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(71) Applicants and
(72) Inventors: **FINNEN, Michael** [GB/GB]; University of Edinburgh, Edinburg Research & Innovation Limited, 47 Little France Crescent, Edinburgh EH16 4TJ (GB). **WELLER, Richard** [GB/GB]; The University of Edinburgh, Lauriston Building, Lauriston Place, Edinburgh EH3 9HA (GB).

(74) Agent: **MURGITROYD & COMPANY**; Scotland House, 165-169 Scotland Street, Glasgow G5 8PL (GB).

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(54) **Title:** METHOD & COMPOSITION FOR THE TREATMENT OF ACNE AND SEBUM DEPENDENT PILOSEBACEOUS DISORDERS

(57) **Abstract:** A method for the treatment of acne or other disorders of the pilosebaceous unit by administering a therapeutically effective amount of 4,4'- diisoamyloxydiphenylthiourea, one of its derivatives or a mixture thereof to a subject afflicted with such a disorder is disclosed. The invention further relates to the use of a composition comprising 4,4'- diisoamyloxydiphenylthiourea, one of its derivatives or a mixture thereof for the treatment of acne or other disorders of the pilosebaceous unit and to a topical pharmaceutical composition comprising a therapeutically effective amount of 4,4'-diisoamyloxydiphenylthiourea, one of its derivative or a mixture thereof, and a pharmaceutically acceptable carrier.

METHOD & COMPOSITION FOR THE TREATMENT OF ACNE AND SEBUM DEPENDENT PILOSEBACEOUS DISORDERS

Field of the Invention

The present invention relates to a method for the treatment of disorder of the pilosebaceous unit such as acne by administering a phenylthiourea compound, one of its derivatives or a mixture thereof. It further relates to the use of the compound, one of its derivatives or a mixture thereof in the manufacture of a medicament for treatment of disorders of the pilosebaceous unit such as acne and to a pharmaceutical topical composition comprising a therapeutically effective amount of the active compound, one its derivative or a mixture thereof for the treatment of acne and other disorders of the pilosebaceous unit.

Background of the Invention

Acne vulgaris, also called Acne, is the most common disease of the pilosebaceous unit of the skin. Approximately 40 percent of all teenagers have acne of sufficient severity to require medical treatment. Acne affects 25 percent of all adult men and 50 percent of adult women sometimes in their adult lives. In addition to teenagers, adults can develop acne, or have a recurrence of acne, in their 30s, 40s, and sometimes beyond that. Acne is most commonly distributed on the face and to a lesser degree on the back and chest. It can persist for years and may result in disfigurement and permanent scarring of the skin. The past few decades have seen very little progress toward the development of medicines with potent efficacy and low toxicity to treat acne.

Acne is characterised by increased sebum excretion from the sebaceous gland. However, this alone need not cause acne; patients with

acromegaly, or with Parkinson's disease, have high sebum excretion rates but no acne. Furthermore, sebum excretion often remains high long after the acne has gone away. However, acne is always associated with increased levels of sebum production. The condition is also familiar in about half of those with acne. There is a high concordance of the sebum excretion rate and acne in monozygotic, but not dizygotic, twin.

It generally accepted that multiple factors combine to cause acne resulting in chronic inflammation around pilosebaceous follicles. However, *Propionibacterium acnes*, a normal skin commensal, plays a central pathogenic part. *Propionibacterium acnes* colonizes the pilosebaceous ducts, breaks down triglycerides of sebum releasing free fatty acids, produces substances chemotactic for inflammatory cells and induces the ductal epithelium to secrete pro-inflammatory cytokines via activation of Toll like receptor 2 (TLR2). The inflammatory reaction is sustained by a foreign body reaction to follicular contents of the ruptured follicle and a type IV immune reaction to one or more antigens in the follicular contents.

Poral occlusion is also a contributory factor in acne development. Both genetic and environmental factors (e.g. some cosmetics) can cause the epithelium to overgrow the follicular surface. Follicles then retain sebum that can develop an increased concentration of bacteria and free fatty acids. Rupture of these follicles is associated with intense inflammation and tissue damage, mediated by oxygen free radicals and enzymes such as elastase released by white cells

Many variants of acne are known including:

Acne conglobate, more commonly known as nodular or cystic acne, is a more severe form of acne than acne vulgaris. In the case of nodular acne, the sebum builds up in the gland, mixes with dead cells, and eventually

ruptures the follicle wall, which typically forms a deep cyst under the skin. Scarring often results from these deep cysts (Roche Laboratories Inc., Important Information Concerning Your Treatment with Accutane, 6th ed., 1996).

Other forms of acne are:

- infantile acne which may follow transplacental stimulation of a child's sebaceous glands by maternal androgens;
- mechanical acne. Excessive scrubbing, picking, or the rubbing of chin straps or a fiddle can rupture occluded follicles; and
- acne associated with virilisation, including clitoromegaly, may be caused by an androgen-secreting tumour of the adrenals, ovaries or testes or, rarely, to congenital adrenal hyperplasia caused by mild 21-hydroxylase deficiency;
- acne accompanying the polycystic ovarian syndrome is caused by modestly raised circulating androgen levels;
- drug-induced acne. Corticosteroids, androgenic and anabolic steroids, gonadotrophins, oral contraceptives, lithium, iodides, bromides, antituberculosis and anticonvulsant therapy can all cause an acneiform rash; and
- tropical acne. Heat and humidity are responsible for this variant, which affects Caucasians with a tendency to acne.

Topical Treatment

Many over the counter and prescription topical treatments are available for acne. Most of the over the counter medications contain salicylic acid, sulfur, benzyl peroxide, etc. Most can only treat the minor aspects of acne and are of limited efficacy. These topical creams, lotions, ointments and cleansers can only attack the end result of acne, but not the causes. They do not treat the causes of acne and cannot prevent future outbreaks.

The prescribed topical formulations like retinol and derivatives are moderately more effective than over the counter treatments but the side effects that they cause often outweigh the benefits. They are astringent, peel off layers of the skin, dry and irritate skin and make skin more susceptible to photosensitivity. As a result of severe teratogenicity topical retinoids should not be prescribed for pregnant woman with acne or women who are at risk of becoming pregnant.

Topical antibiotics are also frequently prescribed. These include topical clindamycin, erythromycin and sulfacetamide but antibacterial resistance of *P. acnes* is a growing problem, with most erythromycin-resistant strains being cross-resistant to clindamycin. Whilst addressing the problem of *P.acnes* topical antibiotics do not resolve the excess sebum production associated with acne.

Thus, although there are several dozen topical treatments on the market, most are only effective for a short period of time, possess many side effects and do not treat the underlying causes of acne.

Systemic Treatment

Systemic antibiotics are often used to treat acne. However, the incidence of antibiotic resistant *P. acnes*, particularly to erythromycin, is rising even in patients never previously exposed to it. This resistance can lead to therapeutic failure. In addition systemic antibiotics need to be taken at high doses for prolonged periods of time (up to 2 years) for a therapeutic effect to be seen. Moreover serious side effects and absorption problems (some compounds have to be taken on an empty stomach) add to the limitations of such treatments. The systemic antibiotics used are, for example, a combination of oxytetracycline and tetracycline, minocycline, doxycycline, tetracyclines.

Hormonal treatments (for example co-cyprindiol, a combined antiandrogen - oestrogen treatment) are also used to treat acne. The incidence of venous thrombo-embolism is higher than for the low dose OCP, and the course should not go on for more than three months after the acne has cleared, at which point the drug should be replaced by a low oestrogen/low progestogen oral contraceptive. Of course such treatments are not available for males.
Retinoids (such as isotretinoin is an oral retinoid) are an effective treatment for severe acne but their use is severely limited by toxicity and side effects and is often a last resort after other treatments have failed.

Thus while there are dozens of acne medications on the market, there are none that actually address the multifactorial aetiology of the disease and actually treat the multiple causes of acne. While some medications are clinically effective their use is limited by severe side effects and toxicity.

It is thereof an object of the invention to provide means of alleviating at least one of the problems associated with these treatments.

Summary of the Invention

It has now been found that 4,4'-diisoamyloxydiphenylthiourea significantly reduces sebum production in human skin and also has a negative effect on the growth of *P.acnes*.

4,4'-diisoamyloxydiphenylthiourea (ISO), also known as thiocarlide or as 4,4'-diisoamyloxythiocarbanilide, is a thiourea chemical that was used in the 1960s to successfully treat tuberculosis (TB). Thioureas specifically inhibit mycolic acid synthesis (see "*Antimicrobacterial activities of Isoxyl and new derivatives through the inhibition of Mycolyc acid Synthesis*" 1999 May;43(5):1042-51). Mycolic acids are long chain fatty acids only found in

the cell walls of the mycolata taxon, a group of bacteria which includes *Mycobacterium tuberculosis*, the causative agent of the disease tuberculosis (Curr Pharm Biotechnol. 2002 Sep;3(3):197-225).

Propionibacterium acnes does not synthesize mycolic acids as part of its cell wall. Thus the inhibitory activity of 4,4'-diisoamyloxydiphenylthiourea (ISO) upon the growth of *P.acnes* was unexpected and surprising.

Moreover, despite previous extensive clinical use of 4,4'-diisoamyloxydiphenylthiourea (ISO) in the treatment of Tuberculosis, no reports of an effect on sebum production have been previously documented. Thus, the finding that 4,4'-diisoamyloxydiphenylthiourea (ISO) substantially and rapidly reduced sebum production is also unexpected and surprising.

According to one embodiment of the invention it is provided a method for the treatment of a disorder of the pilosebaceous unit or apparatus and, in particular, acne such as acne vulgaris, said method comprising the step of administering a therapeutically effective amount of a compound chosen in the group consisting of 4,4'-diisoamyloxydiphenylthiourea, one of its derivative and mixtures thereof to a subject afflicted with such a disorder.

According to another embodiment of the invention it is provided the use of 4,4'-diisoamyloxydiphenylthiourea, one of its derivative or a mixture thereof in the manufacture of a medicament for the treatment of a disorder of the pilosebaceous unit and, in particular, acne.

According to another embodiment of the invention it is provided a composition, preferably a topical one, for the treatment of a disorder of the pilosebaceous unit and, in particular, acne such as acne vulgaris, said composition comprising a therapeutically effective amount of 4,4'-

diisoamyloxydiphenylthiourea, one of its derivative or a mixture thereof together with a pharmaceutically acceptable carrier.

According to an aspect of the invention the method, use and composition reduce the production of sebum and/or inhibits growth of *Propionibacterium acnes.*

In the context of the present invention the term "treatment" includes any regime that can be of benefit to the human or non-human animal. Treatment may include curative, alleviation or prophylactic effects. Thus, in a method of treatment of the present invention, the term "treating" shall encompass the means for ameliorating or preventing a skin syndrome, disorder or disease described herein with a thiourea derivative or prodrug or metabolite thereof, which would obviously be included within the scope of the invention albeit not specifically disclosed for certain of the instant compounds.

In a preferred embodiment, the active compound is administered to a mammal in an amount therapeutically effective in resolving skin lesions and preventing their reappearance. The invention also relates to a method for treating acne by administering a topical composition comprising said compound in an amount therapeutically effective in resolving or alleviating acne lesions.

While acne is the preferred condition to be treated by the method/use and composition of the invention, it is also an object of the invention to treat other cutaneaous disorders, especially those associated with excessively oily or greasy skin or sebbhorea and/or overgrowth of *P.acnes*. Such diseases include, but are not limited to, Sebbhorea, rosecea; Acne

conglobate, Acne vulgaris, Infantile acne, Acne associated with virilization, Acne accompanying the polycystic ovarian syndrome, Drug-induced acne.

The term "derivatives" encompasses the usual pharmaceutically or cosmetically acceptable variants of the chemical compound, such as, without limitation, its pharmaceutically acceptable salts, stereoisomer, crystalline, polymorph, amorphous, solvate, hydrate, ester, prodrug or metabolite form. Thus, the expression "derivatives" encompasses all such compound forms and mixtures thereof, including active compounds in the form of essentially pure enantiomers, racemic mixtures, pure geometric isomers (such as cis and trans stereoisomers), mixtures of geometric isomers and tautomers.

The compound of the present invention may be present in the form of pharmaceutically acceptable salt. For use in medicaments, the "pharmaceutically acceptable salts" of the compounds of this invention refer to non-toxic acidic/anionic or basic/cationic salt forms. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore when the active compound of the present invention carries an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

Thus, representative pharmaceutically acceptable salts include the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, camsylate (or camphosulfonate), carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, fumarate, gluconate, glutamate, hydrabamine, hydrobromine, hydrochloride, iodide, isothionate, lactate, malate, maleate, mandelate, mesylate, nitrate, oleate, pamoate, palmitate, phosphate/diphosphate, salicylate, stearate, sulfate, succinate, tartrate, tosylate.

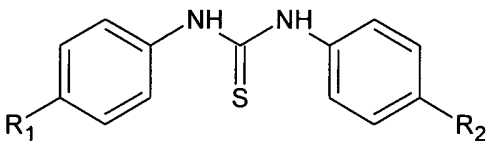
The present invention includes within its scope prodrugs and metabolites of the compounds of this invention. In general, such prodrugs and metabolites will be functional derivatives of the compounds that are readily convertible *in vivo* into an active compound.

The term "prodrug" means a pharmaceutically acceptable form of a functional derivative of a compound of the invention (or a salt thereof), wherein the prodrug may be: 1) a relatively active precursor which converts in vivo to an active prodrug component; 2) a relatively inactive precursor which converts in vivo to an active prodrug component; or 3) a relatively less active component of the compound that contributes to therapeutic biological activity after becoming available *in vivo* (i.e. as a metabolite). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in, for example, "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The term "metabolite" means a pharmaceutically acceptable form of a metabolic derivative of a compound of the invention (or a salt thereof), wherein the derivative is a relatively less active component of the compound that contributes to therapeutic biological activity after becoming available *in vivo*.

According on embodiment of the invention the active compound which can be used in the invention also extend to a *para*-phenyl thiourea compound having the general formula I:

Formula I



Preferably R_1 and R_2, identical or different, branched or not, are chosen in the group consisting of para-alkoxy, para-alkylthio and para-alkyl and oxygen radicals, preferably in C_1-C_{10}, more particularly in C_1 to C_6 and even more preferably in C_2 to C_5.

Amongst these phenyl thiourea compounds it is further preferred that R_1 and R_2 are chosen amongst the following radicals: methanolate, ethanolate, propane-1-olate, butan-1-olate, 3-methylbutan-1-olate, methanthiolate, ethanthiolate, propane-1-thiolate, butan-1-thiolate, 3-methylbutan-1-thiolate, butanyl and *ter*-butyl. It is further preferred that:

- R_1 and R_2 are butan-1-olate,
- R_1 and R_2 are propane-1-olate,
- R_1 and R_2 are methanolate,
- R_1 and R_2 are 3-methyl butan-1-thiolate,
- R_1 and R_2 are butan-1-thiolate,
- R_1 and R_2 are propan-1-thiolate,
- R_1 and R_2 are methanthiolate,
- R_1 and R_2 are *ter*-butyl,
- R_1 and R_2 are propyl,

- R_1 and R_2 are pentan-1-thiolate,
- R_1 and R_2 are ethanolate,
- R_1 and R_2 are 3-methyl propan-1-thiolate,
-when R_1 is 3-methylbutan-1-olate, R_2 is propane-1-thiolate,
-when R_1 is butyl, R_2 is 3-methylbutan-1-olate,
-when R_1 is butyl, R_2 is oxygen,
-when R_1 is butyl, R_2 is propane-1-thiolate.

Dosage

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject and it will vary with the age, weight and response of the particular patient. The dosages below are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are used.

The concentration of the composition in the active ingredient may vary from 0.01µg/ml to 50mg/ml, preferably between 0.03 µg/ml to 30mg/ml and more preferably between 5 to 15 mg/ml.

Depending upon the need, the agent may be administered at a dose of from 0.01 to 100 mg/kg body weight, such as from 0.1 to 100 mg/kg, more preferably from 0.5 to 10 mg/kg body weight and, even more preferably, 0.1 to 0.01 mg/kg body weight.

Administration

By way of example, the compound of the present invention may be administered in accordance with a regimen of 1 to 4 times per day, preferably once or twice per day. The specific dose level and frequency of

dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Formulation

Formulations can be systemic or topical.

The compositions of the present invention may be administered by direct injection. The composition may be formulated for parenteral, mucosal, intramuscular, intravenous, subcutaneous, intraocular or transdermal administration.

The composition of this invention is preferably in the form of a topical product that can be applied externally to the skin and can be prepared in accordance with conventional techniques known to those of ordinary skill in the art. The composition of the invention may take a variety of physical forms such as, for example, creams, dressings, gels, lotions, ointments or liquids. A cream, a gel and a lotion are the preferred forms. The composition can also conveniently be used in a spray applicator.

The composition of the invention includes a suitable topical carrier or excipient. Typical carriers include water and/or alcohols and/or emollients such as hydrocarbon oils and waxes, silicone oils, hyaluronic acid, vegetable, animal or marine fats or oils, glyceride derivatives, fatty acids or fatty acid esters or alcohols or alcohol ethers, lanolin and derivatives, polyhydric alcohols or esters, wax esters, sterols, phospholipids and the like, and generally also emulsifiers (nonionic, cationic or anionic), although some of the emollients inherently possess emulsifying properties. These

same general ingredients can be formulated into a cream as well as a lotion, or into gels, or into solid sticks by utilization of different proportions of the ingredients and/or by inclusion of thickening agents such as gums or other forms of hydrophilic colloids. Such compositions are referred to herein as pharmaceutically acceptable carriers. Preferably, the carrier should be a gel base formula without lipid materials that would exacerbate the oiliness of acne prone skin. However, a moisturizer emulsion base may be preferred by individuals that have particularly dry skin yet still suffer from acne lesions.

The compositions according to the invention preferably contain an effective stabilizing amount of an emulsifier. Preferably, the emulsifier is present at from about 1.0% to about 10.0%, more preferably from about 3.0% to about 6.0%, by weight, based on the total composition. Any emulsifier that is compatible with the components of the composition can be employed. Suitable emulsifiers include stearic acid, acetyl alcohol, stearyl alcohol, Steareth 2, Steareth 20, Acrylates/C10-30, alkyl acrylate Crosspolymer.

In another preferred embodiment, the compositions used in the methods of present invention contain a pH-buffering agent. Preferably, the amount of buffering agent should be that which would result in compositions having a pH ranging from about 4.5 to about 8.5, more preferably from about 5.5 to about 8.5, most preferably from about 6.5 to about 8.0. The buffering agent can be any of the known buffering agents commonly found in cosmetic or pharmaceutical compositions provided that they are physically and chemically stable with the other ingredients of the composition. Suitable buffering agents include organic acids such as, but not intended to be restricted to, citric acid, malic acid, and glycolic acid.

Detailed Description of the Invention

The present invention is illustrated by the following non-limiting examples in which:

Fig. 1 shows the semi-developed formula of 4,4'-diisoamyloxydiphenylthiourea (ISO).

Figs. 2a and 2b shows a comparative study of the effect of a topical placebo (Fig. 2a) on sebum production compared to the effect of topical application of 4,4'-diisoamyloxydiphenylthiourea (ISO) (Fig. 2b).

Fig. 3 shows the mean reduction in sebum excretion for patients after 10 weeks treatment

Fig. 4 shows the effect of 4,4'-diisoamyloxydiphenylthiourea (ISO) on the growth of *P.acnes*.

Effect of ISO on Sebum Production in Human

Ten healthy volunteers were recruited in order to measure the affects of 4,4'-diisoamyloxydiphenylthiourea on sebum production. The only exclusion criteria were volunteers on oral retinoids or using a topical acne preparation.

Sebum was measured using the Sebumeter SM815 (C-K Electronics, Cologne, Germany). Following initial degreasing of the forehead, the volunteers were kept seated in a room for an hour before Sebum forehead measurements were taken. This ensured production of sebum would be

reflective of production in an hour and also so temperature and humidity would remain constant throughout the trial.

Basal levels of sebum production on the left hand side and the right hand side of the forehead were measured at the start of the trial (Week 0). No significant differences in basal sebum production between left and right sides of the forehead were evident (Figs 2a and 2b).

Treatment involved the application of placebo aqueous base cream to the right hand side of the forehead and aqueous cream containing 4% 4,4'-diisoamyloxydiphenylthiourea to the left hand side of the forehead. Creams were applied twice a day, once in the morning and once in the evening, for one week. Volunteers were blinded during the study and received two weighed pots of creams. They were also instructed not to apply other moisturizers or cosmetics to their foreheads during this period and to bring back the pots on their day of sebum measurement. Creams were weighed at the end of treatment and usage determined.

One week treatment with a placebo aqueous cream (left hand side) did not reduce sebum production (Fig 2a). The effects of treatment with 4% 4,4'-diisoamyloxydiphenylthiourea for one week are shown in Fig 2b. In all 10 patients, a decrease in sebum production on the treated side of the forehead was evident.

The mean reduction in sebum excretion for patients after 10 weeks treatment is shown in Fig. 3. The treatment caused a statistically significant inhibition of sebum excretion. Thus the initial rapid reduction in sebum secretion after one week of treatment was maintained after 10 weeks of treatment.

Growth inhibitory effect of ISO on *P. acnes*

Test substance or vehicle (DMSO) was added to test wells containing P.acnes (ATCC 6919; 1 x 10-4 to 5 x 10-5 CFU/ml) in reinforced Clostridial medium. After 2 days at 37°C, growth of the culture was examined and scored positive (0% growth) for inhibition of growth or turbidity or negative (100% growth) for no effect upon growth or turbidity (Misiek, M., Pursiano, T.A., Leitner, F. and Price, K.E. (1973) Antimicrobial Agents Chemotherapy 3: 40-48: Enza Di Modugno, Isabelle Erbetti, Livia Ferrari, Gianluca Galassi, Stephen M. Hammond, and Luigi xerri (1994) Antimicrobial Agents and Chemotherapy, 38: 2362-2368, 1994.)

As shown in Fig.4, the minimal total inhibitory concentration for of 4,4'-diisoamyloxydiphenylthiourea was 0.03 µg/ml. In identical experiments the minimal total inhibitory concentration for tetracycline was found to be 1 µg/ml and for vancomycin 1 µg/ml.

Specificity of ISO anti-microbial activity

The anti microbial action of 4,4'-diisoamyloxydiphenylthiourea also shows a high specificity and appears restricted to the facultative anaerobe *P.acnes.* Table 1 shows that testing carried out against a wide range of other organisms did not reveal significant anti microbial effects.

Table 1

ORGANISM	ATCC	Minimum Inhibitory Conc.
Cornebacterium minutissimum	ATCC23347	n.a. >100µg/ml

Pityrosporum ovale	ATCC38593	n.a. >100µg/ml
Staphylococcus aureus	ATCC27660	n.a. >100µg/ml
Staphylococcus aureus	ATCC33591	n.a. >100µg/ml
Streptococcus pneumoniae	ATCC6301	n.a. >100µg/ml
Bacillus subtillis	ATCC43223	n.a. >100µg/ml
Propionobacterium acnes	ATCC6919	0.03 µg/ml

n.a. : not active.

It is therefore shown that, unexpectedly, the thiourea compound 4,4'-diisoamyloxydiphenylthiourea both effectively reduces the production of sebum by human skin and has a potent inhibitory effect on the growth of P.acnes. The effect on sebum production is unexpectedly rapid occurring after one week of treatment and maintained thereafter. It is further shown that application of the compound to the skin results in a dramatic and rapid improvement in the condition of acne. Moreover, the inhibitory effects on the growth of *P.acnes* are specific for this facultative anaerobe and not observed with other commonly occurring bacteria.

CLAIMS

1. Use of 4,4'-diisoamyloxydiphenylthiourea, one of its derivative or a mixture thereof for the treatment of a disorder of the pilosebaceous apparatus.

2. The use according to claim 1, wherein said disorder is sebbhorea, rosecea, acne conglobate, acne vulgaris, infantile acne, acne associated with virilization, acne accompanying the polycystic ovarian syndrome, or drug-induced acne.

3. The use according to claim 2, wherein said disorder is acne vulgaris.

4. The use according to any one of claims 1 to 3, wherein the concentration for of 4,4'-diisoamyloxydiphenylthiourea is equal or superior to 0.03 µg/ml.

5. The use according to any one of claims 1 to 4, wherein 4,4'-diisoamyloxydiphenylthiourea is administered at a dose of 0.01 to 100 mg/kg body weight of a patient.

6. The use according to any one of claims 1 to 5, wherein said use is topical.

7. A pharmaceutical composition, said composition comprising a therapeutically effective amount of 4,4'-diisoamyloxydiphenylthiourea, one of its derivative or a mixture thereof together with a pharmaceutically acceptable carrier.

8. The composition according to claim 7 wherein said composition is a topical composition which comprises a topically acceptable carrier.

9. The composition of claims 7 or 8, wherein said carrier is chosen in the group consisting of water, alcohols, emollients and mixtures thereof.

10. The composition of claim 7, wherein such carrier is chosen in the group consisting of hydrocarbon oils and waxes, silicone oils, hyaluronic acid, vegetable, animal or marine fats or oils, glyceride derivatives, fatty acids or fatty acid esters or alcohols or alcohol ethers, lanolin and derivatives, polyhydric alcohols or esters, wax esters, sterols, phospholipids.

11. The composition according to any one of claims 7 to 10, wherein the concentration for of 4,4'-diisoamyloxydiphenylthiourea is equal or superior to 0.03 µg/ml.

Fig. 1

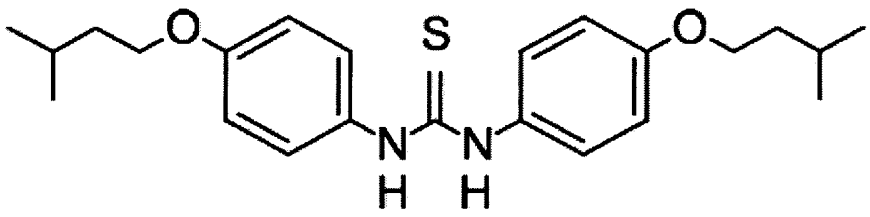


Fig. 2a

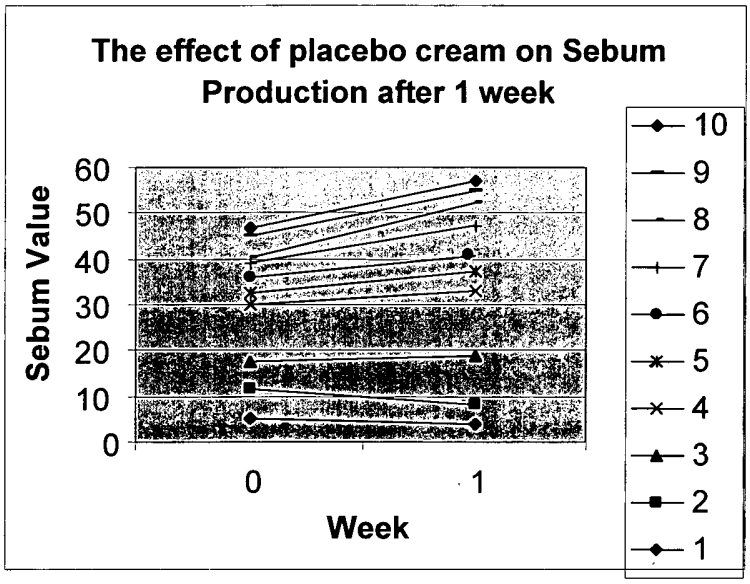

The effect of placebo cream on Sebum Production after 1 week
Sebum Value
60
50
40
30
20
10
0
0
1
Week
10
9
8
7
6
5
4
3
2
1

Fig. 2b

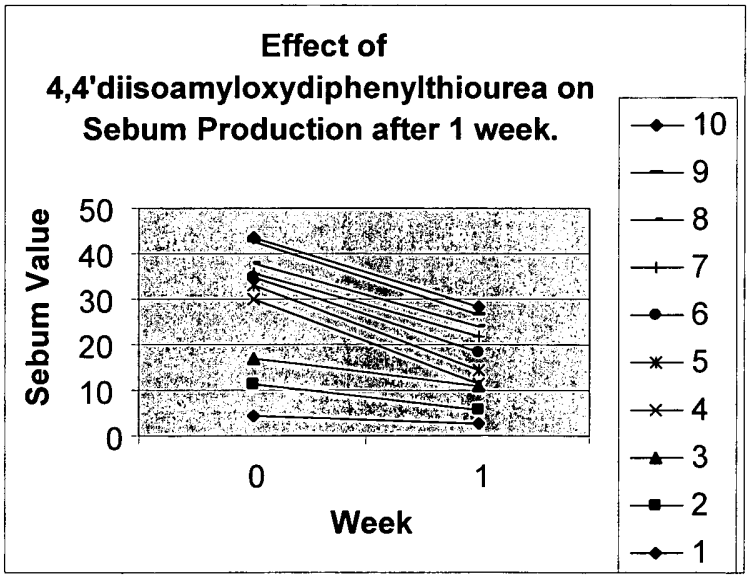

Effect of 4,4'diisoamyloxydiphenylthiourea on Sebum Production after 1 week.
Sebum Value
50
40
30
20
10
0
0
1
Week
10
9
8
7
6
5
4
3
2
1

Fig. 3

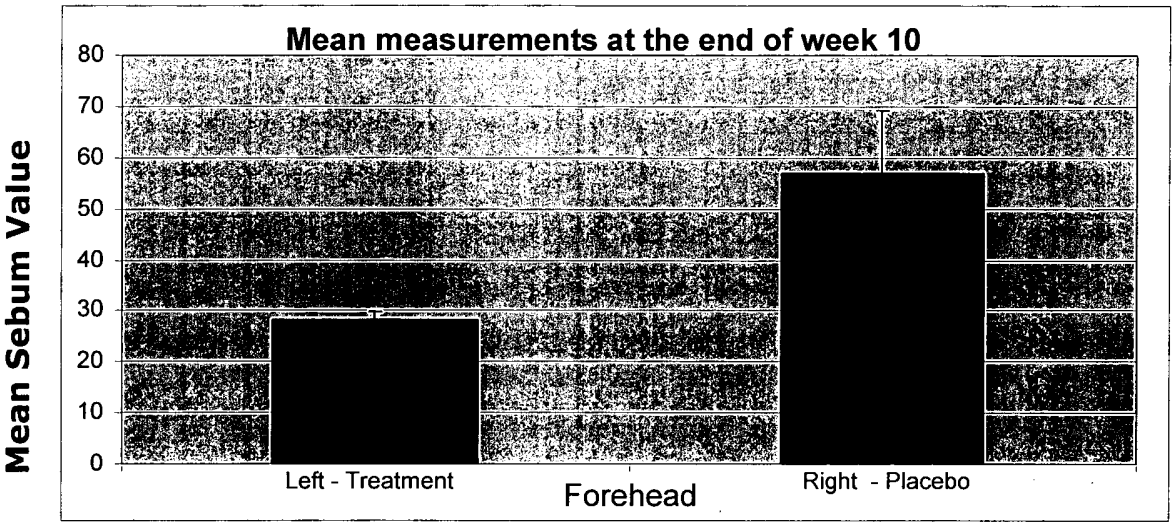
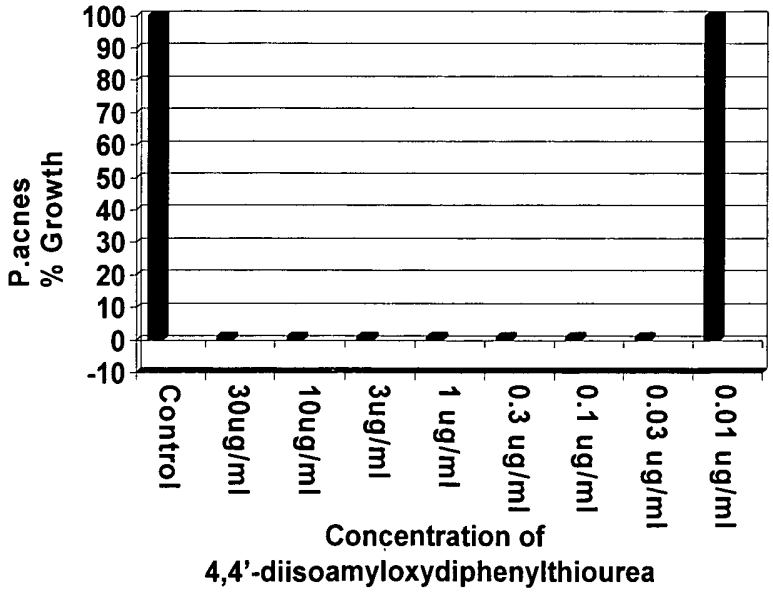

Mean measurements at the end of week 10
Mean Sebum Value
80
70
60
50
40
30
20
10
0
Left - Treatment
Forehead
Right - Placebo

Fig. 4


P.acnes
% Growth
100
90
80
70
60
50
40
30
20
10
0
-10
Control
30ug/ml
10ug/ml
3ug/ml
1 ug/ml
0.3 ug/ml
0.1 ug/ml
0.03 ug/ml
0.01 ug/ml
Concentration of
4,4'-diisoamyloxydiphenylthiourea

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003289

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/17 A61P17/00 A61P17/08 A61P17/10

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 A61P

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 practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/080179 A (XANTECH PHARMACEUTICALS INC [US]; DEES H CRAIG [US]; WACHTER ERIC [US]) 23 September 2004 (2004-09-23) page 8, paragraphs 27,28 page 9, paragraph 32-36 page 10, paragraph 37 page 22, paragraph 66 page 26, paragraph 76 page 28, paragraph 86 page 30; claims 1,4-8 page 31; claims 9,12-16	1,4-11

-/--

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

[X] See patent family annex.

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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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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2008	16/12/2008

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	Opravz, Petra

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003289

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHETSUKSIRI BENJAWAN ET AL: "Unique mechanism of action of the thiourea drug isoxyl on Mycobacterium tuberculosis." THE JOURNAL OF BIOLOGICAL CHEMISTRY 26 DEC 2003, vol. 278, no. 52, 26 December 2003 (2003-12-26), pages 53123-53130, XP002506273 ISSN: 0021-9258 abstract page 53123 page 53128	7,11
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Information on patent family members

International application No
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