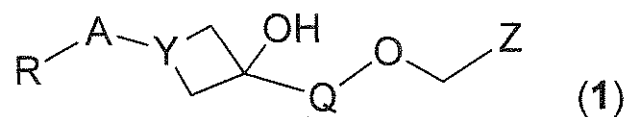


In one aspect, there is provided a compound according to the following Formula (1), an enantiomer, diastereomer, tautomer or pharmaceutical acceptable salt thereof



wherein

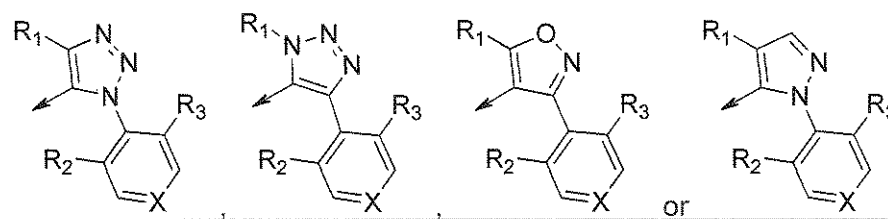
R is selected from the group consisting of COOR₆, CONR₇R₈, tetrazolyl, SO₂NR₇R₈, C₁₋₆ alkyl, SO₂-C₁₋₆ alkyl and H, with R₆ independently selected from the group consisting of H or C₁₋₆ alkyl, and R₇ and R₈ independently from each other selected from the group consisting of H, C₁₋₆ alkyl, halo-C₁₋₆ alkyl, C₁₋₆ alkylene-R₉, SO₂-C₁₋₆ alkyl, wherein R₉ is selected from the group consisting of COOH, OH and SO₃H;

A is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazolyl, indolyl, thienyl, benzothienyl, indazolyl, benzisoxazolyl, benzofuranyl, benzotriazolyl, furanyl, benzothiazolyl, thiazolyl, oxadiazolyl, each optionally substituted with one or two groups independently selected from the group consisting of OH, O-C₁₋₆ alkyl, O-halo-C₁₋₆ alkyl, C₁₋₆ alkyl, halo-C₁₋₆ alkyl, C₃₋₆ cycloalkyl and halogen;

Q is selected from the group consisting of phenyl, pyridyl, thiazolyl, thiophenyl, pyrimidyl, each optionally substituted with one or two groups independently selected from the group consisting of C₁₋₆ alkyl, halo-C₁₋₆ alkyl, halogen and CF₃;

Y is selected from N or CH;

Z is selected from



wherein

X = CH, N, NO;

R₁ is selected from the group consisting of hydrogen, C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₄₋₅ alkylcycloalkyl, wherein C₁₋₃ alkyl is optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy or C₁₋₆ alkoxy;

R₂ and R₃ are independently selected from the group consisting of hydrogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy and halogen.

In another aspect, there is provided a pharmaceutical composition comprising the compound as disclosed above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present ~~invention~~-disclosure is directed to a compound according to Formula (1) for use as a medicament.

In another aspect, there is provided a compound as disclosed above for use as a medicament.

In another embodiment, the present ~~disclosure~~invention is directed to a compound according to Formula (1) for use in the prophylaxis and/or treatment of diseases mediated by FXR.

In another embodiment, the present ~~disclosure~~invention is directed to the use of a compound according to Formula (1) for the preparation of a medicament for the prophylaxis and/or treatment of diseases mediated by FXR.

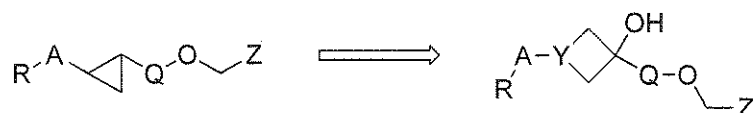
In another aspect, there is provided use of a compound as disclosed above for the preparation of a medicament for the prophylaxis and/or treatment of diseases mediated by FXR.

In another embodiment in combination with any of the above or below embodiments, the disease is selected from chronic intrahepatic or some forms of extrahepatic cholestatic conditions; liver fibrosis; obstructive or chronic inflammatory disorders of the liver; liver cirrhosis; liver steatosis and associated syndromes, cholestatic or fibrotic effects that are associated with alcohol-induced cirrhosis or with viral-borne forms of hepatitis; liver failure or liver ischemia after major liver resection; chemotherapy associated steatohepatitis (CASH); acute liver failure; and/or Inflammatory Bowel Diseases.

In another embodiment in combination with any of the above or below embodiments, the disease is selected from lipid and lipoprotein disorders; Type II Diabetes and clinical complications of Type I and Type II Diabetes, including diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and other observed effects of clinically manifest long term Diabetes; conditions and diseases which result from chronic fatty and fibrotic degeneration of organs due to enforced lipid and specifically triglyceride accumulation and subsequent activation of profibrotic pathways, such as Non-Alcoholic Fatty Liver Disease (NAFLD), or Non-Alcoholic Steatohepatitis (NASH); obesity or metabolic syndrome (combined conditions of dyslipidemia, diabetes or abnormally high body-mass index); and/or acute myocardial infarction, acute stroke or thrombosis which occurs as an endpoint of chronic obstructive atherosclerosis.

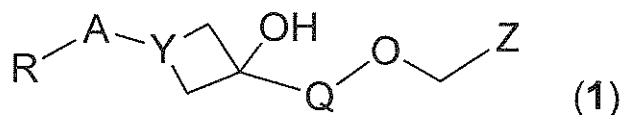
In another embodiment in combination with any of the above or below embodiments, the disease is selected from non-malignant hyperproliferative disorders and malignant hyperproliferative disorders, specifically of hepatocellular carcinoma, colon adenoma and polyposis, colon adenocarcinoma, breast cancer, pancreas adenocarcinoma, Barrett's esophagus or other forms of neoplastic diseases of the gastrointestinal tract and the liver.

The improved physico-chemical properties have been achieved by the introduction of a polar hydroxyl group on a 1,3-cyclobutylidene or 1,3-azetidinylidene group replacing the former 1,2-cyclopropylidene ring.



Claims

1. A compound according to the following Formula (1), an enantiomer, diastereomer, tautomer, solvate, prodrug or pharmaceutical acceptable salt thereof



wherein

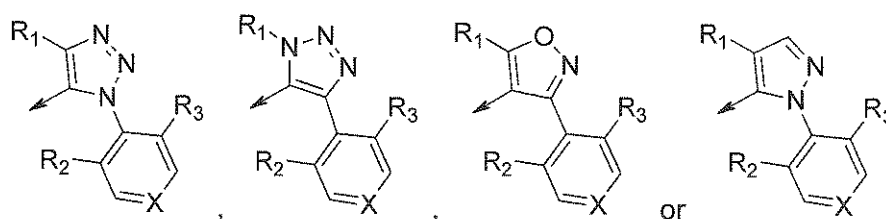
R is selected from the group consisting of COOR₆, CONR₇R₈, tetrazolyl, SO₂NR₇R₈, C₁₋₆ alkyl, SO₂-C₁₋₆ alkyl and H, with R₆ independently selected from the group consisting of H or C₁₋₆ alkyl, and R₇ and R₈ independently from each other selected from the group consisting of H, C₁₋₆ alkyl, halo-C₁₋₆ alkyl, C₁₋₆ alkylene-R₉, SO₂-C₁₋₆ alkyl, wherein R₉ is selected from the group consisting of COOH, OH and SO₃H;

A is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazolyl, indolyl, thienyl, benzothienyl, indazolyl, benzisoxazolyl, benzofuranyl, benzotriazolyl, furanyl, benzothiazolyl, thiazolyl, oxadiazolyl, each optionally substituted with one or two groups independently selected from the group consisting of OH, O-C₁₋₆ alkyl, O-halo-C₁₋₆ alkyl, C₁₋₆ alkyl, halo-C₁₋₆ alkyl, C₃₋₆ cycloalkyl and halogen;

Q is selected from the group consisting of phenyl, pyridyl, thiazolyl, thiophenyl, pyrimidyl, each optionally substituted with one or two groups independently selected from the group consisting of C₁₋₆ alkyl, halo-C₁₋₆ alkyl, halogen and CF₃;

Y is selected from N or CH;

Z is selected from

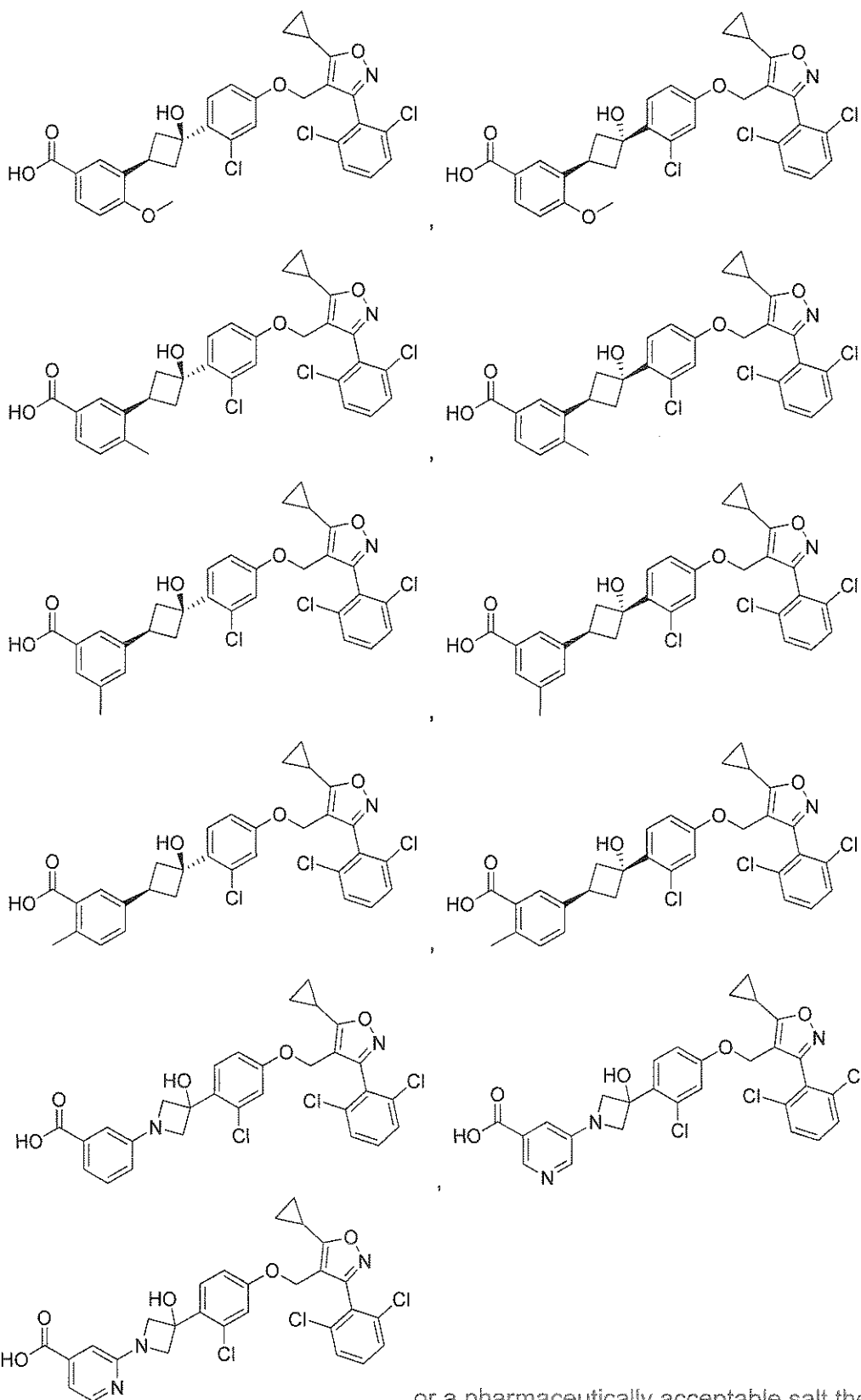


wherein

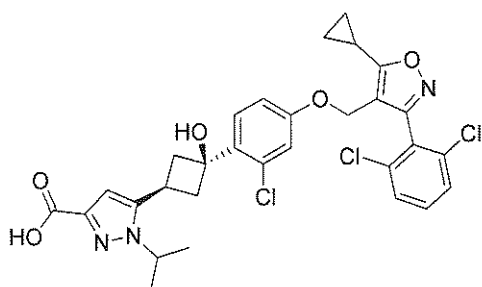
X = CH, N, NO;

R₁ is selected from the group consisting of hydrogen, C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₄₋₅ alkylcycloalkyl, wherein C₁₋₃ alkyl is optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy or C₁₋₆ alkoxy;

R₂ and R₃ are independently selected from the group consisting of hydrogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy and halogen.

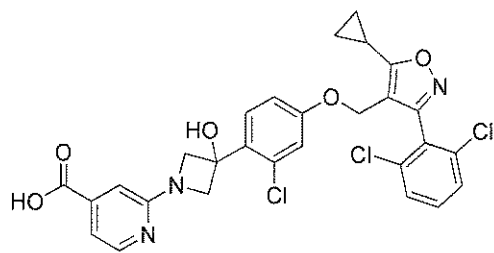


6. The compound according to any of claims 1 to 5 having the following structure



or a pharmaceutically acceptable salt thereof.

7. The compound according to any of claims 1 to 5 having the following structure



or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising the compound according to any of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

96. A compound according to any of claims 1 to 75 for use as a medicament.

7. A compound according to any of claims 1 to 5 for use in the prophylaxis and/or treatment of diseases mediated by FXR.
8. The compound for use according to claim 7 wherein the disease is selected from chronic intrahepatic or some forms of extrahepatic cholestatic conditions;
liver fibrosis;
obstructive or chronic inflammatory disorders of the liver;
liver cirrhosis;
liver steatosis and associated syndromes, cholestatic or fibrotic effects that are associated with alcohol-induced cirrhosis or with viral borne forms of hepatitis;
liver failure or liver ischemia after major liver resection;
chemotherapy-associated steatohepatitis (CASH);
acute liver failure; and/or
Inflammatory Bowel Diseases.
9. The compound for use according to claim 7 wherein the disease is selected from lipid and lipoprotein disorders;
Type II Diabetes and clinical complications of Type I and Type II Diabetes, including diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and other observed effects of clinically manifest long term Diabetes;
conditions and diseases which result from chronic fatty and fibrotic degeneration of organs due to enforced lipid and
specifically triglyceride accumulation and subsequent activation of profibrotic pathways, such as Non-Alcoholic Fatty Liver Disease (NAFLD), or Non-Alcoholic Steatohepatitis (NASH);
obesity or metabolic syndrome (combined conditions of dyslipidemia, diabetes or abnormally high body mass index); and/or
acute myocardial infarction, acute stroke or thrombosis which occurs as an endpoint of chronic obstructive atherosclerosis.
10. The compound for use according to claim 7 wherein the disease is selected from

~~non-malignant hyperproliferative disorders and malignant hyperproliferative disorders, specifically of hepatocellular carcinoma, colon adenoma and polypsis, colon adenocarcinoma, breast cancer, pancreas adenocarcinoma, Barrett's esophagus or other forms of neoplastic diseases of the gastrointestinal tract and the liver.~~

1044. Use of a compound according to any of claims 1 to 75 for the preparation of a medicament for the prophylaxis and/or treatment of diseases mediated by FXR.

1142. The use according to claim 1044 wherein the disease is selected from

chronic intrahepatic or some forms of extrahepatic cholestatic conditions;

liver fibrosis;

obstructive or chronic inflammatory disorders of the liver;

liver cirrhosis;

liver steatosis and associated syndromes, cholestatic or fibrotic effects that are associated with alcohol-induced cirrhosis or with viral-borne forms of hepatitis;

liver failure or liver ischemia after major liver resection;

chemotherapy associated steatohepatitis (CASH);

acute liver failure; and/or

Inflammatory Bowel Diseases.

1243. The use according to claim 1044 wherein the disease is selected from

lipid and lipoprotein disorders;

Type II Diabetes and clinical complications of Type I and Type II Diabetes, including diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and other observed effects of clinically manifest long term Diabetes;

conditions and diseases which result from chronic fatty and fibrotic degeneration of organs due to enforced lipid and specifically triglyceride accumulation and subsequent activation of profibrotic pathways; such as Non-Alcoholic Fatty Liver Disease (NAFLD) or Non-Alcoholic Steatohepatitis (NASH);

obesity or metabolic syndrome (combined conditions of dyslipidemia, diabetes or abnormally high body-mass index); and/or

acute myocardial infarction, acute stroke or thrombosis which occurs as an endpoint of chronic obstructive atherosclerosis.

1314. The use according to claim 1044 wherein the disease is selected from

non-malignant hyperproliferative disorders and malignant hyperproliferative disorders, specifically of hepatocellular carcinoma, colon adenoma and polyposis, colon adenocarcinoma, breast cancer, pancreas adenocarcinoma, Barrett's esophagus or other forms of neoplastic diseases of the gastrointestinal tract and the liver.