In another aspect, there is provided a pharmaceutically acceptable salt of a compound of formula I as defined above.

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.

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 as defined herein or a pharmaceutically acceptable salt as defined herein for use as a medicament.

In another aspect, there is provided a compound as defined herein or a pharmaceutically acceptable salt 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 as defined herein or a pharmaceutically acceptable salt 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 as defined herein or a pharmaceutically acceptable salt 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 as defined herein or a pharmaceutically acceptable salt 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 as defined herein or a pharmaceutically acceptable salt as defined herein.

In another aspect, there is provided use of a compound as defined herein or a pharmaceutically acceptable salt as defined herein in the manufacture of a medicament for the treatment or prevention of diseases 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.

In another aspect, there is provided use of a compound as defined herein or a pharmaceutically acceptable salt as defined herein in the manufacture of a medicament for the treatment or prevention of diseases 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).

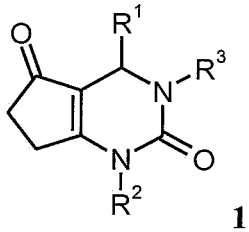
In another aspect, there is provided use of a compound as defined herein or a pharmaceutically acceptable salt as defined herein in the manufacture of a medicament for the treatment or prevention of diseases selected from the group consisting of obesity and related inflammation, insulin resistence, diabetes, fatty liver and liver steatosis.

In another aspect, there is provided use of a compound as defined herein or a pharmaceutically acceptable salt as defined herein in the manufacture of a medicament for the treatment or prevention of diseases selected from the group consisting of traumatic brain injury, abdominal aortic aneurism and Graft vs. Host Disease (GvHD).

In another aspect, there is provided a pharmaceutical composition comprising additionally to a compound as defined herein or a pharmaceutically acceptable salt 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

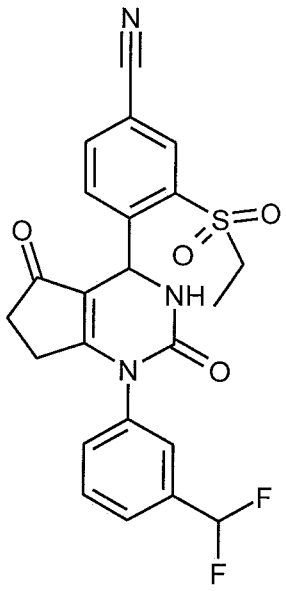
wherein

R^1 is phenyl,
substituted with CN and
substituted with a second substituent $R^{1.1}$,

and R^3 is CH_3.

2. A pharmaceutically acceptable salt of a compound of formula 1 according to claim 1.

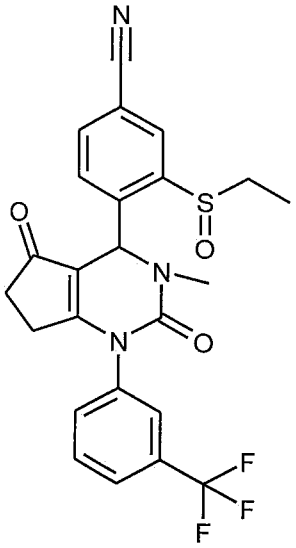
3. A compound according to claim 1, of formula **1.a**



1.a.

4. A pharmaceutically acceptable salt of a compound of formula **1.a** according to claim 3.

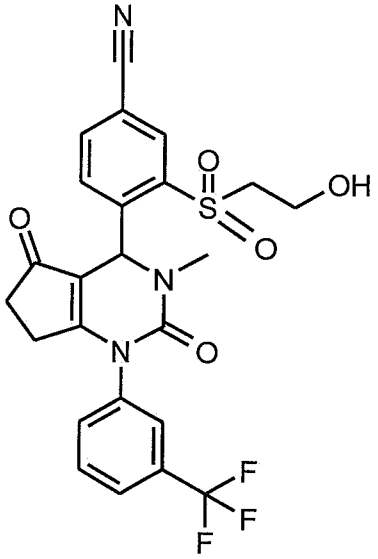
5. A compound according to claim 1, of formula **1.b**



1.b.

6. A pharmaceutically acceptable salt of a compound of formula **1.b** according to claim 5.

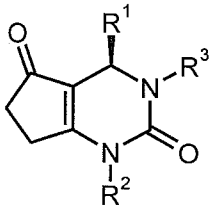
7. A compound according to claim 1, of formula **1.c**



1.c.

8. A pharmaceutically acceptable salt of a compound of formula **1.c** according to claim 7.

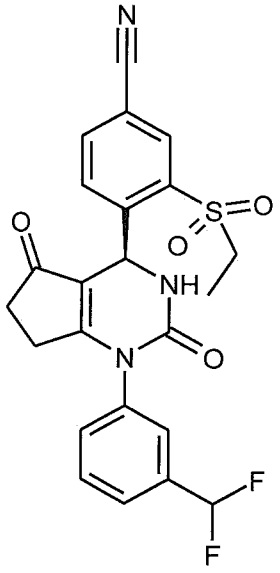
9. A compound according to claim 1, wherein the configuration of formula **1** is formula **1'**



1'.

10. A pharmaceutically acceptable salt of a compound wherein the configuration of formula **1** is formula **1'** according to claim 9.

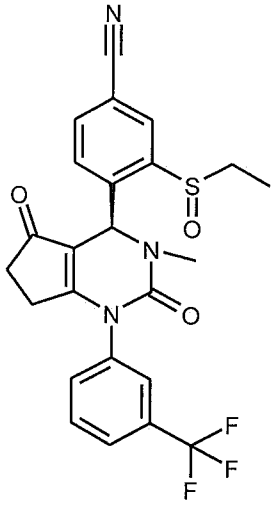
11. A compound according to claim 1, of formula **1.a'**



1.a'.

12. A pharmaceutically acceptable salt of a compound of formula **1.a'** according to claim 11.

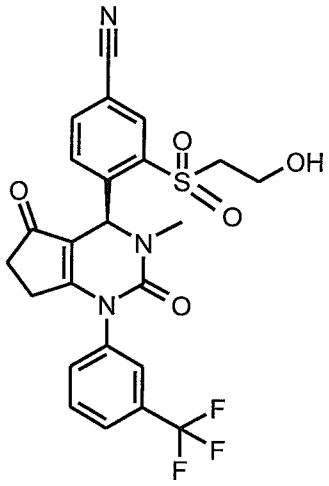
13. A compound according to claim 1, of formula **1.b'**



1.b'.

14. A pharmaceutically acceptable salt of a compound of formula **1.b'** according to claim 13.

15. A compound according to claim 1, of formula **1.c'**



1.c'.

16. A pharmaceutically acceptable salt of a compound of formula **1.c'** according to claim 15.

17. A compound according to any one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 for use as a medicament.

18. A compound according to any one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 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.

19. A compound according to any one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 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).

20. A compound according to any one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 for use as a medicament for the treatment of obesity and related inflammation, insulin resistence, diabetes, fatty liver and liver steatosis.

21. A compound according to any one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 for use as a medicament for the treatment of traumatic brain injury, abdominal aortic aneurism and Graft vs. Host Disease (GvHD).

22. Pharmaceutical composition, characterised in that it contains one or more compounds according to any one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 .

23. Use of a compound according to one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 in the manufacture of a medicament for the treatment or prevention of diseases 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.

24. Use of a compound according to one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 in the manufacture of a medicament for the treatment or prevention of diseases 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).

25. Use of a compound according to one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 in the manufacture of a medicament for the treatment or prevention of diseases selected from the group consisting of obesity and related inflammation, insulin resistence, diabetes, fatty liver and liver steatosis.

26. Use of a compound according to one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16 in the manufacture of a medicament for the treatment or prevention of diseases selected from the group consisting of traumatic brain injury, abdominal aortic aneurism and Graft vs. Host Disease (GvHD).

27. A pharmaceutical composition comprising additionally to a compound according to any one of claims 1, 3, 5, 7, 9, 11, 13 or 15 or a pharmaceutically acceptable salt according to any one of claims 2, 4, 6, 8, 10, 12, 14 or 16, a pharmaceutically active compound selected from the group consisting of betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors,