CLAIMS

1. A combination product comprising:

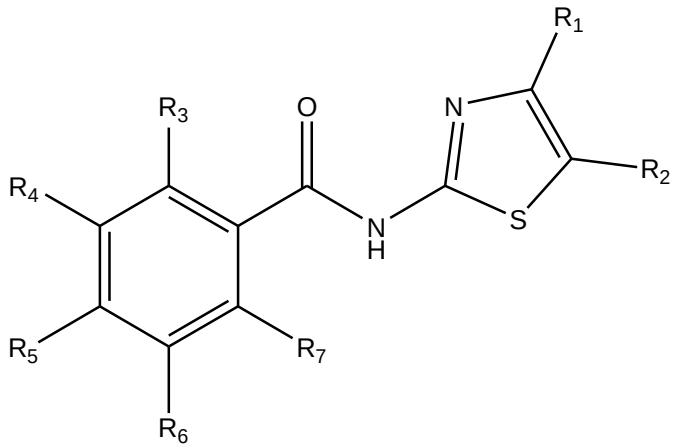
(i) a compound selected from NTZ and an analogue thereof ; and

(ii) an anti-NASH, anti-fibrotic or anti-cholestatic agent,

wherein component (ii) is a ROCK2 inhibitor (in particular KD-025), an ACC inhibitor, a dual inhibitor of NADPH oxidase isoforms NOX4 and NOX1 (in particular GKT-831), an ASK1 inhibitor (in particular selonsertib), a Fatty Acid Bile Acid Conjugate, an FXR agonist, and a CCR antagonist.

2. The combination product according to claim 1, wherein component (ii) is obeticholic acid, aramchol, SHP-625, emricasan, IMM-124-E, GS-9674, NGM-282, A-4250, cenicriviroc, GR-MD-02, GS-4997, Tropifexor (LJN-452), F-351, solithromycin, remogliflozin, BTT-1023, KD-025, PEG-FGF21, tipelukast, VK-2809, MGL-3196, GS-0976, RG-125, volixibat, ursodeoxycholic acid, semaglutide, GSK2330672, or a pharmaceutical salt thereof.

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



(I)

or a pharmaceutical acceptable salt thereof, in which :

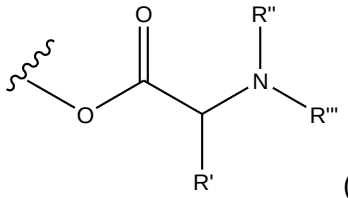
R1 represents a hydrogen atom (H), a deuterium atom (D), a halogen atom, a (C6-C14)aryl group, a heterocyclic group, a (C3-C14)cycloalkyl group, a (C1-C6)alkyl group, a sulfonyl group, a sulfoxyde group, a (C1-C6)alkylcarbonyl group, a (C1-C6)alkyloxy, a carboxylic group, a carboxylate group, a nitro group (NO2), an amino group (NH2), 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, R4, R5, R6, and R7, identical or different, represent a hydrogen atom, a deuterium atom, a halogen atom, a hydroxyl 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 group, a sulfonylaminoalkyle group, an NH2 group, an amino(C1-C6)alkyl group, an (C1-C6)alkylcarbonylamino group, a carboxylic group, a carboxylate group, or a R9 group;

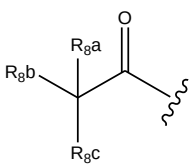
R9 represents a O-R8 group or an amino-acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or a moiety of formula (A):



(A)

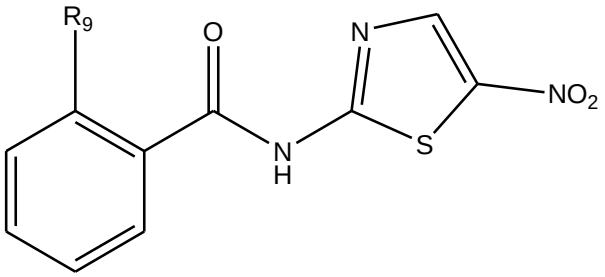
wherein R' represents an (C1-C6)alkyl group, an (C2-C6)alkenyl group, an (C2-C6)alkynyl group, a (C3-C14)cycloalkyl group, (C3-C14)cycloalkylalkyl group, a (C3-C14)cycloalkyl(C2-C6)alkenyl group, a (C3-C14)cycloalkenyl group, a (C3-C14)cycloalkenyl(C1-C6)alkyl group, a (C3-C14)cycloalkenyl(C2-C6)alkenyl 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;



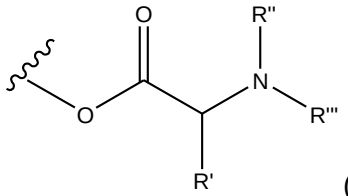
R8 represents a hydrogen atom, a deuterium atom, a glucuronidyl group, or a group wherein, R8a, R8b and R8c, identical or different, represent a hydrogen atom or a deuterium atom.

4. The combination product of any one of claims 1 to 3, 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, 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.

5. The combination product according to any one of claims 1 to 4, 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, 2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl (d1) ethanoate, 2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3,3-dimethylbutanoate, 2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3-methylpentanoate, 2-(5-chlorothiazol-2-ylcarbamoyl)phenyl 2-amino-3,3-dimethylbutanoate, 2-(5-chlorothiazol-2-ylcarbamoyl)phenyl 2-amino-3-methylpentanoate or a pharmaceutically acceptable salt thereof.

6. The combination product according to any one of claims 1 to 5, wherein component (i) is nitazoxanide or a pharmaceutically acceptable salt thereof.

7. The combination product according to any one of claims 1 to 6, 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, 2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3,3-dimethylbutanoate, 2-(5-nitrothiazol-2-ylcarbamoyl)phenyl 2-amino-3-methylpentanoate, 2-(5-chlorothiazol-2-ylcarbamoyl)phenyl 2-amino-3,3-dimethylbutanoate, 2-(5-chlorothiazol-2-ylcarbamoyl)phenyl 2-amino-3-methylpentanoate; or from a pharmaceutical salt thereof; and

(ii), GS-0976, GS-4997 (Selonsertib), GKT-831 (formerly GKT137831), KD-025, Cenicriviroc (CVC), Aramchol, and Tropifexor (LJN-452) or a pharmaceutically acceptable salt thereof.

8. The combination product according to any one of claims 1 to 7, wherein the combination product is a composition comprising components (i) and (ii) and a pharmaceutically acceptable carrier.

9. A kit of parts comprising components (i) and (ii) as defined according to any one of claims 1 to 9, for sequential, separate or simultaneous use.

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

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

12. The combination product according to any one of claims 1 to 10, for use in a method for treating an inflammatory, metabolic, fibrotic and cholestatic disease.

13. The combination product for use according to claim 12, 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, penis, 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, eye and joint fibrosis.

14. The combination product for use according to claim 12, wherein the disease is selected in 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), Primary Biliary Cholangitis (PBC), biliary atresia, familial intrahepatic cholestasis type 3 (PFIC3), inflammatory bowel diseases, Crohn's disease, ulcerative colitis, keloid, old myocardial infarction, scleroderma/systemic sclerosis, inflammatory diseases, neurodegenerative diseases, cancers, liver cancer, hepatocallular carcinoma, gastrointestinal cancer, gastric cancer, meningioma associated with neurofibromatosis, pancreatic neuroendocrine tumors, pancreatic exocrine tumors, leukemia, myeloproliferative/myelodisplastic diseases, mastocytosis, dermatofibrosarcoma, solid tumors including breast, lung, thyroid or colorectal cancer, a prostate cancer, liver fibrosis or cirrhosis of any origin, metabolic disease-induced liver fibrosis or cirrhosis, NAFLD-induced fibrosis or cirrhosis, NASH-induced fibrosis or cirrhosis, alcohol-induced liver fibrosis or cirrhosis, drug-induced liver fibrosis or cirrhosis, infectious agent-induced liver fibrosis or cirrhosis, parasite infection-induced liver fibrosis or cirrhosis, bacterial infection-induced liver fibrosis or cirrhosis, viral infection-induced fibrosis or cirrhosis, HBV-infection induced liver fibrosis or cirrhosis, HCV-infection induced liver fibrosis or cirrhosis, HIV-infection induced liver fibrosis or cirrhosis, dual HCV and HIV-infection induced liver fibrosis or cirrhosis, radiation- or chemotherapy-induced fibrosis or cirrhosis, biliary tract fibrosis, liver fibrosis or cirrhosis due to any chronic cholestatic disease, gut fibrosis of any etiology, Crohn's disease-induced fibrosis, ulcerative colitis-induced fibrosis, intestine (e.g. small intestine) fibrosis, colon fibrosis, stomach fibrosis, skin fibrosis, epidermis fibrosis, endodermis fibrosis, skin fibrosis due to scleroderma/systemic sclerosis, lung fibrosis, lung fibrosis consecutive to chronic inflammatory airway diseases, such

as COPD, asthma, emphysema, smoker's lung,tuberculosis, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), heart fibrosis, kidney fibrosis, nephrogenic systemic fibrosis, muscle fibrosis, soft tissue (e.g. mediastinum or retroperitoneum) fibrosis, bone marrow fibrosis, joint fibrosis, tendon fibrosis, cartilage fibrosis, pancreas fibrosis, uterus fibrosis, nervous system fibrosis, testis fibrosis, ovary fibrosis, adrenal gland fibrosis, artery fibrosis, vein fibrosis, eye fibrosis, endomyocardial fibrosis, mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis (a complication of coal workers' pneumoconiosis), proliferative fibrosis, neoplastic fibrosis, peri-implantational fibrosis and asbestosis, arthrofibrosis, adhesive capsulitis.

15. The combination product for use according to claim 12, wherein the disease is selected in the group consisting of, the disease is selected in 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), Primary Biliary Cholangitis (PBC), biliary atresia, familial intrahepatic cholestasis type 3 (PFIC3), inflammatory bowel diseases, Crohn's disease, ulcerative colitis, liver cancer, hepatocallular carcinoma, gastrointestinal cancer, gastric cancer, colorectal cancer, metabolic disease-induced liver fibrosis or cirrhosis, NAFLD-induced fibrosis or cirrhosis, NASH-induced fibrosis or cirrhosis, alcohol-induced liver fibrosis or cirrhosis, drug-induced liver fibrosis or cirrhosis, infectious agent-induced liver fibrosis or cirrhosis, parasite infection-induced liver fibrosis or cirrhosis, bacterial infection-induced liver fibrosis or cirrhosis, viral infection-induced fibrosis or cirrhosis, HBV-infection induced liver fibrosis or cirrhosis, HCV-infection induced liver fibrosis or cirrhosis, HIV-infection induced liver fibrosis or cirrhosis, dual HCV and HIV-infection induced liver fibrosis or cirrhosis, radiation- or chemotherapy-induced fibrosis or cirrhosis, biliary tract fibrosis, liver fibrosis or cirrhosis due to any chronic cholestatic disease, gut fibrosis of any etiology, Crohn's disease-induced fibrosis, ulcerative colitis-induced fibrosis, intestine (e.g. small intestine) fibrosis, colon fibrosis, stomach fibrosis, lung fibrosis, lung fibrosis consecutive to chronic inflammatory airway diseases, such as COPD, asthma, emphysema, smoker's lung, tuberculosis, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF).

16. Use of a combination product comprising (i) a compound selected from NTZ and an analogue thereof ; and

(ii) an anti-NASH, anti-fibrotic or anti-cholestatic agent, for the manufacture of a medicament for treating an inflammatory, metabolic, fibrotic and cholestatic disease

wherein component (ii) is a ROCK2 inhibitor (in particular KD-025), an ACC inhibitor, a dual inhibitor of NADPH oxidase isoforms NOX4 and NOX1 (in particular GKT-831), an ASK1 inhibitor (in particular selonsertib), a Fatty Acid Bile Acid Conjugate, an FXR agonist, and a CCR antagonist

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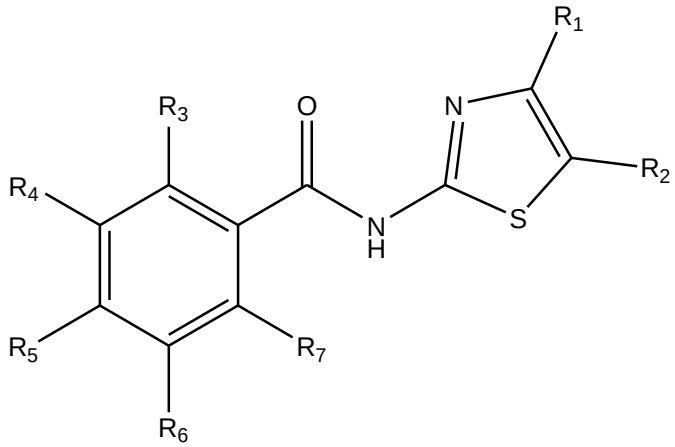
17. Use according to claim 16, wherein component (i) is a compound of formula (I):



(I)

or a pharmaceutical acceptable salt thereof, in which :

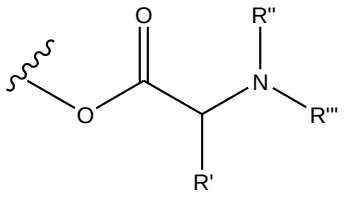
R1 represents a hydrogen atom (H), a deuterium atom (D), a halogen atom, a (C6-C14)aryl group, a heterocyclic group, a (C3-C14)cycloalkyl group, a (C1-C6)alkyl group, a sulfonyl group, a sulfoxyde group, a (C1-C6)alkylcarbonyl group, a (C1-C6)alkyloxy, a carboxylic group, a carboxylate group, a nitro group (NO2), an amino group (NH2), 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, R4, R5, R6, and R7, identical or different, represent a hydrogen atom, a deuterium atom, a halogen atom, a hydroxyl 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 group, a sulfonylaminoalkyle group, an NH2 group, an amino(C1-C6)alkyl group, an (C1-C6)alkylcarbonylamino group, a carboxylic group, a carboxylate group, or a R9 group;

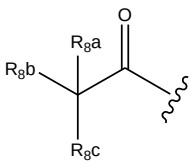
R9 represents a O-R8 group or an amino-acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or 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)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, a glucuronidyl group, or a group wherein, R8a, R8b and R8c, identical or different, represent a hydrogen atom or a deuterium atom.

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