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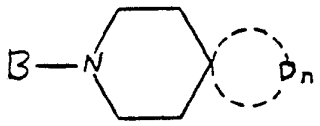

(I)

(57) Abstract

The present invention provides novel compounds as well as known compounds which have been discovered to have important hair growth promoting properties, but which have much less toxicity and antihypertensive properties as compared to minoxidil and can be used at higher concentrations having formula (I) including active isomers, precursors and metabolites thereof, wherein B is a disubstituted heterocyclic N-oxide moiety selected from the group consisting of pyridines, pyrimidines, and triazines, and D_n forms a homocyclic carbon ring or a heterocyclic ring of n members in addition to the para carbon atom of the piperidinyl ring, wherein n equals 2 to 8, and at least two of the ring members D are carbon atoms and the reminder of the ring members, if any, are selected from the group consisting of oxygen, nitrogen, carbon and sulfur, the ring being saturated or unsaturated, and the carbon and nitrogen ring members being substituted or unsubstituted, with the possibility that the substituents, if any, form an additional ring.

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SPIROAZA DERIVATIVES OF HETEROCYCLIC N-OXIDES AND THEIR USE IN HAIR GROWTH PROMOTION

Field of the Invention

This invention relates to novel compositions of matter and methods of their preparation, as well as to known compounds which have now been surprisingly discovered to be useful as hair growth enhancers. These compounds are useful in mammals (e.g. humans and domestic animals) for promotion of hair growth.

Background of the Invention

Various preparations have heretofore been proposed for the treatment of male pattern baldness. It is also a matter of common knowledge, however, that none of the so-called "hair growth formulae" have proven to be very efficacious.

In contrast to most epithelial structures, the hair follicle does not grow continuously throughout its life, but passes through a cycle called the pilar cycle. The pilar cycle comprises essentially three phases -- namely, the anagen or growth phase during which hair is produced, normally lasting about three to seven years; the catagen phase when growth stops and the follicle atrophies, lasting about three to four weeks; and the telogen phase, which is a rest period for the follicle during which the hair

progressively separates and finally falls out, and normally lasting about three to four months. Normally 80 to 95 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. Whereas the telogen phase hair is uniform in diameter with a slightly bulbous, non-pigmented root, the anagen phase hair has a large colored bulb at its root.

Alopecia results when the pilar cycle is disturbed, resulting in excessive hair loss. The most frequent phenomenon is a shortening of the hair growth 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. This shortening of the growth or anagen phase of the pilar cycle may have different origins, among which are very diverse pathological origins such as febrile conditions, mental stresses, hormonal problems (such as androgenetic alopecia due to male hormone sensitivity) and secondary effects of drugs. Alopecia may also be due to age and to a slowing down of mitotic activity. This dysfunction of the biological mechanism of hair growth leading to alopecia may be regarded as a disease. While there are other causes of alopecia such as greasy or oily scalp due to seborrhea and the dandruff accompanying it, the present invention is not directed to treating these extraneous causes of

alopecia, but rather to treating the organic dysfunction of the hair follicle.

Minoxidil, a potent antihypertensive, is well known in the literature as a hair growth promoting agent (see U.S. Patents 3,461,461; 3,973,016; and 3,464,987). However, it has many undesirable systemic side effects. When the topical compound is absorbed, the systemic side effects include fluid retention, tachycardia, dyspnoea, gynaecomastia, fatigue, nausea and cardiotoxicity.

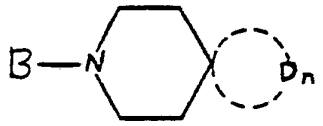
There is presently a search for analogs, derivatives or other compounds of the minoxidil type which would still possess hair growth activity without the undesirable systemic effects associated with minoxidil. My prior published PCT patent applications US85/00556 (WO85/04577) and US85/01329 (WO86/00616) describe certain pyrimidine oxides (oxamates and carbamates) which are similar to minoxidil and have been found to be useful in hair growth promotion.

Brief Summary of the Invention

The present invention provides novel compounds as well as known compounds which have been discovered to have important hair growth promoting properties, particularly increasing and stimulating hair growth on mammalian skins, prolonging the anagen phase of the hair cycle, and converting vellus hair to growth as terminal hair, but which have much less toxicity and

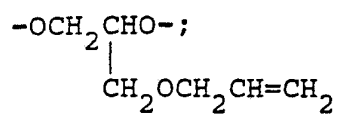
antihypertensive properties as compared to minoxidil and can be used at higher concentrations.

According to the present invention, novel compounds have been found of the formula:



(I)

including active isomers, precursors and metabolites thereof, wherein B is a disubstituted heterocyclic N-oxide moiety selected from the group consisting of pyridines, pyrimidines, and triazines, and D_n forms a homocyclic carbon ring or a heterocyclic ring of n members in addition to the para carbon atom of the piperidinyl ring, wherein n equals 2 to 8, and at least two of the ring members D are carbon atoms and the reminder of the ring members, if any, are selected from the group consisting of oxygen, nitrogen, carbon and sulfur, the ring being saturated or unsaturated, and the carbon and nitrogen ring members being substituted or unsubstituted, with the possibility that the substituents, if any, form an additional ring, but when B is 2,4-diamino-pyrimidine-3-oxide, D_n is not any of the following: $-CONHCONH-$; $-CH_2NHCOO-$; $-(CH_2)_5-$; $-O(CH_2)_3O-$; $-OCH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}-CH_2O-$ (with CH_2OH on the quaternary carbon); $-O(CH_2)_2O-$; $-OCH_2\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}HO-$; $-OCH_2\underset{\displaystyle CH_2OH}{\overset{\displaystyle |}{C}}HO-$;



$-OCH_2CHO-$; $-S(CH_2)_2S-$

$CH_2OCH_2CH=CH_2$

Moreover, it has been unexpectedly found that the above novel compounds, as well as the known compounds specifically excluded from the above formula, are useful in increasing the rate of hair growth on mammalian skins by applying to the skin an effective amount of a composition containing the compound. The hair growth promotion compositions of the invention may also contain a retinoid.

Detailed Description of the Preferred Embodiments

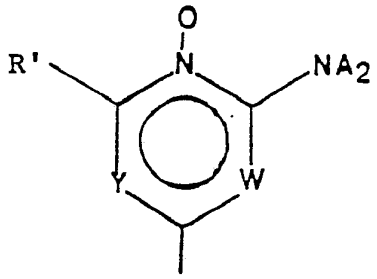
The present invention provides an important advance in the search for compounds which will be more effective for promoting hair growth, and can be used topically at higher concentrations than is possible with minoxidil. As used herein, when referring to the promotion of hair growth or increasing the rate of hair growth, it will be understood that one of more of the following is meant: increasing the rate of hair growth on the scalp; stimulating hair follicles of the skin; prolonging the anagen phase of the hair cycle; converting vellus hair to growth as terminal hair; and/or treating alopecias caused by organic dysfunction of the hair follicle.

As indicated by Formula I above, the novel and known compounds of the present invention are formed by the union of an N-oxide moiety or

subunit represented by the letter B and a spiroaza moiety in which the nitrogen atom of the piperidinyl ring of the spiroaza moiety is attached to the N-oxide moiety. It is believed that the N-oxide site is a primary active site in compounds capable of promoting hair growth.

Many of the N-oxide subunits are known per se in the art and are described particularly as parts of molecules useful in the treatment of hypertension. Such compounds include the N-oxide pyrimidines, which are described for example in U.S. Patents 3,461,461; 3,973,016; and 3,464,987, and British Patent 1,486,682. N-oxide pyridines are disclosed for example in U.S. Patent 4,021,562. Further, the known compounds of Formula I, which are excluded by the definition following formula I, are described in A. Catto, et al., "2,4 Diamino-6-Piperidinil e 6-Piperazinilpirimidine 3-Ossido, Nuovi Analoghi Del Minossidile" Boll. Chim. Farm., 121:16-26 (1982). However, in this article, these compounds are described only as useful in the treatment of hypertension, and not in the promotion of hair growth.

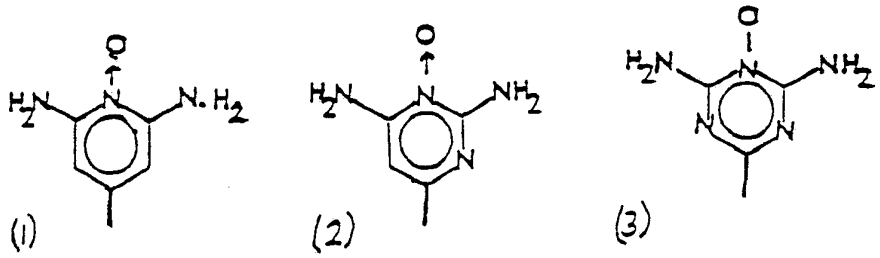
The B moieties useful in the compounds of Formula I are generally described as di-substituted heterocyclic N-oxide moieties, which are similar to those present in minoxidil and its analogs. Such N-oxide moieties may be represented by the following formula:



(II)

wherein W and Y are nitrogen or carbon atoms and may be the same or different; each A may be independently selected from hydrogen or substituted or unsubstituted alkyl, cycloalkyl, alkoxy, halo, haloalkyl, haloalkoxy, haloaryl, alkenyl or aryl groups, wherein the substituents on these groups may be alkyl, halo or alkoxy; R' is A or NA_2. Preferably, the A groups are either hydrogen or lower alkyl, but other substituents include, for example, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower alkaryl, lower aralkyl, lower alkaralkyl, lower alkoxyaralkyl, lower haloaralkyl, lower alkylphenylthio, and halophenylthio, and may additionally be carboxyacyl. As used herein, the term "lower" means C_{1-8} for aliphatic substituents and C_{6-16} for aromatic substituents. The unattached bond at the ring position para to the N-oxide group is the position for attachment of the B moiety to the spiroaza moiety of Formula I.

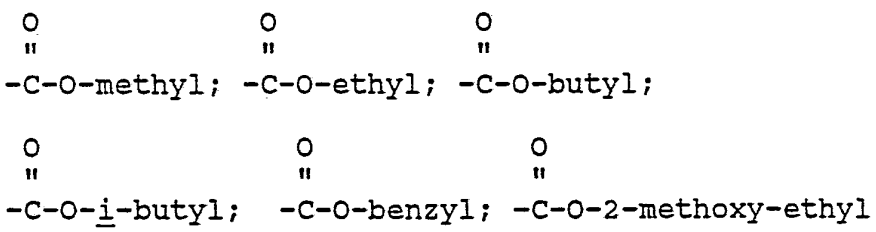
Exemplary B moieties of the present invention are illustrated as follows:



(1) (2) (3)

Thus, where Y and W are both carbon, the heterocylic B moieties have a single nitrogen atom in the ring and may be referred to as pyridines; where one of Y and W is carbon and the other is nitrogen, the heterocyclic rings have two nitrogen atoms and may be referred to as pyrimidines; and where Y and W are both nitrogen, the heterocyclic rings have three nitrogen atoms and may be referred to as triazines.

As shown in the above exemplary Formulas (1), (2) and (3), both A groups are preferably hydrogen. Other preferred substituents on the heterocyclic N-oxide B moieties are amines substituted with carboxyacyl groups. Examples of such pyrimidine B moieties are described in my published PCT patent applications US85/00556 (WO85/04577) and US85/01329 (WO86/00616), the disclosures of which are incorporated herein by reference. In such B moieties, one of the A groups on each amine substituent is hydrogen, while the other is a carboxyacyl group. The carboxyacyl groups may be, for example:



in which case the substituents are referred to as carbamates, or the carboxyacyl groups may be, for example:

O O O
" " "
-C-C-O-methyl; -C-C-O-ethyl; -C-C-O-butyl;

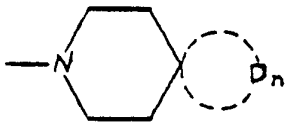
O O
" "
-C-C-O-i-butyl; -C-C-O-benzyl;

O
"
-C-C-O-2-methoxy-ethyl

in which case the substituents are referred to as oxamates.

While compounds (1), (2) and (3), as well as Formula (II) set forth above, are shown in the standard unsaturated ring form, it will be understood that the tautomeric forms of the compounds in which an amino substituent adjacent to the N-oxide group becomes an imino substituent are also included, as well as the solvated forms of the compounds.

The spiroaza moieties useful in the present invention are of the formula:



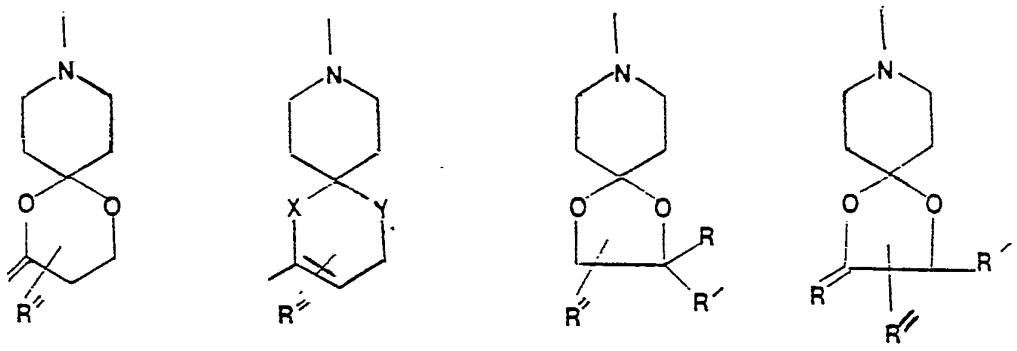
(III)

wherein D_n is as described above and the unattached bond from the nitrogen atom is attached to a B moiety of Formula II as shown in Formula I.

The spiroaza moieties represented by Formula III have a ring which may contain n=2 to

n=8 members which may be homocyclic carbon rings or heterocyclic analogues in which the spirocyclic ring D_n may incorporate one or more similar or dissimilar heteroatoms including oxygen, sulfur or nitrogen. In addition, the spiro ring may also incorporate one or more trigonal centers on which an exocyclic substituent may reside, such as methylene, oxygen, sulfur and nitrogen components. This is dictated by thermodynamic factors and available sites. The alkenyl exocyclic double bond may also be endocyclic as thermodynamic or chemical factors dictate.

For example, ring D_n may bear one or more alkyl substituents. These substituents may be isomeric in character including cis/trans counterparts where appropriate and/or bear substituent groups taken from the list below. Examples of such spiroaza moieties are shown below:



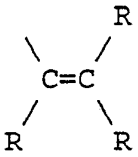
wherein R, R′ and R′′ may be the same or different and are preferably alkyl but may be selected from

the groups below, and X and Y may be carbon, nitrogen, oxygen or sulfur.

Similar or dissimilar alkyl substituents may occupy positions on ring D_n where appropriate and may be geminal (on same sites) in character or occupy various different positions on the ring.

In like manner, substituents other than alkyl may be introduced in the manner prescribed for alkyl groups and may include in addition to alkyl and substituted alkyl one or more groups chosen from the series detailed below:

Alkenyl, mono, Di and Tri substituted alkenyl



Hydroxy and substituted hydroxyl (-OH and -OR)

Amino and Sec-Amino ($-NH_2$ and -NHR)

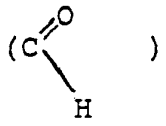
Sulfides (-S-)

Halo (-F, -Cl, -Br)

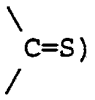
Nitro ($-NO_2$)

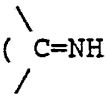
Alkynyl and substituted alkynyl (-C≡C-H and -C≡C-R)

Formyl

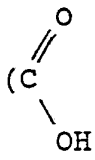
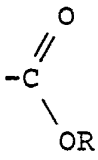


Keto and substituted keto ()

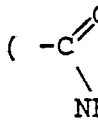
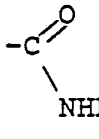
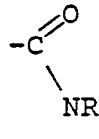
Thioketones and substituted thioketones ()

Imino and substituted Imino ( and C=N-R)

Carboxy and substituted carboxy

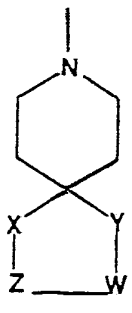
 and 

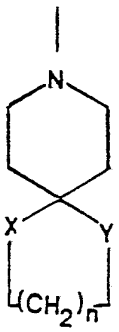
Carboxyamides mono and disubstituted carboxyamides

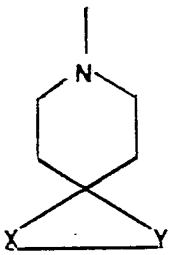
( ,  , )

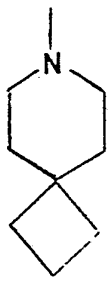
Cyano (-C=N)

Further examples of spiroaza moieties include:

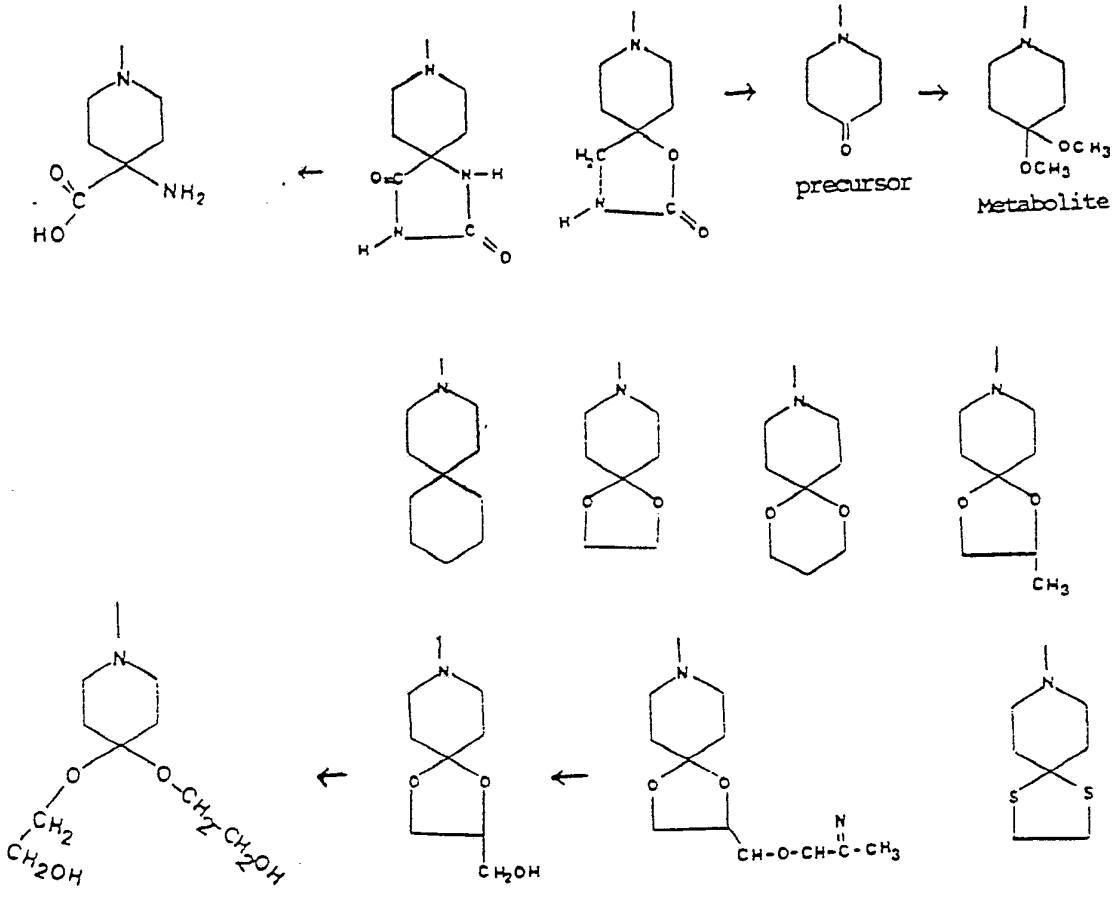


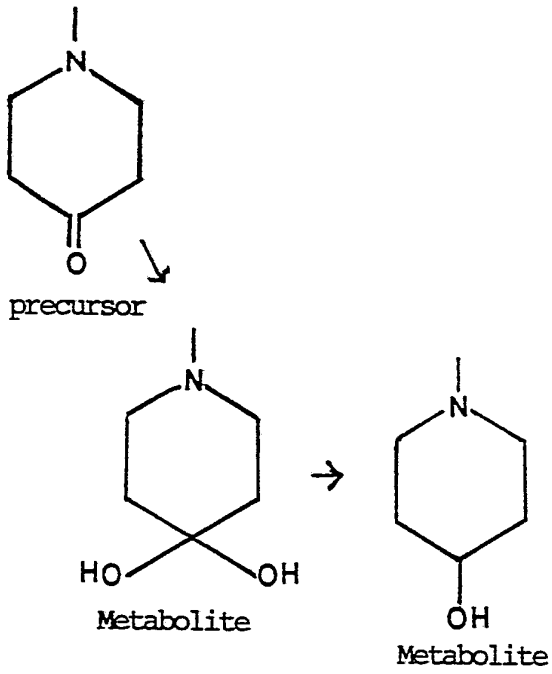


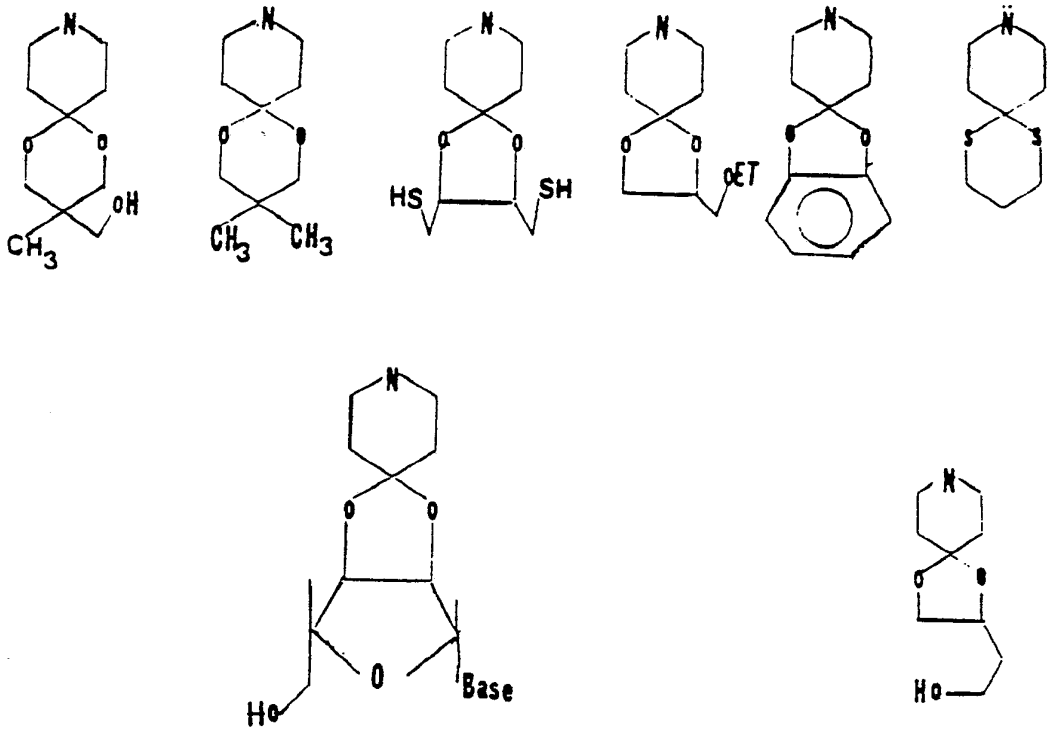




X, Y, Z and W may be different or may be methylene. Still further examples of spiroaza moieties as well as their precursors and metabolites are shown below:

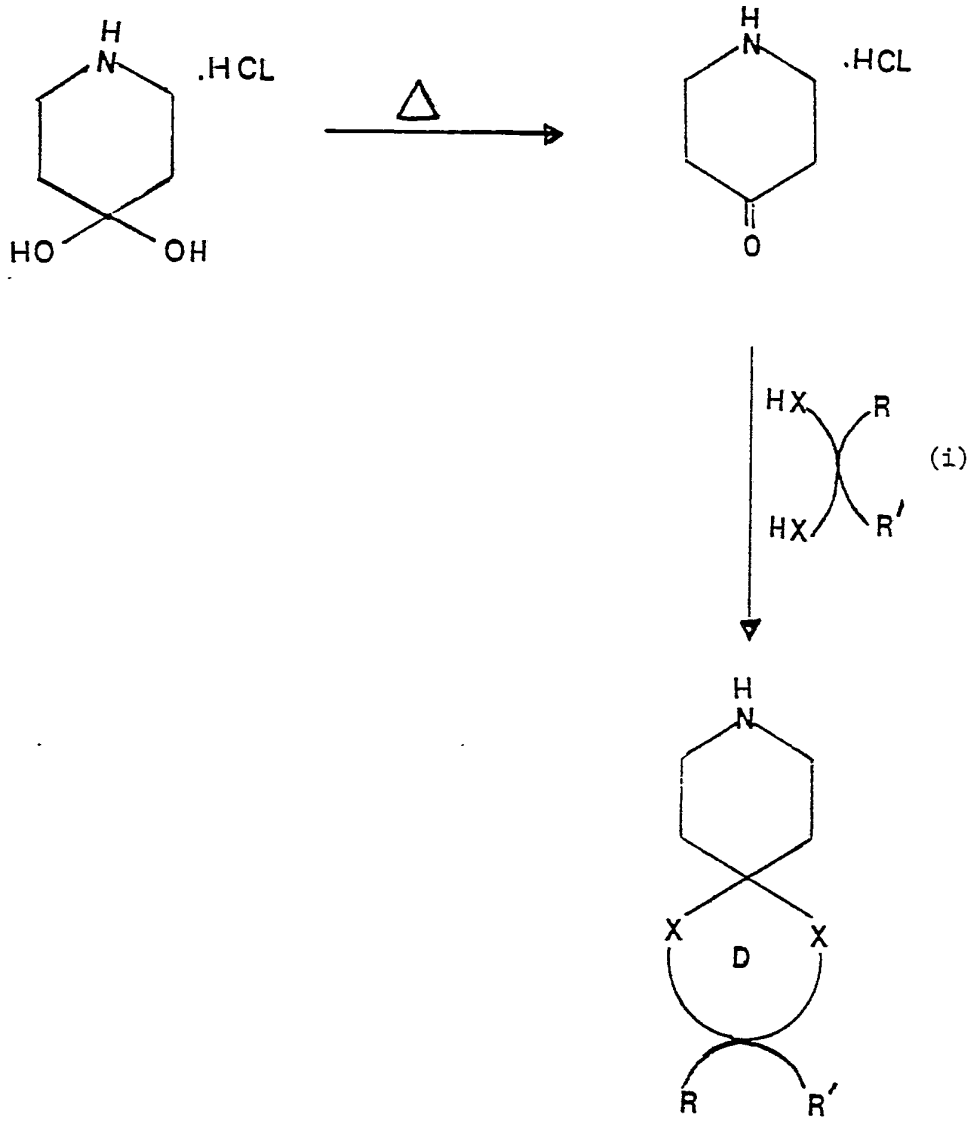



N
O
precursor
N
HO
OH
Metabolite
N
OH
Metabolite



The novel compounds of the invention, as well as the known compounds useful in the methods of the invention, can be formed by generally straightforward processes either known in the art or which will be evident to those of ordinary skill in the art. For example, halogenated compounds of Formula II, wherein the substituent para to the N-oxide group is a chlorine or bromine atom, for example, may be reacted with hydrides of the spiroaza moieties, i.e., compounds in which the spiroaza moieties have hydrogen atoms on the nitrogen bonds to which the B moieties are to be attached. Preferably, the compounds are reacted in the presence of an unreactive solvent.

The spiroaza moieties may be readily produced by methods known in the art, such as the following:

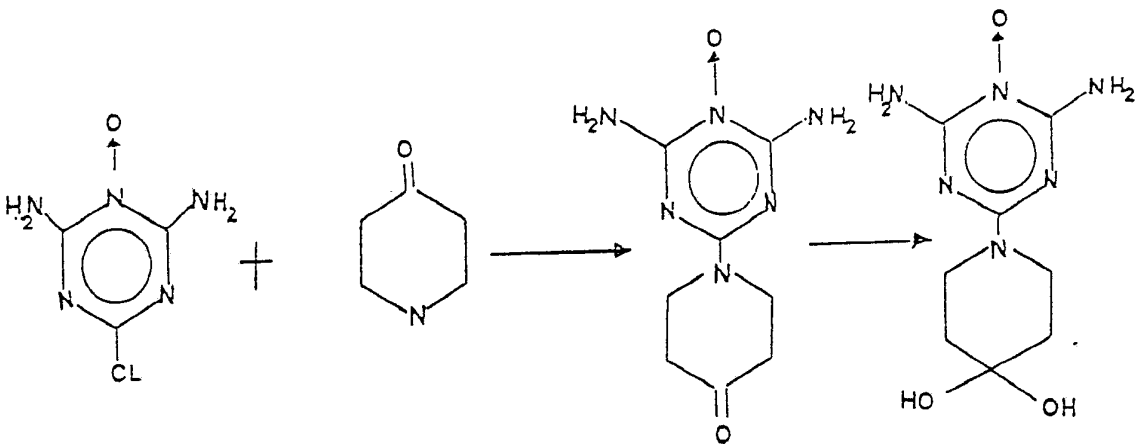


X = O, S, N or C

R = H, alkyl, aryl, substituted with any polar functional groups such as OH, COOH, COOR, NH_2 or ester.

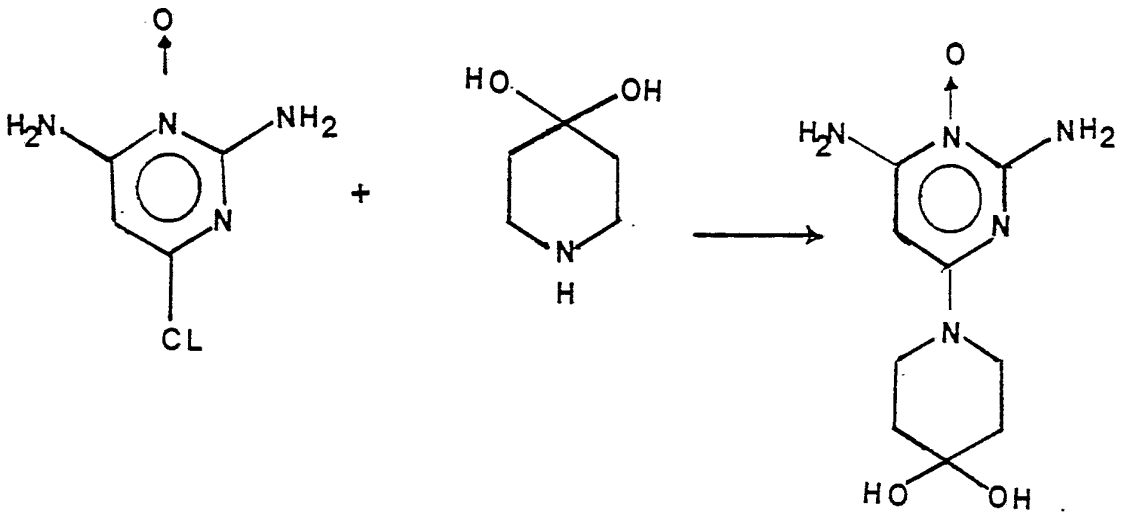
Preparation Example A

A mixture of 2,6-diamino, 4-chloro-triazine-N-oxide 1 (10g) and 4-piperidone (12g) in isopropyl alcohol and 100 ml potassium carbonate (20g, 142 mmole) and water (5 ml) was stirred under reflux for 20 hours. The resulting mixture was cooled and filtered. The filtrate was concentrated to one fourth of its original volume. Acetone (200 ml) was added. A white solid was obtained, recrystallization was accomplished with isopropyl alcohol-petroleum ether, then with H_2O to yield white crystals.

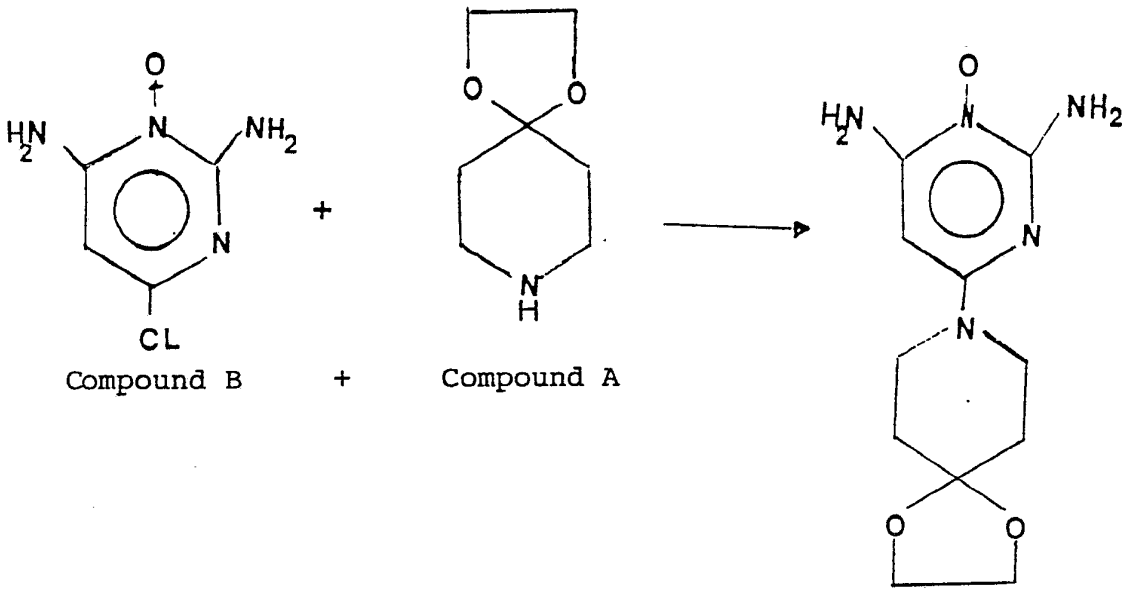


Preparation Example B

A mixture of 2,6-diamino, 4-chloro-pyrimidine-N-oxide 1 (10g, 67 mmole) and 4,4-dihydroxypiperidine HCl (12g, 100 mmole), and isopropyl alcohol, 100 ml potassium carbonate (20g, 142 mmole) and water (5 ml) was stirred under reflux for 20 hours. The resulting mixture was cooled and filtered. The filtrate was concentrated to one fourth of its original volume. Acetone (200 ml) was added. A white solid was obtained.



Preparation Example C



Compound B + Compound A

A mixture of 2,6-diamino, 4-chloro-pyrimidine-N-oxide 1 (Compound B) (10g, 67 mmole) and Compound A above (100 mmole) + isopropyl alcohol + 100 ml potassium carbonate (20g, 142 mmole) and water (5 ml) was stirred under reflux for 20 hours. The resulting mixture was cooled and filtered. The filtrate was concentrated to one fourth of its original volume. Acetone (200 ml) was added. A white solid was obtained, recrystallization was accomplished with isopropyl alcohol-petroleum ether, then with H_2O to yield white crystals.

Where it is desired to form carboxyacylates, e.g., carbamates or oxamates of these compounds, the reaction product described above can be reacted with a suitable carboxyacylating agent.

Although substantially any carboxyacylating agent can be used to produce these carboxyacylates, especially suitable are the anhydrides, mixed anhydrides and acid chlorides of alkanoic, cycloalkanoic, alkenoic, cycloalkenoic, aralkanoic, aromatic and heterocyclic carboxylic acids. These anhydrides and acid chlorides can also have substituents on any carbon except the carbonyl carbon with any of a wide variety of atomic or molecular moieties unreactive with the amine groups on the B moieties. Examples of such substituents are alkyl, e.g., methyl, butyl, decyl; alkoxy, e.g., methoxy, ethoxy, pentyloxy; aklythio, e.g., methylthio, propylthio, heptylthio; dialkylamino, e.g., dimethylamino, diethylamino, dihexylamino; alkoxycarbonyl, e.g., methoxycarbonyl, propoxycarbonyl, nonoxycarbonyl; carboxyacyl, e.g., acetyl, butyryl; carboxamido, e.g., benzamido, aetamido; nitro; fluoro; cyano and the like. Chlorine, bromine and iodine can also be substituents on aromatic portions of carboxyacylating agents.

Examples of suitable anhydrides which can be reacted as the carboxyacylating reagents are acetic anhydride, propionic anhydride, butyric anhydride, isobutyric anhydride, acrylic anhydride, crotonic anhydride, cyclohexane-carboxylic anhydride, benzoic anhydride, napthoic anhydride, furoic anhydride and the like, as well as the corresponding anhydrides substituted with one or more of the above-mentioned substituents. Examples of suitable acid chlorides are acetyl chloride,

propionyl chloride, butyryl chloride, isobutyryl chloride, decanoyl chloride, acryloyl chloride, crotonoyl chloride, cyclohexanecarbonyl chloride, 3-cyclohexenecarbonyl chloride, phenylacetyl chloride, succinyl chloride, benzoyl chloride, naphthoyl chloride, furoyl chloride, ethyl oxalyl chloride, ethyl chloroformate, 3-pyridinecarbonyl chloride, phthaloyl chloride and the like, as well as the corresponding acid chlorides substituted with one or more of the above-mentioned substituents.

At least one molecular equivalent of carboxyacylating agent should be used for the introduction of each carboxyacyl moiety. When reactive carboxyacylating agents such as acetic anhydride are used, a diacyl compound is usually obtained even with only one molecular equivalent of carboxyacylating agent. In such cases, some of the amine groups on the B moieties do not form carboxyacylates.

The carboxyacylation usually takes place rapidly in the range of -20 to about +50^{o}C. Suitable diluents are ethers; e.g., diethyl ether or tetrahydrofuran; ketones, e.g., acetone or methylethyl ketone; esters, e.g., methyl acetate or ethyl acetate; acetonitrile; pyridine and the like. The desired carboxyacylate often separates from the reaction mixture in crystalline form and can be separated in the usual manner; for example, by filtration or centrifugation. Alternatively, the diluent can be evaporated, preferably at reduced pressure. The carboxyacylates can be purified by

conventional techniques; for example, by recrystallization from a suitable solvent or mixture of solvents.

Use in Hair Growth Promotion

The novel compounds of the invention as described above, as well as the similar compounds described by Catto, et al., are relatively weak and non-toxic when administered orally as antihypertensive agents. It has been unexpectedly discovered that the subject compounds, when applied topically to mammalian skin, in an effective amount, can stimulate or improve the rate of hair growth and prolong the anagen phase of the hair cycle. Moreover, these compounds can be used in high concentrations in topical solutions and can be effective in treatment of alopecia. Typically, these compounds are useful as the active ingredients of different types of preparations such as lotions, solutions, ointments, creams, sprays and the like.

Moreover, the compounds of the present invention which form the active ingredients in the hair treatment preparations can be used in combinations with retinoids as described in my published PCT patent applications US81/00338 (WO82/02833) and US82/01593 (WO83/02558), in that these combinations can exhibit synergism. The combinations can improve or stimulate the rate of hair growth to a greater extent than the individual active ingredients of the combinations alone. Suitable retinoid active ingredients for use in

this invention include, for example, derivatives of retinoic acid which have been described in PCT applications US81/00338 and US82/01593, the disclosures of which are incorporated herein by reference.

Preparations such as lotions, creams, conditioners, and the like, including the aforementioned compounds as the active ingredients, can be applied topically to the skin for stimulating or improving the rate of hair growth. It has surprisingly been discovered that the compounds of the present invention are not very toxic, in comparison with minoxidil, and when applied topically to the skin in high concentration have excellent penetration and a long lasting effect, in producing hair growth in an animal model for androgenetic alopecia. Furthermore, retinoids in combination with the subject compounds of this application can exhibit synergism in the animal model studied.

The term "topical" as employed herein, relates to the use of the above compounds, incorporated in a suitable pharmaceutical carrier, and applied at the site of baldness for exertion of local action. Accordingly, such topical compositions include those pharmaceutical forms in which the compound is applied externally by contact with the skin surface to be treated. Conventional pharmaceutical forms for this purpose include ointments, lotions, pastes, jellies, sprays, aerosols, and the like. The term "ointment" embraces formulations (including creams) having

oleaginous, absorptive, water-soluble and emulsion-type bases; e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

The percentage by weight of the compounds of the invention utilized preferably ranges from about 1% to about 20% of the pharmaceutical preparations; the aforesaid pharmaceutical carriers for topical application constitute a major amount of the preparation.

The active compounds may also be used in a free flowing bead formulation by entrapment with a syneresis-free polymeric network which is hydrophobic. Loading as great as 60-80% should be achieved within the polymeric lattice. In this matrix the functional hair growth agent is held by microsorption and protected from hydrolysis and other modes of decomposition, providing prolonged shelf-life and in a form superior to an emulsion.

In this manner it is possible to hold the functional materials under controlled conditions for availability on demand. This system offers the advantage that retinoids, see PCT US82/01593, can be incorporated as additional functional materials, within a similar polymeric network. The structural integrity of the polymer matrix can be disrupted by mechanical stress or force such as rubbing on application to produce a continuous film of the released active component. This protection is particularly important when one or more of the active ingredients has a short half-life, in the absence of encapsulation and upon release.

The pharmaceutical compositions contemplated by this invention include pharmaceutical compositions suited for topical and systemic action.

The following Examples illustrate the administration vehicles for the present invention. The methods of administration may vary by lotion, cream, ointment, polymeric beadlets, supplement to chow, coating for seeds, etc. These Examples are only meant to be illustrative and do not limit the mode of administration nor the ingredients which can be admixed to the present invention, nor the amount which may be used.

Example 1
Lotion Formulation for
Topical Administration

Ingredients	Wt. Percent
2,4-diamino-6-N-(1,5-dioxa-9-azaspiro[5,5]undecane)-pyrimidine-3-oxide	10.0
Ethanol	q.s. to 100.0
Propylene glycol	15.0
Butylated hydroxytoluene	0.1
Water	20.0

Example 2
Cream Conditioner for
Topical Administration

Ingredients	Wt. Percent
2,4-diamino-6-N-(1,5-dioxa-9-azaspiro[5,5]undecane)-pyrimidine-3-oxide	10.0
Distilled Water	q.s. to 100.0
Cetrimonium Chloride	5.0
Cetyl alcohol	4.0
Ethanol	4.0
Butylated hydroxytoluene	1.0
Hydrolyzed animal protein	0.5
Methylparaben, propylparaben	0.1
Stabilizer	0.1

Example 3
Ointment for Topical Administration

All-trans retinoic acid (0.1 gram) and 10 grams of 2,4-diamino-6-N-(1,5-dioxa-9-azaspiro-[5,5]undecane)-pyrimidine-3-oxide are dissolved in 100 ml of acetone, and the solution admixed with 900 grams of USP grade hydrophilic ointment to a uniform consistency; one gram of butylated hydroxytoluene is added. The water washable cream ointment thus prepared consists of 0.1% retinoic acid and 10% of the N,N-substituted piperazine.

Example 4
Polymeric Beadlets
for Topical Administration

Ingredients	Amount
2,4-diamino-6-N-(1,5-dioxa-9-azaspiro[5,5]undecane)-pyrimidine-3-oxide	10 gram
13-cis retinoic acid	25 mg.
Emolient Base	100 ml.

The active ingredients in this example are entrapped within an acrylate copolymer. The hydrophobic polymer is plasticized by most entrapped ingredients. The degree of plasticization determines whether the beads are soft, spreadable, and film-forming with minimal pressure or hard with the ability to withstand shearing of light intensity.

Hairgrowth Data

A rodent model of hypotrichosis has been developed which is useful as an animal model of androgenetic alopecia. The model displays some of the characteristics of male pattern alopecia in humans.

Extreme hair loss is developed after puberty in males. It is typified by initial hair loss on the crown of the head, continuing to the development of hypotrichosis in these animals, as shown by fewer and smaller hair follicles and greatly enlarged sebaceous glands, especially over the crown of the head and the shoulders and upper back. The limbs tend to remain hairy. The females eventually develop male pattern alopecia but not to the same degree as the males.

On topical application of the active compounds of the invention in up to a 20% concentration in a solution of 20% propylene glycol, 60% ethanol and 20% water, a decrease in hair loss was observed. A significantly prolonged anagen phase of the hair cycle was observed, associated in a dose response fashion with the

topical application of the active compound. An increase in the amount of hair and an increased rate of hair growth were also associated with the topical administration of the active compounds as measured by microscopic measurement of the outgrowth of hair after bleaching or dyeing the hair.

Increases in the rate of hair growth and the amount of hair growth varied with the topical application of the compounds. The active compounds caused an increase of more than 30% in the amount of hair growth found over the amount of growth found in animals treated with the placebo lotion.

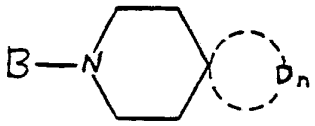
The unexpected novel advantages to be gained from the use of the instant invention are: improved solubility and improved stability and activity of active compounds and the increased percutaneous absorption leading to longer action of compounds; the excellent penetration of skin is due in part to the hydrophilic and lipophilic substituents; and compatibility of compounds with non-polar solvents useful for the preservation of the polar groups while in contact with the skin. Furthermore, the less-toxic nature of these compounds allows a greater concentration of the active compound to be applied topically without unwanted side effects.

Although preferred embodiments have been described and various modifications thereto suggested, the invention is not limited to the preferred embodiments or the suggested

modifications, but is rather defined by the accompanying claims.

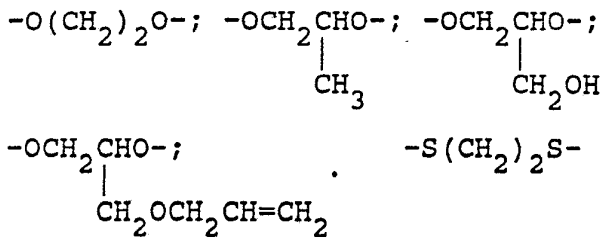
CLAIMS

1. A compound of the formula:

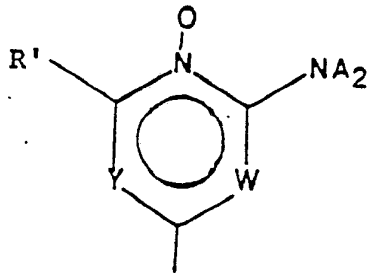


(I)

including active isomers, precursors and metabolites thereof, wherein B is a disubstituted heterocyclic N-oxide moiety selected from the group consisting of pyridines, pyrimidines, and triazines, and D_n forms a homocyclic carbon ring or a heterocyclic ring of n members in addition to the para carbon atom of the piperidinyl ring, wherein n equals 2 to 8, and at least two of the ring members D are carbon atoms and the reminder of the ring members, if any, are selected from the group consisting of oxygen, nitrogen, carbon and sulfur, the ring being saturated or unsaturated, and the carbon and nitrogen ring members being substituted or unsubstituted, with the possibility that the substituents, if any, form an additional ring, but when B is 2,4-diamino-pyrimidine-3-oxide, D_n is not any of the following: $-CONHCONH-$; $-CH_2NHCOO-$; $-(CH_2)_5-$; $-O(CH_2)_3O-$; $-OCH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_2OH}{C}}-CH_2O-$;



2. A compound according to claim 1 where B is a moiety of the formula:



(II)

wherein W and Y are nitrogen or carbon and are the same or different; each A is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyalkyl, cycloalkyl, aryl, aralkyl, alkaryl, alkaralkyl, alkoxyaralkyl, haloaralkyl and carboxyacyl; and R′ is A or NA_2.

3. A compound according to claim 2 wherein both A are hydrogen.

4. A compound according to claim 2 wherein one A on each amine group is hydrogen and the other is carboxyacyl.

5. A compound according to claim 2 wherein W and Y are both carbon, both A and hydrogen.

6. A compound according to claim 2 wherein W and Y are both nitrogen, both A are hydrogen.

7. A compound according to claim 2 wherein one of W and Y is nitrogen.

8. A compound according to claim 2 wherein B is a dicarbamate.

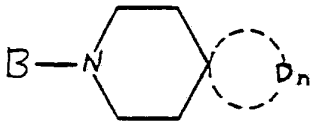
9. A compound according to claim 2 wherein B is a dioxamate.

10. A compound according to claim 1 wherein D_n forms a homocyclic carbon ring.

11. A compound according to claim 1 wherein D_n is $(CH_2)_n$.

12. A compound according to claim 1 wherein D_n forms a heterocyclic ring.

13. A method of increasing the rate of hair growth on mammalian skins which comprises topically applying to the skin an effective amount of a composition comprising a compound of the formula:

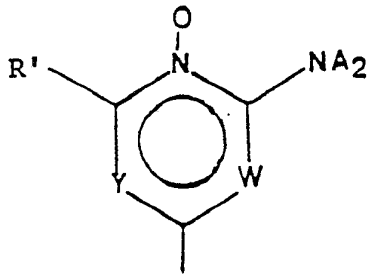


(I)

including active isomers, precursors and metabolites thereof, wherein B is a disubstituted

heterocyclic N-oxide moiety selected from the group consisting of pyridines, pyrimidines, and triazines, and D_n forms a homocyclic carbon ring or a heterocyclic ring of n members in addition to the para carbon atom of the piperidinyl ring, wherein n equals 2 to 8, and at least two of the ring members D are carbon atoms and the reminder of the ring members, if any, are selected from the group consisting of oxygen, nitrogen, carbon and sulfur, the ring being saturated or unsaturated, and the carbon and nitrogen ring members being substituted or unsubstituted, with the possibility that the substituents, if any, form an additional ring.

14. A method according to claim 13 wherein B is a moiety of formula:



(II)

wherein W and Y are nitrogen or carbon and are the same or different; each A is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyalkyl, cycloalkyl, aryl, aralkyl, alkaryl, alkaralkyl, alkoxyaralkyl, haloaralkyl, lower carboxyacyl and R′ is A or NA_2.

15. A method according to claim 14 wherein both A are hydrogen.

16. A method according to claim 14 wherein one A on each amine group is hydrogen and the other is carboxyacyl.

17. A method according to claim 14 wherein said composition also contain a retinoid.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/00658

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC IPC 4: C07D

239/02,239/04,239/70.241/04,295/00,295/02,295.04,295/08,295/22
401/02,401/06,401/08,403/02,403/06.403/14 ,471/00,471/02, *

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	544/14, 245, 255, 312, 323, 358, 359, 364, 374, 382, 546/330 548/262, 325, 335

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X Y	BOLL, CHIM. FARM. 121 (1982) 16-26. "2,4-DIAMINO-6-PIPERIDINIL e 6-PIPERAZINIL-PIRIMIDINE 3-OSSIDO, NUOVI ANALOGHI DEL MINOSSIDIE", CATTO. SEE THE ABSTRACT AND THE TABLE	1-12 1-17
A	HELVETICA CHIMICA ACTA VOL. 65, FASC. 5 (1982) -Nr-142 "REGIOSELECTIVE SYNTHESIS OF 2-OXO-2,8-DIHYDRO_[1,2,4]-OXADIAZOLO-[2,3,-a] PYRIMIDINE-7-CARBAMATES: A NEW CLASS OF ANTIHYPERTENSIVE PERIPHERAL VASODILATORS" MULLER. SEE SCHEME 1 AND SCHEME 2, PAGES 1446 AND 1447.	1-17

* Special categories of cited documents: [10]

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

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

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

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

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

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

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

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 APRIL 1988	19 MAY 1989
International Searching Authority	Signature of Authorized Officer
ISA/US	NATHAN M. NUTTER

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

*

Continued from second sheet

471/08, 471/12, 471/18, 487/02, 487/08,
491/02, 491/08, 498/02, 498/22

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.