

TECHNICAL PROBLEMS UNDERLYING THE PRESENT INVENTION

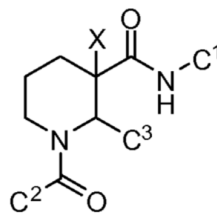
As explained above, there existed a need in the prior art for effective therapies for the treatment of neutrophilic dermatoses, such as Hidradenitis suppurativa (HS), and cutaneous neutrophilic autoimmune diseases.

5 The present inventors have now surprisingly found that molecules inhibiting C5a signaling, e.g. an anti-C5a antibody, are exceptionally well-suited for the treatment of Hidradenitis suppurativa. The present inventors have additionally studied the physiological mechanism leading to neutrophil activation and found out that C5a is the key driver of neutrophil activation.

10 Thus, the present inventors expect that inhibiting C5a activity will be a suitable therapy approach for the treatment of various neutrophilic disorders, especially cutaneous, neutrophilic, inflammatory diseases.

SUMMARY

15 In one aspect the present disclosure refers to the use of a compound in the manufacture of a medicament for treating a cutaneous, neutrophilic, inflammatory disease in a subject, wherein the compound is an inhibitor of C5a activity, and wherein the cutaneous, neutrophilic, inflammatory disease is selected from the group consisting of hidradenitis suppurativa (HS); PASH (PG, acne and hidradenitis suppurativa); PAPASH (pyogenic arthritis, acne, PG and
20 hidradenitis suppurativa), wherein the inhibitor of C5a activity directly binds to a C5a receptor and inhibits the activity of the C5a, wherein the inhibitor of C5a activity is: (a) a monoclonal antibody or antigen binding fragment thereof that specifically binds to a C5a receptor;



(b) a compound according to formula II (II), wherein C¹ is selected from the group consisting of aryl and heteroaryl, wherein the heteroaryl group has from 1-3
25 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;

30 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 heterocycloalkyl group or portion has from 1-3

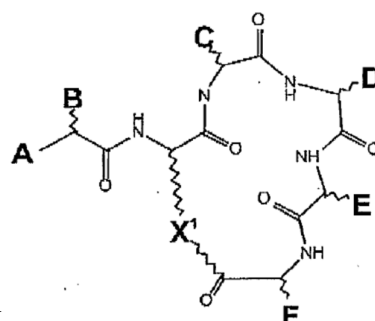
heteroatoms selected from N, O and S, and wherein the heteroaryl group has from 1-3 heteroatoms as ring members selected from N, O and S, and each C³ is optionally substituted with from 1-3 R³ substituents;

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)R^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 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 form a fused five or six- membered carbocyclic or heterocyclic ring;

each R² is independently selected from the group consisting of halogen, -CN, -NO₂, -R^f, -CO₂R^d, -CONR^dR^e, -C(O)R^d, -OC(O)NR^dR^e, -NR^eC(O)R^d, -NR^eC(O)R^f, -NR^dC(O)NR^dR^e, -NR^dC(O)NR^dR^e, -NR^dR^e, -OR^d, and -S(O)₂NR^dR^e; wherein each R^d and R^e 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 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 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 R² groups are on adjacent atoms, they are combined to form a five- or six-membered ring;

each R³ is independently selected from the group consisting of halogen, -CN, -Rⁱ, -CO₂R^g, -CONR^gR^h, -C(O)R^g, -C(O)Rⁱ, -OC(O)NR^gR^h, -NR^hC(O)R^g, -NR^hCO₂Rⁱ, -NR^gC(O)NR^gR^h, -NR^gR^h, -OR^g, -ORⁱ, -S(O)₂NR^gR^h, -X⁴-R^j, -NH-X⁴-R^j, -O-X⁴-R^j, -X⁴-NR^gR^h, -X⁴-NHR^j, -X⁴-CONR^gR^h, -X⁴-NR^hC(O)R^g, -X⁴-CO₂R^g, -O-X⁴-CO₂R^g, -NH-X⁴-CO₂R^g, -X⁴-NR^hCO₂Rⁱ, -O-X⁴-NR^hCO₂Rⁱ, -NHR^j and -NHCH₂R^j, wherein X⁴ is a C₁₋₄ alkylene; each R^g and R^h is independently selected from hydrogen, C₁₋₈ alkyl or heteroalkyl, C₃₋₆ cycloalkyl and C₁₋₈ 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, piperidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, and S,S-dioxo-tetrahydrothiopyranyl, and wherein the aliphatic and 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, -C(O)O- 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; and X is hydrogen or CH_3 ; or



- (c) a compound according to formula IV (IV), wherein
- A is H, alkyl, aryl, NH_2 , NH-alkyl, $N(alkyl)_2$, NH-aryl, NH-acyl, NH-benzoyl, $NHSO_3$, $NHSO_2$ -alkyl, $NHSO_2$ -aryl, OH, O-alkyl, or O-aryl;
- B is an alkyl, aryl, phenyl, benzyl, naphthyl or indole group, or the side chain of a D- or L-amino acid, but is not the side chain of glycine, D-phenylalanine, L-homophenylalanine, L-tryptophan, L-homotryptophan, L-tyrosine, or L-homotyrosine;
- C is the side chain of a D-, L- or homo-amino acid, but is not the side chain of isoleucine, phenylalanine, or cyclohexylalanine;
- D is the side chain of a neutral D-amino acid, but is not the side chain of glycine or D-alanine, a bulky planar side chain, or a bulky charged side chain;
- E is a bulky substituent, but is not the side chain of D-tryptophan, L-N-methyltryptophan, L-homophenylalanine, L-2-naphthyl L-tetrahydroisoquinoline, L-cyclohexylalanine, D-leucine, L-fluorenylalanine, or L-histidine;
- F is the side chain of L-arginine, L-homoarginine, L-citrulline, or L-canavanine, or a bioisostere thereof; and

X^1 is $-(CH_2)_nNH-$ or $(CH_2)_nS-$, where n is an integer of from 1 to 4; $-(CH_2)_2O-$; $-(CH_2)_3O-$; $-(CH_2)_3-$; $-(CH_2)_4-$, $-CH_2-COCHRNH-$ or $-CH_2-CHCOCHRNH-$, where R is the side chain of any common or uncommon amino acid.

In one example, there is disclosed a method for the treatment of a cutaneous, neutrophilic, inflammatory disease in a subject, comprising the step of:

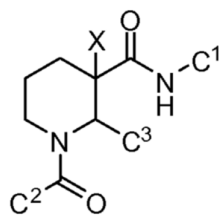
administering to a subject in need thereof a therapeutic amount of a compound, wherein the compound is an inhibitor of C5a activity, and wherein the cutaneous, neutrophilic, inflammatory disease is selected from the group consisting of hidradenitis suppurativa (HS); Pyoderma gangrenosum (PG); PAPA (pyogenic arthritis, PG and acne); PASH (PG, acne and hidradenitis suppurativa); PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa); Sweet syndrome (SS); subcorneal pustular dermatosis (SPD); epidermolysis bullosa acquisita,

CLAIMS

1. Use of a compound in the manufacture of a medicament for treating a cutaneous, neutrophilic, inflammatory disease in a subject, wherein the compound is an inhibitor of C5a activity, and

5 wherein the cutaneous, neutrophilic, inflammatory disease is selected from the group consisting of hidradenitis suppurativa (HS); PASH (PG, acne and hidradenitis suppurativa); PAPASH (pyogenic arthritis, acne, PG and hidradenitis suppurativa), wherein the inhibitor of C5a activity directly binds to a C5a receptor and inhibits the activity of the C5a receptor; and wherein the inhibitor of C5a activity is:

- (a) a monoclonal antibody or antigen binding fragment thereof that specifically binds to a C5a receptor;



- (b) a compound according to formula II (II), wherein

15 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;

20 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;

25 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 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 1-3 R³ substituents;

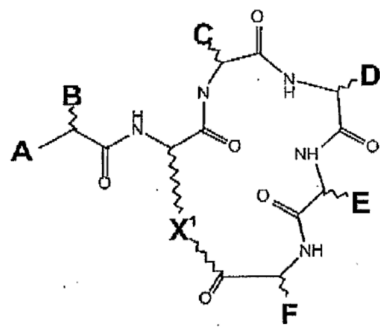
30 each R¹ is independently selected from the group consisting of halogen, -CN, -R^c, -CO₂R^a, -CONR^aR^b, -C(O)R^a, -OC(O)NR^aR^b, -NR^bC(O)R^a, -NR^bC(O)R^c, -NR^a-C(O)NR^aR^b, -NR^aC(O)NR^aR^b, -NR^aR^b, -OR^a, and -S(O)₂NR^aR^b; wherein

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 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 form a fused five or six- membered carbocyclic or heterocyclic ring;

each R² is independently selected from the group consisting of halogen, -CN, -NO₂, -R^f, -CO₂R^d, -CONR^dR^e, -C(O)R^d, -OC(O)NR^dR^e, -NR^eC(O)R^d, -NR^eC(O)₂R^f, -NR^dC(O)NR^dR^e, -NR^dC(O)NR^dR^e, -NR^dR^e, -OR^d, and -S(O)₂NR^dR^e; wherein each R^d and R^e 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 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 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 R² groups are on adjacent atoms, they are combined to form a five- or six-membered ring;

each R³ is independently selected from the group consisting of halogen, -CN, -Rⁱ, -CO₂R^g, -CONR^gR^h, -C(O)R^g, -C(O)Rⁱ, -OC(O)NR^gR^h, -NR^hC(O)R^g, -NR^hCO₂Rⁱ, -NR^gC(O)NR^gR^h, -NR^gR^h, -OR^g, -OR^j, -S(O)₂NR^gR^h, -X⁴-R^j, -NH-X⁴-R^j, -O-X⁴-R^j, -X⁴-NR^gR^h, -X⁴-NHR^j, -X⁴-CONR^gR^h, -X⁴-NR^hC(O)R^g, -X⁴-CO₂R^g, -O-X⁴-CO₂R^g, -NH-X⁴-CO₂R^g, -X⁴-NR^hCO₂Rⁱ, -O-X⁴-NR^hCO₂Rⁱ, -NHR^j and -NHCH₂R^j, wherein X⁴ is a C₁₋₄ alkylene; each R^g and R^h is independently selected from hydrogen, C₁₋₈ alkyl or heteroalkyl, C₃₋₆ cycloalkyl and C₁₋₈ 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, piperidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, and S,S-dioxo-tetrahydrothiopyranyl, and wherein the aliphatic and 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, $-C(O)O-C_{1-8}$ 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; and X is hydrogen or CH_3 ; or



(c) a compound according to formula IV

wherein

A is H, alkyl, aryl, NH_2 , NH-alkyl, $N(alkyl)_2$, NH-aryl, NH-acyl, NH-benzoyl, $NHSO_3$, $NHSO_2$ -alkyl, $NHSO_2$ -aryl, OH, O-alkyl, or O-aryl;

B is an alkyl, aryl, phenyl, benzyl, naphthyl or indole group, or the side chain of a D- or L-amino acid, but is not the side chain of glycine, D-phenylalanine, L- homophenylalanine, L-tryptophan, L-homotryptophan, L- tyrosine, or L-homotyrosine;

C is the side chain of a D-, L- or homo-amino acid, but is not the side chain of isoleucine, phenylalanine, or cyclohexylalanine;

D is the side chain of a neutral D-amino acid, but is not the side chain of glycine or D-alanine, a bulky planar side chain, or a bulky charged side chain;

E is a bulky substituent, but is not the side chain of D-tryptophan, L-N-methyltryptophan, L-homophenylalanine, L-2-naphthyl L-

tetrahydroisoquinoline, L-cyclohexylalanine, D-leucine, L-fluorenylalanine, or L-histidine;

F is the side chain of L-arginine, L-homoarginine, L-citrulline, or L-canavanine, or a bioisostere thereof; and

5 X^1 is $-(CH_2)_nNH-$ or $(CH_2)_nS-$, where n is an integer of from 1 to 4; $-(CH_2)_2O-$; $-(CH_2)_3O-$; $-(CH_2)_3-$; $-(CH_2)_4-$, $-CH_2-COCHRNH-$ or $-CH_2-CHCOCHRNH-$, where R is the side chain of any common or uncommon amino acid.

2. The use of claim 1, wherein the C5a receptor is C5aR and/or C5L2.
- 10 3. The use of any one of claims 1 to 2, wherein the inhibitor of C5a activity is selected from the group consisting of:
 - (a) Avacopan or a compound according to formula II or formula III; or PMX-53;
 - (b) an antibody or an antigen-binding fragment thereof, wherein said antibody or
15 antigen-binding fragment thereof competes with avacopan or PMX-53 for binding to C5aR;
 - (c) clone S5/1 or clone 7H110, or an antigen-binding fragment thereof; and
 - (d) an antibody or an antigen-binding fragment thereof, wherein said antibody or
20 antigen-binding fragment thereof competes with one of the antibodies indicated under (r) for binding to C5aR.
4. The use of any one of claims 1 to 3, wherein the compound is to be administered at a dose of 800 mg once per week or at a dose of 800 mg twice per week.