(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2017 (05.01.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/001434 A1

(51) International Patent Classification:
A61K 31/55 (2006.01) *A61P 17/10* (2006.01)
A61P 17/04 (2006.01)

(21) International Application Number:
PCT/EP2016/065063

(22) International Filing Date:
28 June 2016 (28.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
15306033.0 29 June 2015 (29.06.2015) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2017/001434 A1

(54) Title: CGRP RECEPTOR ANTAGONIST COMPOUNDS FOR TOPICAL TREATMENT OF SKIN DISORDERS

(57) Abstract: The present invention relates to CGRP receptor antagonist compound of formula (I) for topical application for treating and/or preventing skin inflammatory pathologies with a neurogenic component. More specifically the present invention relates to CGRP receptor antagonist compound of formula (I) for topical application for treating and/or preventing rosacea and especially type I rosacea, atopic dermatitis, psoriasis, and/or acne. The preferred compound according to the present invention is: [N-[(3R,6S)-6-(2,3-Difluorophenyl)-2-oxo- 1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1- yl)piperidine-1-carboxamide] also named telcagepant.

CGRP RECEPTOR ANTAGONIST COMPOUNDS FOR TOPICAL TREATMENT OF SKIN DISORDERS

The present invention relates to the use of CGRP receptor antagonist compounds and the pharmaceutical compositions comprising such compounds in dermatological field.

BACKGROUND OF THE INVENTION

CGRP is broadly expressed in the central and peripheral nervous system and is involved in various biological functions. There are more and more evidence that CGRP play a key role as neuromodulator, but it is mostly known as a strong vasodilatator. CGRP activates a heterodimer receptor (CGRP-R) composed of a class B protein-G coupled receptor (CLR or calcitonin-like receptor)) associated with a transmembrane protein modifying the receptor activity (RAMP1 or receptor activity-modifying protein 1). Many studies have been done on CGRP role and CGRP receptor activity. For instance studies have demonstrated that migraine attack was associated to the release of CGRP by meningeal nociceptors of the trigeminal ganglion and that CGRP could play a key role in migraine attack.

The increasing number of evidences that CGRP was linked to migraine attack resulted in a high interest for the development of compounds able to block the effects of this neuropeptide. Important efforts have been made to develop direct small antagonist compounds of CGRP with vasoconstriction activity for treating migraine attack. These compounds are described in the literature for their oral use especially olcegepant, telcagepant and MK-3207. However their development was discontinued since severe hepatotoxicity was associated to these compounds by oral route.

Besides its role in migraine attack, CGRP release by face trigeminal nerves could be involved in neurogenic inflammation responsible especially of permanent erythema in type I rosacea. This hypothesis is done knowing that rosacea and migraine are sharing common characteristics such as a neurogenic component with vasodilation phenomenon, the activation of trigeminal nervous system and the release of neuro-inflammatory peptides (CGRP, P substance...). CGRP would have its vasodilatator action by acting through smooth muscle cells and sub-cutaneous vessels.

The compound ([N-[(3R,6S)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo [4,5-b]pyridin-1-yl)piperidine-1-carboxamide] also named telcagepant or MK-094 developed by Merck & Co, was the first orally bioavailable CGRP receptor antagonist tested in the clinic with a triptan-like efficacy

for the acute treatment of migraine. Because of various toxic effects observed in patients during the clinical development of telcagepant, especially hepatotoxicity, its development has been discontinued.

Inflammatory skin diseases relate to skin diseases associated with inflammatory component. There are different types of inflammatory skin disease, classified by their localization, their causes and their symptoms. These skin disorders are common but their diagnosis can be difficult. Indeed, the skin immune system have limited way to respond to internal and external stimuli and many diseases present an inflammatory profile with few distinctive characteristics.

Rosacea is a common chronic and progressive inflammatory dermatosis associated with vascular relaxation. Rosacea affects principally central part of the face and is characterized by facial flushes, facial erythema, papules, pustules, telangiectasia and sometimes ocular lesions and rhinophyma. Moreover these primary features are associated with a secondary neurogenic component, more specifically to a cutaneous hyperreactivity of face and neck skin, characterized by the apparition of skin redness, prurit, feelings of itching, burning, stinging, and rough, flaky skin sensations.

Rosacea is classified into four subtypes according to the degree of primary features, such as vasomotor flushing, persistent erythema, papules and pustules, telangiectasias:

Erythematotelangiectatic rosacea (ETR) is mainly characterized by vasomotor flushing and persistent central facial erythema (redness). Telangiectasias (visible blood vessels) are commonly observed but are not essential for the diagnosis of this subtype. Central facial edema, burning or stinging sensations and rough, flaky skin are also symptoms that have sometimes been reported. A history of flushing as the only symptom is commonly found in people with erythematotelangiectatic rosacea. Facial flushing is due to the sudden dilatation of the arterioles of the face (which then takes a red appearance) and may be triggered by emotional stress, hot drink, alcohol, spicy food or temperature changes.

Papulopustular rosacea (PPR) is characterized by persistent central facial erythema and transient inflammatory crops of papules and/or pustules in the center of the face. However, the papules and pustules can also occur in periorificial regions, i.e., around the mouth, nose and eyes. The papulopustular subtype resembles acne vulgaris but comedones (specific of acne) are absent in rosacea. Rosacea and acne may coexist in a same patient, in which case comedones may also be present alongside the papules and pustules suggestive of

rosacea. People with papulopustular rosacea sometimes complain of a burning or stinging sensation. Moreover, PPR is also characterized by the presence of inflammatory infiltrates that accompany flares, along with a heightened immune response involving neutrophilic infiltration and increased gene expression of IL8. This subtype is often observed after or at the same time as ETR (including the presence of telangiectasias).

Phymatous rosacea is characterized by a thickening of the skin, irregular surface nodularities and swelling. Patients with this subtype sometimes exhibit prominent, enlarged follicles as well as telangiectasias in the affected areas. The nose is most commonly affected ("rhinophyma") but phymatous rosacea can also involve other areas such as the chin, the forehead, the cheeks and the ears. This subtype essentially affects men and often occurs after or at the same time as ETR or PPR.

Ocular rosacea (or ophthalmic rosacea) exhibits symptoms restricted to the ocular area with blepharitis, conjunctivitis and keratitis. It is characterized by watery or bloodshot eyes (interpalpebral conjunctival hyperemia), foreign body sensation, burning or stinging, dry or itchy eyes, sensitivity to light, blurred vision, conjunctival telangiectasias or eyelid margin telangiectasias or erythema of the eyelid and periocular area. They can occur with or without rosacea. The onset may occur before, during or after the onset of skin lesions.

The pathogenesis of rosacea is complex and not yet completely understood. Its etiology is multifactorial. In addition to exogenous factors (including UV light, temperature changes, alcohol, hormonal or emotional factors), it may be due to a higher density of *Demodex folliculorum* mites in rosacea patients. Such factors activate neurovascular and/or immune responses, and consequently inflammatory cascades. Intermittent flares may contribute to the chronicity of rosacea as they are associated with prolonged vasodilation, perivascular inflammation, edema and exposure to cytokines and cellular infiltrates. Moreover, many people who get rosacea have family history of the disease, suggesting a possible role of genetic.

Typical treatment of rosacea include oral or topical administration of antibiotics such as tetracycline, erythromycin, clindamycin, but also metronidazole (an antibacterial agent), low dose of isotretinoin in severe forms or even anti-infectious agents such as azelaic acid. However these treatments do not allow treating and/or preventing efficiently all the symptoms associated with rosacea, especially, the neurogenic component such as the skin hyperreactivity and redness.

In addition to rosacea, atopic dermatitis, psoriasis and acne belong to the most frequent inflammatory skin diseases.

Dermatitis derives from Greek language with “derma” meaning skin and “itis” meaning inflammation. Thus, dermatitis corresponds to skin inflammation that is classified in several specific and distinct types of dermatitis according to the localization, causes and symptoms thereof. Non exhaustive examples of dermatitis are atopic dermatitis, contact dermatitis, herpetiformis dermatitis, acrodermatitis, exfoliative dermatitis, perioral dermatitis, seborrheic dermatitis, eczema, hand eczema. Atopic dermatitis is a condition of the epidermis which affects a large number of individuals genetically predisposed to atopy, including infants, children and pregnant women.

Atopic dermatitis is an increasingly common pruritic inflammatory skin disorder due to complex interactions between the genetic predispositions and environmental factors. Atopic dermatitis has a complex etiology that involves abnormal immunological and inflammatory pathways that include defective skin barrier, exposure to environmental agents and neuropsychological factors. The diagnosis of atopic dermatitis is based on clinical presentation of skin erythematous plaques, eruption, and/or lichenification, typically in flexural areas accompanied by intense pruritus and cutaneous hypersensitivity. Pathological examination reveals spongiosis, hyperkeratosis and parakeratosis in acute lesions and marked epidermal hyperplasia, acanthosis, and perivascular accumulation of lymphocytes and mast cells (mastocytes) in chronic lesions.

Although the exact pathophysiology of atopic dermatitis has not yet been clearly understood, it has been reported that atopic dermatitis has at least two major components corresponding to a damaged skin barrier and a deregulated immune response.

Several authors have proposed pharmaceutical or dermatological compositions in order to treat symptoms of atopic dermatitis such as dry skin, erythematous plaques, eruption, lichenification, intense pruritus or cutaneous hypersensitivity and, to a greater extent, to compensate for the epithelial barrier deficiency. For example, pyrrolidone carboxylic acid (Takaoka, JP2004168763) and citrulline or certain amino acids such as glycine, methionine and alanine (Harano et al., WO2005/077349) have been used as a moisturizing agent in emollient compositions for treating atopic dermatitis. Tezuka (JP08020525) has proposed shampoos containing a complex of sodium montmorillonite with a moisturizing agent, which itself can be urea, amino acids, proteins, proteins, pyrrolidone carboxylic acid or a silk protein hydrolysate.

Natural or synthetic immune inhibitors, anti-histamine agents, and steroids have also been used in pharmaceutical compositions in order to treat dermatitis atopic by reducing IgE production with the aim to reduce the immune response. For example, cyclosporin A holds the limelight as immune inhibitors or calcineurin inhibitor and is marked by Novartis under the name Sandimmun®. However, the conventional treating agents for atopic dermatitis using steroid and anti-histamine agents can only temporarily relieve symptoms. In addition, when topical or oral steroids are administered for a long term, the skin of a patient wears thin and osteoporosis is induced. Tacrolimus, which is marked under the names Prograf®, Advagraf® and Protopic®, may also be cited for treating atopic dermatitis as a calcineurin inhibitor leader. However, this drug is suspected of carrying a cancer risk and FDA (Food Drug Administration) has even issued a health warning in March 2005.

Psoriasis is an inflammatory skin disease characterized by red, itchy and scaly skin patches covered with white scales on top with a varying severity. These patches are mostly localized on the knees, elbows, scalp, and on lower back but can also affect other parts of the body. In this pathology, skin cells are quickly multiplied and then accumulated to form psoriatic patches. Psoriasis is characterized by an abnormally excessive and rapid growth of the epidermal skin cells which are replaced every 3-5 days rather than between 28-30 days in normal skin. This abnormal production of skin cells is thought to be due to premature maturation of keratinocytes induced by an inflammatory cascade in the dermis involving dendritic cells, macrophages and T cells. These immune cells are moving from the dermis to the epidermis to secrete cytokines which will stimulate keratinocyte proliferation. It has also been suggested that nerves play an important role in the pathogenesis of this disorder since the denervation of skin has shown an improvement in the psoriatic phenotype (Ostrowski et al., J. Invest. Dermatol., 2011, 131(7), 1530-1538).

Psoriasis pathology is multifactorial, with genetic pre-dispositions triggered by many environmental factors such as, stress, tobacco, alcohol, interruption of corticosteroids etc.

The current available treatments permit mostly to control the symptoms with a limited efficacy and may be use only during short time periods. For instance we can refer to topical treatments with corticosteroids, or with vitamin D3 analogous, retinoids, fluocinonides etc. However these treatments are not really efficient and generate several side effects when used during a long time period such as skin irritations and a pathology aggravation after treatment interruption. This disease affects 2-4% of the population without gender distinction.

Acne is also one of the most common inflammatory skin diseases. It is characterized by areas of skin with seborrhea (scaly red skin) and different types of lesions. Currently, acne lesions may be divided into non-inflammatory lesions (microcomedones, open and closed comedones), inflammatory lesions (papules, pustules, nodules, cysts) and possibly residual lesions or scarring (atrophic, hypertrophic and keloid scars). Lesions are most likely to occur on the face, neck, chest, shoulders and back, where there is a higher concentration of pilosebaceous units.

There exist several forms of acne, the common factor of all being attack of the pilosebaceous follicles. For example, we can mention acne vulgaris, neonatal acne, infantile acne, iatrogenic acne, cosmetic acne or severe forms like acne conglobata or acne fulminans. Acne vulgaris, commonly referred as "acne" or polymorphic juvenile acne, is the most common form and starts at puberty. This type of acne can be divided into mild, moderate, moderately severe and severe acne.

Despite extensive research on acne pathogenesis, the exact sequence of events and their possible mechanisms leading to the development of a microcomedone and its transformation into an inflamed lesion has remained unclear. *(Shaheen B and Gonzales M, J of the European Academy of Dermatology and Venereology 2012).* Recent reports unveiled the role of IL-17, and TNF-α pathways in the physiopathology of acne. Importantly, it has been shown that IL-17/Th17 pathway is activated in acne lesions. In addition, the pro-inflammatory cytokine TNF-α was significantly up-regulated in lesional acne *(Kelhala H, Plos One 2014).* Finally, *Kistowska et al* reported that acne patients exhibit stronger Th17 and Th17/Th1 (IFN-γ and TNF-α) responses to *Propionibacterium acnes*, a Gram-positive commensal bacterium thought to be involved in the pathogenesis of acne vulgaris (*Kistowska et al. J Invest Dermatol. 2014).*

Conventional treatments for treating acne include topical retinoids which reduce comedone formation and inflammatory response, topical or systemic antibiotics (such as erythromycin, clindamycin and tetracyclines) which aim is to reduce bacteria population and inflammation, benzoyl peroxide (BPO) which is both anti-bacterial and midly comedolytic. Using multiple agents (combined therapy) has been recommended to target as many pathophysiologic factors of acne. Oral isotretinoin, which targets all the pathophysiological factors involved in acne, is used in most severe and refractory cases because of serious side effects (such as teratogenicity or depression). However, these available therapies are harsh on the skin and can cause dryness, irritation, or redness.

In view of all these various elements, there is a need to find efficient compounds and develop new compositions for treating and/or preventing inflammatory skin pathologies with a neurogenic component such as rosacea, atopic dermatitis, psoriasis and/or acne, on a long-term period and without toxic effects.

SUMMARY OF THE INVENTION

The invention provides a safe treatment to discontinue or decrease skin inflammation, especially linked to a neurogenic inflammation. The invention provides a long-term effect with limited toxic effects especially regarding hepatotoxicity.

Compounds of formula (I), well known for their high activity as CGRP antagonist compounds by oral route but also for their hepatic toxic effects, can be highly effective as CGRP antagonists by topical application besides avoiding their well-known side effects. More specifically, topical application of these CGRP antagonist compounds can be effective for treating and/or preventing skin inflammatory pathologies with a neurogenic component and especially rosacea.

CGRP antagonist compounds have been described by Merck & Co in EP1 638 969 B1, as orally bioavailable drugs useful for treating acute migraine. These compounds are derived from benzodiazepine lead compound, optimized for leading to potent CGRP receptor antagonist compounds.

The applicant found that CGRP receptor antagonist compounds of family (I) can be effective for treating and/or preventing inflammatory skin pathologies with a neurogenic component by topical application. More specifically, compounds of formula (I), particularly telcagepant (MK-094) can be effective for treating and/or preventing skin inflammatory rosacea, especially type I rosacea, atopic dermatitis, psoriasis and/or acne by topical application.

Indeed, the topical application of MK094 allows to decrease the blood vessel dilation by a significant reduction of the blood perfusion with a dose and time dependant manner. Therefore the topical application of compound of formula (I) such as MK094 is useful for treating and/or preventing type I erythema characterized by erythema and skin flushing induced by excessive blood vessel dilatation.

The present invention relates to CGRP receptor antagonist compound of formula (I) for topical application. More specifically the present invention relates to CGRP receptor antagonist compound of formula (I) for topical application for treating and/or preventing inflammatory skin pathologies with a neurogenic component. On another aspect the present invention relates to CGRP receptor antagonist compound of formula (I) for topical application for treating and/or preventing rosacea, atopic dermatitis, psoriasis, and/or acne. The CGRP receptor antagonist compound useful for the present invention is a compound of formula (I). This invention is also directed to a pharmaceutical composition for topical application, comprising at least one CGRP receptor antagonist compound of formula (I) and a pharmaceutically acceptable vehicle for the treatment and/or the prevention of skin inflammatory pathologies with a neurogenic component and especially rosacea, atopic dermatitis, psoriasis and/or acne.

This topical application of CGRP receptor antagonist compound of formula (I) for treating and/or preventing skin inflammatory disorders with a neurogenic component allows to obtain a significant biological activity of CGRP receptor antagonist and a significant skin bioavailability with a significant hepatic metabolism instability allowing to avoid the toxic side effects observed by oral route.

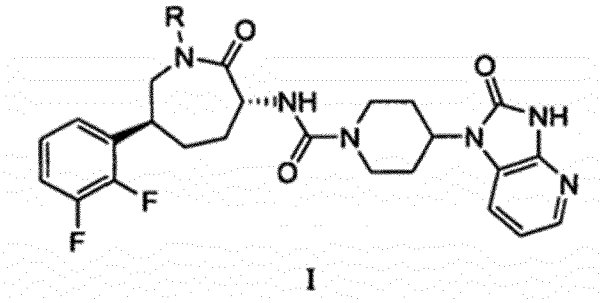
Therefore the present application concerns CGRP receptor antagonist compounds of formula (I) for treating and/or preventing skin inflammatory pathologies with a neurogenic component, by topical application. More specifically the present invention concerns CGRP receptor antagonist compounds of formula (I) for treating and/or preventing rosacea, atopic dermatitis, psoriasis, and/or acne by topical application. On a more specific aspect the present invention telcagepant (MK-094) is the preferred compound. On another embodiment the present invention is also directed to a pharmaceutical composition for topical application, comprising at least one CGRP receptor antagonist compound of formula (I) and a pharmaceutically acceptable vehicle for the treatment and/or the prevention of skin inflammatory pathologies with a neurogenic component, and especially rosacea, atopic dermatitis, psoriasis, and/or acne. On another embodiment the present inventions concerns the topical use of CGRP receptor antagonists of formula (I). On a more specific embodiment the present invention concerns the topical use of CGRP receptor antagonists of formula (I) for treating and/or preventing skin inflammatory pathologies with a neurogenic component, especially rosacea, atopic dermatitis, psoriasis, and/or acne. On another aspect the present invention is directed to the use of a CGRP receptor antagonist of formula (I) for the

manufacture of a medicament destined to treat and/or prevent skin inflammatory pathologies with a neurogenic component by topical application. Another aspect of the invention is directed to a process for treating and/or preventing skin inflammatory pathologies with a neurogenic component, comprising the topical administration of at least one compound of formula (I).The present invention is further directed to a method for the manufacture of a medicament comprising at least a compound of formula (I) with a pharmaceutical carrier or diluent for treating and/or preventing skin inflammatory pathologies with a neurogenic component and more especially type I rosacea, atopic dermatitis, psoriasis, and/or acne.

The present invention also relates to a method for treating and or preventing skin inflammatory pathologies with a neurogenic component and more especially type I rosacea, atopic dermatitis, psoriasis, and/or acne, by topical administration of a composition comprising the compound of formula (I) and more precisely MK094.

CGRP receptor antagonist compounds of formula (I) according to the present invention, have been described in EP1 638 969 B1.

According to the present invention, compounds for use in topically treating and/or preventing a skin inflammatory pathology with a neurogenic component are compounds of formula (I):



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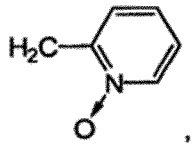
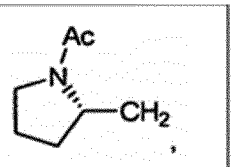
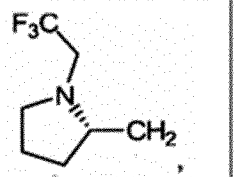
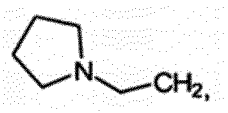
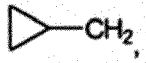
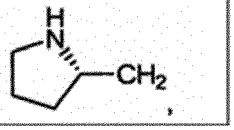
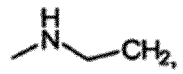
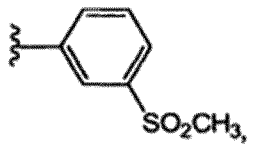
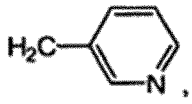
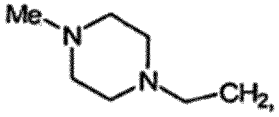
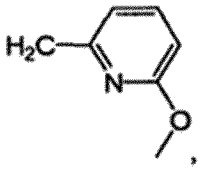
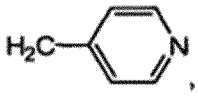
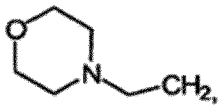
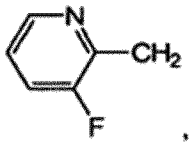
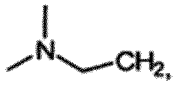
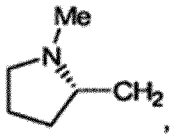
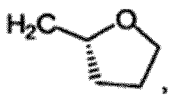
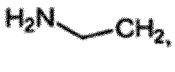
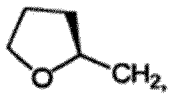
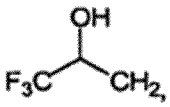
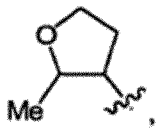
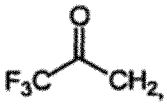
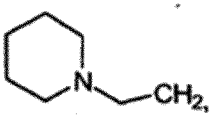
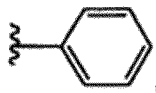
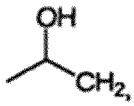
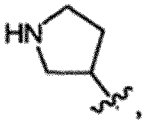
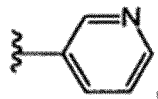
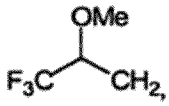
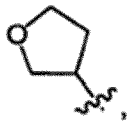
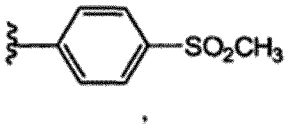
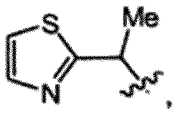
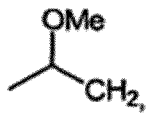
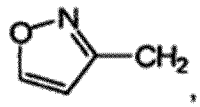
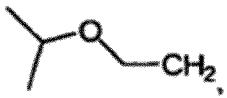
 ,	CH_3,	 ,
$CH_2CH_2SO_2CH_3$,	CH_2CH_3,	 ,
 ,	 ,	 ,

	CH_2CH_2F,	
	CH_2CHF_2,	
$CH_2CO_2CH(CH_3)_2$,		CH_2CH_2OH,
		
	$CH_2CO_2CH_3$,	
		
		
		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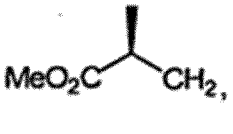
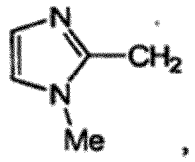
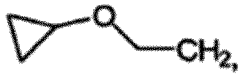
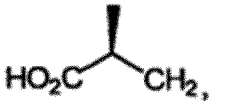
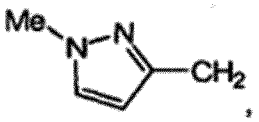
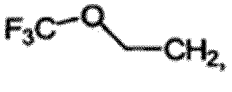
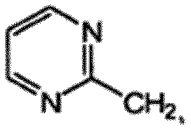
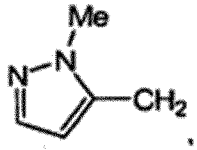
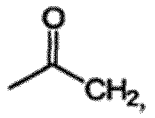
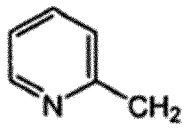
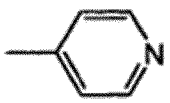
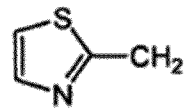
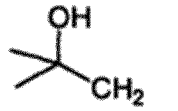
		
		
		CH_2CO_2H,
	CH_2CH_2-S-CH_3	CH_2CH_2-SO-CH_3
CH_2CH_2-O-CH_3	CH_2CF_3	
		

and pharmaceutically acceptable salts and individual stereoisomers thereof.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of formula (I) may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention.

The compounds of formula (I) and their isomeric forms are useful according the present invention. The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. Racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art. Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

Halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo.

As used herein, "alkyl" is intended to mean linear or branched structures having no carbon-to-carbon double or triple bonds. Thus C1-6alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C1-6alkyl specifically includes, but is not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl and hexyl. "Cycloalkyl" is an alkyl, part or all of which which forms a ring of three or more atoms.

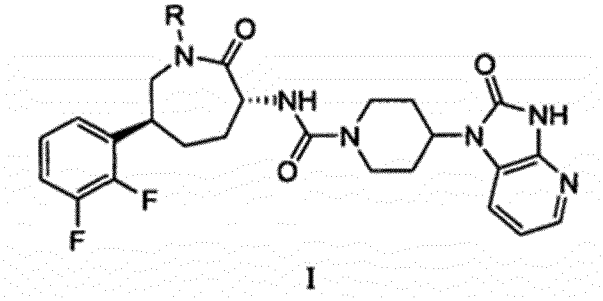
As used herein, "aryl" is intended to mean mono- or bi-cycle with 6 to 12 atoms of carbon of formula $C_nH_{(n-2)}$.

As used herein “heterocycloalkyl” is a cycloalkyl group as defined herein, comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur.

All the chemical synthesis processes of these CGRP receptor antagonist compounds of formula (I) are described by Merck & Co in EP1 638 969 B1 at page 11 to page 29, more specifically by examples 1 to 9 and in table E-4.

According to the present invention "pharmaceutically acceptable vehicle" refers to a vehicle appropriated for topical application, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. As used herein, "pharmaceutically acceptable salts" refer to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. In one aspect of the invention the salts are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of formula (I) are meant to also include the pharmaceutically acceptable salts.

More specifically according to the present invention, compounds for treating and/or preventing skin inflammatory pathology with a neurogenic inflammation are compounds of formula (I):



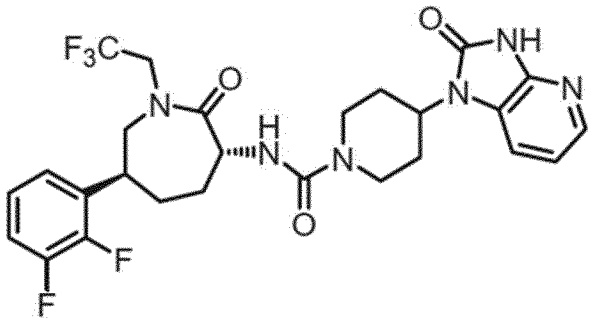
I

wherein R is selected from: -CH2CF3, -CH2CH2F, -CH2CHF2, -CH2CH2CF3 and pharmaceutically acceptable salts and individual stereoisomers thereof.

On a more specific embodiment the preferred CGRP receptor antagonist is compound of formula (I) for treating and/or preventing skin inflammatory pathologies with a neurogenic inflammation wherein R is -CH2CF3.

More specifically the preferred CGRP receptor antagonist compound of formula (I) for treating and/or preventing skin inflammatory pathologies with a neurogenic inflammation is Telcagepant (MK-094) and its pharmaceutically acceptable salts and individual stereoisomers thereof.

The preferred compound of the present invention (telcagepant, MK094), having the following specific formula:



The preferred compound of the present invention is telcagepant (MK094), having the following chemical name: [N-[(3R,6S)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide] and the CAS registry number 781649-09-0.

According to the present invention “pharmaceutical composition” refers preferably to a dermatological composition which can be topically applied. More specifically

"pharmaceutical composition" relates to a pharmaceutical composition comprising a CGRP receptor antagonist compound of formula (I) and a vehicle suitable for a topical application, for the treatment and/or the prevention of skin inflammatory pathology with a neurogenic component. Telcagepant being the preferred CGRP receptor antagonist compound of formula (I) and rosaea, especially type I rosacea being the preferred skin inflammatory pathology with a neurogenic component.

The choice of the concentration of CGRP receptor antagonist compounds of formula (I), preferably telcagepant, and the form of the pharmaceutical composition for the treatment and/or the prevention of a particular skin inflammatory pathology with a neurogenic component can be made depending on the type and severity of the pathology, location of the affected area, and form of the pharmaceutical composition. A person of ordinary skill in the art will be able to determine these different parameters.

The choice of the concentration of CGRP receptor antagonist compounds of formula (I), preferably MK-094, and the form of the pharmaceutical composition for the treatment and/or the prevention of a particular skin inflammatory pathology with a neurogenic component can be made depending on the type and severity of the pathology, location of the affected area, and form of the pharmaceutical composition. A person of ordinary skill in the art will be able to determine these different parameters. As an indication of useful range of concentration, the compound of formula (I) and especially MK-094 can be used in a composition from 0.001 to 10 %, preferentially from 0.001 to 5 %, more preferentially from 0.3 to 3 %, and even more preferentially at 3 % relative to the total weight of the composition.

The pharmaceutical composition is advantageously administered by topical application and, therefore, is in a form suitable for topical application to the skin. For example, it may be in the form of an optionally gelled, oily solution, an optionally two-phase dispersion of the lotion type, an emulsion obtained by dispersion of a fatty phase in an aqueous phase (O/W) or vice versa (W/O), or a triple emulsion (W/O/W or O/W/O) or a vesicular dispersion of ionic and/or non-ionic type. This topical composition may be in anhydrous form, in aqueous form or in the form of an emulsion. These compositions are prepared according to the usual methods. According to this invention, a composition in the form of an emulsion obtained by dispersion of a fatty phase in an aqueous phase (O/W) is preferably used.

This composition may be more or less fluid and may be in the form of salves, emulsions, creams, milks, ointments, impregnated pads, syndets, solutions, gels, sprays or aerosols, foams, suspensions, lotions or sticks. Preferably, the composition used in the present invention is in the form of an emulsion, of a cream, of a lotion type, of a gel, or of a solution, and more preferably in the form of an emulsion.

It is also considered that the pharmaceutical composition according to the present invention can be administered in combination with, or comprise an additional active ingredient or additive. The additional active ingredient is preferably selected from the group comprising antibiotics, antibacterial, antivirrals, antiparasitics, antifungals, anesthetics, analgesics, antiallergic agents, retinoids, free-radical scavengers, anti-pruriginous, the keratolytic agents, antiseborrheic, antihistaminic, sulfides, immunosuppressant products and antiproliferative agents, corticosteroids, intravenous immunoglobulin, anti-angiogenic, anti-inflammatory and/or a mixture thereof.

The additive is preferably selected from the group consisting of sequestering agents, chelating agents, antioxidants, sunscreens, preservatives, fillers, electrolytes, humectants, dyes, conventional acids, or bases, organic or inorganic, perfumes, essential oils, cosmetic active agents, moisturizers, vitamins, essential fatty acids, sphingolipids, self-tanning compounds, soothing and protective agents of the skin, penetrating agents, emulsifiers, gelling agents and a mixture thereof.

In one embodiment, the term "treatment" or "treating" refers to an improvement, the prophylaxis of a disease or disorder, or at least one symptom can be discerned therefrom. In another embodiment, "treatment" or "treating" means an improvement, prevention of at least one measurable physical parameter associated with the disease or disorder being treated, which is not necessarily discernible in the subject. In another further embodiment "treatment" or "treating" refers to inhibiting or slowing the progression of a disease or disorder, physically, e.g., stabilization of a discernible symptom, physiologically, for example, stabilization of a physical parameter, or both. In another embodiment, "treatment" or "treating" refers to delaying the onset of a disease or disorder. In some embodiments, compounds of interest are administered as a preventive measure. In this context, "prevention" or "preventing" refers to a reduction in the risk of acquiring a disease or disorder specified.

The present invention is directed to any mammal, particularly humans, male or female.

According to the present invention "dermatologic disorders" or "skin inflammatory pathologies with a neurogenic component" refers to skin inflammatory pathologies with a neurogenic component chosen among type I erythematous rosacea, type II papulopustular rosacea, atopic dermatitis, hand chronic eczema, psoriasis (vulgaris, scalp, arthritic, pustular, guttate), facial erythema, pudic erythema, hives, utricaria (acute, chronic), any kind of pruritus (for instance senile pruritus, prurigo nodularis) and acne.

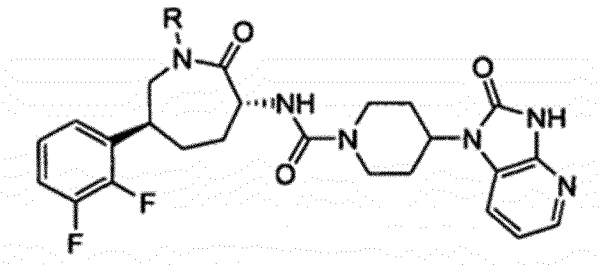
More specifically the skin inflammatory pathologies with a neurogenic component are chosen among type I erythematous rosacea, atopic dermatitis, vulgaris and scalp psoriasis, prurit senile, acne and prurigo nodularis.

On a specific embodiment the skin inflammatory pathology with a neurogenic component according to the present invention is rosacea and especially type I erythemateous rosacea, atopic dermatitis, psoriasis, and/or acne.

Type I erythemateous rosacea according to the present invention is mainly characterized by vasomotor flushing and persistent central facial erythema (redness) and telangiectasias (visible blood vessels). Central facial edema, burning or stinging sensations and rough, flaky skin are also symptoms that have sometimes been reported. Flushing is the only symptom commonly found in people with type I erythemateous rosacea. Facial flushing is due to the sudden dilatation of the arterioles of the face (which then takes a red appearance) and may be triggered by emotional stress, hot drink, alcohol, spicy food or temperature changes.

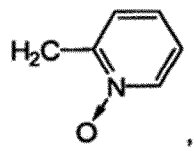
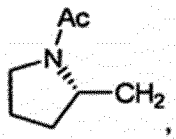
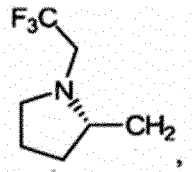
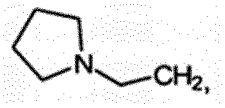
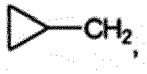
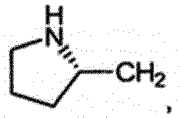
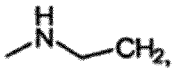
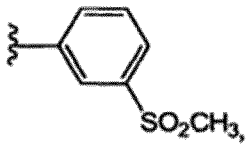
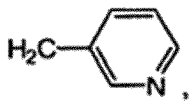
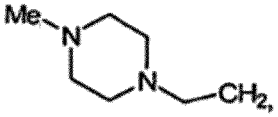
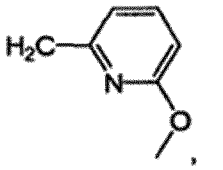
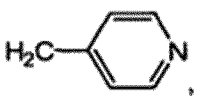
Claims

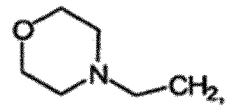
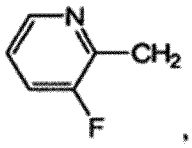
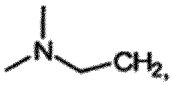
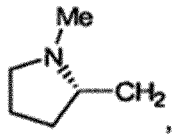
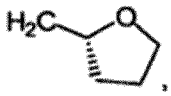
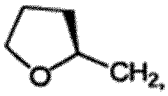
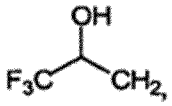
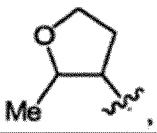
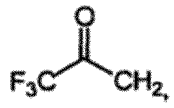
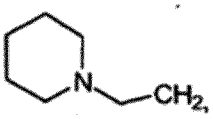
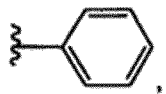
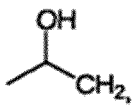
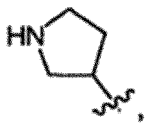
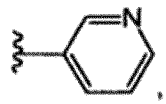
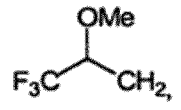
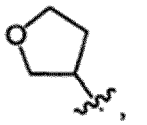
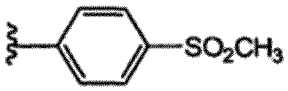
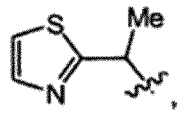
1. Compound for use in topically preventing or treating a dermatological disorder, wherein the compound is of formula I:

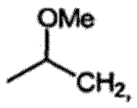
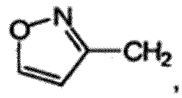
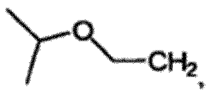


I

wherein R is selected from:

 ,	CH_3,	 ,
$CH_2CH_2SO_2CH_3$,	CH_2CH_3,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,

	CH_2CH_2F,	
	CH_2CHF_2,	
$CH_2CO_2CH(CH_3)_2$,		CH_2CH_2OH,
		
	$CH_2CO_2CH_3$,	
		
		
		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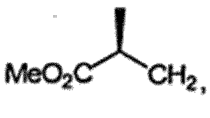
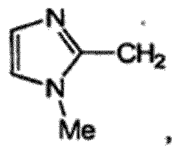
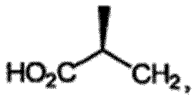
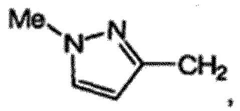
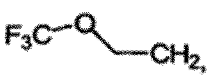
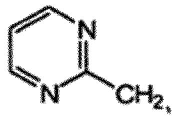
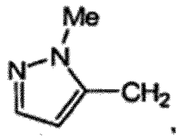
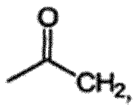
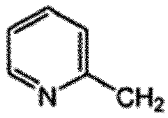
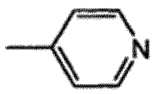
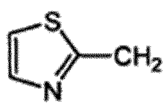
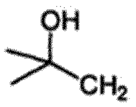
		
		
		CH_2CO_2H,
	CH_2CH_2-S-CH_3	CH_2CH_2-SO-CH_3
CH_2CH_2-O-CH_3	CH_2CF_3	
		

and their pharmaceutically acceptable salts and individual stereoisomers thereof.

2. The compound for use according to claim 1, wherein the dermatological disorder is a skin inflammatory pathology with a neurogenic component.

3. The compound for use according to claim 2 wherein the skin inflammatory pathology with a neurogenic component is selected from the group consisting of rosacea, especially type I erythematous rosacea, type II papulopustular rosacea, atopic dermatitis, hand chronic eczema, psoriasis (vulgaris, scalp, arthritic, pustular, guttate), facial erythema, pudic erythema, hives (acute, senile pruritus, prurigo nodularis) and acne.

4. The compound for use according to claim 2 or 3, wherein the skin inflammatory pathology with a neurogenic component is selected from the group consisting of type I

erythematous rosacea, atopic dermatitis, vulgaris and scalp psoriasis, prurit senile, acne and prurigo nodularis.

5. The compound for use according to any of claims 2 to 4, wherein the skin inflammatory pathology with a neurogenic component is type I erythematous rosacea, atopic dermatitis, psoriasis, and/or acne.

6. The compound for use according to any of the preceding claims, wherein:
- R is -CH2CF3, -CH2CH2F, -CH2CHF2, or -CH2CH2CF3 and their pharmaceutically acceptable salts and individual stereoisomers thereof.

7. The compound for use according to any of the preceding claims, wherein:
- R is - CH2CF3 and its pharmaceutically acceptable salts and individual stereoisomers thereof.

8. The compound for use according to any of the preceding claims which is [N-[(3R,6S)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide].

9. A pharmaceutical topical composition comprising at least a compound as defined in any of claim 1 and claims 6 to 8, and a pharmaceutically acceptable vehicle for topical application.

10. A pharmaceutical composition according to claim 9, wherein the compound as defined in any of claim 1 and claims 6 to 8 is at a concentration ranging from 0.001 to 10 %, preferentially from 0.001 to 5 %, more preferentially from 0.3 to 3 %, and even more preferably 3% relative to the total weight of the composition.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/065063

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/55 A61P17/04 A61P17/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	compounds 82-145 claims 1-20, 24, 28 page 35, lines 16-19, 30-31 page 39, line 3 page 41, lines 25-26 page 41, line 31 - page 42, line 17	1-10
Y	WO 2010/002763 A1 (MERCK & CO INC [US]; MAHJOUR MAJID [US]; ZHANG DAN [US]; MOMENT AARON) 7 January 2010 (2010-01-07) page 1, line 9 - page 3, line 20	1-10
Y	US 2001/051157 A1 (BRETON LIONEL [FR] ET AL) 13 December 2001 (2001-12-13) claims 1, 12-14	1-10

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2016	26/08/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Renard, Delphine

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/065063

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/014351 A2 (SVEINSSON BIRKIR [IS]) 19 February 2004 (2004-02-19) claims 1, 5-6, 8, 9, 11 -----	1-10
Y	EP 0 734 729 A1 (OREAL [FR]) 2 October 1996 (1996-10-02) claims 1-2, 10-11 -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/065063

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