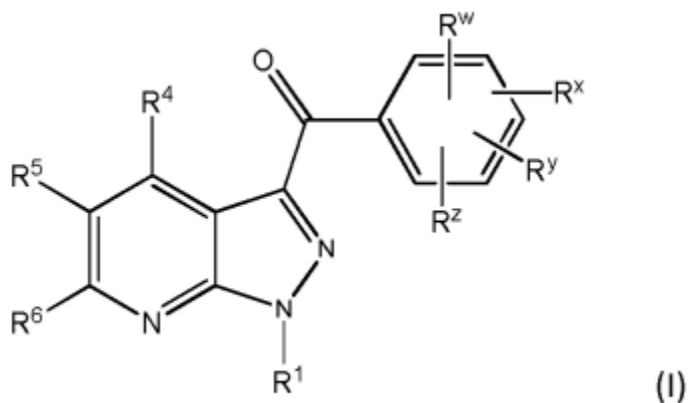


Claims

1. A compound having formula (I)



and the pharmaceutically acceptable salts, prodrugs, biologically active metabolites, solvates and stereoisomers thereof,

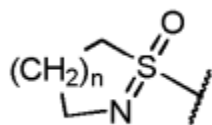
wherein the variables in formula (I) have the meanings as follows:

R¹ is H or alkyl

R⁴ is H or alkyl;

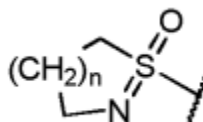
R⁵ is selected from

- a) pyrimidinyl which is substituted with 1 or 2 substituents independently selected from cycloalkyl, alkyl, -COOR¹⁰, -OH, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, tetrazolyl, CN, halogen, alkoxy, -(NR¹⁰)S(=O)-alkyl [S-alkylsulfonimidoyl], and



and

- b1) pyridyl which is substituted with 1 or 2 substituents independently selected from alkyl and halogen and which is optionally further substituted with -OH, alkoxy,



CN, -COOR¹⁰, CF₃, -(NR¹⁰)S(=O)-alkyl, and

and

b2) pyridyl substituted with -COOR¹⁰ and further substituted with -OH, CN, or CF₃;
R⁶ is H or alkyl;
R^w is -NR¹⁰ SO₂ R¹²;
R^x is H, halogen or alkyl;
R^y is H, halogen or alkyl;
R^z is H, halogen or alkyl;
wherein one or two or three of R^x, R^y or R^z are halogen, and the other(s) of R^x, R^y and R^z is H or alkyl;
R¹⁰ at each occurrence is independently H or alkyl;
R¹² is H, alkyl or phenylalkyl; and
n is 1 or 2.

2. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of claim 1, wherein R¹ is H.

3. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of any one of the preceding claims, wherein R⁴ and R⁶ are H.

4. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of any one of the preceding claims, wherein R⁵ is pyrimidinyl substituted with 1 or 2 substituents independently selected from cycloalkyl, alkyl, alkoxy, -OH, alkylsulfanyl, halogen, CN, and tetrazol.

5. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of claim 4, wherein R⁵ is pyrimidinyl substituted with 1 or 2 substituents independently selected from cycloalkyl, alkyl, alkoxy, -OH, alkylsulfanyl, halogen, and CN.

6. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of claim 5, wherein R⁵ is pyrimidinyl substituted with a group selected from cycloalkyl, alkyl, alkoxy, -OH and alkylsulfanyl and further substituted with a group selected from alkyl, alkoxy, and alkylsulfanyl.

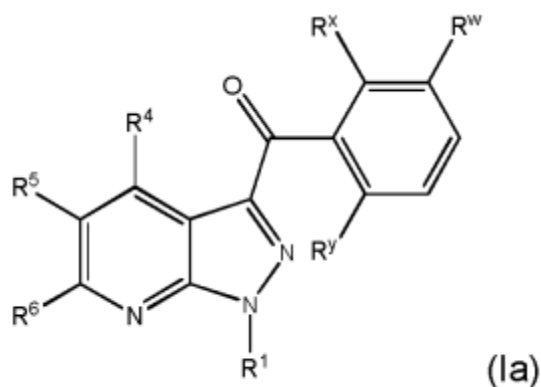
7. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of any one of claims 1 to 3, wherein R⁵ is pyridyl-4-yl (bonded in 4-position to the pyrazolopyridine group) substituted with alkyl or halogen in 3-position.

8. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of any one of the preceding claims, wherein R^{10} is H or alkyl, ~~in~~in particular H.

9. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of any one of the preceding claims, wherein R^{12} is alkyl or phenylalkyl.

10. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of claim 9, wherein R^{12} is C_1 - C_3 -alkyl or benzyl.

11. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of any one of the preceding claims having formula (Ia)



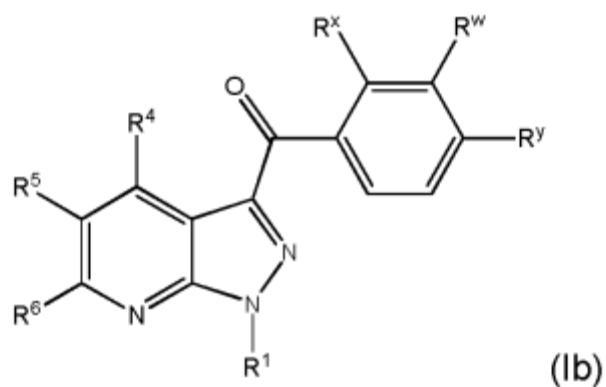
wherein

R^x is halogen;

R^y is halogen; and

R^1 , R^4 , R^5 , R^6 , and R^w are as defined any one of the preceding claims.

12. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of any one of claims 1 to 10 having formula (Ib)



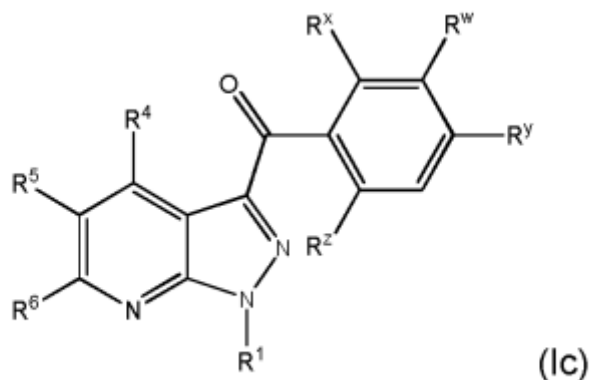
wherein

R^x is halogen;

R^y is halogen; and

R¹, R⁴, R⁵, R⁶, and R^w are as defined any one of claims 1 to 10.

13. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of any one of claims 1 to 10 having formula (Ic)



wherein

R^x is halogen;

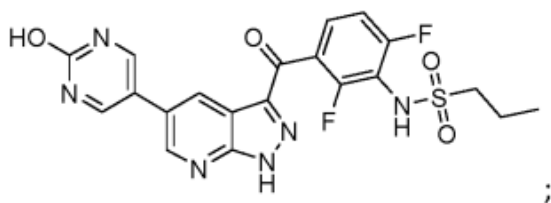
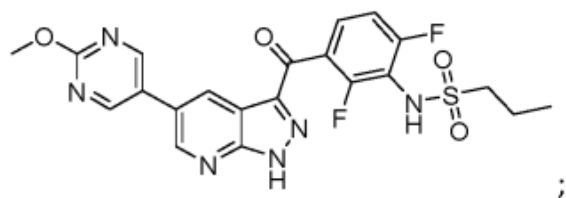
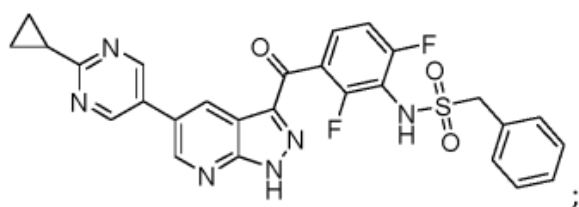
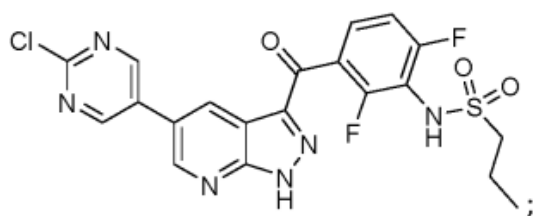
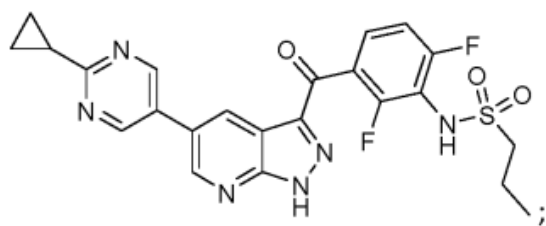
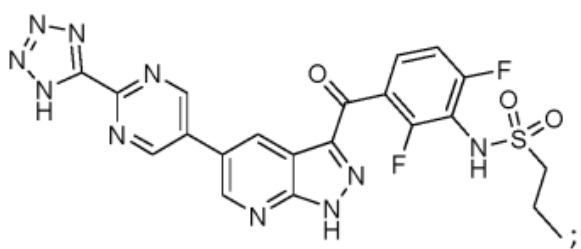
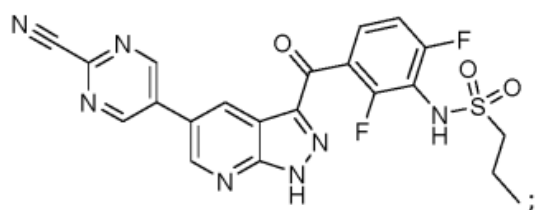
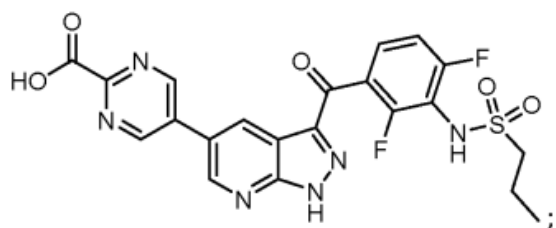
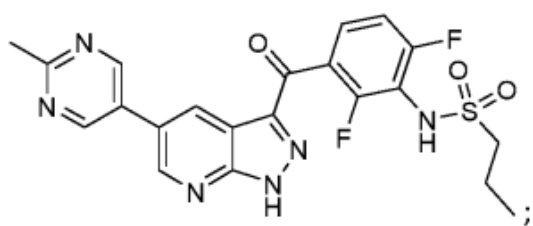
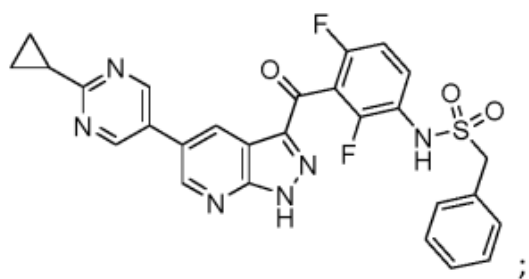
R^y is halogen;

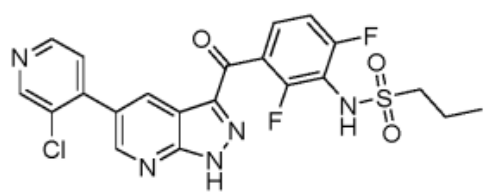
R^z is halogen; and

R¹, R⁴, R⁵, R⁶, and R^w are as defined any one of claims 1 to 10.

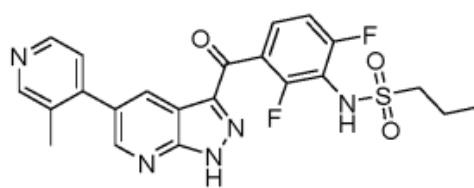
14. The compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof, of any one of claims 11 to 13, wherein R^x, R^y and R^z (if present) are F or Cl, in particular F.

15. A compound of claim 1, selected from

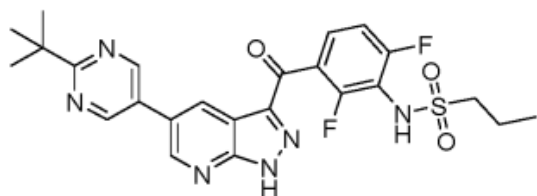




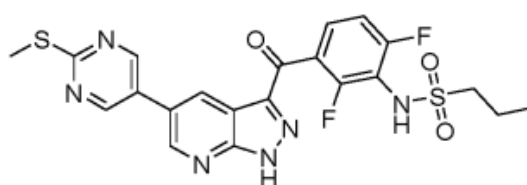
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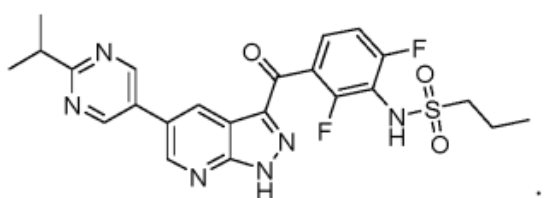
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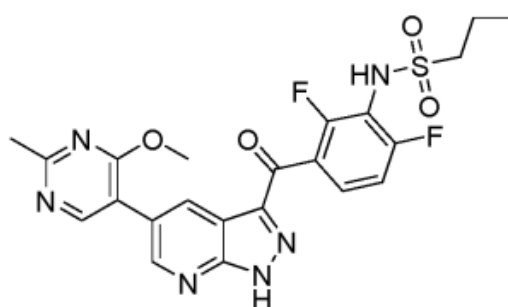
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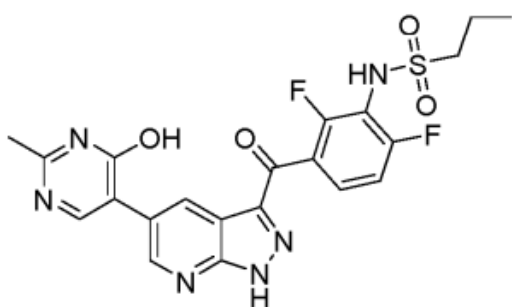
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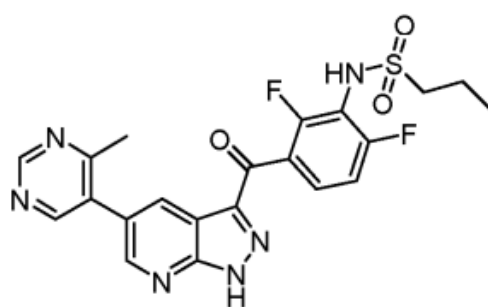
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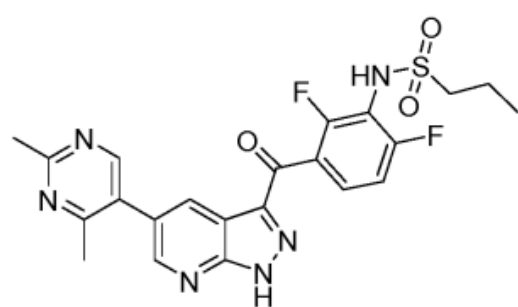
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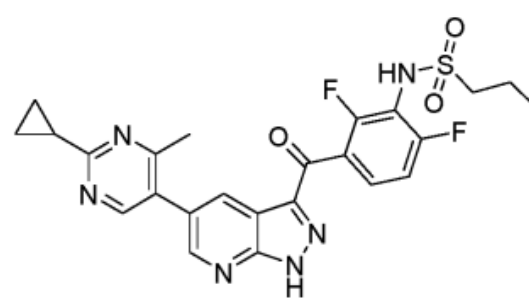
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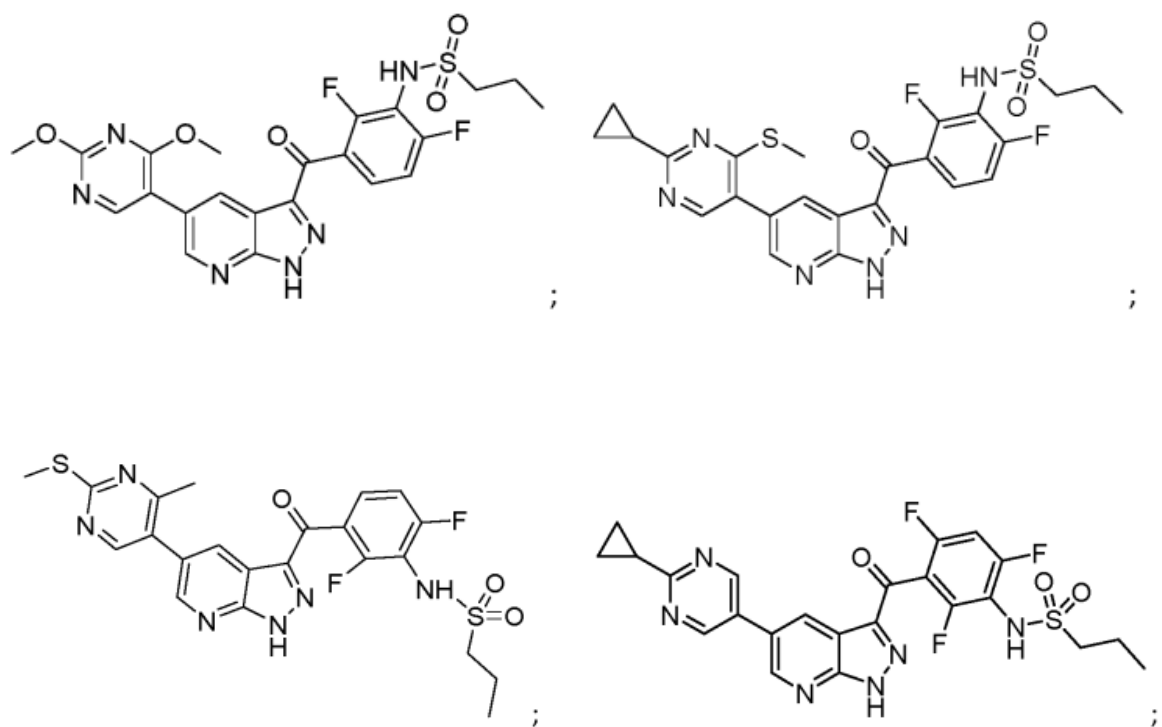
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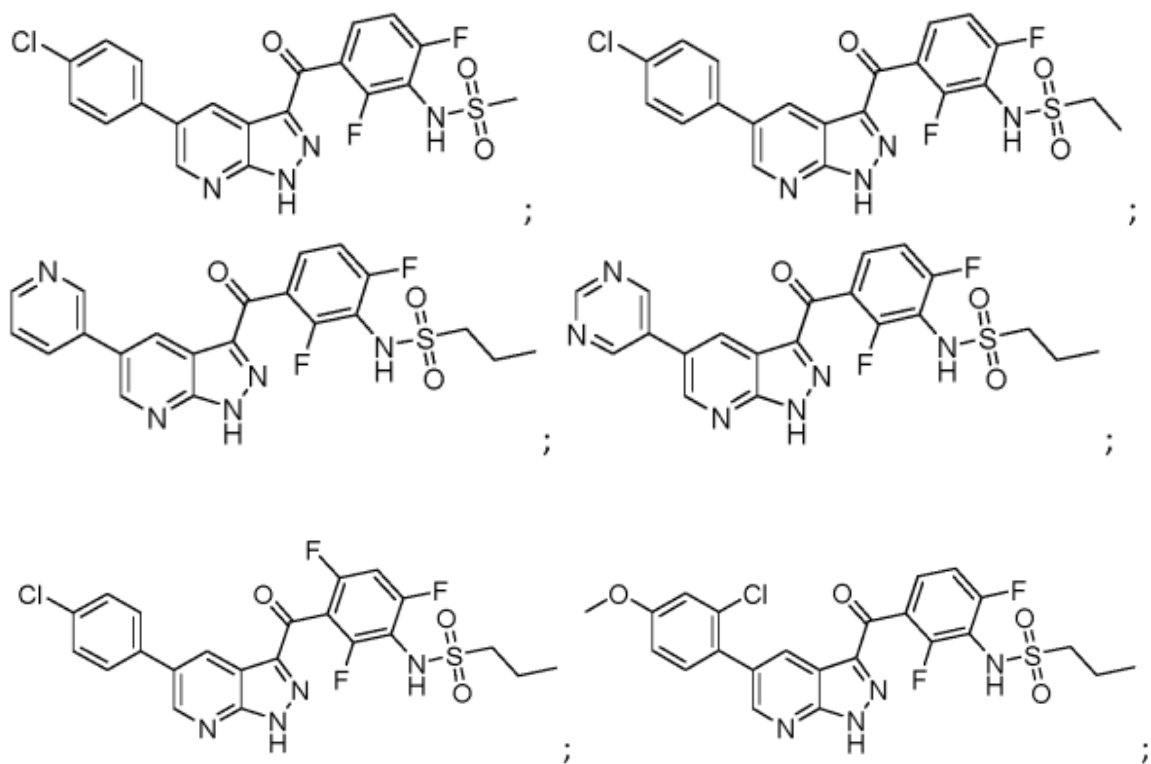


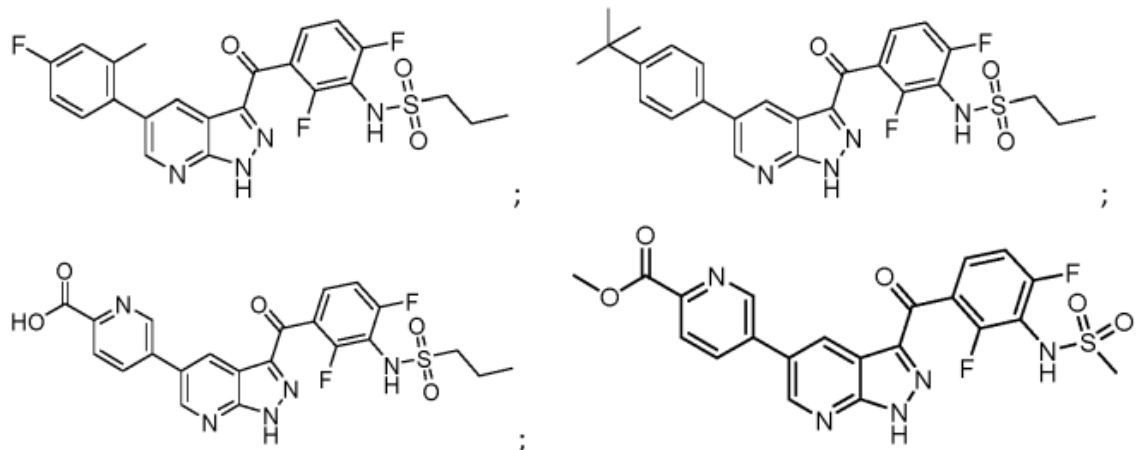
;



and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof.

16. A compound selected from





and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof.

17. A pharmaceutical composition comprising a compound of any one of claims 1 to 16 and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof.

18. Use of Aa compound and the pharmaceutically acceptable salts, prodrugs, solvates and optical isomers thereof according to any one of claims 1 to 16 or a composition of claim 17 ~~for use in~~ in the manufacture of a medicament for

inhibiting protein kinase MKK4 and in particular for ~~use in~~ selectively inhibiting protein kinase MKK4 over protein kinases JNK1 and MKK7;

promoting liver regeneration or reducing or preventing hepatocyte death;

the treatment of acute, acute-on-chronic or chronic liver disease;

treating acute and chronic or acute on chronic liver diseases such as acute and chronic viral hepatitis like hepatitis B, C, E, hepatitis caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus and other viruses, all types of autoimmune hepatitis, primary sclerosing hepatitis, alcoholic hepatitis;

treating metabolic liver diseases such as metabolic syndrome, fatty liver like non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), Morbus Wilson, hemochromatosis, alphas₁-antitrypsin deficiency, glycogen storage diseases;

treating all types of liver cirrhosis, such as primary biliary cirrhosis, ethyl toxic liver cirrhosis, cryptogenic cirrhosis;

treating acute (fulminant) or chronic liver failure such as toxic liver failure like acetaminophen (paracetamol) induced liver failure, alpha-amanitin induced liver failure, drug induced hepatotoxicity and liver failure caused, for example, by antibiotics, nonsteroidal anti inflammatory drugs, anticonvulsants, acute liver failure induced by herbal supplements (kava, ephedra, skullcap, pennyroyal etc), liver disease and failure due to vascular diseases such as Budd-Chiari syndrome, acute liver failure of unknown origin, chronic liver disease due to right heart failure;

treating galactosemia, cystic fibrosis, porphyria, hepatic ischemia perfusion injury, small for size syndrome after liver transplantation, primary sclerosing cholangitis or hepatic encephalopathy;

treating osteoarthritis or rheumatoid arthritis, or CNS-related diseases such as Alzheimer disease and Parkinson disease.

19. The use of the compound and the pharmaceutically acceptable salts, solvates and optical isomers thereof, ~~for use according to claim 18, wherein the compound is~~ is to be administered at a dosage of 0.2 to 15 mg/kg of the subject to be treated over 1 to 12 months weeks.

20. ~~A method of~~

~~inhibiting protein kinase MKK4,~~

~~selectively inhibiting protein kinase MKK4 over protein kinases JNK1 and MKK7, promoting liver regeneration or preventing hepatocyte death,~~

~~treating acute, acute-on-chronic or chronic liver disease, treating acute and chronic or acute-on-chronic liver diseases such as acute and chronic viral hepatitis like hepatitis B, C, E, hepatitis caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus and other viruses, all types of autoimmune hepatitis, primary sclerosing hepatitis, alcoholic hepatitis;~~

~~treating metabolic liver diseases such as metabolic syndrome, fatty liver like non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis~~

~~(ASH), Morbus Wilson, hemochromatosis, alpha-antitrypsin deficiency, glycogen storage diseases;~~

~~—treating all types of liver cirrhosis, such as primary biliary cirrhosis, ethyl toxic liver cirrhosis, cryptogenic cirrhosis;~~

~~—treating acute (fulminant) or chronic liver failure such as toxic liver failure like acetaminophen (paracetamol) induced liver failure, alpha-amanitin induced liver failure, drug induced hepatotoxicity and liver failure caused, for example, by antibiotics, nonsteroidal anti inflammatory drugs, anticonvulsants, acute liver failure induced by herbal supplements (kava, ephedra, skullcap, pennyroyal etc.), liver disease and failure due to vascular diseases such as Budd-Chiari syndrome, acute liver failure of unknown origin, chronic liver disease due to right heart failure;~~

~~—treating galactosemia, cystic fibrosis, porphyria, hepatic ischemia perfusion injury, small for size syndrome after liver transplantation, primary sclerosing cholangitis or hepatic encephalopathy,~~

~~—treating osteoarthritis or rheumatoid arthritis, or CNS-related diseases such as Alzheimer disease and Parkinson disease,~~

~~—which comprises administering an effective amount of a compound or a composition as defined in any one of claim 1 to 17 to a subject in need thereof.~~