RORγ1 is expressed in many tissues and is predominantly expressed in the kidneys, liver, and skeletal muscle. In contrast, expression of RORγt is restricted to some cell types of the immune system and to lymphoid organs such as the thymus and secondary lymphoid tissues (Hirose 1994; Jetten, 2009, Nuclear Receptor Signaling).

RORγt has been identified as a key regulator of Th17 cell differentiation and IL-17 production by γδ T cells, Th17 cells, T cytotoxic (Tc) 17 cells and innate lymphoid cells type 3 (ILC3) cells (Gaffen 2014). Th17 cells are a subset of T helper cells which preferentially produce the cytokines IL-17A, IL-17F, IL-21 and IL-22 (Castro PLOS 2017). T cells lacking RORγt failed to differentiate into Th17 cells even under Th17-polarizing culture conditions, while over-expression of RORγt in naïve CD4+ T cells was sufficient to accelerate the expression of Th17-related cytokines and chemokines (Gaffen 2014, Nat Rev Immunol; Yang 2014, Trend Pharmacol Sci). IL-23 is a vital checkpoint in the generation, maintenance and activation of pathogenic Th17 cells. In response to IL-23 signals, RORγt cooperates with a network of transcription factors (STAT3, IRF4 and BATF) to initiate the complete differentiation program of Th17 cells (Gaffen 2014, Nat Rev Immunol).

Th17 cells and IL-17 immune response have been shown to be associated with the pathology of many human inflammatory and autoimmune disorders. Therapeutic strategies targeting the IL-23–IL-17 axis are being developed in many autoimmune diseases, and some of them have already demonstrated to provide clinical efficacy some diseases (Patel 2015; Krueger 2018 Exp Dermatol) .

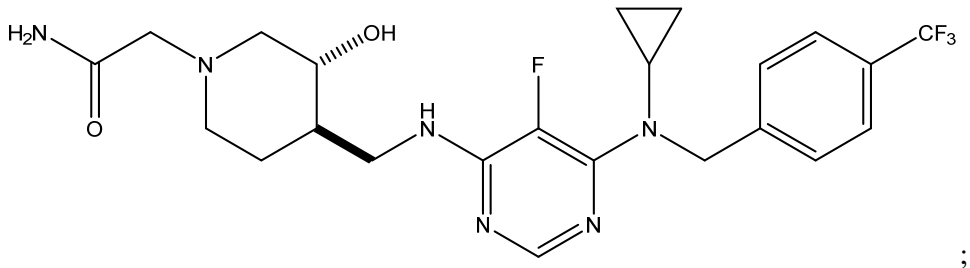
There is thus evidence that RORα, RORβ and RORγ play a role in the pathogenesis of many diseases.

It would be desirable to provide compounds that modulate the activity of RORα and/or RORγ for use in treating inflammatory, metabolic and autoimmune diseases.

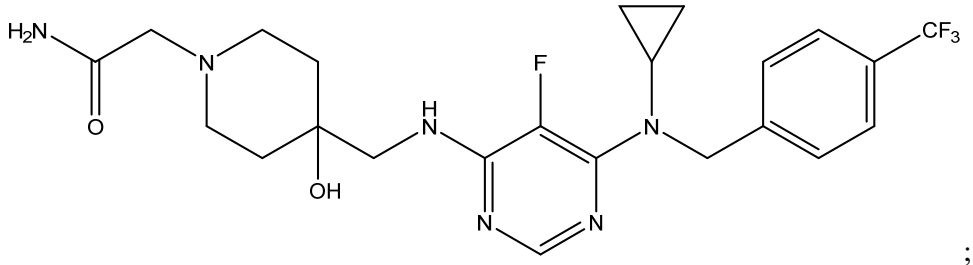
WO2016020288 and WO2016020295 describe compounds that modulate the activity or RORgamma receptors. However, a need still exists for potent RORgamma modulators having improved physicho-chemical properties.

Summary

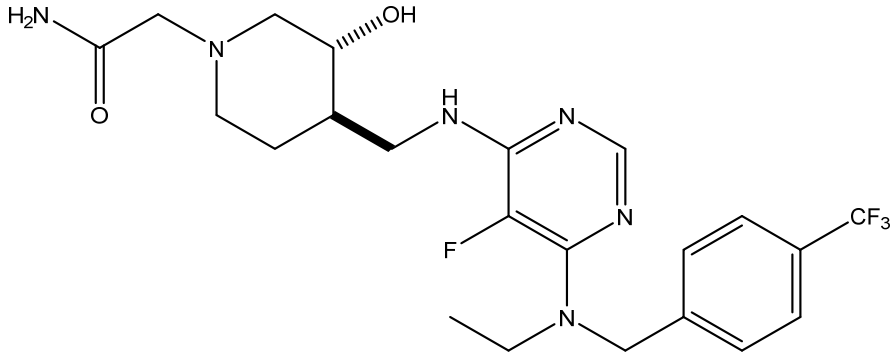
In one aspect of the present disclosure, there is provided a compound, stereoisomer, or salt having a structure selected from the group consisting of:



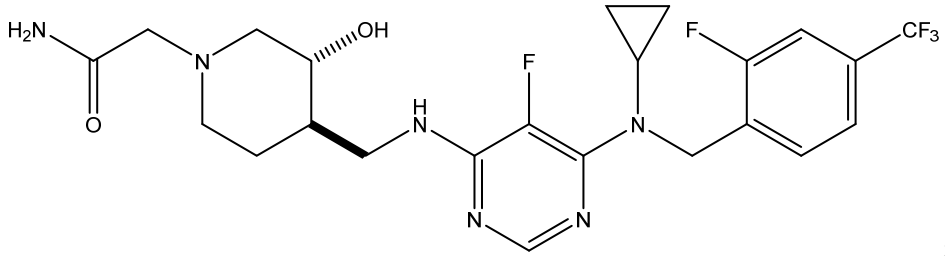
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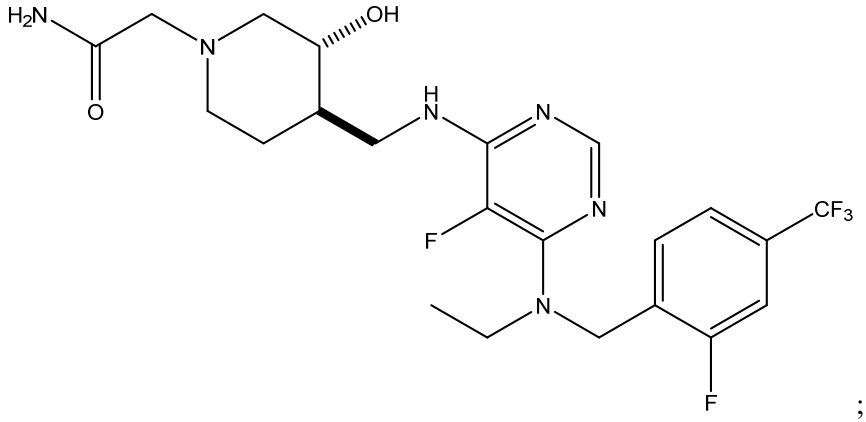
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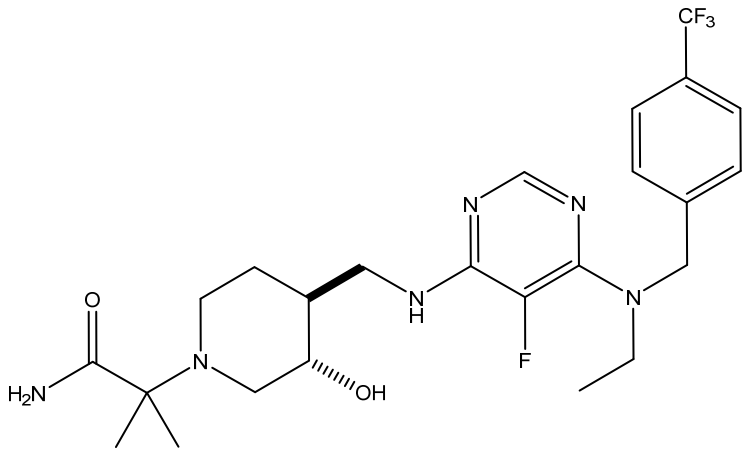
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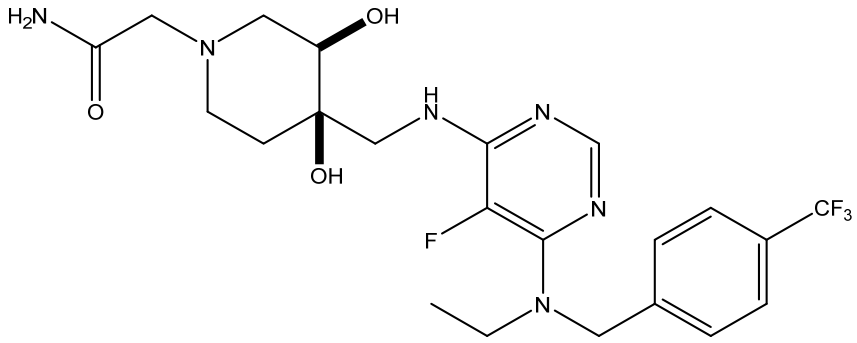
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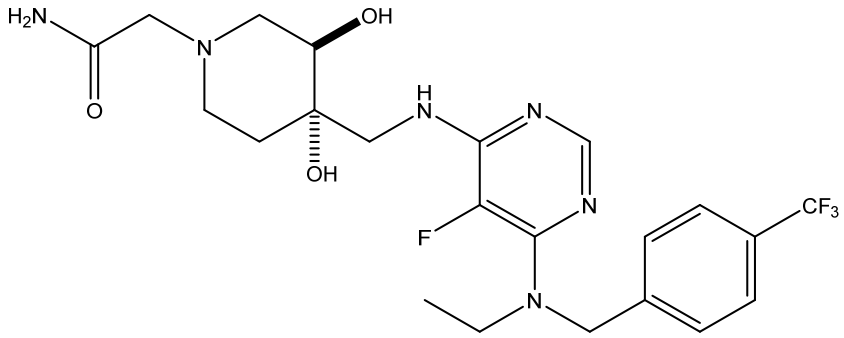
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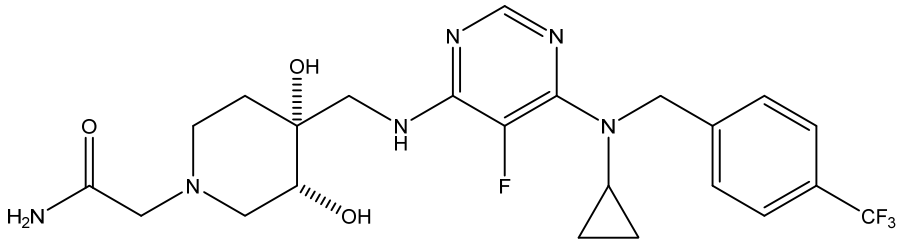
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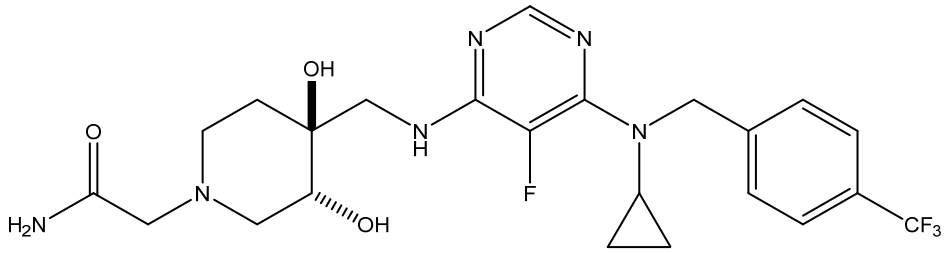
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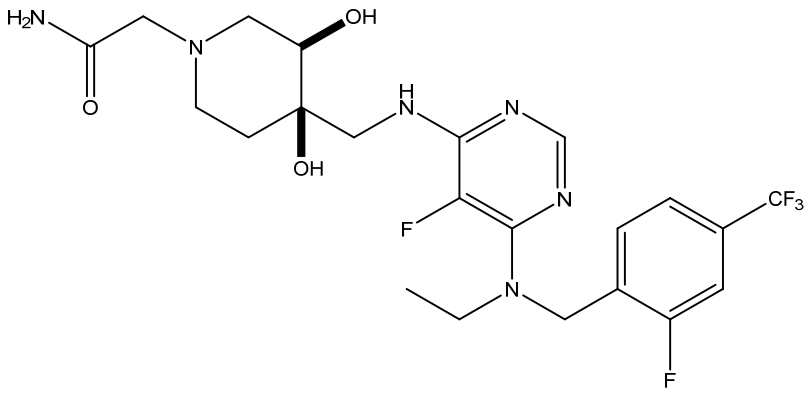


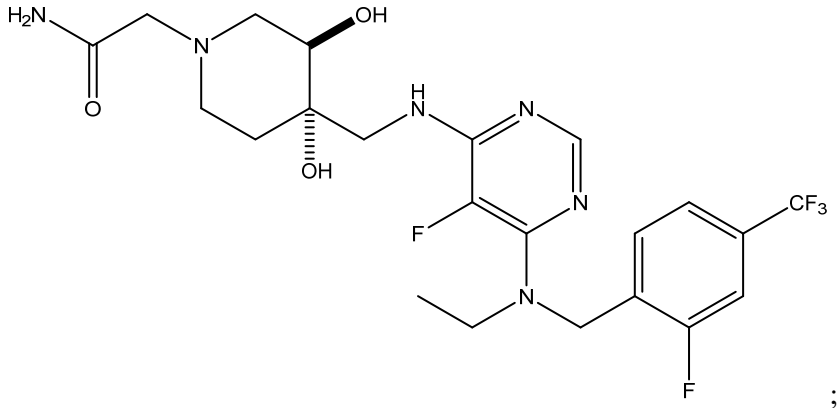
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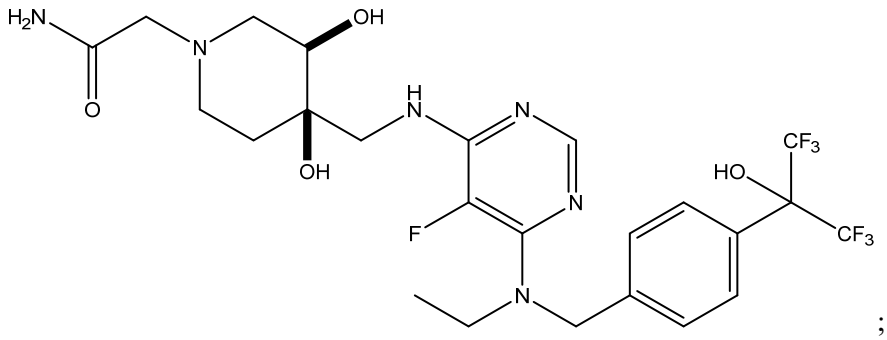


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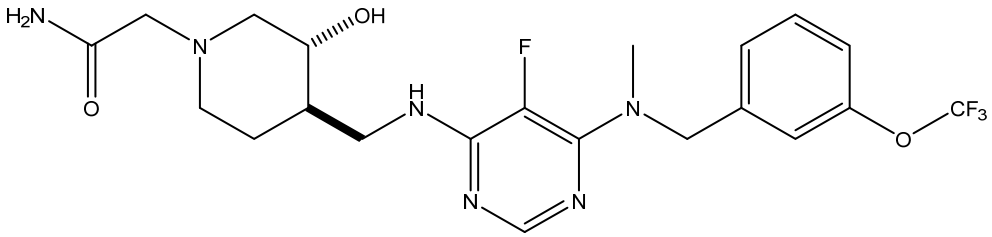

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H2N
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H2N
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and



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In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound, stereoisomer, or salt disclosed herein and at least one pharmaceutical acceptable excipient.

In a further aspect of the present disclosure, there is provided a compound, stereoisomer, or salt disclosed herein or a pharmaceutical composition disclosed herein, for use as a medicament.

In another aspect of the present disclosure, there is provided a use of a compound, stereoisomer, or salt disclosed herein or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for the treatment and/or prevention of an inflammatory, metabolic, oncologic or autoimmune disease.

In one example provided herein are compounds of Formula (I)

R_7 is selected from the group consisting of hydrogen, hydroxyl, CN, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and substituted or unsubstituted heteroaryl;

each R_8 independently is selected from the group consisting of hydrogen, hydroxyl, CN, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and substituted or unsubstituted heteroaryl; and

whenever R_7 is hydrogen and each R_8 present is hydrogen, then R_6 is selected from the group consisting of CN, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-6} hydroxyhaloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and substituted or unsubstituted heteroaryl; and

when substituted, a heteroalicyclyl is substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-6} hydroxyhaloalkyl, hydroxy, C_{1-4} alkoxy, and halogen; and

when substituted, a heteroaryl is substituted with 1 to 3 substitutents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, hydroxy, C_{1-4} alkoxy, cyano, halogen, C_{1-4} haloalkyl, C_{1-4} haloalkoxy and C_{1-6} hydroxyhaloalkyl; and

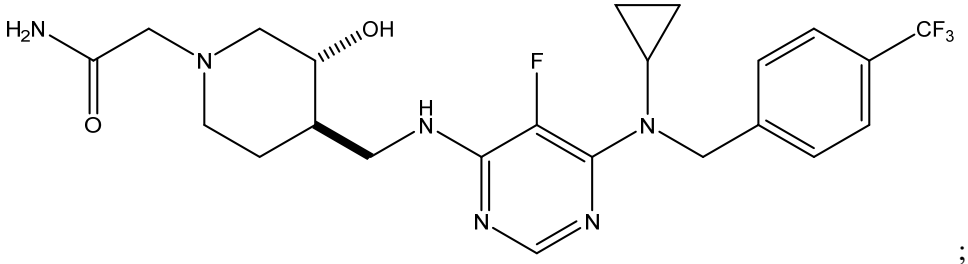
when substituted, a cycloalkyl or cycloalkenyl is substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-4} alkyl and halogen.

In one example provided herein are pharmaceutical compositions comprising a compound of Formula (I) or a stereoisomer thereof, or a pharmaceutically acceptable salt of the compound or stereoisomer of Formula (I) and at least one pharmaceutical acceptable excipient.

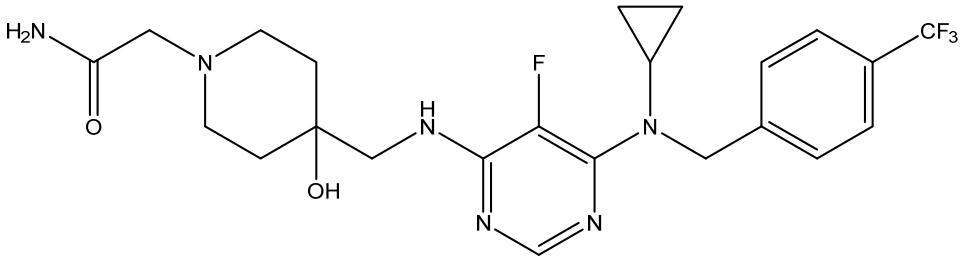
In one example provided herein are compounds of Formula (I) or a stereoisomer thereof, or a pharmaceutically acceptable salt of the compound or stereoisomer of Formula (I), or pharmaceutical compositions thereof for use in treatment and/or prevention of a disease or disorder or a symptom thereof selected from the group consisting of asthma, acne, chronic obstructive pulmonary disease (COPD), bronchitis, atherosclerosis, helicobacter pylori infection, allergic diseases including allergic rhinitis, allergic conjunctivitis and uveitis, sprue and food allergy, atopic dermatitis, lichen planus, cystic fibrosis, lung allograph rejection, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ichthyoses, bullous diseases, hidradenitis suppurativa,

CLAIMS

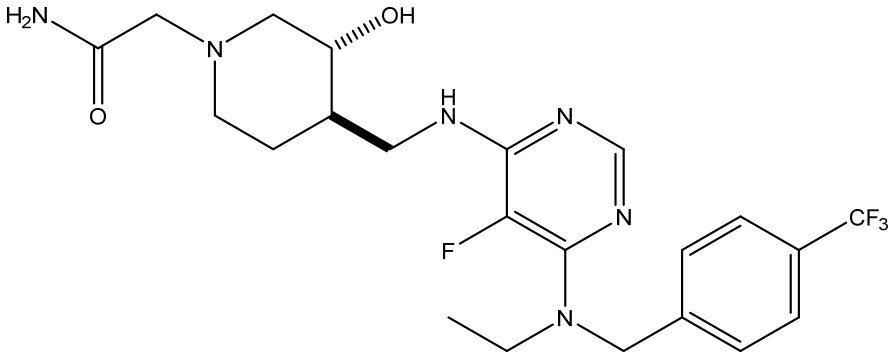
1. A compound, stereoisomer, or salt having a structure selected from the group consisting of:



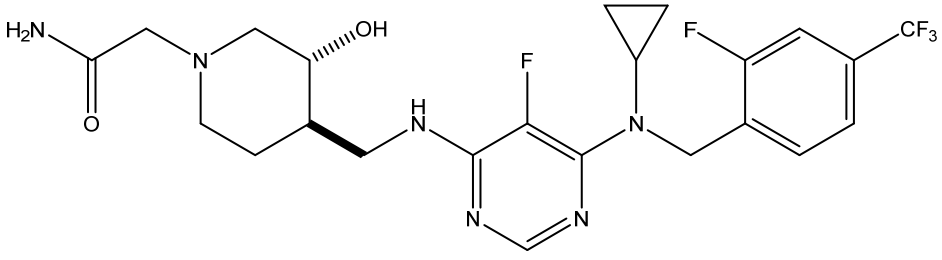
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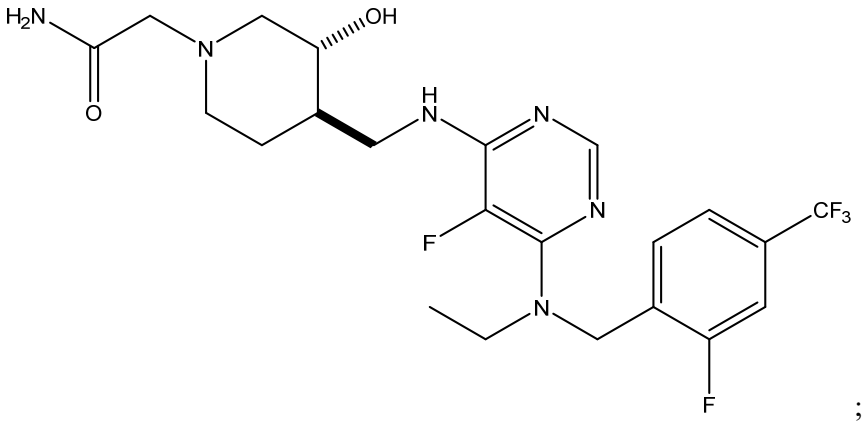
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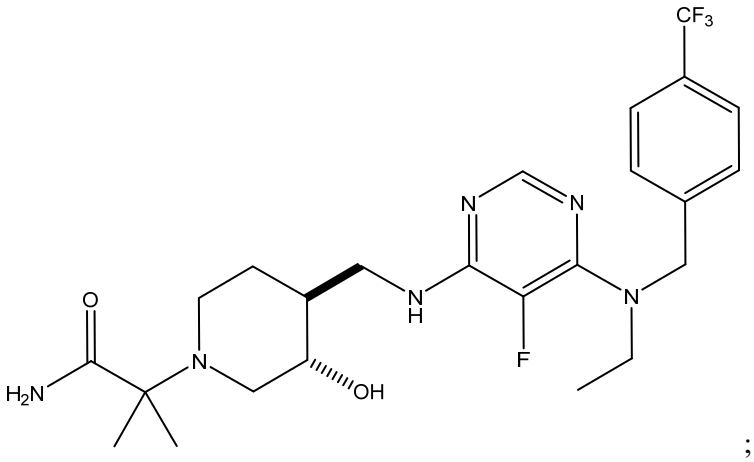
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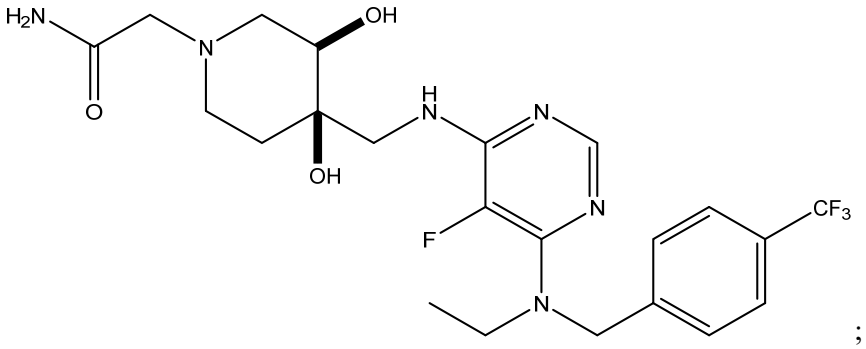
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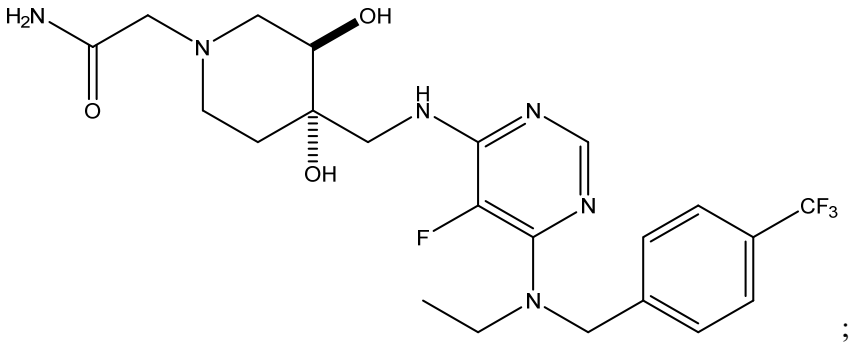
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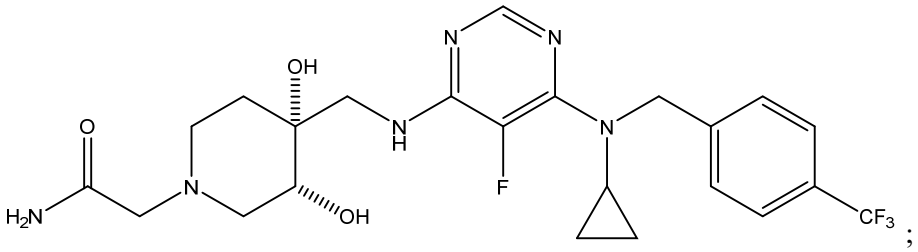


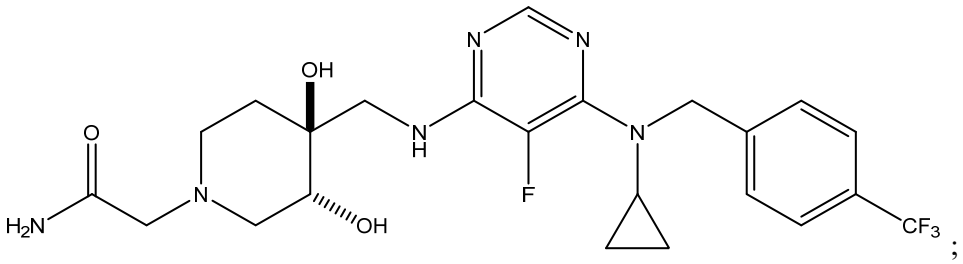
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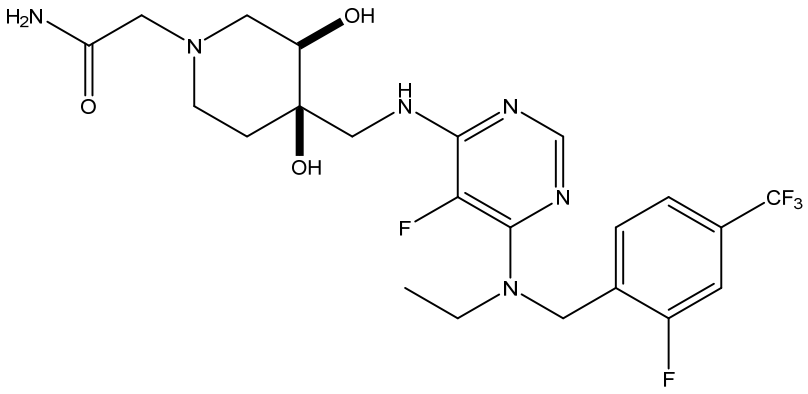


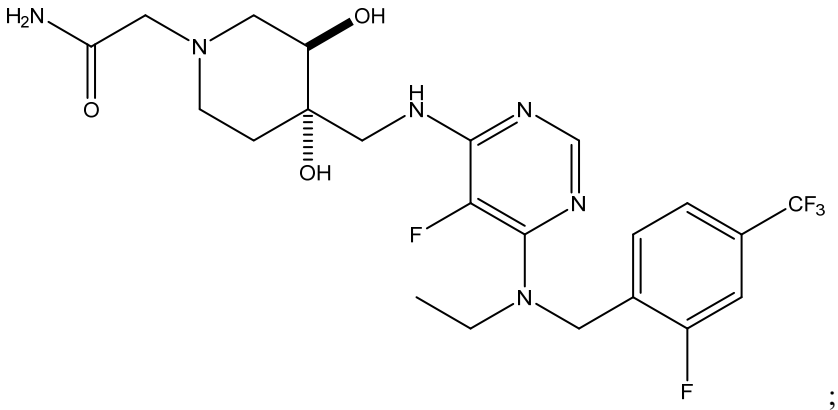
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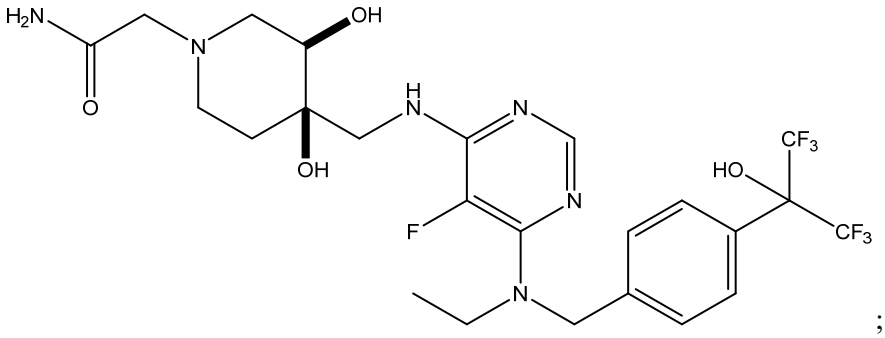

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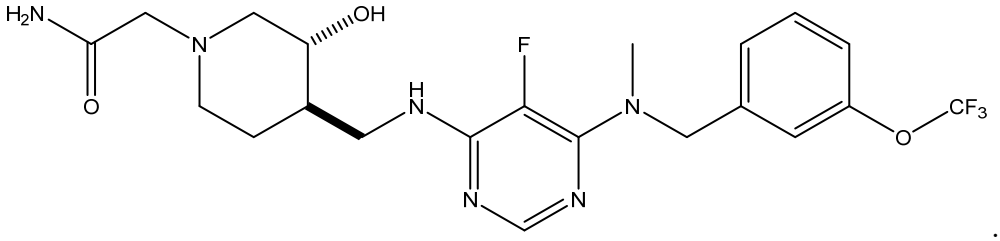


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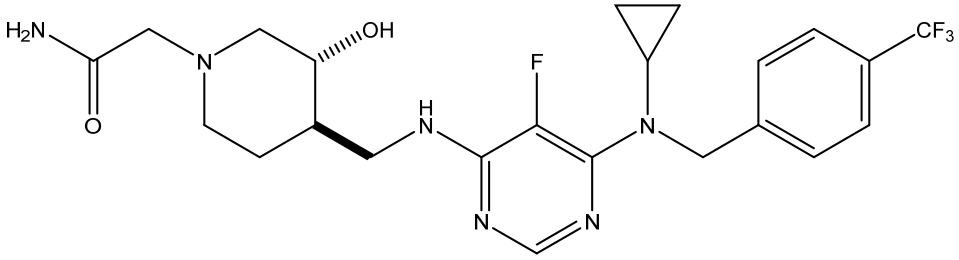
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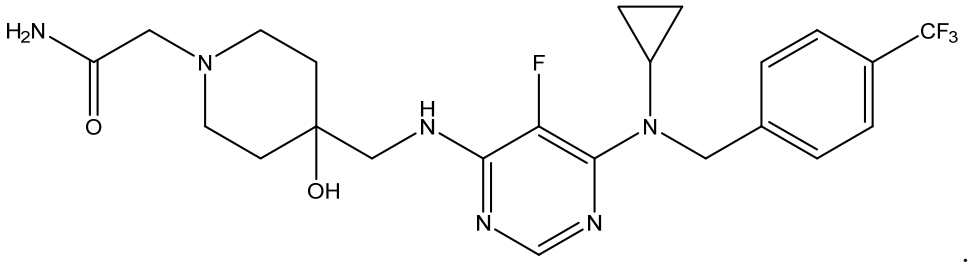
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2. The compound, stereoisomer, or salt according to claim 1, having a structure of:



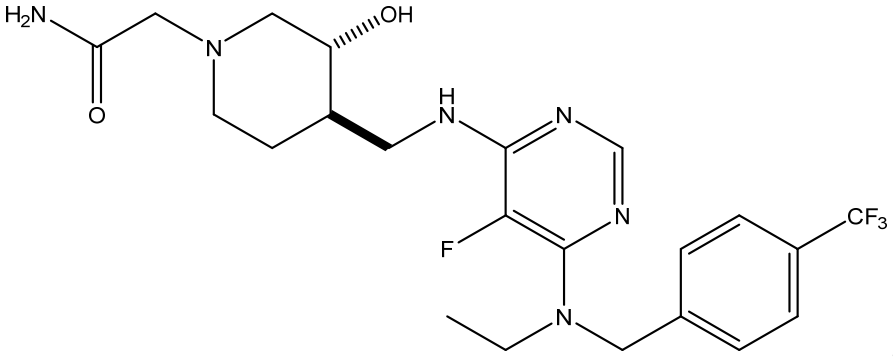
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3. The compound, stereoisomer, or salt according to claim 1, having a structure of:



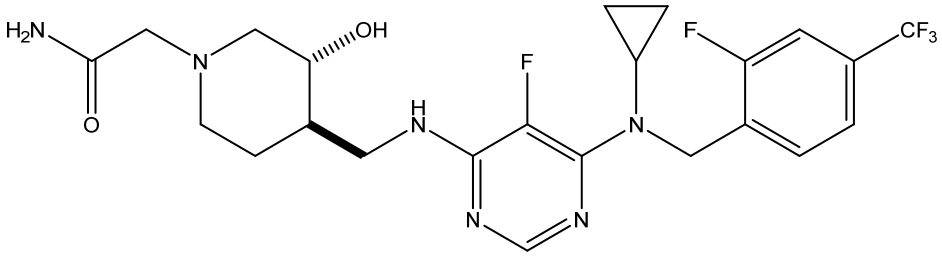
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4. The compound, stereoisomer, or salt according to claim 1, having a structure of:

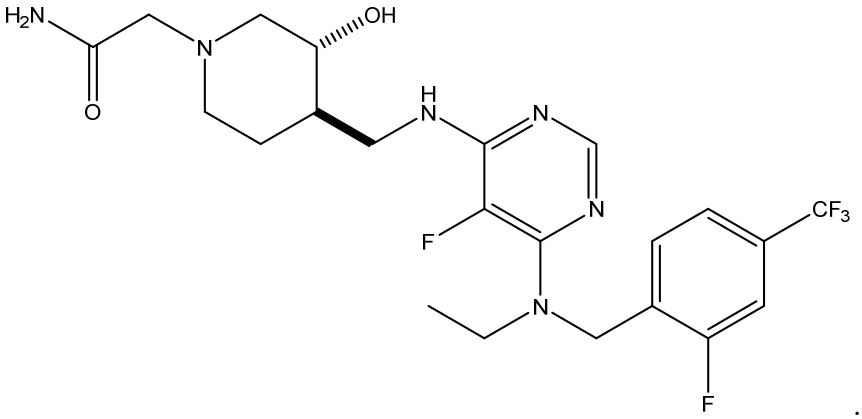


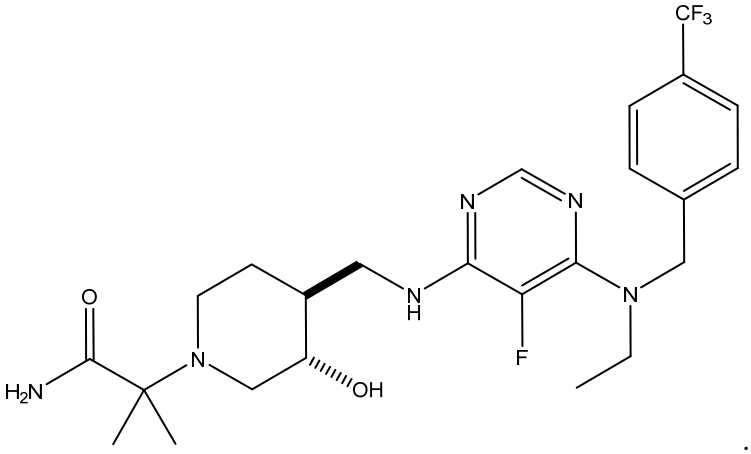
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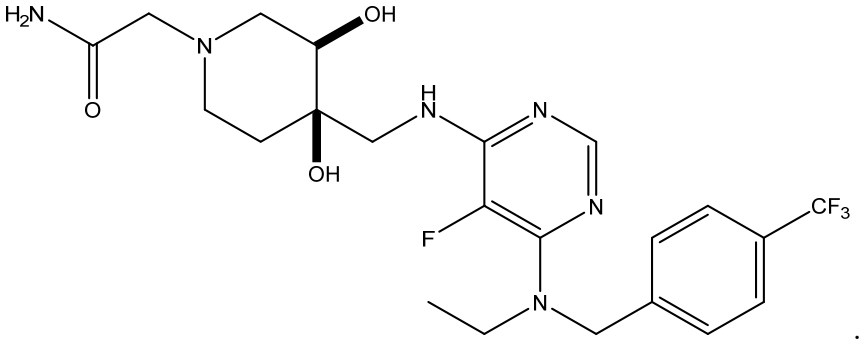
5. The compound, stereoisomer, or salt according to claim 1, having a structure of:

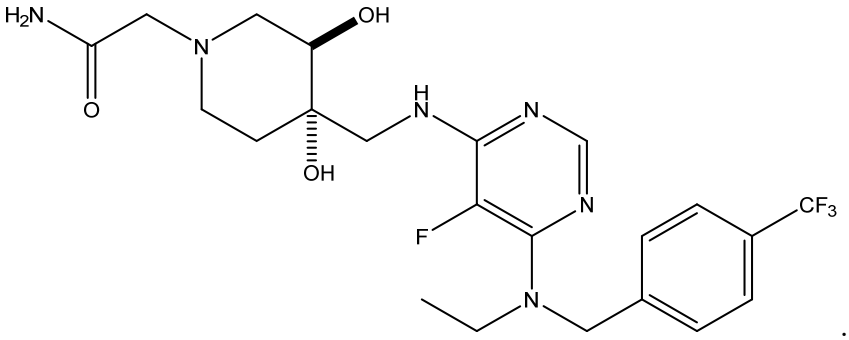


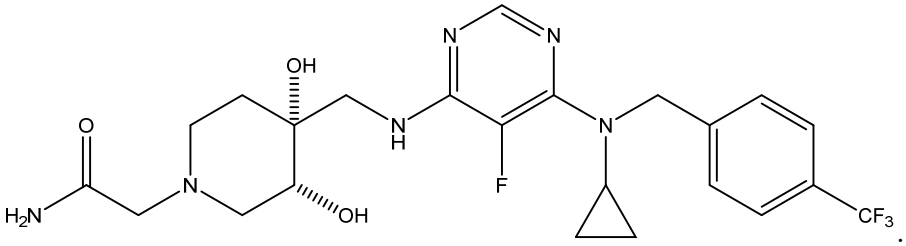
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6. The compound, stereoisomer, or salt according to claim 1, having a structure of: .

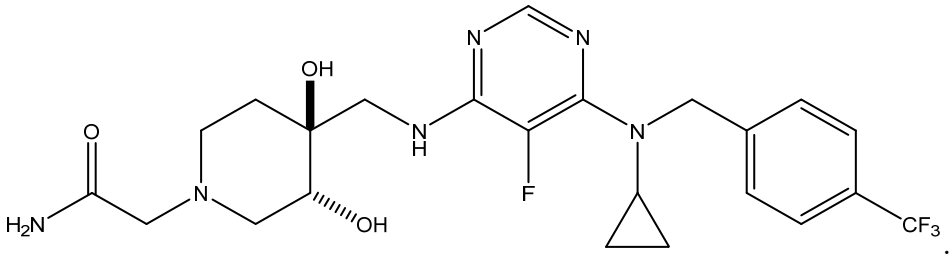
7. The compound, stereoisomer, or salt according to claim 1, having a structure of: .

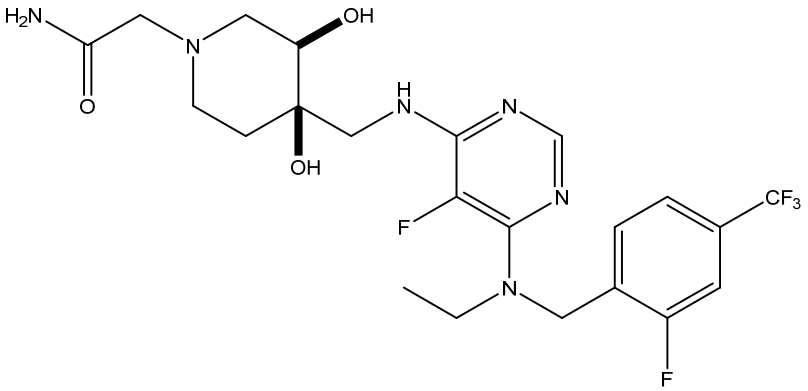
8. The compound, stereoisomer, or salt according to claim 1, having a structure of: .

9. The compound, stereoisomer, or salt according to claim 1, having a structure of: .

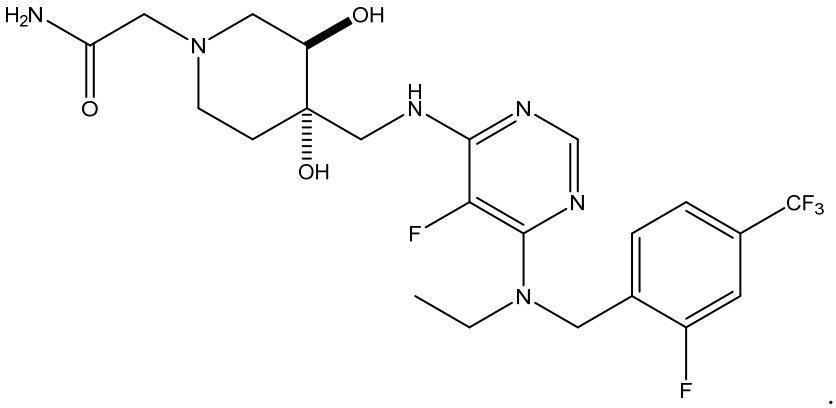
10. The compound, stereoisomer, or salt according to claim 1, having a structure of: .

11. The compound, stereoisomer, or salt according to claim 1, having a structure of:

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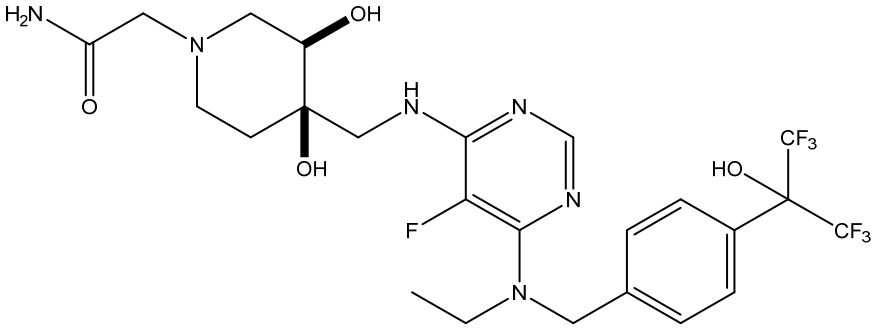
12. The compound, stereoisomer, or salt according to claim 1, having a structure of: .

13. The compound, stereoisomer, or salt according to claim 1, having a structure of:



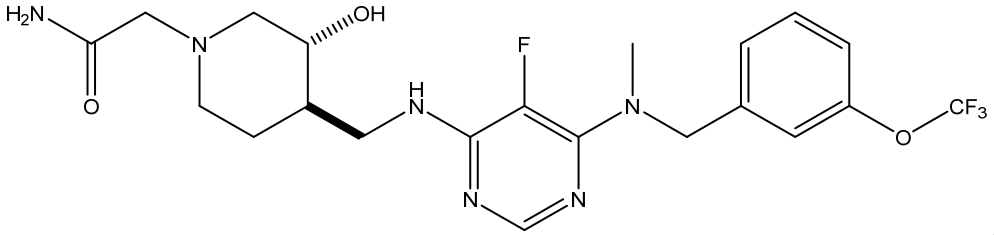
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14. The compound, stereoisomer, or salt according to claim 1, having a structure of:



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15. The compound, stereoisomer, or salt according to claim 1, having a structure of:



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16. A pharmaceutical composition comprising a compound, stereoisomer, or salt according to any one of claims 1-15 and at least one pharmaceutical acceptable excipient.

17. A compound, stereoisomer, or salt according to any one of claims 1-15 or a pharmaceutical composition according to claim 16, for use as a medicament.

18. Use of a compound, stereoisomer, or salt according to any one of claims 1-15 or a pharmaceutical composition according to claim 16, in the manufacture of a medicament for the treatment and/or prevention of an inflammatory, metabolic, oncologic or autoimmune disease.

19. The use according to claim 18, wherein the disease is selected from the group consisting of asthma, acne, chronic obstructive pulmonary disease (COPD), bronchitis, atherosclerosis, helicobacter pylori infection, allergic diseases including allergic rhinitis, allergic conjunctivitis and uveitis, sprue and food allergy, atopic dermatitis, cystic fibrosis, lung allograph rejection, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ichthyoses, bullous diseases, lichen planus, hidradenitis suppurativa, steatosis, steatohepatitis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), lupus erythematosus, Hashimoto's disease, pancreatitis, autoimmune diabetes, autoimmune ocular disease, ulcerative colitis, colitis, Crohn's disease, inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), Sjogren's syndrome, optic neuritis, type I diabetes, neuromyelitis optica, Myastehnia Gravis, Guillain-Barre syndrome, Graves' disease, scleritis, obesity, obesity-induced insulin resistance, type II diabetes, and cancer.

20. The use according to claim 18, wherein the disease is selected from the group consisting of acne, atopic dermatitis, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ichthyoses, bullous diseases, lichen planus, hidradenitis suppurativa, ulcerative colitis, colitis, Crohn’s disease, inflammatory bowel disease (IBD) and lupus erythematosus.