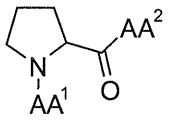
WO2009/000296 describes the use of TPP II inhibitors in the treatment of autoimmune and inflammatory diseases and transplant rejection.

WO2009/000297 discloses the use of TPP II inhibitors for use in combination with chemotherapy for the treatment of cancer.

WO2012/102832 describes the treatment of autism spectrum disorders using glycly-L-2-methylprolyl-L-glutamic acid.

Summary

In one aspect, the present invention refers to a tripeptide compound according to the general formula (1) as shown below or a solvate or hydrate thereof or a pharmaceutically acceptable salt thereof:



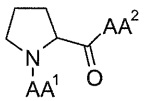
(1)

wherein AA^1 is selected from Lys, Orn, Nle, Phe, N^{α}-methyl-Phe, N^{α},N^{α}-dimethyl-Nle, N^{α},N^{α}-dimethyl-Phe, and N^{α},N^{α}-dimethyl-Lys; and AA^2 is selected from α-aminoisobutyric acid, *t*-butyl glycine, α-aminoisobutyric acid amide, N^{α}-methyl-Thr-OH, N^{α}-methyl-Thr-NH_2, and N^{α}-methyl-Val-OH.

In another aspect, the present invention refers to the tripeptide compound as disclosed herein for use as a medicament. In yet another aspect, the present invention refers to a medicament comprising at least one tripeptide compound as disclosed herein or a solvate or hydrate thereof or a pharmaceutically acceptable salt thereof.

The invention was based on the object to provide novel compounds which can be used as pharmaceutical active compounds, in particular for combating inflammation. Another object of the present invention is the provision of such compounds with increased stability and improved bioavailability being at the same time safe and secure for the patients.

These objects are achieved by the provision of tripeptides compounds (hereinafter also "compounds") according to the general formula (I) as shown below or a solvate or hydrate thereof or a pharmaceutically acceptable salt thereof:



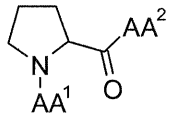
(1)

wherein: AA^1 is selected from α-amino acids, N^{α}-methyl amino acids and N^{α},N^{α}-dimethyl amino acids; and AA^2 is selected from α-aminoisobutyric acid (Aib), *t*-butyl glycine, α-aminoisobutyric acid amide, *t*-butyl glycine amide, N^{α}-methyl amino acids and N^{α}-methyl amino acid amides.

It has surprisingly been found out that these novel compounds of the invention can effectively be used as pharmaceutical active compounds in medicaments, in particular for treating inflammatory diseases, while they at the same time have an increased stability and improved

Claims

1. A tripeptide compound according to the general formula (1) as shown below or a solvate or hydrate thereof or a pharmaceutically acceptable salt thereof:



(1)

wherein:

AA^1 is selected from Lys, Orn, Nle, Phe, N^{α}-methyl-Phe, N^{α},N^{α}-dimethyl-Nle, N^{α},N^{α}-dimethyl-Phe, and N^{α},N^{α}-dimethyl-Lys; and

AA^2 is selected from α-aminoisobutyric acid, *t*-butyl glycine, α-aminoisobutyric acid amide, N^{α}-methyl-Thr-OH, N^{α}-methyl-Thr-NH_2, and N^{α}-methyl-Val-OH.

2. The tripeptide compound according to claim 1, wherein in general formula (1):

AA^1 is selected from Lys, Orn, Nle, Phe, N^{α}-methyl-Phe, N^{α},N^{α}-dimethyl-Nle, and N^{α},N^{α}-dimethyl-Phe; and

AA^2 is α-aminoisobutyric acid, *t*-butyl glycine, and α-aminoisobutyric acid amide.

3. The tripeptide compound according to claim 1 , selected from the group consisting of H-(L)-Lys-(D)-Pro-Aib-OH, H-(L)-Lys-(D)-Pro-N^{α}-methyl-(L)-Thr-OH, H-(L)-Lys-(L)-Pro-Aib-OH, H-(L)-Lys-(L)-Pro-(L)-*t*-butyl-Gly-OH, N^{α},N^{α}-dimethyl-(L)-Lys-(D)-Pro-N^{α}-methyl-(L)-Thr-OH, H-(L)-Lys-(L)-Pro-Aib-NH_2, H-(L)-Orn-(L)-Pro-Aib-OH, H-(L)-Nle-(L)-Pro-Aib-OH, H-(L)-Phe-(L)-Pro-Aib-OH, N^{α},N^{α}-dimethyl-(L)-Lys-(D)-Pro-N^{α}-methyl-(L)-Thr-NH_2, N^{α},N^{α}-dimethyl-(L)-Lys-(D)-Pro-N^{α}-methyl-(L)-Val-OH, N^{α},N^{α}-dimethyl-(L)-Nle-(D)-Pro-N^{α}-methyl-(L)-Thr-OH, N^{α}-methyl-(D)-Phe-(L)-Pro-Aib-OH, H-(D)-Phe-(L)-Pro-Aib-OH, N^{α},N^{α}-dimethyl-(L)-Phe-(L)-Pro-Aib-OH, N^{α},N^{α}-dimethyl-(L)-Nle-(L)-Pro-Aib-OH, or N^{α},N^{α}-dimethyl-(L)-Phe-(D)-Pro-N^{α}-methyl-(L)-Thr-OH or a solvate or hydrate thereof or a pharmaceutically acceptable salt thereof.

4. The tripeptide compound as claimed in one of the preceding claims for use as a medicament.

5. The tripeptide compound for use as a medicament as claimed in claim 4 for the therapeutic and/or prophylactic treatment of diseases chosen from the group comprising acute and chronic inflammatory diseases, acute and chronic pain, pruritus, hyponatremia, edema, ileus, tussis and glaucoma.

6. The tripeptide compound for use as a medicament as claimed in claim 5, wherein the inflammatory diseases are chosen from the group comprising cardiovascular inflammation, neurological inflammation, skeletal inflammation, skin inflammation, muscular inflammation, gastrointestinal inflammation, ocular inflammation, otic inflammation, inflammation due to insect bites and inflammation due to wound healing; atherosclerosis, ischemia, restenosis and vasculitis; asthma, Sjogren's syndrome, pulmonary inflammation, chronic airway inflammation and chronic obstructive pulmonary disease (COPD), allergy, psoriasis, psoriatic arthritis, eczema, scleroderma, atopic dermatitis and systemic lupus erythematosus, arthritis, synovitis, osteomyelitis, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis; septicemia and septic shock, diabetes, glucose intolerance, insulin resistance and obesity, colitis, ulcerative colitis, Crohn's disease, IBD and IBS, and the inflammatory diseases and conditions due to tumor proliferation, tumor metastasis or transplantation rejection.

7. The tripeptide compound for use as a medicament as claimed in claim 5 and/or claim 6, wherein the inflammatory diseases are chosen from the group comprising inflammatory diseases of the gastrointestinal tract, in particular inflammatory bowel diseases, such as Crohn's disease and/or colitis ulcerosa, acute or chronic inflammatory changes with inflammation of the gall bladder, inflammatory pseudopolyps, colitis cystica profunda, pneumatosis cystoides intestinales, pancreatitis, appendicitis, cardiovascular inflammation due to arthereosclerosis, ischemia, restenosis and/or vasculitis, sepsis, septicemia, allergies, asthma, Sjogren's syndrome, pulmonary inflammation, chronic airway inflammation, chronic obstructive pulmonary disease (COPD), tumor proliferation, tumor metastasis, transplant rejection, inflammatory diseases of the joints, such as rheumatoid arthritis, vulvovaginitis, and/or inflammatory diseases of the brain, skin, hair follicle, urogenital tract and of the eyes,

sinusitis, tenosynovitis, bursitis, tendonitis, lateral epicondylitis, adhesive capsulitis, osteomyelitis, osteoarthritic inflammation, ocular inflammation, otitic inflammation and/or autoimmune inflammation, psoriasis, psoriatic arthritis, contact dermatitis, atopic eczema, alopecia areata, scleroderma and other fibrotic diseases, systemic lupus erythematous, urticaria, lichen planus, lymphoma and/or allergic diseases or characterized by mast cell involvements.

8. A medicament comprising at least one tripeptide compound as claimed in one of claims 1 to 3 or a solvate or hydrate thereof or a pharmaceutically acceptable salt thereof.