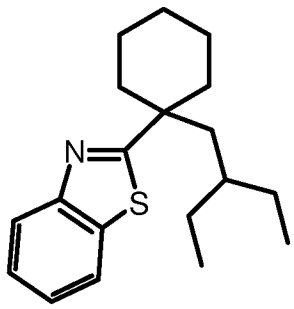
wherein R is H or

with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

In another embodiment the present invention provides a process for the preparation of compounds of formula (I') and Formula(X):



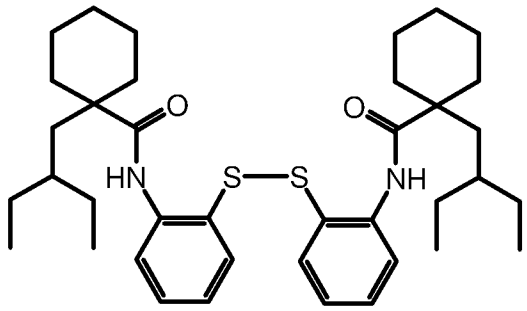
(I')



(X)

:

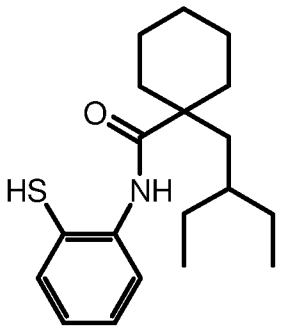
which comprises reacting a compound of formula (II):



(II)

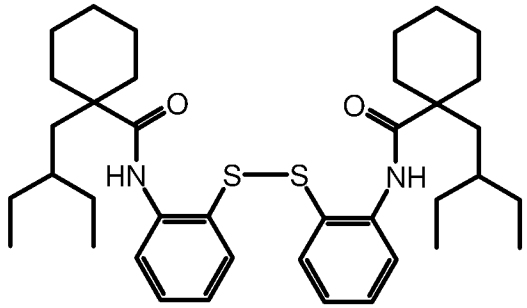
with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

In another embodiment the present invention provides a process for the preparation of a compound of formula (I'):



(I')

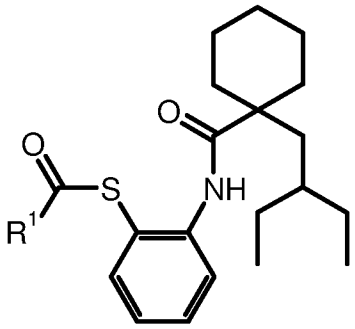
which comprises reacting a compound of formula (II):



(II)

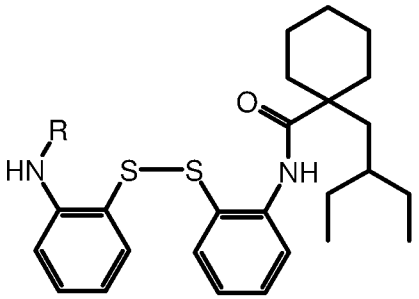
with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

In another embodiment, the present invention provides a process for the preparation of a compound of formula (Ia):

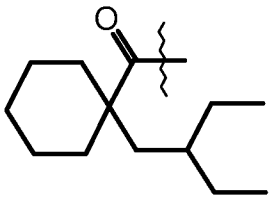


(Ia)

wherein R^1 is (C_1-C_8)alkyl or aryl, in particular R^1 is isopropyl, which comprises reacting a compound of formula (II'):



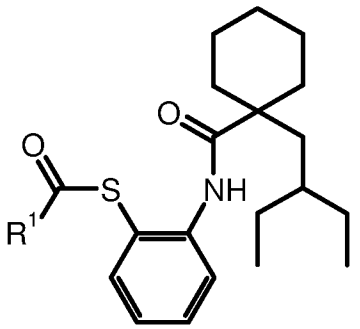
(II')



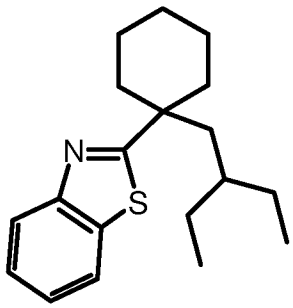
wherein R is H or

with H_2 in the presence of acylating agent such as an anhydride derivative [$((C_1$-$C_8)$alkyl)C(=O)]$_2$O or [aryl(C=O)]$_2$O or a halide derivative ($(C_1$-$C_8)$alkyl)C(=O)halide or aryl(C=O)halide and a heterogeneous transition metal hydrogenation catalyst. In particular, when R^1 is isopropyl, the acylating agent is isobutyric anhydride or isobutyryl halide, in particular isobutyric anhydride.

In another embodiment, the present invention provides a process for the preparation of compounds of formula (Ia) and Formula (X):

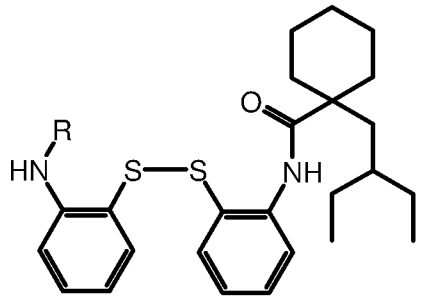


(Ia) and

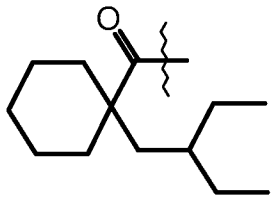


(X)

wherein R^1 is $(C_1$-$C_8)$alkyl or aryl, in particular R^1 is isopropyl, which comprises reacting a compound of formula (II'):



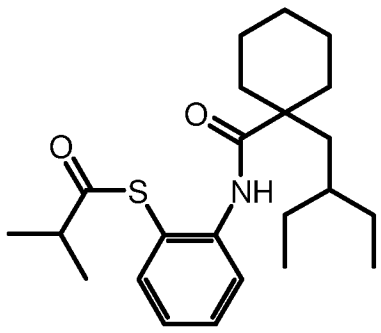
(II')



wherein R is H or

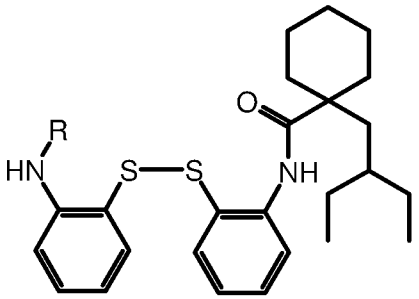
with H_2 in the presence of acylating agent such as an anhydride derivative [((C1-C8)alkyl)C(=O)]2O or [aryl(C=O)]2O or a halide derivative ((C1-C8)alkyl)C(=O)halide or aryl(C=O)halide and a heterogeneous transition metal hydrogenation catalyst. In particular, when R^1 is isopropyl, the acylating agent is isobutyric anhydride or isobutyryl halide, in particular isobutyric anhydride.

In another embodiment, the present invention provides a process for the preparation of a compound of formula (I):

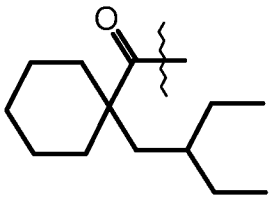


(I)

which comprises reacting a compound of formula (II'):



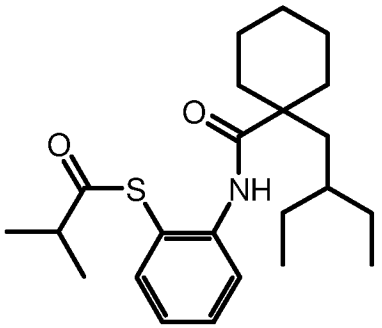
(II')



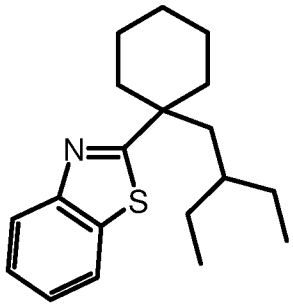
wherein R is H or

with H_2 in the presence of acylating agent such as isobutyric anhydride or isobutyryl halide, more particularly the acylating agent is isobutyric anhydride.

In another embodiment, the present invention provides a process for the preparation of compounds of formula (I) and Formula(X):

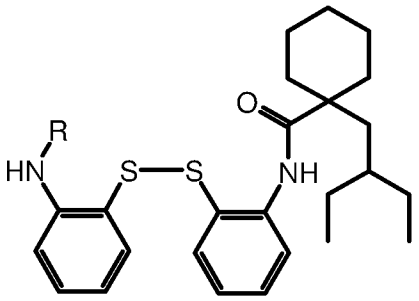


(I) and

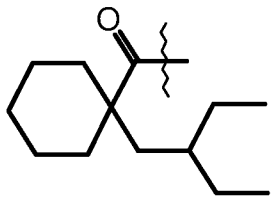


(X)

which comprises reacting a compound of formula (II'):



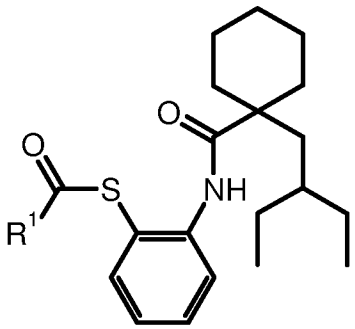
(II')



wherein R is H or

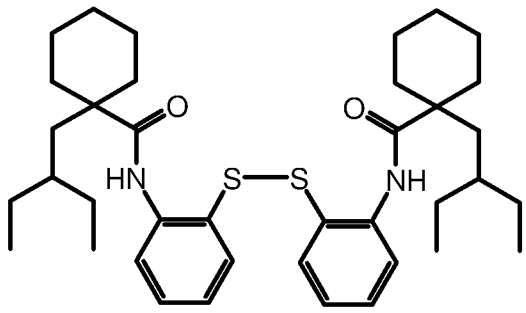
with H_2 in the presence of acylating agent such as isobutyric anhydride or isobutyryl halide, more particularly the acylatign agent is isobutyric anhydride.

In another embodiment, the present invention provides a process for the preparation of a compound of formula (Ia):



(Ia)

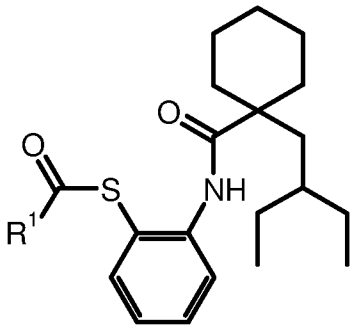
wherein R^1 is (C_1-C_8)alkyl or aryl, in particular R^1 is isopropyl, which comprises reacting a compound of formula (II):



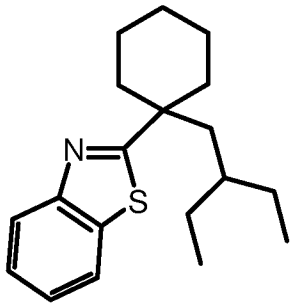
(II)

with H_2 in the presence of acylating agent such as an anhydride derivative [((C_1-C_8)alkyl)C(=O)]$_2$O or [aryl(C=O)]$_2$O or a halide derivative ((C_1-C_8)alkyl)C(=O)halide or aryl(C=O)halide and a heterogeneous transition metal hydrogenation catalyst. In particular, when R^1 is isopropyl, the acylating agent is isobutyric anhydride or isobutyryl halide, in particular isobutyric anhydride.

In another embodiment, the present invention provides a process for the preparation of compounds of formula (Ia) and Formula(X):

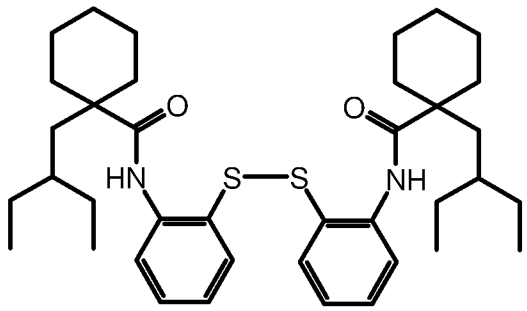


(Ia) and



(X)

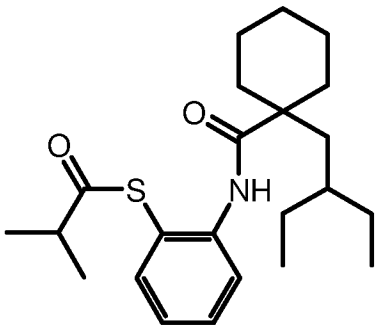
wherein R^1 is (C_1-C_8)alkyl or aryl, in particular R^1 is isopropyl, which comprises reacting a compound of formula (II):



(II)

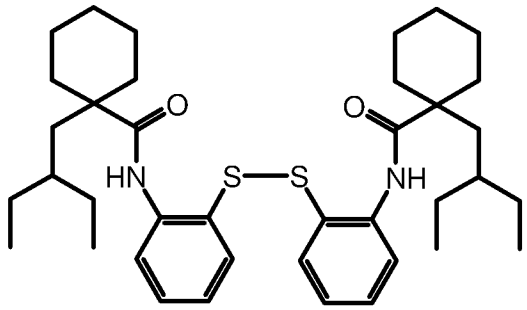
with H_2 in the presence of acylating agent such as an anhydride derivative [((C_1-C_8)alkyl)C(=O)]$_2$O or [aryl(C=O)]$_2$O or a halide derivative ((C_1-C_8)alkyl)C(=O)halide or aryl(C=O)halide and a heterogeneous transition metal hydrogenation catalyst. In particular, when R^1 is isopropyl, the acylating agent is isobutyric anhydride or isobutyryl halide, in particular isobutyric anhydride.

In another embodiment, the present invention provides a process for the preparation of a compound of formula (I):



(I)

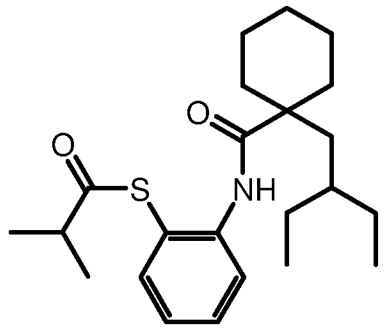
which comprises reacting a compound of formula (II):



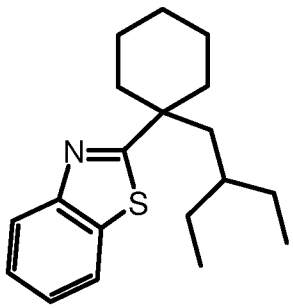
(II)

with H_2 in the presence of acylating agent such as isobutyric anhydride or isobutyryl halide, in particular isobutyric anhydride.

In another embodiment, the present invention provides a process for the preparation of compounds of formula (I) and Formula(X):

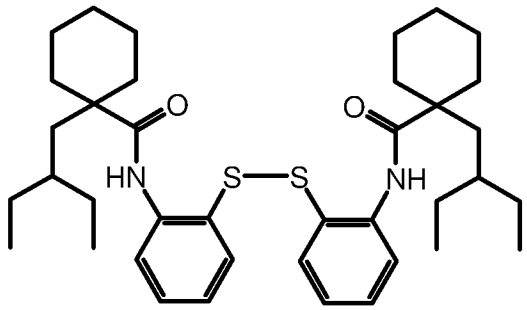


(I) and



(X)

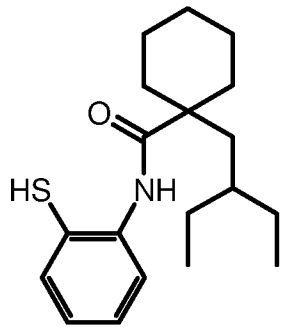
which comprises reacting a compound of formula (II):



(II)

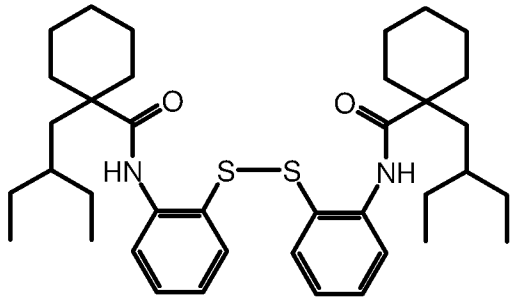
with H_2 in the presence of acylating agent such as isobutyric anhydride or isobutyryl halide, in particular isobutyric anhydride.

In particular embodiment, the present invention provides a process for the preparation of *S*-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate comprising the formation of a compound of formula (I'):



(I')

which comprises reacting a compound of formula (II):



(II)

with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

The present invention as described above may be carried out in the presence of a solvent or a mixture of two or more solvents. In particular the solvent is an organic solvent such as the ether like solvent (e.g. tetrahydrofuran, methyltetrahydrofuran, diisopropyl ether, t-butylmethyl ether or dibutyl ether) ester like solvent (e.g. ethyl acetate, isopropyl acetate butyl acetate), aliphatic hydrocarbon solvent (e.g. hexane, heptane or pentane), saturated alicyclic hydrocarbon solvent (e.g. cyclohexane or cyclopentane) or aromatic solvent (e.g. toluene, o- m- or p-xylene or t-butyl-benzene) or mixture thereof. In particular, the hydrogenation step according to the present invention is carried out in the presence of a solvent selected from ether like solvent, ester like solvent, aliphatic hydrocarbon solvent, saturated alicyclic hydrocarbon solvent or aromatic solvent or mixture thereof, when no acylating agent is present, more particularly the solvent is aliphatic hydrocarbon solvent, saturated alicyclic hydrocarbon solvent or aromatic solvent.

In another embodiment the anhydride derivative can act as a solvent or co-solvent, e.g. molar ratio anhydride/amidodisulfide of 2 to 20, in particular 2 to 5.

In a particular embodiment, the present invention provides a process as described above, wherein the acylating agent is isobutyric anhydride. In particular, 2.0 to 4.0 equivalents of

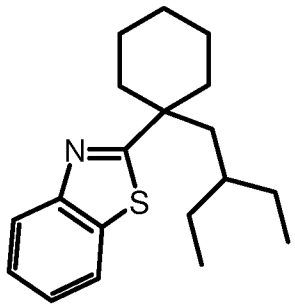
isobutyric anhydride with respect to disulfide of formula (II) are used. More particularly, 2.5 to 3.5 equivalents are used.

In a particular embodiment, the present invention provides a process as described above wherein the reaction is carried out at temperature up to 150°C, in particular between 25°C and 150°C, more particularly between 60°C to 90°C, most particularly at 80°C.

In a particular embodiment, the present invention provides a process as described above wherein the H_2 is added at a pressure of at least 0.1 bar, particularly at a pressure between 0.1 to 100 bar, more particularly at a pressure between 0.2 bar to 30 bar, most particularly 5 to 25 bar.

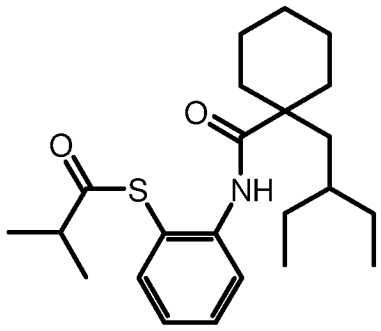
In a particular embodiment, the present invention provides a process as described above wherein the heterogeneous transition metal hydrogenation catalyst is a Raney catalyst, Pd/C, $Pd(OH)_2/C$, Nanoparticulate Palladium(0) microencapsulated in polyurea matrix (NP Pd(0) EncatTM 30),Au/TiO_2, Rh/C, Ru/Al_2O_3, $Ir/CaCO_3$, or Pt/C, or a mixture thereof, particularly the heterogeneous transition metal hydrogenation catalyst is a Raney catalyst, Pd/C, $Pd(OH)_2/C$, Au/TiO_2, Rh/C, Ru/Al_2O_3, $Ir/CaCO_3$, or Pt/C, or a mixture thereof, more particularly the heterogeneous transition metal hydrogenation catalyst is Pd/C, $Pd(OH)_2/C$, Au/TiO_2, Rh/C, Ra-Ni or Pt/C, most particularly the heterogeneous transition metal hydrogenation catalyst is Pd/C or Ra-Ni. The hydrogenation can be run in the presence of a molar excess of palladium towards the disulfide. More conveniently, palladium is used in catalytic amounts, e.g. 0.001 to 0.1 equivalents, preferred 0.01 to 0.1 equivalents with respect to the disulfide. The catalyst can be re-used several times such that the ratio between the disulfide converted and the moles of palladium employed is increased correspondently.

In another embodiment, the present invention provides a compound of formula (X):

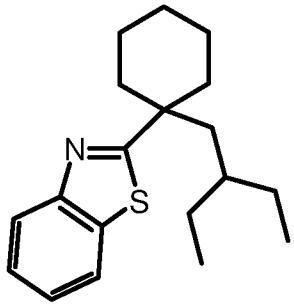


(X).

In another embodiment the present invention provides a compound of formula (I):

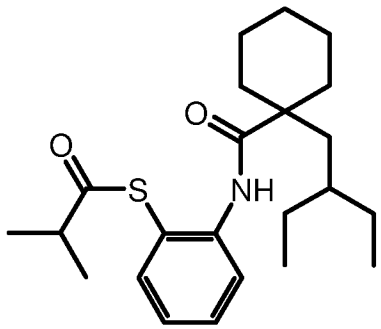


(I) comprising a compound of formula (X)

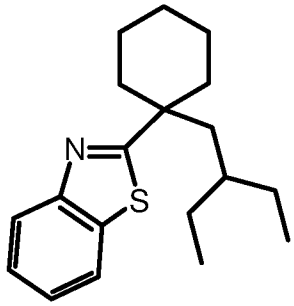


(X) and having less than 0.1 % of the compound of formula (X) by weight.

In another embodiment the present invention provides a compound of formula (I):



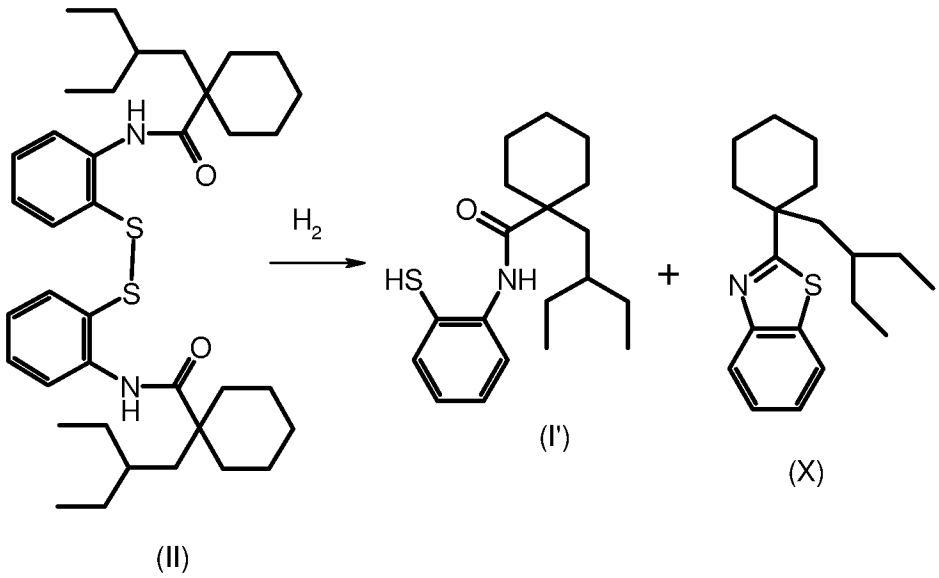
(I) comprising a compound of formula (X)



(X) and having between 1 ppb (parts per billion in weight) and 100 ppm (parts per million in weight) of the compound of formula (X), in particular having between 1 ppb and 1 ppm of the compound of formula (X).

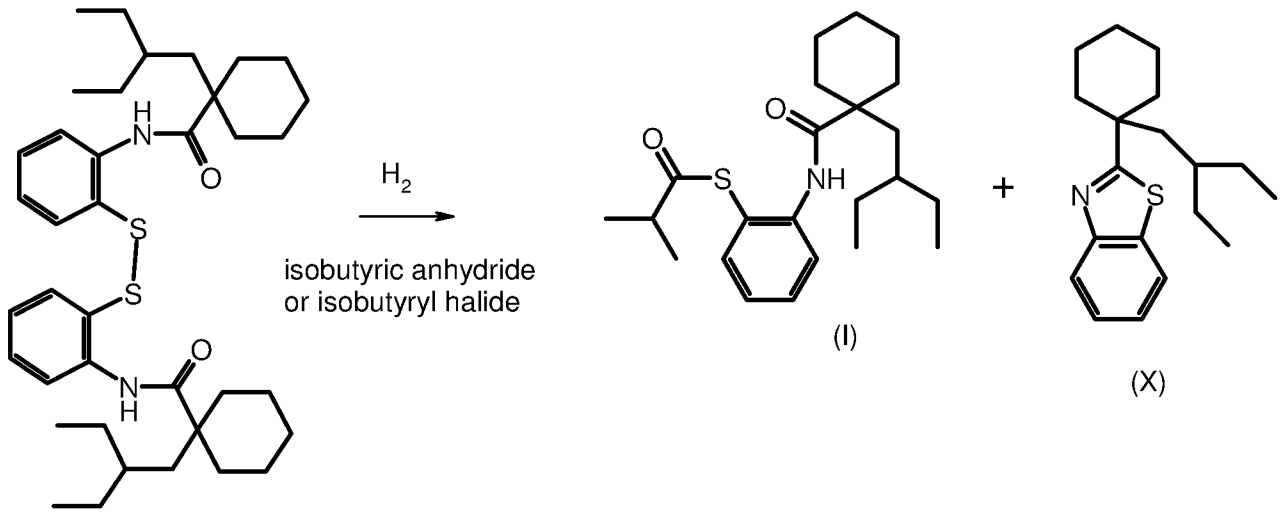
Compounds of formulae (I') and (X) can be prepared according to scheme 1 wherein the process conditions are here above described:

Scheme 1:



Compound of formulae (I) and (X) can be prepared according to scheme 2 wherein the process conditions are here above described:

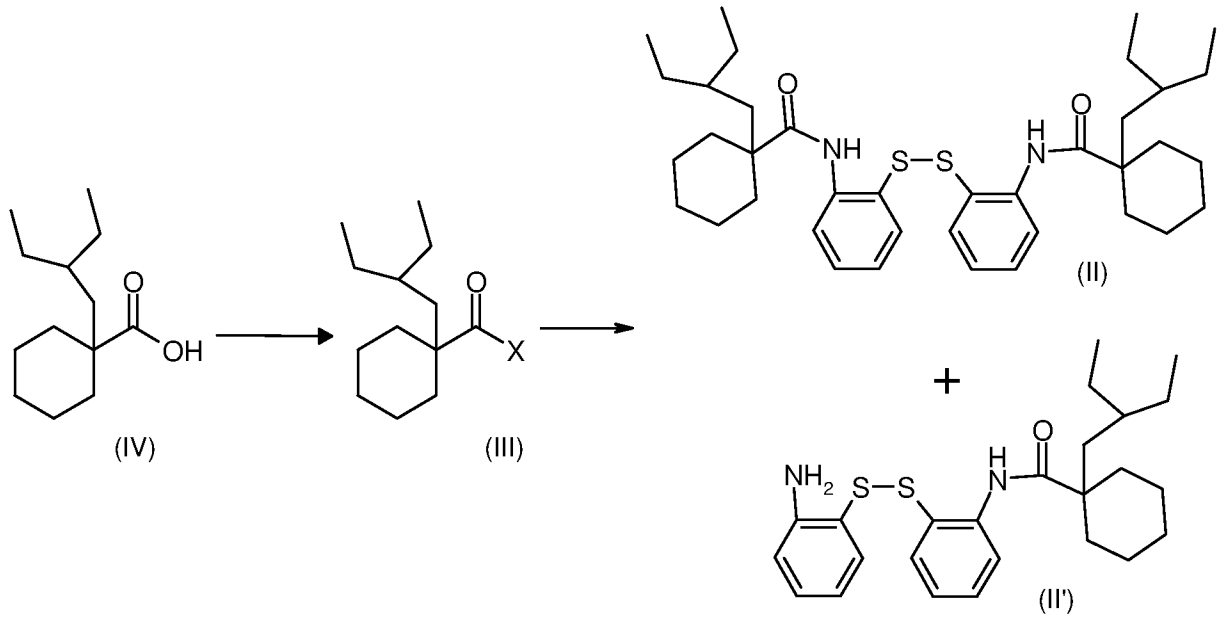
Scheme 2:



(II)

Compounds of formulae (II) and (II') can be prepared according to scheme 3:

Scheme 3:



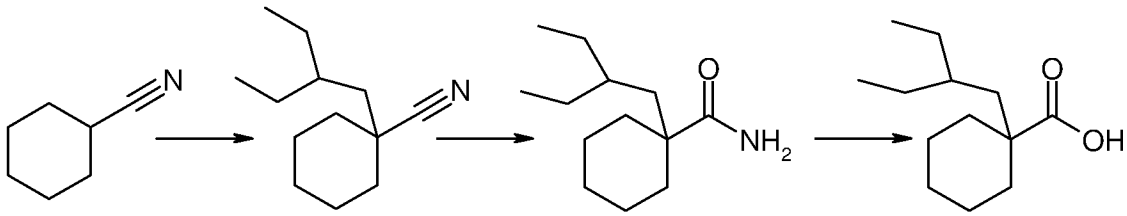
wherein X is I, Br, Cl or F. In particular, the process comprises reacting a cyclohexanecarboxylic acid derivative of formula (IV) with a halogenating agent, such as PX_3, PX_5, SOX_2 or NCX, COX_2 to obtain the acyl halide of formula (III). The halogenating step is preferably carried out in the presence of tri-(C_1-C_5)alkylamine. Furthermore, the process comprises reacting acyl halide with bis(2-aminophenyl)disulfide to acylate the amino

groups of the bis(2-aminophenyl)disulfide in the presence of a base (eg. N-methylmorpholine, di-N-methylpiperazine, pyridine) .

The starting materials, reagents and catalysts, which do not have their synthetic route explicitly disclosed herein, are generally available from commercial sources or are readily prepared using methods known to the person skilled in the art. For instance, the compounds of formulae (II) and (IV) can be prepared according to the procedures described in Shinkai et al., J. Med. Chem. 43:3566-3572 (2000), WO 2007/051714 or WO 2008/074677.

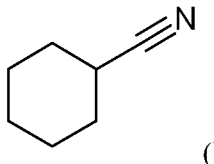
The preparation of the compound of formula (IV) comprises the preparation of a cyclohexanecarbonitrile derivative of formula (VI) followed by the hydrolysis steps as described hereunder and in the following scheme 4.

Scheme 4:



(VII) (VI) (V) (IV)

The compound of formula (VI) can be prepared:by reacting compound of formula (VII)



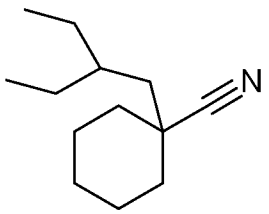
(VII)

with an alkylating agent such as 1-halo-2-ethylbutane, or 2-ethyl-1-butanol and a Grignard reagent, such as (C_1-C_6)alkyl-magnesium-halide, phenyl-magnesium-halide, heteroaryl-magnesium-halide or (C_3-C_6)cycloakyl-magnesium-halide. In particular, the above mentioned coupling reaction is carried out in the presence of a secondary amine. In particular, the Grignard reagent is added to the cyclohexanecarbonitrile, more particularly in the presence of a secondary amine, followed by the addition of an alkylating agent, as defined above. In particular, the above mentioned coupling reaction is followed by a mineral

acid quenching, such as hydrofluoric acid, hydrochloric acid, boric acid, acetic acid, formic acid, nitric acid, phosphoric acid or sulfuric acid, most particularly by hydrochloric acid.

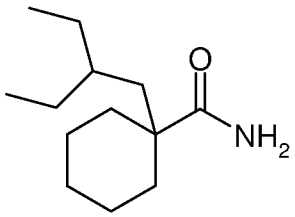
Compound of formula (IV) can be prepared by the following steps:

a) hydrolysis of a cyclohexanecarbonitrile derivative of formula (VI):



(VI)

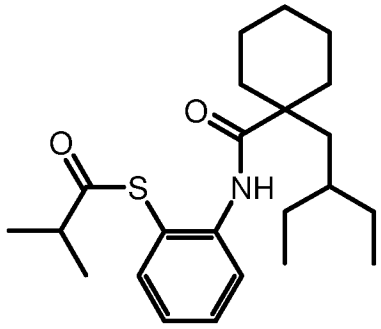
with H_2O in the presence of a strong acid, or with an aqueous base, to obtain a cyclohexanecarboxylic acid amide derivative of formula (V);



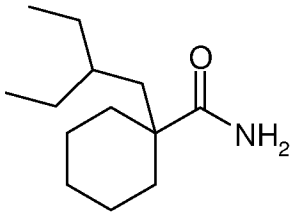
(V)

b) react the said cyclohexanecarboxylic acid amide derivative with a nitrosylating agent, to obtain the compound of formula (IV). The nitrosylating agent can be generated in situ e.g. mixing H2SO4 and nitrous acid (HNO2) or H2SO3/HNO3 or N2O3/H2SO4 or HNO3/SO2 to obtain nitrosulfuric acic (NOHSO4).

In another embodiment the present invention provides a compound of formula (I):

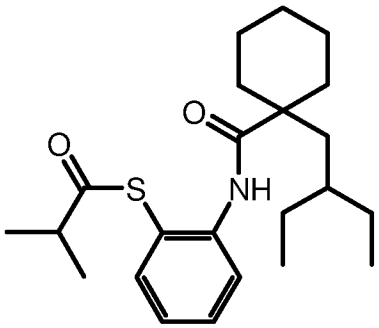


(I) comprising a compound of formula (V)

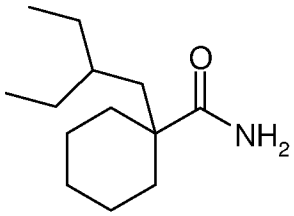


(V) and having less than 0.1 % of the compound of formula (V) by weight.

In another embodiment the present invention provides a compound of formula (I):

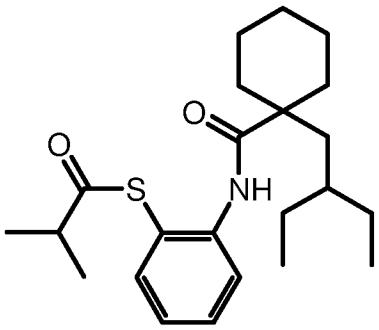


(I) comprising a compound of formula (V)

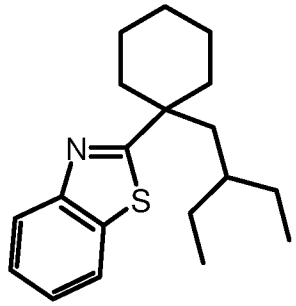


(V) and having between 1 ppb (parts per billion in weight) and 100 ppm (parts per million in weight) of the compound of formula (V), in particular having between 1 ppb and 1 ppm of the compound of formula (V).

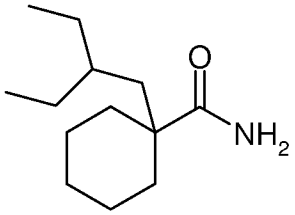
In another embodiment the present invention provides a compound of formula (I):



(I) comprising a compound of formula (X)



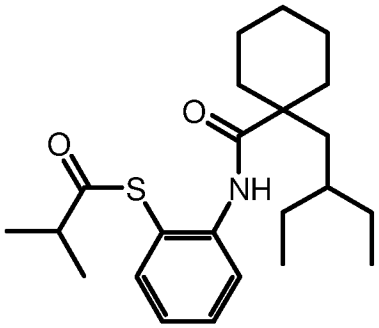
(X) and a compound of formula (V)



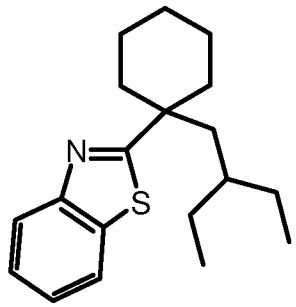
(V)

having less than 0.1 % of the compound of formula (X) by weight and less than 0.1% of the compound of formula (V).

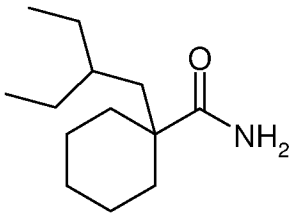
In another embodiment, the present invention provides a compound of formula (I):



(I) comprising a compound of formula (X)



(X) and a compound of formula (V)



(V)

having between 1 ppb (parts per billion in weight) and 100 ppm (parts per million in weight) of the compound of formula (X) and between 1 ppb (parts per billion in weight) and 100 ppm (parts per million in weight) of the compound of formula (V), in particular having between 1 ppb and 1 ppm of the compound of formula (X) and between 1 ppb and 1 ppm of the compound of formula (V)

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I), also known as thioisobutyric acid S-(2-{[1-(2-ethyl-butyl)-cyclohexanecarbonyl]-amino}-phenyl) ester, S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate or as dalcetrapib, and a compound of formula (X). In particular, the composition comprises a compound of formula (I) and between 1 ppb and 100 ppm of compound of formula (X), more particularly between 1ppb and 1 ppm.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I) and a compound of formula (V). In particular, the composition comprises a compound of formula (I) and between 1 ppb and 100 ppm of compound of formula (V), more particularly between 1 ppb and 1ppm.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I), a compound of formula (X) and a compound of formula (V). In particular, the composition comprises a compound of formula (I), between 1 ppb and 100 ppm of compound of formula (X) and between 1 ppb and 100 ppm of compound of formula (V).

In general, the nomenclature used in this Application is based on AUTONOM™ 2000, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. Chemical structures shown herein were prepared using MDL ISIS™ version 2.5 SP2. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom.

The following examples are provided for the purpose of further illustration and are not intended to limit the scope of the claimed invention.

The following abbreviations and definitions are used: Ar (argon); acid chloride (1-(2-ethyl-butyl)-cyclohexanecarbonyl chloride);amidodisulfide (N,N'-(dithiodi-2,1-phenylene)bis[1-(2-ethylbutyl)-cyclohexanecarboxamide]); amidothiophenol (1-(2-ethylbutyl)-N-(2-mercaptophenyl)-cyclohexanecarboxamide); thioester (S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate); DTDA (2,2`-dithiodianiline); d.i. (deionized); eq. (equivalent); EtOH (ethanol); g (gram); HPLC (High-

performance liquid chromatography); GC (gas chromatography); h (hour); M (Molarity [moles/L]); MeOH (methanol); ml (milliliter); RT (room temperature).

The pressure indicated in the experiments is the gauge pressure, i.e. the pressure relative to the local atmospheric pressure.

Example 1: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

A solution of 8.2 g of amidodisulfide (12.9 mmol) in 16.9 g toluene and 6.1 g (38.7 mmol) isobutyric anhydride was transferred together with 552 mg Pd/C (519 µmol Pd, EVONIK E101 N/D 10%) to a 185 mL stainless steel autoclave, which was sealed and 3 times pressurized with 5 bar H_2 and releasing to atmospheric pressure. The autoclave was heated under program control to 80 °C, thereafter charged with 5 bar of H_2. The hydrogenation was carried out under vigorous stirring for 18 hrs at the temperature of 80 °C and 5 bar (0.5 MPa). After this time the autoclave was cooled to RT, the pressure released and the reaction mixture filtered. The filtrate was evaporated under 50 °C/15 mbar and dissolved in 78 g EtOH. Addition of 22 g d.i. H_2O under Ar at RT leads to the precipitation of 9.67 g thioester (yield 96.3%) as white crystals with a melting point of 64.2 - 64.4°C. The observed amount of 1-(2-ethylbutyl)-N-(2-mercaptophenyl)-cyclohexanecarboxamide was less than 0.5%.

Example 2: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

This example was run in an analogous manner to example 1 but using 12.8 g toluene. After work-up and crystallization, 9.63 g of thioester as white crystals (yield 96%) with 100% HPLC area % purity was isolated.

Example 3: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

This example was run in an analogous manner to example 1 but using 26.7 g toluene. After work-up and crystallization, 9.73 g of thioester as white crystals (yield 97%) with 100% HPLC area % purity was isolated.

Example 4: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

8.2 g of amidodisulfide (12.9 mmol) in 16.8 g toluene and 6.1 g (38.7 mmol) isobutyric anhydride was transferred together with 552 mg Pd/C (519 µmol Pd, EVONIK E101 N/D 10%) to a 185 mL stainless steel autoclave. It was hydrogenated under vigorous stirring for 3 hrs at the temperature of 90 °C and 5 bar (0.5 MPa). Work-up according to example 1 afforded 9.63 g of thioester as white crystals (yield 95.9%). HPLC analysis showed a purity of 100 area%.

Example 5: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

This example was run in an analogous manner to example 1 but using 552 mg 20% $Pd(OH)_2/C$ catalyst (519 µmol Pd, wet, ca. 50 weight% H_2O), which was washed 3 times first with THF and then 3 times with Toluene before being transferred in the autoclave. The mixture was hydrogenated under vigorous stirring for 5 hrs at the temperature of 80 °C and 5 bar (0.5 MPa). After work-up according to example 1, 9.76 g of thioester as white crystals (yield 97.2%) were recovered. HPLC analysis showed a purity of 100 area%.

Example 6: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

This example was run in an analogous manner to example 1 but using 1.15g 4.78% nPdnAl2O3/Al2O3 catalyst (519 µmol Pd, SDC materials). The mixture was hydrogenated under vigorous stirring for 5 hrs at the temperature of 80 °C and 5 bar (0.5 MPa). Work-up according to example 1 afforded 9.86 g of thioester as white crystals (yield 98.2%). HPLC analysis showed a purity of 100 area%.

Example 7: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

8.2 g of amidodisulfide (12.9 mmol) in 16.8 g toluene and 6.1 g (38.7 mmol) isobutyric anhydride was transferred together with 552 mg Pd/C (519 µmol Pd, EVONIK E101 N/D 10%) to a 185 mL stainless steel autoclave. It was hydrogenated under vigorous stirring for 18 hrs at the temperature of 80 °C and 0.2 bar (0.02 MPa). Work-up according to example 1 afforded 9.39 g of thioester as white crystals (yield 93.5%). HPLC analysis showed a purity of 100 area%.

Example 8: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

8.2 g of amidodisulfide (12.9 mmol) in 16.8 g ethyl acetate and 6.1 g (38.7 mmol) isobutyric anhydride was transferred together with 552 mg Pd/C (519 µmol Pd, EVONIK E101 N/D 10%) to a 185 mL stainless steel autoclave. The mixture was hydrogenated under vigorous stirring for 18 hrs at the temperature of 80 °C and 5 bar (0.5 MPa). HPLC analysis showed complete conversion. Work-up according to example 1 afforded 8.54 g of thioester as white crystals (yield 85.1%). HPLC analysis showed a purity of 100 area%.

Example 9: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

This example was run in an analogous manner to example 8 but using tert-butyl methyl ether. It was hydrogenated under vigorous stirring for 18 hrs at the temperature of 80 °C and 5 bar (0.5 MPa). HPLC analysis showed complete conversion. Work-up according to example 1 afforded 8.89 g of thioester as white crystals (yield 88.5%). HPLC analysis showed a purity of 100 area%.

Example 10: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

8.2 g of amidodisulfide (12.9 mmol) in 16.8 g toluene and 4.2 g (38.7 mmol) isobutyryl chloride was transferred together with 552 mg Pd/C (519 µmol Pd, EVONIK E101 N/D 10%) to a 185 mL stainless steel autoclave. The mixture was hydrogenated under vigorous stirring for 18 hrs at the temperature of 80 °C and 5 bar (0.5 MPa). Thereafter the reaction mixture was analyzed with HPLC, showed 70.6% conversion of amidodisulfide and 52% thioester HPLC area%. In addition 2.9 area% of 1-(2-ethylbutyl)-N-(2-mercaptophenyl)-cyclohexanecarboxamide and 14.5 area% of 2-[1-(2-ethyl-butyl)-cyclohexyl]-benzothiazole were formed.

Example 11: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate This example was run in an analogous manner to example 10 but using 2.0eq. isobutyric anhydride (4.1 g, 25.8 mmol,) as reagent. The mixture was hydrogenated under vigorous stirring for 18 hrs at the temperature of 80 °C and 5 bar (0.5 MPa). HPLC

analysis showed complete conversion. Work-up according to example 1 afforded 7.05 g of thioester as white crystals (yield 68.5%). HPLC analysis showed a purity of 100 area%.

Example 12: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

8.2 g of amidodisulfide (12.9 mmol) in 22.9 g isobutyric anhydride (145 mmol) was transferred together with 552 mg Pd/C (519 µmol Pd, EVONIK E101 N/D 10%) to a 185 mL stainless steel autoclave. The mixture was hydrogenated under vigorous stirring for 18 hrs at the temperature of 80 °C and 5 bar (0.5 MPa). HPLC analysis showed complete conversion. Work-up according to example 1 afforded 9.57 g of thioester as white crystals (yield 95.3%). HPLC analysis showed a purity of 100 area%.

Example 13 1-(2-ethylbutyl)-N-(2-mercaptophenyl)-cyclohexanecarboxamide

8.2 g of amidodisulfide (12.9 mmol) in 22.9 g toluene was transferred together with 552 mg Pd/C (519 µmol Pd, EVONIK E101 N/D 10%) to a 185 mL stainless steel autoclave. It was hydrogenated under vigorous stirring for 18 hrs at the temperature of 80°C and 10 bar (1.0 MPa). Thereafter the reaction mixture was analyzed with HPLC, showed 100% conversion of amidodisulfide and 99.2% amidothiophenol HPLC area%.

Example 14: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

8.2 g of amidodisulfide (12.9 mmol) in 16.8 g toluene and 6.1 g (38.7 mmol) isobutyric anhydride was transferred together with 327 mg Raney-Ni (2.59 mmol Ni, EVONIK B113 Z 46.5%) to a 185 mL stainless steel autoclave. It was hydrogenated under vigorous stirring for 18 hrs at the temperature of 100 °C and 1 bar (0.1 MPa). Thereafter the reaction mixture was analyzed with HPLC, showing 100% conversion of amidodisulfide and 100% thioester.

Example 15 : Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

8.2 g of amidodisulfide (12.9 mmol) in 16.8 g toluene and 6.1 g (38.7 mmol) isobutyric anhydride was transferred together with 1.35 g Nanoparticulate Palladium(0) microencapsulated in polyurea matrix (NP Pd(0) Encat™ 30, sold by Sigma-Aldrich®)(540

µmol Pd, 0.4 mmol Pd/g) to a 185 mL stainless steel autoclave. It was hydrogenated under vigorous stirring for 18 hrs at the temperature of 90 °C and 30 bar(3 MPa). Thereafter the reaction mixture was analyzed with HPLC, showed complete conversion of amidodisulfide and 100% desired product. This catalyst was reused under the same condition for further 10 times, all of them showed the same result i.e. complete conversion and 100% desired product.

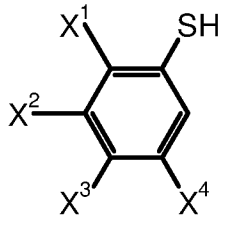
Example 16: Synthesis of S-[2-[1-(2-ethylbutyl)cyclohexanecarbonylamino]-phenyl] 2-methylthiopropionate

In the table hereunder, the reactions were carried in analogous manner to example 1, wherein the reaction conditions were: 0.314 mmol amidodisulfide in 410 mg toluene, 3 eq. isobutyric anhydride, 0.0403 eq. metal catalyst (specifically mentioned in the following table), 80 °C, 5 bar, reaction time 18 hrs. Thereafter the reaction mixture was analyzed with HPLC.

Catalysts	**Conversion HPLC [area%]**	**Yield HPLC [area%]**
3% Au/TiO2	69	65
5% Ru/Al_2O_3	81.1	71.8
5% Pt/C	99.0	73.0
5% Rh/C	87.0	73.0
93% Co_Al (~50%H2O)	49.0	43.0
5% Ir/CaCO3	70.0	65.5

Claims:

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



(I")

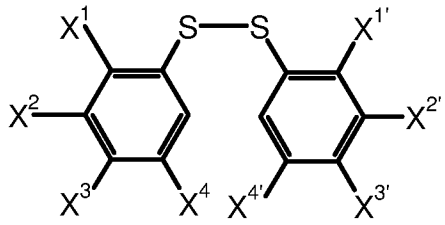
wherein X^1, X^2, X^3 and X^4 are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$; or

two adjacent substituents (i.e. X^1 and X^2 or X^2 and X^3 or X^3 and X^4) together with the carbon atoms to which they are attached form a four, five or six membered cycloalkyl ring that optionally includes an additional heteroatom selected from O, NH and S wherein the heresaid four, five or six membered cycloalkyl ring is optionally substituted with one to three substituents independently selected from with (C_1- C_8)alkyl or aryl;

R^a, R^b, R^c and R^d are independently (C_1- C_8)alkyl, (C_3- C_8)cycloalkyl, aryl or heteroaryl;

each R^e are independently hydrogen, (C_1- C_8)alkyl or aryl;

which comprises reacting a compound of formula (II"):



(II")

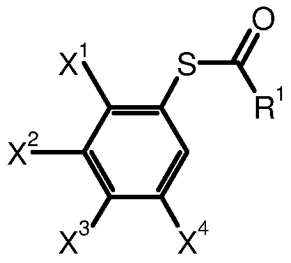
wherein $X^{1'}$, $X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$; or

two adjacent substituents (i.e. $X^{1'}$ and $X^{2'}$ or $X^{2'}$ and $X^{3'}$ or $X^{3'}$ and $X^{4'}$) together with the carbon atoms to which they are attached form a four, five or six membered cycloalkyl ring that optionally includes an additional heteroatom selected from O, NH and S wherein the heresaid four, five or six membered cycloalkyl ring is optionally substituted one to three substituents independently selected from with (C_1- C_8)alkyl or aryl; and

R^a, R^b, R^c, R^d, R^e, X^1, X^2, X^3 and X^4 are as defined above,

with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

2. The process according to claim 1, for the preparation of a compound of formula (I"')



(I'')

wherein X^1, X^2, X^3 and X^4 are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$; or

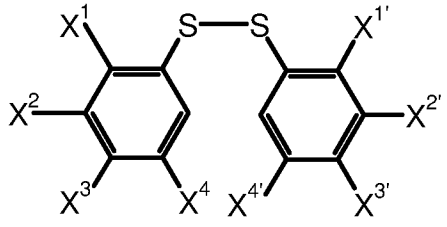
two adjacent substituents (i.e. X^1 and X^2 or X^2 and X^3 or X^3 and X^4) together with the carbon atoms to which they are attached form a four, five or six membered cycloalkyl ring that optionally includes an additional heteroatom selected from O, NH and S wherein the heresaid four, five or six membered cycloalkyl ring is optionally substituted one to three substituents independently selected from with (C_1- C_8)alkyl or aryl;

R^1 is (C_1-C_8)alkyl or aryl;

R^a, R^b, R^c and R^d are independently (C_1- C_8)alkyl, (C_3- C_8)cycloalkyl, aryl or heteroaryl;

each R^e are independently hydrogen, (C_1- C_8)alkyl or aryl;

which comprises reacting a compound of formula (II''):



(II'')

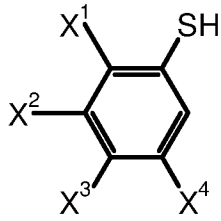
wherein $X^{1'}$, $X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –$NR^e{}_2$; or

two adjacent substituents (i.e. $X^{1'}$ and $X^{2'}$ or $X^{2'}$ and $X^{3'}$ or $X^{3'}$ and $X^{4'}$) together with the carbon atoms to which they are attached form a four, five or six membered cycloalkyl ring that optionally includes an additional heteroatom selected from O, NH and S wherein the heresaid four, five or six membered cycloalkyl ring is optionally substituted one to three substituents independently selected from with (C_1- C_8)alkyl or aryl; and

R^a, R^b, R^c, R^d, R^e, X^1, X^2, X^3 and X^4 are as defined above,

with H_2 in the presence of an acylating agent such as an anhydride derivative [($(C_1$-$C_8)$alkyl)C(=O)]$_2$O or [aryl(C=O)]$_2$O or a halide derivative ($(C_1$-$C_8)$alkyl)C(=O)halide or aryl(C=O)halide and a heterogeneous transition metal hydrogenation catalyst.

3. The process according to claim 1, for the preparation of a compound of formula (I")



(I")

wherein

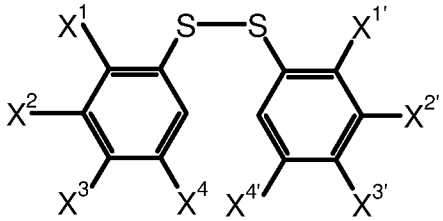
X^1 is -NH-C(=O)R^d, wherein R^d is (C_3-C_8)cycloalkyl substituted by (C_1- C_8)alkyl;

X^2, X^3 and X^4 are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –NR^e_2;

R^a, R^b, R^c and R^d are independently (C_1- C_8)alkyl, (C_3- C_8)cycloalkyl, aryl or heteroaryl;

each R^e are independently hydrogen, (C_1- C_8)alkyl or aryl;

which comprises reacting a compound of formula (II"):



(II")

wherein $X^{1'}$ is -NH-C(=O)R^d or -N$R^{e'}_2$;

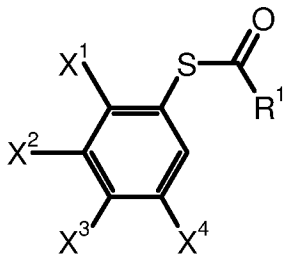
R^d is (C_3- C_8)cycloalkyl substituted by (C_1- C_8)alkyl;

$R^{e'}$ are hydrogen;

$X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –NR^e_2; and

R^a, R^b, R^c, R^d, R^e, X^1, X^2, X^3 and X^4 are as defined above, with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

4. The process according to claim 2, for the preparation of a compound of formula (I"'):



(I''')

wherein

X^1 is -NH-C(=O)R^d, wherein R^d is (C_3- C_8)cycloalkyl substituted by (C_1- C_8)alkyl;

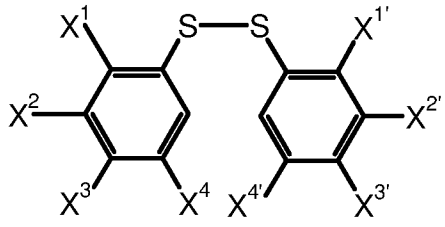
X^2, X^3 and X^4 are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –NR^e_2;

R^a, R^b, R^c and R^d are independently (C_1- C_8)alkyl, (C_3- C_8)cycloalkyl, aryl or heteroaryl;

each R^e are independently hydrogen, (C_1- C_8)alkyl or aryl;

R^1 is (C_1-C_8)alkyl or aryl;

which comprises reacting a compound of formula (II''):



(II'')

wherein $X^{1'}$ is -NH-C(=O)R^d or -$NR^{e'}_2$;

R^d is (C_3- C_8)cycloalkyl substituted by (C_1- C_8)alkyl;

$R^{e'}$ are hydrogen;

$X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen, (C_1- C_8)alkyl, aryl, heteroaryl, -OR^a, -O-C(=O) R^b, -NHR^c, -NH-C(=O)R^d or –NR^e_2; and

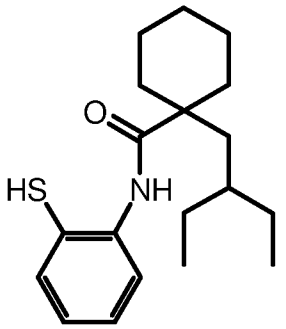
R^a, R^b, R^c, R^d, R^e, X^1, X^2, X^3 and X^4 are as defined above, with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

5. The process according to any one of claims 1 to 4, wherein R^d is (2-Ethyl-butyl)-cyclohexyl.

6. The process according to any one of claims 1 to 5, wherein X^2, X^3 and X^4 are each independently hydrogen or (C_1- C_8)alkyl.

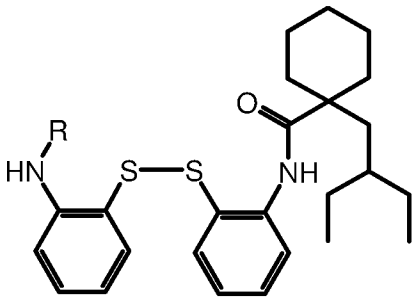
7. The process according to any one of claims 1 to 6, wherein $X^{2'}$, $X^{3'}$ and $X^{4'}$ are each independently hydrogen or (C_1- C_8)alkyl.

8. The process according to either claim 1, 3, 5 or 6, for the preparation of a compound of formula (I'):

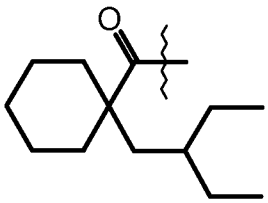


(I')

which comprises reacting a compound of formula (II'):



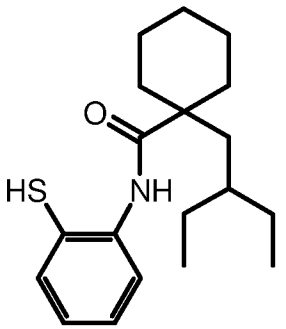
(II')



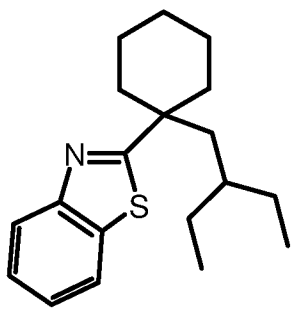
wherein R is H or

with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

9. The process according to any one of claims 1, 3, 5, 6 or 8, for the preparation of compounds of formula (I') and formula(X):

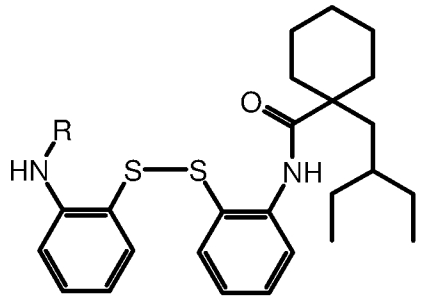


(I')

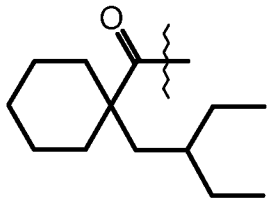


(X)

which comprises reacting a compound of formula (II'):



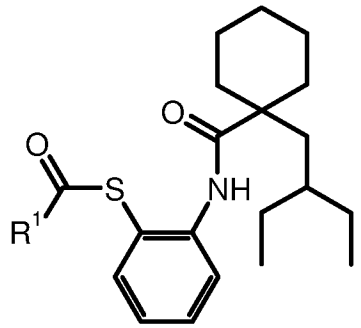
(II')



wherein R is H or

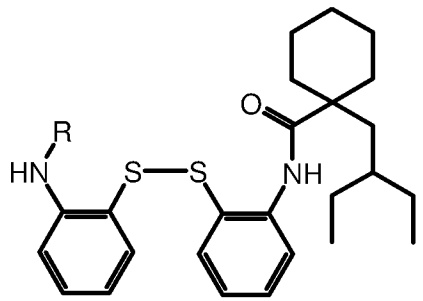
with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

10. The process according to any one of claims 2 , 4, 5 or 6 , for the preparation of a compound of formula (Ia):

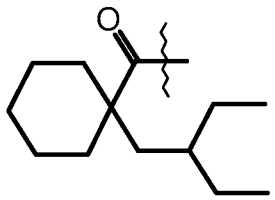


(Ia)

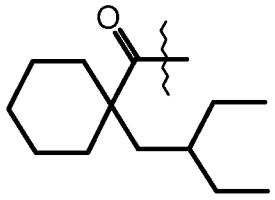
wherein R^1 is (C_1-C_8)alkyl or aryl, in particular R^1 is isopropyl, which comprises reacting a compound of formula (II'):



(II')

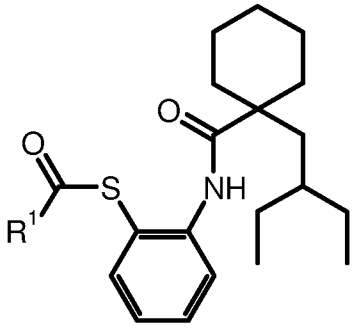


wherein R is H or

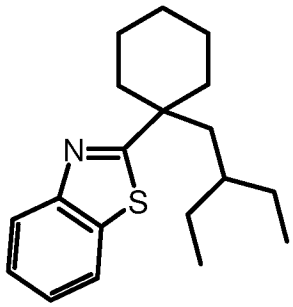


with H_2 in the presence of acylating agent such as an anhydride derivative [$((C_1$-$C_8)$alkyl)C(=O)]$_2$O or [aryl(C=O)]$_2$O or a halide derivative ($(C_1$-$C_8)$alkyl)C(=O)halide or aryl(C=O)halide and a heterogeneous transition metal hydrogenation catalyst.

11 The process according to any one of claims 2, 4, 5, 6, or 10, for the preparation of compounds of formula (Ia) and Formula(X):

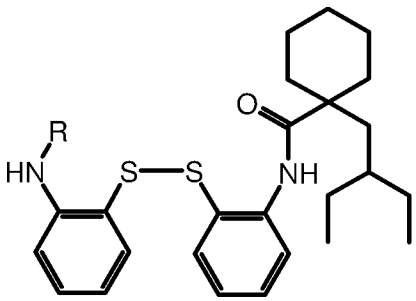


(Ia) and



(X)

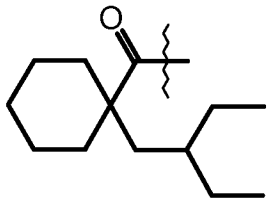
wherein R^1 is (C_1-C_8)alkyl or aryl, in particular R^1 is isopropyl, which comprises reacting a compound of formula (II'):



(II')

wherein R is H or

with H_2 in the presence of acylating agent such as an anhydride derivative [((C1-C8)alkyl)C(=O)]2O or [aryl(C=O)]2O or a halide derivative ((C1-C8)alkyl)C(=O)halide or aryl(C=O)halide and a heterogeneous transition metal hydrogenation catalyst.

12. The process according to any one of claims 8 to 11, wherein R is  .

13. The process according to any one of claims 2, 4 to 7 or 10 to 12, wherein R^1 is isopropyl and the acylating agent is isobutyric anhydride or isobutyryl halide.

14. The process according to any one of claims 2, 4 to 7 or 10 to 13, wherein the acylating agent is isobutyric anhydride.

15. The process according to any one of claims 2, 4 to 7 or 10 to 14, wherein 2.0 to 4.0 equivalents of isobutyric anhydride with respect to disulfide of formula (II) are used.

16. The process according to any one of claims 1 to 15 in the presence of a solvent or a mixture of two or more solvents.

17. The process according to any one of claims 1 to 16, wherein the solvent is an organic solvent.

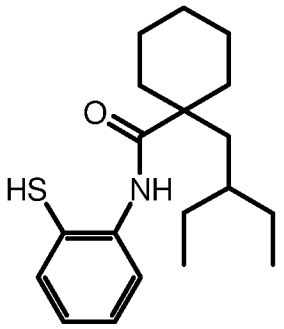
18. The process according to any one of claims 1 to 17, wherein the solvent is the ether like solvent, ester like solvent, aliphatic hydrocarbon solvent, saturated alicyclic hydrocarbon solvent or aromatic solvent or mixture thereof.

19. The process according to any one of claims 1, 3 or 5 to 9, the solvent selected from ether like solvent, ester like solvent, aliphatic hydrocarbon solvent, saturated alicyclic hydrocarbon solvent or aromatic solvent or mixture thereof

20. The process according to any one of claims 19, wherein the solvent is aliphatic hydrocarbon solvent, saturated alicyclic hydrocarbon solvent or aromatic solvent.

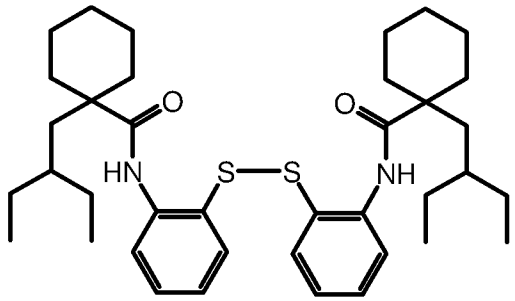
21. The process according to any one of claims 2, 4 to 7 or 10 to 18, wherein the anhydride derivative can act as a solvent or co-solvent with a molar ratio anhydride/amidodisulfide of 2 to 20.

22. A process for the preparation of *S*-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate comprising the formation of a compound of formula (I'):



(I')

which comprises reacting compound of formula (II):



(II)

with H_2 in the presence of a heterogeneous transition metal hydrogenation catalyst.

23. The process according to any one of claims 1 to 22, wherein the H_2 is added at a pressure of at least 0.1 bar, particularly at a pressure between 0.1 to 100 bar, more particularly at a pressure between 0.2 bar to 30 bar, most particularly 5 to 25 bar.

24. The process according to any one of claims 1 to 23, wherein the reaction is carried out at temperature up to 150°C, in particular between 25°C and 150°C, more particularly between 60°C to 90°C, most particularly at 80°C.

25. The process according to any one of claims 1 to 24, wherein the heterogeneous transition metal hydrogenation catalyst is a Raney catalyst, Pd/C, $Pd(OH)_2/C$, Nanoparticulate

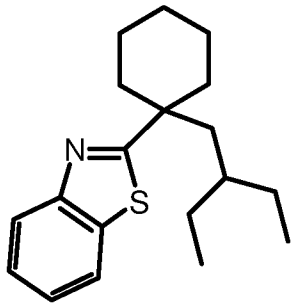
Palladium(0) microencapsulated in polyurea matrix, Au/TiO_2, Rh/C, Ru/Al_2O_3, $Ir/CaCO_3$, Pt/C, or a mixture thereof.

26. The process according to any one of claims 1 to 25, wherein the heterogeneous transition metal hydrogenation catalyst is a Raney catalyst, Pd/C, $Pd(OH)_2/C$, Au/TiO_2, Rh/C, Ru/Al_2O_3, $Ir/CaCO_3$, Pt/C, or a mixture thereof.

27. The process according to any one of claims 1 to 26, wherein the heterogeneous transition metal hydrogenation catalyst is Pd/C, $Pd(OH)_2/C$, Au/TiO_2, Rh/C, Ra-Ni or Pt/C.

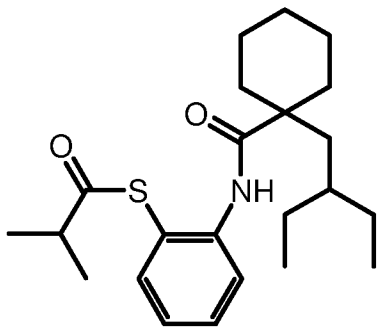
28. The process according to any one of claims 1 to 27, wherein the heterogeneous transition metal hydrogenation catalyst is Pd/C or Ra-Ni.

29. A compound of formula (X):

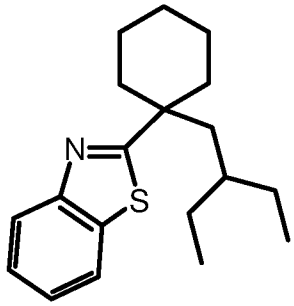


(X).

30. A compound of formula (I):

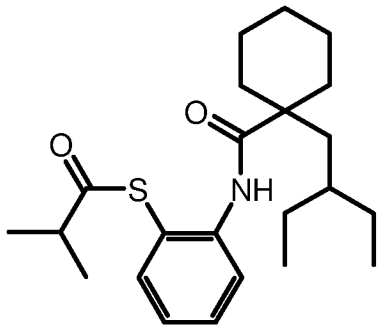


(I) comprising a compound of formula (X)

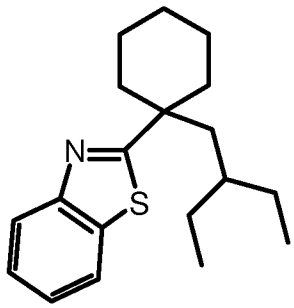


(X) and having less than 0.1 % of the compound of formula (X) by weight.

31. A compound of formula (I) according to claim 29:

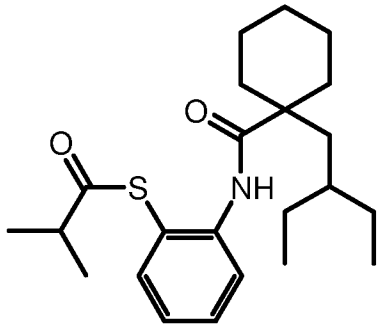


(I) comprising a compound of formula (X)

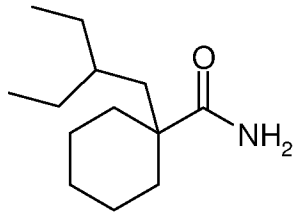


(X) and having between 1 ppb and 100 ppm of the compound of formula (X), in particular having between 1 ppb and 1 ppm of the compound of formula (X).

32. A compound of formula (I):

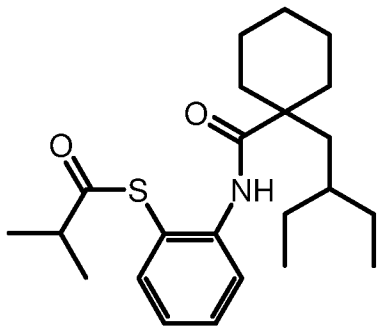


(I) comprising a compound of formula (V)

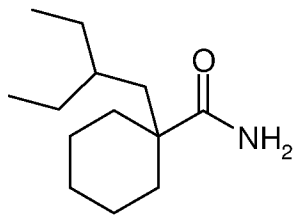


(V) and having less than 0.1 % of the compound of formula (V) by weight.

33. A compound of formula (I) according to claim 31:

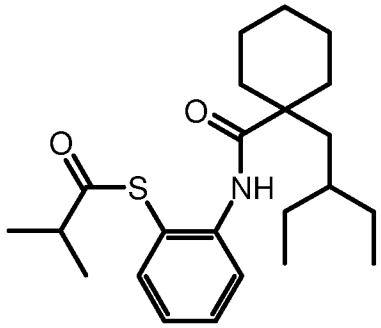


(I) comprising a compound of formula (V)

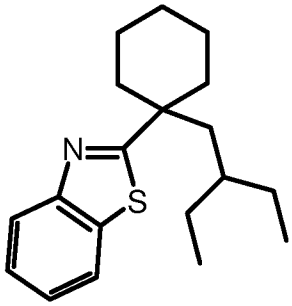


(V) and having between 1 ppb and 100 ppm of the compound of formula (V), in particular having between 1 ppb and 1 ppm of the compound of formula (V).

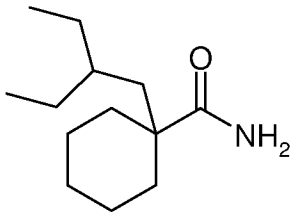
34. A compound of formula (I) according to claim 29 or 31:



(I) comprising a compound of formula (X)



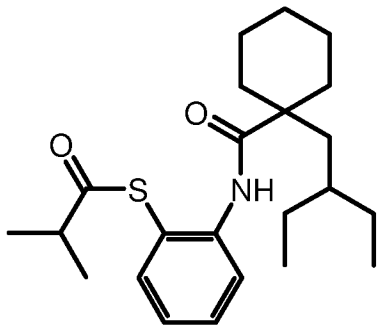
(X) and a compound of formula (V)



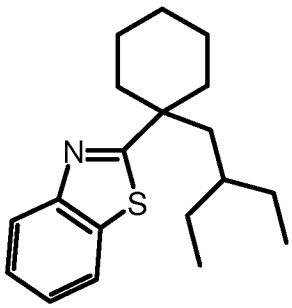
(V)

having less than 0.1 % of the compound of formula (X) by weight and less than 0.1% of the compound of formula (V).

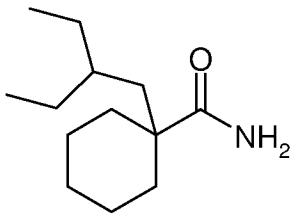
35. A compound of formula (I) according to claim 32:



(I) comprising a compound of formula (X)



(X) and a compound of formula (V)



(V)

having between 1 ppb and 100 ppm of the compound of formula (X) and between 1 ppb and 100 ppm of the compound of formula (V), in particular having between 1 ppb and 1 ppm of the compound of formula (X) and between 1 ppb and 1 ppm of the compound of formula (V)

36. A pharmaceutical composition comprising S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate and a compound of formula (X).

37. The pharmaceutical composition according to claim 36, wherein the composition comprises between 1 ppb and 100 ppm of compound of formula (X), more particularly between 1ppb and 1 ppm.

38. A pharmaceutical composition comprising S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate and a compound of formula (V).

39. The pharmaceutical composition according to claim 37, wherein the composition comprises between 1 ppb and 100 ppm of compound of formula (V) is present, more particularly between 1 ppb and 1ppm.

40. The pharmaceutical composition according to any one of claims 36 to 39, wherein the pharmaceutical composition comprises S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, a compound of formula (X) and a compound of formula (V).

41. The pharmaceutical composition according to any one of claims 36 to 40, wherein the composition comprises S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate, between 1 ppb and 100 ppm of compound of formula (X) and between 1 ppb and 100 ppm of compound of formula (V).

42. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/072470

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C319/06 C07C323/40 C07C327/30 C07D277/64
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CALAIS C ET AL: "Selective reduction of diphenyldisulphides catalysed by sulphides - influence of the nature of the catalyst", JOURNAL OF CATALYSIS, vol. 144, 1993, pages 160-174, XP002227637, ISSN: 0021-9517, DOI: DOI:10.1006/JCAT.1993.1321	1,6,7, 16-20, 23,25,26
Y	abstract page 163, column 2, paragraph C. page 172, column 1, paragraph 2 figures 8,9; table 4	1-42

Y	US 2 483 447 A (HOWELLS VINTON WILLIAM) 4 October 1949 (1949-10-04) column 1, lines 40-48; claims 2-4	1-42

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2012	08/05/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kiernan, Andrea

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International application No
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