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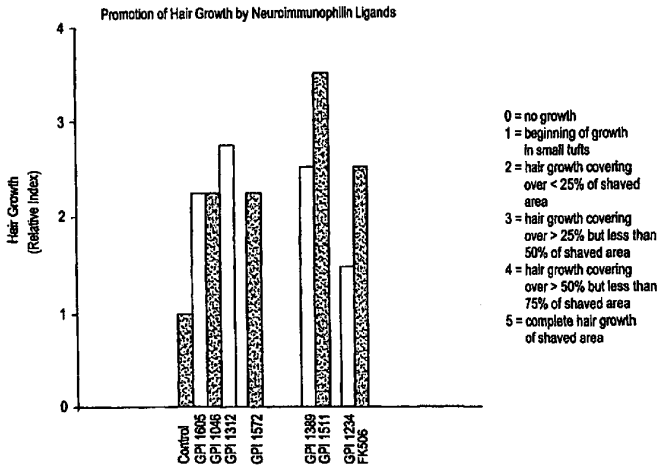


(57) Abstract

This invention relates to pharmaceutical compositions and methods for treating alopecia and promoting hair growth using heterocyclic esters or amides.

HETEROCYCLIC ESTER AND AMIDE HAIR GROWTH COMPOSITIONS AND USES

This application is a continuation-in-part of U.S. Patent Application No. 08/869,426, filed on June 4, 1997, the entire contents of which are herein incorporated by reference.

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to pharmaceutical compositions and methods for treating alopecia and promoting hair growth using low molecular weight, small molecule heterocyclic esters or amides.

2. Description of Related Art

Hair loss occurs in a variety of situations. These situations include male pattern alopecia, alopecia senilis, alopecia areata, diseases accompanied by basic skin lesions or tumors, and systematic disorders such as nutritional disorders and internal secretion disorders. The mechanisms causing hair loss are very complicated, but in some instances can be attributed to aging, genetic disposition, the activation of male hormones, the loss of blood supply to hair follicles, and scalp abnormalities.

The immunosuppressant drugs FK506, rapamycin and cyclosporin are well known as potent T-cell specific

immunosuppressants, and are effective against graft rejection after organ transplantation. It has been reported that topical, but not oral, application of FK506 (Yamamoto et al., J. Invest. Dermatol., 1994, 102, 160-164; Jiang et al., J. Invest. Dermatol. 1995, 104, 523-525) and cyclosporin (Iwabuchi et al., J. Dermatol. Sci. 1995, 9, 64-69) stimulates hair growth in a dose-dependent manner. One form of hair loss, alopecia areata, is known to be associated with autoimmune activities; hence, topically administered immunomodulatory compounds are expected to demonstrate efficacy for treating that type of hair loss. The hair growth stimulating effects of FK506 have been the subject of an international patent filing covering FK506 and structures related thereto for hair growth stimulation (Honbo et al., EP 0 423 714 A2). Honbo et al. discloses the use of relatively large tricyclic compounds, known for their immunosuppressive effects, as hair revitalizing agents.

The hair growth and revitalization effects of FK506 and related agents are disclosed in many U.S. patents (Goulet et al., U.S. Patent No. 5,258,389; Luly et al., U.S. Patent No. 5,457,111; Goulet et al., U.S. Patent No. 5,532,248; Goulet et al., U.S. Patent No. 5,189,042; and Ok et al., U.S. Patent No. 5,208,241; Rupprecht et al., U.S. Patent No. 5,284,840; Organ et al., U.S. Patent No. 5,284,877). These patents claim FK506 related compounds. Although

they do not claim methods of hair revitalization, they disclose the known use of FK506 for effecting hair growth. Similar to FK506 (and the claimed variations in the Honbo et al. patent), the compounds claimed in these patents are relatively large. Further, the cited patents relate to immunomodulatory compounds for use in autoimmune related diseases, for which FK506's efficacy is well known.

Other U.S. patents disclose the use of cyclosporin and related compounds for hair revitalization (Hauer et al., U.S. Patent No. 5,342,625; Eberle, U.S. Patent No. 5,284,826; Hewitt et al., U.S. Patent No. 4,996,193). These patents also relate to compounds useful for treating autoimmune diseases and cite the known use of cyclosporin and related immunosuppressive compounds for hair growth.

However, immunosuppressive compounds by definition suppress the immune system and also exhibit other toxic side effects. Accordingly, there is a need for non-immunosuppressant, small molecule compounds which are useful as hair revitalizing compounds.

Hamilton and Steiner disclose in U.S. Patent No. 5,614,547 novel pyrrolidine carboxylate compounds which bind to the immunophilin FKBP12 and stimulate nerve growth, but which lack immunosuppressive effects. Unexpectedly, it has been discovered that

these non-immunosuppressant compounds promote hair growth with an efficacy similar to FK506. Yet their novel small molecule structure and non-immunosuppressive properties differentiate them from FK506 and related immunosuppressive compounds found in the prior art.

SUMMARY OF THE INVENTION

The present invention provides a method for treating alopecia or promoting hair growth in an animal in need thereof, comprising administering an effective amount of a nitrogen-containing heterocyclic compound having two or more heteroatoms,

wherein said compound has a substituent -C(W)-C(Y)- which is attached to a nitrogen atom of the heterocyclic ring,

wherein W and Y are independently selected from the group consisting of O, S, CH_2, and two hydrogen atoms, and

wherein said compound is additionally substituted with a ester or amide substituent attached to the heterocyclic ring,

provided that said amide substituent is linked to the heterocyclic ring with a carbon-carbon bond,

wherein R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl, or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

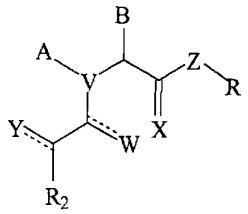
wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro,

trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

The present invention also provides a method for treating alopecia or promoting hair growth in an animal in need thereof, comprising administering an effective amount of compound of formula IV



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is N;

A and B, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR;

R is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_9 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_3,

wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched

chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar_4;

Ar_3 and Ar_4 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the individual ring size is 5-8 members,

and wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S;

X is O or S;

Z is O, NH, or NR_1;

W and Y are independently O, S, CH_2, or two hydrogen atoms;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl,

wherein said R_1 is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

Ar_1 is independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

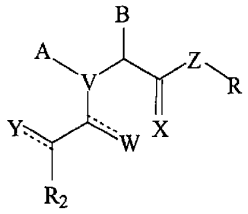
and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkyl, and hydroxy.

The present invention further relates to a pharmaceutical composition which comprises:

(i) an effective amount of a compound for treating alopecia or promoting hair growth in an animal, wherein the compound is of formula IV



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is N;

A and B, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR;

R is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_9 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_3,

wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar_4;

Ar_3 and Ar_4 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the individual ring size is 5-8 members,

and wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S;

X is O or S;

Z is O, NH, or NR_1;

W and Y are independently O, S, CH_2, or two hydrogen atoms;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl,

wherein said R_1 is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

Ar_1 is independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

(ii) a pharmaceutically acceptable carrier.

The invention further provides use of a compound for the preparation of a medicament for treating alopecia or promoting hair growth in an animal in need thereof, wherein said compound is a nitrogen-containing heterocyclic compound having two or more heteroatoms,

wherein said compound has a substituent -C(W)-C(Y)- which is attached to a nitrogen atom of the heterocyclic ring,

wherein W and Y are independently selected from the group consisting of O, S, CH_2, and two hydrogen atoms, and

wherein said compound is additionally substituted with a ester or amide substituent attached to the heterocyclic ring,

provided that said amide substituent is linked to the heterocyclic ring with a carbon-carbon bond,

wherein R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl, or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

The hetero cyclic esters and amides used in the inventive methods and pharmaceutical compositions have an affinity for FKBP-type immunophilins and do not exert any significant immunosuppressive activity.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a photograph of C57 Black 6 mice before being shaved for the hair regeneration experiment.

FIG. 2 is a photograph of mice treated with a vehicle after six weeks. FIG. 2 shows that less than

3% of the shaved area is covered with new hair growth when the vehicle (control) is administered.

FIG. 3 is a photograph of mice treated with 10 μM of GPI 1046, a related non-immunosuppressive neuroimmunophilin FKBP ligand, after six weeks. FIG. 3 shows the remarkable effects of neuroimmunophilin FKBP ligands, wherein 90% of the shaved area is covered with new hair growth.

FIG. 4 is a photograph of mice treated with 30 μM of GPI 1046, a related non-immunosuppressive neuroimmunophilin FKBP ligand, after six weeks. FIG. 4 shows the remarkable ability of neuroimmunophilin FKBP ligands to achieve, essentially, complete hair regrowth in the shaved area.

FIG. 5 is a bar graph depicting the relative hair growth indices for C57 Black 6 mice treated with a vehicle, FK506, and various non-immunosuppressive neuroimmunophilin FKBP ligands, including GPI 1572, 14 days after treatment with each identified compound. Figure 5 demonstrates the remarkable early hair growth promoted by a wide variety of non-immunosuppressive neuroimmunophilin FKBP ligands.

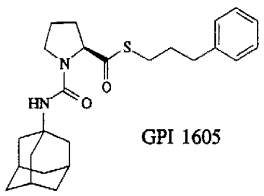
DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alopecia" refers to deficient hair growth and partial or complete loss of hair, including without limitation androgenic alopecia (male pattern

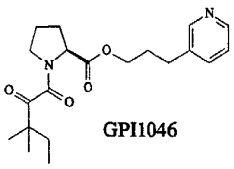
baldness), toxic alopecia, alopecia senilis, alopecia areata, alopecia pelada and trichotillomania. Alopecia results when the pilar cycle is disturbed. The most frequent phenomenon is a shortening of the hair growth or anagen phase due to cessation of cell proliferation. This results in an early onset of the catagen phase, and consequently a large number of hairs in the telogen phase during which the follicles are detached from the dermal papillae, and the hairs fall out. Alopecia has a number of etiologies, including genetic factors, aging, local and systemic diseases, febrile conditions, mental stresses, hormonal problems, and secondary effects of drugs.

"GPI 1605" refers to a compound of formula



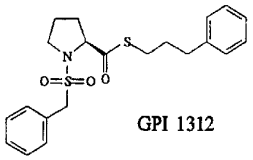
GPI 1605

"GPI 1046" refers to 3-(3-pyridyl)-1-propyl (2s)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidine-carboxylate, a compound of formula



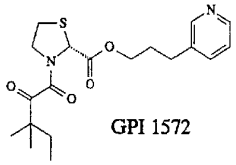
GPI1046

"GPI 1312" refers to a compound of formula



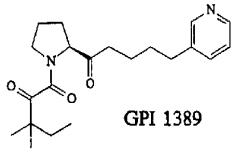
GPI 1312

"GPI 1572" refers to a compound of formula



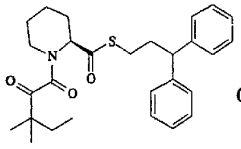
GPI 1572

"GPI 1389" refers to a compound of formula



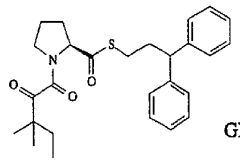
GPI 1389

"GPI 1511" refers to a compound of formula



GPI 1511

"GPI 1234" refers to a compound of formula



GPI 1234

"Isomers" refer to different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. "Diastereoisomers" are stereoisomers which are not mirror images of each other. "Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

"Pharmaceutically acceptable salt, ester, or solvate" refers to a salt, ester, or solvate of a subject compound which possesses the desired pharmacological activity and which is neither biologically nor otherwise undesirable. A salt, ester, or solvate can be formed with inorganic acids such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate,

ethanesulfonate, fumarate, glucoheptanoate, gluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, naphthylate, 2-naphthalenesulfonate, nicotinate, oxalate, sulfate, thiocyanate, tosylate and undecanoate. Examples of base salts, esters, or solvates include ammonium salts; alkali metal salts, such as sodium and potassium salts; alkaline earth metal salts, such as calcium and magnesium salts; salts with organic bases, such as dicyclohexylamine salts; N-methyl-D-glucamine; and salts with amino acids, such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quarternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides; aralkyl halides, such as benzyl and phenethyl bromides; and others. Water or oil-soluble or dispersible products are thereby obtained.

"Pilar cycle" refers to the life cycle of hair follicles, and includes three phases:

(1) the anagen phase, the period of active hair growth which, insofar as scalp hair is concerned, lasts about three to five years;

(2) the catagen phase, the period when growth stops and the follicle atrophies which, insofar as scalp hair is concerned, lasts about one to two weeks; and

(3) the telogen phase, the rest period when hair progressively separates and finally falls out which, insofar as scalp hair is concerned, lasts about three to four months.

Normally 80 to 90 percent of the follicles are in the anagen phase, less than 1 percent being in the catagen phase, and the rest being in the telogen phase. In the telogen phase, hair is uniform in diameter with a slightly bulbous, non-pigmented root. By contrast, in the anagen phase, hair has a large colored bulb at its root.

"Promoting hair growth" refers to maintaining, inducing, stimulating, accelerating, or revitalizing the germination of hair.

"Treating alopecia" refers to:

(i) preventing alopecia in an animal which may be predisposed to alopecia; and/or

(ii) inhibiting, retarding or reducing alopecia; and/or

(iii) promoting hair growth; and/or

(iv) prolonging the anagen phase of the hair cycle; and/or

(v) converting vellus hair to growth as terminal hair. Terminal hair is coarse, pigmented, long hair in which the bulb of the hair follicle is seated deep in the dermis. Vellus hair, on the other hand, is fine, thin, non-pigmented short hair in which the hair bulb is located superficially in the dermis. As alopecia progresses, the hairs change from the terminal to the vellus type.

Methods of the Present Invention

The present invention relates to a method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a heterocyclic ester or amide.

The inventive method is particularly useful for treating male pattern alopecia, alopecia senilis, alopecia areata, alopecia resulting from skin lesions or tumors, alopecia resulting from cancer therapy such as chemotherapy and radiation, and alopecia resulting from systematic disorders such as nutritional disorders and internal secretion disorders.

Pharmaceutical Compositions of the Present Invention

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of a heterocyclic ester or amide for treating alopecia or promoting hair growth in an animal; and

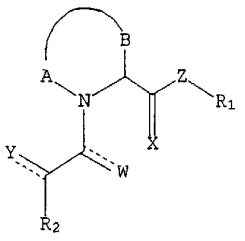
(ii) a pharmaceutically acceptable carrier.

HETEROCYCLIC ESTERS AND AMIDES

The heterocyclic esters and amides used in the methods and pharmaceutical compositions of the present invention are low molecular weight, small molecule compounds having an affinity for an FKBP-type immunophilin, such as FKBP12. When a heterocyclic ester or amide binds to an FKBP-type immunophilin, it has been found to inhibit the prolyl-peptidyl *cis-trans* isomerase, or rotamase, activity of the binding protein. Unexpectedly, the compounds have also been found to stimulate hair growth. The compounds are devoid of any significant immunosuppressive activity.

FORMULA I

The heterocyclic ester or amide may be a compound of formula I



I

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to the nitrogen atom, one or more additional O, S, SO, SO_2, N, NH or NR_1 heteroatom(s);

X is O or S;

Z is O, NH or NR_1;

W and Y are independently O, S, CH_2 or H_2;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

R_2 is either C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain or alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl,

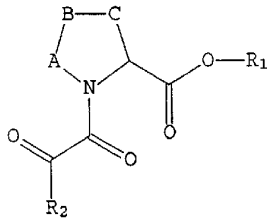
C_2-C_4 straight or branched chain alkenyl, and hydroxyl; and

Ar_1 and Ar_2 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

Suitable carbo- and heterocyclic rings include without limitation naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, fluorenyl and phenyl.

FORMULA II

Additionally, the heterocyclic ester or amide may be a compound of formula II



II

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B and C are independently CH_2, O, S, SO, SO_2, NH or NR_1;

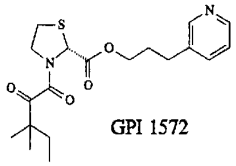
R_1 is C_1-C_5 straight or branched chain alkyl or C_2-C_5 straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$ and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$;

n is 1 or 2;

R_2 is either C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

In a preferred embodiment of the compounds of formula II, the heterocyclic ester or amide is the compound GPI 1572, of the formula



GPI 1572

In a particularly preferred embodiment of formula II compounds:

A is CH_2;

B is CH_2 or S;

C is CH_2 or NH;

R_1 is selected from the group consisting of 3-phenylpropyl and 3-(3-pyridyl)propyl; and

R_2 is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, and *tert*-butyl.

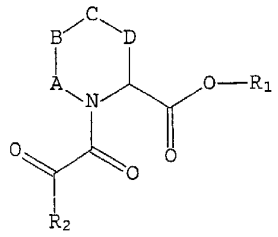
Specific examples of this embodiment are presented in TABLE I.

TABLE I

No.	A	B	C	R_1	R_2
1	CH_2	S	CH_2	3-phenylpropyl	1,1-dimethylpropyl
2	CH_2	S	CH_2	3-(3-pyridyl)propyl	1,1-dimethylpropyl
3	CH_2	S	CH_2	3-phenylpropyl	cyclohexyl
4	CH_2	S	CH_2	3-phenylpropyl	*tert*-butyl
5	CH_2	CH_2	NH	3-phenylpropyl	1,1-dimethylpropyl
6	CH_2	CH_2	NH	3-phenylpropyl	cyclohexyl
7	CH_2	CH_2	NH	3-phenylpropyl	*tert*-butyl

FORMULA III

The heterocyclic ester or amide may also be a compound of formula III



III

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B, C and D are independently CH_2, O, S, SO, SO_2, NH or NR_1;

R_1 is C_1-C_5 straight or branched chain alkyl or C_2-C_5 straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$ and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$;

n is 1 or 2;

R_2 is either C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one

or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

In a particularly preferred embodiment of formula III compounds:

A is CH_2;

B is CH_2;

C is S, O or NH;

D is CH_2;

R_1 is selected from the group consisting of 3-phenylpropyl and (3,4,5-trimethoxy)phenylpropyl; and

R_2 is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, *tert*-butyl, phenyl, and 3,4,5-trimethoxyphenyl.

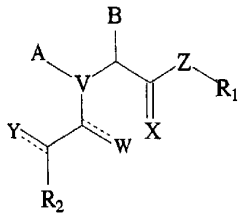
Specific examples of this embodiment are presented in TABLE II.

TABLE II

No.	A	B	C	D	R_1	R_2
8	CH_2	CH_2	S	CH_2	3-phenylpropyl	1,1-dimethylpropyl
9	CH_2	CH_2	O	CH_2	3-phenylpropyl	1,1-dimethylpropyl
10	CH_2	CH_2	S	CH_2	3-phenylpropyl	cyclohexyl
11	CH_2	CH_2	O	CH_2	3-phenylpropyl	cyclohexyl
12	CH_2	CH_2	S	CH_2	3-phenylpropyl	phenyl
13	CH_2	CH_2	O	CH_2	3-phenylpropyl	phenyl
14	CH_2	CH_2	NH	CH_2	3-phenylpropyl	1,1-dimethylpropyl
15	CH_2	CH_2	NH	CH_2	3-phenylpropyl	phenyl

FORMULA IV

The heterocyclic ester or amide may also be a compound of formula IV



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is C, N, or S;

A and B, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group

consisting of O, S, SO, SO_2, N, NH, and NR;

R is either C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_9 cycloakyl, C_5-C_7 cycloalkenyl, or Ar_3, wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar_4;

Ar_3 and Ar_4 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring; wherein the individual ring size is 5-8 members; wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R_1, R_2, W, X, Y, and Z are as defined in Formula I above.

All the compounds of Formulas I-IV possess asymmetric centers and thus can be produced as mixtures of stereoisomers or as individual R- and S-stereoisomers. The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage

of the synthesis, or by resolving the compounds of Formulas I-IV. It is understood that the compounds of Formulas I-IV encompass individual stereoisomers as well as mixtures (racemic and non-racemic) of stereoisomers. Preferably, S-stereoisomers are used in the pharmeceutical compositions and methods of the present invention.

Affinity for FKBP12

The compounds used in the inventive methods and pharmaceutical compositions have an affinity for the FK506 binding protein, particularly FKBP12. The inhibition of the prolyl peptidyl *cis-trans* isomerase activity of FKBP may be measured as an indicator of this affinity.

K_i Test Procedure

Inhibition of the peptidyl-prolyl isomerase (rotamase) activity of the compounds used in the inventive methods and pharmaceutical compositions can be evaluated by known methods described in the literature (Harding et al., *Nature*, 1989, 341:758-760; Holt et al. *J. Am. Chem. Soc.*, 115:9923-9938). These values are obtained as apparent K_i's and are presented for representative compounds in TABLE III.

The *cis-trans* isomerization of an alanine-proline bond in a model substrate, N-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide, is monitored spectrophotometrically in

a chymotrypsin-coupled assay, which releases *para*-nitroanilide from the *trans* form of the substrate. The inhibition of this reaction caused by the addition of different concentrations of inhibitor is determined, and the data is analyzed as a change in first-order rate constant as a function of inhibitor concentration to yield the apparent K_i values.

In a plastic cuvette are added 950 mL of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10 mL of FKBP (2.5 mM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25 mL of chymotrypsin (50 mg/ml in 1 mM HCl) and 10 mL of test compound at various concentrations in dimethyl sulfoxide. The reaction is initiated by the addition of 5 mL of substrate (succinyl-Ala-Phe-Pro-Phe-*para*-nitroanilide, 5 mg/mL in 2.35 mM LiCl in trifluoroethanol).

The absorbance at 390 nm versus time is monitored for 90 seconds using a spectrophotometer and the rate constants are determined from the absorbance versus time data files.

TABLE III

In Vitro Test Results - Formulas I to IV

Compound	K_i (nM)
1	215
2	638

Route of Administration

To effectively treat alopecia or promote hair growth, the compounds used in the inventive methods and pharmaceutical compositions must readily affect the targeted areas. For these purposes, the compounds are preferably administered topically to the skin.

For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in, for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated into suitable lotions or creams containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Other routes of administration known in the pharmaceutical art are also contemplated by this invention.

Dosage

Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with

preferred levels of about 0.1 mg to about 1,000 mg. The specific dose level for any particular patient will vary depending upon a variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease being treated; and the form of administration. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art.

The compounds can be administered with other hair revitalizing agents. Specific dose levels for the other hair revitalizing agents will depend upon the factors previously stated and the effectiveness of the drug combination.

EXAMPLES

The following examples are illustrative of the present invention and are not intended to be limitations thereon. Unless otherwise indicated, all percentages are based upon 100% by weight of the final composition.

25

Example 1

Synthesis of 3-phenyl-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (1)

1-(1,2-dioxo-2-methoxyethyl)2-(4-thiazolidine)-carboxylate

A solution of L-thioproline (1.51 g; 11.34 mmol) in 40 mL of dry methylene chloride was cooled to 0°C and treated with 3.3 mL (2.41 g; 23,81 mmol) of triethylamine. After stirring this mixture for 30 minutes, a solution of methyl oxalyl chloride (1.81 g; 14.74 mmol) was added dropwise. The resulting mixture was stirred at 0°C for 1.5 hours, filtered through Celite to remove solids, dried and concentrated. The crude material was purified on a silic gel column, eluting with 10% MeOH in methylene chloride, to obtain 2.0 g of the oxamate as an orange-yellow solid.

3-phenyl-1-propyl(2*S*)-1-(1,2-dioxo-2-methoxyethyl)2-(4-thiazolidine)carboxylate

1-(1,2-dioxo-2-methoxyethyl)2-(4-thiazolidine)-carboxylate (500 mg; 2.25 mmol), 3-phenyl-1-propanol (465 mg; 3.42 mmol), dicyclohexylcarbodiimide (750 mg; 3.65 mmol), 4-dimethylaminopyridine (95 mg; 0.75 mmol) and camphorsulfonic acid (175 mg; 0.75 mmol) in 30 mL of methylene chloride were stirred together overnight. The mixture was filtered through Celite to remove solids and chromatographed (25% ethyl acetate/hexane) to obtain 690 mg of material. ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.92-2.01 (m, 2H); 2.61-2.69 (m, 2H); 3.34 (m, 1H);

4.11-4.25 (m, 2H); 4.73 (m, 1H); 5.34 (m, 1H); 7.12 (m, 3H); 7.23 (m, 2H).

3-phenyl-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (1)

A solution of 3-phenyl-1-propyl(2*S*)-1-(1,2-dioxo-2-methoxyethyl)2-(4-thiazolidine)carboxylate (670 mg; 1.98 mmol) in tetrahydrofuran (10 mL) was cooled to -78°C and treated with 2.3 mL of a 1.0 M solution of 1,1-dimethylpropylmagnesium chloride in ether. After stirring the mixture for 3 hours, it was poured into saturated ammonium chloride, extracted into ethyl acetate, and the organic phase was washed with water, dried and concentrated. The crude material was purified on a silica gel column, eluting with 25% ethyl acetate in hexane, to obtain 380 mg of the compound of Example 1 as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): d 0.86 (t, 3H); 1.21 (s, 3H); 1.26 (s, 3H); 1.62-1.91 (m, 3H); 2.01 (m, 2H); 2.71 (m, 2H); 3.26-3.33 (m, 2H); 4.19 (m, 2H); 4.58 (m, 1H); 7.19 (m, 3H); 7.30 (m, 2H). Analysis calculated for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.23; N, 3.71. Found: C, 64.29; H, 7.39; N, 3.46.

Example 2

Synthesis of 3-(3-pyridyl)-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine) carboxylate (2)

The compound of Example 2 was prepared according

to the procedure of Example 1, using 3-(3-pyridyl)-1-propanol in the final step, to yield 3-(3-pyridyl)-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, J = 7.3); 1.25 (s, 3H); 1.28 (s, 3H); 1.77 (q, 2H, J = 7.3); 2.03 (tt, 2H, J = 6.4, 7.5); 2.72 (t, 2H, J = 7.5); 3.20 (dd, 1H, J = 4.0, 11.8); 3.23 (dd, 1H, J = 7.0, 11.8); 4.23 (t, 2H, J = 6.4); 4.55 (d, 2H, J = 8.9); 5.08 (dd, 1H, J = 4.0, 7.0); 7.24 (m, 1H); 8.48 (m, 2H). Analysis calculated for $C_{19}H_{26}N_2O_4S$ - 0.5 H_2O: C, 58.89; H, 7.02; N, 7.23. Found: C, 58.83; H, 7.05; N, 7.19.

Example 3

In Vivo **Hair Generation Tests With C57 Black 6 Mice**

Experiment A: C57 black 6 mice were used to demonstrate the hair revitalizing properties of a low molecular weight, small molecule, non-immunosuppressive neuroimmunophilin FKBP ligand, GPI 1046, which is related to heterocyclic esters and amides. Referring now to FIGS. 1 and 2 of the drawings, C57 black 6 mice, approximately 7 weeks old, had an area of about 2 inches by 2 inches on their hindquarters shaved to remove all existing hair. Care was taken not to nick or cause abrasion to the underlaying dermal layers. The animals were in anagen growth phase, as indicated by the pinkish color of the skin. Referring now to FIGS. 2, 3 and 4, four animals per

group were treated by topical administration with 20% propylene glycol vehicle (FIG. 2), 10 μM GPI 1046 (FIG. 3) or 30 μM GPI 1046 (FIG. 4) dissolved in the vehicle. The animals were treated with vehicle or GPI 1046 every 48 hours (3 applications total over the course of 5 days) and the hair growth was allowed to proceed for 6 weeks. Hair growth was quantitated by the percent of shaved area covered by new hair growth during this time period.

FIG. 2 shows that animals treated with vehicle exhibited only a small amount of hair growth in patches or tufts, with less than 3% of the shaved area covered with new growth. In contrast, FIG. 3 shows that animals treated with 10 μM GPI 1046 exhibited dramatic hair growth, covering greater than 90% of the shaved area in all animals. Further, FIG. 4 shows that mice treated with 30 μM GPI 1046 exhibited essentially complete hair regrowth and their shaved areas were indistinguishable from unshaven C57 black 6 mice.

Experiment B: C57 Black 6 mice were used to demonstrate the hair revitalizing properties of a variety of low molecular weight, small molecule, non-immunosuppressive neuroimmunophilin FKBP ligands, including GPI 1572. C57 Black 6 mice, 55 to 75 days old, had an area of about 2 inches by 2 inches on their hindquarters shaved to remove all existing hair. Care was taken not to nick or cause abrasion to the

underlying dermal layers. The animals were in a anagen growth phase when shaved. Five animals per group were treated by topical administration with vehicle, FK506, or one of the low molecular weight, small molecule, non-immunosuppressive neuroimmunophilin FKBP ligands (GPI 1605, 1046, 1312, 1572, 1389, 1511, and 1234) at a concentration of one micromole per milliliter to the shaved area. The animals were treated three times per week, and hair growth was evaluated 14 days after initiation of treatment. Hair growth was quantitated by the percent of shaved area covered by new hair growth, as scored by a blinded observer, on a scale of 0 (no growth) to five (complete hair regrowth in shaved area).

Figure 5 shows that after 14 days, the animals treated with vehicle exhibited the beginning of growth in small tufts. In contrast, animals treated with one of the low molecular weight, small molecule, non-immunosuppressive neuroimmunophilin FKBP ligands, including GPI 1572, exhibited dramatic hair growth.

Example 4

A lotion comprising the following composition may be prepared.

	(%)
95% Ethanol	80.0
a heterocyclic ester or amide as defined above	10.0
α-Tocopherol acetate	0.01
Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
purified water	9.0
perfume and dye	q.s.

Into 95% ethanol are added a heterocyclic ester or amide, α-tocopherol acetate, ethylene oxide (40 mole) adducts of hardened castor oil, perfume and a dye. The resulting mixture is stirred and dissolved, and purified water is added to the mixture to obtain a transparent liquid lotion.

5 ml of the lotion may be applied once or twice per day to a site having marked baldness or alopecia.

Example 5

A lotion comprising the following composition shown may be prepared.

	(%)
95% Ethanol	80.0
a heterocyclic ester or amide as defined above	0.005
Hinokitol	0.01
Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
Purified water	19.0
Perfume and dye	q.s.

Into 95% ethanol are added a heterocyclic ester or amide, hinokitol, ethylene oxide (40 mole) adducts of hardened castor oil, perfume, and a dye. The resulting mixture is stirred, and purified water is added to the mixture to obtain a transparent liquid lotion.

The lotion may be applied by spraying once to 4 times per day to a site having marked baldness or alopecia.

Example 6

An emulsion may be prepared from A phase and B phase having the following compositions.

(A phase)	(%)
Whale wax	0.5
Cetanol	2.0
Petrolatum	5.0
Squalane	10.0
Polyoxyethylene (10 mole) monostearate	2.0
Sorbitan monooleate	1.0
a heterocyclic ester or amide as defined above	0.01
(B phase)	(%)
Glycerine	10.0
Purified water	69.0
Perfume, dye, and preservative	q.s.

The A phase and the B phase are respectively heated and melted and maintained at 80°c. Both phases are then mixed and cooled under stirring to normal temperature to obtain an emulsion.

The emulsion may be applied by spraying once to four times per day to a site having marked baldness or alopecia.

Example 7

A cream may be prepared from A phase and B phase having the following compositions.

(A Phase)	(%)
Fluid paraffin	5.0
Cetostearyl alcohol	5.5
Petrolatum	5.5
Glycerine monostearate	33.0
Polyoxyethylene (20 mole) 2-octyldodecyl ether	3.0
Propylparaben	0.3
(B Phase)	(%)
a heterocyclic ester or amide as defined above	0.8
Glycerine	7.0
Dipropylene glycol	20.0
Polyethylene glycol 4000	5.0
Sodium Hexametaphosphate	0.005
Purified water	44.895

The A phase is heated and melted, and maintained at 70°c. The B phase is added into the A phase and the mixture is stirred to obtain an emulsion. The emulsion is then cooled to obtain a cream.

The cream may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 8

A liquid comprising the following composition may be prepared.

	(%)
Polyoxyethylene butyl ether	20.0
Ethanol	50.0
a heterocyclic ester or amide as defined above	0.001
Propylene glycol	5.0
Polyoxyethylene hardened castor oil derivative (ethylene oxide 80 mole adducts)	0.4
Perfume	q.s.
Purified water	q.s.

Into ethanol are added polyoxypropylene butyl ether, propylene glycol, polyoxyethylene hardened castor oil, a heterocyclic ester or amide, and perfume. The resulting mixture is stirred, and purified water is added to the mixture to obtain a liquid.

The liquid may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 9

A shampoo comprising the following composition may be prepared.

	(%)
Sodium laurylsulfate	5.0
Triethanolamine laurylsulfate	5.0
Betaine lauryldimethylaminoacetate	6.0
Ethylene glycol distearate	2.0
Polyethylene glycol	5.0
a heterocyclic ester or amide as defined above	5.0
Ethanol	2.0
Perfume	0.3
Purified water	69.7

Into 69.7 of purified water are added 5.0 g of sodium laurylsulfate, 5.0 g of triethanolamine laurylsulfate, 6.0 g of betaine lauryldimethyl-aminoacetate. Then a mixture obtained by adding 5.0 g of a heterocyclic ester or amide, 5.0 g of polyethylene glycol, and 2.0 g of ethylene glycol distearate to 2.0 g of ethanol, followed by stirring, and 0.3 g of perfume are successively added. The resulting mixture is heated and subsequently cooled to obtain a shampoo.

The shampoo may be used on the scalp once or twice per day.

Example 10

A patient is suffering from alopecia senilis. A heterocyclic ester or amide as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 11

A patient is suffering from male pattern alopecia. A heterocyclic ester or amide as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 12

A patient is suffering from alopecia areata. A heterocyclic ester or amide as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 13

A patient is suffering from hair loss caused by skin lesions. A heterocyclic ester or amide as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 14

A patient is suffering from hair loss caused by tumors. A heterocyclic ester or amide as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 15

A patient is suffering from hair loss caused by a systematic disorder, such as a nutritional disorder or an internal secretion disorder. A heterocyclic ester or amide as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 16

A patient is suffering from hair loss caused by chemotherapy. A heterocyclic ester or amide as identified above, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 17

A patient is suffering from hair loss caused by radiation. A heterocyclic ester or amide as identified above, or a pharmaceutical composition

comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification, they are to be interpreted as specifying the presence of the stated features, integers, steps or components referred to, but not to preclude the presence or addition of one or more other feature, integer, step, component or group thereof.

The claims defining the invention are as follows:

1. A method for treating alopecia or promoting hair growth in an animal in need thereof, comprising administering an effective amount of a nitrogen-containing heterocyclic compound having two or more heteroatoms,

wherein said compound has a substituent $-C(W)-C(Y)-R_2$ which is attached to a nitrogen atom of the heterocyclic ring,

wherein W and Y are independently selected from the group consisting of O, S, CH_2, and two hydrogen atoms, and

wherein said compound is additionally substituted with an ester or amide substituent attached to the heterocyclic ring,

provided that said amide substituent is linked to the heterocyclic ring with a carbon-carbon bond,

wherein R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl, or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

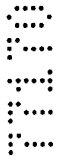
Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

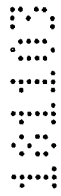
wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

2. The method of claim 1, wherein the compound is of formula I





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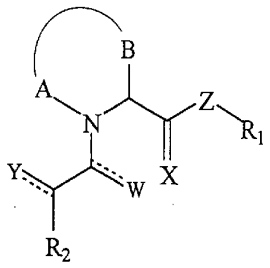


I

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to the nitrogen atom, one or more additional O, S, SO, SO_2, N, NH, or NR_1 heteroatom(s);

X is O or S;

Z is O, NH, or NR_1;

W and Y are independently O, S, CH_2, or two hydrogen atoms;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl,

wherein said R_1 is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-

C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl, or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

Ar_1 and Ar_2 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

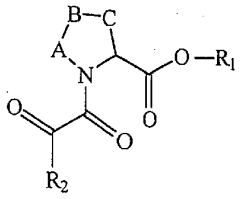
wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

3. The method of claim 2, wherein said Ar_1 or Ar_2 is selected from the group consisting of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, fluorenyl, and phenyl.

4. The method of claim 2, wherein the one or more additional heteroatom(s) in the 5-7 membered saturated or unsaturated heterocyclic ring is NH or NR_1.

5. The method of claim 1, wherein the compound is of formula II



II

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B, and C are independently CH_2, O, S, SO, SO_2, NH, or NR_1, provided that A, B and C are not all CH_2;

R_1 is C_1-C_5 straight or branched chain alkyl or C_2-C_5 straight or branched chain alkenyl,

wherein said R_1 is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$ and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$;

n is 1 or 2;

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

6. The method of claim 5, wherein:

A is CH_2;

B is CH_2 or S;

C is CH_2 or NH;

R_1 is selected from the group consisting of 3-phenylpropyl and 3-(3-pyridyl)propyl; and

R_2 is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, and *tert*-butyl.

7. The method of claim 6, wherein:

B is CH_2;

C is NH; and

R_1 is 3-phenylpropyl.

8. The method of claim 6, wherein:

B is S; and

C is CH_2.

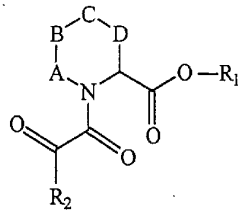
9. The method of claim 5, wherein the compound is selected from the group consisting of:

3-phenyl-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate; and

3-(3-pyridyl)-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine) carboxylate;

or a pharmaceutically acceptable salt, ester, or solvate thereof.

10. The method of claim 1, wherein the compound is of formula III



III

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B, C, and D are independently CH_2, O, S, SO, SO_2, NH, or NR_1, provided that A, B, C and D are not all CH_2;

R_1 is C_1-C_5 straight or branched chain alkyl or C_2-C_5 straight or branched chain alkenyl,

wherein said alkyl or alkenyl is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$ and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$;

n is 1 or 2;

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

11. The method of claim 10, wherein:

A is CH_2;

B is CH_2;

C is S, O or NH;

D is CH_2;

R_1 is selected from the group consisting of 3-phenylpropyl and (3,4,5-trimethoxy)phenylpropyl; and

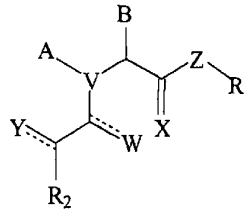
R_2 is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, *tert*-butyl, phenyl, and 3,4,5-trimethoxyphenyl.

12. The method of claim 11, wherein:

C is NH; and

R_2 is 1,1-dimethylpropyl or phenyl.

13. A method for treating alopecia or promoting hair growth in an animal in need thereof, comprising administering an effective



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is N;

A and B, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR;

R is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_9 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_3,

wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar_4;

Ar_3 and Ar_4 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the individual ring size is 5-8 members,

and wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S;

X is O or S;

Z is O, NH, or NR_1;

W and Y are independently O, S, CH_2, or two hydrogen atoms;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl,

wherein said R_1 is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

Ar_1 is independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more

substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy.

14. The method of any one of claims 1-13, wherein the compound is non-immunosuppressive.

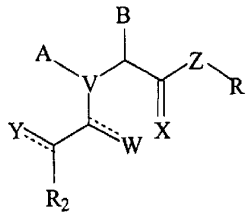
15. The method of any one of claims 1-13, wherein the compound has an affinity for an FKBP-type immunophilin.

16. The method of claim 15, wherein the FKBF-type immunophilin is FKBP-12.

17. The method of any one of claims 1-13, wherein the compound is immunosuppressive.

18. A pharmaceutical composition which comprises:

(i) an effective amount of a compound for treating alopecia or promoting hair growth in an animal, wherein the compound is of formula IV



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is N;

A and B, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR;

R is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_9 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_3,

wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar_4;

Ar_3 and Ar_4 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the individual ring size is 5-8 members,

and wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S;

X is O or S;

Z is O, NH, or NR_1;

W and Y are independently O, S, CH_2, or two hydrogen atoms;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl,

wherein said R_1 is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

Ar_1 is independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

(iii) a pharmaceutically acceptable carrier.

19. The pharmaceutical composition of claim 18, wherein the compound is non-immunosuppressive.

20. The pharmaceutical composition of claim 18, wherein the compound has an affinity for an FKBP-type immunophilin.

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21. The pharmaceutical composition of claim 20, wherein the FKBP-type immunophilin is FKBP-12.

22. The pharmaceutical composition of claim 18, wherein the compound is immunosuppressive.

23. Use of a compound for the preparation of a medicament for treating alopecia or promoting hair growth in an animal in need thereof, wherein said compound is a nitrogen-containing heterocyclic compound having two or more heteroatoms,

wherein said compound has a substituent $-C(W)-C(Y)-R_2$ which is attached to a nitrogen atom of the heterocyclic ring,

wherein W and Y are independently selected from the group consisting of O, S, CH_2, and two hydrogen atoms, and

wherein said compound is additionally substituted with an ester or amide substituent attached to the heterocyclic ring,

provided that said amide substituent is linked to the heterocyclic ring with a carbon-carbon bond,

wherein R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl, or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

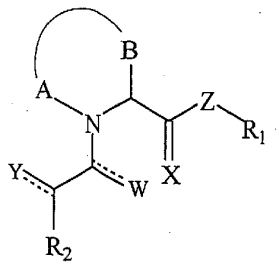
wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6

straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

24. The use of claim 23, wherein the compound is of formula I



I

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to the nitrogen atom, one or more additional O, S, SO, SO_2, N, NH, or NR_1 heteroatom(s);

X is O or S;

Z is O, NH, or NR_1;

W and Y are independently O, S, CH_2, or two hydrogen atoms;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl,

wherein said R_1 is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6

straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl, or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

Ar_1 and Ar_2 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

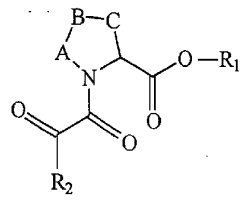
wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

25. The use of claim 24, wherein said Ar_1 or Ar_2 is selected from the group consisting of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, fluorenyl, and phenyl.

26. The use of claim 24, wherein the one or more additional heteroatom(s) in the 5-7 membered saturated or unsaturated heterocyclic ring is NH or NR_1.

27. The use of claim 23, wherein the compound is of formula II



II

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B, and C are independently CH_2, O, S, SO, SO_2, NH, or NR_1, provided that A, B and C are not all CH_2;

R_1 is C_1-C_5 straight or branched chain alkyl or C_2-C_5 straight or branched chain alkenyl,

wherein said R_1 is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$ and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$;

n is 1 or 2;

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

28. The use of claim 27, wherein:

A is CH_2;

B is CH_2 or S;

C is CH_2 or NH;

R_1 is selected from the group consisting of 3-phenylpropyl and 3-(3-pyridyl)propyl; and

R_2 is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, and *tert*-butyl.

29. The use of claim 28, wherein:

B is CH_2;

C is NH; and

R_1 is 3-phenylpropyl.

30. The use of claim 28, wherein:

B is S; and

C is CH_2.

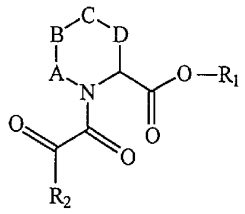
31. The use of claim 27, wherein the compound is selected from the group consisting of:

3-phenyl-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate; and

3-(3-pyridyl)-1-propyl(2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine) carboxylate;

or a pharmaceutically acceptable salt, ester, or solvate thereof.

32. The use of claim 23, wherein the compound is of formula III



III

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B, C and D are independently CH_2, O, S, SO, SO_2, NH, or NR_1, provided that A, B, C and D are not all CH_2;

R_1 is C_1-C_5 straight or branched chain alkyl or C_2-C_5 straight or branched chain alkenyl,

wherein said alkyl or alkenyl is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$ and C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$;

n is 1 or 2;

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1; and

Ar_1 is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or

substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members,

and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

33. The use of claim 32, wherein:

A is CH_2;

B is CH_2;

C is S, O or NH;

D is CH_2;

R_1 is selected from the group consisting of 3-phenylpropyl and (3,4,5-trimethoxy)phenylpropyl; and

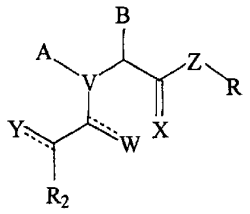
R_2 is selected from the group consisting of 1,1-dimethylpropyl, cyclohexyl, *tert*-butyl, phenyl, and 3,4,5-trimethoxyphenyl.

34. The use of claim 33, wherein:

C is NH; and

R_2 is 1,1-dimethylpropyl or phenyl.

35. Use of a compound for the preparation of a medicament for treating alopecia or promoting hair growth in an animal in need thereof, wherein said compound is of formula IV



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is N;

A and B, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO_2, N, NH, and NR;

R is C_1-C_9, straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_9 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_3,

wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar_4;

Ar_3 and Ar_4 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the individual ring size is 5-8 members, and

wherein said heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S;

X is O or S;

Z is O, NH, or NR_1;

W and Y are independently O, S, CH_2, or two hydrogen atoms;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl,

wherein said R_1 is substituted with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

Ar_1 is independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino,

wherein the individual ring size is 5-6 members, and

wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; and

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy.

36. The use of any one of claims 23-35, wherein the compound is non-immunosuppressive.

37. The use of any one of claims 23-35, wherein the compound has an affinity for an FKBP-type immunophilin.

38. The use of claim 37, wherein the FKBP-type immunophilin is FKBP-12.

39. The use of any one of claims 23-35, wherein the compound is immunosuppressive.

40. The method of any one of claims 1-17, substantially as herein described with reference to any one of the Examples.

41. The pharmaceutical composition of any one of claims 18-22, substantially as herein described with reference to any one of the Examples.

42. The use of the compounds of any one of claims 23-39, substantially as herein described with reference to any one of the Examples.

DATED this 17th day of November, 2003

GPI NIL HOLDINGS, INC.
By their Patent Attorneys:
CALLINAN LAWRIE

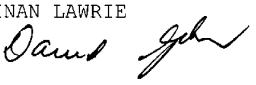


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FIG. 1

FIG.2

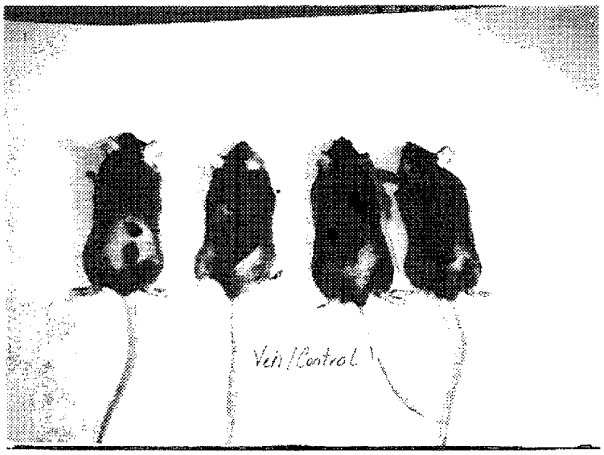


FIG.3

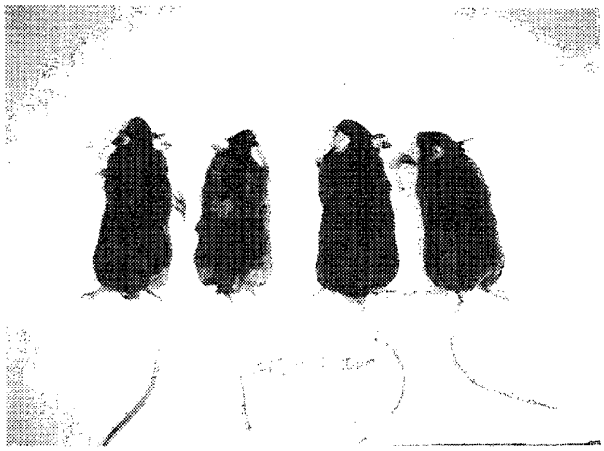


FIG.4

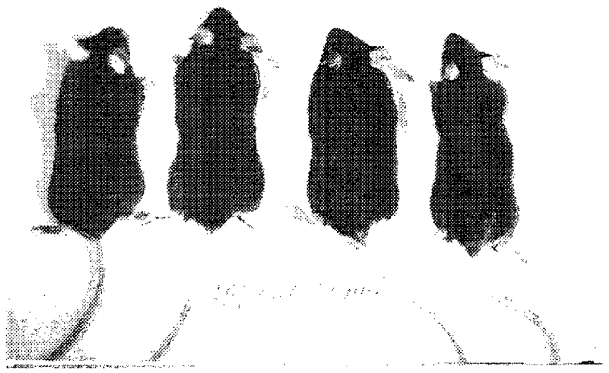
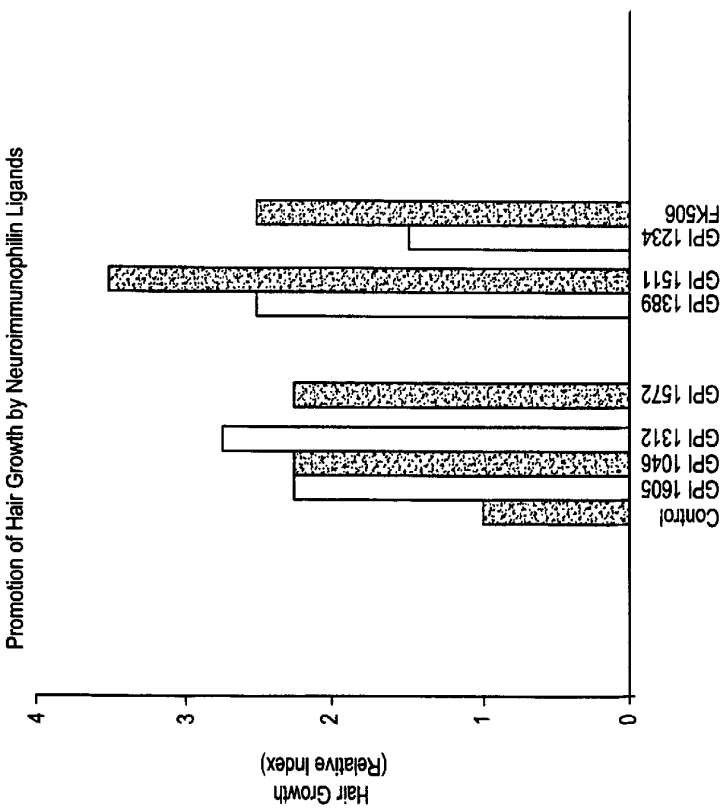


FIG. 5


Promotion of Hair Growth by Neuroimmunophilin Ligands
Hair Growth
(Relative Index)
0
1
2
3
4
Control
GPI 1605
GPI 1046
GPI 1312
GPI 1572
GPI 1389
GPI 1511
GPI 1234
FK506
0 = no growth
1 = beginning of growth in small tufts
2 = hair growth covering over < 25% of shaved area
3 = hair growth covering over > 25% but less than 50% of shaved area
4 = hair growth covering over > 50% but less than 75% of shaved area
5 = complete hair growth of shaved area