5-[3-[PIPERAZIN-1-YL]-3-OXO-PROPYL]-IMIDAZOLIDINE-2,4-DIONE DERIVATIVES AS ADAMTS 4 AND 5 INHIBITORS FOR TREATING E.G. OSTEOARTHRITIS

FIELD OF THE INVENTION

[0001] The present invention relates to hydantoin compounds, and their use in the prophylaxis and/or treatment of inflammatory diseases, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In a particular aspect, the present compounds are ADAMTS inhibitors, particularly ADAMTS-5 and/or ADAMTS-6. The present invention also provides methods for the production of a compound of the invention, pharmaceutical compositions comprising a compound of the invention, methods for the prophylaxis and/or treatment of inflammatory diseases, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis by administering a compound of the invention.

BACKGROUND OF THE INVENTION

[0002] Cartilage is an avascular tissue of which chondrocytes are the main cellular component. One of the functional roles of cartilage in the joint is to allow bones to articulate on each other smoothly. Loss of articular cartilage, therefore, causes the bones to rub against each other leading to pain and loss of mobility, and is the hallmark of various diseases, among which rheumatoid arthritis and osteoarthritis are the most prominent.

[0003] The chondrocytes in normal articular cartilage occupy approximately 5% of the tissue volume, while the extra-cellular matrix makes up the remaining 95% of the tissue. The chondrocytes secrete the components of the matrix, mainly proteoglycans (including aggrecan) and collagens, which in turn supply the chondrocytes with an environment suitable for their survival under mechanical stress. Collagen type II, together with collagen type IX, is arranged in solid fibril-like structures, and provides cartilage with high mechanical strength properties, whereas aggrecan and other proteoglycans can absorb water and provide the resilient and shock-absorbing properties of the cartilage.

[0004] Under physiological conditions, cartilage homeostasis is maintained by a balance between the production (anabolism) and degradation (catabolism) of aggrecan and collagen. However, in OA and other joint disorders, this balance shifts toward catabolism. Loss of aggrecan occurs early in the onset of cartilage destruction, initially at the joint surface then spreading more deeply at more advanced stages (Pond and Nuki, 1973).

[0005] Osteoarthritis (also referred to as OA, or wear-and-tear arthritis) is the most common form of arthritis and is characterized by loss of articular cartilage, often associated with the subchondral bone re-modelling and pain. The disease mainly affects hands, spine and weight-bearing joints such as knees, and hips. During the disease process, the cartilage progressively deteriorates, which can be graded. At more advanced stages, the deeper layers of cartilage are affected, leading to calcification and exposure of the subchondral bone (Wieland et al., 2005).

[0006] The clinical manifestations of the development of the osteoarthritis condition include: increased volume of the joint, pain, crepitation and functional disability that lead to pain and reduced mobility of the joints. When disease further develops, pain at rest emerges. If the condition persists without correction and/or therapy, the joint is destroyed leading to disability.

[0007] Osteoarthritis is difficult to treat. At present, no cure is available and treatment focuses on relieving pain and preventing the affected joint from becoming deformed. Common treatments are currently limited to steroidal and non-steroidal anti-inflammatory drugs (NSAIDS), which provide symptomatic relief for pain and inflammation but do not arrest or slow down the progression of the disease (Mobasheri, 2013).

[0008] Therapeutic methods for the correction of the articular cartilage lesions that appear during the osteoarthritic disease have been developed, but so far none of them have been able to slow down the disease progression or to promote the regeneration of articular cartilage in situ and in vivo.

[0009] Although some dietary supplements as chondroitin and glucosamine sulfate have been advocated as safe and effective options for the treatment of osteoarthritis, a clinical trial revealed that both treatments did not reduce pain associated to osteoarthritis (Clegg et al., 2006).

[0010] In severe cases, joint replacement may be necessary. This is especially true for hips and knees. If a joint is extremely painful and cannot be replaced, it may be fused. This procedure stops the pain, but results in the permanent loss of joint function, making walking and bending difficult.

[0011] Another possible treatment is the transplantation of cultured autologous chondrocytes. Here chondral cellular material is taken from the patient, sent to a laboratory where it is expanded. The material is then implanted in the damaged tissues to cover the tissue's defects.

[0012] Yet another treatment includes the intra-articular instillation of Hylan G-F 20 (Synvisc, Hyalgan, Artz etc.), a substance that improves temporarily the rheology of the synovial fluid, producing an almost immediate sensation of free movement and a marked reduction of pain.

[0013] Other methods include application of tendinous, periosteal, facial, muscular or perichondral grafts; implantation of fibrin or cultured chondrocytes; implantation of synthetic matrices, such as collagen, carbon fiber; and administration of electromagnetic fields. All of these have reported minimal and incomplete effects, resulting in a poor quality tissue that can neither support the weighted load nor allow the restoration of an articular function with normal movement.

[0014] The ADAMTS family of secreted zinc metalloproteinases includes nineteen members that are known to bind and degrade extra cartilage matrix (ECM) components (Shiomi et al., 2010). Several members of the ADAMTS family have been found to cleave aggrecan, the major proteoglycan component of cartilage: ADAMTS-1, -4, -5, -8, -9, -15, -16 and -18. Since the expression and/or aggrecanase degrading activity of ADAMTS-1, -8, -9, -15, -16 and -18 are quite low, ADAMTS-4 (aggrecanase-1) and ADAMTS-5 (aggrecanase-2) are believed to be the two major functional aggrecanases (Tortorella and Malfait, 2008).

[0015] Although the role of ADAMTS-6 remains unclear, it has been recently associated with inguinal hernia (Jorgenson et al., 2015), vertebral disc degeneration diseases (Gruber et al., 2010), and Fabry disease (Shin et al., 2015).

[0016] ADAMTS-5 was identified in 1999 (Abbaszade et al., 1999). In 2005, two independent groups identified