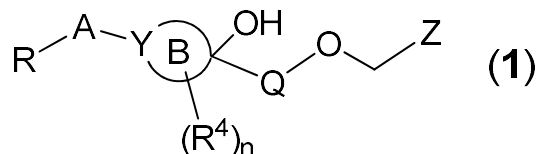


Claims

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



5 wherein

R is selected from the group consisting of hydrogen, halogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-R⁷, C₀₋₆-alkylene-O-R⁷, C₀₋₆-alkylene-CN, C₀₋₆-alkylene-NR⁷R⁸, O-C₃₋₁₀-cycloalkyl, O-C₁₋₆-alkylene-O-R⁷, O-C₃₋₁₀-heterocycloalkyl, C₀₋₆-alkylene-CO₂R⁷, C₀₋₆-alkylene-C(O)R⁷, C₀₋₆-alkylene-C(O)NR⁷R⁸, C₀₋₆-alkylene-C(O)NR⁷SO₂R⁷, C₀₋₆-alkylene-N(R⁷)C(O)R⁷, C₀₋₆-alkylene-SO_x-R⁷, C₀₋₆-alkylene-SO₃H, C₀₋₆-alkylene-SO₂-NR⁷R⁸, C₀₋₆-alkylene-SO₂-NR⁸COR⁷, C₀₋₆-alkylene-N(R⁷)SO₂-R⁸, and C₀₋₆-alkylene-SO₂-C₃₋₁₀-heterocycloalkyl,

15 wherein alkylene, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted by 1 to 4 substituents independently selected from the group consisting of halogen, CN, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, oxo, CO₂H, SO₃H, O-C₁₋₃-alkyl and O-halo-C₁₋₃-alkyl;

R⁷ is independently selected from the group consisting of hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and phenyl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, CO₂H, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₃H and SO₂-C₁₋₃-alkyl;

R⁸ is selected from the group consisting of hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

25 or R⁷ and R⁸ when taken together with the nitrogen to which they are attached may complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

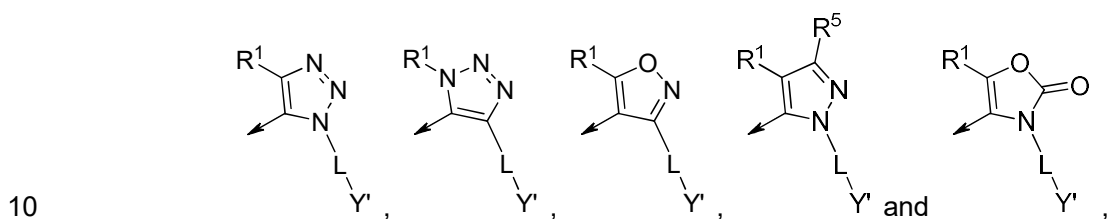
30 A is a 6-10 membered mono- or bicyclic aryl or a 5-10 membered mono- or bicyclic heteroaryl containing 1 to 5 heteroatoms independently selected from the group consisting of N, O and S, wherein aryl and heteroaryl are unsubstituted or substituted with one or two groups independently selected from the group consisting of OH, halogen, CN, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₆-cycloalkyl and halo-C₃₋₆-cycloalkyl;

B is a C₅₋₈-cycloalkyl ring or, if Y is N, then is B a C₄₋₈-heterocycloalkyl or bridged C₄₋₈-heterocycloalkyl containing one nitrogen atom, and wherein the substituent Q is not directly adjacent to substituent A;

Q is selected from the group consisting of phenyl, pyridyl, thiazolyl, thiophenyl, pyrimidyl, oxazolyl, pyrazolyl, imidazolyl and triazolyl, each unsubstituted or substituted with one or two groups independently selected from the group consisting of halogen, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy or halo-C₁₋₄-alkoxy;

Y is N, CH or CF;

Z is selected from



wherein

L is selected from the group consisting of a bond, C₁₋₃-alkylene and C₁₋₃-alkylene-O-;

Y' is selected from phenyl, pyridyl, pyridyl-N-oxide, pyrimidyl, pyridinonyl, pyrimidinonyl, C₄₋₈-cycloalkyl, and C₄₋₈-heterocycloalkyl, wherein phenyl, pyridyl, pyridyl-N-oxide, pyrimidyl, pyridinonyl, pyrimidinonyl, C₄₋₈-cycloalkyl and C₄₋₈-heterocycloalkyl are substituted with R² and R³ and optionally substituted with one or two groups independently selected from fluoro, chloro, CN, NH₂, NH(C₁₋₃-alkyl), N(C₁₋₃-alkyl)₂, C₁₋₃-alkyl, fluoro-C₁₋₃-alkyl, OH, C₁₋₃-alkoxy, fluoro-C₁₋₃-alkoxy, C₃₋₆-cycloalkyl and fluoro-C₃₋₆-cycloalkyl;

R¹ is selected from the group consisting of C₁₋₄-alkyl and C₃₋₆-cycloalkyl, wherein C₁₋₄-alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy, C₁₋₃-alkoxy and fluoro-C₁₋₃-alkoxy, and C₃₋₆-cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy, C₁₋₃-alkyl, fluoro-C₁₋₃-alkyl, C₁₋₃-alkoxy and fluoro-C₁₋₃-alkoxy;

R² and R³ are independently selected from the group consisting of hydrogen, halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, C₁₋₃-alkoxy, halo-C₁₋₃-alkoxy, cyclopropyl and fluoro-cyclopropyl;

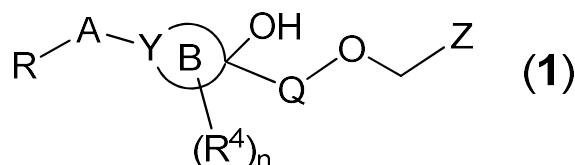
R⁴ is independently selected from halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, C₁₋₃-alkoxy, halo-C₁₋₃-alkoxy, C₃₋₆-cycloalkyl, and fluoro-C₃₋₆-cycloalkyl;

R⁵ is selected from the group consisting of hydrogen, fluoro, CH₃, CHF₂ and CF₃;

n is selected from 0, 1, 2, 3 and 4; and

x is selected from 0, 1 and 2.

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



wherein

R is selected from the group consisting of hydrogen, halogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-O-R⁷, C₀₋₆-alkylene-CN, C₀₋₆-alkylene-NR⁷R⁸, O-C₃₋₁₀-cycloalkyl, O-C₁₋₆-alkylene-O-R⁷, O-C₃₋₁₀-heterocycloalkyl, C₀₋₆-alkylene-CO₂R⁷, C₀₋₆-alkylene-C(O)R⁷, C₀₋₆-alkylene-C(O)NR⁷R⁸, C₀₋₆-alkylene-C(O)NR⁷SO₂R⁷, C₀₋₆-alkylene-N(R⁷)C(O)R⁷, C₀₋₆-alkylene-SO_x-R⁷, C₀₋₆-alkylene-SO₃H, C₀₋₆-alkylene-SO₂-NR⁷R⁸, C₀₋₆-alkylene-SO₂-NR⁸COR⁷, C₀₋₆-alkylene-N(R⁷)SO₂-R⁸, and C₀₋₆-alkylene-SO₂-C₃₋₁₀-heterocycloalkyl,

wherein alkylene, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted by 1 to 4 substituents independently selected from the group consisting of halogen, CN, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, oxo, CO₂H, SO₃H, O-C₁₋₃-alkyl and O-halo-C₁₋₃-alkyl;

R⁷ is independently selected from the group consisting of hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and phenyl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, CO₂H, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₃H and SO₂-C₁₋₃-alkyl;

R⁸ is selected from the group consisting of hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

or R⁷ and R⁸ when taken together with the nitrogen to which they are attached may complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

A is a 6-10 membered mono- or bicyclic aryl or a 5-10 membered mono- or bicyclic heteroaryl containing 1 to 5 heteroatoms independently selected from the group consisting of N, O and S, wherein aryl and heteroaryl are unsubstituted or substituted with one or two groups independently selected from the group consisting of OH, halogen, CN, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₆-cycloalkyl and halo-C₃₋₆-cycloalkyl;

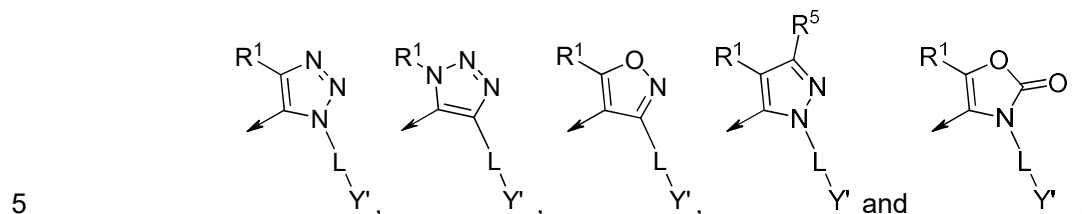
B is a C₅₋₈-cycloalkyl ring or, if Y is N, then is B a C₅₋₈-heterocycloalkyl containing one nitrogen atom, and wherein the substituent Q is not directly adjacent to substituent A;

Q is selected from the group consisting of phenyl, pyridyl, thiazolyl, thiophenyl, pyrimidyl, oxazolyl, pyrazolyl, imidazolyl and triazolyl, each unsubstituted or substituted with one or two

groups independently selected from the group consisting of halogen, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy or halo-C₁₋₄-alkoxy;

Y is N, CH or CF;

Z is selected from



wherein

L is selected from the group consisting of a bond, C₁₋₃-alkylene and C₁₋₃-alkylene-O-;

Y' is selected from phenyl, pyridyl, pyridyl-*N*-oxide, pyrimidyl, pyridinonyl, pyrimidinonyl, C₄₋₈-cycloalkyl, and C₄₋₈-heterocycloalkyl, wherein phenyl, pyridyl, pyridyl-*N*-oxide, pyrimidyl, pyridinonyl, pyrimidinonyl, C₄₋₈-cycloalkyl and C₄₋₈-heterocycloalkyl are substituted with R² and R³ and optionally substituted with one or two groups independently selected from fluoro, chloro, CN, NH₂, NH(C₁₋₃-alkyl), N(C₁₋₃-alkyl)₂, C₁₋₃-alkyl, fluoro-C₁₋₃-alkyl, OH, C₁₋₃-alkoxy, fluoro-C₁₋₃-alkoxy, C₃₋₆-cycloalkyl and fluoro-C₃₋₆-cycloalkyl;

10

R¹ is selected from the group consisting of C₁₋₄-alkyl and C₃₋₆-cycloalkyl, wherein C₁₋₄-alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy, C₁₋₃-alkoxy and fluoro-C₁₋₃-alkoxy, and C₃₋₆-cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy, C₁₋₃-alkyl, fluoro-C₁₋₃-alkyl, C₁₋₃-alkoxy and fluoro-C₁₋₃-alkoxy;

15

R² and R³ are independently selected from the group consisting of hydrogen, halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, C₁₋₃-alkoxy, halo-C₁₋₃-alkoxy, cyclopropyl and fluoro-cyclopropyl;

20

R⁴ is independently selected from halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, C₁₋₃-alkoxy, halo-C₁₋₃-alkoxy, C₃₋₆-cycloalkyl, and fluoro-C₃₋₆-cycloalkyl;

R⁵ is selected from the group consisting of hydrogen, fluoro, CH₃, CHF₂ and CF₃;

n is selected from 0, 1, 2, 3 and 4; and

25 x is selected from 0, 1 and 2.

3. The compound according to claim 1 or 2 wherein

R is selected from the group consisting of CO₂H, SO₃H, CONR⁷R⁸, tetrazolyl, 1,2,4-oxadiazol-5(4H)-one-3-yl and SO₂NHCOR⁷;

30 R⁷ is selected from the group consisting of hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₁₋₆-alkylene-R⁹, and SO₂-C₁₋₃-alkyl;

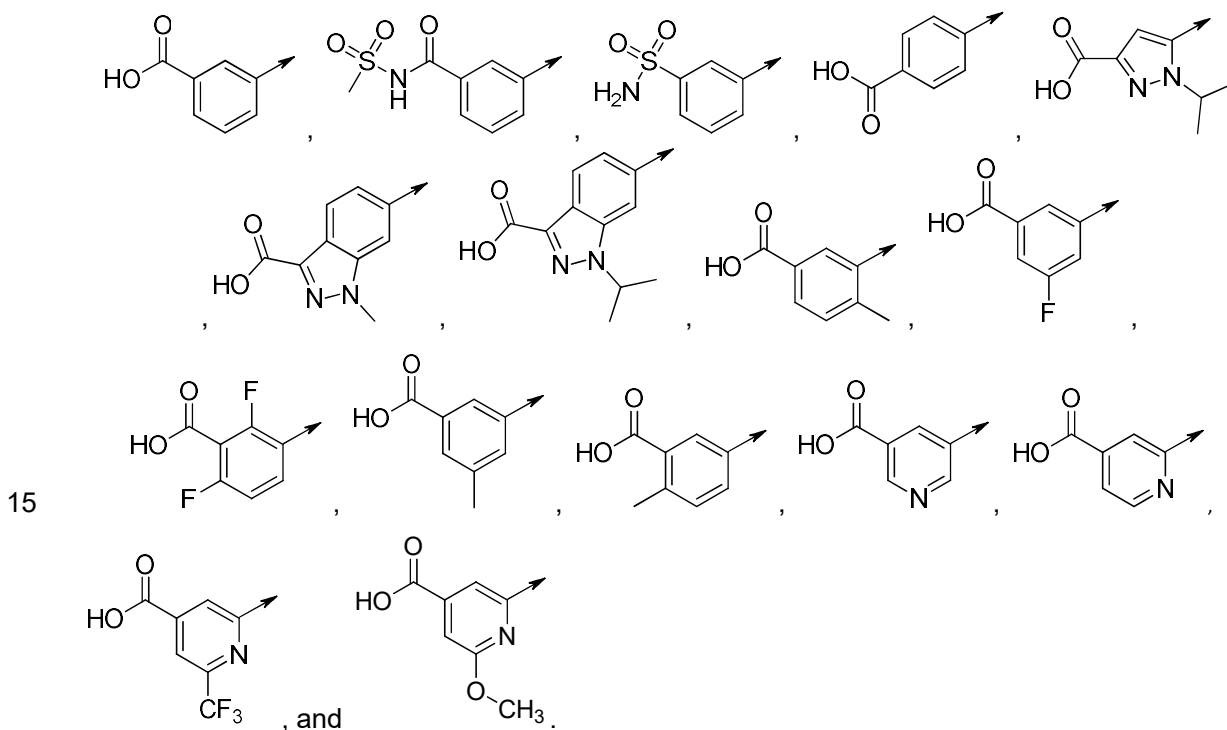
R⁸ is selected from the group consisting of hydrogen, C₁₋₆-alkyl, and halo-C₁₋₆-alkyl; and

R⁹ is selected from the group consisting of COOH, OH and SO₃H.

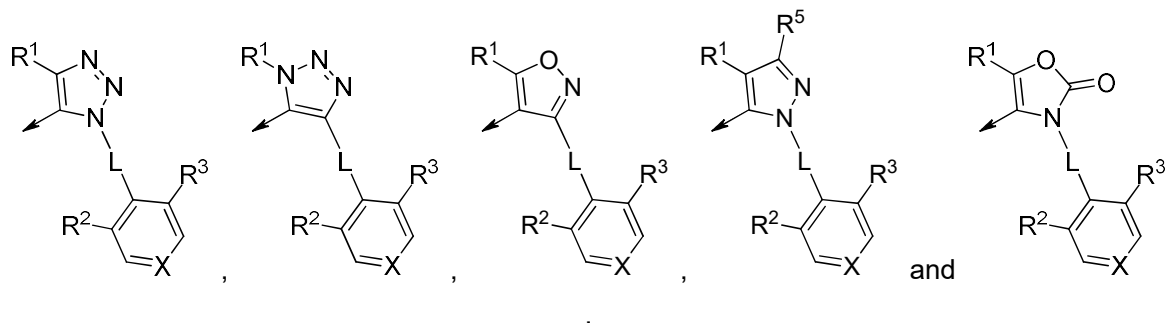
4. The compound according to any of claims 1 to 3 wherein

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

5. The compound according to any of claims 1 to 4 wherein R-A is selected from



6. The compound according to any of claims 1 to 5 wherein Z is selected from



wherein

L is selected from the group consisting of a bond, C₁₋₃-alkylene and C₁₋₃-alkylene-O-;

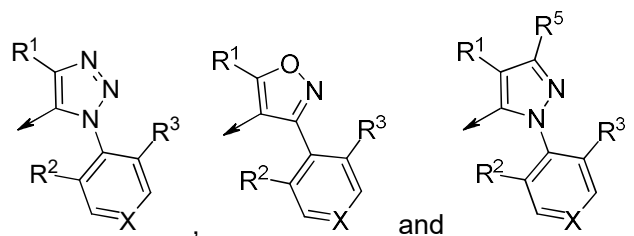
X is selected from the group consisting of CH, CF, N and NO;

5 R¹ is selected from the group consisting of C₁₋₄-alkyl and C₃₋₆-cycloalkyl, wherein C₁₋₄-alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy, C₁₋₃-alkoxy and fluoro-C₁₋₃-alkoxy, and C₃₋₆-cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy, C₁₋₃-alkyl, fluoro-C₁₋₃-alkyl, C₁₋₃-alkoxy and fluoro-C₁₋₃-alkoxy;

10 R² and R³ are independently selected from the group consisting of hydrogen, halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, C₁₋₃-alkoxy, halo-C₁₋₃-alkoxy, cyclopropyl and fluoro-cyclopropyl; and

R⁵ is selected from the group consisting of hydrogen, fluoro, CH₃, CHF₂ and CF₃.

7. The compound according to any of claims 1 to 6 wherein Z is selected from



15 wherein

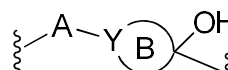
X is selected from the group consisting of CH, CF, N and NO;

R¹ is selected from the group consisting of CF₃, CHF₂, isopropyl and cyclopropyl, wherein isopropyl and cyclopropyl are unsubstituted or substituted with one or two fluoro or one hydroxy;

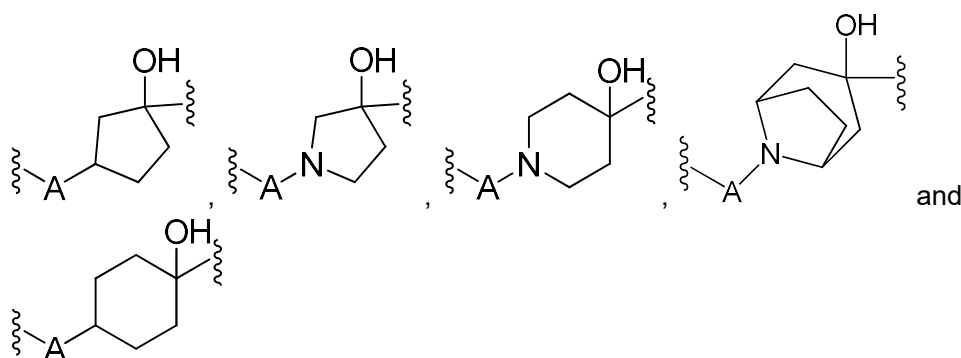
R² is selected from the group consisting of fluoro, chloro, CH₃, CHF₂, CF₃, OCHF₂ and OCF₃;

20 R³ is selected from the group consisting of hydrogen, fluoro, chloro, CH₃, CHF₂, CF₃, OCHF₂ and OCF₃; and

R⁵ is selected from the group consisting of hydrogen, fluoro, CH₃, CHF₂ and CF₃.

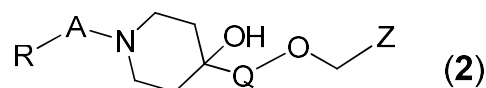


8. The compound according to any of claims 1 to 7 wherein is selected from



9. The compound according to claim 1 or 2 with Formula (2)

5



wherein

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

R is selected from the group consisting of CO₂H, SO₃H, CONR⁷R⁸, tetrazolyl, 1,2,4-oxadiazol-5(4H)-one-3-yl and SO₂NHCOR⁷, wherein

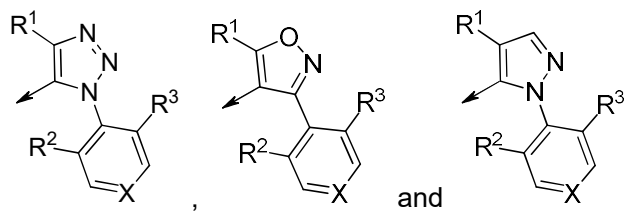
R⁷ is selected from the group consisting of hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₁₋₆-alkylene-R⁹, and SO₂-C₁₋₃-alkyl;

R⁸ is selected from the group consisting of hydrogen, C₁₋₆-alkyl, and halo-C₁₋₆-alkyl; and

R⁹ is selected from the group consisting of COOH, OH and SO₃H;

Q is selected from the group consisting of phenyl, pyridyl, thiazolyl, thiophenyl and pyrimidyl, each unsubstituted or substituted with one or two groups independently selected from the group consisting of fluoro, chloro, CH₃, CHF₂ and CF₃;

Z is selected from



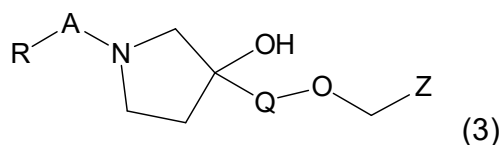
X is selected from the group consisting of CH, N and NO;

R¹ is selected from the group consisting of isopropyl and cyclopropyl, wherein isopropyl and cyclopropyl are unsubstituted or substituted with one or two fluoro or one hydroxy;

R² is selected from the group consisting of fluoro, chloro, CH₃, CHF₂, CF₃, OCHF₂ and OCF₃; and

- 5 R³ is selected from the group consisting of hydrogen, fluoro, chloro, CH₃, CHF₂, CF₃, OCHF₂ and OCF₃.

10. The compound according to claim 1 or 2 with Formula (3)



10 wherein

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

R is selected from the group consisting of CO₂H, SO₃H, CONR⁷R⁸, tetrazolyl, 1,2,4-oxadiazol-5(4H)-one-3-yl and SO₂NHCOR⁷, wherein

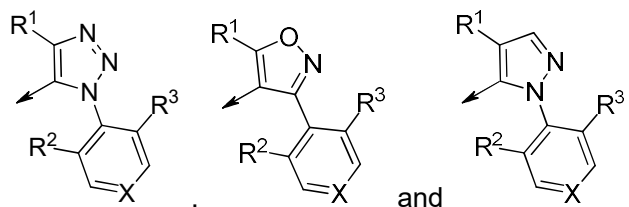
20 R⁷ is selected from the group consisting of hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₁₋₆-alkylene-R⁹, and SO₂-C₁₋₃-alkyl;

R⁸ is selected from the group consisting of hydrogen, C₁₋₆-alkyl, and halo-C₁₋₆-alkyl; and

R⁹ is selected from the group consisting of COOH, OH and SO₃H;

25 Q is selected from the group consisting of phenyl, pyridyl, thiazolyl, thiophenyl and pyrimidyl, each unsubstituted or substituted with one or two groups independently selected from the group consisting of fluoro, chloro, CH₃, CHF₂ and CF₃;

Z is selected from



X is selected from the group consisting of CH, N and NO;

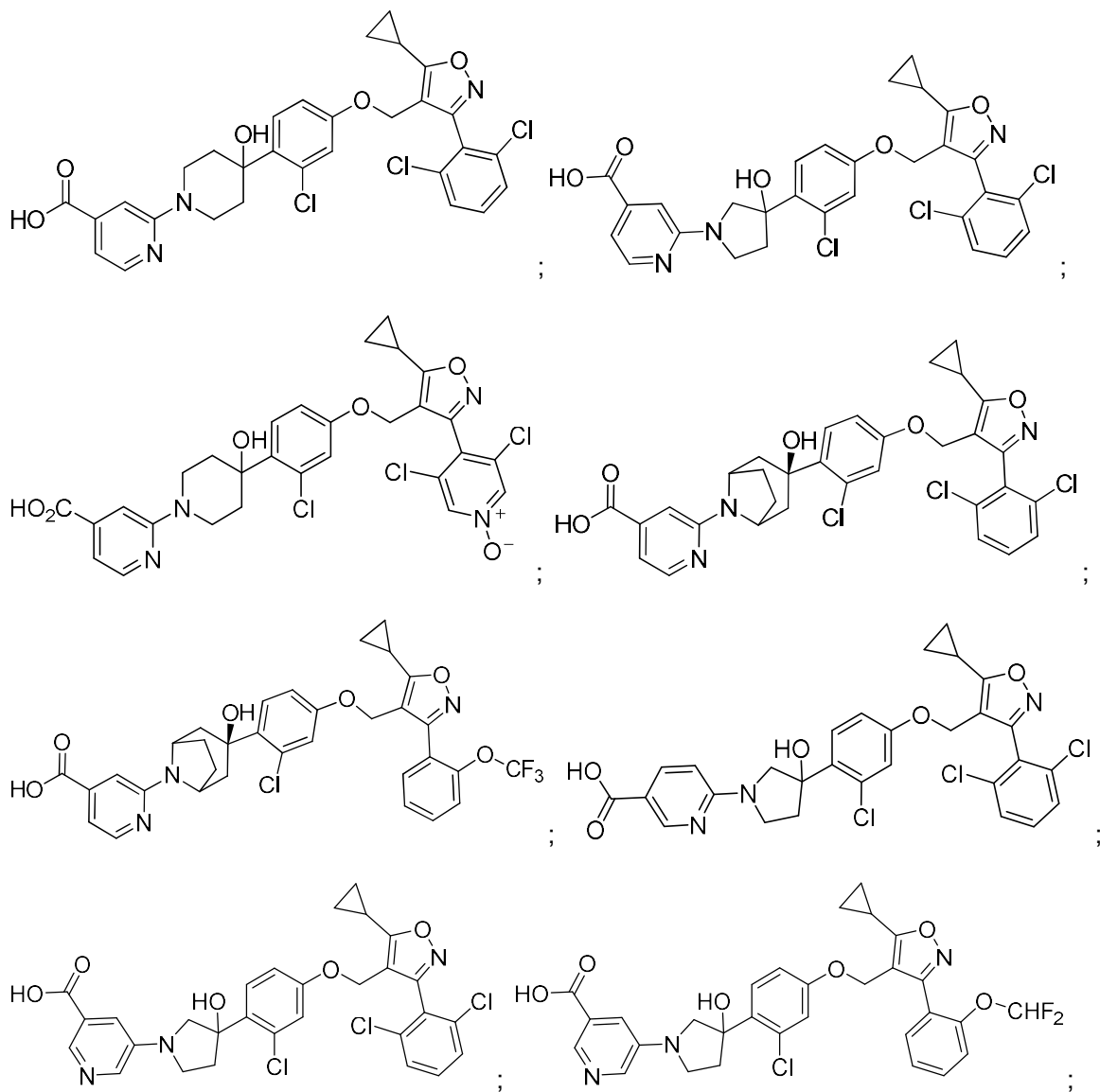
R¹ is selected from the group consisting of isopropyl and cyclopropyl, wherein isopropyl and cyclopropyl are unsubstituted or substituted with one or two fluoro or one hydroxy;

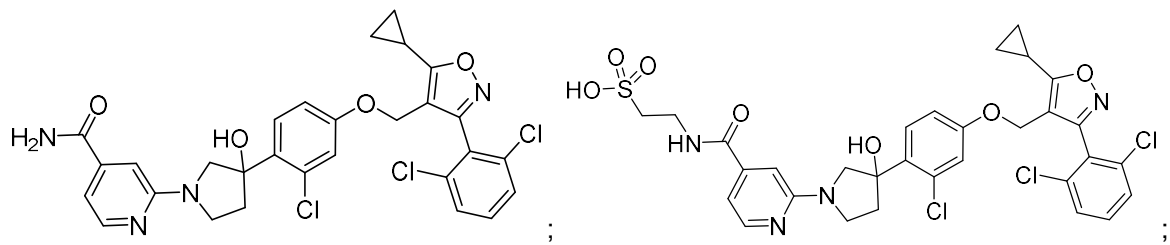
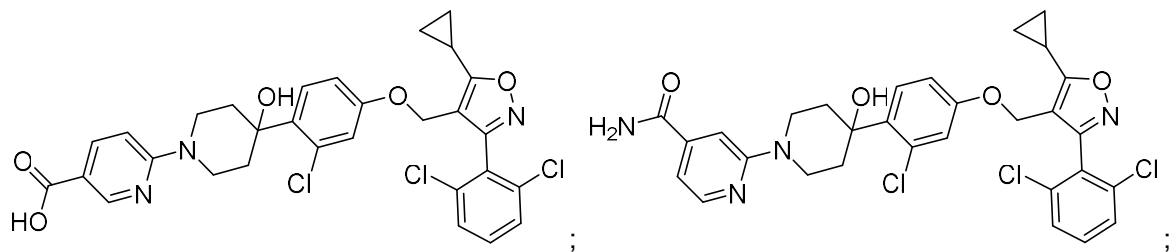
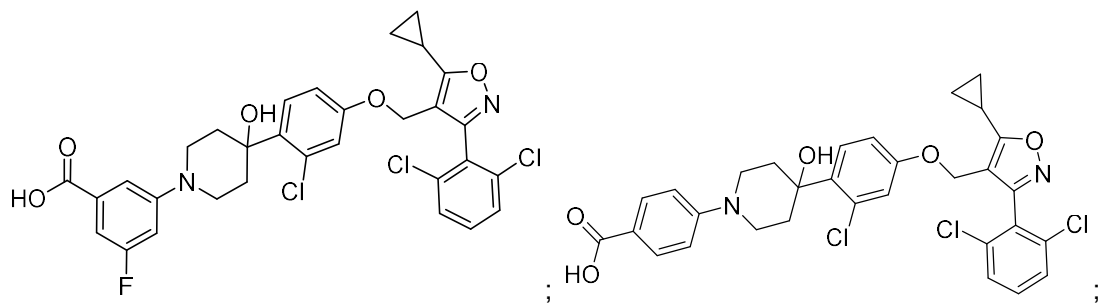
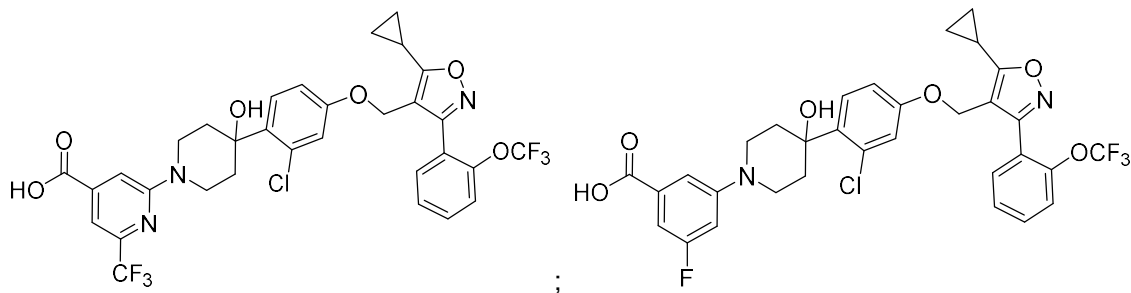
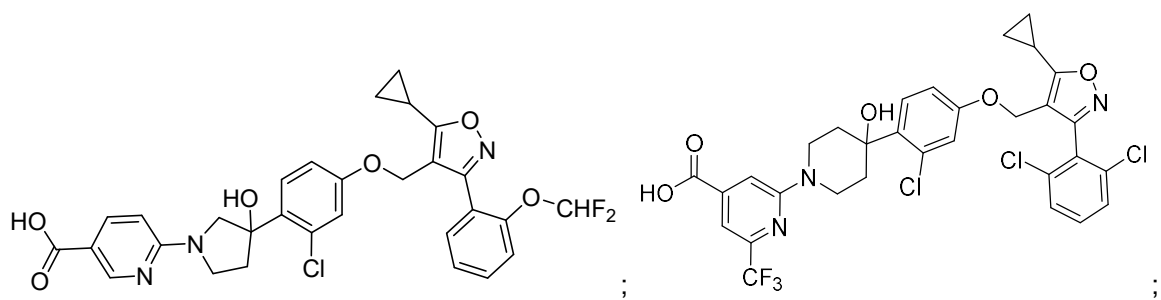
R² is selected from the group consisting of fluoro, chloro, CH₃, CHF₂, CF₃, OCHF₂ and OCF₃;
and

- 5 R³ is selected from the group consisting of hydrogen, fluoro, chloro, CH₃, CHF₂, CF₃, OCHF₂ and OCF₃.

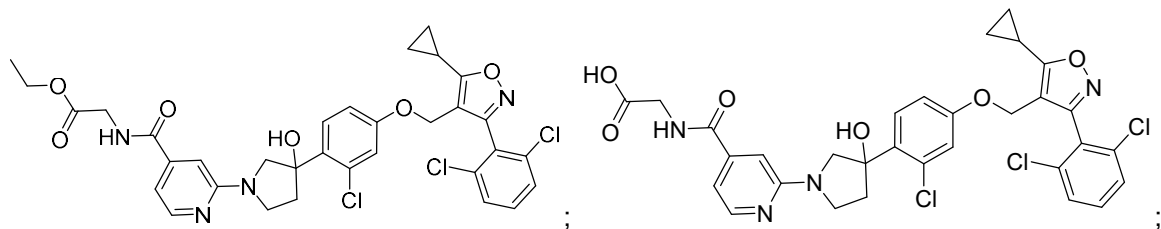
11. A compound selected from the group consisting of:

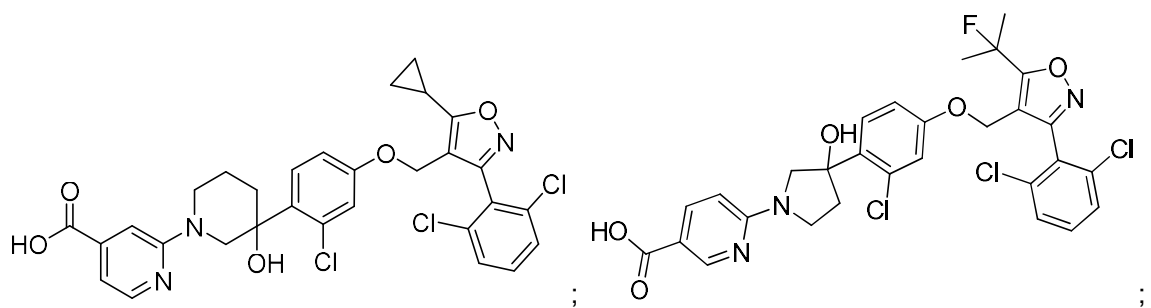
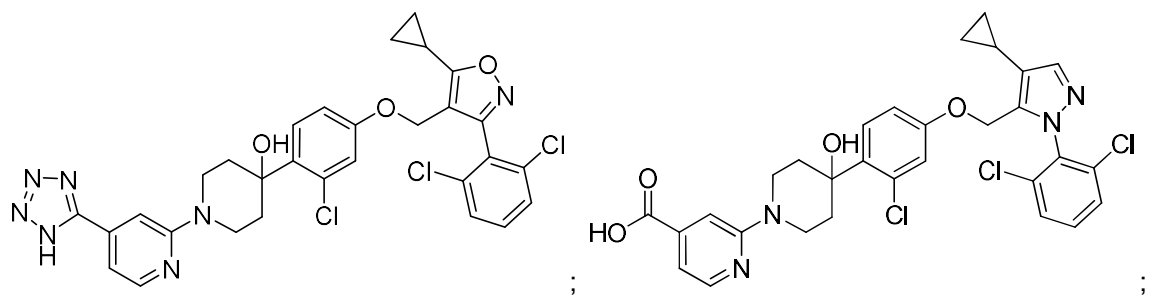
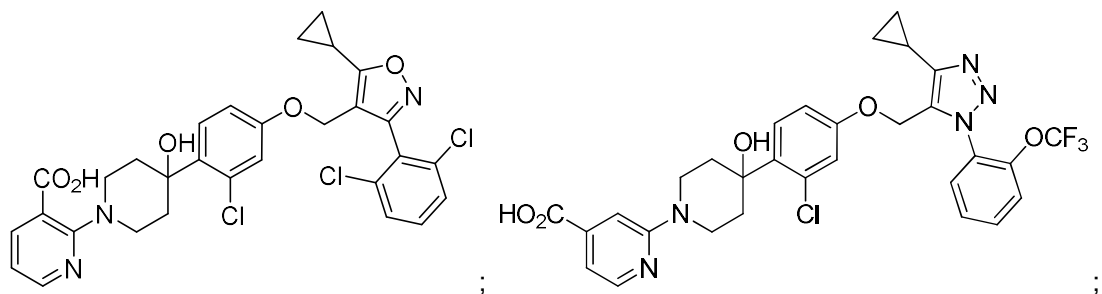
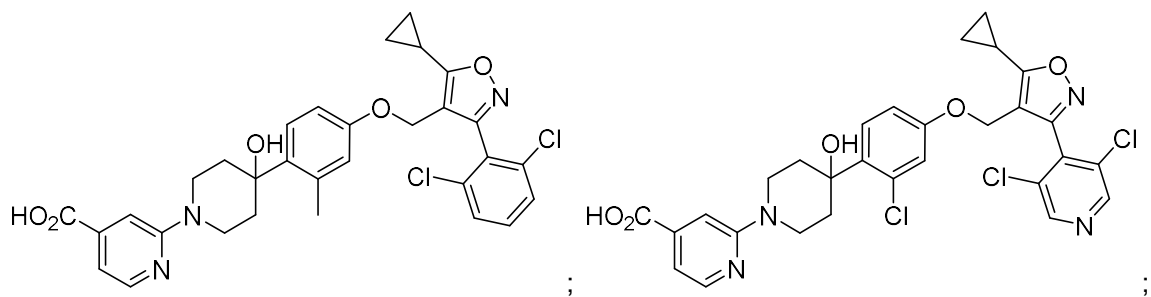
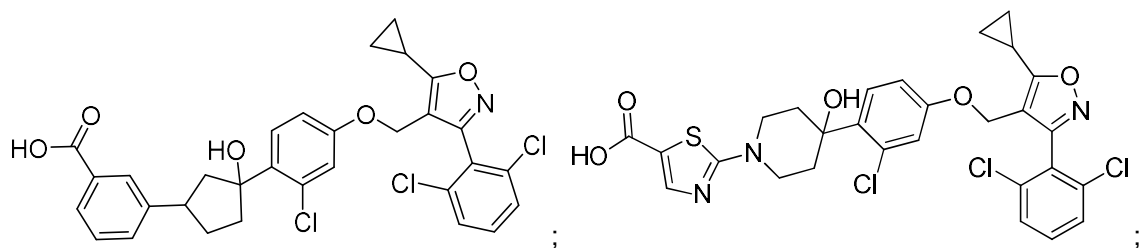
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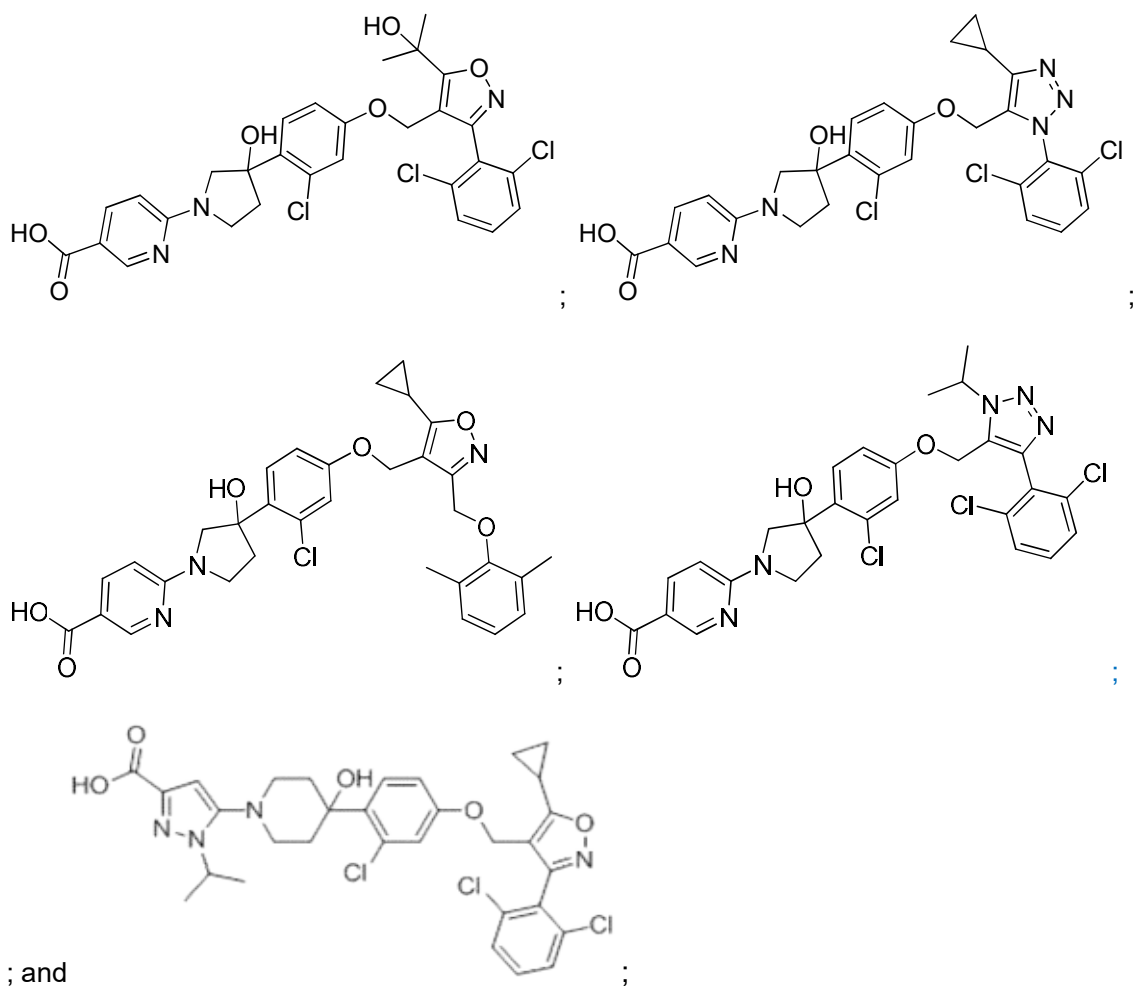


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or an enantiomer, diastereomer, tautomer, solvate or pharmaceutical acceptable salt thereof.

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12. A compound according to any of claims 1 to 11 as a medicament.

13. Use of a compound according to any of claims 1 to 11 for the preparation of a medicament for the prophylaxis and/or treatment of diseases mediated by FXR.

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14. The use according to claim 13 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;

15 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

Inflammatory Bowel Diseases.

5

15. The use according to claim 13 wherein the disease is selected from

lipid and lipoprotein disorders;

Type II Diabetes and clinical complications of Type I and Type II Diabetes;

10 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;

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

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

16. The use according to claim 15, wherein the clinical complications of Type I and Type II Diabetes is diabetic nephropathy, diabetic neuropathy, diabetic retinopathy or other observed effects of clinically manifest long term Diabetes.

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17. The use according to claim 15, wherein 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 is Non-Alcoholic Fatty Liver Disease (NAFLD), or Non-Alcoholic Steatohepatitis (NASH).

25

18. The use according to claim 13 wherein the disease is selected from

non-malignant hyperproliferative disorders and malignant hyperproliferative disorders.

30 19. The use according to claim 18, wherein the disease is 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.