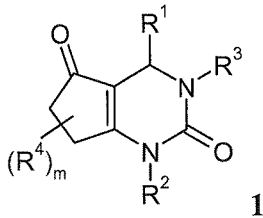
- For a review on various inhibitors of neutrophil elastase see: P. Sjö (*Future Med. Chem.* **2012**, *4*, 651-660).

BRIEF SUMMARY

Neutrophil elastase (NE) is a 29 kDa serine protease. It is expressed in bone marrow precursor cells, stored in the granula of peripheral blood granulocytes at high concentrations and it is released upon cellular activation. To the substrates of NE belong major elements of the extracellular matrix: elastin, fibronectin, laminin, collagen and proteoglycans. Neutrophil elastase activity leads to ECM degradation, increases migration and chemotaxis of monocytes and vascular smooth muscle cells and directly affects components of the coagulation and fibrinolytic pathways (PAI-1 and TFPI). Increased activity of neutrophil elastase is associated with chronic inflammatory and fibrotic diseases of several organs. Inhibitors of neutrophil elastase will therefore have an important role for the treatment of different diseases like COPD, idiopathic pulmonary fibrosis and other fibrotic diseases, cancer, acute lung injury, acute respiratory distress syndrome, bronchiectasis, cystic fibrosis, alpha1-antitrypsin deficiency and others.

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



1

wherein

R^1 is phenyl or a five- or six-membered heteroaryl, containing ~~wherein~~ one, two or three elements ~~are replaced by an element independently~~ selected from ~~the group consisting of~~ N, O or S; each ring optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, O_2N-, NC-, H_2N-, HO-, $R^{1.1}$, $R^{1.1}O$-, $R^{1.2}$, $R^{1.3}S$-, $R^{1.3}(O)S$- and $R^{1.3}(O)_2S$-;

$R^{1.1}$ is independently selected from the group consisting of C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl- and C_{3-6}-halocycloalkyl;

$R^{1.2}$ is HO-C_{1-6}-alkyl- or $R^{1.1}$-O-C_{1-6}-alkyl-;

$R^{1.3}$ is independently selected from the group consisting of H, HO-, $R^{1.1}$ and $R^{1.2}$;

R^2 is phenyl or a five- or six-membered heteroaryl, containing ~~wherein~~ one or two elements ~~are replaced by an element independently~~ selected from ~~the group consisting of~~ N, O or S; each ring optionally substituted with a substituent independently selected from the group consisting of halogen, C_{1-4}-alkyl-, C_{1-4}-haloalkyl- and C_{1-4}-alkyl-O-;

R^3 is a residue independently selected from the group consisting of

- $R^{3.1}$-;
- $R^{3.2}(O)C$-;
- $R^{3.2}O(O)C$-;
- $R^{3.2}O(O)C$-A-;
- $R^{3.2}S$-; $R^{3.2}(O)S$-; $R^{3.2}(O)_2S$-;
- $(R^{3.2})_2N(O)C$ and
- $(R^{3.2})_2N(O)C$-A-;

$R^{3.1}$ is independently selected from the group consisting of H, $R^{3.3}$, $R^{3.4}$, C_{1-6}-alkyl-C_{3-6}-cycloalkyl- and C_{3-6}-cycloalkyl-C_{1-6}-alkyl-, each optionally substituted with one or two substituents independently selected from $R^{3.1.1}$-;

$R^{3.1.1}$ is selected from the group consisting of HO-, halogen, NC-, $R^{3.3}O$-, $R^{3.5}$, $R^{3.6}$and $R^{3.7}$ or

$R^{3.1.1}$ denotes a ring independently selected from phenyl and a four-membered heterocyclic ring containing one element independently selected from among N, O, S, S(O) and $S(O)_2$;

$R^{3.1.1}$ denotes a five- or six-membered heterocyclic or heteroaryl ring containing one, two or three elements independently selected from among N, O, S, S(O) and $S(O)_2$;

each of the rings optionally substituted with one or two substituents independently selected from among HO-, O=, halogen, NC-, $R^{3.3}$, $R^{3.3}O$-, $R^{3.3}$-(O)C-, $R^{3.4}$, $R^{3.5}$, $R^{3.6}$ and $R^{3.7}$ or two substituents are together $R^{3.8}$;

$R^{3.2}$ is independently selected from among $R^{3.1}$, phenyl and a five- or six-membered heterocyclic or heteroaryl ring containing one, two or three elements

or a salt thereof.

In another aspect, there is provided a compound according to the present disclosure for use as a medicament.

~~In another aspect, there is provided a compound according to the present disclosure 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 and rheumatoid arthritis.~~

In another aspect, there is provided a pharmaceutical composition, characterised in that it contains one or more compounds of formula **1** according to the present disclosure or a pharmaceutically active salt thereof.

In another aspect, there is provided use of a compound of formula **1** according to the present disclosure in the manufacture of a medicament for the treatment or prevention of a diseases in which neutrophil elastase inhibitors have a therapeutic benefit, wherein said disease is selected from the group consisting of asthma and allergic diseases, gastrointestinal inflammatory diseases, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes and rheumatoid arthritis..

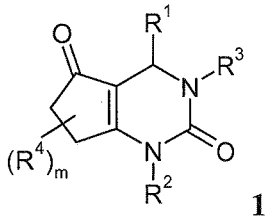
In another aspect, there is provided a pharmaceutical composition comprising additionally to a compound of formula **1**, according the present disclosure, a pharmaceutically active compound selected from the group consisting of betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, Cathepsin C inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor antagonists and SYK-inhibitors, but also combinations of two or three active substances.

The compounds according to the present disclosure, including the physiologically acceptable salts, are effective as inhibitors of neutrophil elastase and exhibit favourable inhibitory potency, as determined by the half maximal inhibitory concentration (IC_{50}), in an enzymatic inhibition assay.

Some compounds according to the present disclosure, including the physiologically acceptable salts, are additionally effective as inhibitors of neutrophil serin

WHAT WE CLAIM

1. A compound of formula 1



1

wherein

R^1 is phenyl or a five- or six-membered heteroaryl, ~~wherein~~ containing one, two or three elements ~~are replaced by an element independently~~ selected from ~~the group consisting of~~ N, O or S; each ring optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, O_2N-, NC-, H_2N-, HO-, $R^{1.1}$, $R^{1.1}O$-, $R^{1.2}$, $R^{1.3}S$-, $R^{1.3}(O)S$- and $R^{1.3}(O)_2S$-;

$R^{1.1}$ is independently selected from the group consisting of C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl- and C_{3-6}-halocycloalkyl;

$R^{1.2}$ is HO-C_{1-6}-alkyl- or $R^{1.1}$-O-C_{1-6}-alkyl-;

$R^{1.3}$ is independently selected from the group consisting of H, HO-, $R^{1.1}$ and $R^{1.2}$;

R^2 is phenyl or a five- or six-membered heteroaryl, ~~wherein~~ containing one or two elements ~~are replaced by an element independently~~ selected from ~~the group consisting of~~ N, O or S; each ring optionally substituted with a substituent independently selected from the group consisting of halogen, C_{1-4}-alkyl-, C_{1-4}-haloalkyl- and C_{1-4}-alkyl-O-;

R^3 is a residue independently selected from the group consisting of

- $R^{3.1}$-;
- $R^{3.2}(O)C$-;
- $R^{3.2}O(O)C$-;
- $R^{3.2}O(O)C$-A-;
- $R^{3.2}S$-; $R^{3.2}(O)S$-; $R^{3.2}(O)_2S$-;

2. A compound of formula **1**, according to claim 1, wherein R^1 is $R^{1.c}$ and $R^{1.c}$ is phenyl or pyridinyl; each ring optionally substituted by one, two or three residues independently selected from the group consisting of F, Cl, Br-, ,NC-, $R^{1.1}$, $R^{1.3}(O)S$- and $R^{1.3}(O)_2S$-;

$R^{1.1}$ is independently selected from the group consisting of C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl- and C_{3-6}-halocycloalkyl;

$R^{1.2}$ is HO-C_{1-6}-alkyl- or $R^{1.1}$-O-C_{1-6}-alkyl-;

$R^{1.3}$ is independently selected from the group consisting of H, HO-, $R^{1.1}$ and $R^{1.2}$;

or a salt thereof.

3. A compound of formula **1**, according to claim1, wherein R^1 is $R^{1.e}$ and $R^{1.e}$ is phenyl or pyridinyl; each ring optionally substituted by one or two residues independently selected from the group consisting of NC-, Me(O)S-, $Me(O)_2S$ and $Et(O)_2S$; or a salt thereof.

4. A compound of formula **1**, according to one of the claims 1 to 3, wherein R^2 is $R^{2.b}$ and $R^{2.b}$ is phenyl or a six-membered heteroaryl; wherein one or two elements are ~~replaced by~~ N; each ring optionally substituted with a substituent independently selected from the group consisting of halogen, C_{1-4}-alkyl- and C_{1-4}-haloalkyl-; or a salt thereof.

5. A compound of formula **1**, according to one of the claims 1 to 3, wherein R^2 is $R^{2.f}$ and $R^{2.f}$ is pyridinyl, optionally substituted with a substituent independently selected from the group consisting of F_3C- and F_2HC-, or a salt thereof.

6. A compound of formula **1**, according to one of the claims 1 to 5, wherein A is A^b and A^b is -CH_2-, optionally substituted with one or two substituents independently selected from the group consisting of F, Me, Et, i-Pr, MeO, EtO, $HOCH_2O$- and $MeOCH_2$-; or a salt thereof.

7. A compound of formula **1**, according to one of the claims 1 to 6, wherein R^4 is $R^{4.a}$ and $R^{4.a}$ is selected from the group consisting of halogen, C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl- and C_{3-6}-halocycloalkyl; or a salt thereof.

or a salt thereof.

12. A compound of formula **1** according to any one claims 1 to 11 for use as a medicament.

~~13. A compound of formula 1 according to any one claims 1 to 11 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 and rheumatoid arthritis.~~

~~14~~13. Pharmaceutical composition, characterised in that it contains one or more compounds of formula **1** according to any one of claims 1 to 11 or a pharmaceutically active salt thereof.

~~15~~14. Use of a compound of formula **1** according to one of claims 1 to 11 in the manufacture of a medicament for the treatment or prevention of a diseases in which neutrophil elastase inhibitors have a therapeutic benefit, wherein said disease is selected from the group consisting of asthma and allergic diseases, gastrointestinal inflammatory diseases, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes and rheumatoid arthritis.

~~16~~15. A pharmaceutical composition comprising additionally to a compound of formula **1**, according to any one of claims 1 to 11, a pharmaceutically active compound selected from the group consisting of betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, Cathepsin C inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor antagonists and SYK-inhibitors, but also combinations of two or three active substances.