IBAT INHIBITORS FOR THE TREATMENT OF LIVER DISEASES

BACKGROUND OF THE INVENTION

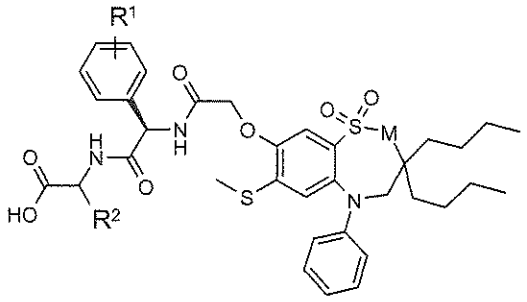
Ileal bile acid transporter (IBAT) is the main mechanism for re-absorption of bile acids from the GI tract. Partial or full blockade of that mechanism will result in lower concentration of bile acids in the small bowel wall, portal vein, liver parenchyma, intrahepatic biliary tree, extrahepatic biliary tree, including gall bladder.

Diseases which may benefit from partial or full blockade of the IBAT mechanism may be those either having as a primary pathophysiological defect, causing or having symptoms of too high concentration of bile acids in serum and in the above organs. WO 2008/058630 describes the effect of certain ileal bile acid transport (IBAT) in the treatment of liver disease related to fat disorders.

SUMMARY OF THE INVENTION

The present invention regards specific IBAT inhibitors in the prophylaxis and/or treatment of a liver disease.

In one aspect, there is provided use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;

$\mathbf{R^1}$ is H or hydroxy;

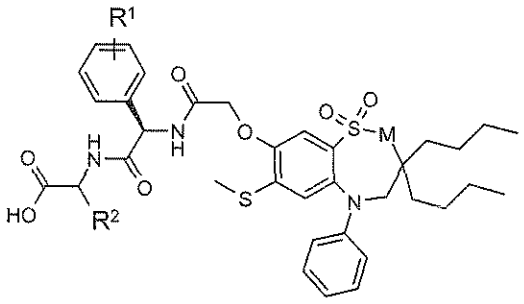
$\mathbf{R^2}$ is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$,

$-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

In one aspect, there is provided use of a pharmaceutical composition comprising a compound of Formula (II)



Formula II

wherein

M is CH_2 or NH;

$\mathbf{R^1}$ is H or hydroxy;

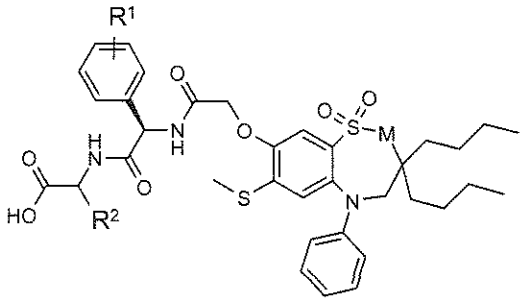
$\mathbf{R^2}$ is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$,

$-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

In one aspect, there is provided use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;

$\mathbf{R^1}$ is H or hydroxy;

$\mathbf{R^2}$ is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$,

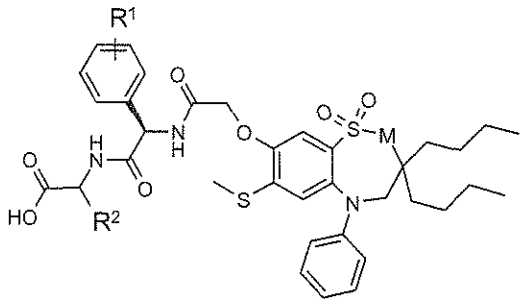
$-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

or a pharmaceutically acceptable salt thereof;

and ursodeoxycholic acid,

in the manufacture of a combination for simultaneous or sequential administration in the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

In one aspect, there is provided use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;

R^1 is H or hydroxy;

R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$,

$-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

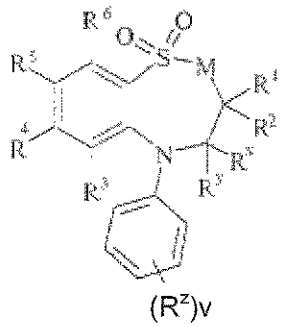
or a pharmaceutically acceptable salt thereof,

and nor-ursodeoxycholic acid,

in the manufacture of a combination for simultaneous or sequential administration in the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

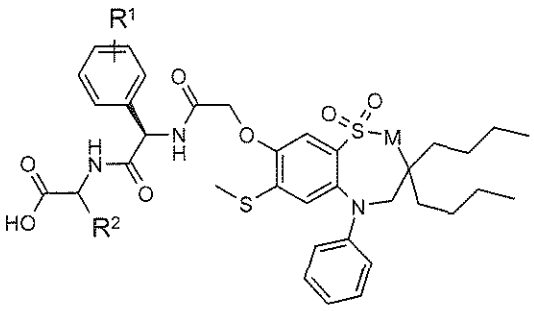
DETAILED DESCRIPTION OF THE INVENTION

The invention relates to IBAT inhibitor compounds of formula (I):



CLAIMS

1. Use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;

R^1 is H or hydroxy;

R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

2. Use according to claim 1, wherein the compound of formula II is selected from the group consisting of:

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- (N-{(R)-α-[N'-((S)-1-carboxyethyl) carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

3. Use according to claim 1 or 2, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, or a pharmaceutically acceptable salt thereof.

4. Use according to claim 1 or 2, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)carbamoyl]methyl}-carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, or a pharmaceutically acceptable salt thereof.

5. Use according to any one of claims 1 to 4, wherein the liver disease is Alagille syndrome (ALGS).

6. Use according to any one of claims 1 to 4, wherein the liver disease is progressive familial intrahepatic cholestasis (PFIC).

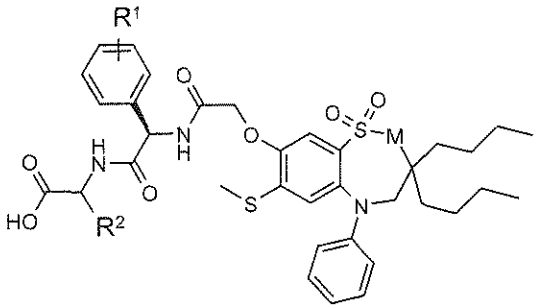
7. Use according to any one of claims 1 to 4, wherein the liver disease is primary biliary cirrhosis (PBC).

8. Use according to any one of claims 1 to 4, wherein the liver disease is primary sclerosing cholangitis (PSC).

9. Use according to any one of claims 1 to 4, wherein the liver disease is non-alcoholic steatohepatitis (NASH).

10. Use according to any one of claims 1 to 4, wherein the liver disease is pruritus of cholestatic liver disease.

11. Use of a pharmaceutical composition comprising a compound of Formula (II)



Formula II

wherein

M is CH_2 or NH;

R^1 is H or hydroxy;

R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

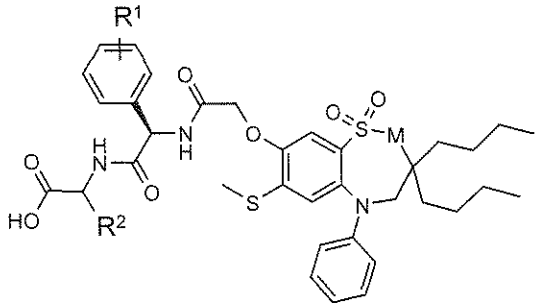
or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

12. Use according to claim 11, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}-carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, or a pharmaceutically acceptable salt thereof.

13. Use according to claim 11, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)carbamoyl]methyl}-carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, or a pharmaceutically acceptable salt thereof.

14. Use of a compound of formula II



Formula II

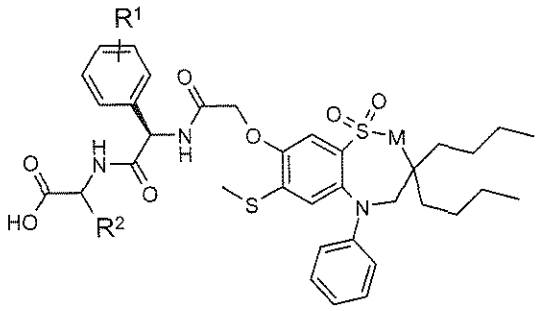
wherein

M is CH_2 or NH;
R^1 is H or hydroxy;
R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;
or a pharmaceutically acceptable salt thereof;

and ursodeoxycholic acid,

in the manufacture of a combination for simultaneous or sequential administration in the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

15. Use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;
R^1 is H or hydroxy;
R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;
or a pharmaceutically acceptable salt thereof,

and nor-ursodeoxycholic acid,

in the manufacture of a combination for simultaneous or sequential administration in the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

16. Use according to claim 14 or 15, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, or a *pharmaceutically acceptable salt thereof.*

17. Use according to claim 14 or 15, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)carbamoyl]methyl}-carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, or a pharmaceutically acceptable salt thereof.