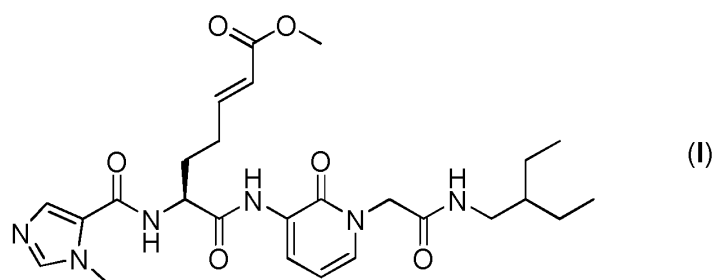


Claims

1. A systemic formulation containing (S,E)-methyl-7-(1-(2-(2-ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate of the formula (I):



or an enantiomer, a solvate, a hydrate or a pharmaceutically acceptable salt thereof, and at least one polymeric precipitation inhibitor.

2. The systemic formulation according to claim 1, wherein the systemic formulation is an oral formulation.
3. The systemic formulation according to claim 1 or 2, wherein the systemic formulation further comprises at least one acidifier and/or at least one binder.
4. The systemic formulation according to any of claims 1 to 3, wherein the at least one polymeric precipitation inhibitor is selected from the group consisting of L-hydroxypropyl cellulose, hydroxypropyl cellulose, a combination of L-hydroxypropyl cellulose and hydroxypropyl cellulose, polyethylene glycol, poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, ethylcellulose, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, and sodium carboxymethyl cellulose.
5. The systemic formulation according to claim 3 or 4, wherein the at least one acidifier is selected from the group consisting of ascorbic acid, organic dicarboxylic acid such as oxalic acid, malonic acid, succinic acid, glutaric acid, tartaric acid, fumaric acid, maleic acid, malic acid, adipic acid, or

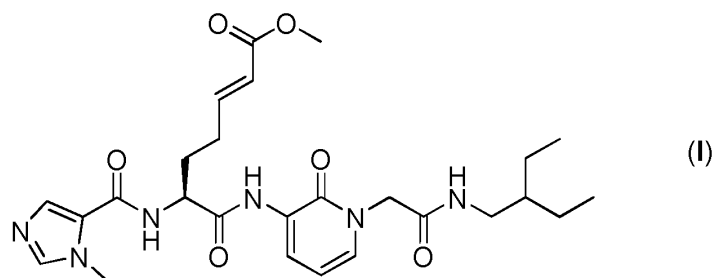
glutamic acid, and organic tri-carboxylic acid such as citric acid, or sodium hydrogen citrate.

- 5 6. The systemic formulation according to any one of claims 3 to 5, wherein the
at least one binder is selected from the group consisting of sugar, sucrose,
polysaccharides, xanthan gum, guar gum, carrageenan, starches derived
from wheat, corn, rice and potatoes, preagglutinated (modified) starch
derived from wheat, corn, rice and potatoes, sodium starch glycolate,
10 natural gums, acacia gum, gelatin, tragacanth, derivatives of sea weed,
alginic acid, sodium alginate, ammonium calcium alginate, cellulose,
cellulose derivatives, hydroxypropyl cellulose, L-hydroxypropyl cellulose,
low-substituted hydroxypropyl cellulose, methyl cellulose, sodium
carboxymethylcellulose, hydroxypropyl methylcellulose,
15 polyvinylpyrrolidone, povidone K25.
7. The systemic formulation according to any one of the claims 1 to 6, wherein
(S,E)-methyl-7-(1-(2-(2-ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-
pyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-
20 enoate particles have a particle size distribution which is defined by $d(0.95) \leq 25 \mu\text{m}$.
8. The systemic formulation according to any one of the claims 1 to 7, wherein
the systemic formulation is a tablet, coated tablet, capsule, powder, or
25 granule.
9. The systemic formulation according to any one of the claims 3 to 8, wherein
the systemic formulation comprises 1 to 15 m/m acidifier, 0.1 to 7 m/m
polymeric precipitation inhibitor, wherein m/m (mass ratio) of said
compounds is calculated relative to mass of (S,E)-methyl-7-(1-(2-(2-
30 ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-
methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate.
10. The systemic formulation according to any one of claims 1 to 9, wherein the
formulation comprises 0.1 wt% to 45 wt% (S,E)-methyl-7-(1-(2-(2-
35 ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-
methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate, 3 wt% to 75 wt%
acidifier, 2 wt% to 35 wt% polymeric precipitation inhibitor, 0 wt% to 12 wt%
binder, 2 wt% to 35 wt% disintegrant, and 1 wt% to 9 wt% lubricant/glidant.

11. The systemic formulation according to any one of claims 1 to 10, wherein the systemic formulation comprises 0.1 wt% to 45 wt% (S,E)-methyl-7-(1-(2-(2-ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate, 3 wt% to 75 wt% adipic acid, 2 wt% to 35 wt% L-hydroxypropyl cellulose and/or hydroxypropyl cellulose, 0 wt% to 12 wt% povidone K25, 2 wt% to 35 wt% sodium croscarmellose, and 1 wt% to 9 wt% talc or silicon dioxide.
12. A systemic formulation according to any one of the claims 1 to 11 for use in the prophylaxis and/or treatment of TG2-related diseases.
13. The systemic formulation for use according to claim 12, wherein the TG2-related disease is selected from the group consisting of nephropathy, fibrotic liver diseases including NAFLD, NASH, cirrhosis, cholestatic liver diseases such as primary sclerosing cholangitis and primary biliary cholangitis, autoimmune hepatitis, alcoholic steatohepatitis, cystic fibrosis, pulmonary fibrosis, idiopathic pulmonary fibrosis, radiation-induced lung injury, bridging fibrosis, cardiac fibrosis, systemic sclerosis, collagen induced arthritis, rheumatoid arthritis, atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, vascular stiffening, vascular calcification, fibroproliferative diseases, elevated blood pressure, gliar scar, arterial stiffness, arthrofibrosis, Dupuytren's contracture, keloid, medistinal fibrosis, myelofibrosis, Peyronie's disease, nephrogenic systemic fibrosis, IgA nephropathy (IgA-N), progressive massive fibrosis, retroperitoneal fibrosis, systemic sclerosis, and adhesive capsulitis preferably in human.
14. The systemic formulation for use according to claim 12 or 13, wherein the TG2-related disease is selected from the group consisting of nephropathy, NASH and/or cystic fibrosis.
15. The systemic formulation for use according to any one of the claims 12 to 14, wherein the TG2-related disease is diabetes related fibrosis.

16. A compound (S,E)-methyl-7-(1-(2-(2-ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate of the formula (I):

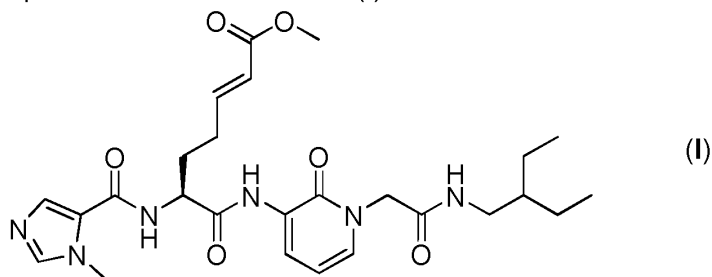
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or an enantiomer, a solvate, a hydrate or a pharmaceutically acceptable salt thereof for use as a hepatoprotectant.

- 10 17. The compound for use according to Claim 16 in the protection of the liver against hepatotoxicity, in the improvement of liver function, in the protection/repair of liver injury, and/or in the prophylaxis or treatment of a liver disease or liver disorder.
- 15 18. The compound for use according to claim 16 or 17, wherein the compound reduces serum levels of at least one hepatic enzyme.
19. The compound for use according to claim 18, wherein the at least one hepatic enzyme is selected from alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP).
- 20 20. The compound for use according to any one of the claims 17 to 19, wherein the liver disease or liver disorder is liver fibrosis, alcoholic hepatitis, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), cirrhosis, cholestatic liver diseases such as primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), alcoholic steatohepatitis (ASH), or liver inflammation.
- 25 21. The compound for use according to any one of the claims 17 to 20, wherein the hepatotoxicity, the liver injury, the liver disease or liver disorder is caused by at least one hepatotoxicant, celiac disease, or a viral infection.
- 30

22. The compound for use according to claim 21, wherein the at least one hepatotoxicant is selected from the group comprising or consisting of toxic chemicals, xenobiotics, anticancer drugs, immunosuppressant drugs, analgesic drugs, anti-inflammatory drugs, anti-tubercular drugs, biologicals, radiations, heavy metals, mycotoxin, galactosamine, and lipopolysaccharides; celiac disease associated with a specific genetic phenotype (HLA DQ2/DQ8) and a pathobiology promoted by transglutaminase 2 (TG2); and/or the viral infection with hepatitis A, B, C viruses.
23. The compound for use according to any one of the claims 17 to 22, wherein the liver disease or liver disorder is liver fibrosis.
24. The compound for use according to any one of the claims 17 to 23, wherein the compound is administered orally.
25. A pharmaceutical composition comprising a compound (S,E)-methyl-7-(1-(2-(2-ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate of the formula (I):



or an enantiomer, a solvate, a hydrate or a pharmaceutically acceptable salt thereof for use as a hepatoprotectant.

26. The pharmaceutical composition according to claim 25 for use in the protection of the liver against hepatotoxicity, in the improvement of liver function, in the protection/repair of liver injury, and/or in the prophylaxis or treatment of a liver disorder/disease.
27. The pharmaceutical composition for use according to claim 25 or 26, wherein the compound reduces serum levels of at least one hepatic enzyme.

28. The pharmaceutical composition for use according to claim 27, wherein the at least one hepatic enzyme is selected from alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP).
- 5 29. The pharmaceutical composition for use according to any one of the claims 26 to 28, wherein the liver disorder/disease is liver fibrosis, alcoholic hepatitis, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), cirrhosis, cholestatic liver diseases such as primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC),
10 autoimmune hepatitis (AIH), alcoholic steatohepatitis (ASH), or liver inflammation.
30. The pharmaceutical composition for use according to any one of claims 26 to 29, wherein the hepatotoxicity, liver injury, the liver disease or liver
15 disorder is caused by at least one hepatotoxicant, celiac disease, or a viral infection.
31. The pharmaceutical composition for use according to claim 30, wherein the at least one hepatotoxicant is selected from the group comprising or
20 consisting of toxic chemicals, xenobiotics, anticancer drugs, immunosuppressant drugs, analgesic drugs, anti-inflammatory drugs, anti-tubercular drugs, biologicals, radiations, heavy metals, mycotoxin, galactosamine, and lipopolysaccharides, celiac disease associated with a specific genetic phenotype (HLA DQ2/DQ8) and a pathobiology promoted
25 by transglutaminase 2 (TG2) and/or a viral infection with hepatitis A, B, C viruses.
32. The pharmaceutical composition for use according to any one of the claims 25 to 31, wherein the pharmaceutical composition further comprises at least
30 one polymeric precipitation inhibitor.
33. The pharmaceutical composition for use according to any one of the claims 25 to 32, wherein the pharmaceutical composition further comprises at least
35 one acidifier and/or at least one binder.
34. The pharmaceutical composition for use according to claim 32 or 33, wherein the at least one polymeric precipitation inhibitor is selected from the group consisting of L-hydroxypropyl cellulose, hydroxypropyl cellulose, a

- combination of L-hydroxypropyl cellulose and hydroxypropyl cellulose, polyethylene glycol, poly(ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide), polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, ethylcellulose, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer and sodium carboxymethyl cellulose.
- 5
35. The pharmaceutical composition for use according to claim 33 or 34, wherein the at least one acidifier is selected from the group consisting of ascorbic acid, organic di-carboxylic acid such as oxalic acid, malonic acid, succinic acid, glutaric acid, tartaric acid, fumaric acid, maleic acid, malic acid, adipic acid, or glutamic acid, and organic tri-carboxylic acid such as citric acid, or sodium hydrogen citrate.
- 10
36. The pharmaceutical composition for use according to any one of the claims 33 to 35, wherein the at least one binder is selected from the group consisting of sugar, sucrose, polysaccharides, xanthan gum, guar gum, carrageenan, starches derived from wheat, corn, rice and potatoes, preagglutinated (modified) starch derived from wheat, corn, rice and potatoes, sodium starch glycolate, natural gums, acacia gum, gelatin, tragacanth, derivatives of sea weed, alginic acid, sodium alginate, ammonium calcium alginate, cellulose, cellulose derivatives, hydroxypropyl cellulose, L-hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, methyl cellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, povidone K25.
- 15
- 20
- 25
37. The pharmaceutical composition for use according to any one of the claims 25 to 36, wherein (S,E)-methyl-7-(1-(2-(2-ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate particles have a particle size distribution which is defined by $d(0.95) \leq 25 \mu\text{m}$.
- 30
38. The pharmaceutical composition for use according to any one of the claims 25 to 37, wherein the pharmaceutical composition is an oral formulation.
- 35
39. The pharmaceutical composition for use according to claim 38, wherein the oral formulation is a tablet, coated tablet, capsule, powder, or granule.

40. The pharmaceutical composition for use according to any one of the claims 32 to 39, wherein the pharmaceutical composition comprises 1 to 15 m/m acidifier, 0.1 to 7 m/m polymeric precipitation inhibitor, wherein m/m (mass ratio) of said compounds is calculated relative to mass of (S,E)-methyl-7-(1-(2-(2-ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate.
41. The pharmaceutical composition for use according to any one of the claims 32 to 40, wherein the pharmaceutical composition comprises 0.1 wt% to 45 wt% (S,E)-methyl-7-(1-(2-(2-ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate, 3 wt% to 75 wt% acidifier, 2 wt% to 35 wt% polymeric precipitation inhibitor, 0 wt% to 12 wt% binder, 2 wt% to 35 wt% disintegrant, and 1 wt% to 9 wt% lubricant/glidant.
42. The pharmaceutical composition for use according to any one of the claims 32 to 41, wherein the pharmaceutical composition comprises 0.1 wt% to 45 wt% (S,E)-methyl-7-(1-(2-(2-ethylbutylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate, 3 wt% to 75 wt% adipic acid, 2 wt% to 35 wt% L-hydroxypropyl cellulose and/or hydroxypropyl cellulose, 0 wt% to 12 wt% povidone K25, 2 wt% to 35 wt% sodium croscarmellose, and 1 wt% to 9 wt% talc or silicon dioxide.
43. The pharmaceutical composition for use according to any one of the claims 26 to 42, wherein the liver disease or liver disorder is liver fibrosis.