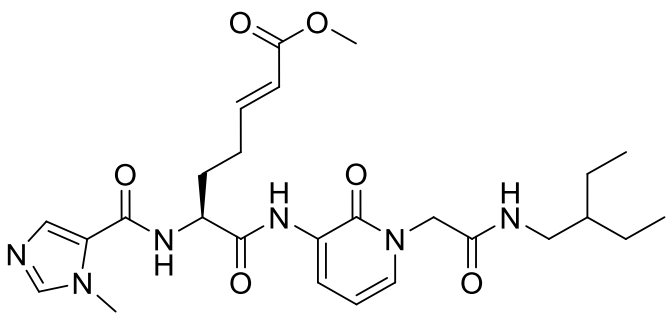
Claims

1. A systemic formulation comprising Compound 1 of formula (**I**):



(**I**),

or an enantiomer, a solvate, a hydrate or a pharmaceutically acceptable salt thereof, and at least one polymeric precipitation inhibitor,
wherein mass ratio (m/m) of the at least one polymeric precipitation inhibitor relative to Compound 1 or an enantiomer, a solvate, a hydrate or a pharmaceutically acceptable salt thereof ranges from 0.05 to 10 m/m.

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 di-carboxylic acid, and organic tri-carboxylic acid.

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, 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, and povidone K25.

7. The systemic formulation according to any one of the claims 1 to 6, wherein Compound 1 particles have a particle size distribution which is defined by d(0.95) ≤ 25 µm.

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 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, and 0.1 to 7 m/m polymeric precipitation inhibitor, wherein m/m is calculated relative to mass of Compound 1.

10. The systemic formulation according to any one of claims 1 to 9, wherein the formulation comprises 0.1 wt% to 45 wt% Compound 1, 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% Compound 1, 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.

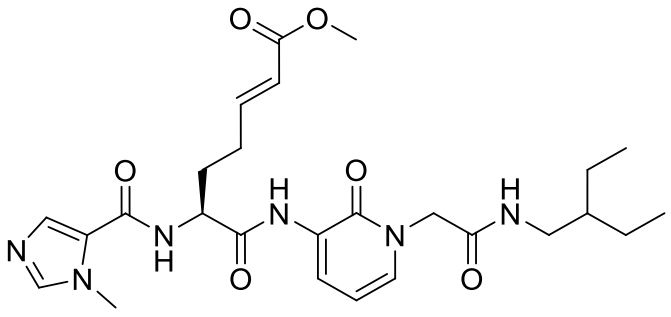
12. Use of the systemic formulation according to any one of the claims 1 to 11 for manufacture of a medicament for prophylaxis and/or treatment of TG2-related diseases, wherein the TG2-related disease is nephropathy, fibrotic liver diseases, cholestatic liver diseases, autoimmune hepatitis, alcoholic 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, hypertension, gliar scar, arterial stiffness, arthrofibrosis, Dupuytren's contracture, keloid, medistinal fibrosis, myelofibrosis, Peyronie's disease, nephrongenic systemic fibrosis, IgA nephropathy (IgA-N), progressive massive fibrosis, retroperitoneal fibrosis, systemic sclerosis, or adhesive capsulitis.

13. The use according to claim 12, wherein the TG2-related disease is non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), cirrhosis, primary sclerosing cholangitis (PSC), or primary biliary cholangitis (PBC).

14. The use according to claim 12 or 13, wherein the TG2-related disease is nephropathy, NASH, or cystic fibrosis.

15. The use according to any one of the claims 12 to 14, wherein the TG2-related disease is diabetes related fibrosis.

16. Use of Compound 1 of formula (**I**):



(**I**)

,

or an enantiomer, a solvate, a hydrate or a pharmaceutically acceptable salt thereof for manufacture of a medicament for protection of liver against

hepatotoxicity, protection/repair of liver injury, and/or prophylaxis or treatment of a liver disease or liver disorder.

17. The use according to claim 16, wherein Compound 1 reduces serum levels of at least one hepatic enzyme.

18. The use according to claim 17, wherein the at least one hepatic enzyme is selected from alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP).

19. The use according to any one of the claims 16 to 18, wherein the liver disease or liver disorder is liver fibrosis, alcoholic hepatitis, NASH, NAFLD, cirrhosis, cholestatic liver diseases, autoimmune hepatitis (AIH), alcoholic steatohepatitis (ASH), or liver inflammation.

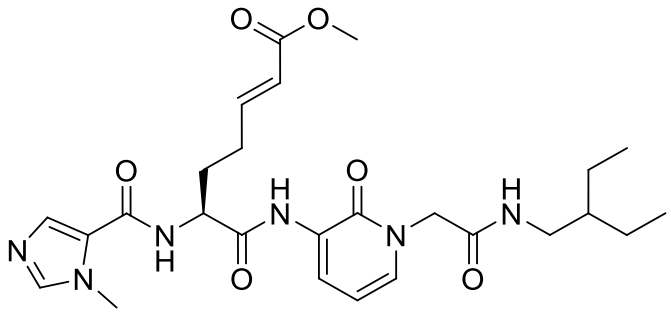
20. The use according to any one of the claims 16 to 19, wherein the hepatotoxicity, the liver injury, the liver disease or liver disorder is caused by at least one hepatotoxicant, celiac disease, or a viral infection.

21. The use according to claim 20, wherein the at least one hepatotoxicant is selected from the group consisting of toxic chemicals, xenobiotics, anticancer drugs, immunosuppressant drugs, analgesic drugs, anti-inflammatory drugs, anti-tubercular drugs, biologicals, radiations, heavy metals, mycotoxin, galactosamine, lipopolysaccharides, celiac disease associated with a specific genetic phenotype (HLA DQ2/DQ8) and a pathobiology promoted by transglutaminase 2 (TG2), and viral infection with hepatitis A, B, C viruses.

22. The use according to any one of the claims 16 to 21, wherein the liver disease or liver disorder is liver fibrosis.

23. The use according to any one of the claims 16 to 22, wherein Compound 1 is administered orally.

24. Use of a pharmaceutical composition comprising
Compound 1 of formula (**I**):



(**I**)

,

or an enantiomer, a solvate, a hydrate or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, for manufacture of a medicament for protection of liver against hepatotoxicity, protection/repair of liver injury, and/or prophylaxis or treatment of a liver disease or liver disorder.

25. The use according to claim 24, wherein Compound 1 reduces serum levels of at least one hepatic enzyme.

26. The use according to claim 25, wherein the at least one hepatic enzyme is selected from ALT, AST, and ALP.

27. The use according to any one of the claims 24 to 26, wherein the liver disorder/disease is liver fibrosis, alcoholic hepatitis, NASH, NAFLD, cirrhosis, cholestatic liver diseases, AIH, ASH, or liver inflammation.

28. The use according to claim 24, wherein the hepatotoxicity, liver injury, the liver disease or liver disorder is caused by at least one hepatotoxicant, celiac disease, or a viral infection.

29. The use according to claim 28, wherein the at least one hepatotoxicant is selected from the group consisting of toxic chemicals, xenobiotics, anticancer drugs, immunosuppressant drugs, analgesic drugs, anti-inflammatory drugs, anti-tubercular drugs, biologicals, radiations, heavy metals, mycotoxin, galactosamine, lipopolysaccharides, celiac disease associated with a specific genetic phenotype (HLA DQ2/DQ8) and a pathobiology promoted by transglutaminase 2 (TG2), and a viral infection with hepatitis A, B, C viruses.

30. The use according to any one of the claims 24 to 29, wherein the pharmaceutical composition further comprises at least one polymeric precipitation inhibitor.

31. The use according to any one of the claims 24 to 30, wherein the pharmaceutical composition further comprises at least one acidifier and/or at least one binder.

32. The use according to claim 30 or 31, 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.

33. The use according to claim 31 or 32, wherein the at least one acidifier is selected from the group consisting of ascorbic acid, organic di-carboxylic acid, and organic tri-carboxylic acid.

34. The use according to any one of the claims 31 to 34, 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, and povidone K25.

35. The use according to any one of the claims 24 to 34, wherein Compound 1 particles have a particle size distribution which is defined by d(0.95) ≤ 25 µm.

36. The use according to any one of the claims 24 to 35, wherein the pharmaceutical composition is an oral formulation.

37. The use according to claim 36, wherein the oral formulation is a tablet, coated tablet, capsule, powder, or granule.

38. The use according to any one of the claims 24 to 37, wherein the pharmaceutical composition comprises 1 to 15 m/m acidifier, and 0.1 to 7 m/m polymeric precipitation inhibitor, wherein m/m is calculated relative to mass of Compound 1.

39. The use according to any one of the claims 24 to 38, wherein the pharmaceutical composition comprises 0.1 wt% to 45 wt% Compound 1, 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.

40. The use according to any one of the claims 24 to 39, wherein the pharmaceutical composition comprises 0.1 wt% to 45 wt% Compound 1, 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.

41. The use according to any one of the claims 24 to 40, wherein the liver disease or liver disorder is liver fibrosis.

42. The systemic formulation according to claim 5, wherein the organic di-carboxylic acid is oxalic acid, malonic acid, succinic acid, glutaric acid, tartaric acid, fumaric acid, maleic acid, malic acid, adipic acid, or glutamic acid; and the organic tri-carboxylic acid is citric acid or sodium hydrogen citrate.

43. The use according to claim 33, wherein the organic di-carboxylic acid is oxalic acid, malonic acid, succinic acid, glutaric acid, tartaric acid, fumaric acid, maleic acid, malic acid, adipic acid, or glutamic acid; and the organic tri-carboxylic acid is citric acid or sodium hydrogen citrate.