Even though they are anti-inflammatory in other settings, topical glucocorticoids cannot be used because one of their side effects is actually delayed wound healing [Hengge UR (2006) J Am Acad Dermatol 54:1-15]. Therefore, as a dogma in the prior art, topical glucocorticoids are described to impair wound healing [Wicke C et al (2000) Arch Surg 135:1265-1270; Anderson K et al (2014) J Am Coll Clin Wound Spec 4:84–91]. Further, non-steroidal anti-inflammatory drugs, e.g. ibuprofen, are only effective in ameliorating wound pain [Dissemond J et al (2014), supra].

There is therefore an ongoing and strong medical need for reliable and effective therapies for the treatment of impaired skin wound healing in patients.

Summary

In one aspect, the present disclosure refers to the use of a Selective Glucocorticoid Receptor ~~Modulator~~ Activator (~~SEGRM~~SERGA) which is a glucocorticoid receptor agonist, or a pharmaceutically acceptable salt thereof, in the manufacture of a pharmaceutical composition for treating impaired skin wound healing in a subject.

In another aspect, the present disclosure refers to an *in vitro* method for identifying a subject suffering from impaired skin wound healing to be responsive to the treatment with the pharmaceutical composition of the disclosure, comprising performing steps i) and/or ii):

i) measuring the proliferation of fibroblast cells, and optionally the amount of at least one IL-1 cytokine marker in the supernatant of fibroblast cells, in the presence of:

(1) a wound exudate sample or wound biofilm sample obtained from the skin wound of said subject, and

(2) the ~~SEGRM~~ SERGA comprised in the pharmaceutical composition of the disclosure;

ii) measuring the fibroblast-derived matrix formation by fibroblast cells in the presence of:

(1) a wound exudate sample or wound biofilm sample obtained from the skin wound of said subject, and

(2) the ~~SEGRM~~SERGA comprised in the pharmaceutical composition of the disclosure;

wherein the subject is identified to be responsive to the the pharmaceutical composition of the disclosure,

in case the value of proliferation of fibroblast cells measured in step i) and/or the value of the fibroblast-derived matrix formation by fibroblast cells measured in step ii) is at least 20% above a control value established in the absence of the ~~SEGRM~~SERGA comprised in the pharmaceutical composition of (2) and, optionally, in case the value for the amount of the at least one IL-1 cytokine marker in the supernatant of fibroblast cells obtained in step i) is below a control value established in the absence of the ~~SEGRM~~SERGA comprised in pharmaceutical composition of (2).

In another aspect, the present disclosure refers to a kit or kit-of-parts, comprising:

(a) a pharmaceutical composition comprising at least one Selective Glucocorticoid Receptor Activator~~Modulator~~ (~~SEGRM~~SERGA) which is a glucocorticoid receptor (GR) agonist, or a pharmaceutically acceptable salt thereof, and

(b) a diagnostic kit comprising one or more of the following:

i) fibroblast cells,

ii) a support having a plurality of defined areas or cavities, wherein a subset of areas or cavities are (i) coated with adhesion enhancing agent, and/or (ii) are filled with fibroblast-derived matrix (FDM),

iii) a matrix promoting supplement.

Detailed description of the invention

It was surprisingly found in the present application, as shown in the examples and corresponding Figures, that Selective Glucocorticoid Receptor Modulators (SEGRMs) exhibit an outstanding fibroblast proliferation (2D) enhancing and fibroblast derived matrix formation (3D) enhancing effect, increase Collagen-1 and -3 expression and inhibit IL-1beta secretion in a human-linked *ex vivo* wound healing model using wound exudates from chronic wound patients. For example, the effect of mapracorat, as exemplary SEGRM, was studied on fibroblast proliferation in the presence of >80 human wound exudates, leading to increases of >120%.

Moreover, it was found that mapracorat reduced the wound score from days 6 to 12 in wounds treated with wound exudates from chronic human wounds and/or the TLR 7/8 agonist R848 (resiquimod) as inducers of delayed wound healing in a pig model of delayed wound healing (Figure 13).

In addition, it was found in the examples that BI-653048, but not its inactive analogue BI-3047, dose-dependently enhanced fibroblast proliferation in the presence of different aggressive wound exudates (Figure 1) and inhibited IL-1ß secretion in these cultures (Figure 2). The chemically different SEGRMs mapracorat, ZK216348 and HY14234 had similar effects on proliferation and IL-1ß secretion or mRNA expression in the presence of wound exudates (Figures 5, 8, and 9 – 11). While qualitatively similar, the magnitude of effects differed depending on the SEGRM compound and the individual wound exudate. Therefore, in a preferred embodimenta personalized medicine approach with *in vitro* pretesting of patient exudates against different compounds can be performed by using methods of the invention described herein. Expression of collagen 1 and collagen 3 mRNAs in the fibroblast proliferation assay with wound exudate, but not medium, was increased by BI-653048 and mapracorat (Figures 3 and 6 – 8). The effect was reversed by the glucocorticoid receptor antagonist mifepristone (Figure 4).

Further, a positive effect was observed in 3D fibroblast culture with wound exudate from a patient with a chronic, non-healing wound with a plurality of structurally different SEGRMs, including BI-653048 (but not its inactive analogue BI-3047), mapracorat, ZK216348, AZD7594, and HY14234 (Figure 12). The fibroblast proliferation assay (2D) as well as the

Claims

1. Use of a Selective Glucocorticoid Receptor ~~Modulator~~Activator ~~–~~Activator (SEGRA~~SEGRM~~) which is glucocorticoid receptor (GR) agonist, or a pharmaceutically acceptable salt thereof, in the manufacture of a pharmaceutical composition for treating impaired skin wound healing in a subject.

2. The use of claim 1, wherein the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition is a non-steroidal Selective Glucocorticoid Receptor ~~Modulator~~Activator (~~SEGRM~~SEGRA),
and:
   - the ~~SEGRM~~SEGRA specifically binds to a Glucocorticoid Receptor (GC) with an affinity (KD) of less than 100 nM, and/or
   - the competition factor for the ~~SEGRM~~SEGRA i) is lower than 20 for Glucocorticoid Receptor (GC), and ii) is at least 5 for progesterone receptor (PR), androgen receptor (AR) and mineralocorticoid receptor (MR), wherein the competition factor is defined as IC_{50} value of the ~~SEGRM~~SEGRA/IC_{50} of a reference compound, and wherein the reference compound for GC is dexamethasone, the reference compound for PR is progesterone, the reference compound for AR is metribolone, and the reference compound for MR is aldosterone, and/or
   - the EC_{50} value for transactivation activity of the ~~SEGRM~~SEGRA upon binding to a Glucocorticoid Receptor (GC) in a cell is at least 20-fold higher than the EC_{50} value for transactivation activity of dexamethasone and/or the the IC_{50} value for transrepression activity of the ~~SEGRM~~SEGRA upon binding to a Glucocorticoid Receptor (GC) in a cell is at most 100-fold higher than the IC_{50} value for transrepression activity of dexamethasone.

3. The use of claim 1 or 2, wherein the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition:
   - specifically binds to a Glucocorticoid Receptor (GC) with an affinity (KD) of less than 100 nM, and/or
   - is a non-steroidal ~~SEGRM~~SEGRA, and/or
   - effects translocation of the glucocorticoid receptor from the cytoplasm into the nucleus in primary human fibroblasts in an *in vitro* culture at a concentration of the ~~SEGRM~~SEGRA of 10 nM at 37°C, and/or
   - is a glucocorticoid receptor (GR) agonist.

4. The use of any of claims 1 to 3,
wherein the skin wound is selected from a wound of a diabetic patient, a skin wound which is infected by at least one microorganism, an ischemic wound, a wound in a patient suffering from deficient blood supply or venous stasis, an ulcer, such a diabetic ulcer, venous ulcer, arterial ulcer, such as ulcus cruris arteriosum, mixed ulcer, or pressure ulcer, a neuropathic wound, ulcus cruris, surgical wound, burn, dehiscence, neoplastic ulcer, a bullous skin disease, such as epidermolysis bullosa, and rare ulcer.

5. The use of any of claims 1 to 4, wherein the subject suffers from at least one co-morbidity associated with impaired skin wound healing, in particular diabetes, and/or wherein the subject is treated with at least one immunosuppressive drug.

6. The use of any of claims 1 to 5, wherein the subject suffers from diabetes and/or has at least one diabetic ulcer, and or wherein the subject
(i) has undergone transplantation of a graft, and/or
(ii) obtains immunosuppressive therapy,
and optionally suffers from diabetes.

7. The use of any of claims 1 to 6, wherein the subject is identified to be responsive to the treatment of impaired skin wound healing by performing steps i) and/or ii):
i) measuring the proliferation of fibroblast cells, and optionally the amount of at least one IL-1 cytokine marker in the supernatant of fibroblast cells, in the presence of:
(1) a wound exudate sample or wound biofilm sample obtained from the skin wound of said subject, and
(2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1;
ii) measuring the fibroblast-derived matrix formation by fibroblast cells in the presence of:
(1) a wound exudate sample or wound biofilm sample obtained from the skin wound of said subject, and
(2) the ~~SEGRM~~SEGRA comprised in the the pharmaceutical composition of claim 1.

8. The use of claim 7,
wherein the subject is identified to be responsive to the treatment of impaired skin wound healing with the pharmaceutical composition of claim 1,
in case the value of proliferation of fibroblast cells measured in step i) and/or the value of the fibroblast-derived matrix formation by fibroblast cells measured in step ii) is at least 20% above a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2), and, optionally, in case the value for the amount of the at least one IL-1 cytokine marker in the supernatant of fibroblast cells obtained in step i) is below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2).

9. The use of claim 7 or 8, wherein in addition step iiia) and/or one, two, three or four of the following steps iiib) to iiie) are performed:
iiia) measuring the proliferation of keratinocyte cells in the presence of:
(1) a wound exudate sample, or wound biofilm sample, obtained from the skin wound of said subject, and
(2) the ~~SEGRM~~SEGRA comprised in the the pharmaceutical composition of claim 1,
iiib) measuring the amount(s) of one or more M1 marker(s) and one or more M2 marker(s) in the supernatant of macrophages incubated with
(1) a wound exudate sample or wound biofilm sample obtained from said skin wound, and
(2) the ~~SEGRM~~SEGRA comprised in the the pharmaceutical composition of claim 1,
wherein the macrophages are in co-culture with fibroblasts, and
wherein the one or more M1 markers are selected from CXCL10 and IL-23p19, and the one or more M2 markers are selected from CCL22 and CCL18,

iiic) measuring the amount(s) and/or frequency distribution(s) of one or more M1 cell surface marker(s) and one or more M2 cell surface marker(s) on macrophages incubated with
(1) a wound exudate sample or wound biofilm sample obtained from said skin wound, and
(2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1,
wherein the macrophages are in co-culture with fibroblasts, and

wherein the one or more M1 cell surface markers are selected from CD38, CD64 and CD197, and wherein the one or more M2 cell surface markers are selected from CD200 receptor, CD206 and CD209,

iiid) measuring the expression level(s) of one or more M1 marker mRNA(s) and one or more M2 marker mRNA(s) in macrophages incubated with

(1) a wound exudate sample or wound biofilm sample obtained from said skin wound, and

(2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1,

wherein the macrophages are in co-culture with fibroblasts, and

wherein the one or more M1 marker mRNA(s) are selected from CD38, CD64, CD197, CXCL10 and IL-23p19, and the one or more M2 marker mRNA(s) are selected from CD200 receptor (CD200R), CD206, CD209, CCL22 and CCL18,

iiie) measuring the amount(s) of one or more cytokine markers in the supernatant of macrophages incubated

(1) with a wound exudate sample or wound biofilm sample obtained from said skin wound, and

(2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1,

wherein the macrophages are in co-culture with fibroblasts, and

wherein the one or more cytokine markers are selected from IL-1alpha, IL-1beta and TNF-alpha,

and

wherein the subject is identified to be responsive to the treatment with the pharmaceutical composition of claim 1, in case the value of proliferation of fibroblast cells measured in step i) and/or the value of the fibroblast-derived matrix formation by fibroblast cells measured in step ii) and/or the value of the proliferation of keratinocyte cells in step iiia) is at least 20% above a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2), and, optionally, in case the value for the amount of the at least one IL-1 cytokine marker in the supernatant of fibroblast cells obtained in step i) is below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2),

and/or in case one or more of the following applies:

- the ratio of amount(s) of one or more M1 marker(s) to the amount(s) of one or more M2 marker(s) obtained in iiib) is/are below a control value

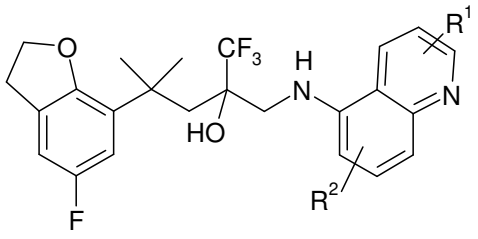
established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2),

- the ratio of amount(s) and/or frequency distribution(s) of one or more M1 cell surface marker(s) to the amount(s) and/or frequency distribution(s) of one or more M2 cell surface marker(s) obtained in iiic) is/are below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2), in particular wherein the ratio is selected from a CD38/CD209 ratio, a CD197/CD209 ratio and a CD197/CD206 ratio,
- the ratio of expression level(s) of one or more M1 marker mRNA(s) to the expression level(s) of one or more M2 marker mRNA(s) obtained in iiid) is/are below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2),
- the value obtained in iiie) is below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2).

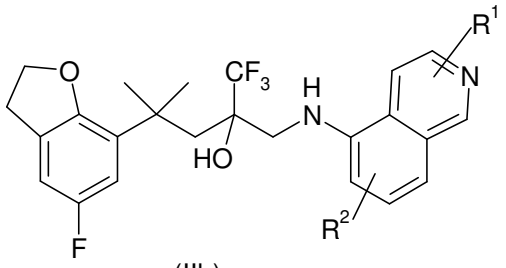
10. The use of any of claims 1 to 9, wherein the pharmaceutical composition is
    (i) formulated for systemic, preferably oral or intravenous administration, or
    (ii) formulated for local administration, in particular for topical, mucosal, ocular, intradermal or subcutaneous administration.

11. The use of claim 10, wherein the pharmaceutical composition is formulated for local administration, wherein said pharmaceutical composition comprises at least one Selective Glucocorticoid Receptor ~~Modulator~~Activator (~~SEGRM~~SEGRA) and a) oleyl alcohol, b) cetearyl octanoate and c) a vegetable oil.

12. The use of any of claims 1 to 11, wherein the ~~SEGRM~~SEGRA is selected from:
    (i) a compound of formula (IIa) or (IIb) below:



(IIa)



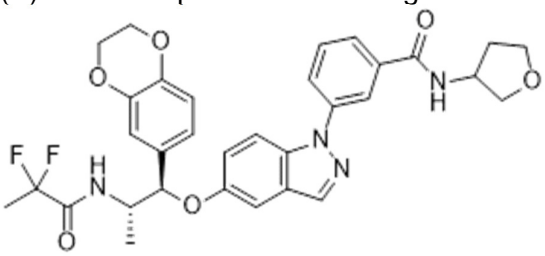
(IIb)

in which

R^1 and R^2, independently of one another, can be a hydrogen atom, a C_{1-3}-alkyl group, a halogen atom, a cyano group, a C_{1-3}-alkoxy group or a hydroxy group, as well as their racemates or separately present stereoisomers and optionally their pharmaceutically acceptable salts ~~or their prodrugs~~;

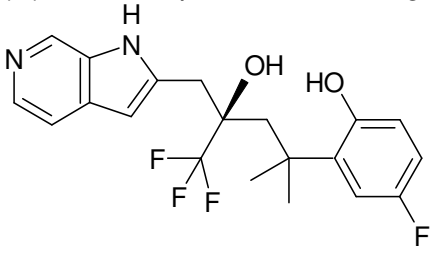
(ii) the compound (R)-2-(4-((5-(Ethylsulfonyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)methyl)-5,5,5-trifluoro-4-hydroxy-2-methylpentan-2-yl)-5-fluorobenzamide, or a pharmaceutically acceptable salt thereof;

(iii) the compound of following formula below:



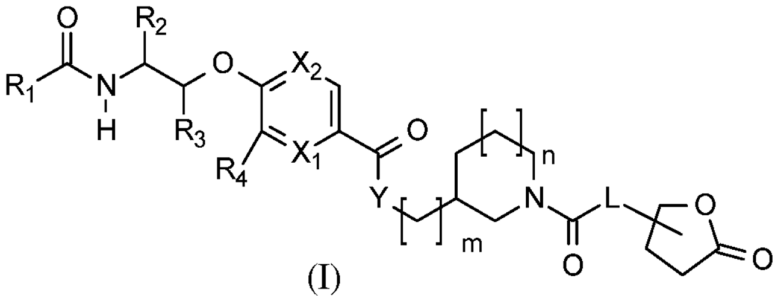
, or a pharmaceutically acceptable salt thereof;

(iv) the compound of following formula below:



, or a pharmaceutically acceptable salt thereof;

(v) a compound of following formula (I) below:



(I)

,

wherein

R_1 is selected from the group consisting of 5- and 6- membered heteroaryl, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, (4-6)-membered heterocycloalkyl and phenyl, wherein said 5- and 6-membered heteroaryl, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, (4-6)-membered heterocycloalkyl and phenyl is optionally substituted with one or more substituents independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halogen, hydroxyl and cyano;

R_2 is selected from $(C_1\text{-}C_3)$alkyl and halo$(C_1\text{-}C_3)$alkyl;

R_3 is selected from phenyl, 5-membered heteroaryl and 6-membered heteroaryl, wherein said phenyl, 5-membered heteroaryl and 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from R_5;

R_4 is selected from hydrogen, halogen, $(C_1\text{-}C_4)$alkyl and halo$(C_1\text{-}C_4)$alkyl;

R_5 is selected from halogen, cyano, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, phenyl, 5-membered heteroaryl, 6-membered heteroaryl and $-S(O)_2R_a$, wherein R_a represents $(C_1\text{-}C_4)$alkyl;

X_1 is selected from CH, C(R_b) and N, wherein R_b represents halogen, $(C_1\text{-}C_4)$alkyl or halo$(C_1\text{-}C_4)$alkyl;

X_2 is selected from CH and N;

Y is selected from -NH- and -O-;

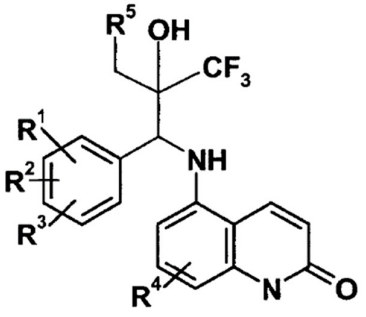
m is 0 or 1; n is 0 or 1;

L represents a bond, -O-, -NH- or $-N(R_c)-$, wherein R_c represents $(C_1\text{-}C_4)$alkyl;

or pharmaceutically acceptable salts, hydrates or solvates thereof;

and

(vi) a compound of following formula (III) below:



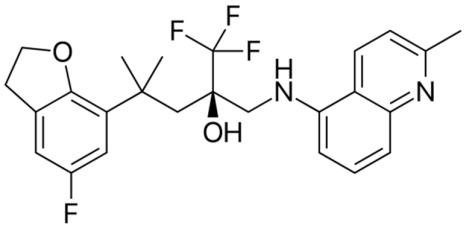
(III), wherein

$R^1$and R^2 independently of one another, mean a hydrogen atom, a hydroxy group, a halogen atom, an optionally substituted $(C_1\text{-}C_{10})$-alkyl group, an optionally substituted $(C_1\text{-}C_{10})$-alkoxy group, a $(C_1\text{-}C_{10})$-alkylthio group, a $(C_1\text{-}C_5)$-perfluoroalkyl group, a cyano group, a nitro group,

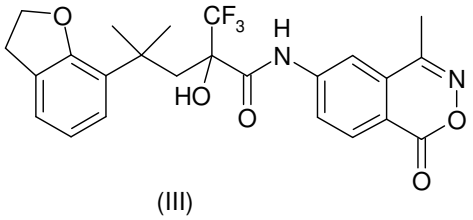
or R^1 and R^2
together mean a group that is selected from the groups -O-$(CH_2)_p$-O-,
-O-$(CH_2)_p$-CH_2-, -O-CH=CH-, -$(CH_2)_{p+2}$-, -NH-$(CH_2)_{p+1}$,
-N(C_1-C_3-alkyl)-$(CH_2)_{p+1}$, and -NH-N=CH-,
whereby p = 1 or 2, and the terminal oxygen atoms and/or carbon atoms
and/or nitrogen atoms are linked to directly adjacent ring-carbon atoms,
or NR^6R^7,
whereby R^6 and R^7, independently of one another, mean
hydrogen, C_1-C_5-alkyl or (CO)-(C_1-C_5)-alkyl,
R^3 means a hydrogen atom, a hydroxy group, a halogen atom, a cyano
group, an optionally substituted (C_1-C_{10})-alkyl group, a (C_1-C_{10})-alkoxy group,
a (C_1-C_{10})-alkylthio group, or a (C_1-C_5)-perfluoroalkyl group,
R^4 means a hydrogen, halogen, hydroxy, (C_1-C_5)-alkyl, (C_1-C_5)alkoxy,
(C_1-C_5)-alkylthio, (C_1-C_5)-perfluoroalkyl, cyano, nitro, NR^6R^7, $COOR^9$,
(CO)NR^6R^7 or a (C_1-C_5-alkylene)-O-(CO)-(C_1-C_5)alkyl group,
R^5 means a group selected from
-(C_1-C_{10})alkyl, which may be optionally partially or completely halogenated,
-(C_2-C_{10})alkenyl,
-(C_2-C_{10})alkynyl,
(C_3-C_7)cycloalkyl-(C_1-C_8)alkyl,
(C_3-C_7)cycloalkyl-(C_1-C_8)alkyenyl,
(C_3-C_7)cycloalkyl-(C_2-C_8)alkynyl,
heterocyclyl-(C_1-C_8)alkyl,
heterocyclyl-(C_1-C_8)alkenyl,
heterocyclyl-(C_2-C_8)alkynyl,
-R^8,
R^8-(C_1-C_8)alkyl,
R^8-(C_2-C_8)alkenyl,
R^8-(C_2-C_8)alkynyl,
-S-(C_1-C_{10})-alkyl,
-SO_2-(C_1-C_{10})-alkyl,
-S-R^8,
-SO_2-R^8,
-CN,
-Hal,
-O-(C_1-C_{10})-alkyl,
-NR^6R^7 wherein R^6, R^7 have the meaning defined above,

-O-R^8,
-OH,
with the exception of -$CH(CH_3)_{2)}$ or -$C(CH_3)=CH_2$,
R^8 means an aryl group which may optionally be substituted by 1-3 hydroxy, halogen, C_1-C_5-alkyl, C_1-C_5-alkoxy, cyano, CF_3, nitro, $COO(C_1$-C_5-alkyl) or $C(O)OCH_2$-phenyl or a heteroaryl group whereby the heteroaryl group may contain 1-3 hetero atoms which may optionally be substituted by 1-3 alkyl groups, hydroxy, halogen, cyano or C_1-C_5-alkoxy groups,
and their salts, solvates or salts of solvates.

13. The use of any of claims 1 to 12, wherein the ~~SEGRM~~SEGRA is selected from following compounds:

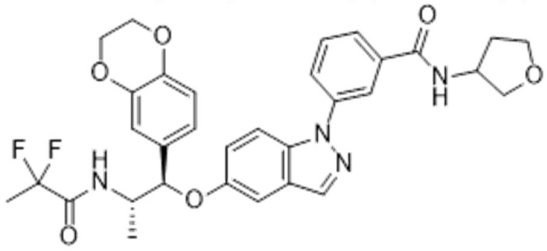


;

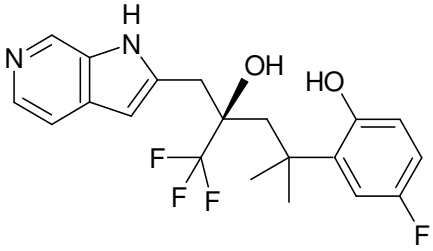


(III) ;

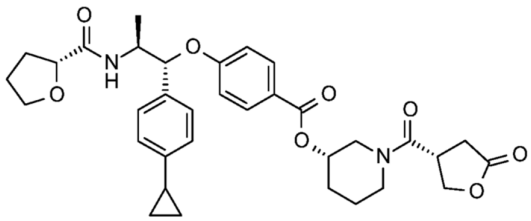
(R)-2-(4-((5-(Ethylsulfonyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)methyl)-5,5,5-trifluoro-4-hydroxy-2-methylpentan-2-yl)-5-fluorobenzamide;



;



;



;

[(3S)-1-[(3R)-5-oxotetrahydrofuran-3-carbonyl]-3-piperidyl] 4- [(1R,2S)-1-(4-cyclopropylphenyl)-2-[[(2R)-tetrahydrofuran-2-carbonyl] amino] propoxy] benzoate;

5-{[(1S,2S)-1-(2-chloro-3-fluoro-4-methoxyphenyl)-3,3,3-trifluoro-2-hydroxy-2-(methoxymethyl)propyl]amino}-7-fluoro-1H-quinolin-2-one;

5-{(1S,2S)[1-(2-chloro-3-fluoro-4-methoxyphenyl)-3,3,3-trifluoro-2-hydroxy-2-(hydroxymethyl)propyl]amino}-7-fluoro-1H-quinolin-2-one, and

5-{(1S,2S)[1-(2-chloro-3-fluoro-4-methoxyphenyl)-3,3,3-trifluoro-2-hydroxy-2-(hydroxymethyl)propyl]amino}-7-fluoro-1H-quinolin-2-one,

or a pharmaceutically acceptable salt thereof.

14. An *in vitro* method for identifying a subject suffering from impaired skin wound healing to be responsive to the treatment with the pharmaceutical composition of claim 1, comprising performing steps i) and/or ii):

i) measuring the proliferation of fibroblast cells, and optionally the amount of at least one IL-1 cytokine marker in the supernatant of fibroblast cells, in the presence of:
   (1) a wound exudate sample or wound biofilm sample obtained from the skin wound of said subject, and
   (2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1;

ii) measuring the fibroblast-derived matrix formation by fibroblast cells in the presence of:
   (1) a wound exudate sample or wound biofilm sample obtained from the skin wound of said subject, and
   (2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1;

wherein the subject is identified to be responsive to the pharmaceutical composition of claim 1,

in case the value of proliferation of fibroblast cells measured in step i) and/or the value of the fibroblast-derived matrix formation by fibroblast cells measured in step ii) is at least 20% above a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2) and, optionally, in case the value for the amount of the at least one IL-1 cytokine marker in the supernatant of fibroblast cells obtained in step i) is below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in pharmaceutical composition of (2)~~.~~

preferably

~~15. The *in vitro* method of claim 14,~~ wherein in addition step iiia) and/or one, two, three or four of the following steps iiib) to iiie) are performed:

iiia) measuring the proliferation of keratinocyte cells in the presence of:

(1) a wound exudate sample, or wound biofilm sample, obtained from the skin wound of said subject, and

(2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1,

iiib) measuring the amount(s) of one or more M1 marker(s) and one or more M2 marker(s) in the supernatant of macrophages incubated with

(1) a wound exudate sample or wound biofilm sample obtained from said skin wound, and

(2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1,

wherein the macrophages are in co-culture with fibroblasts, and

wherein the one or more M1 markers are selected from CXCL10 and IL-23p19, and the one or more M2 markers are selected from CCL22 and CCL18,

iiic) measuring the amount(s) and/or frequency distribution(s) of one or more M1 cell surface marker(s) and one or more M2 cell surface marker(s) on macrophages incubated with

(1) a wound exudate sample or wound biofilm sample obtained from said skin wound, and

(2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1,

wherein the macrophages are in co-culture with fibroblasts, and

wherein the one or more M1 cell surface markers are selected from CD38, CD64 and CD197, and wherein the one or more M2 cell surface markers are selected from CD200 receptor, CD206 and CD209,

iiid) measuring the expression level(s) of one or more M1 marker mRNA(s) and one or more M2 marker mRNA(s) in macrophages incubated with

(1) a wound exudate sample or wound biofilm sample obtained from said skin wound, and

(2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1,

wherein the macrophages are in co-culture with fibroblasts, and

wherein the one or more M1 marker mRNA(s) are selected from CD38, CD64, CD197, CXCL10 and IL-23p19, and the one or more M2 marker mRNA(s) are selected from CD200 receptor (CD200R), CD206, CD209, CCL22 and CCL18,

iiie) measuring the amount(s) of one or more cytokine markers in the supernatant of macrophages incubated

(1) with a wound exudate sample or wound biofilm sample obtained from said skin wound, and

(2) the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of claim 1,

and

wherein the subject is identified to be responsive to the treatment with the pharmaceutical composition of claim 1, in case the value of proliferation of fibroblast cells measured in step i) and/or the value of the fibroblast-derived matrix formation by fibroblast cells measured in step ii) and/or the value of the proliferation of keratinocyte cells in step iiia) is at least 20% above a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2), and/or in case one or more of the following applies:

- the ratio of amount(s) of one or more M1 marker(s) to the amount(s) of one or more M2 marker(s) obtained in iiib) is/are below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2),
- the ratio of amount(s) and/or frequency distribution(s) of one or more M1 cell surface marker(s) to the amount(s) and/or frequency distribution(s) of one or more M2 cell surface marker(s) obtained in iiic) is/are below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in the pharmaceutical composition of (2), in particular wherein the ratio is selected from a CD38/CD209 ratio, a CD197/CD209 ratio and a CD197/CD206 ratio,

- the ratio of expression level(s) of one or more M1 marker mRNA(s) to the expression level(s) of one or more M2 marker mRNA(s) obtained in iiid) is/are below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in pharmaceutical composition of (2),
- the value obtained in iiie) is below a control value established in the absence of the ~~SEGRM~~SEGRA comprised in pharmaceutical composition of (2)~~,~~.

more preferably wherein the *in vitro* method is characterized by the features of claims 2 to 13.

~~16~~15. A kit or kit-of-parts, comprising:

(a) a pharmaceutical composition comprising at least one Selective Glucocorticoid Receptor ~~Modulator~~Activator (~~SEGRM~~SEGRA) which is a glucocorticoid receptor (GR) agonist, or a pharmaceutically acceptable salt thereof, and

(b) a diagnostic kit comprising one or more of the following:

i) fibroblast cells,

ii) a support having a plurality of defined areas or cavities, wherein a subset of areas or cavities are (i) coated with adhesion enhancing agent, and/or (ii) are filled with fibroblast-derived matrix (FDM),

iii) a matrix promoting supplement~~,~~.

preferably wherein

~~17. The *in vitro* method of claim 14 or 15, or~~ the kit or kit-of-parts ~~of claim 16,~~is characterized by the features of any of claims 2 to 13.