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Use of angiogenesis suppressors for inhibiting hair growth

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(54) Title: USE OF ANGIOGENESIS SUPPRESSORS FOR INHIBITING HAIR GROWTH

(57) Abstract

A method of inhibiting hair growth in a mammal includes applying, to an area of skin from which reduced hair growth is desired, a dermatologically acceptable composition containing a non-steroidal suppressor of angiogenesis.

USE OF ANGIOGENESIS SUPPRESSORS FOR INHIBITING HAIR GROWTH

The invention relates to a method of the inhibition of unwanted hair growth in mammals.

A main function of mammalian hair is to provide environmental protection. However, that function has largely been lost in humans, in whom hair is kept or removed from various parts of the body essentially for cosmetic reasons. For example, it is generally preferred to have hair on the scalp but not on the face.

Various procedures have been employed to remove unwanted hair, including shaving, electrolysis, depilatory creams or lotions, waxing, plucking, and therapeutic antiandrogens. These conventional procedures generally have drawbacks associated with them. Shaving, for instance, can cause nicks and cuts, and can leave a perception of an increase in the rate of hair regrowth. Shaving also can leave an undesirable stubble. Electrolysis, on the other hand, can keep a treated area free of hair for prolonged periods of time, but can be expensive, painful, and sometimes leaves scarring. Depilatory creams, though very effective, typically are not recommended for frequent use due to their high irritancy potential. Waxing and plucking can cause pain, discomfort, and poor removal of short hair. Finally, antiandrogens -- which have been used to treat female hirsutism -- can have unwanted side effects.

It has previously been disclosed that the

rate and character of hair growth can be altered by applying to the skin inhibitors of certain enzymes. These inhibitors include inhibitors of 5-alpha reductase, ornithine decarboxylase, S-adenosylmethionine decarboxylase, gammaglutamyl transpeptidase, and transglutaminase. See, for example, Breuer et al., U.S. Pat. No. 4,885,289; Shander, U.S. Pat. No. 4,720,489; Ahluwalia, U.S. Pat. No. 5,095,007; Ahluwalia et al., U.S. Pat. No. 5,096,911; Shander et al., U.S. Pat. No. 5,132,293; and Shander et al., U.S. Pat. No. 5,143,925.

Angiogenesis, the development of new blood vessels, is the cumulative effect of many biochemical processes and occurs mainly during embryonic growth, wound healing, and the cyclical development of the uterine endometrium. Angiogenesis also plays a role in diabetic retinopathy, atherosclerosis, and tumor growth. Angiogenesis involves the degradation of both the parent vessel basement membrane and the interstitial matrix to provide a passage for the new vessel; migration of endothelial cells toward an angiogenic stimulus; formation of a lumen and the initiation of blood flow. These processes are under the control of growth factors, cytokines, peptides, immunomodulators, as well as other factors that may act as direct stimulants of angiogenesis or as indirect stimulants by attracting inflammatory factors.

There are at least seven major pathways thought to contribute to angiogenesis.

The first pathway involves heparin sulfate proteoglycans (HSPG). HSPG binds basic fibroblast growth factor (bFGF), and stimulates angiogenesis in the presence of copper ions. HSPG is formed from heparin by the enzyme sulfotransferase.

The second pathway involves histamine, which may stimulate angiogenesis after binding to specific histamine receptors. Histamine is formed from the

amino acid histidine by the enzyme histidine decarboxylase (HDC). This synthetic reaction takes place in mast cells, and histamine is released from mast cells upon their degranulation.

The third pathway involves angiotensin II, which stimulates angiogenesis after binding to angiotensin II receptors. Angiotensin II is formed from angiotensin I by angiotensin converting enzyme (ACE).

The fourth pathway involves prostaglandin E1, which stimulates angiogenesis. Prostaglandin E1 synthesis is catalyzed by the enzyme prostaglandin synthase.

The fifth pathway involves Substance P, an endogenous molecule that functions as a neurotransmitter and in the regulation of inflammation. Substance P also posses angiogenic properties by acting through the neurokinin 1 receptor (NK1).

The sixth pathway involves platelet activating factor (PAF), an endogenous protein that binds to a specific receptor and stimulates chemotaxis and leukocyte infiltration, which can lead to the stimulation of angiogenesis.

The seventh pathway involves the arachidonic acid metabolite 12(R)-HETrE, which is angiogenic through its effects on capillary permeability, neutrophil chemotoxin, vasodilation, and endothelial cell mitogenesis. The metabolite 12(R)-HETrE is formed from 5HETE by the enzyme cytochrome P450 reductase.

One aspect of the invention is the use of non-steroidal suppressors of angiogenesis to inhibit hair growth. It has now been found that unwanted mammalian (including human) hair growth -- particularly androgen-stimulated hair growth -- can be inhibited by applying to the skin a dermatologically acceptable composition including a non-steroidal suppressor of angiogenesis in an amount effective to reduce hair

growth. The unwanted hair growth which is reduced may be normal hair growth, or hair growth that results from an abnormal or diseased condition.

Accordingly, a first aspect of the present invention provides a cosmetic method of reducing mammalian hair growth comprising:

selecting an area of skin from which reduced hair growth is desired; and

applying to said area of skin a dermatologically acceptable composition comprising a non-steroidal suppressor of angiogenesis in an amount effective to inhibit hair growth.

A second aspect of the present invention provides the use of a non-steroidal suppressor of angiogenesis for the manufacture of a medicament for inhibiting mammalian hair growth.

A third aspect of the present invention provides a method of producing a composition for inhibiting mammalian hair growth, which comprises selecting a non-steroidal suppressor of angiogenesis, and combining said suppressor, in an amount effective to reduce hair growth, with a non-toxic, dermatologically acceptable vehicle or carrier.

A fourth aspect of the present invention provides a composition when used for inhibiting mammalian hair growth, which includes a non-steroidal suppressor of angiogenesis in an amount effective to reduce hair growth and a non-toxic, dermatologically acceptable vehicle or carrier.

Suppressors of angiogenesis include compounds that interfere with one or more of the seven major angiogenesis pathways described previously. There are at least 12 classes of compounds that have been found to interfere with one of these pathways, and thus can be used to inhibit hair growth. The 12 classes of compounds are set forth in the Figure.

Referring to the Figure, the first class of compounds inhibit the enzyme sulfotransferase. Examples include p-nitrocatechol and catechin. Inhibiting sulfotransferase interferes with the transformation of heparin to HSPG.

The second class of compounds are heparin binding antagonists, which inhibit the binding of HSPG to bFGF. Examples include pentosan polysulfate and quinacrine.

The third class of compounds are copper chelators, which also inhibit the binding of HSPG to bFGF. Examples include bathocuproine disulfonate and diethylenetriamine pentaacetic acid.

The fourth class of compounds inhibit the enzyme HDC. Examples include O-p-nitrohydroxylamine and α-fluoromethylhistidine. Inhibiting HDC interferes with the conversion of histidine to histamine.

The fifth class of compounds inhibit mast cell degranulation, and this interferes with the release of histamine from mast cells. Examples include mycophenolic acid, bromocryptine, and cromoglycate.

The sixth class of compounds are histamine receptor antagonists which interfere with the binding of histamine to specific histamine receptors. Examples include terfenadine, tripelennamine, chlorpheniramine, and cimetidine.

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The seventh class of compounds inhibit ACE.

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Examples include enalapril and lisinopril. Inhibiting ACE interferes with the conversion of angiotensin I to angiotensin II.

The eighth class of compounds are angiotensin II receptor antagonists, which interfere with the binding of angiotensin II to specific angiotensin II receptors. Examples include 1,4-substituted indoles such as those described in Poss et al., Bioorganic & Medicinal Chemistry Letters, 4:145-150 (1994); dihydropyridine derivatives like nifedipine and others described in Webster et al., Bioorganic & Medicinal Chemistry Letters, 4:133-138 (1994); 2,4-dihydro-3H-1,2,4-triazol-3-ones (triazolinone) derivatives bearing a side chain at N^4 position as described by Chang et al. (Bioorganic & Medicinal Chemistry Letters, 4:115-120 (1994)); tetrahydroisoquinoline carboxylic acids; imidazopyridine derivatives like tetrahydroimidazopyridine carboxylic acid analogs; and Losartan.

The ninth class of compounds inhibit the enzyme prostaglandin synthetase. An example is piracetam. Inhibiting prostaglandin synthetase interferes with the formation of prostaglandin E1.

The tenth class of compounds are NK1 receptor antagonists, which interfere with the binding of Substance P to the NK1 receptor. Examples include (3aR,7aR)-7,7,-diphenyl-2-[1-imino-2-(2-methoxyphenyl)ethyl] perhydroisoindol-4-one and cis-2-(diphenylmethyl)-N-[(2-methoxy-phenyl)methyl]-1-azabicyclo[2,2,2]octan-3-amine.

The eleventh class of compounds are PAF receptor antagonists, which interfere with the binding of PAF to the PAF receptors. Examples include tioconazole and (3-[4-(2-chlorphenyl)-9-methyl-6H-thieno[2-f]-[1,2,4]triazolo-[4,3-a][1,4]-diazepin-2-yl-1-(4-morpholinyl)-1-propanone.

The twelfth class of compounds are inhibitors

of the enzyme cytochrome P450 reductase. An example is clotrimazole. Inhibiting cytochrome P450 reductase interferes with the formation of 12(R)-HETrE from 5HETE.

Additional non-steroidal compounds that may inhibit angiogenesis -- but which may not be members of one of the twelve classes of compounds described above -- include phenyl-ethylene derivatives such as tamoxifen and nafoxidine; irsogladine; the synthetic laminin peptide, CDPGYIGSR-NH_2; radicicol; eponemycin; fumagillin (O-(chloroacetyl-carbamoyl) fumagillol) and synthetic analogues thereof; recombinant human platelet factor-4 and related peptides; protamine; sulfated chitin derivatives; diaminoanthraquinone derivatives; thrombospondin; quinoline-3-carboxamide (linomide); analogues of diatamycin A; and aurintricarboxylic acid.

The above compounds are known and some are commercially available.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including an inhibitor of sulfotransferase.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including a heparin binding antagonist.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including a copper chelator.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including an inhibitor of HDC.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition

including an inhibitor of mast cell degranulation.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including a histamine receptor antagonist.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including an inhibitor of ACE.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including an angiotensin II receptor antagonist.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including an inhibitor of prostaglandin synthetase.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including an NK1 receptor antagonist.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including a PAF receptor antagonist.

Another aspect of the invention features inhibiting mammalian hair growth by applying to the skin a dermatologically acceptable composition including an inhibitor of cytochrome P450 reductase.

Inhibitors of enzymes, and receptor antagonists, may be irreversible or reversible. Reversible inhibitors may be competitive or non-competitive.

"Non-steroidal", as used herein, means a compound that lacks the 17-carbon ring structure found typically in a steroid.

Other features and advantages of the

invention will be apparent from the description of the embodiments thereof, and from the claim.

The Figure is a summary of twelve classes of compounds that interfere with angiogenesis.

The hair growth inhibiting compound is incorporated in a non-toxic dermatologically acceptable topical composition which preferably includes a vehicle or carrier which is adapted to be spread upon the skin. Examples of suitable vehicles are acetone, alcohols, or a cream, lotion, or gel which can effectively deliver the active compound. One such vehicle is disclosed in co-pending application PCT/US93/0506A. In addition, a penetration enhancer may be added to the vehicle to further enhance the effectiveness of the formulation.

The concentration of the hair growth inhibiting compound in the composition may be varied over a wide range up to a saturated solution, preferably from 0.1% to 30% by weight or even more; the reduction of hair growth increases as the amount of compound applied increases per unit area of skin. The maximum amount effectively applied is limited only by the rate at which the hair growth inhibiting compound penetrates the skin. Generally, the effective amounts range from 100 to 3000 micrograms or more per square centimeter of skin.

The composition should be topically applied to a selected area of the body from which it is desired to inhibit hair growth. For example, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper lip, and chin. The composition can also be applied to the legs, arms, torso or armpits. The composition is particularly suitable for inhibiting the growth of unwanted hair in women suffering from hirsutism or other conditions. In humans, the composition should be applied once or twice a day, or even more frequently, for at least three months to achieve a perceived

reduction in hair growth. Reduction in hair growth is demonstrated when the frequency or hair removal is reduced, or the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed by shaving (i.e., hair mass) is reduced.

Male intact Golden Syrian hamsters are considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to androgens in the hamster. To evaluate the effectiveness of a composition including a hair growth inhibiting compound, the flank organs of each of a group of hamsters are depilated by applying a thioglycolate based chemical depilatory (Surgex). To one organ of each animal 25 μl of vehicle alone once a day is applied, while to the other organ of each animal an equal amount of vehicle containing a hair growth inhibiting compound is applied. After thirteen applications (one application per day for five days a week), the flank organs are shaved and the amount of recovered hair (hair mass) from each is weighed. Percent-reduction of hair growth is calculated by subtracting the hair mass (mg) value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained is then divided by the hair mass value of the vehicle treated side, and the resultant number is multiplied by 100.

The above-described assay will be referred to herein as the "Golden Syrian hamster" assay. Preferred compositions provide an inhibition in hair growth of at least about 20%, more preferably at least about 40%, and most preferably at least about 60% when tested in the Golden Syrian hamster assay. A number of

compositions were tested in the Golden Syrian hamster assay; the results are provided in the Table.

TABLE

Compound	Dose	Vehicle*	pH	Hair Mass Treated (mg)	Hair Mass Control (mg)	%Inhibition
bathocuproine	10%	A	7.0	0.41 ± .06	2.23 ± .20	81 ± 3
p-nitrocatechol sulfate	10%	A	9.0	0.58 ± .08	2.39 ± .21	74 ± 5
aurintricarboxylic acid	10%	A	4.0	0.92 ± .08	2.70 ± .29	66 ± 2
mycophenolic acid	10%	D	4.0	0.60 ± .13	1.85 ± .19	65 ± 8
nafoxidine	10%	A	5.0	0.76 ± .19	1.70 ± .14	59 ± 8
tamoxifen	10%	A	4.5	0.72 ± .17	1.65 ± .24	56 ± 12
catechin	10%	A	4.5	0.56 ± .12	1.31 ± .12	56 ± 8
quinacrine	10%	A	6.0	1.27 ± .23	2.50 ± .40	50 ± 8
O-p-nitrohydroxylamine	10%	A	4.0	0.94 ± .17	1.82 ± .21	50 ± 5
diethylenetriamine pentaacetic acid	7.5%	B	4.0	1.31 ± .22	2.44 ± .28	49 ± 8
cimetidine	10%	A	8.0	0.95 ± .14	1.85 ± .23	46 ± 7
lisinopril	7.5%	A	5.0	0.79 ± .14	1.50 ± .23	44 ± 10
piracetam	10%	A	6.0	0.89 ± .18	1.44 ± .22	38 ± 10
enalapril	10%	C	5.0	1.25 ± .16	2.06 ± .11	38 ± 9
pentosan polysulfate	10%	A	6.5	1.07 ± .16	1.57 ± .12	33 ± 7

TABLE (continued)

Compound	Dose	Vehicle*	pH	Hair Mass Treated (mg)	Hair Mass Control (mg)	%Inhibition
terfenadine	5%	B	8.0	1.50 ± .26	2.18 ± .26	32 ± 8
tripelennamine	10%	A	6.5	1.20 ± .23	1.80 ± .23	30 ± 9
chlorfeniramine	10%	A	6.0	0.92 ± .16	1.40 ± .21	29 ± 12
tranexamic acid	10%	A	5.5	1.47 ± .13	2.01 ± .15	21 ± 12

*vehicle A = 68% H_2O; 16% ethanol; 5% propylene glycol; 4% benzyl alcohol; 2% propylene carbonate

B = 80% H_2O; 10% dipropylene glycol; 10% ethanol

C = 80% ethanol; 17.5% H_2O; 2% propylene glycol dipelargonate; 0.5% propylene glycol

D = 70% ethanol; 30% dimethylsulfoxamine

It will be appreciated by those skilled in the art that the invention can be performed within a wide range of equivalent parameters of composition and conditions without departing from the spirit or scope of the invention or of any embodiment thereof.

C L A I M S

1. A cosmetic method of reducing mammalian hair growth comprising:

selecting an area of skin from which reduced hair growth is desired; and

applying to said area of skin a dermatologically acceptable composition comprising a non-steroidal suppressor of angiogenesis in an amount effective to inhibit hair growth.

2. The method of claim 1, wherein said suppressor is a compound that interferes with the action of heparin sulfate proteoglycans.

3. The method of claim 2, wherein said compound is an inhibitor of sulfotransferase.

4. The method of claim 2, wherein said compound is a heparin binding antagonist.

5. The method of claim 2, wherein said compound is a copper chelator.

6. The method of claim 1, wherein said suppressor is a compound that interferes with the action of histamine.

7. The method of claim 6, wherein said compound is an inhibitor of histidine decarboxylase.

8. The method of claim 6, wherein said compound is an inhibitor of mast cell degranulation.

9. The method of claim 6, wherein said compound is a histamine receptor antagonist.

10. The method of claim 1, wherein said suppressor is a compound that interferes with the action of angiotensin II.

11. The method of claim 10, wherein said compound is an inhibitor of angiotensin converting enzyme.

12. The method of claim 10, wherein said compound is an angiotensin II receptor antagonist.

13. The method of claim 1, wherein said suppressor is a compound that interferes with the action of prostaglandin E1.

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14. The method of claim 1, wherein said compound is an inhibitor of prostaglandin synthetase.

15. The method of claim 1, wherein said suppressor interferes with the action of Substance P.

16. The method of claim 15, wherein said compound is an NK1 receptor antagonist.

17. The method of claim 1, wherein said suppressor interferes with the action of platelet activating factor.

18. The method of claim 17, wherein said compound is a platelet activating factor receptor antagonist.

19. The method of claim 1, wherein said suppressor interferes with the action of 12-HETrE.

20. The method of claim 19, wherein said compound is an inhibitor of cytochrome P450 reductase.

21. The method of claim 1, wherein said composition further comprises vehicle.

22. The method of claim 1, wherein the concentration of said suppressor in said composition is between 1% and 30% by weight.

23. The method of claim 1, wherein the composition provides a reduction in hair growth of at least 20% when tested in the Golden Syrian hamster assay.

24. The method of claim 1, wherein the composition provides a reduction in hair growth of at least 50% when tested in the Golden Syrian hamster assay.

25. The method of claim 1, wherein the composition provides a reduction in hair growth of at least 70% when tested in the Golden Syrian hamster assay.

26. The method of claim 1, wherein the suppressor is applied to the skin in an amount of from 100 to 3000 micrograms of said inhibitor per square centimeter of skin.

27. The method of claim 1, wherein said mammal is

a human.

28. The method of claim 27, wherein said area of skin is on the face of the human.

29. The method of claim 28, wherein said human is a woman suffering from hirsutism.

30. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises an inhibitor of sulfotransferase in an amount effective to inhibit hair growth.

31. The method of claim 30, wherein said inhibitor is p-nitrocatechol.

32. The method of claim 30, wherein said inhibitor is catechin.

33. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises a heparin binding antagonist in an amount effective to inhibit hair growth.

34. The method of claim 33, wherein said antagonist is pentosan polysulfate.

35. The method of claim 33, wherein said antagonist is quinacrine.

36. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises a copper chelator in an amount effective to inhibit hair growth.

37. The method of claim 36, wherein said copper chelator is bathocuproine disulfonate.

38. The method of claim 36, wherein said copper chelator is diethylenetriamine pentaacetic acid.

39. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises an inhibitor of histidine decarboxylase in an amount effective to inhibit hair growth.

40. The method of claim 39, wherein said inhibitor is O-p-nitrohydroxylamine.

41. The method of claim 39, wherein said inhibitor is α-fluoromethylhistidine.

42. The method of claim 1, wherein the non-

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steroidal suppressor of angiogenesis comprises an inhibitor of mast cell degranulation in an amount effective to inhibit hair growth.

43. The method of claim 42, wherein said inhibitor is mycophenolic acid.

44. The method of claim 42, wherein said inhibitor is bromocryptine.

45. The method of claim 42, wherein said inhibitor is cromoglycate.

46. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises a histamine receptor antagonist in an amount effective to inhibit hair growth.

47. The method of claim 46, wherein said antagonist is terfenadine.

48. The method of claim 46, wherein said antagonist is tripelennamine.

49. The method of claim 46, wherein said antagonist is chlorpheniramine.

50. The method of claim 46, wherein said antagonist is cimetidine.

51. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises an inhibitor of angiotensin converting enzyme in an amount effective to inhibit hair growth.

52. The method of claim 51, wherein said inhibitor is enalapril.

53. The method of claim 51, wherein said inhibitor is lisinopril.

54. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises an angiotensin II receptor antagonist in an amount effective to inhibit hair growth.

55. The method of claim 54, wherein said antagonist is a 1,4- substituted indole.

56. The method of claim 54, wherein said antagonist is a dihydropyridine derivative.

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57. The method of claim 56, wherein said antagonist is nifedipine.

58. The method of claim 54, wherein said antagonist is a triazolinone derivative.

59. The method of claim 58, wherein said triazolinone derivative has a side chain at the N^4 position.

60. The method of claim 54, wherein said antagonist is a tetrahydroisoquinoline carboxylic acid.

61. The method of claim 54, wherein said antagonist is an imidazopyridine derivative.

62. The method of claim 61, wherein said imidazopyridine derivative is a tetrahydroimidazopyridine carboxylic acid analog.

63. The method of claim 54, wherein said antagonist is Losantan.

64. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises an inhibitor of prostaglandin synthetase in an amount effective to inhibit hair growth.

65. The method of claim 64, wherein said inhibitor is piracetam.

66. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises an NK1 receptor antagonist in an amount effective to inhibit hair growth.

67. The method of claim 66, wherein said antagonist is (3aR,7aR)-7,7,-diphenyl-2-[1-imino-2-(2-methoxyphenyl) ethyl]perhydroisoindol-4-one.

68. The method of claim 66, wherein said antagonist is cis-2-(diphenylmethyl)-N-[(2-methoxy-phenyl)methyl]-1-azabicyclo[2,2,2]octan-3-amine.

69. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises a platelet activating factor receptor antagonist in an amount effective to inhibit hair growth.

70. The method of claim 69, wherein said

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antagonist is tioconazole.

71. The method of claim 69, wherein said antagonist is (3-[4-(2-chlorphenyl)-9-methyl-6H-thieno[2-f]-[1,2,4]triazolo-[4,3-a][1,4]-diazepin-2-yl-1-(4-morpholinyl)-1-propanone.

72. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises an inhibitor of cytochrome P450 reductase in an amount effective to inhibit hair growth.

73. The method of claim 72, wherein said inhibitor is clotrimazole.

74. The method of claim 1, wherein the non-steroidal suppressor of angiogenesis comprises an amount effective to reduce hair growth, a compound selected from the group consisting of phenyl-ethylene derivatives such as tamoxifen and nafoxidine; irsogladine; the synthetic laminin peptide, CDPGYIGSR-NH_2; radicicol; eponemycin; fumagillin (O-(chloroacetyl-carbamoyl)fumagillol) and synthetic analogues thereof; recombinant human platelet factor-4 and related peptides; protamine; sulfated chitin derivatives; diaminoanthroquinone derivatives; thrombospondin; quinoline-3-carboxamide (linomide); analogues of diatamycin A; and aurintricarboxylic acid.

75. The use of a non-steroidal suppressor of angiogenesis for the manufacture of a medicament for inhibiting mammalian hair growth.

76. The use according to claim 75, wherein said suppressor is as defined in any one of claims 2 to 74.

77. A method of producing a composition for inhibiting mammalian hair growth, which comprises selecting a non-steroidal suppressor of angiogenesis, and combining said suppressor, in an amount effective to reduce hair growth, with a non-toxic, dermatologically acceptable vehicle or carrier.

78. A method according to claim 77, wherein said vehicle or carrier is adapted to be spread upon the skin of a mammal.

79. A method according to claim 77, wherein said suppressor is as defined in any one of claims 2 to 74.

80. The new use of a non-steroidal suppressor of angiogenesis for reducing hair growth.

81. A composition when used for inhibiting mammalian hair growth, which includes a non-steroidal suppressor of angiogenesis in an amount effective to reduce hair growth and a non-toxic, dermatologically acceptable vehicle or carrier.

82. A composition according to claim 81, wherein said suppressor is as defined in any one of claims 2 to 74.

Dated 1 March, 2000
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SPRUSON & FERGUSON

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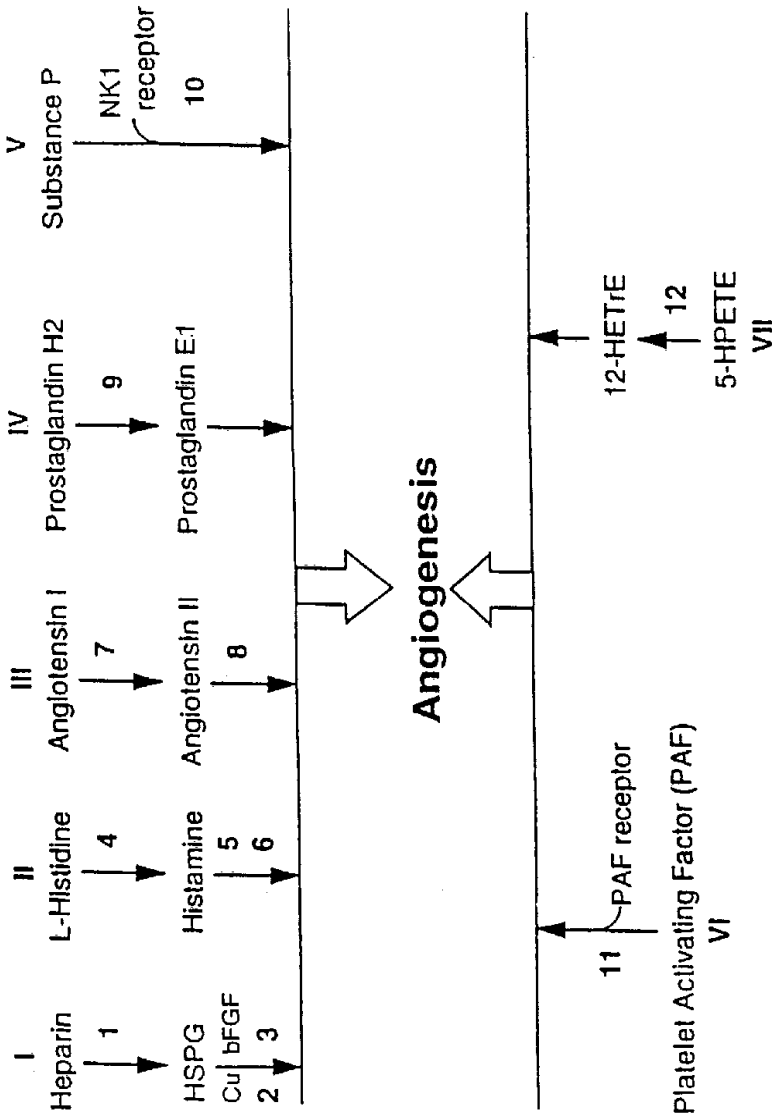
I
Heparin
1
HSPG
Cu bFGF
2 3
II
L-Histidine
4
Histamine
5 6
III
Angiotensin I
7
Angiotensin II
8
IV
Prostaglandin H2
9
Prostaglandin E1
V
Substance P
NK1 receptor
10
Angiogenesis
12-HETrE
12
5-HPETE
VII
11
PAF receptor
Platelet Activating Factor (PAF)
VI