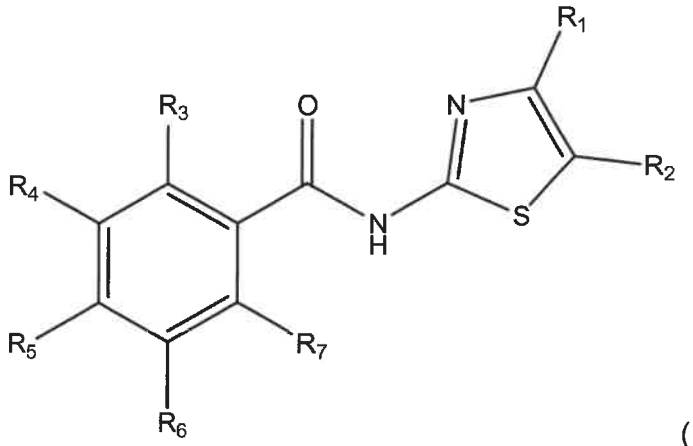
CLAIMS

1. A combination product comprising:

(i) a compound selected from NTZ and an analogue thereof ; and

(ii) at least one PPAR agonist.

2. The combination product according to claim 1, wherein component (i) is a compound of formula (I):



(I)

or a pharmaceutical acceptable salt thereof, in which :

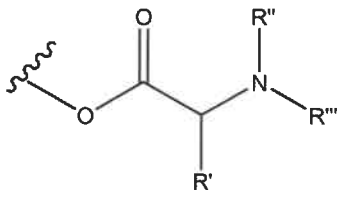
R1 represents a hydrogen atom (H), a deuterium atom (D), a halogen atom, a (C6-C14)aryl group, a heterocyclic group, a (C3-C14)cycloalkyl group, a (C1-C6)alkyl group, a sulfonyl group, a sulfoxyde group, a (C1-C6)alkylcarbonyl group, a (C1-C6)alkyloxy, a carboxylic group, a carboxylate group, a NO_2 group, a NH2 group, a (C1-C6)alkylamino group, an amido group, a (C1-C6)alkylamido group, a (C1-C6)dialkylamido group.

R2 represents a hydrogen atom, a deuterium atom, a NO2 group, a (C6-C14)aryl group, a heterocyclic group, a halogen atom, a (C1-C6)alkyl group, a (C3-C14)cycloalkyl group, a (C2-C6)alkynyl group, a (C1-C6)alkyloxy group, a (C1-C6)alkylthio group, a (C1-C6)alkylcarbonyl group, a (C1-C6)alkylcarbonylamino group, a (C6-C14)arylcarbonylamino group, a carboxylic or carboxylate group, an amido group, a (C1-C6)alkylamido group, a (C1-C6)dialkylamido group, a NH_2 group, a (C1-C6)alkylamino group,

or R1 and R2, together with the carbon atoms to which they are attached, form a substituted or unsubstituted 5- to 8- membered cycloalkyl, heterocyclic or aryl group,

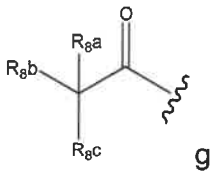
R3 represents a hydrogen atom, a deuterium atom, a halogen atom, a O-R8 group, a (C1-C6)alkylcarbonyl group, an (C1-C6)alkyl group, an (C1-C6)alkyloxy group, an (C1-C6)alkylthio group, an (C1-C6)alkylcarbonyloxy group, an (C6-C14)aryloxy group, a (C6-C14)aryl group, a heterocyclic group, a (C3-C14)cycloalkyl group a NO2, a

sulfonylaminoalkyle group, an NH2 group, an amino(C1-C6)alkyl group, an (C1-C6)alkylcarbonylamino group, a carboxylic group, a carboxylate group, an aminoacid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a moiety of formula (A):

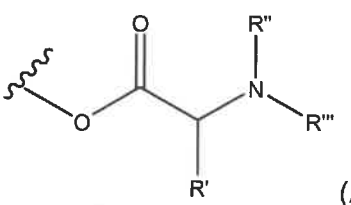


(A)

wherein R' represents an (C1-C6)alkyl group, an (C2-C6)alkenyl group, an (C2-C6)alkynyl group, a (C3-C14)cycloalkyl group, (C3-C14)cycloalkylalkyl group, a (C3-C14)cycloalkyl(C2-C6)alkenyl group, a (C3-C14)cycloalkenyl group, a (C3-C14)cycloalkenyl(C1-C6)alkyl group, a (C3-C14)cycloalkenyl(C2-C6)alkenyl group, a (C3-C14)cycloalkenyl(C2-C6)alkynyl group; R'' and R''', independently, represent hydrogen atom, an (C1-C6)alkyl group, or a nitrogen protecting group.

R8 represents a hydrogen atom, a deuterium atom, or a  group wherein, R8a, R8b and R8c, identical or different, represent a hydrogen atom or a deuterium atom.

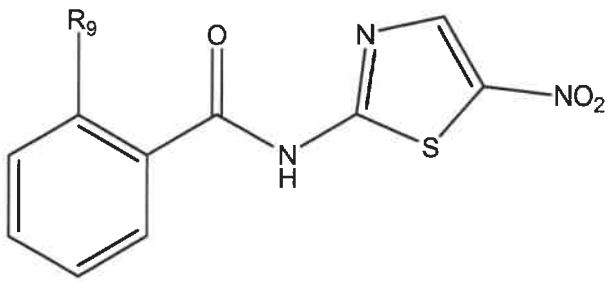
R4, R5, R6, and R7, identical or different, represent a hydrogen atom, a deuterium atom, a halogen atom, a hydroxyl group, an (C1-C6)alkylcarbonyl group, an (C1-C6)alkyl group, an (C1-C6)alkyloxy group, an (C1-C6)alkylthio group, an (C1-C6)alkylcarbonyloxy group, an (C6-C14)aryloxy group, an (C6-C14)aryl group, a heterocyclic group, a (C3-C14)cycloalkyl group, a NO2, a sulfonylamino(C1-C6)alkyl group, an NH2 group, an amino(C1-C6)alkyl group, an (C1-C6)alkylcarbonylamino group, a carboxylic group, a carboxylate group, an aminoacid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a moiety of formula (A):



(A)

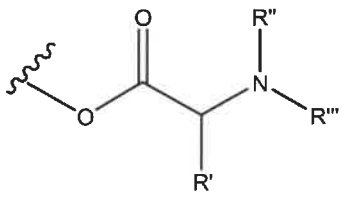
wherein R' represents an (C1-C6)alkyl group, an (C2-C6)alkenyl group, an (C2-C6)alkynyl group, a (C3-C14)cycloalkyl group, (C3-C14)cycloalkyl(C1-C6)alkyl group, a (C3-C14)cycloalkyl(C1-C6)alkenyl group, a (C3-C14)cycloalkenyl group, a (C3-C14)cycloakenyl(C1-C6)alkyl group, a (C3-C14)cycloalkenyl(C2-C6)alkenyl group, a (C3-C14)cycloalkenyl(C2-C6)alkynyl group; R" and R"', independently, represent a hydrogen atom, an (C1-C6)alkyl group, or a nitrogen protecting group;
or a pharmaceutically acceptable salt thereof.

3. The combination production of claim 1 or 2, wherein component (i) is a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, in which R9 represents a hydrogen atom, a deuterium atom, a O-R8 group (R8 is defined above), or an aminoacid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a moiety of formula (A):



(A);

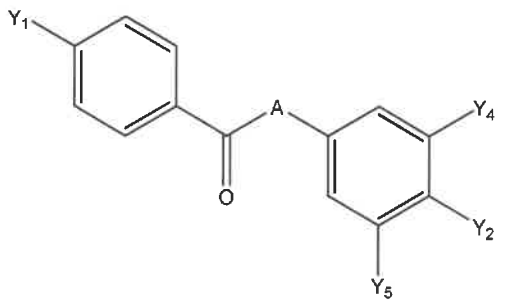
wherein R' represents an (C1-C6)alkyl group, an (C2-C6)alkenyl group, an (C2-C6)alkynyl group, a (C3-C14)cycloalkyl group, (C3-C14)cycloalkyl(C1-C6)alkyl group, a (C3-C14)cycloalkyl(C1-C6)alkenyl group, a (C3-C14)cycloalkenyl group, a (C3-C14)cycloakenyl(C1-C6)alkyl group, a (C3-C14)cycloalkenyl(C2-C6)alkenyl group, a (C3-C14)cycloalkenyl(C2-C6)alkynyl group; R" and R"', independently, represent a hydrogen atom, an (C1-C6)alkyl group, or a nitrogen protecting group
or a pharmaceutically acceptable salt thereof.

4. The combination product according to any one of claims 1 to 3, wherein component (i) is selected from nitazoxanide, tizoxanide, [(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d3)ethanoate, 2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d2) ethanoate; or 2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d1) ethanoate, ((S)-2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3,3-dimethylbutanoate hydrochloride) and ((2S,3S)-2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3-methylpentanoate hydrochloride), or pharmaceutically acceptable salt thereof.

5. The combination product according to any one of claims 1 to 4, wherein component (ii) is selected from:

- at least one PPAR-alpha agonist;
- at least one PPAR-gamma agonist;
- at least one PPAR-delta agonist;
- at least one PPAR-alpha/delta dual agonist;
- at least one PPAR-alpha agonist and at least one PPAR delta agonist;
- at least one PPAR-alpha/gamma dual agonist;
- at least one PPAR-alpha agonist and at least one PPAR gamma agonist;
- at least one PPAR-gamma/delta dual agonist;
- at least one PPAR-gamma agonist and at least one PPAR delta agonist;
- at least one PPAR-alpha/gamma/delta pan agonist; and
- at least one PPAR-alpha agonist, at least one PPAR-gamma agonist and at least one PPAR-delta agonist.

6. The combination product according to any one of claims 1 to 5, wherein the at least one PPAR agonist is a compound of formula (III), or a pharmaceutically acceptable salt thereof:



(III)

in which:

Y1 represents a halogen, a Ra, or Ga-Ra group;

A represents a CH=CH or a CH2-CH2 group;

Y2 represents a Gb-Rb group;

Ga and Gb, identical or different, represent an atom of oxygen or sulfur;

Ra represents a hydrogen atom, an unsubstituted (C1-C6)alkyl group, a (C6-C14)aryl group or a (C1-C6)alkyl group that is substituted by one or more halogen atoms, a (C1-C6)alkoxy or a (C1-C6)alkylthio group, (C3-C14)cycloalkyl groups, (C3-C14)cycloalkylthio groups or heterocyclic groups;

Rb represents a (C1-C6)alkyl group substituted by at least a –COORc group, wherein Rc represents a hydrogen atom, or a (C1-C6)alkyl group that is substituted or not by one or more halogen atoms, (C3-C14)cycloalkyl groups, or heterocyclic groups; and

Y4 and Y5, identical or different, representing a (C1-C6)alkyl group that is substituted or not by one or more halogen atoms, (C3-C14)cycloalkyl groups or heterocyclic groups.

7. The combination product according to any one of claims 1 to 6, wherein component (ii) is selected from Elafibranor, Seladelpar, Saroglitazar, and Lanifibranor, or a pharmaceutical salt thereof.

8. The combination product according to any one of claims 1 to 7, comprising:

(i) a compound selected from nitazoxanide, tizoxanide, [(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d3)ethanoate, 2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d2) ethanoate; or 2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d1) ethanoate, ((S)-2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3,3-dimethylbutanoate hydrochloride) and ((2S,3S)-2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3-methylpentanoate hydrochloride); or from a pharmaceutical salt thereof; and

(ii) Elafibranor or a pharmaceutically acceptable salt thereof.

9. The combination product according to any one of claims 1 to 8, wherein the combination product is a composition comprising components i) and ii) and a pharmaceutically acceptable carrier.

10. The combination product according to any one of claims 1 to 9, wherein the combination product is a kit of parts comprising components i) and ii), for sequential, separate or simultaneous use.

11. The combination product according to any one of claims 1 to 10, further comprising at least one therapeutically active agent with known antifibrotic activity selected from

pirfenidone or receptor tyrosine kinase inhibitors (RTKIs) such as Nintedanib, Sorafenib and other RTKIs, or angiotensin II (AT1) receptor blockers, or CTGF inhibitor, or any antifibrotic compound susceptible to interfere with the TGFβ and BMP-activated pathways including activators of the latent TGFβ complex such as MMP2, MMP9, THBS1 or cell-surface integrins, TGFβ receptors type I (TGFBRI) or type II (TGFBRII) and their ligands such as TGFβ, Activin, inhibin, Nodal, anti-Müllerian hormone, GDFs or BMPs, auxiliary co-receptors (also known as type III receptors), or components of the SMAD-dependent canonical pathway including regulatory or inhibitory SMAD proteins, or members of the SMAD-independent or non-canonical pathways including various branches of MAPK signaling, TAK1, Rho-like GTPase signaling pathways, phosphatidylinositol-3 kinase/AKT pathways, TGFβ-induced EMT process, or canonical and non-canonical Hedgehog signaling pathways including Hh ligands or target genes, or any members of the WNT, or Notch pathways which are susceptible to influence TGFβ.

12. The combination product according to any one of claims 1 to 11, further comprising at least one therapeutically active agent selected from JAK/STAT inhibitors and other anti-inflammatory and/or immunosuppressant agents.

13. The combination product according to claim 12, wherein the therapeutically active agent is selected from glucocorticoids, NSAIDS, cyclophosphamide, nitrosoureas, folic acid analogs, purine analogs, pyrimidine analogs, methotrexate, azathioprine, mercaptopurine, ciclosporin, myriocin, tacrolimus, sirolimus, mycophenolic acid derivatives, fingolimod and other sphingosine-1-phosphate receptor modulators, monoclonal and/or polyclonal antibodies against such targets as proinflammatory cytokines and proinflammatory cytokine receptors, T-cell receptor and integrins.

14. The combination product according to any one of claims 1 to 13, wherein components (i) and (ii) are formulated in an injectable suspension, a gel, an oil, a pill, a tablet, a suppository, a powder, a capsule, an aerosol, an oinment, a cream, a patch, or means of galenic forms for a prolonged and/or slow release.

15. The combination product according to any one of claims 1 to 14, for use as a medicament.

16. The combination product according to any one of claims 1 to 14, for use in a method for treating an inflammatory, metabolic, fibrotic or cholestatic disease.

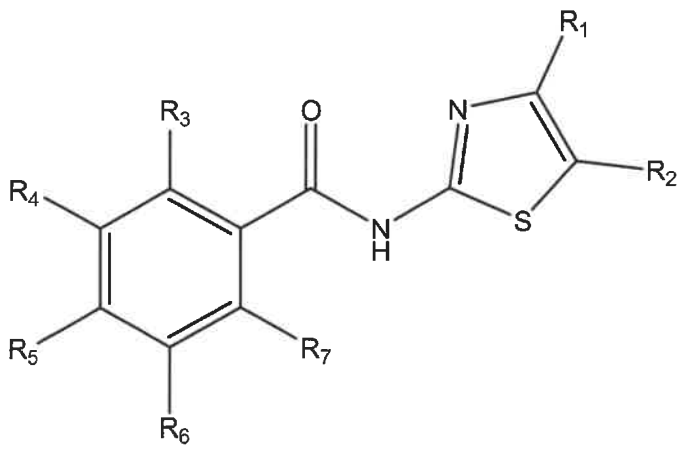
17. The combination product for use according to claim 16, wherein the fibrotic disorder is selected in the group consisting of liver, kidney, skin, epidermis, endodermis, muscle, tendon, cartilage, heart, pancreas, lung, uterus, nervous system, testis, ovary, adrenal gland, artery, vein, colon, intestine (e.g. small intestine), biliary tract, soft tissue (e.g. mediastinum or retroperitoneum), bone marrow, joint and stomach fibrosis, in particular liver, gut, lung, heart, kidney, muscle, skin, soft tissue, bone marrow, intestinal, and joint fibrosis.

18. The combination product for use according to claim 16, wherein the disease is selected from the group consisting of, metabolic liver diseases, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), drug-induced liver diseases, alcohol-induced liver diseases, infectious agent induced liver diseases, inflammatory liver diseases, immune system dysfunction-mediated liver diseases, dyslipidemia, cardiovascular diseases, restenosis, syndrome X, metabolic syndrome, diabetes, obesity, hypertension, chronic cholangiopathies such as Primary Sclerosing Cholangitis (PSC) and Primary Biliary Cholangitis (PBC).

19. Use of (i) a compound selected from NTZ and an analogue thereof; and

(ii) at least one PPAR agonist in the preparation of a combination product for the treatment of an inflammatory, metabolic, fibrotic or cholestatic disease.

20. Use according to claim 19, wherein component (i) is a compound of formula (I):



(I)

or a pharmaceutical acceptable salt thereof, in which :

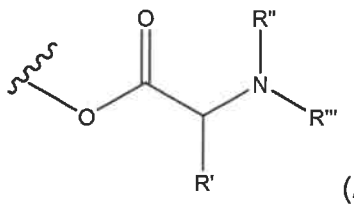
R1 represents a hydrogen atom (H), a deuterium atom (D), a halogen atom, a (C6-C14)aryl group, a heterocyclic group, a (C3-C14)cycloalkyl group, a (C1-C6)alkyl group, a sulfonyl

group, a sulfoxyde group, a (C1-C6)alkylcarbonyl group, a (C1-C6)alkyloxy, a carboxylic group, a carboxylate group, a NO_2 group, a NH2 group, a (C1-C6)alkylamino group, an amido group, a (C1-C6)alkylamido group, a (C1-C6)dialkylamido group.

R2 represents a hydrogen atom, a deuterium atom, a NO2 group, a (C6-C14)aryl group, a heterocyclic group, a halogen atom, a (C1-C6)alkyl group, a (C3-C14)cycloalkyl group, a (C2-C6)alkynyl group, a (C1-C6)alkyloxy group, a (C1-C6)alkylthio group, a (C1-C6)alkylcarbonyl group, a (C1-C6)alkylcarbonylamino group, a (C6-C14)arylcarbonylamino group, a carboxylic or carboxylate group, an amido group, a (C1-C6)alkylamido group, a (C1-C6)dialkylamido group, a NH_2 group, a (C1-C6)alkylamino group,

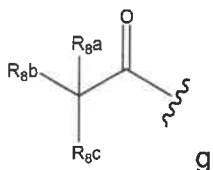
or R1 and R2, together with the carbon atoms to which they are attached, form a substituted or unsubstituted 5- to 8- membered cycloalkyl, heterocyclic or aryl group,

R3 represents a hydrogen atom, a deuterium atom, a halogen atom, a O-R8 group, a (C1-C6)alkylcarbonyl group, an (C1-C6)alkyl group, an (C1-C6)alkyloxy group, an (C1-C6)alkylthio group, an (C1-C6)alkylcarbonyloxy group, an (C6-C14)aryloxy group, a (C6-C14)aryl group, a heterocyclic group, a (C3-C14)cycloalkyl group a NO2, a sulfonylaminoalkyle group, an NH2 group, an amino(C1-C6)alkyl group, an (C1-C6)alkylcarbonylamino group, a carboxylic group, a carboxylate group, an aminoacid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a moiety of formula (A):



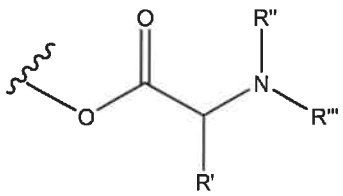
(A)

wherein R' represents an (C1-C6)alkyl group, an (C2-C6)alkenyl group, an (C2-C6)alkynyl group, a (C3-C14)cycloalkyl group, (C3-C14)cycloalkylalkyl group, a (C3-C14)cycloalkyl(C2-C6)alkenyl group, a (C3-C14)cycloalkenyl group, a (C3-C14)cycloalkenyl(C1-C6)alkyl group, a (C3-C14)cycloalkenyl(C2-C6)alkenyl group, a (C3-C14)cycloalkenyl(C2-C6)alkynyl group; R" and R"', independently, represent hydrogen atom, an (C1-C6)alkyl group, or a nitrogen protecting group.

R8 represents a hydrogen atom, a deuterium atom, or a 

group wherein, R8a, R8b and R8c, identical or different, represent a hydrogen atom or a deuterium atom.

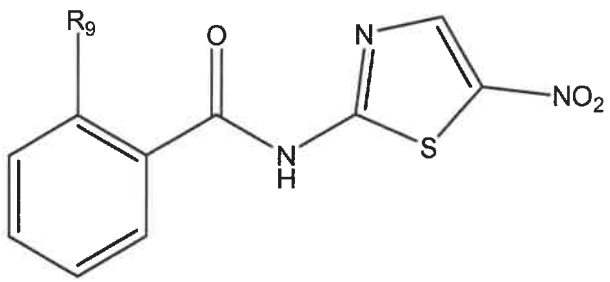
R4, R5, R6, and R7, identical or different, represent a hydrogen atom, a deuterium atom, a halogen atom, a hydroxyl group, an (C1-C6)alkylcarbonyl group, an (C1-C6)alkyl group, an (C1-C6)alkyloxy group, an (C1-C6)alkylthio group, an (C1-C6)alkylcarbonyloxy group, an (C6-C14)aryloxy group, an (C6-C14)aryl group, a heterocyclic group, a (C3-C14)cycloalkyl group, a NO2, a sulfonylamino(C1-C6)alkyl group, an NH2 group, an amino(C1-C6)alkyl group, an (C1-C6)alkylcarbonylamino group, a carboxylic group, a carboxylate group, an aminoacid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a moiety of formula (A):



(A)

wherein R' represents an (C1-C6)alkyl group, an (C2-C6)alkenyl group, an (C2-C6)alkynyl group, a (C3-C14)cycloalkyl group, (C3-C14)cycloalkyl(C1-C6)alkyl group, a (C3-C14)cycloalkyl(C1-C6)alkenyl group, a (C3-C14)cycloalkenyl group, a (C3-C14)cycloakenyl(C1-C6)alkyl group, a (C3-C14)cycloalkenyl(C2-C6)alkenyl group, a (C3-C14)cycloalkenyl(C2-C6)alkynyl group; R'' and R''', independently, represent a hydrogen atom, an (C1-C6)alkyl group, or a nitrogen protecting group;
or a pharmaceutically acceptable salt thereof.

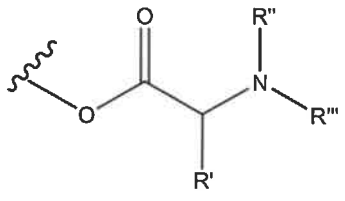
21. Use according to claim 19 or 20, wherein component (i) is a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, in which R9 represents a hydrogen atom, a deuterium atom, a O-R8 group (R8 is defined above), or an aminoacid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic

acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a moiety of formula (A):



(A);

wherein R' represents an (C1-C6)alkyl group, an (C2-C6)alkenyl group, an (C2-C6)alkynyl group, a (C3-C14)cycloalkyl group, (C3-C14)cycloalkyl(C1-C6)alkyl group, a (C3-C14)cycloalkyl(C1-C6)alkenyl group, a (C3-C14)cycloalkenyl group, a (C3-C14)cycloakenyl(C1-C6)alkyl group, a (C3-C14)cycloalkenyl(C2-C6)alkenyl group, a (C3-C14)cycloalkenyl(C2-C6)alkynyl group; R'' and R''', independently, represent a hydrogen atom, an (C1-C6)alkyl group, or a nitrogen protecting group

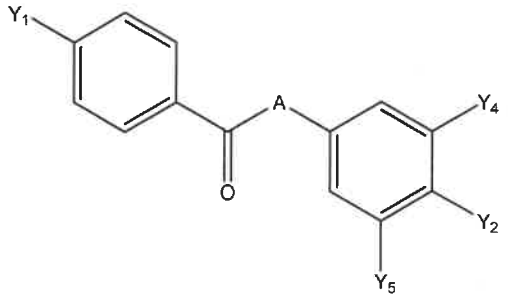
or a pharmaceutically acceptable salt thereof.

22. Use according to any one of claims 19 to 21, wherein component (i) is selected from nitazoxanide, tizoxanide, [(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d3)ethanoate, 2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d2) ethanoate; or 2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d1) ethanoate, ((S)-2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3,3-dimethylbutanoate hydrochloride) and ((2S,3S)-2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3-methylpentanoate hydrochloride), or pharmaceutically acceptable salt thereof.

23. Use according to any one of claims 19 to 22, wherein component (ii) is selected from:

- at least one PPAR-alpha agonist;
- at least one PPAR-gamma agonist;
- at least one PPAR-delta agonist;
- at least one PPAR-alpha/delta dual agonist;
- at least one PPAR-alpha agonist and at least one PPAR delta agonist;
- at least one PPAR-alpha/gamma dual agonist;
- at least one PPAR-alpha agonist and at least one PPAR gamma agonist;
- at least one PPAR-gamma/delta dual agonist;
- at least one PPAR-gamma agonist and at least one PPAR delta agonist;
- at least one PPAR-alpha/gamma/delta pan agonist; and
- at least one PPAR-alpha agonist, at least one PPAR-gamma agonist and at least one PPAR-delta agonist.

24. Use according to any one of claims 19 to 23, wherein the at least one PPAR agonist is a compound of formula (III), or a pharmaceutically acceptable salt thereof:



(III)

in which:

Y1 represents a halogen, a Ra, or Ga-Ra group;

A represents a CH=CH or a CH2-CH2 group;

Y2 represents a Gb-Rb group;

Ga and Gb, identical or different, represent an atom of oxygen or sulfur;

Ra represents a hydrogen atom, an unsubstituted (C1-C6)alkyl group, a (C6-C14)aryl group or a (C1-C6)alkyl group that is substituted by one or more halogen atoms, a (C1-C6)alkoxy or a (C1-C6)alkylthio group, (C3-C14)cycloalkyl groups, (C3-C14)cycloalkylthio groups or heterocyclic groups;

Rb represents a (C1-C6)alkyl group substituted by at least a –COORc group, wherein Rc represents a hydrogen atom, or a (C1-C6)alkyl group that is substituted or not by one or more halogen atoms, (C3-C14)cycloalkyl groups, or heterocyclic groups; and

Y4 and Y5, identical or different, representing a (C1-C6)alkyl group that is substituted or not by one or more halogen atoms, (C3-C14)cycloalkyl groups or heterocyclic groups.

25. Use according to any one of claims 19 to 24, wherein component (ii) is selected from is selected from Elafibranor, Seladelpar, Saroglitazar, and Lanifibranor, or a pharmaceutical salt thereof.

26. Use according to any one of claims 19 to 25, comprising (i) a compound selected from nitazoxanide, tizoxanide, [(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d3)ethanoate, 2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d2) ethanoate; or 2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d1) ethanoate, ((S)-2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3,3-dimethylbutanoate hydrochloride) and ((2S,3S)-2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3-methylpentanoate hydrochloride); or from a pharmaceutical salt thereof; and

(ii) Elafibranor or a pharmaceutically acceptable salt thereof.

27. Use according to any one of claims 19 to 26, wherein the fibrotic disorder is selected in the group consisting of liver, kidney, skin, epidermis, endodermis, muscle, tendon, cartilage, heart, pancreas, lung, uterus, nervous system, testis, ovary, adrenal gland, artery, vein, colon, intestine (e.g. small intestine), biliary tract, soft tissue (e.g. mediastinum or retroperitoneum), bone marrow, joint and stomach fibrosis, in particular liver, gut, lung, heart, kidney, muscle, skin, soft tissue, bone marrow, intestinal, and joint fibrosis.

28. Use according to any one of claims 19 to 27, wherein the disease is selected from the group consisting of, metabolic liver diseases, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), drug-induced liver diseases, alcohol-induced liver diseases, infectious agent induced liver diseases, inflammatory liver diseases, immune system dysfunction-mediated liver diseases, dyslipidemia, cardiovascular diseases, restenosis, syndrome X, metabolic syndrome, diabetes, obesity, hypertension, chronic cholangiopathies such as Primary Sclerosing Cholangitis (PSC) and Primary Biliary Cholangitis (PBC).