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(54) **Title:** NEW USE OF ANGIOTENSIN II RECEPTOR AGONIST

(57) **Abstract:** There is provided N-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5- isobutylthiophene-2-sulfonamide (C21), or a salt thereof in a method of inhibition of hair growth, as well as compositions comprising C21 and medical and cosmetic methods of inhibition of hair growth in subjects.

NEW USE OF ANGIOTENSIN II RECEPTOR AGONIST

Field of the Invention

This invention relates to the new use of a known compound in medicine and/or in cosmetics, and to compositions comprising it. In particular, the invention relates to the use of the compound and those compositions in the inhibition of hair growth.

Background and Prior Art

Hair is a characteristic feature of all mammals, including humans. It is primarily composed of proteins, in particular keratin, and is produced in hair follicles, which are epidermal appendages within the skin.

Hair production occurs in three phases, anagen (the growth phase), catagen (the transitional phase) and telogen (resting or shedding phase).

Hair growth during anagen is relatively constant (1 cm/month), which means that anagen duration (typically 3 years in a normal human scalp) determines the final length of the hair.

The hair follicle begins to involute as it enters catagen, which generally lasts about two weeks, during which time the lower two-thirds of the follicle undergoes complete involution.

Telogen follows catagen, whereupon the follicle remains dormant for approximately three months. During telogen, the hair fiber is shed from the scalp in a process called exogen. Telogen terminates with the commencement of the next anagen phase of the next hair cycle.

There are obviously many reasons why individuals wish to remove some or all hair from specific sites of the body.

In Western societies in particular, the removal of unwanted hair has mainly been the preserve of women, but these days the frequency of epilation for cosmetic reasons is increasing in men. Other motives for hair removal include

reasons connected to professions (e.g. models, actors, etc.) and sport (e.g. swimmers, cyclists, etc.).

Hair removal is typically carried out by mechanical removal (epilation) or chemical degradation (depilation) of the hair.

Epilation includes shaving or plucking and/or waxing, which latter two processes work by pulling the hair out from the roots. Shaving can result in skin irritation, and removing hair by the root can be very painful. This is because the hair follicle is surrounded by a small muscle that is attached to nerve endings.

Chemical depilation removes hair by cleavage of disulfide bonds in the hair fiber, as well as denaturation of the associated protein matrix. Thioglycolates are the most commonly employed, but thiolactates and sulfides are also used. All work by acting as reducing agents.

Although such a process avoids the pain associated with waxing, the hair merely 'breaks' near the skin surface, and re-growth occurs within a relatively short period of time. Thus, continuous use of products is required. Further, because thioglycolates only work at high pH values (e.g. about pH 12 to 13), such preparations necessarily include strong bases, which can cause irritant dermatitis. Sulfide-based depilatories (which are powders) are more effective hair removers but are even more irritating than thioglycolates, produce an unpleasant odour on application, and are poisonous if ingested.

Examples of therapeutic applications in which inhibition of hair growth would be desirable, include the presence of dermatological disorders (e.g. pseudofolliculitis barbae), hirsuitism and/or hypertrichosis, in which individuals suffer from excess hair growth for various reasons. Individuals who have hair bearing naevi may also wish to achieve partial or total inhibition of hair growth.

Some medications are known to cause hair loss. For example, anagen effluvium is a form of diffuse hair loss that follows administration of anticancer chemotherapeutic agents, radiation treatment, and various chemicals. Chemotherapy-induced alopecia (CIA) has an estimated incidence of 65%. CIA results from the direct toxic insult to the rapidly dividing hair follicle cells in

anagen, leading to abrupt cessation of mitotic activity. As a result, the growing hair shaft is only partially keratinized, causing hair fiber breakage.

The Renin-Angiotensin System (RAS) is a key regulator of blood pressure homeostasis. Renin, a protease, cleaves its only known substrate (angiotensinogen) to form angiotensin I (Ang I), which in turn serves as substrate to angiotensin converting enzyme (ACE) to form angiotensin II (Ang II). The endogenous hormone Ang II is a linear octapeptide (Asp^1-Arg^2-Val^3-Tyr^4-Ile^5-His^6-Pro^7-Phe^8), and is an active component of the RAS.

The angiotensin II type 1 (AT1) receptor is expressed in most organs, and is believed to be responsible for the majority of the pathological effects of Ang II.

Several studies in adult individuals appear to demonstrate that, in the modulation of the response following Ang II stimulation, activation of the Ang II type 2 (AT2) receptor has opposing effects to those mediated by the Ang II Type I (AT1) receptor.

The AT2 receptor has also been shown to be involved in apoptosis and inhibition of cell proliferation (de Gasparo M. *et al.*, *Pharmacol. Rev.*, 52, 415 (2000)).

International patent application WO 2002/096883 describes the preparation of imidazolyl, triazolyl, and tetrazolyl thiophene sulfonamides and derivatives as AT2 receptor agonists. Of the compounds described in that document (as Example 1) is N-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (Compound 21 or, as used hereinafter 'C21'), which was selected for clinical development from a group of about 20 related analogues as a selective AT2 receptor agonist. C21 is now in clinical development for treatment of disorders in which treatment with an AT2 receptor agonist is believed to be beneficial, including idiopathic pulmonary fibrosis (IPF) (see, for example, international patent application WO 2016/139475).

C21 has also been indicated to be of potential use in the treatment of *inter alia*, stroke, spinal cord injury, sickle cell disease, muscular dystrophy, cancer treatment-related cardiotoxicity, peripheral neuropathy and systemic sclerosis (see, for example, international patent applications WO 2004/046141, WO

2016/092329, WO 2016/107879, WO 2016/139475, WO 2017/221012, WO 2019/008393, and US patent application US 2012/035232).

During a Phase I clinical trial, conducted to investigate the safety, tolerability and pharmacokinetics of C21, it was surprisingly discovered that its administration induced hair loss. No other adverse side effects were observed and, after cessation of treatment, hair grew back.

The expected pharmacological effects of agonism of the AT2 receptor are described in general in de Gasparo *et al supra*. It is not mentioned in that document, or anywhere else to the applicant's knowledge, that agonism of the AT2 receptor may induce hair loss. Indeed, normal human hair follicles do not express the AT2 receptor (see Takeda *et al, Brit. J. Dermatol.*, **147**, 276 (2002)), which makes the finding reported herein even more remarkable.

Disclosure of the Invention

According to the invention, there is provided C21 or a pharmaceutically- or cosmetically-acceptable salt thereof for use in a method of inhibition of hair growth.

By 'inhibition of hair growth', we include stopping hairs from growing by any mechanism, as well as the inducement of loss (i.e. removal) of existing hairs by any mechanism. In this respect, inhibition of hair growth includes both the inhibition or prevention of anagen growth phase, and/or the enhancement or promotion of catagen and/or telogen phases.

Thus, there is further provided:

(a) C21 or a cosmetically-acceptable salt thereof for use as a cosmetic and/or in cosmetic preparations, and/or as part of a medical device, which cosmetics, preparations or devices are suitable for use in the inhibition of hair growth; and

(b) a method of medical treatment and/or cosmetic treatment comprising inhibition of hair growth, which method comprises administering C21 or a cosmetically-acceptable salt thereof to a subject in need of such treatment.

C21 and salts thereof that are disclosed herein for use in any medical indication, cosmetic application, pharmaceutical formulation, cosmetic preparation or other use connected with the inhibition of hair growth are referred to hereinafter together as 'the compounds of the invention'.

Salts of C21 that may be mentioned include pharmaceutically- and/or cosmetically-acceptable acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of free compound with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of active ingredient in the form of a salt with another counter-ion, for example using a suitable ion exchange resin. Preferred salts of C21 include acid addition salts, such as HCl salts, alkaline earth salts, such as magnesium and calcium salts, and alkali metal salts, such as potassium or, preferably, sodium salts.

Although C21 and salts thereof may possess biological activity as such, certain pharmaceutically- or cosmetically-acceptable (e.g. 'protected') derivatives of C21 may exist or be prepared which may not possess such activity, but may be administered and thereafter be metabolised in the body to form C21. Such compounds (which may possess some biological activity, provided that such activity is appreciably lower than that of C21) may therefore be described as 'precursors' or 'prodrugs' of C21.

As used herein, references to precursors or prodrugs will include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time, following administration. All precursors and prodrugs of C21 are included within the scope of the invention.

Compounds of the invention are particularly useful in the inhibition of hair growth, including the removal of hairs from a subject.

'Removal' of hairs includes the inducement or acceleration of loss of hairs, and/or of hair growth inhibition, in a subject that has either a medical need for

such hair loss or hair growth inhibition, or wishes to induce such hair loss or hair growth inhibition for other (e.g. cosmetic) reasons.

Medical conditions in which inhibition of hair growth or inducement of hair loss may be desired or required include any condition characterised by abnormal hair growth, including all forms of hypertrichosis (including congenital hypertrichosis lanuginose, congenital hypertrichosis terminalis, nevoid hypertrichosis and acquired hypertrichosis) and hirsutism. Also included are conditions in which individuals have hair bearing naevi, or pseudofolliculitis barbae, pseudofolliculitis, hair from grafted donor sites, and men undergoing sex-change operations.

As described above, the use of C21 and salts thereof in the inhibition of hair growth, and/or in the inducement of hair loss, in subjects is not just limited to those that have a medical need, but also may include any individual who may wish to inhibit hair growth, or to remove hairs from any part of their body, for any reason, including a cosmetic reason, a psychological reason or a professional reason (e.g. models, actors, swimmers, cyclists, etc.).

According to several further aspects of the invention there is provided a compound of the invention for use as a depilatory; a depilatory preparation comprising a compound of the invention; as well as a method of inhibiting hair growth and/or inducing hair loss in a subject which method comprises the administration of a compound of the invention to a subject in need thereof.

'Subjects' include mammalian (particularly human) subjects.

In accordance with the invention, compounds of the invention may be administered locally or systemically, for example orally, intravenously or intraarterially (including by intravascular and other perivascular devices/dosage forms (e.g. stents)), intramuscularly, cutaneously, subcutaneously, transmucosally (e.g. sublingually or buccally), rectally, intravaginally, transdermally, nasally, pulmonarily (e.g. tracheally or bronchially), topically, or by any other parenteral route, in the form of a pharmaceutical preparation comprising the compound(s) in pharmaceutically- or cosmetically-acceptable dosage form(s).

Inhibition of hair growth or inducement of hair loss may be induced by systemic administration of a compound of the invention, for example by way of oral administration (e.g. as described hereinafter), by way of a parenteral route (e.g. by injection), or by way of pulmonary administration, for example as described in international patent application WO 2020/095042.

Other modes of delivery of compounds of the invention include topical administration. In such a mode of administration, absorption of compound of the invention into systemic circulation may occur, or the compound of the invention may act locally at the site at which inhibition hair growth and/or inducement of hair loss is desired or required (e.g. the mucosa or, more preferably, the skin).

Compounds of the invention are administered in an appropriate (for example topically-acceptable) vehicle suitable for application to said site. In this respect, compounds of the invention will generally be administered in the form of one or more formulations in admixture with a (e.g. pharmaceutically- or cosmetically-acceptable) adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration (e.g. topically to the mucosa or, preferably, the skin) and standard pharmaceutical, cosmetic, or other, practice. Acceptable carriers may be chemically inert to the active compounds and may have limited (or preferably no) detrimental side effects or toxicity under the conditions of use. Such carriers may also impart an immediate, or a modified, release of the active ingredient.

Suitable pharmaceutical formulations may be commercially available or may otherwise be prepared according to techniques that are described in the literature, for example, Remington *The Science and Practice of Pharmacy*, 22nd edition, Pharmaceutical Press (2012) and *Martindale – The Complete Drug Reference,* 38th Edition, Pharmaceutical Press (2014) and the documents referred to therein, the relevant disclosures in all of which documents are hereby incorporated by reference.

Otherwise, the preparation of suitable (e.g. cosmetic) formulations including compounds of the invention may be achieved non-inventively by the skilled person using routine techniques.

Compounds of the invention may be in the form of an aqueous formulation such as an emulsion, a suspension and/or a solution (e.g. an (optionally) buffered aqueous formulation, such as a physiological saline-containing formulation, a phosphate-containing formulation, an acetate-containing formulation or a borate-containing formulation).

Active ingredient may further be combined with appropriate excipients to prepare creams, foams, gels, pastes, ointments, lotions, liquids, etc.

Suitable carrier materials for use in creams or foams include hydroxypropyl methyl cellulose, corn gluten powder, sodium dodecyl sulfate, acrylamide, sodium fatty alcohol polyoxyethylene ether sulfonate, gelatin, polyethylene glycols. Suitable gel-forming materials include alginates, hyaluronic acid, gummi tragacanthae, gelatin, pectin, glycerin, propanediol, carrageenan, gellan gum, cellulose derivatives, carbomer and starch, Xanthan gum, cationic guar gum, agar, noncellulosic polysaccharides, saccharides such as glucose, vinyl polymers, acrylic resins, polyvinyl alcohol, carboxyvinyl polymer. Suitable excipients for use in pastes or ointments include glycerin, vaseline, paraffin, polyethylene glycols, etc. Suitable ingredients for use in lotions include polyethylene glycols, propanediol cellulose derivatives, glycerin, noncellulosic polysaccharides. Liquid formulations may include viscosity modifiers, hyaluronic acid, sugars such as glucose and lactose, emulsifiers, buffering agents, alcohols, preservatives, etc.

Topical formulations comprising compositions of the invention may include surfactants, emulsifiers and/or penetration enhancers, such as polyoxyethylene esters, including polyoxyl 8 stearate, polyoxyl 32 stearate, polyoxyl 40 stearate, polyoxyl 100 stearate and polyoxyl 15 hydroxystearate; hexadecanol (cetyl alcohol); fatty acids (e.g. stearic acid); monoacyl glycerides (e.g. glyceryl monostearate); polyethoxylated alcohols; polyvinyl alcohols; polyol esters; polyoxyethylene alkyl ethers, including polyoxyl cetostearyl ether, polyoxyl lauryl ether, polyoxyethylene sorbitan monooleate and polyoxyl stearyl ether; polyoxylglycerides, including lauroyl polyoxylglycerides and stearoyl polyoxylglycerides; sorbitan esters, including sorbitan oleate. sorbitan monopalmitate and sorbitan monostearate; sodium lauryl sulfate; polysorbates, including polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate),

polysorbate 60 (polyoxyethylene (20) sorbitan monostearate), polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate) and polysorbate 80 (polyoxyethylene (20) sorbitan monooleate); polyoxyethylene castor oil derivatives; ethoxylated fatty acid esters; polyoxylglycerides; lauryl dimethyl amine oxide; bile salts (e.g. sodium deoxycholate, sodium cholate); phospholipids; N,N-dimethyldodecylamine-N-oxide; hexadecyltrimethyl-ammonium bromide; poloxamers; lecithin; sterols (e.g. cholesterol); and the like.

Topical formulations comprising compositions of the invention may further include thickening agents, such as acryloyldimethyltaurate/VP copolymer; moisturizing agents, including paraffin oil, silicone oil, glycerol, glycerin, polyethylene glycol, trehalose, glycerol, petrolatum, hyaluronic acid and salts (e.g. sodium and potassium salts) thereof, octanoic/caprylic triglyceride, and the like; as well as pH modifiers, such as acids, bases and pH buffers; antioxidants, such as vitamins and glutathione; and preservatives, such as phenoxyethanol, ethylhexyl glycerin, and the like.

According to a further aspect of the invention there is provided a composition comprising a compound of the invention and one or more pharmaceutically- or cosmetically-acceptable excipient, such as an adjuvant, diluent or carrier. Preferred formulations are suitable for application locally to e.g. the mucosa or, more preferably, the skin, and therefore comprise a topically-acceptable adjuvant, diluent or carrier.

Formulations comprising compounds of the invention may thus be suitable for, adapted for, and/or packaged and presented for, topical administration for use in the inhibition of hair growth and/or the promotion of hair loss by way of direct topical administration of that formulation.

Administration of active ingredients may be continuous or intermittent.

The mode of administration may also be determined by the timing and frequency of administration, but is also dependent, in the case of the therapeutic treatment of a medical condition, on the severity of that condition, or otherwise on the need for hair removal.

The amount of active ingredient in a formulation will depend on the severity of the need for hair loss, and on the subject, to be treated, but may be determined by the skilled person.

In any event, the practitioner, or other skilled person, will be able to determine routinely the actual dosage, which will be most suitable for an individual subject. Dosages mentioned herein are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Doses may be administered between once and four times (e.g. between 1 and 3 times) daily for up to three (e.g. two) weeks, e.g. up to one week, such as 4 days or 3 days. Such treatment periods may be repeated as appropriate. The hair loss may occur during or up to 4 weeks after treatment, e.g. up to 3 weeks after treatment, such as 1 or 2 weeks after treatment.

Suitable oral daily doses (calculated as the free base) of C21 in adult subjects (average weight e.g. 70 kg), may be up to about 600 mg, including about 400 mg and about 200 mg, and no lower than about 50 mg .

Appropriate concentrations of compounds of the invention in a topical formulation as described above may be about 0.00001 mg/mL (e.g. about 1 mg/mL, such as 10 mg/mL) up to about 200 mg/mL, in all cases calculated as the free (non-salt) compound.

Appropriate topical doses of compounds of the invention are in the range of about 5 ng/cm^2 to about 20 mg/cm^2 of treated area, such as up to 10 µg/cm^2 of treated area, in all cases calculated as the free (non-salt) compound.

In any event, the dose administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a response in the subject over a reasonable timeframe (as described hereinbefore). One skilled in the art will recognize that the selection of the exact dose and composition and the most appropriate delivery regimen will also be influenced by *inter alia* the pharmacological properties of the formulation, the nature and severity of the condition being treated, and the physical condition of the recipient, as well as the age, condition, body weight, sex and response of the subject to be

treated, and the stage/severity of the disease, as well as genetic differences between subjects.

In the uses and methods described herein, compounds of the invention may also be combined with one or more other depilatory agents. Subjects may thus also (and/or already) be receiving said depilatory agents, by which we mean receiving a prescribed dose of one or more of those depilatory agents mentioned herein, prior to, in addition to, and/or following, treatment with a compound of the invention.

Such depilatory agents that may be used in combination with compounds of the invention in the inhibition of hair growth and/or promotion of hair loss include salts (e.g. sodium, potassium or calcium salts) of thioglycolic acid or thiolactic acid, and sulfides of strontium, calcium or barium.

When compounds of the invention are 'combined' with other depilatory agents, the active ingredients may be administered together in the same formulation, or administered separately (simultaneously or sequentially) in different formulations.

Such combination products provide for the administration of compounds of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the other depilatory agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other depilatory agent).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention; another depilatory agent; and a pharmaceutically- or cosmetically-acceptable adjuvant, diluent or carrier (which formulation is hereinafter referred to as a 'combined preparation'); and

(2) a kit of parts comprising components:

(A) a pharmaceutical formulation including a compound of the invention in admixture with a pharmaceutically- or cosmetically-acceptable adjuvant, diluent or carrier; and

(B) a pharmaceutical formulation including another depilatory agent, in admixture with a pharmaceutically- or cosmetically-acceptable adjuvant, diluent or carrier,

which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other.

According to a further aspect of the invention, there is provided a method of making a kit of parts as defined above, which method comprises bringing component (A), as defined above, into association with a component (B), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

By bringing the two components 'into association with' each other, we include that components (A) and (B) of the kit of parts may be:

(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination treatment; or

(ii) packaged and presented together as separate components of a 'combination pack' for use in conjunction with each other in combination treatment.

Thus, there is further provided a kit of parts comprising:

(I) one of components (A) and (B) as defined herein; together with

(II) instructions to use that component in conjunction with the other of the two components.

The kits of parts described herein may comprise more than one formulation including an appropriate quantity/dose of a compound of the invention, and/or more than one formulation including an appropriate quantity/dose of another depilatory agent, in order to provide for repeat dosing. If more than one formulation (comprising either active compound) is present, such formulations may be the same, or may be different in terms of the dose of either compound, chemical composition(s) and/or physical form(s).

With respect to the kits of parts as described herein, by 'administration in conjunction with', we include that respective formulations comprising a compound of the invention and other depilatory agent are administered, sequentially, separately and/or simultaneously, over the course of treatment of the condition.

Thus, in respect of the combination product according to the invention, the term 'administration in conjunction with' includes that the two components of the combination product (compound of the invention and other depilatory agent) are administered (optionally repeatedly), either together, or sufficiently closely in time, to enable a beneficial effect for the subject, that is greater, over the course of the treatment of the condition, than if either a formulation comprising compound of the invention, or a formulation comprising the other depilatory agent, are administered (optionally repeatedly) alone, in the absence of the other component, over the same course of treatment. Determination of whether a combination provides a greater beneficial effect in respect of, and over the course of treatment will depend upon the condition to be treated, but may be achieved routinely by the skilled person.

Further, in the context of a kit of parts according to the invention, the term 'in conjunction with' includes that one or other of the two formulations may be administered (optionally repeatedly) prior to, after, and/or at the same time as, administration of the other component. When used in this context, the terms 'administered simultaneously' and 'administered at the same time as' include that individual doses of the relevant compound of the invention and other depilatory agent are administered within 48 hours (e.g. 24 hours) of each other.

In a further aspect of the invention, there is provided a process for the preparation of a combined preparation as hereinbefore defined, which process comprises bringing into association a compound of the invention, the other depilatory agent, and at least one (e.g. pharmaceutically- or cosmetically-acceptable) excipient.

Wherever the word 'about' is employed herein, for example in the context of amounts, such as concentrations and/or doses of active ingredients, pHs, etc. it will be appreciated that such variables are approximate and as such may vary by ± 10%, for example ± 5% and preferably ± 2% (e.g. ± 1%) from the

numbers specified herein. In this respect, the term 'about 10%' means e.g. ±10% about the number 10, i.e. between 9% and 11%.

Compounds of the invention have the advantage that they have considerably less side effects, and/or are much safer than current depilatory agents that are known to inhibit hair growth and/or to induce hair loss, whether those prior art agents are administered topically or systemically.

The uses and methods described herein may also have the advantage that, in the inhibition of hair growth or the inducement of hair loss, they may be more convenient for the subject than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or that it/they may have other useful pharmacological properties over, similar methods (treatments) known in the prior art, whether for use in the inhibition of hair growth/inducement of hair loss or otherwise.

The invention is illustrated by the following example.

Example

Clinical Trial

A Phase 1, randomized, double-blind, placebo-controlled study was conducted in healthy male and female volunteers to investigate the safety, tolerability and pharmacokinetics of ascending single and multiple oral doses of C21, with an open label arm to investigate the effect of food.

The highest dose of C21 previously tested in healthy male volunteers was 100 mg once daily for 1 or 8 days.

Part A of the study involved administering to 10 male and female subjects (8 active and 2 placebo) daily dose regimens of either 100 mg b.i.d., 200 mg q.d. or 200 mg b.i.d. of C21 for assessments of safety, tolerability, and pharmacokinetics of C21 and its major metabolite (known as 'M1').

Additionally, the effect of food on the pharmacokinetics of C21 was investigated in an open label manner in an additional 10 male and female subjects at a single oral dose of 75 mg. Subjects received two single doses of 75 mg of C21 at least

3 days apart in a randomized fashion in either in fasted or fed states. A US FDA-recommended high-fat breakfast was used to investigate maximum effects

Part B was a randomized, double-blind, placebo-controlled ascending multiple dose study in healthy male and female volunteers. Prior to commencing Part B, the safety and pharmacokinetics was analyzed from Part A, and it was verified that the dose strengths and the different daily regimens could be safely administered to humans without the risk of accumulation.

Each dose level was investigated with a different cohort of eight subjects (6 on active drug and 2 on placebo). Subjects received multiple doses of C21 b.i.d. for 8 days. All daily dose regimens were multiples of 100 or 200 mg dose strength as tested in Part A.

Multiple doses were administered in an escalating manner. A staggered dosing approach was used, in which two subjects (1 active and 1 placebo) were dosed first and, if there were no safety concerns with the two sentinel subjects, the remaining 6 subjects (5 active and 1 placebo) were dosed.

Safety was monitored throughout the study by the documenting of adverse events and serious adverse events, as well as clinical laboratory tests (hematology, clinical chemistry and urinalysis), vital signs (pulse rate, respiratory rate, supine blood pressure and body temperature), 12-lead electrocardiograms (ECG; cardiac intervals, PR, QRS, QT and corrected QT [QTc] interval), continuous 12-lead ECG telemetry, physical examination and slit lamp examination.

The investigational product was a solution of C21, 2.5 mg/ml (as parent), for oral administration, the composition of which is described in the table below:

Components	Function	Quantity per mL
C21	Active Pharmaceutical Ingredient	2.6 mg

Sodium carbonate, anhydrous	Buffer component	0.50 mg
Sodium hydrogen carbonate	Buffer component	1.8 mg
Sodium carbonate (1 M aqueous solution)	pH Regulator	q.s. to pH 9 – 10
Sodium hydrogen carbonate (1 M aqueous solution)	pH Regulator	q.s. to pH 9 – 10
Water, purified	Solvent	q.s. to 1 mL

The carbonate buffer was prepared by dissolving sodium carbonate and sodium hydrogen carbonate in purified water at ambient temperature. C21 was added and the mixture was stirred at ambient temperature until a complete solution was obtained. The pH was checked and, if needed, corrected by addition of 1 M sodium hydrogen carbonate or 1 M sodium carbonate to pH 9-10.

The placebo solution was an aqueous solution of citric acid buffer containing denatonium benzoate, the composition of which is described in the table below:

Components	Function	Quantity per mL
Citric acid monohydrate	Buffer component	2 mg
Denatonium benzoate (8.55% solution in ethanol)	Flavouring agent	3 µg*
Hydrochloric acid	pH Regulator	q.s. to pH 2.0-3.5
Sodium hydroxide	pH Regulator	q.s. to pH 2.0-3.5
Water, purified	Solvent	To 1.0 ml

* As denatonium benzoate

The placebo solution was prepared by dissolving citric acid monohydrate and denatonium benzoate in purified water at ambient temperature. The pH was checked and, if needed, adjusted with sodium hydroxide or hydrochloric acid to pH 2.0-3.5.

In subjects that received 200 mg C21 b.i.d. (total daily dose: 400 mg), there were no serious adverse events reported, and no clinically significant ECG changes, post dose trends, changes in vital signs, abnormal read-outs in clinical laboratory tests (liver transaminases, bilirubin, serum creatinine, neutropenia, lymphopenia or thrombocytopenia), clinically significant findings in 12-lead ECG telemetry or slit lamp experiments, were noted. However, unexpected hair loss was noted in most of the subjects.

One subject was abroad during that time and could not return for an unscheduled visit. He reported by phone that he could pull out his hair in tufts without any pressure or pulling. After showering, there was a lot of hair in the tray. Remaining body hair (chest, armpits, legs, pubic hair) could easily be pulled out, without applying force and without pain. During further follow-up call a couple of weeks later, the subject reported beginning of hair re-growth.

A second subject reported that he could pull out his hair without much force. He reported that his nose hair had fallen out as had that of his beard. Remaining body hair (chest, armpits, legs, pubic hair) was easily pulled out, without any pressure or pain. The subject was referred to a dermatologist. Again, a few days later, the subject reported the beginning of hair re-growth.

A third subject did not show any signs of hair loss at a first, unscheduled, visit but, during a follow-up telephone call a few days later reported hair loss on his head, as well as his beard, chest and armpit. A couple of weeks later, the subject reported a mild improvement of the symptoms.

A fourth subject noticed that his hair could be pulled out quite easily, without resistance, but did not seem to be falling out by itself. Visually, hair loss was not noticeable. During the examination, beard hair and the hair on the legs could be easily pulled out. The subject was referred to a dermatologist. The subject reported the beginning of hair re-growth during the follow-up phone calls a week or two later.

A fifth subject noticed at first that a lot of hair was on his T-shirt when undressing. Later, he noticed that hair stuck to his hands when brushing through. Hair on his arms and beard hair could be easily pulled out without resistance. In other parts of his body, the subject had not noticed any changes. The subject was referred to a dermatologist. During phone contacts a week or two later, the subject reported the beginning of hair re-growth on his head and beard and that his hair could not be easily pulled out anymore.

A sixth subject noticed whilst showering that hair loss was occurring, which increased in intensity on the next day. While washing his hair, he suddenly had hair in his hand. The subject was referred to a dermatologist and, about 10 days later, reported the beginning of hair re-growth on his head and legs.

All these 6 patients with hair loss were treated with C21, while the two subjects on placebo treatment did not show any signs of hair loss.

A couple of weeks after reporting that hair had started to re-grow, all of the subjects returned for the planned slit lamp examination (8 weeks post-dosing). The remaining six subjects showed an improvement in their symptoms. Hair re-growth was documented in all subjects, although hair was still very short and thin/soft.

Claims

1. *N*-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-isobutylthiophene-2-sulfonamide, or a salt thereof, for use in a method of inhibition of hair growth.

2. A method of inhibition of hair growth in a subject, which method comprises administering *N*-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-isobutyl-thiophene-2-sulfonamide, or a salt thereof, to a subject in need of such treatment.

3. A composition comprising *N*-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-isobutylthiophene-2-sulfonamide, or a salt thereof, in admixture with one or more adjuvant, diluent or carrier, which composition is suitable for use in a method of inhibition of hair growth in a subject.

4. A compound for use as claimed in Claim 1, a method as claimed in Claim 2, or a composition as claimed in Claim 3, wherein the method comprises topical administration.

5. A composition as claimed in Claim 3 or Claim 4, wherein the composition is a topical composition.

6. A composition as claimed in Claim 5, wherein the composition is a cream, a foam, a gel, a paste, an ointment, a lotion or a liquid.

7. A compound for use, method or composition as claimed in any one of the preceding claims, wherein the method is a medical method of treatment and the salt is pharmaceutically-acceptable, and (if appropriate) the composition is a pharmaceutical formulation, in which the one or more adjuvant, diluent or carrier is pharmaceutically-acceptable.

8. A compound for use, method, or composition as claimed in Claim 7, wherein the treatment is of a medical condition selected from hypertrichosis, hirsutism, hair bearing naevi, pseudofolliculitis barbae, pseudofolliculitis, grafted hair and of a man undergoing a sex-change operation.

9. A compound for use, method, or composition as claimed in any one of Claims 1 to 6, wherein the method is a cosmetic method of treatment and the salt is cosmetically-acceptable, and (if appropriate) the composition is a cosmetic preparation, in which the one or more adjuvant, diluent or carrier is cosmetically-acceptable.

10. A compound for use, method, or composition as claimed in any one of the preceding claims, wherein the inhibition of hair growth comprises stopping hairs from growing, inducement of loss and/or removal of existing hairs, by way of inhibition of anagen and/or promotion of catagen and/or telogen.

11. A compound for use, method, or composition as claimed in any one of the preceding claims, wherein the salt is a sodium salt.

12. A process for the preparation of a composition as defined in any one of Claims 3 to 11, which process comprises bringing into association *N*-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-isobutylthio-phene-2-sulfonamide, or salt thereof, with the one or more adjuvant, diluent or carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2020/053031

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61Q7/02 A61K8/49
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)
A61Q 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/096883 A1 (VICORE PHARMA AB [SE]; MCNEENEY STEPHEN PHILLIP [GB] ET AL.) 5 December 2002 (2002-12-05)	1,3-6, 9-12
Y	claim 26; example 1	1-12

Y	WO 2011/014649 A1 (UNIV DUKE [US]; DELONG MITCHELL A [US]; OLSEN ELISE A [US]) 3 February 2011 (2011-02-03) paragraph [0002]; claim 1	1-12

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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 :

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
25 February 2021	05/03/2021
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Briand, Benoit

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2020/053031

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International application No
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