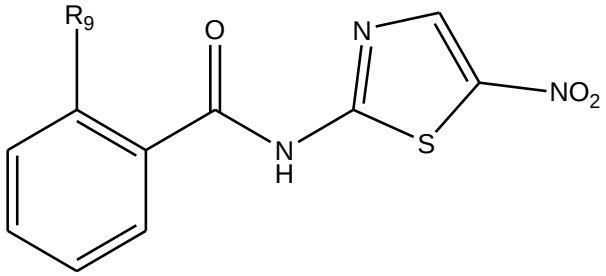
CLAIMS

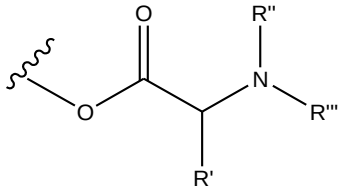
1. A combination product comprising:

(i) 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 amino acid 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 ; and

(ii) at least one compound selected from Elafibranor, Seladelpar, Saroglitazar, and Lanifibranor, or a pharmaceutical salt thereof.

2. The combination product according to claim 1, 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.

3. The combination product according to claim 1 or 2, 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.

4. The combination product according to any one of claims 1 to 3, wherein the combination product is a composition comprising components (i) and (ii) and a pharmaceutically acceptable carrier.

5. The combination product according to any one of claims 1 to 3, wherein the combination product is a kit of parts comprising components (i) and (ii), for sequential, separate or simultaneous use.

6. The combination product according to any one of claims 1 to 5, 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.

7. The combination product according to any one of claims 1 to 6, further comprising at least one therapeutically active agent selected from JAK/STAT inhibitors and other anti-inflammatory and/or immunosuppressant agents.

8. The combination product according to claim 7, 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.

9. The combination product according to any one of claims 1 to 8, 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.

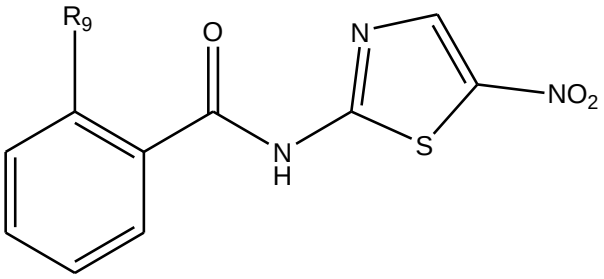
10. The combination product according to any one of claims 1 to 9, for use as a medicament.

11. The combination product according to any one of claims 1 to 9, for use in a method for treating an inflammatory, metabolic, fibrotic or cholestatic disease.

12. The combination product for use according to claim 11, 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.

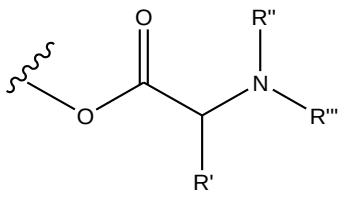
13. The combination product for use according to claim 11, wherein the disease is selected from the group consisting of, metabolic liver diseases, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), drug-induced liver diseases, alcohol-induced liver diseases, infectious agent 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).

14. Use of (i) 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; and

(ii) at least one compound selected from Elafibranor, Seladelpar, Saroglitazar, and Lanifibranor, or a pharmaceutical salt thereof;

in the preparation of a combination medicament for the treatment of an inflammatory, metabolic, fibrotic or cholestatic disease.

15. Use according to claim 14, 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.

16. Use according to claim 14 or 15, 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.

17. Use according to any one of claims 14 to 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. Use according to any one of claims 14 to 17, 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).