

FUSED PIPERIDINYL BICYCLIC AND RELATED COMPOUNDS FOR USE IN THE TREATMENT OF DISEASES

FIELD OF THE INVENTION

5 The present invention relates to fused piperidiny bicyclic, meta-substituted piperidiny and their related compounds that modulate activities of mammalian C5a receptor by directly binding to the C5a receptor for use in treating diseases, in particular monosodium urate (MSU)-inducible diseases, neutrophil-driven inflammatory kidney diseases, cutaneous neutrophilic inflammatory diseases, and immune complex diseases.

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BACKGROUND OF THE INVENTION

C5a generated by activation of complement system

 The complement system is an important branch of innate immunity and plays a critical role in host defense against invading microbials. These functions are carried out by functionally-related proteins that sequentially detect, tag and eliminate pathogens and pathogen-affected cells. Complement proteins are primarily present in plasma of circulating blood to perform their immune surveillant functions. These proteins are inactive in steady state and are activated through enzyme cascades in response to infections, pathogenic mechanisms and artificial triggers, such as organ transplantations.

20 The complement proteins are activated by three canonical pathways that differ by initial activation mechanisms. The three pathways are the classical, alternative, and lectin-binding pathways. The classical pathway is activated by antibody complexes. The alternative pathway is initiated by foreign surfaces, such as certain molecules present on the membrane of microbials, altered host cell surfaces in lesions, artificial surfaces encountered during kidney dialysis. The lectin-binding pathway is triggered by the binding of mannose-binding lectin protein or ficolin to microbial carbohydrate structures. Upon initiation, the progression and amplification of all three pathways utilize the same underlying mechanism involving a cascade of enzymatic cleavage of complement proteins. All three pathways converge in the formation of C3 convertases, which result in proteolysis of C3 into bioactive fragments, C3a and C3b, which in turn lead to cleavage of C5 [1].

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 C5 is a 190 kDa protein comprising an alpha chain (~120 kDa) and a beta chain (~75 kDa). Enzymatic cleavage of the N-terminus of the alpha chain yields C5a. Human C5a is a globular protein with 74 amino acids, comprising a core structure and a flexible C-terminus. A

saccharide chain conjugated to Asn residue at position 64 has a highly variable structure leading to molecular weight of human C5a ranging from 10 kDa to 15 kDa.

In addition to C5a, proteolysis of C5 also gives rise to C5b, which subsequently forms C5b-9 (MAC, membrane attack complex) with other complement components. C3a, C5a and
5 MAC are terminal effectors of complement activation. MAC forms trans-cell membrane channels on pathogens or damaged host cells, leading to cell lysis. C3a and C5a are regarded as anaphylatoxins due to their potent proinflammatory effects, in which C5a is much more potent than C3a.

10 C5a functions

C5a is a key driver for rapid innate immune responses to infections and injuries. C5a induces releases of histamine and TNF-alpha. C5a activates granulocytes. Particularly, C5a stimulates a spectrum of neutrophil activities. At lower concentrations, C5a is a potent chemoattractant of neutrophils. At higher concentrations, C5a induces the release of granular
15 enzymes, the generation of oxidants by triggering oxidative burst. C5a stimulates production and release of pro-inflammatory cytokines, which in turn cause vasodilation, increase vascular permeability, and further enhance neutrophil extravasation. Neutrophils are a double-edged sword. On one hand, they defend against infections; on the other hand, they directly cause acute or chronic tissue damage when there is excessive activity of C5a.

20 C5a also plays a role in complex regulation of adaptive immunity. C5a is involved in the interactions between antigen-presenting cells and T cells. C5a can modulate T cell differentiation, survival, and proliferation. For instance, C5a-mediated priming and differentiation of Th-17 cell and IL-17 production have been proposed to be underlying mechanisms of some autoimmune diseases [2].

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C5a functions are largely mediated by C5a receptor 1

C5a exerts its function via its cognate receptor, C5a receptor 1 (C5aR1), and later identified C5a receptor-like 2 (C5aR2). Both receptors consist of seven helical transmembrane domains and share approximately 35% homology in the primary sequence. C5aR1 is expressed
30 by immune cells, including granulocytes and monocytes, as well as non-myeloid immune cells, such as T cells. C5aR1 is also found in non-immune cells in many organs, such as kidney, liver and lungs. C5aR1 is a G protein coupled receptor and linked to several G protein coupled downstream signaling transduction pathways, such as cAMP and calcium mediated pathways. Loss-of-function approaches including C5aR1 deficient animal models and pharmacological

inhibition have shown that C5aR1 mediates multifaceted C5a functions in various pathophysiological contexts, which warrants the exercise of C5aR1 inhibitors, such as antibodies and antagonists, in pharmaceutical development and clinics with the goal to treat C5a-related disorders [3].

5 C5aR2 localizes both intracellularly and on the cell membrane. Because C5aR2 is not associated with G proteins, it was historically viewed as a non-functional decoy receptor and thus received much less attention compared with C5aR1. However, accumulating experimental observations have indicated that C5aR2 may have both pro- and anti-inflammatory effects depending on the biological contexts.

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C5a-C5aR1 axis is a promising therapeutic target for various disorders.

C5a has been linked to a wide variety of diseases, including but not limited to: kidney-related disorders, cardiovascular disorders, respiratory diseases, skin disorders, arthritis, neurodegenerative disorders (Alzheimer's, dementia), ischemia-reperfusion injury, multiple sclerosis, transplant rejection, age-related macular degeneration, neutrophilic dermatoses, and cancer. In accordance with this view, preclinical and clinical data have highlighted the potential benefits of inhibiting C5a-C5aR1 interaction in several disorders [4-7].

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Targeting C5a or C5a receptors versus targeting C5 or C3.

20 In principle, there are multiple ways to block pathogenic C5a functions. It can be blocked by direct neutralizing C5a, such as using anti-C5a antibody, or by C5aR1 inhibitors. It can also be achieved by blocking C5a generation by inhibiting cleavage of C5, which can be achieved by targeting C5 per se or its upstream activators, such as C3. However, blocking C5a functions by targeting its upstream complement molecules is inherently confounded by the existence of extrinsic pathways. Extrinsic pathways refer to pathways other than the three canonic pathways that lead to cleavage of C5 and subsequent generation of C5a. Extrinsic pathways utilize a wide spectrum of proteases that are outside of complement realm. These proteases include proteases released by microbials, associated with coagulant cascade or activated during inflammatory responses and tissue damage [8].

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30 Therefore, modalities targeting C3 or C5 do not block C5 cleavage by extrinsic pathways, and thus do not completely block C5a generation, which could lead to compromised therapeutic effects.

In addition, targeting C5a or C5a receptors versus targeting C5 and C3 has other potential clinical benefits. For instance, inhibiting C5 or C3 not only blocks C5a but also C5b

and subsequent formation of MAC. Whereas targeting C5a or C5a receptors leaves MAC generation intact, which could be an advantage because MAC plays an important role in maintenance of homeostasis via its microbiocidal and tumoricidal effects. Clinical interventions targeting C5a or C5a receptors may carry less risks of infection complications than
5 interventions targeting C5 or C3.

Fused piperidinyl bicyclic, meta-substituted piperidinyl and their related compounds that excellently modulate activities of mammalian C5a receptor by directly binding to the C5a receptor are disclosed in WO 2020/182384 A1.

10 TECHNICAL PROBLEMS UNDERLYING THE PRESENT INVENTION

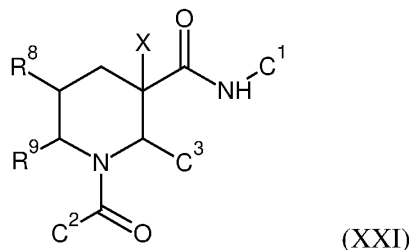
While, as explained above, the C5a-C5aR1 axis is considered a promising therapeutic target for the treatment of various disorders, it is unknown which particular diseases or disorders can actually be treated by using compounds that modulate activities of the mammalian C5a receptor, in particular which diseases or disorders can be treated by C5aR1 inhibitors.

15 For example, it is reported in literature that blocking the receptor for C5a with the C5a receptor antagonist PMX53 in patients with rheumatoid arthritis did not reduce synovial inflammation (Vergunst, 2007). Further, it is reported that C5aR inhibition with the C5a receptor antagonist PMX53 in the early inflammatory phase did not affect bone regeneration in a model of uneventful fracture healing (Ehrnthaller, 2016). As a further example, it has been
20 reported that complement 5a receptor deficiency did not influence adverse cardiac remodeling after pressure-overload in mice (de Haan, 2017). There are several further data published in the art indicating that blocking the receptor for C5a does not necessarily lead to therapeutic success.

The present inventors have now surprisingly found that specific diseases or disorders can advantageously be treated by specific compounds that directly target the C5a receptor,
25 thereby avoiding the drawbacks associated with the targeting of C5 or C3. In particular, the diseases or disorders which can be treated are monosodium urate (MSU)-inducible diseases, neutrophil-driven inflammatory kidney diseases, cutaneous neutrophilic inflammatory diseases, and immune complex diseases.

SUMMARY OF THE INVENTION

In an aspect the present invention relates to a compound having the general formula (XXI)



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and pharmaceutically acceptable salts, hydrates and rotamers thereof;

wherein

C¹ is selected from the group consisting of aryl and heteroaryl, wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups are optionally substituted with from 1 to 3 R¹ substituents;

C² is selected from the group consisting of aryl and heteroaryl, wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups are optionally substituted with from 1 to 3 R² substituents;

C³ is selected from the group consisting of C₁₋₈ alkyl or heteroalkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, heterocycloalkyl or heterocycloalkyl-C₁₋₄ alkyl, wherein the heteroalkyl group has from 1-3 heteroatoms selected from N, O and S, wherein the heterocycloalkyl group or portion has from 1-3 heteroatoms selected from N, O and S, and wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S, and each C³ is optionally substituted with from 1 to 3 R³ substituents;

each R¹ is independently selected from the group consisting of halogen, —CN, —R^c, —CO₂R^a, —CONR^aR^b, —C(O)R^a, —OC(O)NR^aR^b, —NR^bC(O)R^a, —NR^bC(O)₂R^c, —NR^a—C(O)NR^aR^b, —NR^aC(O)NR^aR^b, —NR^aR^b, —OR^a, and —S(O)₂NR^aR^b; wherein each R^a and R^b is independently selected from hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and is optionally substituted with one or two oxo; each R^c is independently selected from the group consisting of C₁₋₈ alkyl or heteroalkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, heterocycloalkyl, aryl and heteroaryl, and wherein the aliphatic and/or cyclic portions of R^a, R^b and R^c are optionally further substituted with

from one to three halogen, hydroxy, methyl, amino, alkylamino and dialkylamino groups; and optionally when two R^1 substituents are on adjacent atoms, are combined to form a fused five or six-membered carbocyclic or heterocyclic ring;

each R^2 is independently selected from the group consisting of halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{R}^f$,
 5 $-\text{CO}_2\text{R}^d$, $-\text{CONR}^d\text{R}^e$, $-\text{C}(\text{O})\text{R}^d$, $-\text{OC}(\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^e\text{C}(\text{O})\text{R}^d$, $-\text{NR}^e\text{C}(\text{O})_2\text{R}^f$,
 $-\text{NR}^d\text{C}(\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^d\text{R}^e$, $-\text{OR}^d$, and $-\text{S}(\text{O})_2\text{NR}^d\text{R}^e$; wherein each R^d and R^e is
 independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached
 10 to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-
 membered ring having from 0 to 2 additional heteroatoms as ring members selected
 from N, O or S, and is optionally substituted with one or two oxo; each R^f is
 independently selected from the group consisting of C_{1-8} alkyl or heteroalkyl, C_{1-8}
 haloalkyl, C_{3-6} cycloalkyl, heterocycloalkyl, aryl and heteroaryl, and wherein the
 aliphatic and/or cyclic portions of R^d , R^e and R^f are optionally further substituted with
 15 from one to three halogen, hydroxy, methyl, amino, alkylamino and dialkylamino
 groups, and optionally when two R^2 groups are on adjacent atoms, they are combined to
 form a five- or six-membered ring;

each R^3 is independently selected from the group consisting of halogen, $-\text{CN}$, $-\text{R}^i$, $-\text{CO}_2\text{R}^g$,
 $-\text{CONR}^g\text{R}^h$, $-\text{C}(\text{O})\text{R}^g$, $-\text{C}(\text{O})\text{R}^i$, $-\text{OC}(\text{O})\text{NR}^g\text{R}^h$, $-\text{NR}^h\text{C}(\text{O})\text{R}^g$, $-\text{NR}^h\text{CO}_2\text{R}^i$,
 20 $-\text{NR}^g\text{C}(\text{O})\text{NR}^g\text{R}^h$, $-\text{NR}^g\text{R}^h$, $-\text{OR}^g$, $-\text{OR}^j$, $-\text{S}(\text{O})_2\text{NR}^g\text{R}^h$, $-\text{X}^4-\text{R}^j$, $-\text{NH}-\text{X}^4-\text{R}^j$,
 $-\text{O}-\text{X}^4-\text{R}^j$, $-\text{X}^4-\text{NR}^g\text{R}^h$, $-\text{X}^4-\text{NHR}^j$, $-\text{X}^4-\text{CONR}^g\text{R}^h$, $-\text{X}^4-\text{NR}^h\text{C}(\text{O})\text{R}^g$,
 $-\text{X}^4-\text{CO}_2\text{R}^g$, $-\text{O}-\text{X}^4-\text{CO}_2\text{R}^g$, $-\text{NH}-\text{X}^4-\text{CO}_2\text{R}^g$, $-\text{X}^4-\text{NR}^h\text{CO}_2\text{R}^i$, $-\text{O}-$
 $\text{X}^4-\text{NR}^h\text{CO}_2\text{R}^i$, $-\text{NHR}^j$ and $-\text{NHCH}_2\text{R}^j$, wherein X^4 is a C_{1-4} alkylene; each R^g and
 R^h is independently selected from hydrogen, C_{1-8} alkyl or heteroalkyl, C_{3-6} cycloalkyl
 25 and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with
 the nitrogen atom to form a four-, five- or six-membered ring having from 0 to 2
 additional heteroatoms as ring members selected from N, O or S and is optionally
 substituted with one or two oxo; each R^i is independently selected from the group
 consisting of C_{1-8} alkyl or heteroalkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, heterocycloalkyl,
 aryl and heteroaryl; and each R^j is selected from the group consisting of C_{3-6} cycloalkyl,
 30 imidazolyl, pyrimidinyl, pyrrolinyl, pyrrolyl, piperidinyl, morpholinyl,
 tetrahydrofuranyl, tetrahydropyranyl, and S,S-dioxo-tetrahydrothiopyranyl, and
 wherein the aliphatic and/or cyclic portions of R^g , R^h , R^i and R^j are optionally further
 substituted with from one to three halogen, methyl, CF_3 , hydroxy, C_{1-4} alkoxy, C_{1-4}
 alkoxy- C_{1-4} alkyl, $-\text{C}(\text{O})\text{O}-\text{C}_{1-8}$ alkyl, amino, alkylamino and dialkylamino groups,

and optionally when two R³ groups are on adjacent atoms, they are combined to form a five- or six-membered ring;

X is hydrogen or CH₃; and

R⁸ and R⁹ are independently from each other selected from the group consisting of hydrogen, halogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, and C₁-C₈ alkoxy or R⁸ and R⁹ are combined to form a fused saturated or unsaturated mono- or multi-ring carbocycle in which one or more of the ring carbon atoms may be replaced independently from each other by N, S, or O,

for use in the treatment or prevention of a disease or disorder selected from the group consisting of

- monosodium urate (MSU)-inducible diseases,
- neutrophil-driven inflammatory kidney diseases, including ischemic nephropathy, ischemic reperfusion renal injury, and obstructive nephropathy,
- cutaneous neutrophilic inflammatory diseases, and
- immune complex diseases.

Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1. Hamster Neutropenia model *in vivo*. % inhibition of C5a-induced neutropenia (C5a 100μg/kg) in hamsters is given at 8 hr after administration of INF054 and INF052 (both 10 mg/kg oral). ** indicates p<0.01 .

Fig. 2. MSU-induced peritonitis model *in vivo*. Quantification of **A** monocytes (mono), **B** neutrophils (neut), **C** white blood cells (WBC), and **D** lymphocytes (lymph) taken from peritoneal lavage fluid. Group G1 is treatment naive, group G2 were injected with monosodium urate (MSU) crystal into the abdominal cavity and received vehicle only, and group G3 received MSU injection as well as INF052 (20 mg/kg). ** indicates p<0.01.

Fig. 3. Inhibition of ischemic reperfusion renal injury. Histopathological status of kidneys after ischemic reperfusion injury (IRI). Group G1 received INF052 (100 mg/kg) after IRI, group G2 received vehicle only after IRI, and group G3 is treatment naive. * indicates p<0.05.

Fig. 4. Unilateral ureteral obstruction (UUO) induced nephropathy. Blood urea nitrogen (BUN) levels at day 1, 3, 7 and 14 after UUO surgery. Group G1 is treatment naive, group G2 received UUO treatment and received vehicle only, and group G3 received UUO treatment as well as INF052 (20 mg/kg).

Fig. 5. Unilateral ureteral obstruction (UUO) induced nephropathy. Histopathological status of kidneys H&E staining. Group G1 is treatment naive, group G2 received UUO treatment and received vehicle only, and group G3 received UUO treatment as well as INF052 (20 mg/kg). * indicates $p < 0.05$.

5 **Fig. 6. Inhibition of Immune Complex-Induced Neutrophil Activation in Human Whole Blood.** The flow cytometer detected neutrophil CD11b expression levels (Mean fluorescence intensity (MFI) emitted by FITC-conjugated anti-CD11b antibody on the surface of neutrophils) under non-activating (HBSS and single primary antibodies) and activating (non-PMN-specific or PMN-specific immune complexes) conditions. The different levels of
10 CD11b upregulated were efficiently blocked by 0.25 μM (grey bars) and 1 μM (black bars) INF052.

Fig. 7. Blocking the CD11b upregulation on neutrophils induced by *Hidradenitis suppurativa* patients' plasma. Activation of neutrophils to upregulate CD11b expression in whole blood with the HS patient (pat 088) plasma and its blockade *via* different concentrations
15 of C5aR antagonist INF052. The addition of 15 nM C5a spiked normal healthy human plasma to whole blood in the absence and presence of INF052 was used as the activation and blocking controls, respectively.

Fig. 8. Blocking the CD11b upregulation on neutrophils induced by *Hidradenitis suppurativa* patients' plasma. Activation of neutrophils to upregulate CD11b expression in
20 whole blood with three HS patients' plasma and their blockade *via* different concentrations of C5aR antagonist INF052. The addition of 15 nM C5a spiked normal healthy human plasma to whole blood in the absence and presence of INF052 was used as the activation and blocking controls, respectively.

25 DETAILED DESCRIPTION OF THE INVENTION

Definitions

Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose
30 of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Kölbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland).

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Several documents (for example: patents, patent applications, scientific publications, manufacturer's specifications, instructions, GenBank Accession Number sequence submissions etc.) are cited throughout the text of this specification. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention. Some of the documents cited herein are characterized as being "*incorporated by reference*". In the event of a conflict between the definitions or teachings of such incorporated references and definitions or teachings recited in the present specification, the text of the present specification takes precedence.

In the context of the present invention, C5a particularly refers to human C5a. The amino acid sequence of human C5 can be found under the accession number UniProtKB P01031 (CO5_HUMAN).

In the context of the present invention, the expression "C5a receptor" refers to any potential C5a binding ligand on the cell surface, especially to any receptor protein to which C5a may bind and elicit a reaction on said receptor (e.g. activation or inhibition of the receptor). The term "C5a receptor" particularly encompasses the two receptors C5aR and C5L2. Alternative names for C5aR are C5aR1 and CD88. An alternative name for C5L2 is C5aR2. Certain embodiments of the present invention refer to a compound modulating C5a receptor activity (e.g. by binding to a C5a receptor). In these contexts, the term "C5a receptor" can refer to (i) C5aR or to (ii) C5L2 or to (iii) both C5aR and C5L2. This means that some compounds modulate the activity of only one of the C5a receptors (i.e. either C5aR or C5L2), while other compounds modulate the activities of both C5a receptors (i.e. both C5aR and C5L2).

As used herein, a first compound (e.g. a compound of the invention) is considered to "bind" to a second compound (e.g. a target protein), if it has a dissociation constant K_d to said second compound of 1 mM or less, preferably 100 μ M or less, preferably 50 μ M or less, preferably 30 μ M or less, preferably 20 μ M or less, preferably 10 μ M or less, preferably 5 μ M or less, more preferably 1 μ M or less, more preferably 900 nM or less, more preferably 800 nM or less, more preferably 700 nM or less, more preferably 600 nM or less, more preferably

500 nM or less, more preferably 400 nM or less, more preferably 300 nM or less, more preferably 200 nM or less, even more preferably 100 nM or less, even more preferably 90 nM or less, even more preferably 80 nM or less, even more preferably 70 nM or less, even more preferably 60 nM or less, even more preferably 50 nM or less, even more preferably 40 nM or less, even more preferably 30 nM or less, even more preferably 20 nM or less, and even more preferably 10 nM or less.

The term “binding” according to the invention preferably relates to a specific binding. “Specific binding” means that a compound (e.g. a protein ligand or nucleic acid aptamer) binds stronger to a target (e.g. a target protein or a target epitope) for which it is specific compared to the binding to another target. A compound binds stronger to a first target compared to a second target, if it binds to the first target with a dissociation constant (K_d) which is lower than the dissociation constant for the second target. Preferably the dissociation constant (K_d) for the target to which the compound binds specifically is more than 10-fold, preferably more than 20-fold, more preferably more than 50-fold, even more preferably more than 100-fold, 200-fold, 500-fold or 1000-fold lower than the dissociation constant (K_d) for the target to which the compound does not bind specifically.

As used herein, the term “ K_d ” (usually measured in “mol/L”, sometimes abbreviated as “M”) is intended to refer to the dissociation equilibrium constant of the particular interaction between a compound (e.g. a compound of the invention) and a target molecule.

Methods for determining binding affinities of compounds, i.e. for determining the dissociation constant K_d , are known to a person of ordinary skill in the art and can be selected for instance from the following methods known in the art: Surface Plasmon Resonance (SPR) based technology, Bio-layer interferometry (BLI), enzyme-linked immunosorbent assay (ELISA), flow cytometry, isothermal titration calorimetry (ITC), analytical ultracentrifugation, radioimmunoassay (RIA or IRMA) and enhanced chemiluminescence (ECL). Typically, the dissociation constant K_d is determined at 20°C, 25°C, 30°C, or 37°C. If not specifically indicated otherwise, the K_d values recited herein are determined at 20 °C by SPR.

The term “naturally occurring”, as used herein, as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally occurring.

As used herein, a “patient” means any mammal or bird who may benefit from a treatment with the compound described herein (i.e. with an inhibitor of C5a receptor activity described herein). Preferably, a “patient” is selected from the group consisting of laboratory

animals (e.g. mouse or rat), domestic animals (including e.g. guinea pig, rabbit, chicken, turkey, pig, sheep, goat, camel, cow, horse, donkey, cat, or dog), or primates including monkeys and apes (e.g. African green monkeys, chimpanzees, bonobos, gorillas) and human beings. It is particularly preferred that the “patient” is a human being. The terms “patient” and “subject to be treated” (or in short: “subject”) are used interchangeably herein.

As used herein, “treat”, “treating” or “treatment” of a disease or disorder means accomplishing one or more of the following: (a) reducing the severity and/or duration of the disorder; (b) limiting or preventing development of symptoms characteristic of the disorder(s) being treated; (c) inhibiting worsening of symptoms characteristic of the disorder(s) being treated; (d) limiting or preventing recurrence of the disorder(s) in patients that have previously had the disorder(s); and (e) limiting or preventing recurrence of symptoms in patients that were previously symptomatic for the disorder(s).

As used herein, “prevent”, “preventing”, “prevention”, or “prophylaxis” of a disease or disorder means preventing that a disorder occurs in a subject for a certain amount of time. For example, if a compound of the invention (or a pharmaceutical composition comprising the compound) is administered to a subject with the aim of preventing a disease or disorder, said disease or disorder is prevented from occurring at least on the day of administration and preferably also on one or more days (e.g. on 1 to 30 days; or on 2 to 28 days; or on 3 to 21 days; or on 4 to 14 days; or on 5 to 10 days) following the day of administration.

As used herein, “administering” includes *in vivo* administration, as well as administration directly to tissue *ex vivo*, such as vein grafts.

A “pharmaceutical composition” according to the invention may be present in the form of a composition, wherein the different active ingredients and diluents and/or carriers are admixed with each other, or may take the form of a combined preparation, where the active ingredients are present in partially or totally distinct form. An example for such a combination or combined preparation is a kit-of-parts.

An “effective amount” is an amount of a therapeutic agent sufficient to achieve the intended purpose. The effective amount of a given therapeutic agent will vary with factors such as the nature of the agent, the route of administration, the size and species of the animal to receive the therapeutic agent, and the purpose of the administration. The effective amount in each individual case may be determined empirically by a skilled artisan according to established methods in the art.

The term “alkyl”, by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms

designated (e.g. C₁-C₈ alkyl, i.e. C₁-C₈ means one to eight carbons, preferably C₁-C₆ alkyl, most preferably C₁-C₄ alkyl). Preferred examples of C₁-C₄ alkyl mean methyl, ethyl, n-propyl, isopropyl, n-butyl and tert-butyl. More preferred, C₁-C₄ alkyl is a methyl group or an ethyl group, in particular a methyl group. In one embodiment, alkyl is preferably a C₂-C₆ alkyl, more preferably C₂-C₄ alkyl group. The term "alkenyl" refers to an unsaturated alkyl group having one or more double bonds. Similarly, the term "alkynyl" refers to an unsaturated alkyl group having one or more triple bonds. The term "cycloalkyl" refers to hydrocarbon rings having the indicated number of ring atoms (e.g., C₃₋₆ cycloalkyl) and being fully saturated or having no more than one double bond between ring vertices. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings. The term "heterocycloalkyl" refers to a cycloalkyl group that contains from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The heterocycloalkyl may be a monocyclic, a bicyclic or a polycyclic ring system. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom.

15 The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having four or fewer carbon atoms. Similarly, "alkenylene" and "alkynylene" refer to the unsaturated forms of "alkylene" having double or triple bonds, respectively.

20 The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Similarly, the terms "heteroalkenyl" and "heteroalkynyl" by itself or in combination with another term, means, unless otherwise stated, an alkenyl group or alkynyl group, respectively, that contains the stated number of carbons and having from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, and S may be placed at any interior position of the heteroalkyl group.

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The term "heteroalkylene" by itself or as part of another substituent means a divalent radical, saturated or unsaturated or polyunsaturated, derived from heteroalkyl. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like).

5 The terms "alkoxy," "alkylamino," and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. Additionally, for dialkylamino groups, the alkyl portions can be the same or different and can also be combined to form a 3-7 membered ring with the nitrogen atom to which each is attached.

10 The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "C₁₋₄ haloalkyl" is meant to include trifluoromethyl, and the like.

15 The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon group, e.g. a C₆-C₁₀ aryl group, which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings), e.g. a C₄-C₁₀ heteroaryl group, that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the
20 remainder of the molecule through a heteroatom. Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl, while non-limiting examples of heteroaryl groups include furyl, thienyl, pyrrolyl, pyridyl, quinolinyl, quinolyl, isoquinolyl, and the like. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

25 For brevity, the term "aryl" when used in combination with other terms (e.g.: aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group.

30 The above terms (e.g., "alkyl," "aryl" and "heteroaryl"), in some embodiments, will include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below. For brevity, the terms aryl and heteroaryl will refer to substituted or unsubstituted versions as provided below, while the term "alkyl" and related aliphatic radicals is meant to refer to unsubstituted versions, unless indicated to be substituted.

Substituents for the alkyl radicals (including those groups often referred to as alkylene, alkenyl, alkynyl and cycloalkyl) can be a variety of groups selected from: -halogen, -OR', -NR'R'', -SR', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NR'S(O)₂R'', -CN and -NO₂ in a number ranging from zero to (2 m'+1), where m' is the total number of carbon atoms in such radical. R', R'' and R''' each independently refer to hydrogen, unsubstituted C₁₋₆ alkyl, unsubstituted heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted C₁₋₆ alkyl, C₁₋₈ alkoxy or C₁₋₆ thioalkoxy groups, or unsubstituted aryl-C₁₋₄ alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. The term "acyl" as used by itself or as part of another group refers to an alkyl radical wherein two substituents on the carbon that is closest to the point of attachment for the radical is replaced with the substituent =O.

Similarly, substituents for the aryl and heteroaryl groups are varied and are generally selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'-C(O)NR''R''', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NR'S(O)₂R'', -N₃, perfluoro(C₁₋₄)alkoxy, and perfluoro(C₁₋₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl, C₂₋₈ alkynyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-C₁₋₄ alkyl, and unsubstituted aryloxy-C₁₋₄ alkyl. Other suitable substituents include each of the above aryl substituents attached to a ring atom by an alkylene tether of from 1-4 carbon atoms.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -

S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or unsubstituted C₁₋₆ alkyl.

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), and sulfur (S).

5 As used herein, the term "CYCLE" means a saturated or unsaturated mono- or multi-ring carbocycle, preferably 5, 6 or 7-membered (cycle), in which one or more (e.g. 1, 2, 3, or 4) of the ring carbon atoms may be replaced independently from each other by N, S, or O. The term "CYCLE" refers to fully saturated and unsaturated ring systems as well as partially unsaturated ring systems and is intended to include all the possible isomeric forms of the carbocycle (for example, pyrrolyl comprises 1H-pyrrolyl and 2H-pyrrolyl). Examples of where
10 CYCLE is a monocyclic or bicyclic aryl group include phenyl and naphthyl. Examples of where CYCLE is a monocyclic or bicyclic cycloalkyl group include, but are not limited to, cyclopentyl and cyclohexyl. Examples of where CYCLE is a monocyclic or bicyclic saturated heterocycle include, but are not limited to, tetrahydrofuranyl, pyrrolidinyl, tetrahydrothienyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and the like. Examples of where CYCLE is a
15 monocyclic, bicyclic or tricyclic partially saturated heterocycle include, but are not limited to, pyrrolinyl, imidazolinyl, pyrazolinyl, and the like. Examples of where CYCLE is a monocyclic, bicyclic or tricyclic aromatic heterocycle include, but are not limited to, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, and the like.
20

Throughout this specification, index numbers are used to distinguish different substituents in the compounds of the invention. Such index numbers are used as superscript numbers or as subscript numbers without denoting any particular meaning to the superscript or subscript usage. In other words, superscript index numbers and subscript index numbers are
25 used interchangeably. For example, formulae (I), (XI) and (XXI) all contain the substituents C₁, C₂ and C₃. In some formulae and reaction schemes, these substituents are shown as C₁, C₂, and C₃; in other formulae and reaction schemes, these substituents are shown as C¹, C², and C³. But C¹ and C₁ is the same substituent; C² and C₂ is the same substituent; and C³ and C₃ is the same substituent.

30 "Pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the

particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge, S. M., et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the compounds used according to the present invention may be in a prodrug form. Prodrugs of the compounds described herein are those compounds that

readily undergo chemical changes under physiological conditions to provide the compounds used according to the present invention. Additionally, prodrugs can be converted to the compounds used according to the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds used according to the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

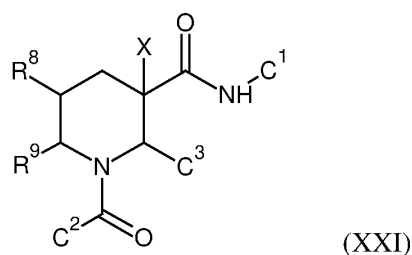
Certain compounds used according to the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be used within the scope of the present invention. Certain compounds used according to the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds used according to the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. The compounds used according to the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds (for example ^2H (i.e. deuterium, D) in place of ^1H). The compounds may also be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds used according to the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

Embodiments of the Invention

The present invention will now be further described. In the following passages different aspects of the invention are defined in more detail. Each aspect defined below may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

In an aspect the present invention is directed to a compound having the general formula (XXI)



and pharmaceutically acceptable salts, hydrates and rotamers thereof;

wherein

- 5 C¹ is selected from the group consisting of aryl and heteroaryl, wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups are optionally substituted with from 1 to 3 R¹ substituents;
- C² is selected from the group consisting of aryl and heteroaryl, wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said
- 10 aryl and heteroaryl groups are optionally substituted with from 1 to 3 R² substituents;
- C³ is selected from the group consisting of C₁₋₈ alkyl or heteroalkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, heterocycloalkyl or heterocycloalkyl-C₁₋₄ alkyl, wherein the heteroalkyl group has from 1-3 heteroatoms selected from N, O and S, wherein the heterocycloalkyl group or
- 15 portion has from 1-3 heteroatoms selected from N, O and S, and wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S, and each C³ is optionally substituted with from 1 to 3 R³ substituents;
- each R¹ is independently selected from the group consisting of halogen, —CN, —R^c, —CO₂R^a, —CONR^aR^b, —C(O)R^a, —OC(O)NR^aR^b, —NR^bC(O)R^a, —NR^bC(O)₂R^c, —NR^a—
- 20 C(O)NR^aR^b, —NR^aC(O)NR^aR^b, —NR^aR^b, —OR^a, and —S(O)₂NR^aR^b; wherein each R^a and R^b is independently selected from hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and is optionally substituted with one or two oxo;
- 25 each R^c is independently selected from the group consisting of C₁₋₈ alkyl or heteroalkyl, C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, heterocycloalkyl, aryl and heteroaryl, and wherein the aliphatic and/or cyclic portions of R^a, R^b and R^c are optionally further substituted with from one to three halogen, hydroxy, methyl, amino, alkylamino and dialkylamino groups; and optionally when two R¹ substituents are on adjacent atoms, are combined to
- 30 form a fused five or six-membered carbocyclic or heterocyclic ring;

each R^2 is independently selected from the group consisting of halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{R}^f$, $-\text{CO}_2\text{R}^d$, $-\text{CONR}^d\text{R}^e$, $-\text{C}(\text{O})\text{R}^d$, $-\text{OC}(\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^e\text{C}(\text{O})\text{R}^d$, $-\text{NR}^e\text{C}(\text{O})_2\text{R}^f$, $-\text{NR}^d\text{C}(\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^d\text{R}^e$, $-\text{OR}^d$, and $-\text{S}(\text{O})_2\text{NR}^d\text{R}^e$; wherein each R^d and R^e is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and is optionally substituted with one or two oxo; each R^f is independently selected from the group consisting of C_{1-8} alkyl or heteroalkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, heterocycloalkyl, aryl and heteroaryl, and wherein the aliphatic and/or cyclic portions of R^d , R^e and R^f are optionally further substituted with from one to three halogen, hydroxy, methyl, amino, alkylamino and dialkylamino groups, and optionally when two R^2 groups are on adjacent atoms, they are combined to form a five- or six-membered ring;

each R^3 is independently selected from the group consisting of halogen, $-\text{CN}$, $-\text{R}^i$, $-\text{CO}_2\text{R}^g$, $-\text{CONR}^g\text{R}^h$, $-\text{C}(\text{O})\text{R}^g$, $-\text{C}(\text{O})\text{R}^i$, $-\text{OC}(\text{O})\text{NR}^g\text{R}^h$, $-\text{NR}^h\text{C}(\text{O})\text{R}^g$, $-\text{NR}^h\text{CO}_2\text{R}^i$, $-\text{NR}^g\text{C}(\text{O})\text{NR}^g\text{R}^h$, $-\text{NR}^g\text{R}^h$, $-\text{OR}^g$, $-\text{OR}^j$, $-\text{S}(\text{O})_2\text{NR}^g\text{R}^h$, $-\text{X}^4-\text{R}^j$, $-\text{NH}-\text{X}^4-\text{R}^j$, $-\text{O}-\text{X}^4-\text{R}^j$, $-\text{X}^4-\text{NR}^g\text{R}^h$, $-\text{X}^4-\text{NHR}^j$, $-\text{X}^4-\text{CONR}^g\text{R}^h$, $-\text{X}^4-\text{NR}^h\text{C}(\text{O})\text{R}^g$, $-\text{X}^4-\text{CO}_2\text{R}^g$, $-\text{O}-\text{X}^4-\text{CO}_2\text{R}^g$, $-\text{NH}-\text{X}^4-\text{CO}_2\text{R}^g$, $-\text{X}^4-\text{NR}^h\text{CO}_2\text{R}^i$, $-\text{O}-\text{X}^4-\text{NR}^h\text{CO}_2\text{R}^i$, $-\text{NHR}^j$ and $-\text{NHCH}_2\text{R}^j$, wherein X^4 is a C_{1-4} alkylene; each R^g and R^h is independently selected from hydrogen, C_{1-8} alkyl or heteroalkyl, C_{3-6} cycloalkyl and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a four-, five- or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S and is optionally substituted with one or two oxo; each R^i is independently selected from the group consisting of C_{1-8} alkyl or heteroalkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, heterocycloalkyl, aryl and heteroaryl; and each R^j is selected from the group consisting of C_{3-6} cycloalkyl, imidazolyl, pyrimidinyl, pyrrolinyl, pyrrolyl, piperidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, and S,S-dioxo-tetrahydrothiopyranyl, and wherein the aliphatic and/or cyclic portions of R^g , R^h , R^i and R^j are optionally further substituted with from one to three halogen, methyl, CF_3 , hydroxy, C_{1-4} alkoxy, C_{1-4} alkoxy- C_{1-4} alkyl, $-\text{C}(\text{O})\text{O}-\text{C}_{1-8}$ alkyl, amino, alkylamino and dialkylamino groups, and optionally when two R^3 groups are on adjacent atoms, they are combined to form a five- or six-membered ring;

X is hydrogen or CH_3 ; and

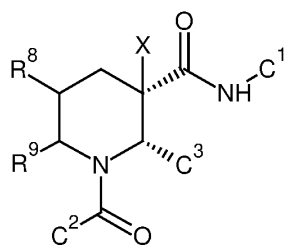
R⁸ and R⁹ are independently from each other selected from the group consisting of hydrogen, halogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, and C₁-C₈ alkoxy or R⁸ and R⁹ are combined to form a fused saturated or unsaturated mono- or multi-ring carbocycle in which one or more of the ring carbon atoms may be replaced independently from each other by N, S, or O,

for use in the treatment or prevention of a disease or disorder selected from the group consisting of

- monosodium urate (MSU)-inducible diseases, including peritonitis and gout,
- neutrophil-driven inflammatory kidney diseases, including ischemic nephropathy, ischemic reperfusion renal injury, and obstructive nephropathy,
- cutaneous neutrophilic inflammatory diseases, including hidradenitis suppurativa (HS), pyoderma gangrenosum (PG), PASH (PG, acne, and hidradenitis suppurativa), PAPASH (pyogenic arthritis, acne, PG, and hidradenitis suppurativa), chronic spontaneous urticaria, and bullous pemphigoid, and
- immune complex diseases.

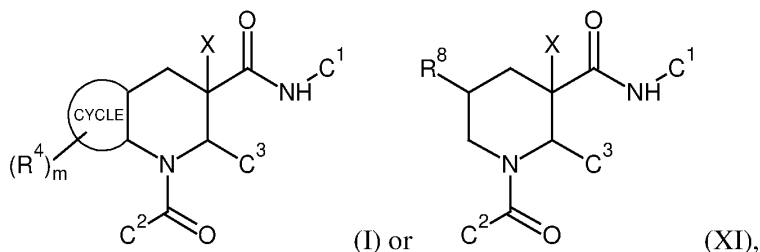
In some embodiments of this aspect, at least one of R⁸ and R⁹ is **not** hydrogen and/or X is hydrogen. Preferably, R⁸ is not hydrogen. Preferably, X is hydrogen.

In some embodiments of this aspect, the compound has formula (XXIa)



(XXIa)

In some embodiments of the first aspect, the compound has formula (I) or formula (XI):



wherein

X, C¹, C², and C³ are defined as above;

R⁸ in Formula (XI) is defined as above;

R^4 is selected from the group consisting of cyano, halo, nitro, hydroxyl, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) alkyl-OH, (C_1-C_6) -alkyl- NR^5R^6 , trifluoromethyl, (C_1-C_6) alkoxy, (C_1-C_6) thioalkoxy, phenoxy, COR^7 , NR^5R^6 , $NHCO(C_1-C_6)$ alkyl, SO_3H , $SO_2(C_1-C_6)$ alkyl and $SO_2NR^5R^6$;

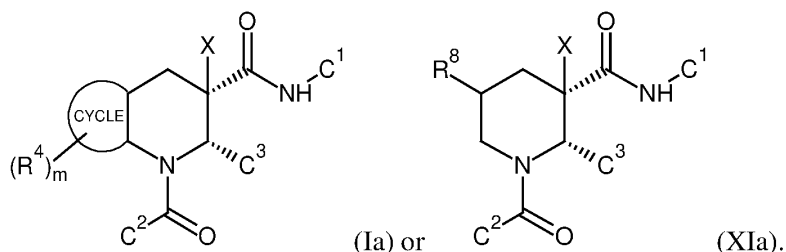
- 5 R^5 and R^6 are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl and (C_3-C_6) cycloalkyl;

R^7 is independently hydroxyl, (C_1-C_6) alkoxy, phenoxy or $-NR^5R^6$;

m is 0-4; and

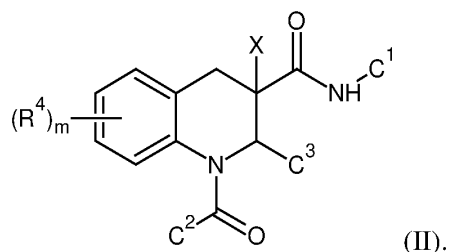
- 10 CYCLE is a saturated or unsaturated mono- or multi-ring carbocycle in which one or more of the ring carbon atoms may be replaced independently from each other by N, S, or O.

In further embodiments, the compound has formula (Ia) or formula (XIa):



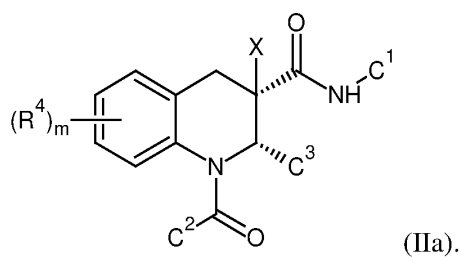
- 15 In some embodiments, CYCLE is a saturated or unsaturated mono- or multi-ring, preferably 5, 6 or 7-membered, carbocycle in which from one to four (preferably from 1 to 3, more preferably 1 or 2, even more preferably 1) of the ring carbon atoms may be replaced independently from each other by N, S, or O.

In some embodiments, the compound has formula (II):

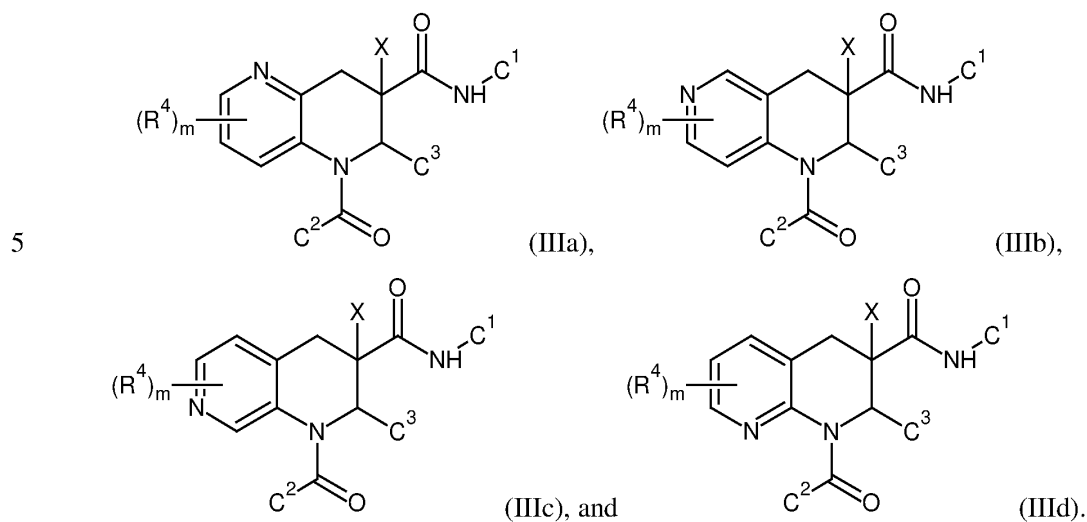


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In further embodiments, the compound has formula (IIa):

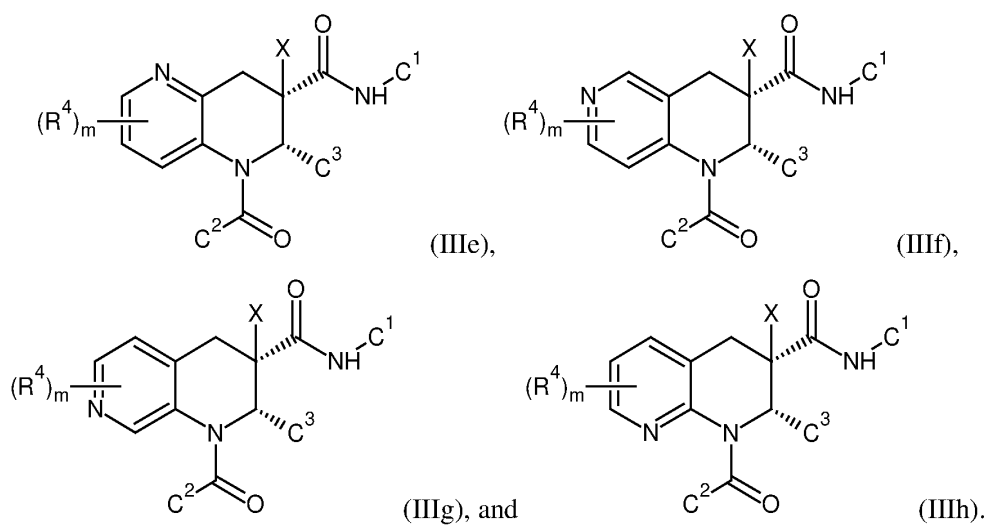


In some embodiments, the compound has a formula selected from the group consisting of (IIIa), (IIIb), (IIIc), and (IIId):



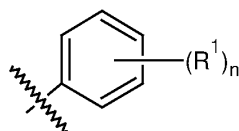
In further embodiments, the integer m is 0. In these embodiments, there is no substituent R⁴.

10 In further embodiments, the compound has a formula selected from the group consisting of (IIIe), (IIIf), (IIIg), and (IIIh):



In further embodiments, the integer m is 0, i.e. in these embodiments, there is no substituent R^4 .

In some embodiments, C^1 is



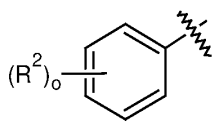
5 wherein

R^1 is defined as above (at each occurrence, R^1 is independently selected, i.e. differing residues R^1 might be present at the phenyl ring), and

n is an integer selected from 0, 1, 2, or 3, preferably 2.

10 In further embodiments, each R^1 is independently selected from the group consisting of $-OH$, halogen, C_{1-6} alkyl, hydroxy (C_{1-6}) alkyl, and halo (C_{1-6}) alkyl. In preferred embodiments, each R^1 is independently selected from the group consisting of $-OH$, chloro, methyl, $-CH_2-OH$, and CF_3 .

In some embodiments of the first aspect, C^2 is



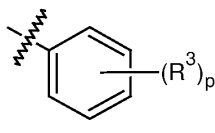
15 wherein

R^2 is defined as above (at each occurrence, R^2 is independently selected, i.e. differing residues R^2 might be present at the phenyl ring), and

o is an integer selected from 0, 1, 2, or 3.

20 In further embodiments, each R^2 is independently selected from the group consisting of C_{1-6} alkyl and halogen. In preferred embodiments, each R^2 is independently selected from the group consisting of methyl, fluoro, and chloro.

In some embodiments of the first aspect, C^3 is



wherein

25 R^3 is defined as above (at each occurrence, R^3 is independently selected, i.e. differing residues R^3 might be present at the phenyl ring), and

p is an integer selected from 0, 1, 2, or 3.

In preferred embodiments, p is 1 and R^3 is C_1 - C_8 hydroxyalkyl (preferably hydroxypentyl), C_1 - C_8 hydroxyalkoxy (preferably hydroxybutoxy), or NHR^j as defined above. In further preferred embodiments, R^j is selected from the group consisting of C_1 - C_8 alkyl, C_1 - C_8 hydroxyalkyl, C_3 - C_6 cycloalkyl and tetrahydropyranyl. In further preferred embodiments, R^j is selected from the group consisting of isopropyl, hydroxybutyl, cyclobutyl, cyclopentyl and tetrahydropyranyl.

In some embodiments of the first aspect, R_8 is selected from the group consisting of halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, and C_1 - C_4 alkoxy. In preferred embodiments, R_8 is selected from the group consisting of fluoro, chloro, methyl, trifluoromethyl, and methoxy.

In some embodiments, the compound is selected from the group consisting of INF004, INF011, INF014, INF015, INF022, INF023, INF024, INF025, INF030, INF033, INF034, INF035, INF038, INF039, INF040, INF041, INF045, INF046, INF047, INF048, INF049, INF050, INF051, INF052, INF053, INF054, INF055, INF056, INF058, INF067, INF068, INF069, INF070, INF071, INF072, INF075, INF077, and INF080. The structural formulas and the chemical names of these compounds are shown below in chapter “C. Results” of the Example section.

It is preferred that the compounds used according to the invention have an IC_{50} of 1 μM or lower in a Ca^{2+} mobilization assay. Ca^{2+} mobilization assays are well known in the art. A preferred Ca^{2+} mobilization assay uses human monocytes like, e.g. U-937 (ATCC® CRL-1593.2™). A Ca^{2+} mobilization assay suitable to determine the IC_{50} is described in the Examples. Preferably the compounds has an IC_{50} of 500 nM or lower, more preferably of 200 nM or lower and even more preferably of 100 nM or lower in a Ca^{2+} mobilization assay.

-

The compounds used according to the invention are used in the treatment or prevention of a disease or disorder selected from the group consisting of

- monosodium urate (MSU)-inducible diseases, including peritonitis and gout,
- neutrophil-driven inflammatory kidney diseases, including ischemic nephropathy, ischemic reperfusion renal injury, and obstructive nephropathy,
- cutaneous neutrophilic inflammatory diseases, including neutrophilic dermatoses (ND), such as hidradenitis suppurativa (HS), pyoderma gangrenosum (PG), PASH (PG, acne, and hidradenitis suppurativa), and PAPASH (pyogenic arthritis, acne, PG, and

hidradenitis suppurativa), as well as chronic spontaneous urticaria and bullous pemphigoid, and

- immune complex diseases.

5 Uric acid crystals [monosodium urate (MSU)] have emerged as an important factor for both gouty arthritis and immune regulation. This simple crystalline structure appears to activate innate host defense mechanisms in multiple ways and triggers robust inflammation and immune activation. The recognition mechanisms of MSU following its phase change from soluble uric acid are diverse, involving both protein receptors and non-specific plasma membrane
10 attachment. Upon contact with host cells, MSU induces a set of membrane events that trigger Syk and PI3K activation, phagocytosis, and cytokine production. It is assumed that this further leads to active C5a formation and IL-1 β production, as well as recruiting of circulating neutrophils to the site of MSU-induced inflammation within 4-6 hours.

 It has been surprisingly found that while MSU crystal dramatically increased the number
15 of white blood cells (WBC) in peritoneal lavage fluid (but not in blood) when injected, co-administration of a compound used according to the invention reduced the cell counts of WBC, monocytes, neutrophils, and lymphocytes in peritoneal lavage fluid. Without wishing to be bound by theory, it is assumed that the recruitment of WBC, especially neutrophils at the site of inflammation could be inhibited by the presence of a compound used according to the
20 invention. This finding is aligned with the knowledge of C5aR being expressed on neutrophils. This MSU-induced disease model (in particular peritonitis as shown in Example 3) thus suggests that the compounds used according to the invention have the potential to inhibit the effects of MSU-induced and neutrophil-driven inflammation *in vivo*.

 In a preferred embodiment, the monosodium urate (MSU)-inducible diseases include
25 peritonitis and gout. For these, the monosodium urate (MSU)-induced inflammation is established as cause for the inflammation, which as shown in Example 3, can be significantly reduced by the compounds used according to the invention.

 While inflammatory kidney diseases, like glomerulonephritis, is typically caused by
30 bacterial or viral infection, several further causes may lead to an inflammatory response of the kidney tissue. E.g., renal ischemia reperfusion (I/R) injury is the most common cause of acute renal failure as seen after renal transplantation, major abdominal and vascular surgery, coronary bypass surgery, and in trauma and sepsis. The complement system has been shown to mediate renal ischemia-reperfusion (I/R) injury. C5aR was found expressed on mesangial, as well as on

tubular epithelial cells in kidneys of healthy mice. After I/R injury, C5aR expression was up-regulated in tubular epithelial cells and kidneys were heavily infiltrated by neutrophils.

It has been surprisingly found that administration of a compound used according to the invention significantly reduced loss of renal function in an ischemic reperfusion renal injury model (see Example 4) and in a unilateral ureteral obstruction (UUO) induced nephropathy model (see Example 5).

Not wishing to be bound by theory, it is assumed that this is achieved mainly through neutrophil-dependent but may also be by neutrophil-independent pathways. This finding suggests that the compound used according to the invention have the potential to inhibit the effects of neutrophil-driven inflammatory kidney diseases, including ischemic nephropathy, ischemic reperfusion renal injury, and obstructive nephropathy *in vivo*.

Hidradenitis suppurativa (HS) is a chronic devastating skin disorder affecting areas rich in apocrine glands, and it is considered as one of neutrophil-associated cutaneous inflammatory diseases. Nodules appear in the affected areas, and they progressively become swollen and rupture with the release of pus. This process occurs repeatedly leading to sinus tract formation and scars. This disease course creates a frustrating situation for the patients but also for physicians. The point prevalence is reported to range between 1% and 4%. The exact pathophysiology of HS is not well defined. Smoking, dietary habits and genetic predisposition have all been linked with HS. The percentage of NK cells was increased and that of CD4-lymphocytes decreased compared to healthy controls probably implying the existence of an autoimmune predilection for the disorder. IL-1 β and IL-17 have been found to be upregulated in the lesion of HS, being associated with the activation of inflammasome. Hidradenitis suppurativa (HS) is presented with the high number of neutrophil infiltrates in the inflamed skin, especially in the late stage of disease. Activated neutrophils could be an important effector cell type causing tissue damage through direct harmful effect or indirect regulatory effect toward other effect cells such as active T cells and TH17 in this disease setting.

A hypothesis for the implication of some autoimmune or autoinflammatory mechanism in the pathogenesis of HS has been created over the last years. The hypothesis is further reinforced by positive results from the administration of TNF antagonists in prospective, placebo-controlled studies, which result in the approval of Adalimumab (an antibody directed against tumor necrosis factor α) in patients with moderate to severe HS. One major, yet unanswered question is how neutrophils are recruited to the affected skin lesion and to what extent activated neutrophils would contribute to the disease development.

The wide range of possible pathogenic mechanisms suggested by different studies may imply that HS is associated with host mechanisms rather than exogenous factors. Taking into account of the paradox that both anti-infectious (antibiotics) and pro-infectious (anti-TNF, corticosteroids, immunosuppressive drugs) therapies may be helpful, HS may appear as an auto-inflammatory disease based on a defect in the hair follicle innate immunity, which is supported by the fact that pro-inflammatory cytokines such as interleukin (IL)-1 β , and tumor necrosis factor- α (TNF- α) are markedly increased in lesional and perilesional skin.

Neutrophilic dermatoses (ND) are a group of disorders characterized by skin lesions for which histologic examination reveals intense inflammatory infiltrates composed primarily of neutrophils with no evidence of infection. ND include pyoderma gangrenosum (PG) and other well-defined entities, such as Sweet's syndrome, subcorneal pustular dermatosis (SPD), erythema elevatum diutinum (EED), or neutrophilic urticarial dermatosis (NUD), and their atypical or transitional forms. Hidradenitis suppurativa (HS) has recently been assigned to the family of ND based on the high number of neutrophil infiltrates observed in the inflamed skin.

Pyoderma gangrenosum (PG) and hidradenitis suppurativa (HS) are prototypic neutrophilic dermatoses that are regarded as autoinflammatory disease in origin with the hallmark of the accumulation of neutrophils in the skin [12]. Autoinflammatory Syndrome represents an emerging group of inflammatory conditions that are distinct from autoimmune, allergic, and infectious disorders. From a pathophysiological perspective, all the autoinflammatory syndromes such as PAPA (pyogenic arthritis, PG and acne), PASH (PG, acne and hidradenitis suppurativa) or PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa) share common mechanisms consisting of over-activation of the innate immune system and 'sterile' neutrophil-rich cutaneous inflammation [13].

Neutrophilic urticarial dermatosis (NUD), such as chronic spontaneous urticaria (autoimmune), is a rare form of dermatosis. In clinical terms, it consists of a chronic or recurrent eruption comprising slightly elevated, pink to reddish plaques or macules. The elementary lesion lasts 24 to 48 hours and resolves without leaving any residual pigmentation. Extra-cutaneous signs are common, particularly fever or arthralgia. At histopathology, the dermis contains dense neutrophilic interstitial infiltrate with leukocytoclasia, but without fibrinoid necrosis of vessel walls. NUD often occurs in a setting of underlying systemic disease. The most commonly associated diseases are adult-onset Still's disease, Schnitzler syndrome, lupus erythematosus and cryopyrin-associated periodic syndromes. Treatment of NUD depends on the clinical context. Dapsone and colchicine are often effective, but additional treatment options would be desirable.

Generally, bullous autoimmune dermatoses (also known as autoimmune bullous diseases (AIBD)), such as bullous pemphigoid (BP), are a clinically and immunopathologically heterogeneous group of diseases, characterized clinically by blisters or erosions of the skin and/or mucous membranes. In AIBD, autoantibodies are directed against structural proteins of the skin; in pemphigus diseases, they are directed against desmosomal proteins, which connect neighboring keratinocytes/epithelial cells, and in pemphigoid diseases, against proteins of the basement membrane zone, which connect the epidermis/epithelium and the dermis/lamina propria. Bullous pemphigoid (BP) is an inflammatory subepidermal blistering disease, which is considered to be associated with an IgG autoimmune response to the hemidesmosomal protein, BP180.

It has been surprisingly found that administration of a compound used according to the invention is suitable to ameliorate NDs (see Example 7). Not wishing to be bound by theory, it is assumed that this is achieved mainly through neutrophil-dependent but may also be by neutrophil-independent pathways. This finding suggests that the compound used according to the invention have the potential to inhibit the effects of cutaneous neutrophilic inflammatory diseases, including hidradenitis suppurativa (HS), pyoderma gangrenosum (PG), PASH (PG, acne, and hidradenitis suppurativa), and PAPASH (pyogenic arthritis, acne, PG, and hidradenitis suppurativa), as well as neutrophilic urticarial dermatosis (NUD) and autoimmune bullous diseases (AIBD) *in vivo*.

Immune complex diseases are a group of conditions resulting from inflammation and tissue damage induced in tissues where immune complexes are formed or deposited. An immune complex, sometimes called an antigen-antibody complex or antigen-bound antibody, is a molecule formed from the binding of multiple antigens to antibodies. The bound antigen and antibody act as a unitary object, effectively an antigen of its own with a specific epitope. After an antigen-antibody reaction, the immune complexes can be subject to any of a number of responses, including complement deposition, opsonization, phagocytosis, or processing by proteases. Immune complex deposition is a prominent feature of several autoimmune diseases, including rheumatoid arthritis, scleroderma, and Sjögren's syndrome. An inability to degrade immune complexes in the lysosome and subsequent accumulation on the surface of immune cells has been associated with systemic lupus erythematosus. Further relevant immune complex diseases are IgA nephritis (or IgA nephropathy, derives its name from deposits of immunoglobulin A (IgA) in a granular pattern in the mesangium); lupus nephritis (an inflammation of the kidneys caused by systemic lupus erythematosus (SLE), an autoimmune

disease); ANCA (Anti-neutrophilic cytoplasmic antibody) vasculitis; C3 glomerulopathy (C3G), characterized by the dominant deposition of the third component of complement (C3) in the renal glomerulus; Atypical hemolytic uremic syndrome (aHUS), also known as complement-mediated hemolytic uremic syndrome, which is usually caused by chronic, uncontrolled activation of the complement system; Goodpasture syndrome (also known as anti-glomerular basement membrane disease, is a rare autoimmune disease in which antibodies attack the basement membrane in lungs and kidneys); crescentic glomerulonephritis; focal segmental glomerulosclerosis (FSGS); rheumatic fever (an inflammatory disease believed to involve the production of auto-antibodies); dermatomyositis (DM); chronic inflammatory demyelinating polyneuropathy (CIDP) (also called chronic relapsing polyneuropathy (CRP) or chronic inflammatory demyelinating polyradiculoneuropathy); chemotherapy-induced peripheral neuropathy (CIPN); and transplantation rejection.

Dermatomyositis (DM) is an acquired autoimmune disease in which skeletal muscle is targeted by the immune system, which is a subset of idiopathic inflammatory myopathy (IIM). DM is characterized primarily by muscle inflammation, proximal muscle weakness, and cutaneous involvement. Additionally, the disease may present with extra-muscular symptoms affecting various organs including the heart, joints, lungs, and gastrointestinal tract. Recent studies seem to confirm the relevancy of immune cells infiltration for myocardial injury in dermatomyositis [14].

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common, heterogeneous, immune-mediated neuropathy, characterized by predominant demyelination of motor and sensory nerves. CIDP follows a relapsing–remitting or a progressive course and causes substantial disability. The pathogenesis of CIDP involves a complex interplay of multiple aberrant immune responses, creating a pro-inflammatory environment, subsequently inflicting damage on the myelin sheath. The complement system appears to play a role in promoting macrophage-mediated demyelination. [15]

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurologic complication of chemotherapy that causes pain, sensory loss, and numbness in the hands and feet. In many cases, acute CIPN leads to stopping of the chemotherapeutic treatment and the condition may last for months or years until it becomes chronic. Changes in chemotherapy regimen or treatment dismissal are necessary when pain is too severe, thus resulting in the risk of reducing the therapeutic efficacy. Chemotherapeutic drugs are used to block the progression of cancer owing to their ability to kill cancer cells. However, these drugs also affect healthy cells, causing side effects such as anemia, diarrhea, nausea, and also leading to serious

complications, such as infertility, infections, and pain. At the same time, chemotherapeutic agents may impact nervous system structures and, depending on the compound and its mechanism of action, they are responsible for a variety of neuropathies, such as peripheral neuropathy. Alterations in immune signaling and ion channel expression, neurotoxicity, 5 mitochondrial dysfunction, and axonal degeneration are considered among the most relevant mechanisms involved in CIPN, and several studies highlight immune system and immune-mediated neuroinflammation as key events in its development.

It has been surprisingly found that administration of a compound used according to the invention significantly reduced neutrophil activation driven by immune complexes in an 10 immune complex model in human whole blood (see Example 6).

Pharmaceutical compositions and Modes of Administration

In practice the compound used according to the present invention may be in a pharmaceutical composition, and the compound or the pharmaceutical composition comprising 15 the compound may be administered to a patient by any route established in the art which provides a sufficient level of the compound in the patient. It can be administered systemically or locally. Such administration may be parenterally, transmucosally, e.g., orally, nasally, rectally, intravaginally, sublingually, submucosally, transdermally, or by inhalation. Preferably, administration is parenteral, e.g., via intravenous or intraperitoneal injection, and also 20 including, but is not limited to, intra-arterial, intramuscular, intradermal and subcutaneous administration. If the compound described herein or a pharmaceutical composition comprising the compound is administered locally, it can be injected directly into the organ or tissue to be treated.

Pharmaceutical compositions adapted for oral administration may be provided as 25 capsules or tablets; as powders or granules; as solutions, syrups, amorphous dispersion in polymers, waxy solids or suspensions (in aqueous or non-aqueous liquids); as edible foams or whips; or as emulsions. Tablets or hard gelatine capsules may comprise lactose, starch or derivatives thereof, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, stearic acid or salts thereof. Soft gelatine capsules may comprise vegetable oils, waxes, fats, 30 semi-solid or liquid polyols etc. Solutions and syrups may comprise water, polyols and sugars.

An active agent intended for oral administration may be coated with or admixed with a material that delays disintegration and/or absorption of the active agent in the gastrointestinal tract (e.g., glyceryl monostearate or glyceryl distearate may be used). Thus, the sustained release of an active agent may be achieved over many hours and, if necessary, the active agent

can be protected from being degraded within the stomach. Pharmaceutical compositions for oral administration may be formulated to facilitate release of an active agent at a particular gastrointestinal location due to specific pH or enzymatic conditions.

Pharmaceutical compositions adapted for transdermal administration may be provided
5 as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Pharmaceutical compositions adapted for topical administration may be provided as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils. For topical administration to the skin, mouth, eye or other external tissues a topical ointment or cream is preferably used. When formulated in an ointment, the
10 active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water base or a water-in-oil base. Pharmaceutical compositions adapted for topical administration to the eye include eye drops. In these compositions, the active ingredient can be dissolved or suspended in a suitable carrier, e.g., in an aqueous solvent. Pharmaceutical compositions adapted for
15 topical administration in the mouth include lozenges, pastilles and mouthwashes.

Pharmaceutical compositions adapted for nasal administration may comprise solid carriers such as powders (preferably having a particle size in the range of 20 to 500 microns). Powders can be administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nose from a container of powder held close to the nose. Alternatively, compositions
20 adopted for nasal administration may comprise liquid carriers, e.g., nasal sprays or nasal drops. These compositions may comprise aqueous or oil solutions of the active ingredient. Compositions for administration by inhalation may be supplied in specially adapted devices including, but not limited to, pressurized aerosols, nebulizers or insufflators, which can be constructed so as to provide predetermined dosages of the active ingredient. Pharmaceutical
25 compositions may also be administered via the nasal cavity to the lungs.

Pharmaceutical compositions adapted for rectal administration may be provided as suppositories or enemas. Pharmaceutical compositions adapted for vaginal administration may be provided as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical compositions adapted for parenteral administration include aqueous and
30 non-aqueous sterile injectable solutions or suspensions, which may contain antioxidants, buffers, bacteriostats and solutes that render the compositions substantially isotonic with the blood of an intended recipient. Other components that may be present in such compositions include water, alcohols, polyols, glycerine and vegetable oils, for example. Compositions adapted for parenteral administration may be presented in unit-dose or multi-dose containers,

for example sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of a sterile liquid carrier, e.g., sterile saline solution for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

5 In a preferred embodiment, a compound used according to the invention as described herein is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine
10 to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically-sealed container such as an ampule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where
15 the composition is administered by injection, an ampule of sterile saline can be provided so that the ingredients may be mixed prior to administration.

 In another embodiment, for example, a compound used according to the invention as described herein or a pharmaceutical composition comprising the compound can be delivered in a controlled-release system. For example, the compound may be administered using
20 intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used (see Sefton (1987) *CRC Crit. Ref. Biomed. Eng.* **14**: 201; Buchwald et al. (1980) *Surgery* **88**:507; Saudek et al. (1989) *N. Eng. J. Med.* **321**: 574). In another embodiment, the compound can be delivered in a vesicle, in particular a liposome (see Langer (1990) *Science* **249**:1527-1533; Treat et al. (1989) in
25 Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, N.Y., 353-365; WO 91/04014; U.S. 4,704,355). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release (1974) Langer and Wise (eds.), CRC Press: Boca Raton, Fla.; Controlled Drug Bioavailability, Drug Product Design and Performance, (1984) Smolen and Ball (eds.), Wiley: N.Y.; Ranger and Peppas (1953) J.
30 Macromol. Sci. Rev. Macromol. Chem. **23**: 61; see also Levy et al. (1985) *Science* **228**:190; During et al. (1989) *Ann. Neurol.* **25**: 351; Howard et al. (1989) *J. Neurosurg.* **71**: 105).

 In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the target cells, tissue or organ, thus requiring only a fraction of the systemic dose (see, e.g., Goodson (1984) 115-138 in Medical Applications of Controlled

Release, vol. 2). Other controlled release systems are discussed in the review by Langer (1990, *Science* **249**: 1527-1533).

In a specific embodiment, it may be desirable to administer a compound used according to the invention as described herein or a pharmaceutical composition comprising the compound locally to the area in need of treatment. This may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as silastic™ membranes, or fibers.

Selection of the preferred effective dose of the compound used according to the invention as described herein will be determined by a skilled artisan based upon considering several factors which will be known to one of ordinary skill in the art. Such factors include the particular form of the pharmaceutical composition, e.g. polypeptide or vector, and its pharmacokinetic parameters such as bioavailability, metabolism, half-life, etc., which will have been established during the usual development procedures typically employed in obtaining regulatory approval for a pharmaceutical compound. Further factors in considering the dose include the condition or disease to be prevented and or treated or the benefit to be achieved in a normal individual, the body mass of the patient, the route of administration, whether administration is acute or chronic, concomitant medications, and other factors well known to affect the efficacy of administered pharmaceutical agents. Thus the precise dosage should be decided according to the judgment of the practitioner and each patient's circumstances, e.g., depending upon the condition and the immune status of the individual patient, according to standard clinical techniques. Typical doses of the compound used according to the invention are in the range of about 0.1 to 100 mg/kg, preferably of about 0.1 to 10mg/kg body weight.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known to those skilled in the art. For examples of methods of preparing pharmaceutical compositions, see Remington: *The Science and Practice of Pharmacy*, Lippincott, Williams & Wilkins, 21st ed. (2005).

In one embodiment of the invention, the compounds used according to the invention may also be combined with at least one additional therapeutic agent.

In one embodiment, the present invention also relates to a method for treating the specific diseases as defined above in a patient in need of such treatment comprising administering a compound used according to the present invention as defined above or a pharmaceutical composition as described herein.

In general, the compounds used according to the present invention can be prepared by the synthetic methods outlined in WO 2020/182384 A1, which is incorporated herein by reference.

5

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention. Compounds used within the scope of this invention can be synthesized as known in the art, e.g. from WO 2020/182384 A1, using a variety of reactions known to the skilled artisan. One skilled in the art will also recognize that alternative methods may be employed to synthesize the target compounds used in this invention. Certain molecules described herein can exist in different enantiomeric and diastereomeric forms and the use of all such variants of these compounds are claimed.

15

Example 1**A. The compounds used according to the invention are inhibitors of C5aR1**

The efficacy of the compounds used in accordance with the present invention to modulate activities of the mammalian C5a receptor by directly binding to the C5a receptor is confirmed by the results as shown below.

20

B. Biological Assays**Calcium⁺⁺ mobilization assay**

U937 cells (ATCC[®] CRL-1593.2) were cultivated in RPMI1640 medium supplemented with 10% fetal bovine serum in a standard cell culture incubator. The day before conducting the assay, Dibutyryl-cAMP (0.5 mM working concentration) was added to cell cultures. Next day, cells were spun and resuspended in RPMI 1640 to a concentration of 40,000 cells per 50 μ l. 40,000 cells were plated in one well in a 96 well poly-D-lysine coated plate for two hours to allow cells to adhere. After cell adherence, cytoplasmic calcium⁺⁺ indicator (FLIPR Calcium 6 Assay Kit, Molecular Devices) was added to each well and incubated for 75 minutes at 37 °C. Test compounds were diluted using a robotic liquid handler. The tips of the robotic liquid handler were changed after each mixing step. Test compounds were added into cell cultures at various concentrations (0.01 nM to 100 μ M) for 15 minutes at 37 °C. The cell culture plates were then incubated at room temperature for 30 minutes before being placed into Flexstation-3 plate reader (Molecular Devices). The Flexstation-3 was programmed to add recombinant

C5a protein at various concentrations (1 nM to 10 nM) to cell culture plates and to monitor the change of fluorescence intensity, which correlates with cytoplasmic calcium concentration. The assay was also performed with the presence of human or animal blood components, such as human or bovine plasma or serum.

5

Chemotaxis assay

U937 cells were cultivated in RPMI1640 medium supplemented with 10% fetal bovine serum in a standard cell culture incubator. The day before conducting the assay, Dibutyl-
cAMP (0.5 mM working concentration) was added to cell cultures. Next day cells were spun
10 and resuspended in RPMI 1640 to a concentration of 50,000 cells per 20 μ l. Cells were
incubated with compounds at various concentrations (0.01 nM to 100 μ M) for 30 minutes at 37
°C. 50,000 cells in 20 μ l of RPMI1640 were added into one well of upper chambers of a 96
well chemotaxis plate (the chemotaxis plates containing cell filters with 8 micrometer pores
were purchased from Neuroprobe). C5a or other chemoattractants with preferred concentration
15 in 29 μ l of HBSS buffer were added into lower chambers. Cells migrated into lower chambers
after one to three hours were stained using Cell Titer Glo (Invitrogen) and quantified using
FlexStation[®] 3. The assay was also performed with the presence of human or animal blood
components, such as human or bovine plasma or serum.

20 **Beta-arrestin assay**

U2OS (ATCC number HTB-96), an osteosarcoma cell line, was used to generate
genetically engineered cell lines that overexpress two types of fusion proteins in the same cells:
(a) fusion protein, TEV-C5aR1, which was composed of tobacco etch virus (TEV) protease
fused to wild type human C5aR1 or human C5aR1 mutants. C5aR1 mutants carry mutations of
25 amino acid(s) that was/were speculated to mediate the interaction between C5aR1 and test
compounds. (b) fusion protein, Luc-arrestin, which was composed of β -arrestin-2, inactive
permuted luciferase and a peptide constituting the TEV protease cleavage site. The peptide
localized between β -arrestin-2 and luciferase.

The engineered U2OS cell lines were used to access the activity of C5aR1 and to what
30 extent test compounds can modulate the activity of wild type or mutant C5aR1. In principle,
C5a binding to C5aR1 portion of the TEV-C5aR1 at the cell surface activates C5aR1, leading
to binding between the intracellular portion of TEV-C5aR1 to luc-arrestin inside cells, which
allows TEV to cleave the peptide connecting beta-arrestin and luciferase. This cleavage
converts inactive luciferase to active luciferase, which catalyzes added luciferase substrates and

thus generates luminescence signals. The intensity of luminescence signals correlate with the activity of C5aR1.

Experimentally, engineered U2OS cells were cultivated in McCoy's medium supplemented with 10% fetal bovine serum in a standard cell culture incubator. Test compounds were added into cell culture medium and incubated for 30 minutes, followed by adding C5a into cell culture medium and incubating for one to three hours. Cells were then lysed by reagents containing luciferase substrates, such as One-glo or Bright-glo (Promega). The luminescence units (RLU) were recorded using a luminescence plate reader, such as FlexStation® 3 (Molecular Devices).

C5a-induced CD11b expression in whole blood assay

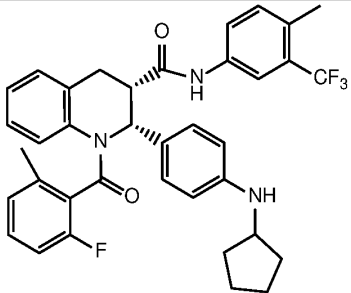
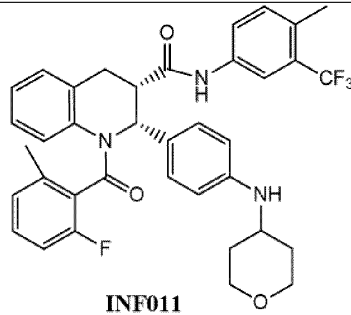
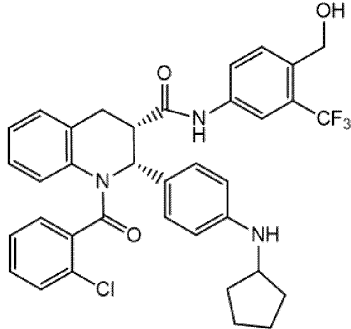
Fresh peripheral blood samples are procured from consented human volunteers. 100 µl whole blood is incubated with test compounds with various concentrations (0.01 nM to 10 µM) for 20 minutes at 37 °C and then incubated with C5a with a preferred concentration ranging from 1 nM to 30 nM for 20 minutes at 37 °C. The samples are ready for immunostaining followed by FACS (fluorescence activated cell sorting) analysis of CD11b expression by white blood cells. The samples are incubated with anti-CD11b antibody (BioLegend) on ice for 30 minutes protected from the light. One milliliter of Red Cell Lysis Buffer (Miltenyi) is added to 100 µl blood sample and incubated at room temperature for 10 minutes. Samples are washed using FACS staining buffer and resuspended in FACS buffer. Samples are analyzed by FACS (Beckman Coulter) for cell surface CD11b expression.

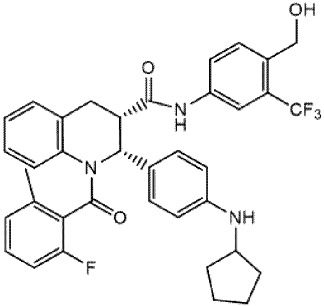
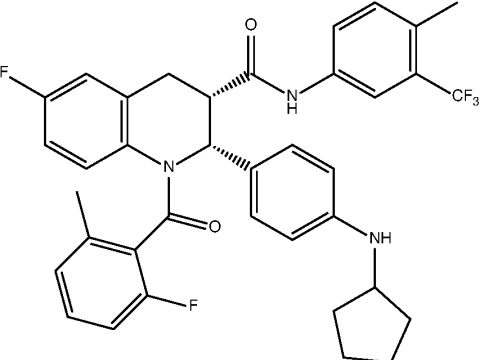
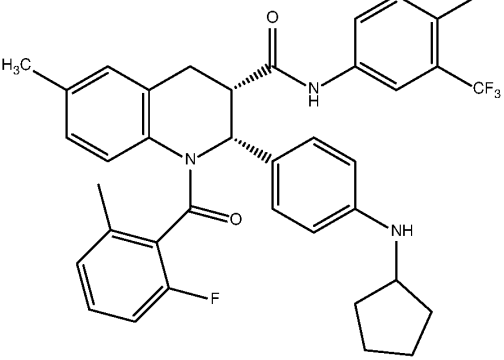
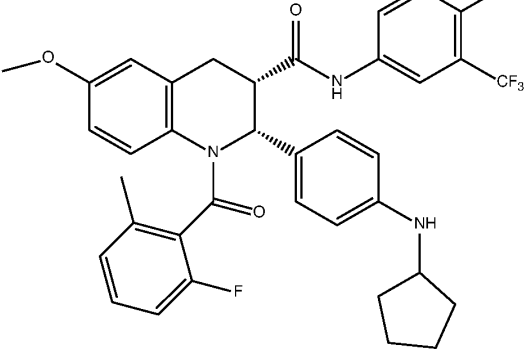
Animal neutropenia assay

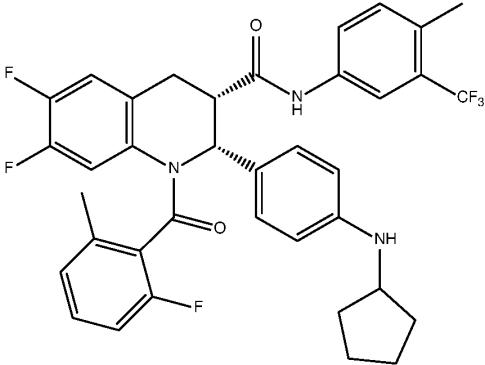
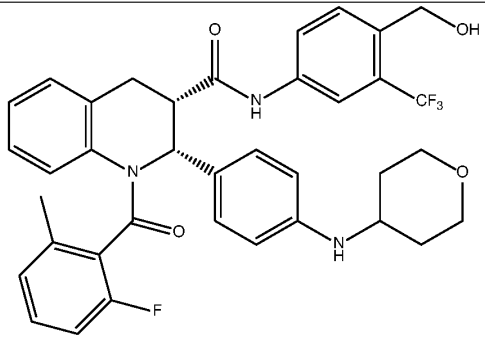
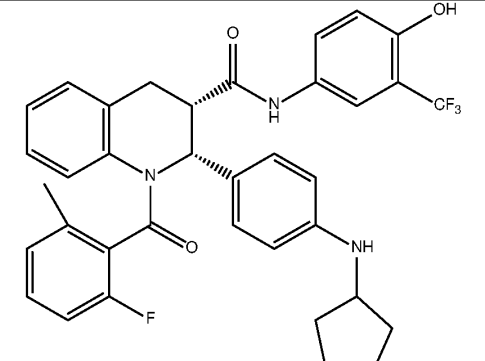
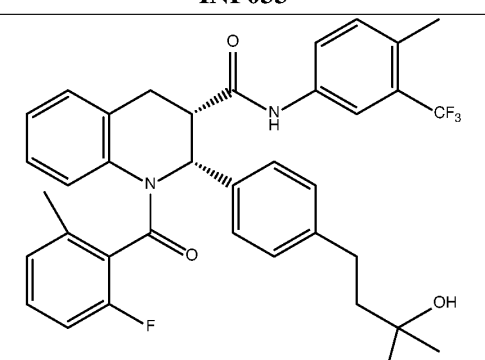
Animals (mouse, rats or Mongolian gerbils) are acclimated for at least three days before being used for experiments. Test compounds (1 to 30 mg/kg) are administrated orally or intravenously. One to three hours later, animals are anaesthetized using a standard procedure, such as intraperitoneal administration of ketamine and xylazine. Animals are catheterized for C5a intravenous administration and blood collection. C5a is constituted in saline and injected intravenously at doses ranging from 30 µg/kg to 120 µg/kg. Blood samples are collected several times over 30 minutes after C5a administration. Blood samples are collected using heparin tubes. White blood cell differentials, such as abundance of neutrophils, in collected blood samples are analyzed by an automated blood cell analyzer (Siemens).

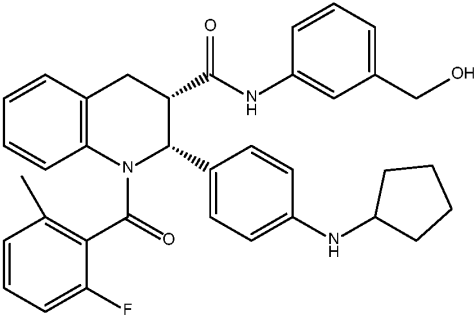
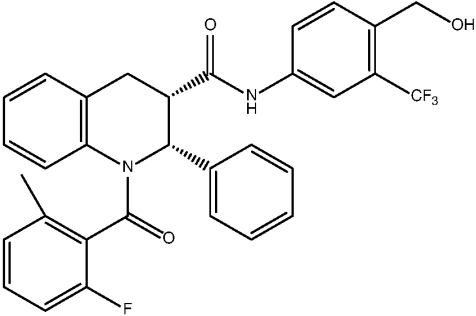
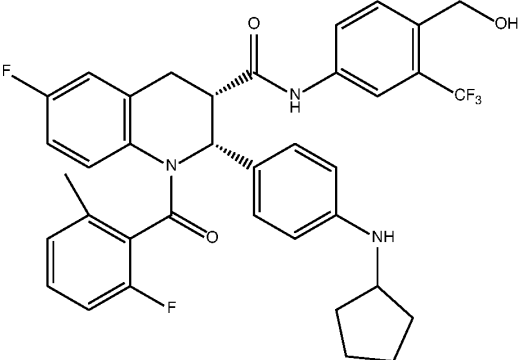
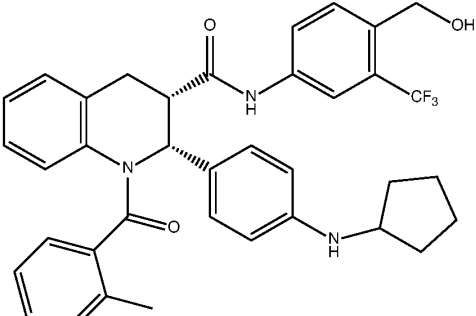
C. Results

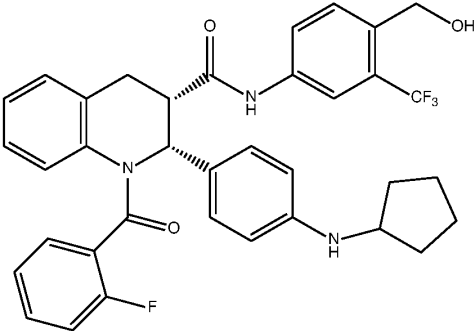
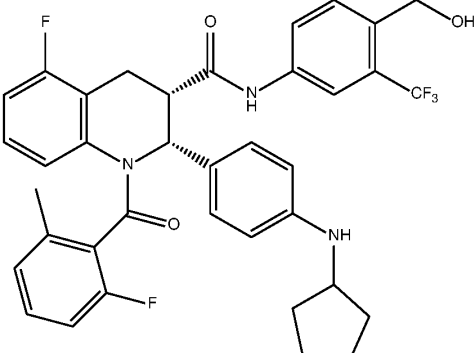
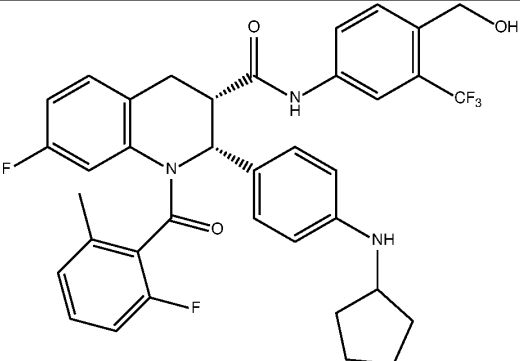
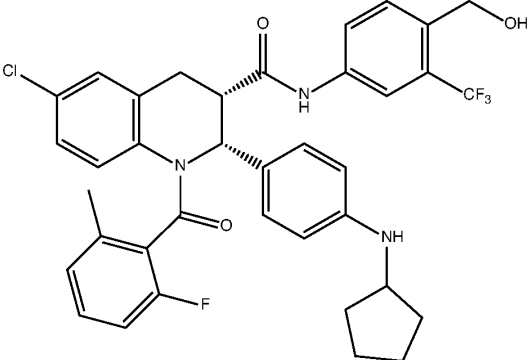
The half maximal inhibitory concentrations, i.e. IC_{50} , were determined in biological assays, such as calcium mobilization assay. Using the calcium mobilization assay the following IC_{50} values were determined by the best dose-response curve fitting method. The curves were plotted using percentage inhibition of C5a-induced calcium mobilization versus various concentrations of compounds.

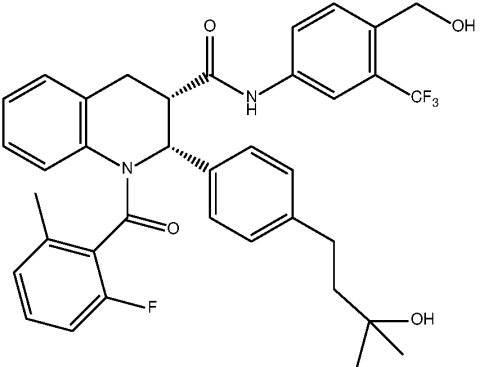
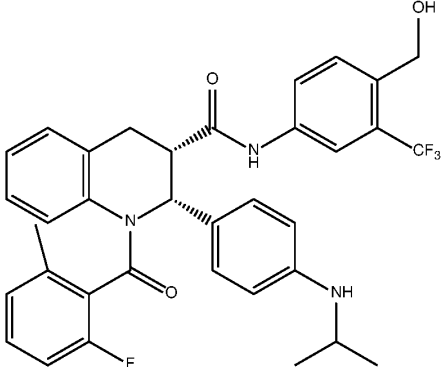
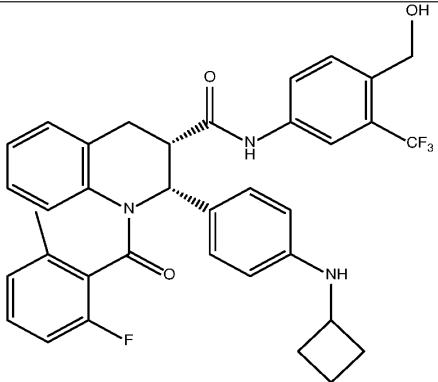
Chemical structure and short name of the compound	IC_{50}
 INF004	< 10 nM
 INF011	100 nM – 1 μ M
 INF014	100 nM – 1 μ M

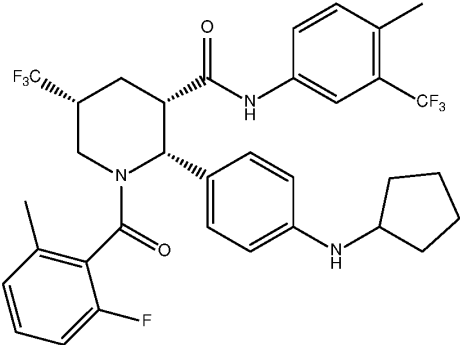
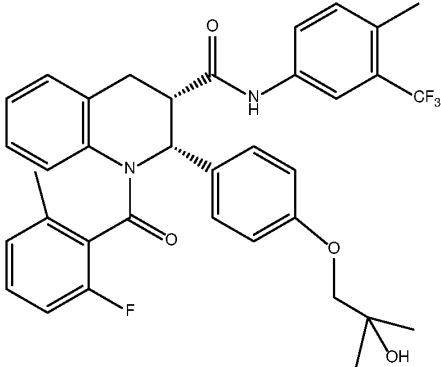
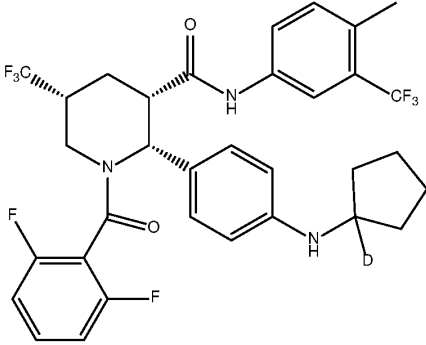
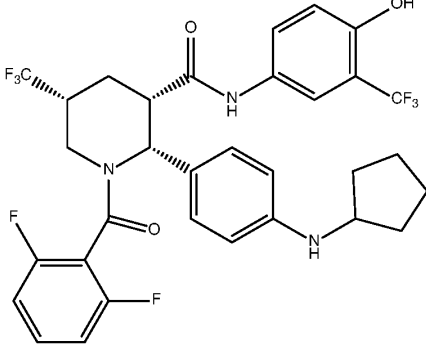
 INF015	< 10 nM
 INF022	< 10 nM
 INF023	< 10 nM
 INF024	< 10 nM

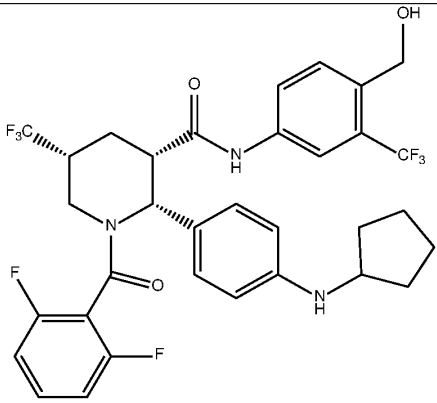
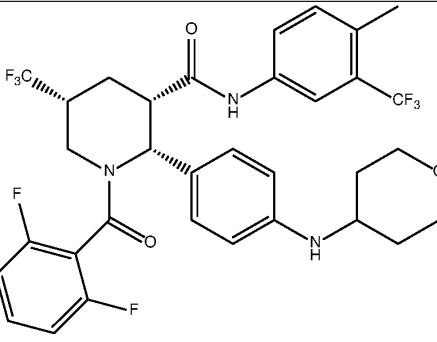
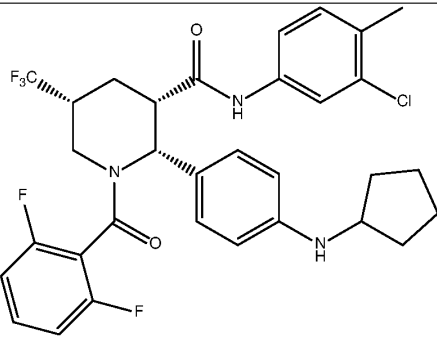
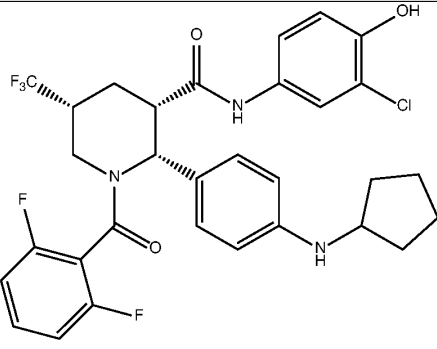
 Chemical structure of INF025: A complex molecule featuring a central piperidine ring substituted with a 2,6-difluorophenyl group, a 2-fluorophenyl group, and a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group. It also contains a 2-(cyclopentylamino)phenyl group and a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group.	10 nM – 100 nM
 Chemical structure of INF030: A complex molecule featuring a central piperidine ring substituted with a 2,6-difluorophenyl group, a 2-fluorophenyl group, and a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group. It also contains a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group and a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group.	1 μ M – 10 μ M
 Chemical structure of INF033: A complex molecule featuring a central piperidine ring substituted with a 2,6-difluorophenyl group, a 2-fluorophenyl group, and a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group. It also contains a 2-(cyclopentylamino)phenyl group and a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group.	< 10 nM
 Chemical structure of INF034: A complex molecule featuring a central piperidine ring substituted with a 2,6-difluorophenyl group, a 2-fluorophenyl group, and a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group. It also contains a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group and a 2-(3-(trifluoromethyl)-4-methylphenyl)amino group.	10 nM – 100 nM

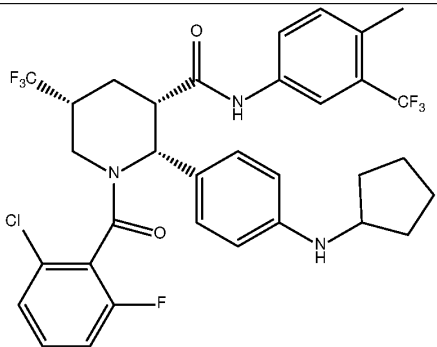
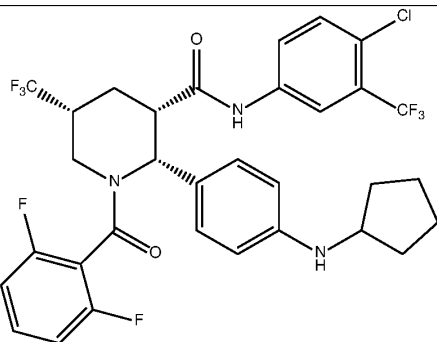
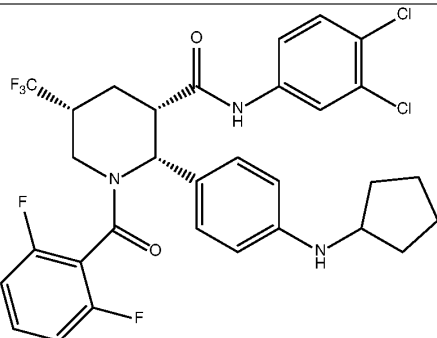
 INF035	1 μ M – 10 μ M
 INF038	100 nM – 1 μ M
 INF039	< 10 nM
 INF040	100 nM – 1 μ M

 INF041	100 nM – 1 μ M
 INF045	< 10 nM
 INF046	100 nM – 1 μ M
 INF047	10 nM – 100 nM

 Chemical structure of INF048: A complex molecule featuring a tricyclic core (a benzene ring fused to a six-membered ring containing a nitrogen atom, which is further fused to another benzene ring). The nitrogen atom is substituted with a 4-(hydroxymethyl)-3-(trifluoromethyl)phenyl group via an amide linkage. The six-membered ring also contains a carbonyl group and is substituted with a 4-(2-hydroxy-2-propyl)phenyl group. INF048	10 nM – 100 nM
 Chemical structure of INF049: Similar to INF048, but the six-membered ring is substituted with an isopropylamino group instead of the 4-(2-hydroxy-2-propyl)phenyl group. INF049	100 nM – 1 μ M
 Chemical structure of INF050: Similar to INF049, but the six-membered ring is substituted with a cyclobutylamino group instead of the isopropylamino group. INF050	10 nM – 100 nM

 INF056	10 nM – 100 nM
 INF058	1 μ M – 10 μ M
 INF067	< 10 nM
 INF068	< 10 nM

 INF069	100 nM – 1 μ M
 INF070	10 nM – 100 nM
 INF071	< 10 nM
 INF072	10 nM – 100 nM

 INF075	1 μ M – 10 μ M
 INF077	100 nM – 1 μ M
 INF080	100 nM – 1 μ M

INF004: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide

INF011: (2R,3S)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-

5 (trifluoromethyl)phenyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide

INF014: (2R,3S)-1-(2-chlorobenzoyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide

10 INF015: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide

- INF022: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-6-fluoro-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 5 INF023: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-6-methyl-N-(4-methyl-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- INF024: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-6-methoxy-N-(4-methyl-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 10 INF025: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-6,7-difluoro-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- INF030: (2R,3S)-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 15 INF033: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- INF034: (2R,3S)-1-(2-fluoro-6-methylbenzoyl)-2-(4-(3-hydroxy-3-methylbutyl)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 20 INF035: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-(hydroxymethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- INF038: (2R,3S)-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 25 INF039: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-6-fluoro-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- INF040: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1-(2-methylbenzoyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 30 INF041: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluorobenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- INF045: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-5-fluoro-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide

- INF046: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-7-fluoro-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 5 INF047: (2R,3S)-6-chloro-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- INF048: (2R,3S)-1-(2-fluoro-6-methylbenzoyl)-2-(4-(3-hydroxy-3-methylbutyl)phenyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 10 INF049: (2R,3S)-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-2-(4-(isopropylamino)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- INF050: (2R,3S)-2-(4-(cyclobutylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 15 INF051: (2R,3S)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((2-hydroxy-2-methylpropyl)amino)phenyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- INF052: (2R,3S,5R)-2-(4-(cyclopentylamino)phenyl)-1-(2,6-difluorobenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)piperidine-3-carboxamide
- 20 INF053: (2R,3S,5R)-2-(4-(cyclopentylamino)phenyl)-1-(2,6-dimethylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)piperidine-3-carboxamide
- INF054: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide;
- INF055: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 25 INF056: (2R,3S,5R)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)piperidine-3-carboxamide
- INF058: (2R,3S)-1-(2-fluoro-6-methylbenzoyl)-2-(4-(2-hydroxy-2-methylpropoxy)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide
- 30 INF067: (2R,3S,5R)-2-(4-((cyclopentyl-1-d)amino)phenyl)-1-(2,6-difluorobenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)piperidine-3-carboxamide

- INF068: (2R,3S,5R)-2-(4-(cyclopentylamino)phenyl)-1-(2,6-difluorobenzoyl)-N-(4-hydroxy-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)piperidine-3-carboxamide
- INF069: (2R,3S,5R)-2-(4-(cyclopentylamino)phenyl)-1-(2,6-difluorobenzoyl)-N-(4-(hydroxymethyl)-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)piperidine-3-carboxamide
- 5 INF070: (2R,3S,5R)-1-(2,6-difluorobenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)-5-(trifluoromethyl)piperidine-3-carboxamide
- INF071: (2R,3S,5R)-N-(3-chloro-4-methylphenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2,6-difluorobenzoyl)-5-(trifluoromethyl)piperidine-3-carboxamide
- INF072: (2R,3S,5R)-N-(3-chloro-4-hydroxyphenyl)-2-(4-(cyclopentylamino)phenyl)-1-10 (2,6-difluorobenzoyl)-5-(trifluoromethyl)piperidine-3-carboxamide
- INF075: (2R,3S,5R)-1-(2-chloro-6-fluorobenzoyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)piperidine-3-carboxamide
- INF077: (2R,3S,5R)-N-(4-chloro-3-(trifluoromethyl)phenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2,6-difluorobenzoyl)-5-(trifluoromethyl)piperidine-3-15 carboxamide
- INF080: (2R,3S,5R)-2-(4-(cyclopentylamino)phenyl)-N-(3,4-dichlorophenyl)-1-(2,6-difluorobenzoyl)-5-(trifluoromethyl)piperidine-3-carboxamide

Example 2 - Inhibition of C5a-Induced Neutropenia

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Hamsters are considered a pharmacologically relevant species having an analogue of human C5aR. Therefore, like in humans, the number of neutrophils in the hamster blood decreases significantly after C5a injection causing neutropenia. Not wishing to be bound by theory, it is assumed that the specific C5a receptor antagonists used according to the invention can ameliorate neutrophil infiltration.

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The effect on inhibition of neutropenia of INF052 and INF054 given by oral (PO) gavage prior to C5a injection was evaluated in Lakeview Golden (LVG) hamsters. C5a injection (100µg/kg, formulated in vehicle 2: saline) was conducted at 8, 24 hours post oral administration of compound (formulated in vehicle 1: 70% PEG-400/30% Solutol HS-15). Blood samples were collected at -1 min (before C5a), and +1 min (post C5a) through jugular vein catheter before and after C5a injections. Neutrophil counting and PK analysis were conducted to study animals.

The study evaluated the effect of INF052 and INF054 at doses of 10, 20, or 30 mg/kg PO (formulated in vehicle 1: 70% PEG-400/30% Solutol HS-15) prior to C5a injection (formulated in vehicle 2: saline) in LVG hamster at 4 (one 30mg/kg study), 8 and 24 h (10, 20, and 30mg/kg studies). Doses of INF052 and INF054 at 10, 20 and 30 mg/kg prior to C5a at 8 and 24 h significantly decreased changes in neutrophil numbers compared with the vehicle 1 + C5a (100 µg/kg) group. The results are summarized in the below Table 1. INF052 at 10 mg/kg demonstrated better potency compared to INF054 in the change in neutrophil numbers at 8 h (see Fig. 1).

Table 1

Formulation	70% PEG-400/30% Solutol HS-15					
C5a	100 µg/kg					
API (Dose)	INF054 (20mg/kg)		INF052 (20mg/kg)		INF071 (20mg/kg)	
Time points	8hr	24 hr	8hr	24 hr	8hr	24 hr
PK, ng/mL	331 ± 50	98 ± 22	922 ± 227	408 ± 216	998 ± 457	399 ± 112
% inhibition	74 ± 3	34 ± 6	84 ± 9	50 ± 5	79 ± 10	39 ± 4

PK: blood samples were collected into tube containing EDTA-K2 as anticoagulant 1 min post C5a injection. The plasma samples were kept at -80°C and the INF054/INF052 concentrations were analyzed by HPLC.

% inhibition: blood samples were collected at -1(prior dose) and 1 min post C5a injection into tube containing EDTA-K2 as anticoagulant, and neutrophils were counted by hematology analyzer (Siemens, ADVIA2120i). The % inhibition was calculated by comparing INF054/INF052-induced change of neutrophil count over the C5a-induced change of neutrophil count.

These results show that the compounds used according to the invention are efficacious in blocking C5a-induced neutropenia.

Example 3 - Inhibition of MSU-induced Peritonitis

Generally, injection of monosodium urate (MSU) crystals into hamster peritoneal cavities triggers the formation of inflammasome complexes and activates the complement cascade, which is assumed to lead to active C5a formation and IL-1β production. The latter leads to recruiting of circulating neutrophils to the site of MSU-induced inflammation, typically within

4 to 6 hours. The effect of INF052 was evaluated on a monosodium urate (MSU) induced acute peritonitis model in hamsters dosed orally with vehicle or 20 mg/kg of INF052 (vehicle: 70% PEG400, 30% Solutol HS15) and then treated with MSU crystal by intraperitoneal (IP) injection at 5 h post dosing. Injection of saline was used as a control. 6 hours post MSU injection, all the study animals were sacrificed. Blood samples and inflammatory exudates recovered from abdominal cavity were used for total cell count and differential analysis. The treatment groups were as follows:

Table 2

Group	Treatment	Dose level(mg/kg)	MSU	N	Frequency	Route
1	Saline	-	No	8	Single	IP
2	Vehicle + MSU	-	Yes	8	Single	P.O.+IP
3	INF052 + MSU	20	Yes	8	Single	P.O.+IP

The cell counts including white blood cells (WBC), neutrophils (Neut), lymphocytes (Lymph) and monocytes (Mono) in peritoneal lavage and blood in the groups (G) were as shown in Table 3 below:

Table 3

G	Peritoneal Lavage				Complete blood count			
	WBC (10 ⁶ cells)	Neut (10 ⁶ cells)	Lymph (10 ⁶ cells)	Mono (10 ⁶ cells)	WBC (10 ⁶ cells)	Neut (10 ⁶ cells)	Lymph (10 ⁶ cells)	Mono (10 ⁶ cells)
1	2.02±1.42**	0.29±0.08**	1.46±1.25**	0.02±0.03**	8.20±2.85	1.88±0.99**	5.51±1.49**	0.57±0.61
2	20.81±6.08	8.49±5.04	10.31±4.31	1.36±0.62	7.16±1.04	5.51±0.97	0.92±0.26	0.61±0.24
3	13.38±3.03**	3.24±2.60**	8.72±2.34	0.99±0.52	6.83±1.22	4.88±0.91	1.14±0.82	0.68±0.22

** p<0.01

The peritoneal lavage liquid volume was as follows:

Table 4

Group	Peritoneal lavage Liquid Volume(mL)
1	5.54±0.37**
2	6.41±0.33
3	6.06±0.29

As shown in the above results, MSU crystal dramatically increased the number of white blood cells in peritoneal lavage fluid, but not in blood. INF052 significantly decreased MSU-induced white blood cells (WBC) and neutrophil (Neut) numbers in peritoneal lavage liquid compared with treatment of MSU + vehicle (see also Fig. 2). In addition, no significant effect on IL-6, IL-1β levels of serum (data not shown), and peritoneal lavage liquid (see above Table 4) has been found. These results confirm that the recruitment of WBC, especially neutrophils at the site of inflammation could be inhibited by the presence of INF052.

In summary, this MSU-induced peritonitis model suggests that the compounds used according to the invention have the potential to inhibit the effects of neutrophil-driven inflammation *in vivo*, in particular monosodium urate (MSU)-induced inflammation.

Example 4 - Inhibition of ischemic reperfusion renal injury

Golden hamsters were dosed with vehicle or INF052 4 hours before surgery. Animals were anesthetized and the right renal artery, vein and ureter were tightened and the right kidney was removed. The left renal pedicle was clipped to stop the blood flow to the left kidney. After 45 minutes, the clip was removed and blood flow restored to the left kidney. The left renal artery was not clipped in the sham-operated group. The animals recovered for two days after surgery. 48 hours after surgery, animals were sacrificed. Blood and kidney tissue samples were collected for analysis. The animal groups are as shown in Table 5 below.

Table 5

Groups		No.	Route	Conc.	Dosage		Regimen
				mg/mL	ml/kg	mg/kg	
1	IRI + INF052	6	p.o.	20	5	100	single dose, 4hrs before surgery

2	IRI + Vehicle	6	p.o.	/	5	/	single dose, 4hrs before surgery
3	Sham- operated group + Vehicle	6	p.o.	/	5	/	single dose, 4hrs before surgery

IRI=ischemic reperfusion injury

The blood biochemistry results at 48 hours after ischemia surgery was as follows:

5 Table 6

Groups		CREA	BUN	CRP	PLT	D-dimer	FDP
		mg/dL	mmol/L	mg/L	10 ⁹ /L	µg/mL	µg/mL
G1-IRI + INF052 (100mg/kg, p.o.)	Mean	109.00	29.74	0.00	761.17	0.03	1.00
	SD	81.08	17.95	0.00	208.88	0.02	0.24
G2-IRI + Vehicle	Mean	409.83	66.07	0.00	802.17	0.02	2.32
	SD	37.87	5.43	0.00	124.60	0.00	1.19
G3-Naive + Vehicle	Mean	17.67	6.83	0.00	721.83	0.02	0.83
	SD	0.82	0.79	0.00	61.65	0.00	0.24

IRI=ischemic reperfusion injury

INF052 significantly reduced plasma levels of creatine (CREA) and blood urea nitrogen (BUN) after the ischemia reperfusion surgery, showing an effect of INF052 in preventing the kidney injury induced by ischemic reperfusion. C-reactive protein (CRP) was not detected, and fibrin/fibrinogen degradation products (FDP) and D-dimer were only detected at minimum detectable dose. Three ELISA assays including plasminogen, suPAR (soluble urokinase-type plasminogen activator receptor) and S100A8/A9 (Calprotectin) (data not shown) also couldn't detect any signal confirming lack of inflammation. Platelet counts remained the same with or without surgery or treatment, indicating platelets were not activated.

The histopathological status of the kidneys is summarized below:

Table 7

Groups		Histopathology					PAS
		Infarction	Dilated tubes	Plugged tubules	Necrotic area	Total	
G1 – IRI+INF052 (100mg/kg, p.o.)	Mean	1.83	2.33	2.17	2.17	8.5	1.67
	SD	0.75	0.52	0.41	0.75	1.64	0.82
G2 – IRI+Vehicle	Mean	2.83	3.17	3	3.33	12.33	2.5
	SD	0.75	0.98	0.89	0.82	3.14	1.05
G3 – Naïve+Vehicle	Mean	0.33	0.33	0.17	0	0.83	0.17
	SD	0.52	0.52	0.41	0	1.33	0.41

IRI=ischemic reperfusion injury

Histopathology Scoring Criteria

Descriptive definition of lesions	Score	Change Percentage
Infarcted area is defined as a portion or a zone of the kidney, showing identifiable tissue profiles and lost cellular details that are stained bright pink by H&E stain.	0	No
	1	<25%
	2	25%-50%
	3	50%-75%
	4	>75%
Dilated tubule is defined as a tubular structure having distended lumen and identifiable epithelial cells.	0	No
	1	<25%
	2	25%-50%
	3	50%-75%
	4	>75%
Plugged tubule is defined as a tubular structure having debris-filled lumen and identifiable epithelial cells.	0	No
	1	<25%
	2	25%-50%
	3	50%-75%
	4	>75%
Necrotic area is defined as a portion or a zone of the kidney other than the infarcted area, showing loss of both tissue profiles and cellular details.	0	No
	1	<25%
	2	25%-50%
	3	50%-75%
	4	>75%

PAS staining shows dilated Bowman's space, atrophic tubuli with protein casts, and tubular atrophy with thickening of the tubular basement membrane.	0	No
	1	<25%
	2	25%-50%
	3	50%-75%
	4	>75%

The results are illustrated in Fig. 3. Administration of INF052 reduced negative effects of ischemic reperfusion on kidneys as confirmed by histopathologic markers and periodic acid-schiff (PAS) staining.

5

In summary, this ischemic reperfusion renal injury model suggests that the compounds used according to the invention have the potential to inhibit the negative effects of neutrophil-driven inflammatory kidney diseases, in particular ischemic reperfusion on kidneys *in vivo*.

10 **Example 5 - Efficacy in unilateral ureteral obstruction (UUO) induced nephropathy**

The unilateral ureteral obstruction (UUO) model is a model of renal interstitial fibrosis. Renal tubular cell expression of the C5aR was sparse in normal renal cortex but markedly upregulated after UUO. It is found that C5 deficiency or inhibition of C5aR led to a significant reduction of extracellular matrix deposition and associated inflammation in the fibrotic kidneys. In this study, the efficacy of INF052 in UUO model was evaluated.

15

Golden Hamsters (8-10 weeks old) were randomly grouped into 3 groups to achieve similar average body weight. Animals in groups 2 and 3 were induced by UUO (Unilateral ureteral obstruction) surgery on day 1. The animals were anesthetized with 2-5% isoflurane. The left kidney was exposed through a flank incision, and the left ureter was tied off at the level of the lower pole with two 3.0 silk ties. Animals received pain medication, buprenorphine hydrochloride (0.05 mg/kg) and gentamicin (20 mg/kg, i.m.) after surgery. All animals were monitored until they regain consciousness. Animals were monitored on daily basis for general health. Animals were given vehicle or active ingredient for a total period of 14 days (see below Table 8).

20

25

Table 8

Groups		No.	Route	Conc.	Dosage		Regimen
				mg/mL	ml/kg	mg/kg	
1	Sham + Vehicle	6-8	p.o.	/	/	/	QD for 14 days
2	UUO + Vehicle	6-8	p.o.	/	5	/	QD for 14 days
3	UUO + INF052 (20mg/kg)	6-8	p.o.	4	5	20*	QD for 14 days

* on day 1, 1st dose was given 5hr before UUO procedure

UUO= unilateral ureteral obstruction

- 5 No significant difference of the left obstructed kidney weight/body weight after INF052 treatment was observed compared to group 2. No mortality was observed till 14-day post-surgery.

10 Serum creatinine levels slightly spiked in groups 2 and 3 about 3 days after surgery, but were normal at day 7 in all groups. Serum creatinine levels are typically not elevated until a substantial loss of kidney function occurred. In the UUO model used, only one kidney was obstructed with progressive fibrosis, but the other one still functions; therefore, no change of creatinine is to be expected.

- 15 As shown in Fig. 4, blood urea nitrogen (BUN) levels were significantly increased in group 2 at day 7 and 14 after UUO surgery. The treatment with INF052 was able to keep BUN levels at a low level very similar to surgery naïve animals, indicating that INF052 interfered with the UUO procedure and avoids inducing higher metabolism or inflammation activity.

- 20 The histopathological status of the kidneys is summarized in Table 9 below:

Table 9

Groups		H&E staining					Masson	α-SMA
		Infarction	Dilated tubes	Plugged tubules	Necrotic area	Total	Fibrosis	α-SMA
G1 – Vehicle only	Mean	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	SD	0.00	0.00	0.00	0.00	0.00	0.00	0.00
G2 – UUO+Vehicle	Mean	0.00	3.17	0.00	0.00	3.17	1.83	1.83
	SD	0.00	0.75	0.00	0.00	0.75	0.41	0.75
G3 – UUO+INF052 (20mg/kg)	Mean	0.00	1.83	0.00	0.00	1.83	1.33	1.50
	SD	0.00	0.75	0.00	0.00	0.75	0.52	0.84

UUO= unilateral ureteral obstruction

INF052 treatment in group 3 significantly attenuated the total score of H&E staining (see Fig. 5) compared to the UUO-vehicle group 2. INF052 further decreased the fibrosis score as determined by Masson’s staining and the score of alpha-SMA positive cells (see Table 9).

In summary, the results of the unilateral ureteral obstruction model suggest that the compounds used according to the invention have the potential to inhibit the negative effects of neutrophil-driven inflammatory kidney diseases, in particular of unilateral ureteral obstruction and thus the potential to treat obstructive nephropathy *in vivo*.

Example 6 - Efficacy in reducing reduced neutrophil activation driven by immune complexes in an immune complex model in human whole blood

The purpose of this study was to evaluate pro-inflammatory effects, such as complement activation and neutrophil stimulation, generated by different immune complexes (IC), as well as to demonstrate the inhibitory function of the C5aR antagonists used in the present invention in these rapid immune responses in a human whole blood model.

The IC involved in this study were formed through a co-incubation of a primary antibody rabbit IgG, either anti-human PMN IgG or irrelevant rabbit IgG, with a goat secondary anti-rabbit IgG to form polymorphonuclear neutrophil (PMN)-specific and non-PMN-specific IC, respectively, prior to whole blood stimulation. Neutrophil activation after mixing the respective IC with whole blood was manifested by an elevated level of C5a in the blood and an upregulation of CD11b expression on the surface of neutrophils. As a C5aR antagonist, INF052 has no impact

on the immediate innate immune response to the release of C5a. Therefore, its anti-inflammatory effect in this whole blood model can only be demonstrated by hindering the CD11b upregulation. The C5a level was determined by the C5a ELISA and CD11b was measured by flow cytometry via fluorescein isothiocyanate (FITC)-conjugated anti-CD11b antibody.

Methods

a. Immune complexes preparation and their application in human whole blood in the presence of or absence of C5a/C5aR axis blocker

Primary antibodies, rabbit IgG specific to PMN and non-PMN-specific, were diluted to a pre-final concentration of 500 µg/mL. Secondary anti-rabbit IgG was diluted to two different prefinal concentrations, 1 mg/mL and 0.5 mg/mL, in order to form two primary-to-secondary antibody ratios (1:2 and 1:1) of the IC. The primary and secondary antibodies, and the buffer HBSS were mixed in a 1:1:1 volumetric ratio. Several control samples were prepared as well, such as no-antibody blank control and the respective single antibody control. Each missing component in the mixture was replaced with equal volume of HBSS. The mixture was incubated at room temperature (RT) for 30 minutes to allow sufficient contact between each component and form the IC on demand. After that, 75 µL of the mixtures were co-incubated with 175 µL freshly withdrawn human whole blood (ACD as anti-coagulant) in the presence of 28 µL of either HBSS, 0.5% DMSO, or INF052, at 37°C for 30 minutes for CD11b upregulation and C5a release. The final in whole blood mixture concentration of the primary antibodies was 45 µg/mL and of the secondary antibodies were 45 µg/mL (primary-to-secondary antibody ratio 1:1) or 90 µg/mL (ratio 1:2).

b. Detection of IC-induced CD11b upregulation on the surface of neutrophils

100 µL of the above-described whole blood samples were placed on ice for 5 minutes. Cell surface CD11b was captured by 2 µL of FITC-conjugated anti-CD11b antibody during the 30 minutes incubation on ice in the dark. Red blood cells were lysed with 1 mL of 1× FACS Lysis Solution at RT for 10 min. After that, 2 mL of Staining Buffer was used to wash the cells twice by spinning at 2500 rpm for 3 min at RT. Cells were resuspended in 500 µL of Staining Buffer. All samples were analyzed within 1 h. Granulocytes were gated in the scatter plot and the mean fluorescence intensity (MFI) of antibody-bound cells was measured.

Results

As shown in Fig. 6, both PMN-specific and non-PMN-specific IgG immune complexes strongly upregulated the CD11b expression levels. PMN-specific IgG-IC induced clearly higher levels of CD11b than non- PMN-specific IgG-IC (3.4 – 5.3 times vs. 2.5 – 4.8 times increase in
5 CD11b signal at baseline). The ratio of antigen to antibody determines the size and shape of an immune complex. This, in turn, plays a role in the effect of the IC. The primary-to-secondary antibody ratio 1:2 showed a much stronger activation effect than ratio 1:1 (1.9-fold and 1.5-fold higher for non- PMN-specific IC and PMN-specific IC, respectively. See Fig. 6). The different levels of CD11b upregulated were efficiently blocked by 0.25 μ M (grey bars, second from
10 right) and 1 μ M (black bars) INF052 in Fig. 6.

Example 7 - Blocking the CD11b upregulation on neutrophils induced by Hidradenitis suppurativa patients' plasma

15 This Example describes the activation of neutrophils (CD11b upregulation) in human whole blood induced by plasma samples collected from four Hidradenitis suppurativa (HS) patients in two clinical studies and the successful blockade of this activation through the C5aR antagonist INF052. It demonstrates that drugs targeting C5aR used according to the present invention, such as INF052, are suitable for blocking the uncontrolled neutrophils activation in
20 Neutrophilic dermatoses (ND).

The purpose of the following study was to demonstrate: i) the plasma collected from patient with Hidradenitis suppurativa (HS) is able to activate neutrophils in human whole blood, which was manifested by the upregulation of CD11b on neutrophils; ii) the C5aR antagonist INF052
25 is highly potent in blocking the inappropriate or uncontrolled activation of neutrophils.

Accumulation of neutrophils at the site of inflammation is dependent on the expression of adhesion molecules, including CD11b. Upregulation and mobilizing of CD11b from intracellular pools to the surface of neutrophils is essential for the rolling action and migration
30 of human neutrophils. Enhanced expression of CD11b therefore reflects an inflammatory triggering event. Activated complement products, especially elevated C5a in HS patient's blood, can strongly upregulate CD11b expression through the binding of C5a to its receptor C5aR on neutrophils. As a consequence, blockade of the C5a-C5aR axis is expected to abolish or attenuate CD11b upregulation on the surface of neutrophils.

The human CD11b assay was conducted using flow cytometry to detect FITC-conjugated anti-CD11b antibody on the surface of neutrophils. The blocking activity of the C5aR antagonist was determined through the reduction of fluorescence intensity emitted by the FITC-conjugated anti-CD11b antibody bound to neutrophils compared to the activated condition.

5

Experimental

Samples

According to the consensus definition, one HS patient’s plasma sample from the Clinic of Pathology, Attiko Univ. General Hospital, Athens and three plasma samples from the Phase IIB Trial SHINE (ClinicalTrials.gov ID: NCT03487276) were applied in this study. The complement system was activated in the pathogenesis of HS as manifested by the elevated levels of C3a, C5a and C5b-9. The C5a levels of the four HS patients are listed below, which are significantly higher than that of a normal healthy human.

10

Patient ID	C5a (ng/mL)
pat 088	93.77
160-0004	251.49
160-0006	219.93
160-0010	122.7

15 The healthy human citrate (Acid Citrate Dextrose) plasma of a single donor was purchased from Biomex GmbH and used as the control of non-activated/non-inflammatory condition. The C5aR antagonist INF052 was used dissolved in DMSO as a 10 mM stock solution and stored at -70°C.

20 **Procedures**

a) Preparation of INF052-spiked human whole blood

Human whole blood was freshly withdrawn from a healthy donor in the presence of 12% citrate-dextrose solution (ACD). INF052 stock solution (10 mM in 100% DMSO) was diluted stepwise in DMSO and then in HBSS to reach the targeted 10-fold concentrated working solutions in HBSS/2.5% DMSO. These working solutions were then diluted 10 times in whole blood to get the final INF052-spiked human whole blood. As the control, 100% DMSO was diluted in the same way and spiked in whole blood. The spiked blood samples were incubated at 37°C for 30 minutes, giving sufficient time for the binding of INF052 to C5aR.

25

b) Human CD11b Potency Assay (Flow Cytometric Assay)

The neutrophil CD11b upregulation blockade by INF052 was performed *ex vivo* in either INF052 (0.25% DMSO) or 0.25% DMSO spiked human whole blood. Recombinant human C5a (rhC5a) at a final concentration of 15 nM was used as the positive control to confirm the activation of neutrophils. Each sample was measured in duplicate.

12 µL of healthy human plasma (huP), HS patient’s plasma or 150 nM rhC5a was added to 80 µL of INF052/DMSO-spiked whole blood, respectively. The final volume of each test sample was filled up to 120 µL with HBSS. Below is the simplest example of samples tested in one assay. In real cases, several patients’ samples as well as several different concentrations of INF052 can be added to one assay.

ID	Sample	HBSS	Plasma	rhC5a	Respectively Spiked Blood
1 / 2	HBSS DMSO	40	–	–	80
3 / 4	HBSS DMSO huP	28	12	–	
5 / 6	HBSS DMSO HS patient’s plasma	28	12	–	
7 / 8	HBSS DMSO huP rhC5a (15 nM)	16	12	12	
9 / 10	HBSS INF052	40	–	–	80
11 / 12	HBSS INF052 huP	28	12	–	
13 / 14	HBSS INF052 HS patient’s plasma	28	12	–	
15 / 16	HBSS INF052 huP rhC5a (15 nM)	16	12	12	
17 / 18	HBSS INF052 huP rhC5a (15 nM)	16	12	12	

All samples were then incubated for 20 min at 37°C to allow time for CD11b expression followed by a 5 min exposure on ice to cease further protein expression. To detect the CD11b expression on neutrophils, 2 µL of FITC-conjugated anti-CD11b antibody was then added to each sample and incubated on ice in the dark for 30 min. Red blood cells (RBC) were lysed using 1 mL 1× FACS Lysing solution at room temperature for 10 min. After RBC lysis, remaining blood cells were washed twice with 2 mL Staining Buffer (SB), centrifuged for 3 min at 1300 g at RT and resuspended in 500 µL SB. Resuspended cells were analyzed within 1 h by flow cytometer. On the FSC vs. SSC dot plot, granulocytes were gated and mean

fluorescence intensity (MFI) of the FITC labeled (*via* anti-CD11b antibody) granulocytes were recorded. The % Blockade of the C5aR antagonist was calculated as follows:

$$\% \text{ Blockade} = \frac{\text{MFI (patient plasma)} - \text{MFI (patient plasma + INF052)}}{\text{MFI (patient plasma)} - \text{MFI (healthy human plasma)}} \times 100$$

5

Results

HS Patients' Plasma Upregulated the CD11b Expression on Neutrophils

CD11b expression on neutrophils was evaluated with the plasma samples from healthy blood donor and several diagnosed HS patients (pat 088, 160-0004, 160-0006 & 160-0010). The mean fluorescence intensity (MFI) of the healthy control was 5412 ± 301.2 (mean $\pm$ SD) in the first assay and 4523.5 ± 41.7 in the second assay with the study samples from SHINE. These were the non-stimulated baseline expression level of CD11b. In the presence of individual HS patient's plasma, a 2.3 – 2.6-fold elevation of CD11b expression was achieved, which was fully comparable to that of the positive control, 15 nM rhC5a (2.2 – 2.4-fold) (Tables 10 & 11, Figs. 7 & 8). These data demonstrated a significantly upregulated CD11b expression on neutrophils mediated by the inflammatory factors in HS patients' plasma.

INF052 successfully blocked the HS- and C5a-Induced CD11b Upregulation

As described above, both HS patients' plasma and 15 nM rhC5a strongly upregulated the CD11b expression on blood neutrophils. The activation could be efficiently blocked *via* incubation of whole blood with C5aR antagonist INF052 prior to the contact of stimulators (i.e., HS patient plasma or C5a) in a dose-dependent manner. In the first experiment employing the plasma sample from a HS patient (pat 088), all three concentrations of INF052, i.e. 50 nM, 250 nM and 1 μ M, presented a >120% blocking effect. A >100% blockade suggests that INF052 not only inhibited the stimulating effects resulted from HS plasma or C5a, but also prevented other indirect or non-specific activations of neutrophils during the long incubation period (Table 10 & Fig. 7). Similar results were obtained in the second experiment by employing other three HS patients' samples from SHINE study, where 100 nM and 250 nM INF052 alone reduced the "baseline" CD11b signals to 20.5% and 51.6%, respectively. As for the CD11b elevations driven by the patient's plasma, 64.4% – 94.8% and 92.6% – 118.8% blocking were achieved from 100 nM and 250 nM INF052, respectively (Table 11 & Fig. 8). All these results demonstrated that C5a/C5aR axis plays a predominantly role in the CD11b expression on neutrophils. Drugs targeting C5aR as used according to the present invention,

such as INF052, are thus suitable for blocking the uncontrolled neutrophils activation in Neutrophilic dermatoses (ND).

Table 10. CD11b expression levels (MFI) on neutrophils, the activation *via* one HS patient (pat 088) plasma and 15 nM rhC5a, and the blocking effect of INF052.

ID	Sample Description	CD11b MFI		Activation (-fold)		Reduction from Baseline (%)		% Blockade	
		Mean	SD	vs. HBSS	vs. HBSS huP	vs. HBSS huP	vs. HBSS huP	vs. HBSS huP	vs. HBSS huP
1/2	HBSS DMSO (Baseline w/o plasma)	5669.5	478.7	1	–	–	–	–	–
3/4	HBSS DMSO huP (Baseline w/ plasma)	5412	301.2	1.0	1	0	–	–	–
5/6	HBSS DMSO pat 088 plasma	12608.5	74.3	2.2	2.3	–	–	–	–
7/8	HBSS DMSO huP rhC5a (15 nM)	13099.5	142.1	2.3	2.4	–	–	–	–
9/10	HBSS INF052 (1 µM)	3384	158.4	–	n.a. (no plasma in this sample)	–	–	–	–
11/12	HBSS INF052 (1 µM) huP	3645	190.9	–	–	32.65	–	–	–
13/14	HBSS INF052 (50 nM) pat 088 plasma	3719.5	113.8	–	–	31.27	123.52	–	–
15/16	HBSS INF052 (250 nM) pat 088 plasma	3870	175.4	–	–	28.49	121.43	–	–
17/18	HBSS INF052 (1 µM) pat 088 plasma	3519	7.1	–	–	34.98	126.30	–	–
19/20	HBSS INF052 (50 nM) huP rhC5a (15 nM)	4858.5	9.2	–	–	10.23	107.20	–	–
21/22	HBSS INF052 (250 nM) huP rhC5a (15 nM)	4575	32.5	–	–	15.47	110.89	–	–
23/24	HBSS INF052 (1 µM) huP rhC5a (15 nM)	4006.5	87.0	–	–	25.97	118.28	–	–

Table 11. CD11b expression levels (MFI) on neutrophils, the activation *via* three HS patients' plasma from SHINE study and 15 nM rhC5a, and the blocking effect of INF052.

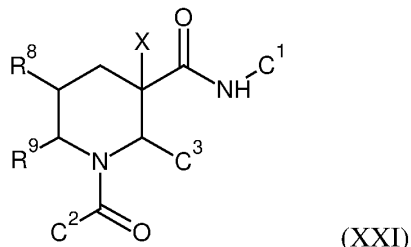
ID	Sample Description	CD11b MFI		Activation (-fold)		Reduction from Baseline (%)		% Blockade
		Mean	SD	vs. HBSS	vs. HBSS huP	vs. HBSS huP	vs. HBSS huP	
1/2	HBSS DMSO (Baseline w/o plasma)	4086.5	153.4	1	–	–	–	–
3/4	HBSS DMSO huP (Baseline w/ plasma)	4523.5	41.7	1.1	1	0	–	–
5/6	HBSS DMSO 160-0004 plasma	11889.5	384.0	2.9	2.6	–		
7/8	HBSS DMSO 160-0006 plasma	10339.5	249.6	2.5	2.3			
9/10	HBSS DMSO 160-0010 plasma	10637	263.0	2.6	2.4			
11/12	HBSS DMSO huP rhC5a (15 nM)	9974.5	301.9	2.4	2.2			
13/14	HBSS INF052 (100 nM)	3217.5	145.0	–	n.a. (no plasma in this sample)			
15/16	HBSS INF052 (100 nM) huP	3597.5	4.9	–		20.47	–	–
17/18	HBSS INF052 (100 nM) 160-0004 plasma	5578.5	24.7			85.7		
19/20	HBSS INF052 (100 nM) 160-0006 plasma	4826	138.6			94.8		
21/22	HBSS INF052 (100 nM) 160-0010 plasma	6697.5	26.2			64.4		
23/24	HBSS INF052 (100 nM) huP rhC5a (15 nM)	5087.5	72.8			89.7		
25/26	HBSS INF052 (250 nM)	2003	14.1	–	n.a. (no plasma in this sample)			–
27/28	HBSS INF052 (250 nM) huP	2187.5	2.1	–		51.64	–	–
29/30	HBSS INF052 (250 nM) 160-0004 plasma	3975	75.0			12.13	107.4	
31/32	HBSS INF052 (250 nM) 160-0006 plasma	3428.5	75.7			24.21	118.8	
33/34	HBSS INF052 (250 nM) 160-0010 plasma	4977.5	103.9			–	92.6	
35/36	HBSS INF052 (250 nM) huP rhC5a (15 nM)	2907.5	27.6			35.72	129.6	

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CLAIMS

1. A compound having the general formula (XXI)



5

and pharmaceutically acceptable salts, hydrates and rotamers thereof;
wherein

C¹ is selected from the group consisting of aryl and heteroaryl, wherein the heteroaryl group
has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said
10 aryl and heteroaryl groups are optionally substituted with from 1 to 3 R¹ substituents;

C² is selected from the group consisting of aryl and heteroaryl, wherein the heteroaryl group
has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said
aryl and heteroaryl groups are optionally substituted with from 1 to 3 R² substituents;

C³ is selected from the group consisting of C₁₋₈ alkyl or heteroalkyl, C₃₋₈ cycloalkyl, C₃₋₈
15 cycloalkyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl,
heterocycloalkyl or heterocycloalkyl-C₁₋₄ alkyl, wherein the heteroalkyl group has from
1-3 heteroatoms selected from N, O and S, wherein the heterocycloalkyl group or
portion has from 1-3 heteroatoms selected from N, O and S, and wherein the heteroaryl
group has from 1-3 heteroatoms as ring members selected from N, O and S, and each
20 C³ is optionally substituted with from 1 to 3 R³ substituents;

each R¹ is independently selected from the group consisting of halogen, —CN, —R^c, —CO₂R^a,
—CONR^aR^b, —C(O)R^a, —OC(O)NR^aR^b, —NR^bC(O)R^a, —NR^bC(O)₂R^c, —NR^a—
C(O)NR^aR^b, —NR^aC(O)NR^aR^b, —NR^aR^b, —OR^a, and —S(O)₂NR^aR^b; wherein each
R^a and R^b is independently selected from hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl, or
25 when attached to the same nitrogen atom can be combined with the nitrogen atom to
form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring
members selected from N, O or S, and is optionally substituted with one or two oxo;
each R^c is independently selected from the group consisting of C₁₋₈ alkyl or heteroalkyl,
C₁₋₈ haloalkyl, C₃₋₆ cycloalkyl, heterocycloalkyl, aryl and heteroaryl, and wherein the
30 aliphatic and/or cyclic portions of R^a, R^b and R^c are optionally further substituted with

from one to three halogen, hydroxy, methyl, amino, alkylamino and dialkylamino groups; and optionally when two R^1 substituents are on adjacent atoms, are combined to form a fused five or six-membered carbocyclic or heterocyclic ring;

each R^2 is independently selected from the group consisting of halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{R}^f$,
 5 $-\text{CO}_2\text{R}^d$, $-\text{CONR}^d\text{R}^e$, $-\text{C}(\text{O})\text{R}^d$, $-\text{OC}(\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^e\text{C}(\text{O})\text{R}^d$, $-\text{NR}^e\text{C}(\text{O})_2\text{R}^f$,
 $-\text{NR}^d\text{C}(\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^d\text{R}^e$, $-\text{OR}^d$, and $-\text{S}(\text{O})_2\text{NR}^d\text{R}^e$; wherein each R^d and R^e is
 independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached
 10 to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-
 membered ring having from 0 to 2 additional heteroatoms as ring members selected
 from N, O or S, and is optionally substituted with one or two oxo; each R^f is
 independently selected from the group consisting of C_{1-8} alkyl or heteroalkyl, C_{1-8}
 haloalkyl, C_{3-6} cycloalkyl, heterocycloalkyl, aryl and heteroaryl, and wherein the
 aliphatic and/or cyclic portions of R^d , R^e and R^f are optionally further substituted with
 15 from one to three halogen, hydroxy, methyl, amino, alkylamino and dialkylamino
 groups, and optionally when two R^2 groups are on adjacent atoms, they are combined to
 form a five- or six-membered ring;

each R^3 is independently selected from the group consisting of halogen, $-\text{CN}$, $-\text{R}^i$, $-\text{CO}_2\text{R}^g$,
 $-\text{CONR}^g\text{R}^h$, $-\text{C}(\text{O})\text{R}^g$, $-\text{C}(\text{O})\text{R}^i$, $-\text{OC}(\text{O})\text{NR}^g\text{R}^h$, $-\text{NR}^h\text{C}(\text{O})\text{R}^g$, $-\text{NR}^h\text{CO}_2\text{R}^i$,
 20 $-\text{NR}^g\text{C}(\text{O})\text{NR}^g\text{R}^h$, $-\text{NR}^g\text{R}^h$, $-\text{OR}^g$, $-\text{OR}^j$, $-\text{S}(\text{O})_2\text{NR}^g\text{R}^h$, $-\text{X}^4-\text{R}^j$, $-\text{NH}-\text{X}^4-\text{R}^j$,
 $-\text{O}-\text{X}^4-\text{R}^j$, $-\text{X}^4-\text{NR}^g\text{R}^h$, $-\text{X}^4-\text{NHR}^j$, $-\text{X}^4-\text{CONR}^g\text{R}^h$, $-\text{X}^4-\text{NR}^h\text{C}(\text{O})\text{R}^g$,
 $-\text{X}^4-\text{CO}_2\text{R}^g$, $-\text{O}-\text{X}^4-\text{CO}_2\text{R}^g$, $-\text{NH}-\text{X}^4-\text{CO}_2\text{R}^g$, $-\text{X}^4-\text{NR}^h\text{CO}_2\text{R}^i$, $-\text{O}-$
 $\text{X}^4-\text{NR}^h\text{CO}_2\text{R}^i$, $-\text{NHR}^j$ and $-\text{NHCH}_2\text{R}^j$, wherein X^4 is a C_{1-4} alkylene; each R^g and
 R^h is independently selected from hydrogen, C_{1-8} alkyl or heteroalkyl, C_{3-6} cycloalkyl
 25 and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with
 the nitrogen atom to form a four-, five- or six-membered ring having from 0 to 2
 additional heteroatoms as ring members selected from N, O or S and is optionally
 substituted with one or two oxo; each R^i is independently selected from the group
 consisting of C_{1-8} alkyl or heteroalkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, heterocycloalkyl,
 aryl and heteroaryl; and each R^j is selected from the group consisting of C_{3-6} cycloalkyl,
 30 imidazolyl, pyrimidinyl, pyrrolinyl, pyrrolyl, piperidinyl, morpholinyl,
 tetrahydrofuranyl, tetrahydropyranyl, and S,S-dioxo-tetrahydrothiopyranyl, and
 wherein the aliphatic and/or cyclic portions of R^g , R^h , R^i and R^j are optionally further
 substituted with from one to three halogen, methyl, CF_3 , hydroxy, C_{1-4} alkoxy, C_{1-4}
 alkoxy- C_{1-4} alkyl, $-\text{C}(\text{O})\text{O}-\text{C}_{1-8}$ alkyl, amino, alkylamino and dialkylamino groups,

and optionally when two R³ groups are on adjacent atoms, they are combined to form a five- or six-membered ring;

X is hydrogen or CH₃; and

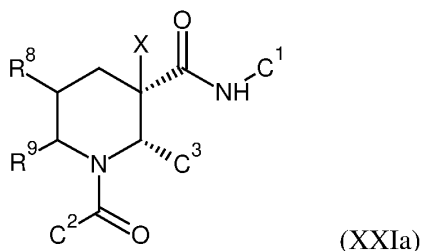
R⁸ and R⁹ are independently from each other selected from the group consisting of hydrogen, halogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, and C₁-C₈ alkoxy or R⁸ and R⁹ are combined to form a fused saturated or unsaturated mono- or multi-ring carbocycle in which one or more of the ring carbon atoms may be replaced independently from each other by N, S, or O,

for use in the treatment or prevention of a disease or disorder selected from the group consisting of

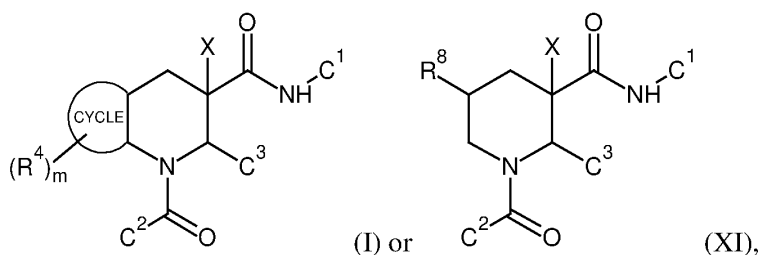
- monosodium urate (MSU)-inducible diseases,
- neutrophil-driven inflammatory kidney diseases,
- cutaneous neutrophilic inflammatory diseases, and
- immune complex diseases.

2. The compound for use according to claim 1, wherein at least one of R⁸ and R⁹ is **not** hydrogen and/or wherein X is hydrogen.

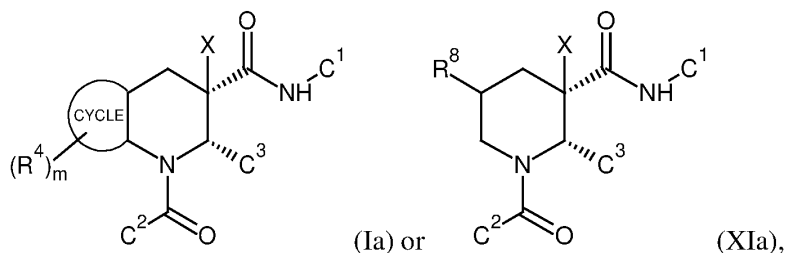
3. The compound for use according to claim 1 or claim 2, wherein the compound has formula (XXIa)



4. The compound for use according to any one of claims 1 to 3, wherein the compound has formula (I) or formula (XI):



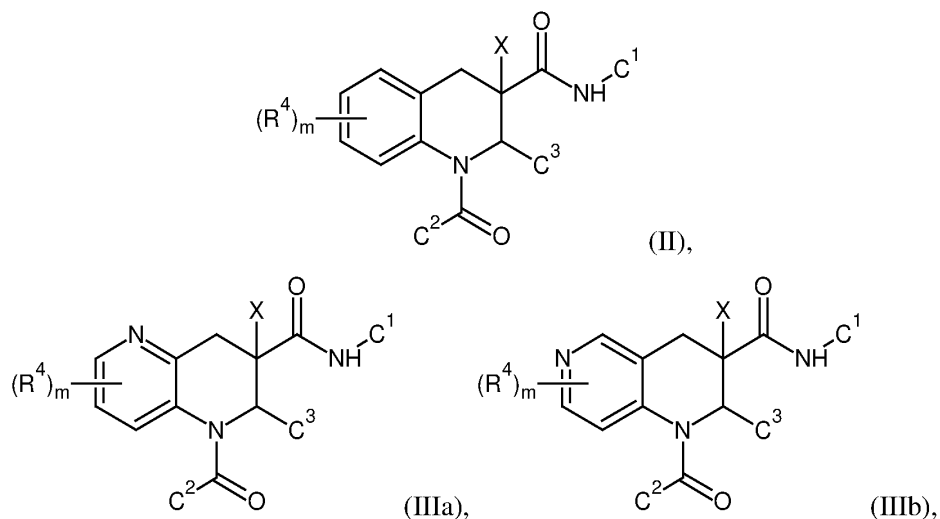
preferably has formula (Ia) or formula (XIa):

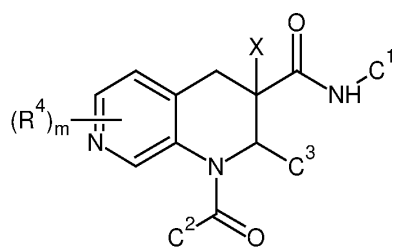


wherein

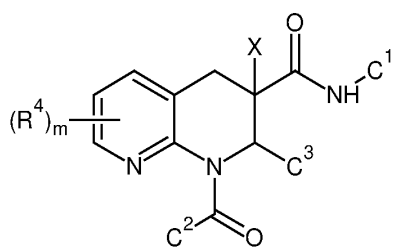
- 5 R^4 is selected from the group consisting of cyano, halo, nitro, hydroxyl, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl-OH, (C₁-C₆)-alkyl-NR⁵R⁶, trifluoromethyl, (C₁-C₆)alkoxy, (C₁-C₆)thioalkoxy, phenoxy, COR⁷, NR⁵R⁶, NHCO(C₁-C₆) alkyl, SO₃H, SO₂(C₁-C₆) alkyl and SO₂NR⁵R⁶;
- R^5 and R^6 are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl and (C₃-C₆)cycloalkyl;
- 10 R^7 is independently hydroxyl, (C₁-C₆)alkoxy, phenoxy or -NR⁵R⁶;
- m is 0-4; and
- CYCLE is a saturated or unsaturated mono- or multi-ring carbocycle in which one or more of the ring carbon atoms may be replaced independently from each other by N, S, or O.

- 15 5. The compound for use according to any one of claims 1 to 4, wherein the compound has a formula selected from the group consisting of (II), (IIIa), (IIIb), (IIIc), and (IIId):





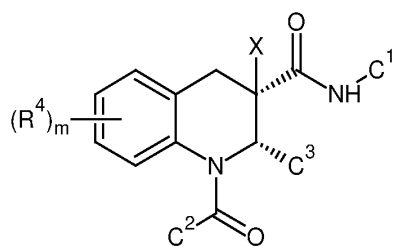
(IIIc), and



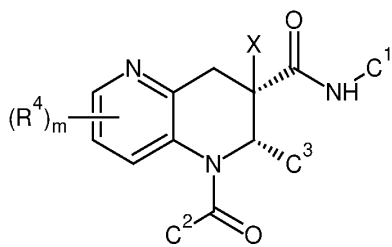
(IIIId),

preferably has a formula selected from the group consisting of (IIa), (IIIc), (IIIe), (IIIg), and (IIIh):

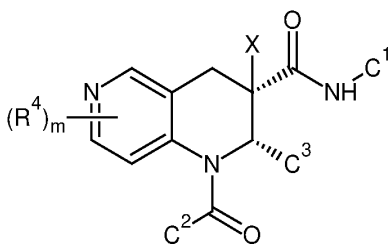
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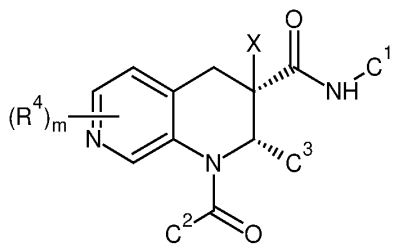
(IIa),



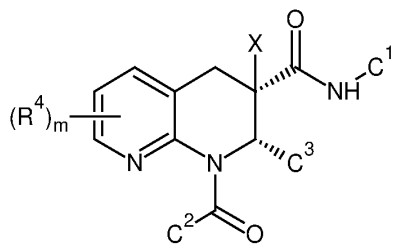
(IIIe),



(IIIff),

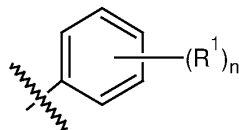


(IIIgg), and



(IIIhh).

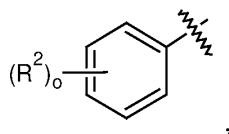
10 6. The compound for use according to any one of claims 1 to 5, wherein C¹ is



wherein

n is an integer selected from 0, 1, 2, or 3.

7. The compound for use according to any one of claims 1 to 6, wherein C² is

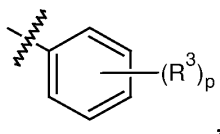


wherein

o is an integer selected from 0, 1, 2, or 3.

5

8. The compound for use according to any one of claims 1 to 7, wherein C³ is



wherein

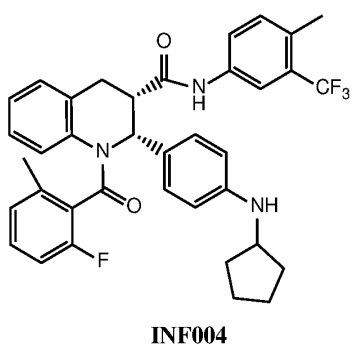
p is an integer selected from 0, 1, 2, or 3.

10

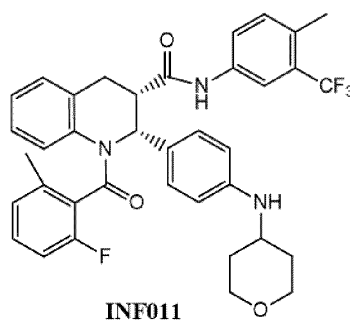
9. The compound for use according to any one of claims 1 to 4, 6, 7 or 8, wherein R₈ is selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkoxy; preferably from the group consisting of fluoro, chloro, methyl, trifluoromethyl, and methoxy.

15

10. The compound for use according to any one of claims 1 to 8, wherein the compound is selected from the group consisting of

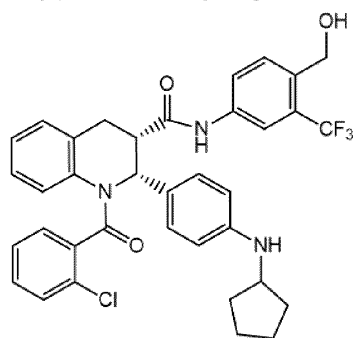


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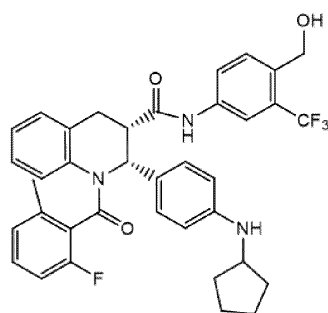


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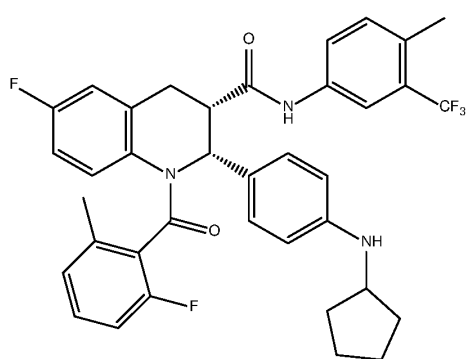
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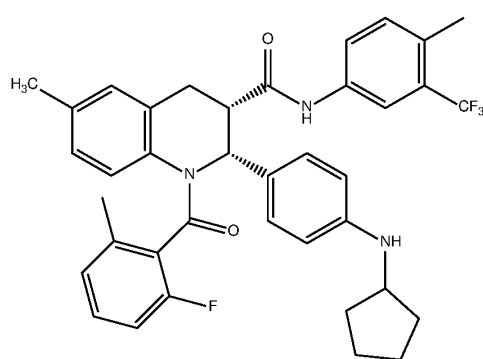
INF014



INF015

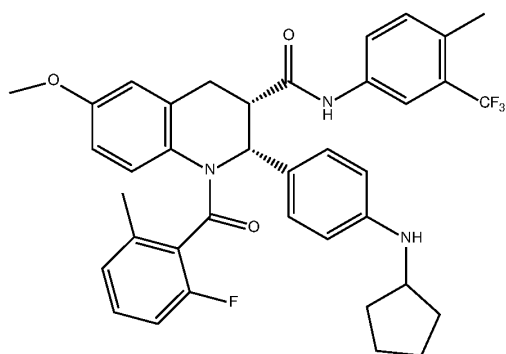


INF022,

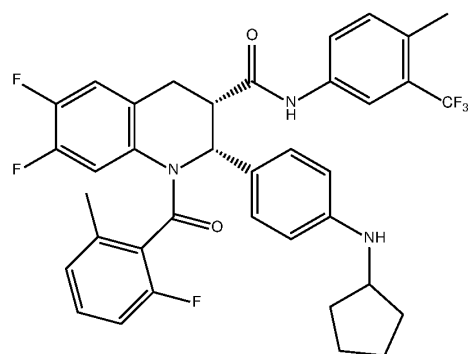


INF023,

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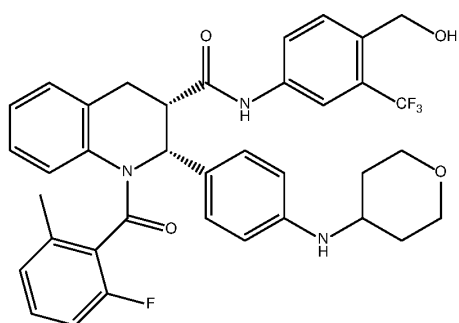


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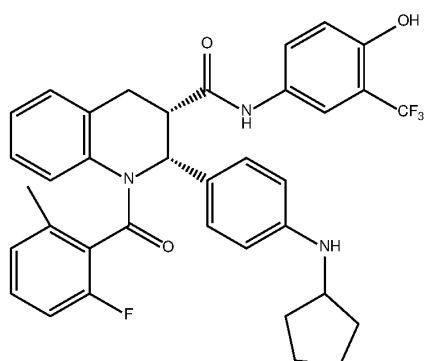


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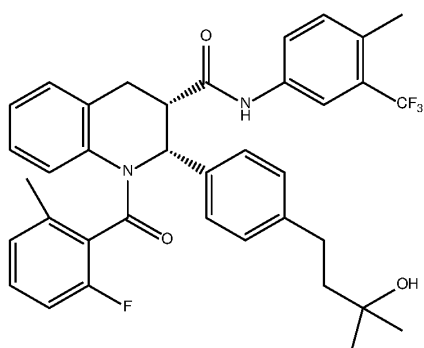
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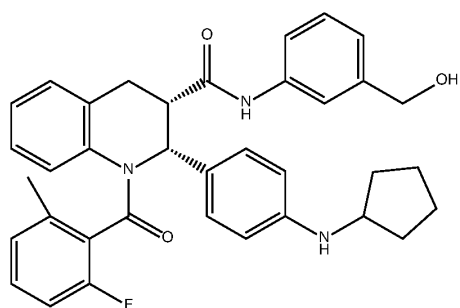
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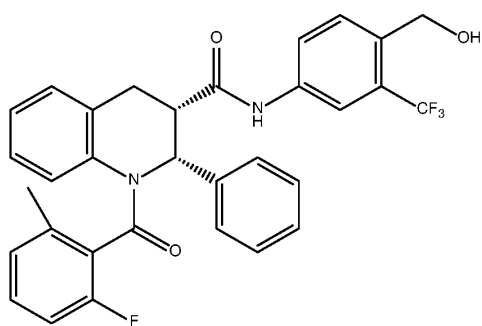
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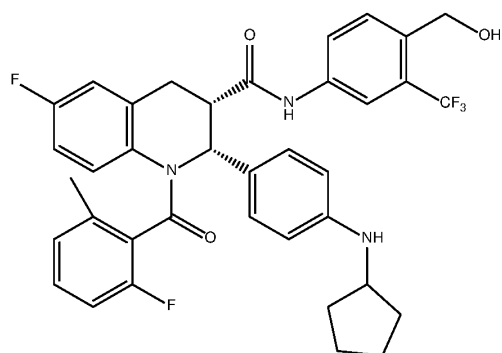
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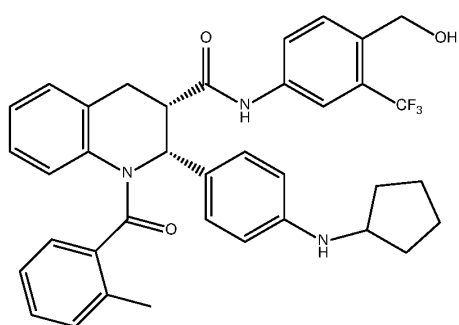
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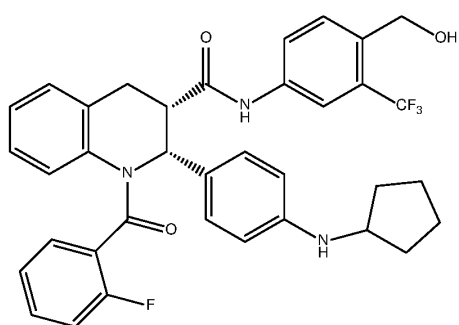
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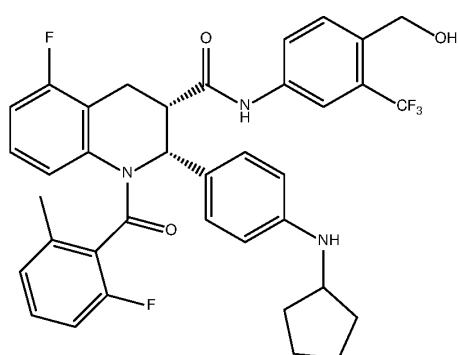
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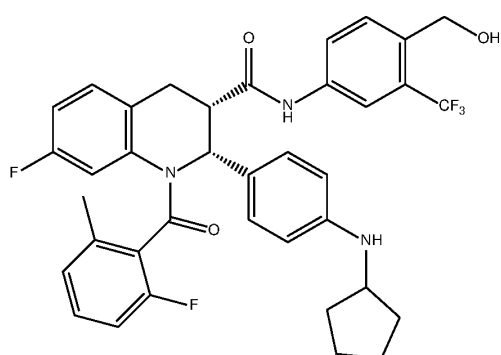
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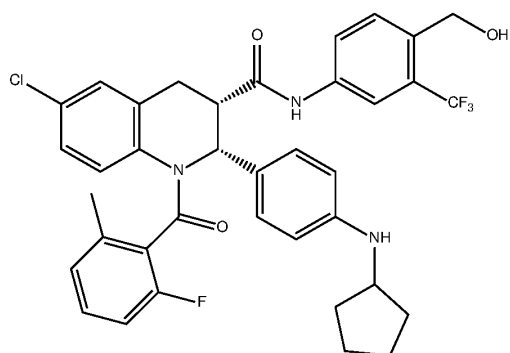
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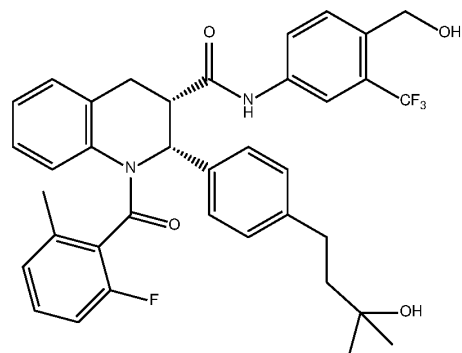
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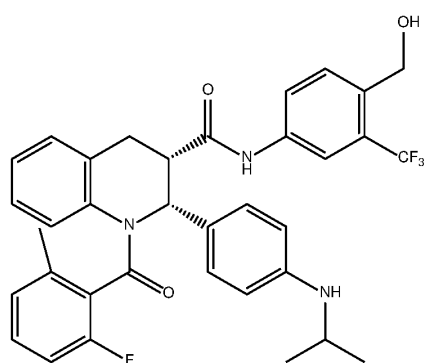
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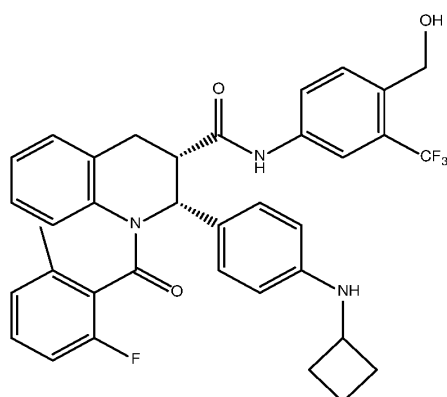
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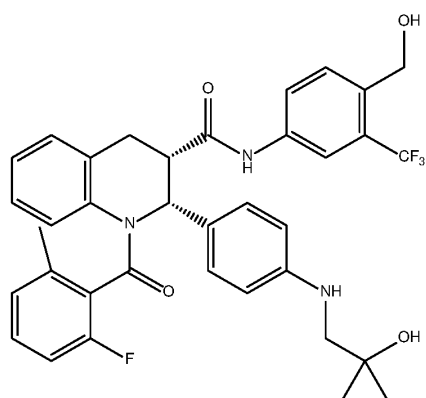
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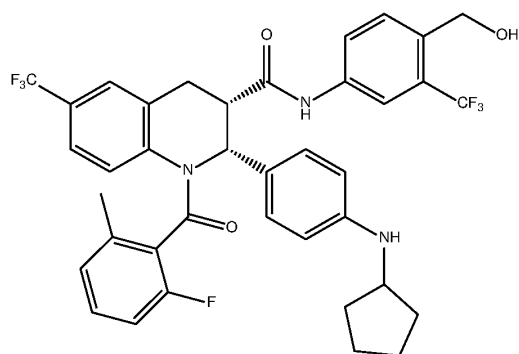
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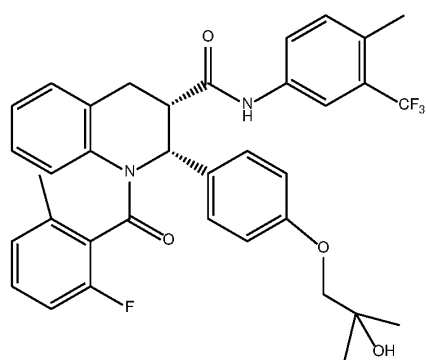
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INF051,

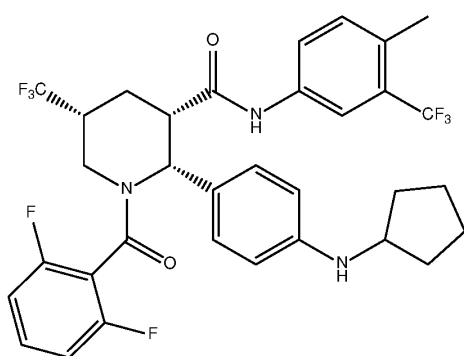


INF055, and

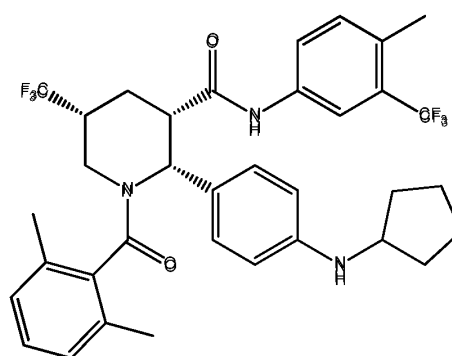


INF058.

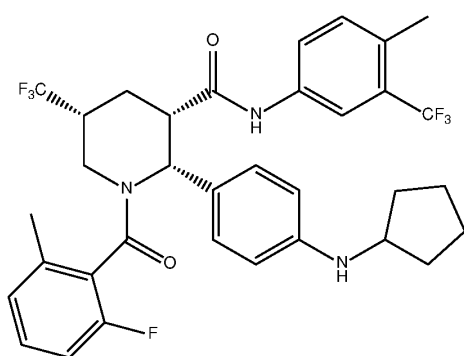
11. The compound for use according to any one of claims 1 to 4, 6, 7, 8, or 9, wherein the compound is selected from the group consisting of



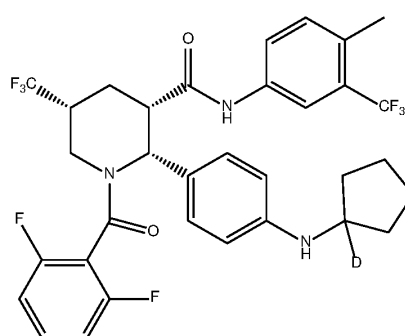
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INF053,

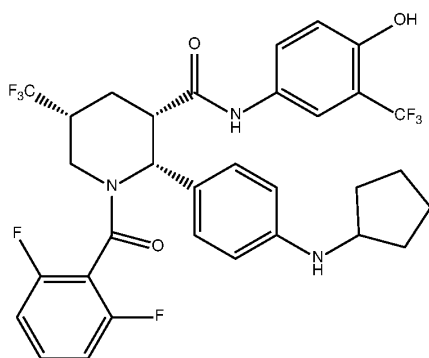


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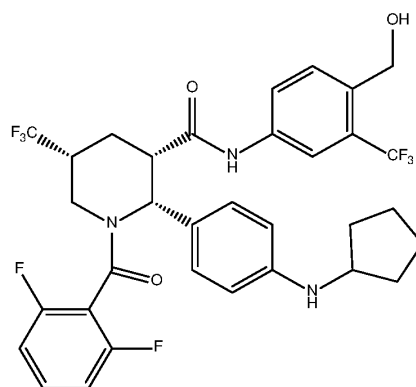


INF067,

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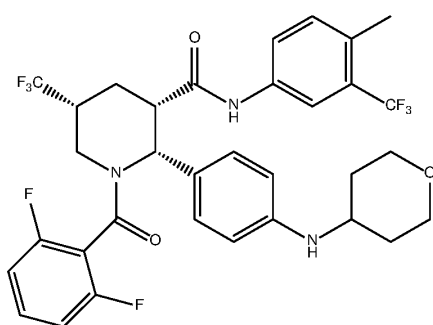


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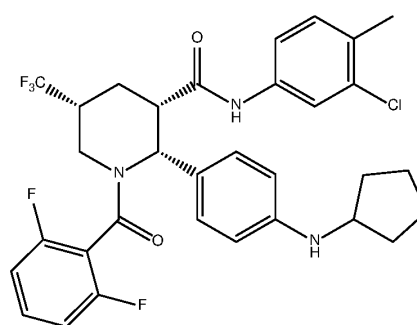


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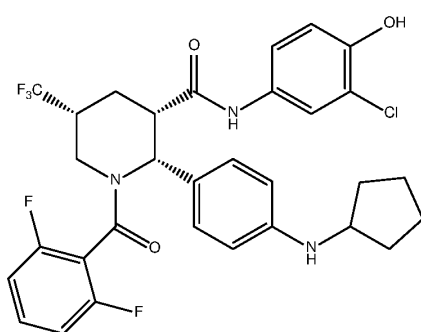
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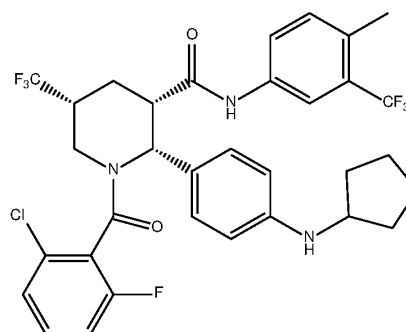
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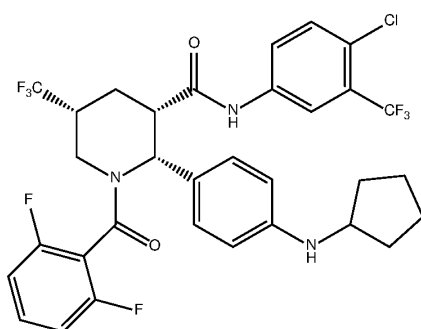
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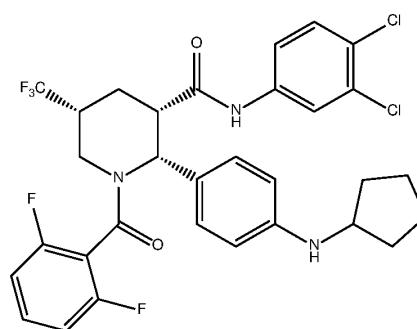
INF072,



INF075,



INF077, and



INF080.

10

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier a compound according to any one of claims 1 to 11 for use in the treatment or prevention of a disease or disorder selected from the group consisting of
- 15
- monosodium urate (MSU)-inducible diseases,
 - neutrophil-driven inflammatory kidney diseases,

- cutaneous neutrophilic inflammatory diseases, and
- immune complex diseases.

13. The compound for use according to any one of claims 1 to 11 or the pharmaceutical
5 composition for use according to claim 12, wherein the disease or disorder is selected from the group consisting of monosodium urate (MSU)-inducible diseases, including peritonitis and gout.
14. The compound for use according to any one of claims 1 to 11 or the pharmaceutical
10 composition for use according to claim 12, wherein the disease or disorder is selected from the group consisting of neutrophil-driven inflammatory kidney diseases, including ischemic nephropathy, ischemic reperfusion renal injury, and obstructive nephropathy, or wherein the disease or disorder is selected from the group consisting of cutaneous neutrophilic inflammatory diseases, including hidradenitis suppurativa (HS), pyoderma gangrenosum (PG), PASH (PG, acne, and hidradenitis suppurativa), PAPASH (pyogenic arthritis, acne, PG, and hidradenitis suppurativa), chronic spontaneous urticaria, and bullous pemphigoid.
15. The compound for use according to any one of claims 1 to 11 or the pharmaceutical
20 composition for use according to claim 12, wherein the disease or disorder is selected from the group consisting of immune complex diseases, including rheumatoid arthritis, systemic lupus erythematosus (SLE), immune-complex mediated glomerulonephritis, IgA nephritis, lupus nephritis, ANCA (Antineutrophilic cytoplasmic antibody) vasculitis, anti-C3 glomerulopathy, atypical haemolytic uraemia syndrome (aHUS),
25 Goodpasture syndrome, crescentic glomerulonephritis, focal segmental glomerulosclerosis (FSGS), rheumatic fever, dermatomyositis, chronic inflammatory demyelinating polyneuropathy, chemotherapy-induced peripheral neuropathy, and transplantation rejection.