- 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 (ECM): 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. The potential of neutrophil elastase inhibitors as anti-inflammatory therapies has been reviewed by P. A. Henriksen in *Current Opinion in Hematology* **2014**, *21*, 23-28. 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.

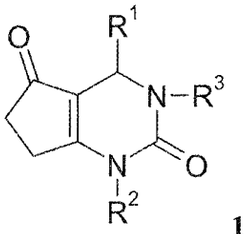
The problem of the present disclosure is to prepare new compounds which on the basis of their pharmaceutical effectiveness as inhibitors of neutrophil elastase activity, may be used therapeutically, that is for the treatment of pathophysiological processes caused by increased activity of neutrophil elastase.

It has surprisingly been found that the compounds of the present disclosure have the following properties which are advantageous in view of the indications of the current disclosure.

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.

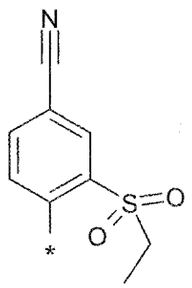
In one aspect, there is provided compound of formula **1**



1

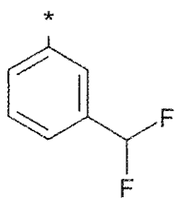
wherein

R^1 is



,

R^2 is

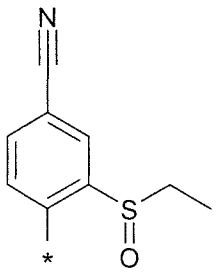


,

and R^3 is H;

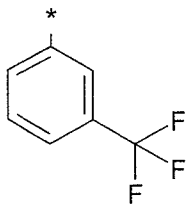
or

R^1 is



,

R^2 is

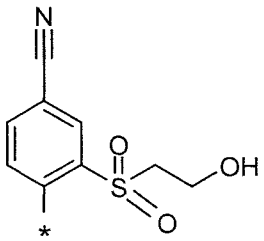


;

and R^3 is CH_3;

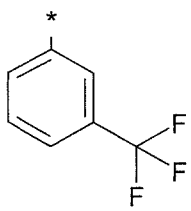
or

R^1 is



,

R^2 is



,

and R^3 is CH_3;

or a pharmaceutically acceptable salt thereof.

Some compounds according to the present disclosure, including the physiologically acceptable salts, are additionally effective as inhibitors of neutrophil serine protease proteinase 3 and exhibit favourable inhibitory potency, as determined by the half maximal inhibitory concentration (IC_{50}), in an enzymatic inhibition assay. This inhibitory activity on a second neutrophil serine protease may be benificial for pharmacological efficacy.

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable inhibitory potency, as determined by the half maximal effective concentration (EC_{50}), in a plasma or whole-blood assay, for instance as described in T. Stevens et al. (*J. Pharm. Exp. Ther.* 2011, *339*, 313-320).

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable in vivo potency, as determined, for example, by the half maximal effective dose (ED_{50}), in models of human neutrophil elastase-induced lung injury in mouse or rat, for instance as described in Tremblay et al. (*Chest* 2002, *121*, 582-588) or T. Stevens et al. (*J. Pharm. Exp. Ther.* 2011, *339*, 313-320).

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable metabolic stability in an in vitro microsomal assay for metabolic stability as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, 2008), chapter 29 and references therein.

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable metabolic stability in an in vitro hepatocytes assay for metabolic stability as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, 2008), chapter 29 and references therein.

An improved metabolic stability in an in vitro test system is expected to translate into a reduced in vivo clearance (CL), because the metabolic conversion in the liver is reduced. Based on the pharmacokinetic equation CL/F_{oral} = Dose / AUC (F_{oral}: oral bioavailability, AUC: area under the curve), a reduced in vivo clearance is expected to lead to higher dose-normalized systemic exposure (AUC) of the drug.

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable permeability in an in vitro Caco-2 cell layer method for permeability as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, 2008), chapter 26 and references therein. For an oral drug, improved permeability is expected to translate into a higher fraction of the drug absorbed in the intestinal tract, thus, resulting in higher dose-normalized systemic exposure (AUC).

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit a favourable, that is low efflux ratio (permeability in the efflux direction divided by the permeability in the influx direction) in an in vitro Caco-2 or MDCK cell layer method as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, 2008), chapter 26 and 27 and references therein. For an oral drug, an improved, that is reduced efflux ratio is expected to translate into a higher fraction of the drug absorbed in the intestinal tract, thus, resulting in higher dose-normalized systemic exposure (AUC).

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable aqueous solubility in a kinetic or thermodynamic solubility method as described in E. Kerns & L. Di (*Drug-like properties: concepts, 15 structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, 2008), chapter 25 and references therein. For an oral drug, improved aqueous solubility is expected to translate into a higher fraction of the drug absorbed in the intestinal tract resulting in higher dose-normalized systemic exposure (AUC) and/or oral bioavailability (F_{oral}) and/or peak plasma concentration after administration (C_{max}). Furthermore, improved aqueous

solubility is expected to reduce the risk of development challenges, such as expensive formulations, increased development time, high drug load.

Comparatively higher dose-normalized systemic exposure (AUC) can be advantageous in several ways: (1) If a certain systemic exposure (AUC) needs to be achieved for efficacy, the drug can be dosed in a lower amount. Lower dosages have the advantages of lower drug load (parent drug and metabolites thereof) for the patient causing potentially less side effects, and lower production costs for the drug product. (2) Comparatively higher dose-normalized systemic exposure (AUC) can lead to increased efficacy or prolonged duration of action of the drug when the same dose is applied.

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable metabolic stability, favourable permeability and favourable aqueous solubility. Accordingly, some compounds of the present disclosure are expected to exhibit favourable pharmacokinetic (PK) properties after oral dosing, in particular favourable systemic exposure (area under the curve, AUC), thus, leading to favourable efficacy in vivo.

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable pharmacokinetic (PK) properties. The PK properties can be determined in pre-clinical animal species, for example mouse, rat, hamster, dog, guinea pig, mini pig, cynomolgus monkey, rhesus monkey. The PK properties of a compound can be described, for example, by the following parameters: Mean residence time (MRT), elimination half-live ($t_{1/2}$), volume-of-distribution (V_D), area under the curve (AUC), clearance (CL) and bioavailability after oral administration (F_{oral}), peak plasma concentration after administration (C_{max}), time to reach Cmax (T_{max}).

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable, that is, low inhibition of cytochrome P450 (CYP) isozymes in corresponding in vitro assays for CYP isozyme inhibition as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, 2008), chapter 32 and references therein. Reduced

inhibition of CYP isozymes is expected to translate into a reduced risk for undesirable drug-drug interactions which is the interference of one drug with the normal metabolic or pharmacokinetic behaviour of a co-administered drug.

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable, that is low Cytochrome P450 (CYP) induction potential. CYP induction can affect the pharmacokinetics of a drug molecule upon multiple dosing, which can result in undesirable pharmacokinetic drug-drug interactions with co-administered drugs. CYP induction can lead to decreased exposure of the inducing compound (e.g. autoinduction) or decreased exposure of a co-administered compound metabolized by the induced enzyme. CYP induction can also lead to an increase in the metabolism of a drug causing changes in pharmacological (active metabolite) and toxicological (toxic metabolite) outcomes.

Some compounds according to the present disclosure, including the physiologically acceptable salts, exhibit favourable, that is low, inhibition of the hERG channel in a patch clamp assay as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, 2008), chapter 34 and references cited therein.

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

In another aspect, there is provided a compound of formula **1** as defined herein for use as a medicament for the treatment of asthma and allergic diseases, gastrointestinal inflammatory diseases, glomerulonephritis, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes and rheumatoid arthritis.

In another aspect, there is provided a compound of formula **1** as defined herein for use as a medicament for the treatment of neutrophilic diseases, cystic fibrosis (CF), non-cystic fibrosis, idiopathic pulmonary fibrosis, bronchiectasis, ANCA-associated vasculitis, lung cancer, non-cyctic fibrosis bronchiectasis, emphysema, chronic bronchitis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary hypertension, pulmonary arterial hypertension (PAH) and Alpha-1-antitrypsin deficiency (AATD).

In another aspect, there is provided a compound of formula **1** as defined herein for use as a medicament for the treatment of obesity and related inflammation, insulin resistence, diabetes, fatty liver and liver steatosis.

In another aspect, there is provided a compound of formula **1** as defined herein for use as a medicament for the treatment of traumatic brain injury, abdominal aortic aneurism and Graft vs. Host Disease (GvHD).

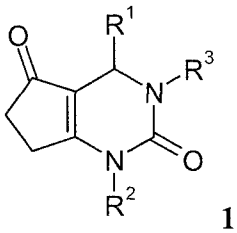
In another aspect, there is provided a pharmaceutical composition, characterised in that it contains one or more compounds of formula **1** as defined herein or a pharmaceutically active salt thereof.

In another aspect, there is provided 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 neutrophil elastase inhibitors have a therapeutic benefit.

In another aspect, there is provided a pharmaceutical composition comprising additionally to a 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, Cathepsin C inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor antagonists and SYK-inhibitors, but also combinations of two or three active substances.

DETAILED DESCRIPTION OF THE INVENTION

A compound of formula 1,



1

wherein

R^1 is phenyl,

substituted with CN and

substituted with a second substituent $R^{1.1}$,

10. A compound of formula **1** according to any one of claims 1 to 8 for use as a medicament for the treatment of asthma and allergic diseases, gastrointestinal inflammatory diseases, glomerulonephritis, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes and rheumatoid arthritis.

11. A compound of formula **1** according to any one of claims 1 to 8 for use as a medicament for the treatment of neutrophilic diseases, cystic fibrosis (CF), non-cystic fibrosis, idiopathic pulmonary fibrosis, bronchiectasis, ANCA-associated vasculitis, lung cancer, non-cyctic fibrosis bronchiectasis, emphysema, chronic bronchitis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary hypertension, pulmonary arterial hypertension (PAH) and Alpha-1-antitrypsin deficiency (AATD).

12. A compound of formula **1** according to any one of claims 1 to 8 for use as a medicament for the treatment of obesity and related inflammation, insulin resistence, diabetes, fatty liver and liver steatosis.

13. A compound of formula **1** according to any one of claims 1 to 8 for use as a medicament for the treatment of traumatic brain injury, abdominal aortic aneurism and Graft vs. Host Disease (GvHD).

14. Pharmaceutical composition, characterised in that it contains one or more compounds of formula **1** according to any one of claims 1 to 8 or a pharmaceutically active salt thereof.

15. Use of a compound of formula **1** according to one of claims 1 to 8 in the manufacture of a medicament for the treatment or prevention of diseases in which neutrophil elastase inhibitors have a therapeutic benefit.

16. The use according to claim 15, wherein said diseases are selected from the group consisting of asthma and allergic diseases, gastrointestinal inflammatory diseases, glomerulonephritis, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes and rheumatoid arthritis.

17. The use according to claim 15, wherein said diseases are selected from the group consisting of neutrophilic diseases, cystic fibrosis (CF), non-cystic fibrosis, idiopathic pulmonary fibrosis, bronchiectasis, ANCA-associated vasculitis, lung cancer, non-cyctic fibrosis bronchiectasis, emphysema, chronic bronchitis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary hypertension, pulmonary arterial hypertension (PAH) and Alpha-1-antitrypsin deficiency (AATD).

18. The use according to claim 15, wherein said diseases are selected from the group consisting of obesity and related inflammation, insulin resistence, diabetes, fatty liver and liver steatosis.

19. The use according to claim 15, wherein said diseases are selected from the group consisting of traumatic brain injury, abdominal aortic aneurism and Graft vs. Host Disease (GvHD).

20. A pharmaceutical composition comprising additionally to a compound of formula **1**, according to any one of claims 1 to 8, a pharmaceutically active compound selected from the group consisting of betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors,