Yamada, Y; Okubo, Y; and Narumi, S. 2009. Review of Diabetic Studies, 6(2): 81-84], myasthenia gravis (MG) [Pease, J.E and Horuk, R. 2009. Expert Opin Ther Patents, 19 (2): 199-221], multiple sclerosis (MS) and other neuroinflammatory diseases [Müller, M; Carter, M.J; Hofert, J; and Campbell, I.L. 2010. Neuropathology and Applied Neurobiology, 36:368-387.], lupus [Lacotte, S; Brun, S; Muller, S; and Dumortier, H. 2009. Autoimmunity: Ann N.Y. Acad. Sci. 1173:310-317.], rheumatoid arthritis (RA) [Brightling, C; Ammit, A.J; Kaur, D; Black, J.L; Wardlaw, A.J; Hughes, J.M; and Bradding, P. 2005. Am J Respir Crit Care Med. 171: 1103-1108.], lichen planus [Meller, S; Gillier, M; and Homey, B. 2009. J. Investigative Dermatology. 129: 315-319.].

Targeting CXCR3 appears a more straightforward way to treat the condition as this abrogates the effects of all three endogenous CXCR3 chemokines at the same time.

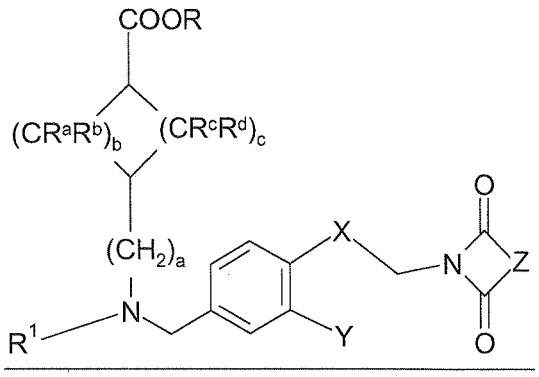
Assorted patent applications and granted patents disclose inhibitors of chemokines or CXCR3 receptor, such as WO2003087063, WO200604924, WO2009094168 and WO2009105435 but the known compounds are structurally very different from the compounds according to the present invention.

We aimed to prepare new CXCR3 receptor antagonist compounds, which have strong antagonistic effect and are selective to the CXCR3 receptor. We also aimed that the stability, bioavailability, metabolism, therapeutic index, toxicity and solubility of the new compounds allow their development into a drug substance. A further aim was that the compounds, due to their favourable enteric absorption, can be administered orally.

Thus, the inventors of the present invention have identified compounds represented by the following formula **1** possessing inhibitory activity against CXCR3 receptors.

SUMMARY

In a first aspect, there is provided a compound of formula **1**

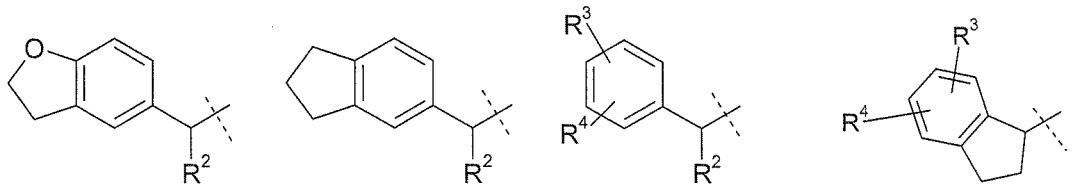


1

- wherein

R represents hydrogen or C_{1-4} alkyl group;

R^1 represents a group selected from the group consisting of



- wherein R^2 represents hydrogen or C_{1-4} alkyl group;

R^3 represents hydrogen, halogen, CF_3, CN or C_{1-4} alkyl; and

R^4 represents hydrogen, halogen or C_{1-4} alkyl;

a = 0, 1 or 2; b = 0, 1, 2 or 3, c = 1, 2 or 3, and

R^a, R^b, R^c and R^d represent independently from each other H or C_{1-4} alkyl;

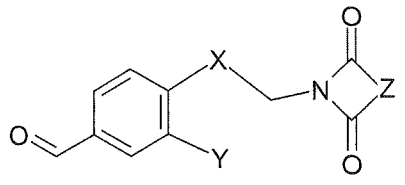
X represents a C_2 aliphatic hydrocarbon bridge optionally containing a double bond or a triple bond or a heteroatom selected from O and S, or –CH(CH_2)CH-;

Y represents hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} hydroxyalkyl;

Z represents a C_{1-4} aliphatic hydrocarbon bridge optionally containing one double bond, and/or one or more heteroatom selected from O, S, N and N(CH_3) or represents a C_{2-4} aliphatic hydrocarbon bridge fused with a C_{3-6} cycloalkyl ring optionally containing one or more double bond or with a phenyl ring or represents a C_{1-4} aliphatic hydrocarbon bridge substituted with a spiro C_{3-6} cycloalkyl ring optionally containing one or more double bond;

or a pharmaceutically acceptable salt or stereoisomer thereof or a pharmaceutically acceptable salt of the stereoisomer.

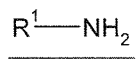
In a second aspect, there is provided a process for the preparation of a compound as disclosed herein or a pharmaceutically acceptable salt or stereoisomer thereof or a pharmaceutically acceptable salt of the stereoisomer, comprising the steps of reductive amination of a benzaldehyde of formula **4**



4

-wherein X, Y and Z have the meaning as defined herein

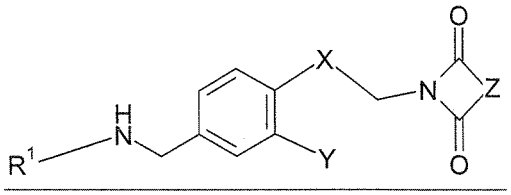
with a primary amine of formula **5**



5

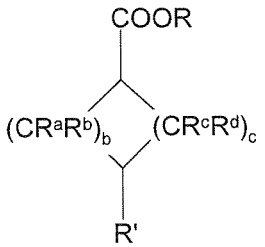
-wherein R^1 has the meaning as defined herein

reacting the obtained secondary amine of formula **2**



2

with a formyl- or oxocycloalkane carboxylic acid ester of formula **3**



3

-wherein R, R^a, R^b, R^c,R^d, b, and c have the meaning as defined herein and R' represents –CHO or =O -

and optionally hydrolyzing the obtained ester of formula **1**.

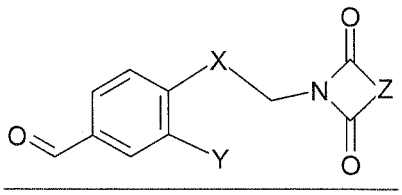
In a third aspect, there is provided a compound as disclosed herein or a pharmaceutically

acceptable salt or stereoisomer thereof or a pharmaceutically acceptable salt of the stereoisomer for use as a medicament.

In a fourth aspect, there is provided a compound as disclosed herein or a pharmaceutically acceptable salt or stereoisomer thereof or a pharmaceutically acceptable salt of the stereoisomer for use in the preventive and/or therapeutic treatment of a CXCR3 receptor mediated disease or disorder.

In a fifth aspect, there is provided pharmaceutical compositions containing at least one compound as disclosed herein or a pharmaceutically acceptable salt or stereoisomer thereof or a pharmaceutically acceptable salt of the stereoisomer and at least one pharmaceutically acceptable excipient.

In a sixth aspect, there is provided a compound of formula **4**,



4

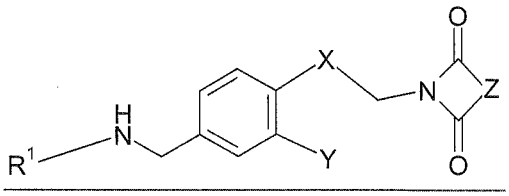
- wherein

X represents a C_2 aliphatic hydrocarbon bridge optionally containing a double bond or a triple bond or a heteroatom selected from O and S, or $-CH(CH_2)CH-$;

Y represents hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} hydroxyalkyl;

Z represents a C_{1-4} aliphatic hydrocarbon bridge optionally containing one double bond, and/or one or more heteroatom selected from O, S, N and $N(CH_3)$ or represents a C_{2-4} aliphatic hydrocarbon bridge fused with a C_{3-6} cycloalkyl ring optionally containing one or more double bond or with a phenyl ring or represents a C_{1-4} aliphatic hydrocarbon bridge substituted with a spiro C_{3-6} cycloalkyl ring optionally containing one or more double bond.

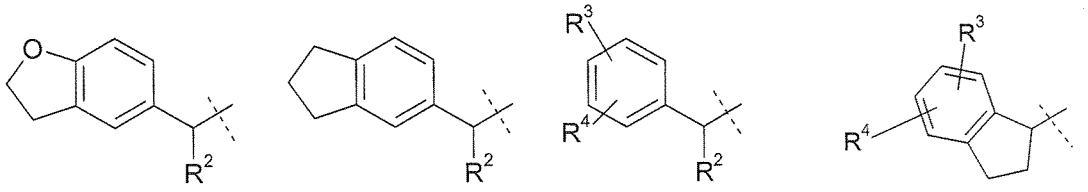
In a seventh aspect, there is provided a compound of formula **2**



2

- wherein

R^1 represents a group selected from the group consisting of



- wherein R^2 represents hydrogen or C_{1-4} alkyl group;

R^3 represents hydrogen, halogen, CF_3, CN or C_{1-4} alkyl; and

R^4 represents hydrogen, halogen or C_{1-4} alkyl;

X represents a C_2 aliphatic hydrocarbon bridge optionally containing a double bond or a triple bond or a heteroatom selected from O and S, or $-CH(CH_2)CH-$;

Y represents hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} hydroxyalkyl;

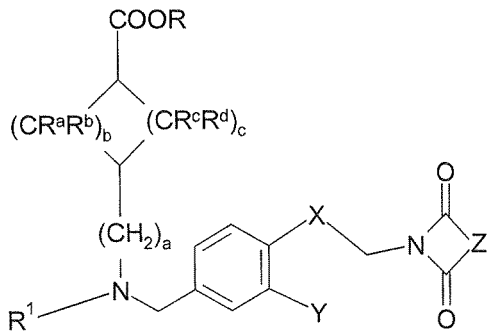
Z represents a C_{1-4} aliphatic hydrocarbon bridge optionally containing one double bond, and/or one or more heteroatom selected from O, S, N and $N(CH_3)$ or represents a C_{2-4} aliphatic hydrocarbon bridge fused with a C_{3-6} cycloalkyl ring optionally containing one or more double bond or with a phenyl ring or represents a C_{1-4} aliphatic hydrocarbon bridge substituted with a spiro C_{3-6} cycloalkyl ring optionally containing one or more double bond;

or a salt thereof.

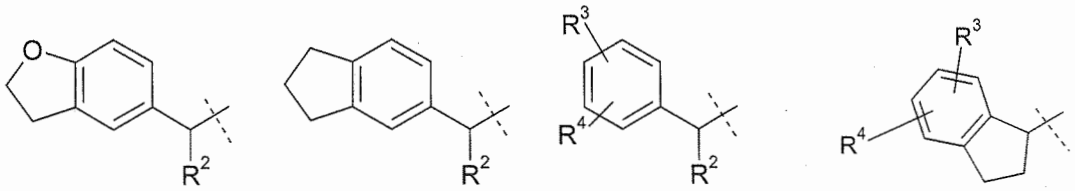
In an eight aspect, there is provided a use of one or more compounds as disclosed herein in the manufacture of a medicament for treating or preventing a CXCR3 receptor mediated disease or disorder.

DETAILED DESCRIPTION

The present invention thus provides a compound of formula **1**



1



- wherein R^2 represents hydrogen or C_{1-4} alkyl group;

R^3 represents hydrogen, halogen, CF_3, CN or C_{1-4} alkyl; and

R^4 represents hydrogen, halogen or C_{1-4} alkyl;

X represents a C_2 aliphatic hydrocarbon bridge optionally containing a double bond or a triple bond or a heteroatom selected from O and S, or $-CH(CH_2)CH-$;

Y represents hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} hydroxyalkyl;

Z represents a C_{1-4} aliphatic hydrocarbon bridge optionally containing one double bond, and/or one or more heteroatom selected from O, S, N and $N(CH_3)$ or represents a C_{2-4} aliphatic hydrocarbon bridge fused with a C_{3-6} cycloalkyl ring optionally containing one or more double bond or with a phenyl ring or represents a C_{1-4} aliphatic hydrocarbon bridge substituted with a spiro C_{3-6} cycloalkyl ring optionally containing one or more double bond;

or a salt thereof.

22. ~~Method of treating or preventing a CXCR3 receptor mediated disease or disorder comprising administering a pharmaceutically effective amount~~ Use of one or more compounds according to any of claims 1 to 13 ~~to a patient in need thereof~~ in the manufacture of a medicament for treating or preventing a CXCR3 receptor mediated disease or disorder.

23. ~~Method~~ The use according to claim 22 wherein the CXCR3 receptor mediated disease or is selected from the group consisting of COPD, psoriasis, graft/transplant rejection, ophthalmological disease, celiac disease, inflammatory bowel disease (IBD), type 1 diabetes, myasthenia gravis (MG), multiple sclerosis (MS) and other neuroinflammatory diseases, lupus, rheumatoid arthritis (RA) or lichen planus.