**Ester de Metronidazole pour le traitement de la Rosacee**

The present invention relates to a compound chosen from the compound of formula (I) below: enantiomers thereof and pharmaceutically acceptable salts thereof, and also to the uses thereof.
Title: METRONIDAZOLE ESTERS FOR TREATING ROSacea

Abstract: The present invention relates to a compound chosen from the compound of formula (I) below: enantiomers thereof and pharmaceutically acceptable salts thereof, and also to the uses thereof.
Metronidazole esters for treating rosacea

The present invention relates to a compound of formula (I), and to its uses as a medicament, especially in the treatment and/or prevention of rosacea and in the treatment and/or prevention of inflammatory pathologies.

Rosacea is a progressive chronic common inflammatory dermatosis associated with vascular relaxation. It mainly affects the central part of the face and is characterized by reddening of the face or hot flushes, facial erythema, papules, pustules, telangiectasia and occasionally ocular lesions known as ocular rosacea. In serious cases, especially in men, the soft tissue of the nose may swell and produce a bulbous swelling known as rhinophyma. Rosacea develops over several years via episodes that are worsened by various stimuli such as temperature variations, alcohol, spices, exposure to sunlight, or emotions.

Rosacea is classified into four subtypes as a function of various clinical characteristics (Wilkin J. et al., JAAD, 2002, 46: 584-587).

The primary characteristics (histamine flushes, persistent erythema, papules and pustules, and telangiectasia) and secondary characteristics (burning or stinging sensation, plaques, dry appearance of the skin, oedema, ocular manifestations, phymatous changes) of rosacea are often observed in combination. The most common modes of exteriorization or combinations of signs are temporarily regrouped into specific subtypes, which are described below. Each category comprises the minimum number of signs that are sufficient to make a diagnosis of the corresponding subtype (although the modes of exteriorization are not necessarily limited to these signs), and it is possible that patients simultaneously present characteristics suggesting more than one subtype of rosacea.

Subtype 1: Erythematotelangiectasic rosacea

Erythematotelangiectasic rosacea is characterized mainly by histamine flushes and persistent central facial erythema. The presence of telangiectasias is common, but not essential to the diagnosis of this subtype. A central facial oedema, burning and
stinging sensations, and redness or desquamation are also occasionally observed. History of histamine flushes alone are common in the case of patients suffering from erythematotelangiectasic rosacea.

Subtype 2: Papulopustular rosacea
Papulopustular rosacea is characterized by persistent central facial erythema and by transient papules and/or pustules distributed in the centre of the face. However, the papules and pustules may also affect the peri-orificial regions (i.e. the perioral, perinasal or periocular areas). The papulopustular subtype resembles common acne, but comedones are absent. Rosacea and acne may coexist, and, besides the papules and pustules resembling rosacea, the patients concerned will also possibly have comedones. Patients suffering from papulopustular rosacea occasionally complain of burning and stinging sensations.

This subtype is often observed before or at the same time as subtype 1 (including the presence of telangiectasias). The telangiectasias risk being masked by the persistent erythema and the papules or pustules.

Subtype 3: Phymatous rosacea
Phymatous roscea is manifested by thickening of the skin, nodules with an irregular surface and tumefaction. Rhinophyma is the commonest presentation, but phymatous rosacea may affect other regions, including the chin, the forehead, the cheeks and the ears. In the case of patients suffering from this subtype, the presence of enlarged and prominent follicular apertures is occasionally reported in the affected region, as are telangiectasias.

This subtype is often observed before or at the same time as subtype 1 or 2 (including the presence of persistent erythema, telangiectasias, papules and pustules). In the case of rhinophyma, these additional stigmata risk being particularly pronounced in the nasal region.

Subtype 4: Ocular rosacea (or ophthalmic rosacea)
The diagnosis of ocular rosacea must be envisaged when a patient has one or more of the following ocular signs and symptoms: teary or bloodshot appearance (interpalpebral conjunctival hyperaemia), sensation of presence of a foreign body, of
burning or stinging, dryness, itching, photosensitivity, blurred vision, telangiectasias of the conjunctiva and of the edge of the eyelid, or erythema of the eyelid and periocular erythema. Blepharitis, conjunctivitis and irregularity of the edges of the eyelid are other signs that may be detected. A chalazion or a chronic staphylococcal infection manifested by a stye and whose cause is a dysfunction of the meibomian glands is a frequent sign of ocular affection related to rosacea. Some patients complain of a reduction in visual acuity, which is due to corneal complications (punctuate keratitis, corneal infiltrates/corneal ulcers or marginal keratitis). By itself, the treatment of cutaneous rosacea may be without effect on the risk of lowering the visual acuity associated with ocular rosacea, and an ophthalmological approach will possibly be required.

Finally, other rarer forms of rosacea exist (variants), in particular granulomatous rosacea.

The diagnosis of ocular rosacea is most often made when cutaneous signs and symptoms are also detected. However, it is not necessary for cutaneous signs and symptoms to be present in order to make the diagnosis, and small-scale studies suggest that up to 20% of patients suffering from ocular rosacea may develop ocular signs and symptoms before cutaneous manifestations appear. Cutaneous lesions are the first to appear in the case of about half of these patients, and manifestations of the two types occur simultaneously in a minority of them.

Rosacea generally occurs between the ages of 25 and 70, and is much more common in people with fair complexion. It more particularly affects women, although this complaint is generally more severe in the case of men.

The pathogenesis of rosacea is poorly understood, and may involve several factors. These are, for example, vascular factors (abnormal vascular reactivity), immune factors, or alternatively exogenous factors such as the presence of follicular microorganisms such as bacteria and Demodex folliculorum mites (Diamantis S. & Waldorf H.A., J. Drug Dermatol., 2006, 5: 8-12; Wilkin J.K., Arch. Dermatol., 1994, 130: 359-362; Buechner S.A., Dermatology, 2005, 210: 100-108).
Moreover, studies, especially clinical studies, tend to suggest that rosacea is an inflammatory pathology (McKeage et al., Am. J. Clin. Dermatol. 2010; 11(3): 217-22).

Conventionally, rosacea is treated orally or topically. Among the agents having a marketing authorization for the "rosacea" indication are topical metronidazole and oral doxycycline (Cribier B., La rosacée, Masson-Eticom, Paris, 2002).

Long-term oral treatments with tetracycline derivatives are problematic for many reasons, in particular on account of their significant side effects. The oral administration of tetracyclines, especially doxycycline, may induce photosensitivity, or even phototoxicity at and above 100 mg/day (Layton A.M., Cunliffe W.J. Phototoxic eruptions due to doxycycline-a dose-related phenomenon. Clin. Exp. Dermatol. 1993; 18:425-427), or alternatively gastrointestinal disorders (Maibach H. Second-generation tetracyclines, a dermatologic overview: clinical uses and pharmacology. Cutis. 1991; 48:411-417).

In addition, these treatments do not make it possible to effectively treat and/or prevent all of the symptoms associated with rosacea. Considering the chronic nature of rosacea, with a typical profile of remission and exacerbation, an ideal treatment requires use that may be prolonged, in a safe and effective manner.

Patent application WO 02/74290 describes the use of at least one non-steroidal anti-inflammatory drug (NSAID) for treating rosacea. This compound may especially be piroxicam, aspirin, ibufenac or naproxen. It may optionally be used in combination with a nitroimidazole. The simultaneous use of an NSAID and of a nitroimidazole has, however, appreciable side effects, especially gastrointestinal and renal effects associated with the use of metronidazole as nitroimidazole (D.I. Edwards, Br. J. Vener. Dis. 1980; 56: 285-290), or ulcers associated with the use of an NSAID (C.J. Hawkey, J. Rheumatology, 2002; 29: 4; 650-652).

There is thus a need for active agents that are effective for treating rosacea, which can be used for long periods, and which have the least possible side effects.
The aim of the present invention is thus to propose an effective treatment for rosacea, which especially reduces the side effects for the patient. Preferably, this treatment is performed topically, which considerably reduces any systemic side effect.

One subject of the present invention is thus a compound chosen from the compound of formula (I) below:

![Chemical Structure](image)

(I)

enantiomers thereof and pharmaceutically acceptable salts thereof.

The compound of formula (I) has the chemical name 2-(2-methyl-5-nitroimidazol-1-yl)ethyl 2-(2-fluorobiphenyl-4-yl)propionate.

This compound contains an ester function, which is specifically cleaved in keratinocytes, as is demonstrated in Example 2. For comparative purposes, other metronidazole esters with NSAIDs, for instance indomethacin, niflumic acid, diflunisal or ketorolac esters, were prepared and tested on keratinocyte cultures. All these compounds are stable in the presence of keratinocytes, unlike the compound of formula (I) according to the invention. This particular instability of the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof is thus surprising and unexpected. Without wishing to be bound by any theory, it is quite likely that this particular surprising instability of the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof makes it possible to obtain the anti-inflammatory activity and the anti-rosacea activity once the compound of formula (I), enantiomers thereof or pharmaceutically acceptable salts thereof has (have) penetrated the skin and become hydrolysed on contact with the keratinocytes.
Effectively, the hydrolysis on contact with keratinocytes of the compound of formula (I), enantiomers thereof or pharmaceutically acceptable salts thereof releases metronidazole and flurbiprofen as indicated in Example 2.

However, surprisingly, the amount of metronidazole and flurbiprofen detected in the plasma, after topical application, is smaller when an amount of the compound of formula (I), an enantiomer thereof or a pharmaceutically acceptable salt thereof is applied compared with when the same amount of an equimolar mixture of metronidazole and flurbiprofen is applied.

By way of example, the application to rat skin of a composition containing 1.4% 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate makes it possible to detect about 2.3 times less metronidazole and about 6.7 times less flurbiprofen in the plasma when compared with application under the same conditions of an equimolar mixture of metronidazole and flurbiprofen. The areas under the curve representing the plasmatic concentration as a function of time are used as an indication of the plasmatic exposure.

This particular and unexpected property of the compound of formula (I), enantiomers thereof or pharmaceutically acceptable salts thereof thus makes it possible to minimize the plasmatic amounts of metronidazole and flurbiprofen, and thus to minimize the adverse side effects associated with these products, while at the same time maintaining useful anti-inflammatory activity in the treatment of rosacea.

By way of example, the (S) and (R) enantiomers corresponding to the general formula (I), namely, respectively, 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate and 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (R)-2-(2-fluorobiphenyl-4-yl)propionate, evaluated at a concentration of 1% in the TPA test in mice as indicated in Example 3, show inhibition, respectively, of 95% and 85% for the TPA-induced inflammation. For comparative purposes, (S)-flurbiprofen and (R)-flurbiprofen show inhibition, respectively, of 70% and 80% when they are tested at the same 1% concentration.

Thus, the compound of formula (I), enantiomers thereof or pharmaceutically acceptable salts thereof have anti-inflammatory activity that is useful in the treatment of rosacea while at the same time being able to reduce the plasmatic concentration of metronidazole and flurbiprofen when compared with the topical application of an equivalent concentration of an equimolar mixture of metronidazole and flurbiprofen.
The present invention also relates to a compound chosen from the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof, for its use as a medicament.

A subject of the present invention is also a compound chosen from the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof, for its use in the treatment and/or prevention of rosacea.

A subject of the present invention is also a compound chosen from the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof, for its use in the prevention and/or treatment of inflammatory pathologies.

A subject of the present invention is also the use of at least one compound chosen from the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof, for preparing a medicament for treating and/or preventing rosacea.

A subject of the present invention is also the use of at least one compound chosen from the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof, for preparing a medicament for treating and/or preventing inflammatory pathologies.

The term "salts of the compound of formula (I) according to the invention or salts of enantiomers thereof" means salts of this compound or of enantiomers thereof with a pharmaceutically acceptable acid.

The pharmaceutically acceptable acid is especially:
- a pharmaceutically acceptable inorganic acid, for instance hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid or hydrobromic acid;
- or a pharmaceutically acceptable organic acid, for instance acetic acid, tartaric acid, maleic acid, hydroxymaleic acid, fumaric acid, citric acid, lactic acid, mucic acid, gluconic acid, benzoic acid, succinic acid, oxalic acid, phenylacetic acid, methanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, salicylic acid, aspartic acid, glutamic acid and ascorbic acid.
Preferably, the salts of the compound of formula (I) are chosen from the hydrochloride, the citrate, the salicylate and the benzoate of the compound of formula (I).

The carbon atom located between the benzene ring and the -COO- group is asymmetric; the molecule is thus chiral. Thus, the term "enantiomers of the compound of formula (I)" means the R and S enantiomers of this compound. The S enantiomer is the preferred form.

Thus, the compound according to the invention is preferably 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate.

Preferably, the salts of the S enantiomer of the compound of formula (I) are chosen from the hydrochloride, the citrate, the salicylate and the benzoate of the said S enantiomer (i.e. 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate hydrochloride, 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate citrate, 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate salicylate and 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate benzoate.

The term "treatment" or "treating" rosacea (or inflammatory pathologies) means reducing and/or inhibiting the development of rosacea (or of inflammatory pathologies) and/or of the symptoms thereof.

The term "prevention" or "preventing" rosacea (or inflammatory pathologies) means reducing and/or avoiding the appearance of the symptoms of rosacea (or of inflammatory pathologies).

The term "inflammatory pathologies" especially means cutaneous inflammatory pathologies, such as psoriasis, atopic dermatitis, acne or eczema.

The term "compound according to the invention" means, indiscriminantly, the compound of formula (I), an enantiomer thereof and/or a pharmaceutically acceptable salt thereof.

More preferentially, the compound according to the invention is the S enantiomer of the compound of formula (I) or 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate of structure corresponding to formula (Ia)
The compound according to the invention may be prepared according to the process given in Example 1.

The compound chosen from the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof may thus be formulated in pharmaceutical compositions for human use. The said compositions comprise, in a pharmaceutically acceptable medium, at least one compound chosen from the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof. The term "pharmaceutically acceptable medium" means a medium that is compatible with the skin, mucous membranes and the integuments.

The pharmaceutical composition that may be used according to the invention may be administered topically, parenterally or orally. Preferably, the compound chosen from the compound of formula (I), enantiomers thereof and pharmaceutically acceptable salts thereof is present in a pharmaceutical composition for topical application. The term "topical application" means application to the skin, mucous membranes and/or the integuments.

The composition according to the invention comprises from 0.001\% to 10\% by weight of compound(s) according to the invention relative to the total weight of the composition. Preferentially, the composition according to the invention contains from 0.1\% to 5\% by weight of compound(s) according to the invention relative to the total weight of the composition.

The topical pharmaceutical composition may be in liquid, pasty or solid form, and more particularly in the form of an ointment, a cream, a milk, a pomade, a powder, an
impregnated pad, a syndet, a wipe, a solution, a gel, a spray, a mousse, a suspension, a lotion, a stick, a shampoo or a washing base. It may also be in the form of a suspension of microspheres or nanospheres or lipid or polymer vesicles or a polymer patch and a hydrogel allowing controlled release. This pharmaceutical composition for topical application may be in anhydrous form, in aqueous form or in the form of an emulsion.

In one preferred variant of the invention, the pharmaceutical composition for topical application is in the form of a solution, a gel or an emulsion.

Such pharmaceutical compositions may be manufactured according to processes that are well known to those skilled in the art.

Various examples of preparation and use of the compounds according to the invention will now be given, for illustrative purposes and with no limiting nature.

EXAMPLES

Example 1: Synthesis of 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate

To a solution of (S)-flurbiprofen (2 g, 8.17 mmol) and metronidazole (1.4 g, 8.17 mmol) in 30 mL of dichloromethane are successively added 50 mg of DMAP (4-dimethylaminopyridine) and then 1.6 g (8.17 mmol) of EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide). The reaction mixture is stirred for 4 hours at room temperature and then quenched with 50 mL of water and extracted with 50 mL of dichloromethane. The organic phase is washed with 2×50 mL of 5% citric acid solution and then with 50 mL of water. The organic phase is dried over magnesium sulfate and then evaporated under reduced pressure. The residue is dissolved in 10 mL of isopropanol and then brought to reflux. After cooling to room temperature, the product crystallizes in the form of white crystals.
2.1 g of 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate are obtained. Yield = 64%.

$^1$H NMR (CDCl$_3$): 7.95 (s, 1H); 7.55 (dd, 2H, J= 1 Hz, J= 7 Hz); 7.48 (t, 2H, J= 5 Hz); 7.41 (m, 2H); 7.05 (m, 2H); 4.60-4.44 (m, 4H); 3.69 (q, 1H, J= 7 Hz); 2.31 (s, 3H); 1.51 (d, 3H, J= 7 Hz).

$^{13}$C NMR (CDCl$_3$): 173.4; 161.0; 158.5; 150.6; 140.9; 140.8; 135.2; 132.2; 131.2; 131.2; 129.0; 128.5; 127.8; 123.4; 115.2; 115.0; 62.9; 45.1; 44.9; 18.3; 13.9.

NB: In order to obtain the compound of formula (I) according to the invention in racemic form, the process described above is used replacing the S-flurbiprofen with racemic flurbiprofen.

Each enantiomer of the compound of formula (I) is identified by chiral HPLC under the following conditions:

Column IC 250×4.6 mm 5 μm
Route A Heptane 75%
Route B Isopropanol 25%
Flow rate = 1.4 ml/min

(S): 12.4 minutes / (R): 14.2 minutes

Example 2: Stabilities evaluated on keratinocyte cultures

The stability on keratinocyte cultures is evaluated using human neonatal keratinocytes (Cell’N Tech) cultured in a 75 cm$^2$ flask and detached at 90-100% of confluence with vegetable trypsin (trypLE GIBCO). The compound of formula (I) was tested at 2 μM in the medium CNT-057 (Cell’N Tech) supplemented with 0.1% pluronic acid in 24-well plates. The final DMSO concentration is 0.1%. Degradation kinetics are performed with a Tecan EVO robot over 24 hours. The samples taken are then assayed by LC/MS/MS (Micromass) in comparison with a calibration range of the test product, prepared under the same conditions as the samples (1/3 culture medium and 2/3 methanol). The chromatographic conditions are optimized for each
product. An assay of the appearance of metronidazole is also performed using these same samples.
The half-life time ($t_{1/2}$) of 2-(2-methyl-5-nitroimidazol-1-yl)ethyl 2-(2-fluorobiphenyl-4-yl)propionate is 6 hours.
That of its S enantiomer, namely 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate, is 18 hours.
For comparative purposes, the metronidazole esters with indomethacin, niflumic acid, diflunisal or ketorolac do not become hydrolysed on the keratinocyte cultures.

**Example 3: Anti-inflammatory activity**

a) Model of acute inflammation on mouse ear: arachidonic acid-induced oedema

The anti-inflammatory activities of the compound of formula (I) in racemic form, of the S enantiomer of the compound of formula (I), of metronidazole and of flurbiprofen were measured in an in vivo test performed on a mouse model. This model consists in inducing inflammation of the mouse ear with a single application of arachidonic acid (AA). Female Balb/c ByJ/Ico mice are used. The oedema is induced by applying to the mouse’s ear 20 µL of AA dissolved to 4% in a 1/1 THF/methanol mixture. The anti-inflammatory activities of the S enantiomer of the compound of formula (I), of the compound of formula (I) in racemic form, of metronidazole and of flurbiprofen were evaluated after topical application onto the inner face of the mouse’s ear of 20µL of a solution of the compound in a 1/1 THF/methanol mixture containing 4% AA.

Solutions containing 0.01%; 0.03%; 0.1%; 0.3%; 1% and 2% of the test compound are thus prepared. The percentages correspond to the weight of the test compound per volume of solution. The oedema is evaluated, 1 hour after application, by measuring the thickness of the ear using an Oditest® micrometer. The oedema induced by AA alone is evaluated, 1 hour after application, by measuring the thickness of the ear using an Oditest® micrometer. It is evaluated relative to a group comprising only the vehicle (1/1 THF/methanol).
The inhibition of the oedema is expressed as a percentage of reduction, by the test molecule and at the test concentration, of the oedema induced by AA alone.
The IC$_{50}$ corresponds to the concentration (or dose) at which 50% inhibition of the oedema induced by AA alone is observed.

The results are as follows:

- metronidazole has no anti-inflammatory activity in this model;

- flurbiprofen (racemic) has an IC$_{50}$ of 0.037%. At a dose of 0.1%, it inhibits 60% of the oedema induced by AA alone.

- the racemic compound of formula (I), namely 2-(2-methyl-5-nitroimidazol-1-yl)ethyl 2-(2-fluorobiphenyl-4-yl)propionate, has, at a dose of 1%, anti-inflammatory activity equivalent to that of flurbiprofen (racemic) at the 0.1% dose presented above.

- the S enantiomer of the compound of formula (I), namely 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate, has an IC$_{50}$ of 1%.

At a dose of 1%, it inhibits 50% of the oedema induced by AA alone.

These results show that at a dose of 1%, the racemic compound of formula (I), namely 2-(2-methyl-5-nitroimidazol-1-yl)ethyl 2-(2-fluorobiphenyl-4-yl)propionate, or its S enantiomer, namely 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate, inhibits at least 50% of the oedema induced by AA in this model of anti-inflammatory activity.

b) Model of acute inflammation on mouse ear: oedema induced by TPA (phorbol 12-myristate-13-acetate)

The anti-inflammatory activities of the compound of formula (I) in racemic form, of metronidazole and of flurbiprofen (racemic) were measured in an in vivo test performed on a mouse model.

The model used is the model of mouse ear inflammation induced by a single application of TPA (phorbol 12-myristate-13-acetate). Female Balb/c ByJlco mice are used.

The oedema is induced by applying to the ear 20 µl of 0.01% TPA dissolved in ethanol.
The racemic compound of formula (I) is dissolved, at the desired concentration, in the 0.01% TPA solution and thus applied to a group of mice at the same time as the TPA.

Similarly, flurbiprofen (racemic) is dissolved, at the desired concentration, in the 0.01% TPA solution and thus applied to another group of mice at the same time as the TPA.

Finally, metronidazole is dissolved, at the desired concentration, in the 0.01% TPA solution and thus applied to another group of mice at the same time as the TPA.

The oedema is evaluated, 6 hours after application, by measuring the thickness of the ear using an Oditest® micrometer.

The TPA-induced oedema is evaluated relative to the ethanol vehicle group. The inhibition, with the racemic compound of formula (I), with flurbiprofen (racemic) or with metronidazole, of the oedema induced by TPA alone is expressed by the IC$_{50}$. The IC$_{50}$ corresponds to the concentration (or dose) at which 50% inhibition of the oedema induced by TPA alone is observed.

The results are as follows:

metronidazole has no anti-inflammatory activity in this model;
flurbiprofen (racemic) has an IC$_{50}$ of 0.22%.

The compound of formula (I) in racemic form, namely 2-(2-methyl-5-nitroimidazol-1-yl)ethyl 2-(2-fluorobiphenyl-4-yl)propionate, itself has the same IC$_{50}$ as flurbiprofen (racemic), i.e. equal to 0.22%.

This compound thus has noteworthy anti-inflammatory activity.

**Example 4: Penetration in rats**

The compound of formula (I), an enantiomer thereof or a pharmaceutically acceptable salt thereof is applied to the skin of Wistar SD rats.

In parallel, an equimolar mixture of metronidazole and flurbiprofen corresponding to the same dose is applied for comparative purposes.
The lateral and dorsal hairs of each of the animals are close-cropped, approximately 24 hours before the single application. The applied volume is 10 microlitres/cm\(^2\) over an area of 41 cm\(^2\) (5.5 \(\times\) 7.5 cm\(^2\)).

The vehicle used is composed of propylene glycol/ethanol/water/Tween 80 in respective weight proportions of 30/44/25/1. Skin and blood samples are collected at 45 minutes, 1 hour 30 minutes, 2 hours 30 minutes, 4 hours, 6 hours, 8 hours, 16 hours and 24 hours on three animals per group. The plasmas are prepared by precipitation in a 2/1 acetonitrile/methanol mixture and the biopsies are crushed using a cryomill system and then analysed by LC/MS/MS.

By way of example, a solution of 1.4\% 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate is applied.

In parallel, a solution containing 0.6\% metronidazole and 0.9\% flurbiprofen is applied.

The amount of metronidazole detected in the plasma is about 2.3 times smaller when the 1.4\% 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate solution is applied, and that of flurbiprofen about 6.7 times smaller in comparison with the application of a solution containing 0.6\% metronidazole and 0.9\% flurbiprofen.
CLAIMS

1. Compound chosen from the compound of formula (I) below:

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\text{(I)}
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enantiomers thereof and pharmaceutically acceptable salts thereof.

2. Compound according to Claim 1, for its use as a medicament.

3. Compound according to Claim 1 or 2, for its use in the prevention and/or treatment of rosacea.

4. Compound according to Claim 1 or 2, for its use in the prevention and/or treatment of inflammatory pathologies.

5. Compound according to one of Claims 1 to 4, characterized in that the salt of the compound of formula (I) or of an enantiomer thereof is chosen from the salts of this compound or of an enantiomer thereof with a pharmaceutically acceptable acid.

6. Compound according to Claim 5, characterized in that the pharmaceutically acceptable acid is chosen from:

- pharmaceutically acceptable inorganic acids, for instance hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid or hydrobromic acid;
- and pharmaceutically acceptable organic acids, for instance acetic acid, tartaric acid, maleic acid, hydroxymaleic acid, fumaric acid, citric acid, lactic acid, mucic acid, gluconic acid, benzoic acid, succinic acid, oxalic acid, phenylacetic acid, methanesulfonic acid, toluenesulfonic acid, benzenesulfonic
acid, salicylic acid, sulfanilic acid, aspartic acid, glutamic acid and ascorbic acid.

7. Compound according to one of Claims 1 to 6, characterized in that it is chosen from the compound of formula (I), the hydrochloride of the compound of formula (I), the citrate of the compound of formula (I), the salicylate of the compound of formula (I), the benzoate of the compound of formula (I), and the S enantiomers of these compounds.

8. Compound according to one of Claims 1 to 7, characterized in that it is 2-(2-methyl-5-nitroimidazol-1-yl)ethyl (S)-2-(2-fluorobiphenyl-4-yl)propionate.

9. Compound according to one of Claims 1 to 8, characterized in that it is in a pharmaceutical composition for topical application.

10. Compound according to Claim 9, characterized in that the pharmaceutical composition is in the form of a solution, a gel or an emulsion.

11. Compound according to one of Claims 1 to 10, characterized in that it is present in an amount of between 0.001% and 10% by weight relative to the total weight of the composition.