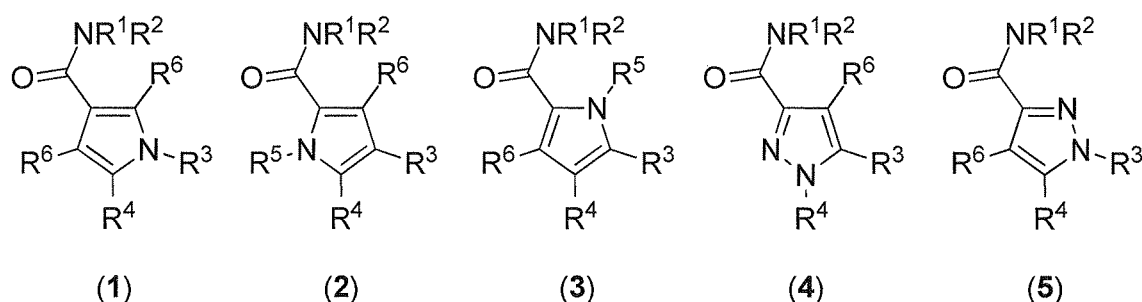


Summary

It is therefore the object of the present disclosure to provide compounds, which bind to the orphan nuclear receptors ROR γ 1 and/or ROR γ t and, thus, to open new methods for treating diseases associated with the modulation of ROR γ , such as autoimmune diseases, inflammatory skin diseases or multiple sclerosis.

This object is solved by claims 1 to 24.

In one aspect of the present disclosure, there is provided a compound represented by Formula (1) to Formula (5)



an enantiomer, diastereomer, tautomer, *N*-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

R¹ is independently selected from C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-(5-membered heteroaryl) and SO₂-C₁₋₁₀-alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR¹¹, O-C₂₋₆-alkylene-OR¹¹, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹¹, COR¹¹, SO_xR¹¹, SO₃H, SO₂NR¹¹R¹², NR¹¹COR¹¹, NR¹¹SO₂R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², C₃₋₁₀-cycloalkyl, O-C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, O-C₃₋₁₀-heterocycloalkyl and NR¹¹R¹²;

R² is R¹ or H;

or R¹ and R² when taken together with the nitrogen to which they are attached 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 halogen, oxo, CN, OR¹¹, SO_xR¹¹, SO₃H, NR¹¹SO₂R¹¹, SO₂NR¹¹R¹², C₀₋₆-alkylene-CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹¹, COR¹¹, NR¹¹-CO-R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², NR¹¹R¹², C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, O-C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl and O-C₃₋₈-heterocycloalkyl,

x is independently selected from 0, 1 and 2;

for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor.

5 In another aspect of the present disclosure, there is provided the compound as disclosed above for use as a medicament.

10 In another aspect of the present disclosure, there is provided the compound as disclosed above for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor, wherein the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, epidermal
15 hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed above and a pharmaceutically acceptable carrier or excipient.

20 In another aspect of the present disclosure, there is provided a use of the compound according to the first aspect for the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor, wherein the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis,
25 chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.
30

Thus, the present disclosure provides carboxamide containing cyclic compounds as ROR γ modulators, which can be used for treating or preventing a disease or disorder associated with the inactivation or activation of the ROR γ receptor.

35 The present disclosure relates to a ROR γ modulator which is based on a cyclic scaffold for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of ROR γ .

When treating the disease or disorder associated with the modulation of the ROR γ receptor, the activity of said receptor is preferably reduced.

5 Preferably, the disease or disorder is selected from the group consisting of autoimmune diseases. Autoimmune diseases comprise a group of diseases with a similar etiology of an overshooting immune response against endogenous targets resulting in chronic inflammation and physical disabilities or other severe symptoms. Autoimmune diseases
comprise e.g. rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease,
10 asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease (COPD) and amyotrophic lateral sclerosis.

The present disclosure provides novel compounds to be used in the treatment of diseases or disorders associated with the inactivation or activation of the ROR γ receptor.

Further, the present disclosure relates to a method for treating autoimmune diseases comprising rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, 5 psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal 10 hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic

6. The compound according to any of claims 1 to 5 wherein

R^3 is a 6-10 membered mono- or bicyclic aryl or a 5-10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from the group consisting of N, O and S

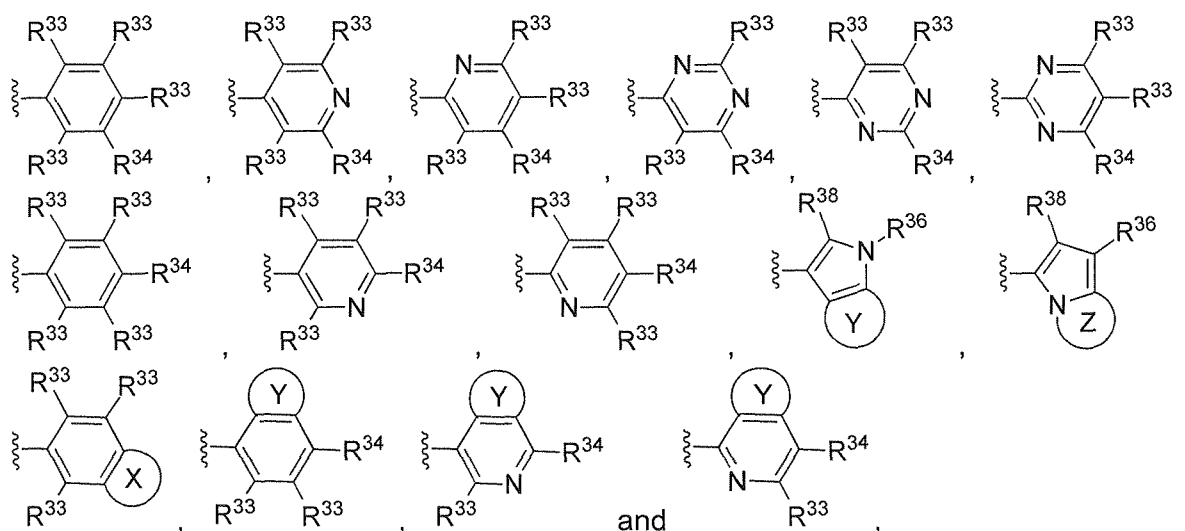
5 wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, OH, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{0-6} -alkylene- C_{3-10} -cycloalkyl, C_{0-6} -alkylene-O- C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene-COOR³¹, C_{0-6} -alkylene-C(O)R³¹, C_{0-6} -alkylene-C(O)N(R³¹)₂, C_{0-6} -alkylene-SO₂-N(R³¹)₂,
10 C_{0-6} -alkylene-SO₂-R³¹, C_{0-6} -alkylene-(5-membered heteroaryl) and C_{0-6} -alkylene-(6-membered heteroaryl),

wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O- C_{1-6} -alkyl and CN,

15 or wherein two adjacent substituents may complete a 3- to 8-membered saturated or partially unsaturated ring containing carbon atoms and optionally containing 1 to 3 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, oxo, OH, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{1-6} -alkyl, C_{3-6} -cycloalkyl and halo- C_{1-6} -alkyl.

20

7. The compound according to any of claims 1 to 6 wherein R^3 is selected from



25

wherein

R^{33} is independently selected from H, halogen, CN, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, OH, O- C_{1-6} -alkyl, O-fluoro- C_{1-6} -alkyl, NH- C_{1-6} -alkyl, NH-fluoro- C_{1-6} -alkyl and C_{3-10} -cycloalkyl,

- 5 wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

- R^{34} is independently selected from H, halogen, CN, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, OH, O- C_{1-6} -alkyl,
10 O-fluoro- C_{1-6} -alkyl, NH- C_{1-6} -alkyl, NH-fluoro- C_{1-6} -alkyl, C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, 5-membered heteroaryl, 6-membered heteroaryl, $C(O)N(R^{37})_2$ and $SO_2N(R^{37})_2$,

- wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1
15 to 3 substituents independently selected from the group consisting of F, C_{1-3} -alkyl, fluoro- C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl and fluoro-O- C_{1-3} -alkyl;

R^{35} is selected from halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl, oxo, OH, O- C_{1-6} -alkyl and O-halo- C_{1-6} -alkyl;

R^{36} is selected from C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, $C(O)N(R^{37})_2$ and $SO_2N(R^{37})_2$;

- 20 R^{37} is independently selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{0-4} -alkylene- C_{3-6} -cycloalkyl and C_{0-4} -alkylene- C_{3-6} -heterocycloalkyl, wherein alkyl and alkylene is unsubstituted or substituted with 1 to 4 substituents selected from the group consisting of halogen, OH, O- C_{1-3} -alkyl, and CN; and wherein cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F,
25 CN, OH, oxo, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

- or wherein two R^{37} when taken together with the nitrogen to which they are attached 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, C_{1-4} -alkyl and halo- C_{1-4} -alkyl;
30

R^{38} is selected from H, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

X is an annelated saturated heterocycle selected from the group consisting of

13. The compound according to any of claims 1 to 11 for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor, wherein the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.
14. A pharmaceutical composition comprising a compound according to any of claims 1 to 11 and a pharmaceutically acceptable carrier or excipient.
15. Use of the compound according to any of claims 1 to 11 for the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor, wherein the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.