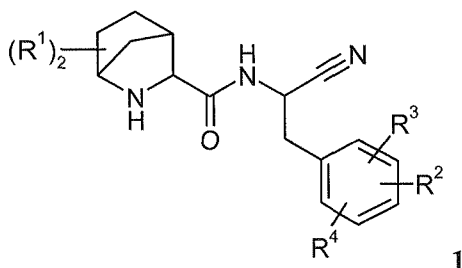


SUBSTITUTED 2-AZA-BICYCLO[2.2.1]HEPTANE-3-CARBOXYLIC ACID (BENZYL-CYANO-METHYL)-AMIDES INHIBITORS OF CATHEPSIN C

5 **FIELD OF INVENTION**

This invention relates to substituted 2-Aza-bicyclo[2.2.1]heptane-3-carboxylic acid (benzyl-cyano-methyl)-amides of formula **1**



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and their use as inhibitors of Cathepsin C, pharmaceutical compositions containing the same, and methods of using the same as agents for treatment and/or prevention of diseases connected with dipeptidyl peptidase I activity, e.g. respiratory diseases.

15 **BACKGROUND INFORMATION**

- WO2004110988 discloses peptidyl nitrile inhibitors as dipeptidyl-peptidase I (DPPI) inhibitors for the treatment of a series of diseases.
 - WO2009074829 and WO2010142985 also disclose peptidyl nitrile inhibitors as
- 20 dipeptidyl-peptidase I (DPPI) inhibitors for the treatment asthma, COPD or allergic rhinitis.

BRIEF SUMMARY OF THE INVENTION

- 25 Dipeptidyl-aminopeptidase I (DPPI or Cathepsin C; EC3.4.141), is a lysosomal cysteine protease capable of removing dipeptides from the amino terminus of protein substrates. DPPI was first discovered by Gutman and Fruton in 1948 (J. Biol. Chem 174: 851-858, 1948). The cDNA of the human enzyme has been described in 1995 (Paris et al.; FEBS Lett 369: 326-330, 1995). The DPPI protein is processed into a mature proteolytically active enzyme consisting of a heavy chain, a light
- 30 chain, and a propeptide that remains associated with the active enzyme (Wolters et al.; J. Biol. Chem. 273: 15514-15520, 1998). Whereas the other cysteine Cathepsins (e.g. B, H, K, L and S) are

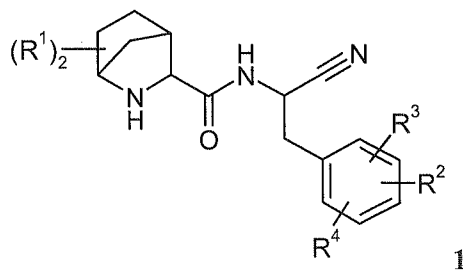
monomers, DPPI is a 200-kD tetramer with 4 identical subunits, each composed of the 3 different polypeptide chains. DPPI is constitutively expressed in many tissues with highest levels in lung, kidney, liver and spleen (Kominami et al.; Biol. Chem. Hoppe Seyler 373: 367-373, 1992).

Consistent with its role in the activation of serine proteases from hematopoietic cells, DPPI is also relatively highly expressed in neutrophils, cytotoxic lymphocytes, natural killer cells, alveolar macrophages and mast cells. Recent data from DPPI deficient mice suggest that, besides being an important enzyme in lysosomal protein degradation, DPPI also functions as the key enzyme in the activation of granule serine proteases in cytotoxic T lymphocytes and natural killer cells (granzymes A and B; Pham et al.; Proc. Nat. Acad. Sci 96: 8627-8632, 1999), mast cells (chymase and tryptase; Wolter et al.; J Biol. Chem. 276: 18551-18556, 2001), and neutrophils (Cathepsin G, elastase and proteinase 3; Adkison et al.; J Clin. Invest. 109: 363.371, 2002). Once activated, these proteases are capable of degrading various extracellular matrix components, which can lead to tissue damage and chronic inflammation.

Thus, inhibitors of Cathepsin C could potentially be useful therapeutics for the treatment of neutrophil-dominated inflammatory diseases such as chronic obstructive pulmonary disease (COPD), pulmonary emphysema, asthma, multiple sclerosis, and cystic fibrosis (Guay et al.; Curr. Topics Med. Chem. 10: 708-716, 2010; Laine and Busch-Petersen; Expert Opin. Ther. Patents 20: 497-506, 2010). Rheumatoid arthritis is also another chronic inflammatory disease where DPPI appears to play a role. Neutrophils are recruited to the site of joint inflammation and release Cathepsin G, elastase and proteinase 3, proteases which are believed to be responsible for cartilage destruction associated with rheumatoid arthritis. Indeed, DPPI deficient mice were protected against acute arthritis induced by passive transfer of monoclonal antibodies against type II collagen (Adkison et al.; J Clin. Invest. 109: 363.371, 2002).

In light of the role DPPI plays in activating certain pro-inflammatory serine proteases, it seems desirable to prepare compounds that inhibit its activity, which thereby inhibit downstream serine protease activity. It has been surprisingly found that the bicyclic compounds of the present invention possess potent Cathepsin C activity, high selectivity against other Cathepsins, e.g. Cathepsin K, and in general desirable pharmacokinetic properties.

In one aspect, there is provided a compound of formula 1



wherein

R^1 is independently selected from H, C_{1-6} -alkyl-, halogen, HO-, C_{1-6} -alkyl-O-, H_2N -,

5 C_{1-6} -alkyl-HN-, $(C_{1-6}$ -alkyl) $_2$ N- and C_{1-6} -alkyl-C(O)HN-;

or two R^1 are together C_{1-4} -alkylene;

R^2 is selected from

- $R^{2.1}$;
- aryl-; optionally substituted with one, two or three residues independently selected
10 from $R^{2.1}$; optionally substituted with one $R^{2.3}$;
- C_{5-10} -heteroaryl-; containing one, two, three or four heteroatoms independently selected
from S, S(O), S(O) $_2$, O and N, wherein carbon atoms of the ring are optionally and
independently from each other substituted with one, two or three $R^{2.1}$; wherein nitrogen
atoms of the ring are optionally and independently from each other substituted with
15 one, two or three $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with
one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$; and
- C_{5-10} -heterocycl-; containing one, two, three or four heteroatoms independently
selected from S, S(O), S(O) $_2$, O and N, wherein the ring is fully or partially saturated,
wherein carbon atoms of the ring are optionally and independently from each other
20 substituted with one, two or three or four $R^{2.1}$; wherein nitrogen atoms of the ring are
optionally and independently from each other substituted with one, two or three $R^{2.2}$;
wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a
nitrogen atom of the ring is optionally substituted with one $R^{2.4}$ or
- R^2 and R^4 are together with two adjacent carbon atoms of the phenyl a 5- or
25 6-membered aryl or heteroaryl, containing one, two or three heteroatoms independently
selected from S, S(O), S(O) $_2$, O and N, wherein carbon atoms of the ring are optionally
and independently from each other substituted with one, two or three $R^{2.1}$; wherein
nitrogen atoms of the ring are optionally and independently from each other substituted
with one, two or three $R^{2.2}$;

R^{2.1} is independently selected from H, halogen, NC-, O=, HO-, H-A-,

H-A-C₁₋₆-alkylene-, R^{2.1.1}-A-, C₁₋₆-alkyl-A-, C₃₋₈-cycloalkyl-A-, C₁₋₆-haloalkyl-A-,

R^{2.1.1}-C₁₋₆-alkylene-A-, C₁₋₆-alkyl-A-C₁₋₆-alkylene-,

C₃₋₈-cycloalkyl-A-C₁₋₆-alkylene-, C₁₋₆-haloalkyl-A-C₁₋₆-alkylene-,

R^{2.1.1}-C₁₋₆-alkylene-A-C₁₋₆-alkylene-, R^{2.1.1}-A-C₁₋₆-alkylene-, HO-C₁₋₆-alkylene-A-,

HO-C₁₋₆-alkylene-A-C₁₋₆-alkylene-, C₁₋₆-alkyl-O-C₁₋₆-alkylene-A- and

C₁₋₆-alkyl-O-C₁₋₆-alkylene-A-C₁₋₆-alkylene-

R^{2.1.1} is independently selected from

• aryl-; optionally substituted independently from each other with one,
two or three R^{2.1.1.1};

• C₅₋₁₀-heteroaryl-; containing one, two, three or four heteroatoms
independently selected from S, S(O), S(O)₂, O and N, wherein carbon
atoms of the ring are optionally and independently from each other
substituted with one, two or three R^{2.1.1.1}; wherein nitrogen atoms of the
ring are optionally and independently from each other substituted with
one, two or three R^{2.1.1.2}; and

• C₅₋₁₀-heterocyclyl-; containing one, two, three or four heteroatoms
independently selected from S, S(O), S(O)₂, O and N, wherein the ring
is fully or partially saturated, wherein carbon atoms of the ring are
optionally and independently from each other substituted with one, two
or three or four R^{2.1.1.1}; wherein nitrogen atoms of the ring are
optionally and independently from each other substituted with one, two
or three R^{2.1.1.2};

R^{2.1.1.1} is independently selected from halogen, HO-, O=, C₁₋₆-alkyl-,

C₁₋₆-alkyl-O-, C₁₋₆-haloalkyl-, C₁₋₆-haloalkyl-O- and

C₃₋₈-cycloalkyl-;

R^{2.1.1.2} is independently selected from O=, C₁₋₆-alkyl-, C₁₋₆-haloalkyl-;

C₃₋₈-cycloalkyl-, C₁₋₆-alkyl-O-C₁₋₆-alkyl-, H(O)C-,

C₁₋₆-alkyl-(O)C-, tetrahydrofuranylmethyl- and

tetrahydropyranylmethyl-;

R^{2.2} is independently selected from H-A-C₁₋₆-alkylene-, C₃₋₈-cycloalkyl-,

C₁₋₆-alkyl-A-C₁₋₆-alkylene-, C₃₋₈-cycloalkyl-A-C₁₋₆-alkylene-,

C₁₋₆-haloalkyl-A-C₁₋₆-alkylene-, R^{2.1.1}-A-C₁₋₆-alkylene-, C₁₋₆-alkyl-S(O)₂- and

C₁₋₆-alkyl-C(O)-, R^{2.1.1}-A-;

$R^{2,3}$ and R^4 are together selected

from -O-, -S-, -N($R^{2,3,1}$)-, -C(O)N($R^{2,3,1}$)-, -N($R^{2,3,1}$)C(O)-, -S(O)₂N($R^{2,3,1}$)-, -N($R^{2,3,1}$)S(O)₂-
 , -C(O)O-, -OC(O)-, -C(O)-, -S(O)-, -S(O)₂-, $R^{2,3}$,
 $R^{2,3}$, -C($R^{2,3,2}$)=C($R^{2,3,2}$)-, -C=N-, -N=C-, -C($R^{2,3,2}$)₂-O-, -O-C($R^{2,3,2}$)₂-, -C($R^{2,3,2}$)₂N($R^{2,3,1}$)-,
 5 and -N($R^{2,3,1}$)C($R^{2,3,2}$)₂- and -C₁₋₄-alkylene-;

$R^{2,3,1}$ is independently selected from H, C₁₋₆-alkyl-, C₁₋₆-haloalkyl-;
 C₃₋₈-cycloalkyl-, HO-C₁₋₄-alkylene-, (C₁₋₄-alkyl)-O-C₁₋₄-alkylene-,
 H₂N-C₁₋₄-alkylene-, (C₁₋₄-alkyl)HN-C₁₋₄-alkylene- and
 (C₁₋₄-alkyl)₂N-C₁₋₄-alkylene-;

10 $R^{2,3,2}$ is independently selected from H, C₁₋₆-alkyl-, C₁₋₆-haloalkyl-;
 C₃₋₈-cycloalkyl-, HO-C₁₋₄-alkylene-, (C₁₋₄-alkyl)-O-C₁₋₄-alkylene-,
 H₂N-C₁₋₄-alkylene-, (C₁₋₄-alkyl)HN-C₁₋₄-alkylene- and
 (C₁₋₄-alkyl)₂N-C₁₋₄-alkylene-;

$R^{2,4}$ and R^4 are together selected

15 from -N($R^{2,4,1}$)-, -C(O)N($R^{2,4,1}$)-, -N($R^{2,4,1}$)C(O)-, -S(O)₂N($R^{2,4,1}$)-, -N($R^{2,4,1}$)S(O)₂-, -C(O)-,
 -S(O)-, -S(O)₂-, -C($R^{2,4,2}$)=C($R^{2,4,2}$)-, -C=N-, -N=C-, -C($R^{2,4,2}$)₂N($R^{2,4,1}$)- and -N($R^{2,4,1}$)C($R^{2,4,2}$)₂-, -C₁₋₄-alkylene-; and

$R^{2,4,1}$ is independently selected from H, C₁₋₆-alkyl-, C₁₋₆-haloalkyl-;
 C₃₋₈-cycloalkyl-, HO-C₁₋₄-alkylene-, (C₁₋₄-alkyl)-O-C₁₋₄-alkylene-,
 20 H₂N-C₁₋₄-alkylene-, (C₁₋₄-alkyl)HN-C₁₋₄-alkylene- and
 (C₁₋₄-alkyl)₂N-C₁₋₄-alkylene-;

$R^{2,4,2}$ is independently selected from H, C₁₋₆-alkyl-, C₁₋₆-haloalkyl-;
 C₃₋₈-cycloalkyl-, HO-C₁₋₄-alkylene-, (C₁₋₄-alkyl)-O-C₁₋₄-alkylene-,
 H₂N-C₁₋₄-alkylene-, (C₁₋₄-alkyl)HN-C₁₋₄-alkylene- and
 25 (C₁₋₄-alkyl)₂N-C₁₋₄-alkylene-;

$R^{2,5}$ and R^4 are together selected from -C($R^{2,5,1}$)=, =C($R^{2,5,1}$)-, -N=; and

$R^{2,5,1}$ is independently selected from H, C₁₋₆-alkyl-, C₁₋₆-haloalkyl-;
 C₃₋₈-cycloalkyl-, HO-C₁₋₄-alkylene-, (C₁₋₄-alkyl)-O-C₁₋₄-alkylene-,
 H₂N-C₁₋₄-alkylene-, (C₁₋₄-alkyl)HN-C₁₋₄-alkylene- and
 30 (C₁₋₄-alkyl)₂N-C₁₋₄-alkylene-;

R^3 is H or F;

R^4 is independently selected from F, Cl, phenyl-H₂C-O-, HO-, C₁₋₆-alkyl-, C₁₋₆-haloalkyl-,
 C₃₋₈-cycloalkyl-, C₁₋₆-alkyl-O-, C₁₋₆-haloalkyl-O-, C₁₋₆-alkyl-HN-, (C₁₋₆-alkyl)₂-HN-,
 C₁₋₆-alkyl-HN-C₁₋₄-alkylene- and (C₁₋₆-alkyl)₂-HN-C₁₋₄-alkylene-;

A is a bond or independently selected

from -O-, -S-, -N(R⁵)-, -C(O)N(R⁵)-, -N(R⁵)C(O)-, -S(O)₂N(R⁵)-, -N(R⁵)S(O)₂-, -S(O)(=N
R⁵)-N(R⁵)-, -N(R⁵)(NR⁵=)

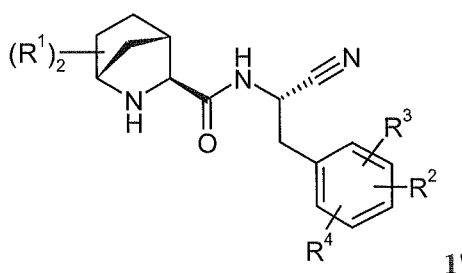
S(O)-, -S(=NR⁵)₂-N(R⁵)-, -N(R⁵)(NR⁵=)₂S-, -C(R⁵)=C(R⁵)-, -C≡C-,

5 , -C(O)O-, -OC(O)-, -C(O)-, -S(O)-, -S(O)₂-, -S(=NR⁵)-, -S(O)(=NR⁵)-, -S(=NR⁵)₂-, -(R⁵)(
O)S=N-, -(R⁵N=)(O)S-, and -N=O)(R⁵)S-;

R⁵ is independently selected from H, C₁₋₆-alkyl- and NC-;

or a salt thereof.

In another aspect, there is provided a compound of formula 1'



wherein R¹, R², R³ and R⁴ have the meaning as defined herein.

In another aspect, there is provided a compound of formula 1 as defined herein for use as a
medicament.

15 In another aspect, there is provided a compound as defined herein for use as a medicament for the
treatment of asthma and allergic diseases, gastrointestinal inflammatory diseases, eosinophilic
diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes, rheumatoid
arthritis and atherosclerosis.

In another aspect, there is provided pharmaceutical composition, characterised in that it contains
20 one or more compounds of formula 1 as defined herein or a pharmaceutically active salt thereof.

In another aspect, there is provided the use of a compound of formula 1 as defined herein in the
manufacture of a medicament for the treatment or prevention of diseases in which DPPI activity
inhibitors have a therapeutic benefit.

In another aspect, there is provided a pharmaceutical composition comprising additionally to a
25 compound of formula 1, as defined herein, a pharmaceutically active compound selected from the
group consisting of betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors,
LTD4-antagonists, EGFR-inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor
antagonists, CCR9 antagonists and SYK-inhibitors, NE-inhibitors, MMP9 inhibitors, MMP12
inhibitors, but also combinations of two or three active substances.

DETAILED DESCRIPTION OF THE INVENTION

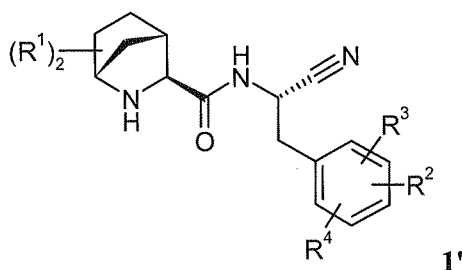
A compound of formula 1

wherein the N-atom is optionally substituted with $-R^{2.2}$, wherein

- $R^{2.2}$ is independently selected from H-A- C_{1-6} -alkylene-, C_{3-8} -cycloalkyl-,
 C_{1-6} -alkyl-A- C_{1-6} -alkylene-, C_{3-8} -cycloalkyl-A- C_{1-6} -alkylene-,
 5 C_{1-6} -haloalkyl-A- C_{1-6} -alkylene-, $R^{2.1.1}$ -A- C_{1-6} -alkylene-, C_{1-6} -alkyl-S(O)₂-,
 C_{1-6} -alkyl-C(O)- and $R^{2.1.1}$ -A-;

or a salt thereof.

- 10 **14.** A compound of formula **1'**



wherein R^1 , R^2 , R^3 and R^4 have the meaning of one of the claims 1 to 12.

- 15 **15.** A compound of formula **1** according to any one claims 1 to 13 for use as a medicament.

- 16.** A compound of formula **1** according to any one claims 1 to 13 for use as a medicament for the treatment of asthma and allergic diseases, gastrointestinal inflammatory diseases, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes, rheumatoid
 20 arthritis and atherosclerosis.

- 17.** Pharmaceutical composition, characterised in that it contains one or more compounds of formula **1** according to any one of claims 1 to 13 or a pharmaceutically active salt thereof.

- 25 **18.** Use of a compound of formula **1** according to one of claims 1-13 in the manufacture of a medicament for the Method of treatment or prevention of diseases in which DPPI activity inhibitors have a therapeutic benefit, which method comprises administration of a therapeutically or preventively effective amount of a compounds of formula **1** according to one of claims 1-13 to a patient in need thereof.