



(43) International Publication Date
2 October 2014 (02.10.2014)

(10) International Publication Number
WO 2014/158943 A1

(51) International Patent Classification:

A61K 31/50 (2006.01) *C07D 237/02* (2006.01)
A61K 31/535 (2006.01)

(21) International Application Number:

PCT/US2014/021020

(22) International Filing Date:

6 March 2014 (06.03.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/779,156 13 March 2013 (13.03.2013) US

(71) Applicant: **AVON PRODUCTS, INC** [US/US]; c/o Joan McGillicuddy, 777 Third Avenue, New York, New York 10017 (US).

(72) Inventors: **HU, Hong**; 25 Marilyn Street, Basking Ridge, New Jersey 07920 (US). **YIM, Sunghan**; 112 Harvest Lane, Lincoln Park, New Jersey 07035 (US). **SANTHANAM, Uma**; 14 North Browning Avenue, Tenafly, New Jersey 07670 (US). **LYGA, John W.**; 105 Old Madisonville Road, Basking Ridge, New Jersey 07920 (US).

(74) Agents: **JOYAL, David M.** et al.; Avon Products, Inc., Avon Place, Suffern, New York 10901 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: TYROSINASE INHIBITORS

(57) Abstract: The compositions and methods of described herein comprise novel ingredients effective to reduce unwanted pigmentation, such as skin discoloration, freckles, age spots, liver spots, sun damage, tans, pigmented acne marks, scars, pigmented birthmarks, hyperpigmentation, post-inflammatory hyperpigmentation, post-injury hyperpigmentation, melasma, cholasma, after-burn scar, nail stain, yellowing of skin, dark circles under eyes, and the like. The composition may include additional ingredients accordingly for a colored cosmetic, moisturizer, cleanser, toner, and the like.



WO 2014/158943 A1

TYROSINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This patent application claims priority to United States Patent Application Serial No. 61/779,156, filed on March 13, 2013. The entirety of the aforementioned application is incorporated herein in its entirety by reference.

FIELD OF INVENTION

[0002] The present invention relates generally to novel compounds, cosmetic formulations, and methods of improving the aesthetic appearance and health of human skin. In particular, the invention relates to substances that reduce unwanted pigmentation in human skin.

BACKGROUND

[0003] Several skin conditions are associated with the overproduction or unwanted production of melanin in the skin, including age spots, freckles, and liver spots. The synthesis of melanin occurs in melanocyte cells in the skin and is a complex process involving several biochemical pathways. Some skin lighteners or depigmenting agents act as inhibitors of tyrosinase, an enzyme that has its catalytically active domain within organelles known as melanosomes. Tyrosinase converts phenols such as tyrosine to ortho-quinones which are subsequently converted to melanin within the melanosomes. Other skin lighteners act by disrupting the transfer of the melanosomes from melanocytes to the keratinocytes where melanin is deposited.

[0004] While these lightening agents do work, they may exhibit in some individuals having sensitivity thereto certain side effects. Some of the side effects of lightening agents include, but are not limited to: redness, itching, stinging, burning, crusting, swelling, unusual discoloration,

[0005] Therefore, there is a continuing need for products that effectively whiten or lighten or otherwise reduce pigmentation of skin. In particular, it treatment of skin that has hyperpigmentation such as age spots, liver spots, sun spots, freckles, scars, and the like. In particular, there is a need for depigmenting products that

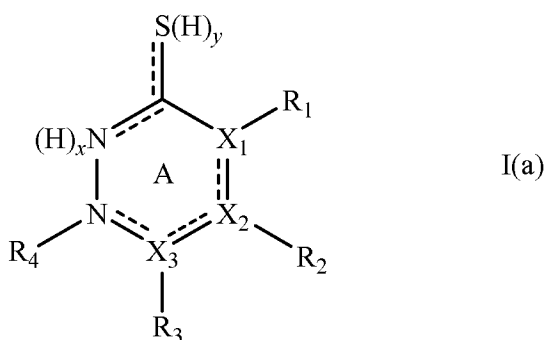
overcome one or more disadvantages of the prior art, including improved effectiveness, and reduced irritation and side effects.

[0006] The foregoing discussion is presented solely to provide a better understanding of nature of the problems confronting the art and should not be construed in any way as an admission as to prior art nor should the citation of any reference herein be construed as an admission that such reference constitutes “prior art” to the instant application. The foregoing discussion is presented solely to provide a better understanding of nature of the problems confronting the art and should not be construed in any way as an admission as to prior art.

SUMMARY OF THE INVENTION

[0007] In accordance with the foregoing objectives and others, the present invention provides compounds and cosmetic formulations thereof that improve one or more signs of dermatological aging and/or skin depigmentation when topically applied to human integuments (skin, lips, nails, hair, etc.), particularly skin. The invention ideally provides compositions and methods for reducing unwanted pigmentation in human skin. The compositions and methods may treat hyperpigmentation conditions, including those associated with UV damage and chronological aging, including without limitation treating, ameliorating, diminishing the appearance of, or preventing age spots, liver spots, freckles, and the like. The compositions and methods are also useful for reducing otherwise unwanted pigmentation, including overall lightening of the skin.

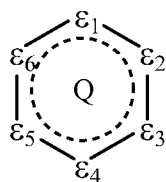
[0008] In one aspect of the invention, cosmetic compositions are provided for improving the aesthetic appearance of human skin comprising a cosmetically acceptable vehicle, and an effective amount of an active agent that reduces pigmentation in keratinous biological substrates, including the skin. The compounds of the invention will have a structure according to formula I(a):



[0009] wherein, “*x*” is an integer 0 or 1 and “*y*” is the absolute value of *x*-1 (*i.e.*, $|x-1|$), such that the compound may be in either the thione or enethiol tautomer;

[0010] X_1 is $-C-$, $-N-$, $-S-$, or $-O-$; and in the case where X_1 is $-S-$ or $-O-$, then R_1 is absent; X_2 is a bond (*i.e.*, it is absent), $-C-$, $-N-$, $-S-$, or $-O-$; and in the case where X_2 is a bond, $-S-$, or $-O-$, then R_2 is absent; and X_3 is $-C-$ or $-N-$;

[0011] at least one (*i.e.*, one, two, three, or four) of R_1 , R_2 , R_3 and R_4 is a five or six membered ring Q, of the form:



[0012] wherein, at least one of ϵ_1 - ϵ_6 is $N-A$, $N-L-A$, $C-A$, or $C-L-A$, where A is ring A of Formula (I) such that one or more of ϵ_1 - ϵ_6 is a point of attachment to ring A, directly or through linker moiety L_1 ; where L_1 is $-X^a-(CH_2)_n-(CH=CH)_m-X^b-(CH_2)_n-(CH=CH)_m-X^c-$, where X^a , X^b , and X^c are independently a bond (*i.e.*, absent), $-O-$, $-S-$, $-NH-$, $-NR^*-$ and “*n*” and “*m*” are independently at each occurrence integers from 0-2, with the proviso that L_1 comprises no more than four atoms in the direct chain between rings A and Q;

[0013] and the remaining ϵ_1 - ϵ_6 are independently selected from $-N-$, $-NH-$, $-NR^*-$, $-NL_2-$, $-O-$, $-S-$, $-CH-$, $-CR-$, $-CR^*-$, $-CL_2-$, and in the case where ring Q is a five membered ring, one of ϵ_1 - ϵ_6 is a bond (*i.e.*, it is absent), and wherein the dashed circle in ring Q indicates that the ring is aromatic, partially unsaturated, or saturated; and wherein L_2 is a linking moiety that forms an additional linkage between

rings A and Q through X_1 , X_2 , or X_3 , where L_2 is group $-X^a-(CH_2)_n-(CH=CH)_m-X^b-(CH_2)_n-(CH=CH)_m-X^c-$, where X^a , X^b , and X^c are independently a bond (*i.e.*, absent), $-O-$, $-S-$, $-NH-$, $-NR^*-$ and “n” and “m” are independently at each occurrence integers from 0-2, with the proviso that L_2 comprises no more than four atoms in the direct chain between rings A and Q;

[0014] and any of R_1 , R_2 , R_3 and R_4 that are not connected to ε_1 - ε_6 are independently selected from groups R, wherein R is selected from hydrogen, $-F$; $-Cl$; $-Br$; $-I$; $-OH$, $-OR^*$; $-NH_2$; $-NHR^*$; $-N(R^*)_2$; $-N(R^*)_3^+$; $-N(R^*)-OH$; $-N(\rightarrow O)(R^*)_2$; $-O-N(R^*)_2$; $-N(R^*)-O-R^*$; $-N(R^*)-N(R^*)_2$; $-C=N-R^*$; $-N=C(R^*)_2$; $-C=N-N(R^*)_2$; $-C(=NR^*)-N(R^*)_2$; $-SH$; $-SR^*$; $-CN$; $-NC$; $-(C=O)-R^*$; $-CHO$; $-CO_2H$; $-CO_2^-$; $-CO_2R^*$; $-(C=O)-S-R^*$; $-O-(C=O)-H$; $-O-(C=O)-R^*$; $-S-(C=O)-R^*$; $-(C=O)-NH_2$; $-(C=O)-N(R^*)_2$; $-(C=O)-NHNH_2$; $-O-(C=O)-NHNH_2$; $-(C=S)-NH_2$; $-(C=S)-N(R^*)_2$; $-N(R^*)-CHO$; $-N(R^*)-(C=O)-R^*$; $-(C=NR)-O-R^*$; $-O-(C=NR^*)-R^*$; $-SCN$; $-NCS$; $-NSO$; $-SSR^*$; $-N(R^*)-C(=O)-N(R^*)_2$; $-N(R^*)-C(=S)-N(R^*)_2$; $-SO_2-R^*$; $-O-S(=O)_2-R^*$; $-S(=O)_2-OR^*$; $-N(R^*)-SO_2-R^*$; $-SO_2-N(R^*)_2$; $-O-SO_3^-$; $-O-S(=O)_2-OR^*$; $-O-S(=O)-OR^*$; $-O-S(=O)-R^*$; $-S(=O)-OR^*$; $-S(=O)-R^*$; $-NO$; $-NO_2$; $-NO_3$; $-O-NO$; $-O-NO_2$; $-N_3$; $-N_2-R^*$; $-N(C_2H_4)$; $-Si(R^*)_3$; $-CF_3$; $-O-CF_3$; $-PR^*_2$; $-O-P(=O)(OR^*)_2$; $-P(=O)(OR^*)_2$; C_1 - C_8 perfluoroalkyl; an aliphatic C_1 - C_8 hydrocarbon radical; a C_1 - C_8 aromatic hydrocarbon radical; or a C_1 - C_8 heteroaryl radical;

[0015] where R^* is independently at each occurrence hydrogen or a straight chained, branched, or cyclic C_1 - C_{20} hydrocarbon radical, which may be saturated, partially saturated, or aromatic, each of which may be optionally substituted with one or more groups R, or optionally substituted with 1-6 heteroatoms selected from nitrogen, oxygen, sulfur, or halogen; and cosmetically acceptable salts of the compounds of Formula I(a).

[0016] The compositions of the invention will typically include a cosmetically or dermatologically acceptable vehicle, which may be in the form of, for example, a serum, a cream, a lotion, a gel, or a stick, and may comprise an emulsion (*e.g.*, water-in-oil, oil-in-water, water-in-silicone, silicone-in-water, polyol-in-silicone, silicone-in-polyol emulsion, etc.), or may comprise an aqueous or ethanolic vehicle, silicone (*e.g.*, cyclomethicone, dimethicone, etc.), hydrocarbon (*e.g.*, petrolatum, isododecane,

etc.), ester oil (isopropyl myristate, myristyl myristate, or the like. The vehicle may further comprise an emulsifier, gelling agent, structuring agent, rheology modifier (*e.g.*, a thickener), film former, or the like. The compositions of the invention may optionally include additional skin benefit agents such as emollients (dimethicone oils, ester oils, or hydrocarbon oils), humectants (*e.g.*, polyols, including propylene glycol, glycerin, etc.), antioxidants (*e.g.*, BHT, ascorbic acid, sodium ascorbate, ascorbyl palmitate, beta-carotene, etc.), vitamins (*e.g.*, tocopherol, tocopheryl acetate, etc.), alpha-hydroxy acids (*e.g.*, glycolic acid), beta-hydroxy acids (*e.g.*, salicylic acid), retinoids (*e.g.*, retinoic acid, all-trans-retinoic acid, retinaldehyde, retinol, and retinyl esters such as acetates or palmitates), other anti-aging ingredients (*e.g.*, collagen stimulators), as well as additional depigmenting agents (*e.g.*, kojic acid, TDPA, Niacinamide, etc.).

[0017] It is a further object of the present disclosure to provide methods comprising topically applying such depigmenting compositions to skin. The composition may be applied once or twice daily, or more frequently, and the treatment regimen may last for as long as required to obtain the desired visible reduction in pigmentation, which may be, for example, one week, four weeks, eight weeks, twelve weeks or longer. The compositions may be applied to human keratinous surfaces, such as skin, to treat, ameliorate, diminish, or prevent, or delay the onset of one or more of dark complexion, pigmented skin discoloration, pigmented birthmarks, hyperpigmentation, post-inflammatory hyperpigmentation, post-injury hyperpigmentation, freckles, age spots, liver spots, sun damage, tans, pigmented acne marks, scars, melasma, cholasma, after-burn scars, nail stains, yellowing of skin, or dark circles under eye.

[0018] Further aspects, features and advantages of the present invention will be better appreciated upon a reading of the following detailed description of the invention and claims.

DETAILED DESCRIPTION OF THE INVENTION

[0019] Detailed embodiments of the present invention are disclosed herein; however, it is to be understood that the disclosed embodiments are merely illustrative of the invention that may be embodied in various forms. In addition, each of the examples given in connection with the various embodiments of the invention are

intended to be illustrative, and not restrictive. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a representative basis for teaching one skilled in the art to variously employ the present invention.

[0020] All terms used herein are intended to have their ordinary meaning unless otherwise provided. By “cosmetically acceptable,” it is meant that a particular component is generally regarded as safe and non-toxic at the levels employed. The term “prevent,” as used herein, includes delaying the onset of or progression of a particular sign of skin aging. The term “thin skin” includes skin that becomes thinner with chronological aging as well as prematurely thinned skin, which may be caused, for example, by photo-aging. In one embodiment, the prematurely thinned skin has been diagnosed as such by a clinician. The phrase “individual in need thereof” refers to a human that could benefit from improved dermal appearance or health, including males or females. In some embodiments, the individual in need thereof is a female. The term “skin” includes, without limitation, the lips, skin of the face, hands, arms, neck, scalp, and chest. As used herein, the term “consisting essentially of” is intended to limit the invention to the specified materials or steps and those that do not materially affect the basic and novel characteristics of the claimed invention, as understood from a reading of this specification.

[0021] The invention provides compositions for reducing pigmentation and/or lightening areas of the integumentary system, including but not limited to, skin, hair, lips, and nails. The compositions are, in one embodiment, topical compositions that once applied to the biological substrate result in a lightening of the biological substrate. As used herein, “skin” refers to the biological substrate of the integumentary system that includes skin, hair, lips, nails, and the like.

[0022] In some embodiments, the composition and methods are for the treatment of hyperpigmentation, which includes reducing, ameliorating, or reversing a degree of subject pigmentation that results from increased presence of one or more of the different types of melanin biosynthesized in skin and/or follicles and deposited in hair or skin, relative to a subject’s baseline pigmentation.

[0023] In some embodiments, the composition and methods are for lightening skin, which includes reducing, ameliorating, and/or reversing a baseline degree of subject pigmentation. Lightening skin may be measured by observing changes in

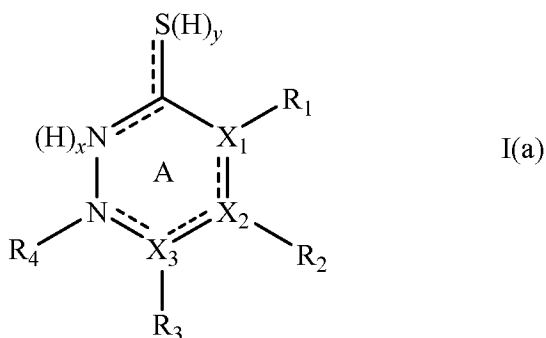
Fitzpatrick scale value of a subject. The Fitzpatrick Scale (aka, Fitzpatrick skin typing test or Fitzpatrick phototyping scale) is a numerical classification schema for the color of skin, and remains a recognized tool for dermatologic research into the color of skin. The Fitzpatrick Scale measures several components, including Genetic Disposition, Reaction to Sun Exposure and Tanning Habits, and classifies skin into six types: Type I (scores 0-7) refers to white, very fair skin, freckles, typical albino skin, that always burns, never tans; Type II (scores 8-16) refers to white, fair skin, that usually burns, or tans with difficulty; Type III (scores 17-24) refers to beige, which is very common, and which sometimes suffers mild burn, gradually tans to a light brown; Type IV (scores 25-30) refers to beige skin with a brown tint, which is typical of Mediterranean Caucasian skin, and which rarely burns, tans with ease to a moderate brown; Type V (scores over 30) refers to dark brown skin which very rarely burns, tans very easily; Type VI refers to Black skin that never burns, tans very easily, and is deeply pigmented. In some embodiments of the invention, the treatments are capable of changing the treated area of skin by at least one or at least two skin type on the Fitzpatrick scale.

[0024] It is to be understood that, as used herein, the terms treating and treatment include and encompass reducing, ameliorating, improving, alleviating, and/or [the dermatological effects of aging and/or environmental stress, or otherwise reducing the appearance of pigmentation in the skin. The present compositions and methods are suitable for use in treating dermatological conditions of the skin in numerous areas of the body, including, without limitation, the face, forehead, lips, neck, arms, hands, legs, knees, feet, chest, back, groin, buttocks, thighs, and the like. In one embodiment, the compositions are applied to the face, chest, and/or hands.

[0025] Specific benefits which may be achieved include, but are not limited to, reducing pigmentation of dark or hyperpigmented skin; reducing age spots or liver spots; reducing pigmented birthmarks, sun damage, tans, pigmented acne marks, scars; evening out or optimizing skin discoloration; decreasing the appearance of dark circles under the eyes; treating melasma, cholasma, freckles, after-burn scars, yellowing of skin, and post-injury hyperpigmentation; lightening hair on the scalp, legs, face, and other areas where whitening and color reduction are desired; and removing or reducing nail stains.

[0026] The present composition and methods of use thereof are not limited by any particular characterization of the physiological and/or chemical effects of lightening agents. Various skin lightening pathways are known and include, for example, those that occur by decreasing melanogenesis by decreasing tyrosinase activity in melanocytes as well as inhibiting melanosome maturation. However, the lightening agents used in the present compositions and methods are believed to lighten by multiple modes of action and by inhibiting the transfer of melanin from the melanocytes to the keratinocytes.

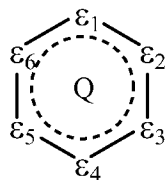
[0027] The compounds of the invention are diazothiones, and more specifically heteroaryl diazothiones. These compounds may have a structure according to formula I(a):



[0028] wherein, “x” is an integer 0 or 1 and “y” is the absolute value of $x-1$ (*i.e.*, $|x-1|$), such that the compound may be in either the thione or enethiol tautomer; and in one embodiment “x” is 1 and “y” is 0 such that the compound is in the thione form;

[0029] X_1 is $-C-$, $-N-$, $-S-$, or $-O-$; and in the case where X_1 is $-S-$ or $-O-$, then R_1 is absent; X_2 is a bond (*i.e.*, it is absent), $-C-$, $-N-$, $-S-$, or $-O-$; and in the case where X_2 is a bond, $-S-$, or $-O-$, then R_2 is absent; and X_3 is $-C-$ or $-N-$; and in one embodiment, X_1 is $-C-$, in another embodiment, X_1 is $-N-$, in another embodiment X_1 is $-O-$; and in one embodiment, X_2 is a bond (*i.e.*, it is absent), and in another embodiment X_2 is $-C-$; and in one embodiment X_3 is $-C-$;

[0030] at least one of R_1 , R_2 , R_3 and R_4 (e.g., only of one of R_1 , R_2 , R_3 and R_4 or two, three, or four of R_1 , R_2 , R_3 and R_4) is a five or six membered ring Q, of the form:



[0031] wherein, at least one (*e.g.*, only one or two) of ε_1 – ε_6 is N–A, N–L–A, C–A, or C–L–A, where “A” is ring A of Formula (I) such that one or more (*e.g.*, only one or two) of ε_1 – ε_6 is a point of attachment to ring A, directly (*i.e.*, by a covalent bond between a ring atom ε_1 – ε_6 to a ring atoms X_1 , X_2 , X_3 , or N of ring A) or through linker moiety L_1 ; where L_1 is $-X^a-(CH_2)_n-(CH=CH)_m-X^b-(CH_2)_n-(CH=CH)_m-X^c-$, where X^a , X^b , and X^c are independently a bond (*i.e.*, absent), –O–, –S–, –NH–, –NR*– and “ n ” and “ m ” are independently at each occurrence integers from 0-2 (*i.e.*, zero, one, or two), with the proviso that L_1 comprises no more than four atoms (*e.g.*, one atom, two atoms, three atoms, or four atoms) in the direct chain between rings A and Q;

[0032] and the remaining ε_1 – ε_6 are independently selected from –N–, –NH–, –NR*–, –NL₂–, –O–, –S–, –CH–, –CR–, –CR*–, –CL₂–, and in the case where ring Q is a five membered ring, one of ε_1 – ε_6 is a bond (*i.e.*, it is absent), and where the dashed circle in ring Q indicates that the ring is aromatic, partially unsaturated, or saturated; and wherein L_2 is a linking moiety that forms an additional linkage between rings A and Q through X_1 , X_2 , or X_3 , where L_2 is group $-X^a-(CH_2)_n-(CH=CH)_m-X^b-(CH_2)_n-(CH=CH)_m-X^c-$, where X^a , X^b , and X^c are independently a bond (*i.e.*, absent), –O–, –S–, –NH–, –NR*– and “ n ” and “ m ” are independently at each occurrence integers from 0-2, with the proviso that L_2 comprises no more than four atoms (*e.g.*, one atom, two atoms, three atoms, or four atoms) in the direct chain between rings A and Q;

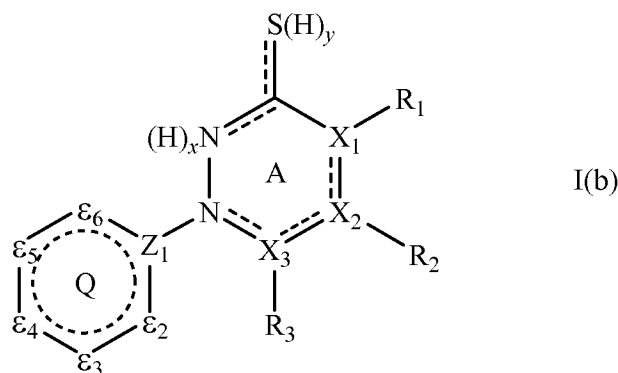
[0033] any of R_1 , R_2 , R_3 and R_4 that are not connected to ε_1 – ε_6 are independently selected from groups R, wherein R is selected from hydrogen, –F; –Cl; –Br; –I; –OH, –OR*; –NH₂; –NHR*; –N(R*)₂; –N(R*)₃⁺; –N(R*)–OH; –N(→O)(R*)₂; –O–N(R*)₂; –N(R*)–O–R*; –N(R*)–N(R*)₂; –C=N–R*; –N=C(R*)₂; –C=N–N(R*)₂; –C(=NR*)–N(R*)₂; –SH; –SR*; –CN; –NC; –(C=O)–R*; –CHO; –CO₂H; –CO₂[–]; –CO₂R*; –(C=O)–S–R*; –O–(C=O)–H; –O–(C=O)–R*; –S–(C=O)–R*; –(C=O)–NH₂; –(C=O)–N(R*)₂; –(C=O)–NHNH₂; –O–(C=O)–NHNH₂; –(C=S)–

NH₂; -(C=S)-N(R*)₂; -N(R*)-CHO; -N(R*)-(C=O)-R*; -(C=NR)-O-R*; -O-(C=NR*)-R*; -SCN; -NCS; -NSO; -SSR*; -N(R*)-C(=O)-N(R*)₂; -N(R*)-C(=S)-N(R*)₂; -SO₂-R*; -O-S(=O)₂-R*; -S(=O)₂-OR*; -N(R*)-SO₂-R*; -SO₂-N(R*)₂; -O-SO₃⁻; -O-S(=O)₂-OR*; -O-S(=O)-OR*; -O-S(=O)-R*; -S(=O)-OR*; -S(=O)-R*; -NO; -NO₂; -NO₃; -O-NO; -O-NO₂; -N₃; -N₂-R*; -N(C₂H₄); -Si(R*)₃; -CF₃; -O-CF₃; -PR*₂; -O-P(=O)(OR*)₂; -P(=O)(OR*)₂; C₁-C₈ perfluoroalkyl; an aliphatic C₁-C₈ hydrocarbon radical; a C₁-C₈ aromatic hydrocarbon radical; or a C₁-C₈ heteroaryl radical;

[0034] where R* is independently at each occurrence hydrogen or a straight chained, branched, or cyclic C₁-C₂₀ hydrocarbon radical, which may be saturated, partially saturated, or aromatic, each of which may be optionally substituted with one or more groups R, or optionally substituted with 1-6 heteroatoms selected from nitrogen, oxygen, sulfur, or halogen;

[0035] and cosmetically acceptable salts thereof, by which is meant salts that are safe for contact with a human integument.

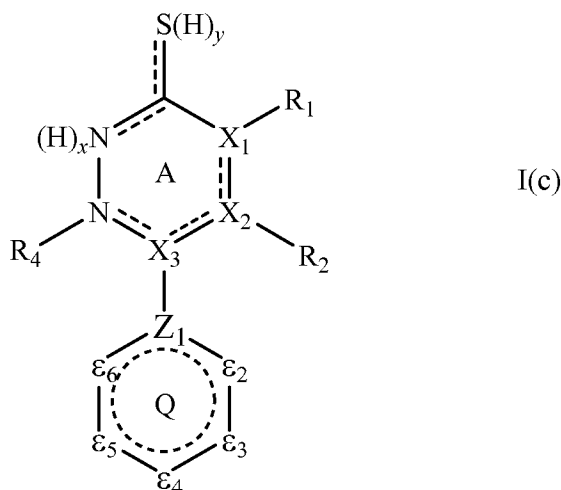
[0036] In one embodiment, the ring Q is attached directly to a ring nitrogen of the heteroaryl diazothione. Such a compound may have a structure according to Formula I(b):



[0037] In this embodiment, Z₁ may be selected from -C-, -CH-, or -N-. In one embodiment, Z₁ is -C- and in another embodiment Z₁ is -N-. In one embodiment, X₁ is -C-, -O-, or -N-; X₂ is -C-; and X₃ is -C-. In another embodiment, X₁ is -C-, -O-, or -N-; X₂ is a bond; and X₃ is -C-. In one embodiment, the bond between X₁ and X₂ is a double bond. In another embodiment, the bond between X₁ and X₂ is a single bond. In one embodiment, X₂ is absent and the bond between X₁ and X₃ is a double bond. In another embodiment, X₂ is absent

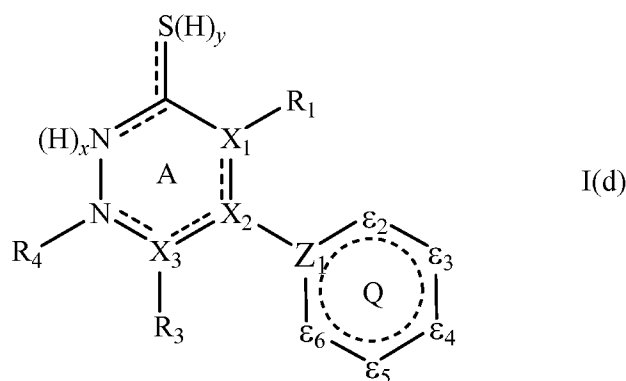
and the bond between X_1 and X_3 is a single bond. In one embodiment, ε_4 is a bond (*i.e.*, absent) such that the ring Q is a five membered ring (*e.g.*, a five membered aryl or heteroaryl ring). In one embodiment, both of rings A and Q are five-membered rings. In one embodiment, both of rings A and Q are six-membered rings (*e.g.*, aryl). In one embodiment, ring A is a five-membered ring and ring Q is a six-membered ring. In one embodiment, ring A is a six-membered ring and ring Q is a five-membered ring.

[0038] In another embodiment, the compound may have a structure according to Formula I(c):



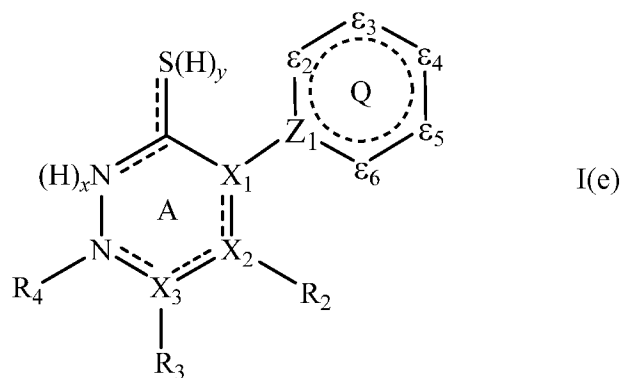
[0039] where Z_1 is typically selected from $-C-$, $-CH-$, or $-N-$. In one embodiment, Z_1 is $-C-$ and in another embodiment Z_1 is $-N-$. In one embodiment, X_1 is $-C-$, $-O-$, or $-N-$; X_2 is $-C-$; and X_3 is $-C-$. In another embodiment, X_1 is $-C-$, $-O-$, or $-N-$; X_2 is a bond; and X_3 is $-C-$. In one embodiment, the bond between X_1 and X_2 is a double bond. In another embodiment, the bond between X_1 and X_2 is a single bond. In one embodiment, X_2 is absent and the bond between X_1 and X_3 is a double bond. In another embodiment, X_2 is absent and the bond between X_1 and X_3 is a single bond. In one embodiment, ε_4 is a bond (*i.e.*, absent) such that the ring Q is a five membered ring (*e.g.*, a five membered aryl or heteroaryl ring). In one embodiment, both of rings A and Q are six-membered rings (*e.g.*, aryl). In one embodiment, ring A is a five-membered ring and ring Q is a six-membered ring. In one embodiment, ring A is a six-membered ring and ring Q is a five-membered ring.

[0040] In another embodiment, the compound has a structure according to Formula I(d):



[0041] where Z_1 is typically selected from $-C-$, $-CH-$, or $-N-$. In one embodiment, Z_1 is $-C-$ and in another embodiment Z_1 is $-N-$. In one embodiment, X_1 is $-C-$, $-O-$, or $-N-$; X_2 is $-C-$; and X_3 is $-C-$. In another embodiment, X_1 is $-C-$, $-O-$, or $-N-$; X_3 is a bond; and X_2 is $-C-$. In one embodiment, the bond between X_1 and X_2 is a double bond. In another embodiment, the bond between X_1 and X_2 is a single bond. In one embodiment, X_3 is absent and the bond between X_2 and the nitrogen adjacent to X_3 is a double bond. In another embodiment, X_2 is absent and the bond between X_2 and the nitrogen adjacent to X_3 is a single bond. In one embodiment, ϵ_4 is a bond (*i.e.*, absent) such that the ring Q is a five membered ring (*e.g.*, a five membered aryl or heteroaryl ring). In one embodiment, both of rings A and Q are six-membered rings (*e.g.*, aryl). In one embodiment, ring A is a five-membered ring and ring Q is a six-membered ring. In one embodiment, ring A is a six-membered ring and ring Q is a five-membered ring.

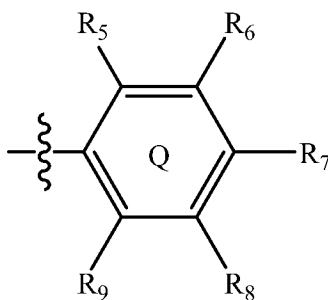
[0042] The compound may also have a structure according to Formula I(e):



[0043] where Z_1 is typically selected from $-C-$, $-CH-$, or $-N-$. In one embodiment, Z_1 is $-C-$ and in another embodiment Z_1 is $-N-$. In one embodiment, X_1 is $-C-$, $-O-$, or $-N-$; X_2 is $-C-$; and X_3 is $-C-$. In another embodiment, X_1 is $-C-$

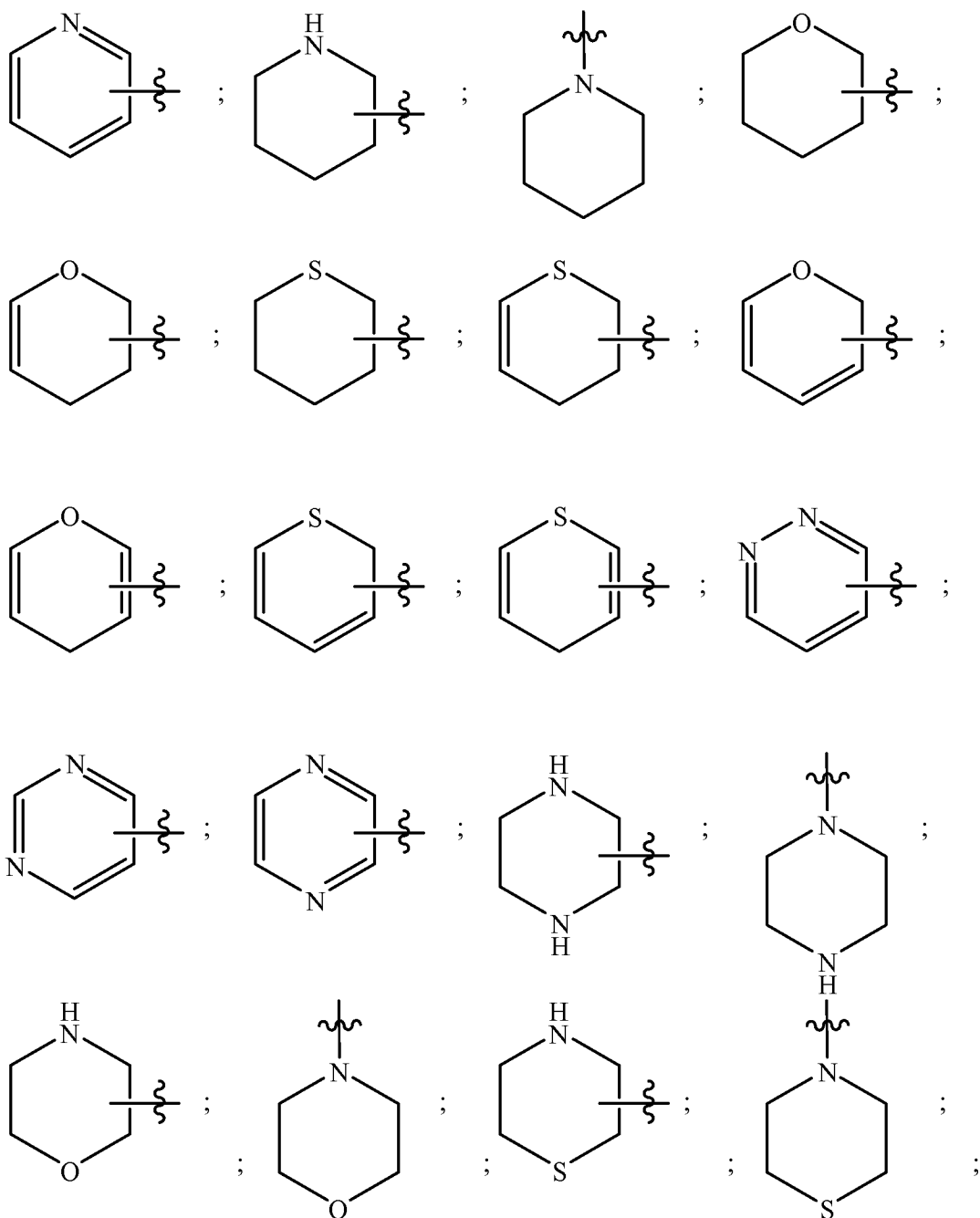
, -O-, or -N-; X_2 is a bond; and X_3 is -C-. In one embodiment, the bond between X_1 and X_2 is a double bond. In another embodiment, the bond between X_1 and X_2 is a single bond. In one embodiment, X_2 is absent and the bond between X_1 and X_3 is a double bond. In another embodiment, X_2 is absent and the bond between X_1 and X_3 is a single bond. In one embodiment, ε_4 is a bond (*i.e.*, absent) such that the ring Q is a five membered ring (*e.g.*, a five membered aryl or heteroaryl ring). In one embodiment, both of rings A and Q are six-membered rings (*e.g.*, aryl). In one embodiment, ring A is a five-membered ring and ring Q is a six-membered ring. In one embodiment, ring A is a six-membered ring and ring Q is a five-membered ring.

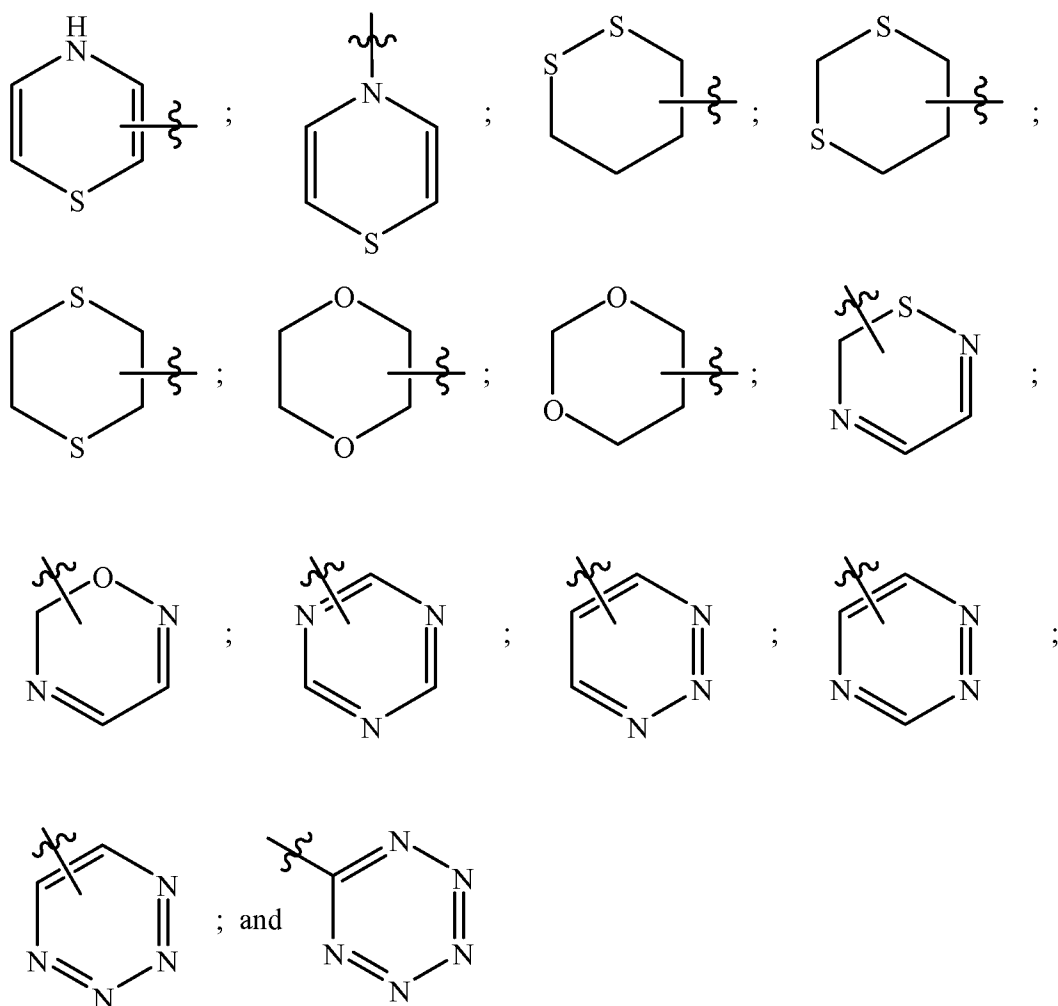
[0044] In some embodiments of the compounds according to formulas I(a)-(e), Z_1 is -C- and Q has the form:



[0045] where R_5 - R_9 are independently selected from hydrogen, R, or L_2 . In one embodiment, all of R_5 - R_9 are hydrogen. In one embodiment, one (or two) of R_5 - R_9 is lower alkyl (*e.g.*, methyl). In one embodiment, one (or two) of R_5 - R_9 is methoxy. In one embodiment, one (or two) of R_5 - R_9 is hydroxyl. In one embodiment, one (or two) of R_5 - R_9 is amino. In one embodiment, one (or two) of R_5 - R_9 is halo. In one embodiment, one (or two) of R_5 - R_9 is cyano. In one embodiment, one (or two) of R_5 - R_9 is carboxyl. In one embodiment, one (or two) of R_5 - R_9 is carbamyl. In one embodiment, one (or two) of R_5 - R_9 is nitro. In one embodiment, one (or two) of R_5 - R_9 is thiol. In one embodiment, one (or two) of R_5 - R_9 is perfluoromethyl. In one embodiment, two adjacent radicals R_5 - R_9 together form a five or six membered ring. In one embodiment, two adjacent radicals R_5 - R_9 together form a five or six membered ring optionally including one, two, or three heteroatoms (*e.g.*, O, N, S) in the ring chain.

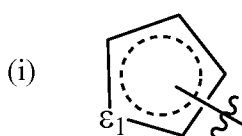
[0046] In some embodiments, ring Q is a six-membered ring which may be aromatic, or which may comprise one or two double bonds, or which may be fully saturated. For example, ring Q may selected from the group consisting of:

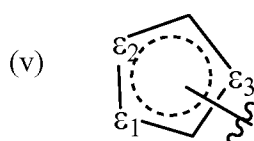
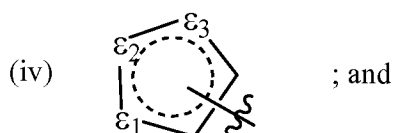
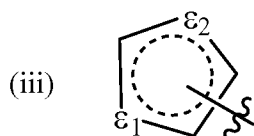
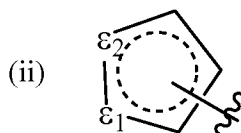




[0047] wherein any available site (e.g., any portion that would otherwise be occupied by hydrogen) on the foregoing six-membered rings may be optionally substituted with a group R (e.g., hydrogen lower alkyl, halo, hydroxyl, methoxyl, cyano, carboxyl, amino, carbamyl, etc.) or may optionally connect with X_1 , X_2 , or X_3 through a group L_2 (e.g., where L_2 comprises no more than four atoms in the chain).

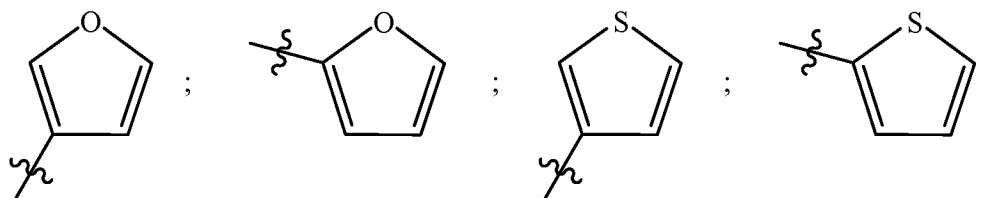
[0048] In some embodiments, ring Q is a five-membered ring which may be aromatic, or which may comprise one or two double bonds, or which may be fully saturated. For example, ring Q may be a five-membered heterocyclic ring selected from the following:

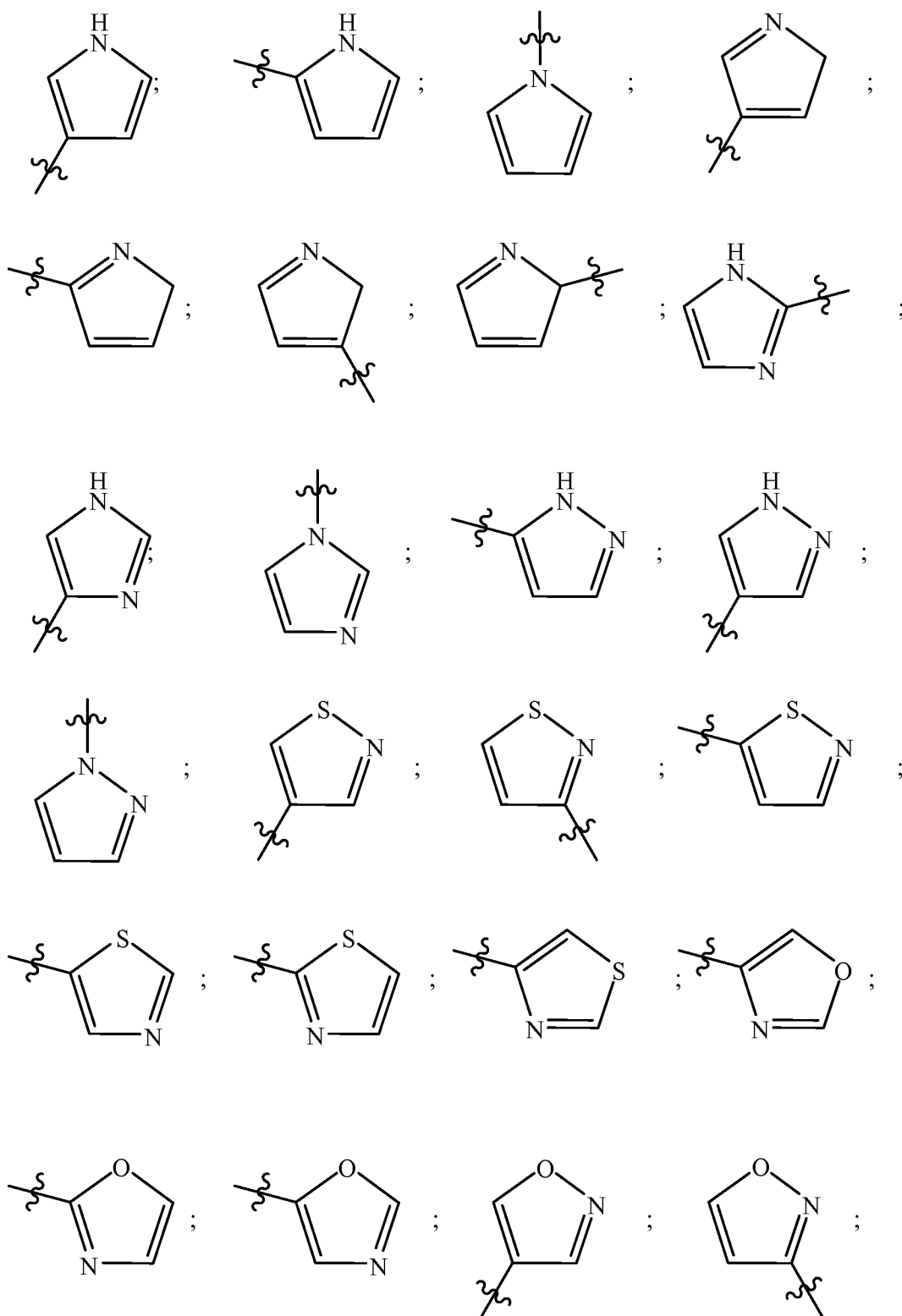


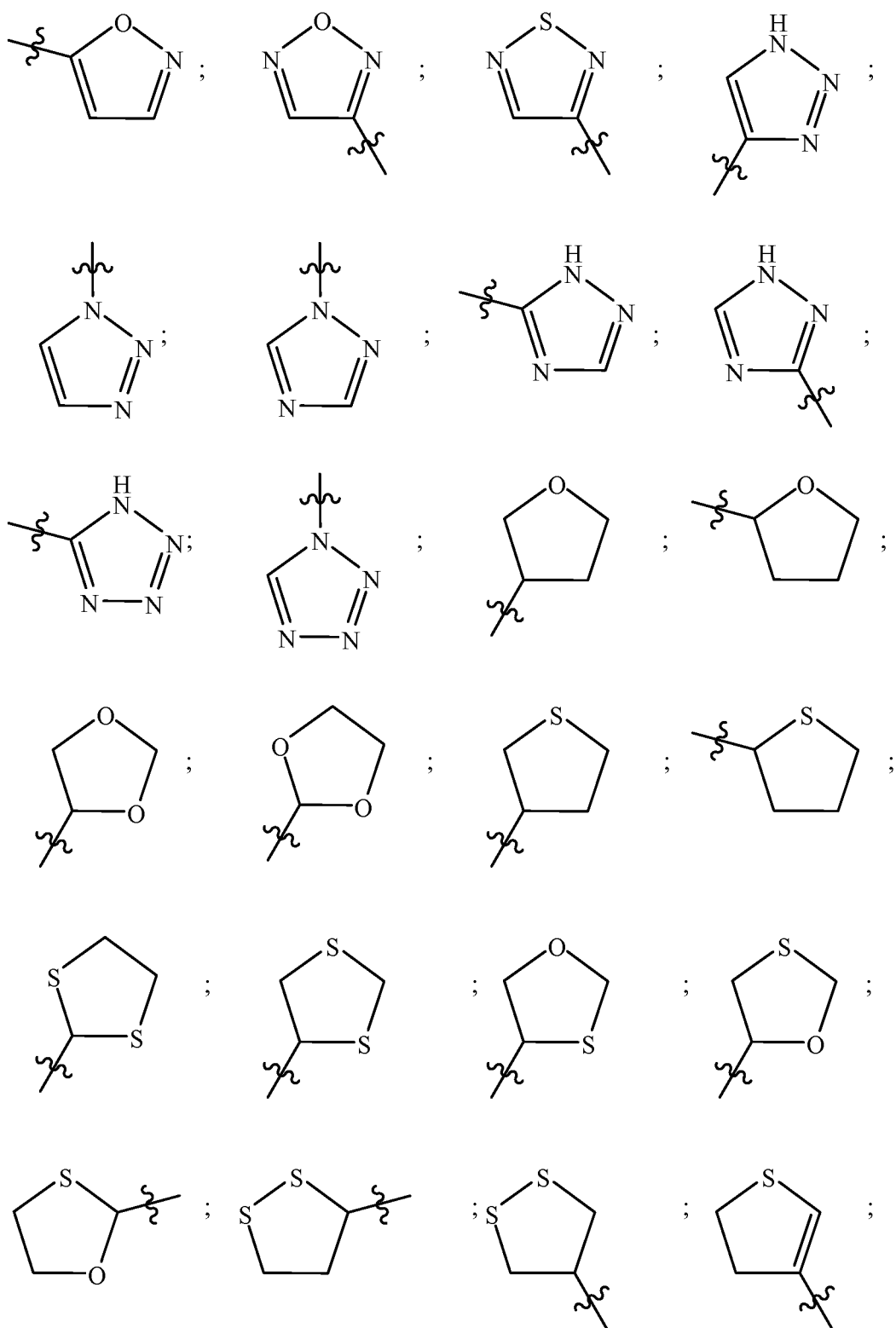


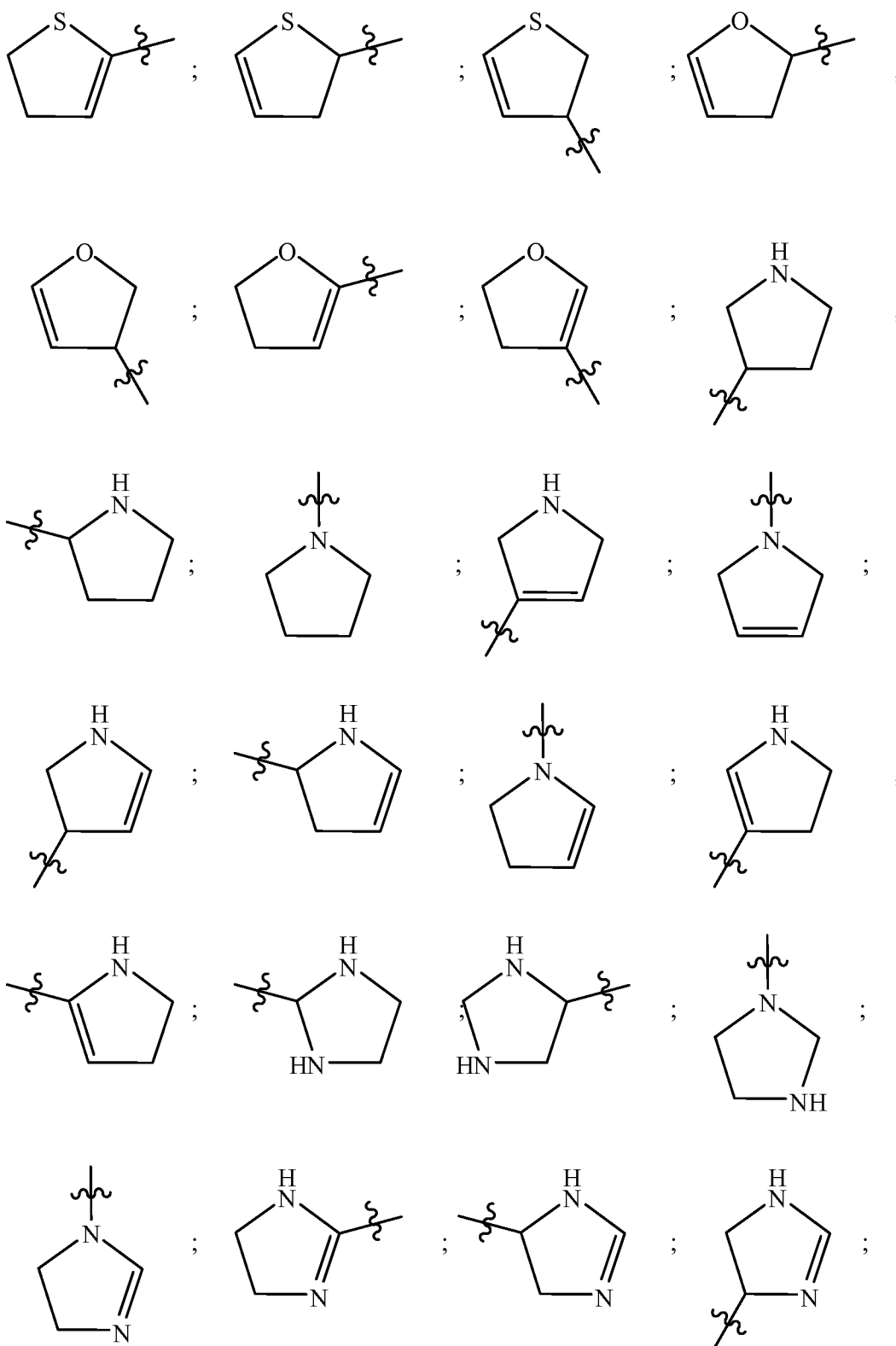
[0049] wherein ϵ_1 , ϵ_2 , and ϵ_3 , are independently selected from N, NH, NR^* , NL_2 , S, and O; with the proviso that where the point of attachment is ϵ_1 , ϵ_2 , or ϵ_3 , then that position represents N; and wherein carbon atoms which are not the point of attachment may be optionally substituted with a group R or L_2 ; and wherein the dashed circles indicate that each ring may comprise zero, one, or two double bonds.

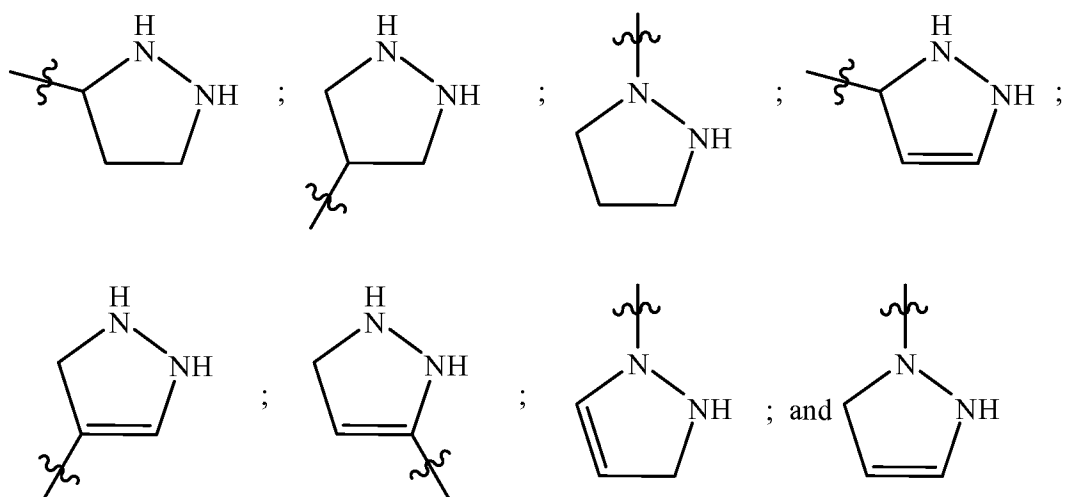
[0050] In specific embodiments of Formulas I(a)-(e), Q may be selected from the group consisting of:





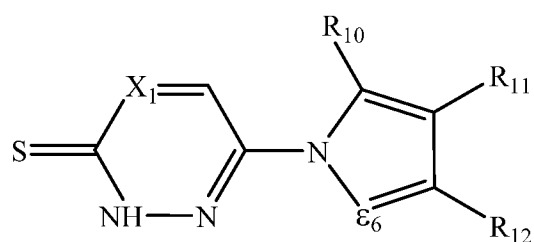






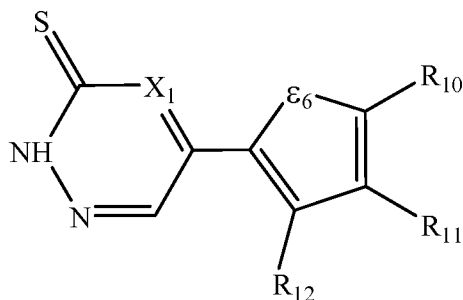
[0051] wherein any available site (e.g., a position otherwise occupied by hydrogen) on the ring Q may be optionally substituted with a group R (e.g., hydrogen, lower alkyl, halo, hydroxyl, methoxyl, cyano, carboxyl, amino, carbamyl, etc.) or may optionally connect with X_1 , X_2 , or X_3 through a group L_2 .

[0052] In one embodiment, the compound has the structure:



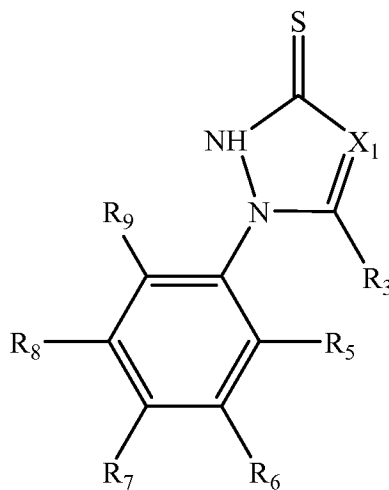
[0053] where X_1 is CH or N; ϵ_6 is CH, CR, or N; and/or R_{10} , R_{11} , and R_{12} are independently a group R (e.g., hydrogen, lower alkyl, halo, hydroxyl, methoxyl, cyano, carboxyl, amino, carbamyl, etc.). In one embodiment, X_1 is N; ϵ_6 is CH; R_{11} is hydrogen, and/or R_{10} and/or R_{12} are independently hydrogen or lower alkyl (e.g., methyl). In one embodiment, X_1 is N; ϵ_6 is N; R_{11} is hydrogen, and/or R_{10} and/or R_{12} are independently hydrogen or lower alkyl (e.g., methyl). In one embodiment, X_1 is CH; ϵ_6 is CH; R_{11} is hydrogen, and/or R_{10} and/or R_{12} are independently hydrogen or lower alkyl (e.g., methyl). In one embodiment, X_1 is CH; ϵ_6 is N; R_{11} is hydrogen, and/or R_{10} and/or R_{12} are independently hydrogen or lower alkyl (e.g., methyl). All such embodiments are and inclusive of either the thione or enethiol tautomer.

[0054] In one embodiment, the compound has the structure:



[0055] where X_1 is CH or N; ϵ_6 is O, S, or NH; and R_{10} , R_{11} , and R_{12} are independently a group R (*e.g.*, hydrogen, lower alkyl, halo, hydroxyl, methoxyl, cyano, carboxyl, amino, carbamyl, etc.). In one embodiment, X_1 is N; ϵ_6 is S; and/or R_{10} , R_{11} and R_{12} are hydrogen. In one embodiment, X_1 is N; ϵ_6 is O; and/or R_{10} , R_{11} and R_{12} are hydrogen. In one embodiment, X_1 is CH; ϵ_6 is S; and/or R_{10} , R_{11} and R_{12} are hydrogen. In one embodiment, X_1 is CH; ϵ_6 is O; and/or R_{10} , R_{11} and R_{12} are hydrogen. All such embodiments are inclusive of either the thione or enethiol tautomer.

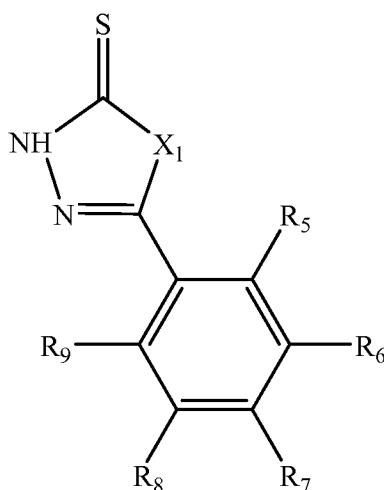
[0056] In one embodiment the compound has the structure:



[0057] where X_1 is CH or N; and R_3 is a group R (*e.g.*, hydrogen, lower alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl, tert-butyl, n-butyl, etc.), halo, hydroxyl, methoxyl, cyano, carboxyl, amino, carbamyl, etc.), and any position R_5 - R_9 of the phenyl group is hydrogen or independently a group R (*e.g.*, lower alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl, tert-butyl, n-butyl, etc.), halo, hydroxyl, methoxyl, cyano,

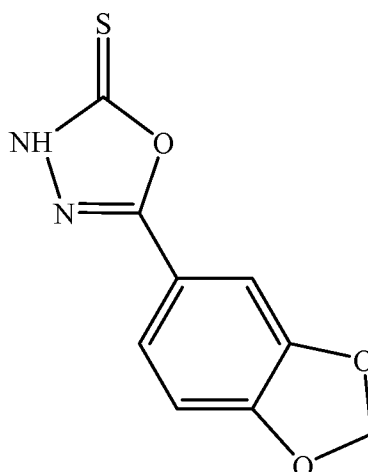
carboxyl, amino, carbamyl, etc.), and wherein any two adjacent substituents R may together form a 5 or 6-membered ring (optionally containing one, two, or three heteroatoms (O, N, S) in the ring). In one embodiment, X_1 is N and R_3 is lower alkyl. In one embodiment, X_1 is CH and R_3 is lower alkyl. In one embodiment, X_1 is N and R_3 is isopropyl. In one embodiment, X_1 is CH and R_3 is isopropyl. In one embodiment, R_3 and R_5 together form a five or six-membered heterocyclic ring (*e.g.*, R_3 and R_5 together comprise $-O-$, $-O-CH_2-$, $-CH_2-O-$, $-CH_2CH_2-$, $-CH=CH-$, $-S-$, $-S-CH_2-$, $-CH_2-S-$, $-NR^*-$, $-NR^*-CH_2-$, $-CH_2-NR^*-$, $-C(=O)-$, etc.). All such embodiments are inclusive of either the thione or enethiol tautomer.

[0058] In one embodiment, the compound has the structure:

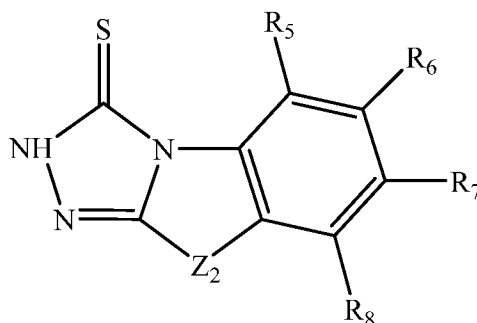


[0059] Where, for example, X_1 is O, S, CH_2 , or NH; and R_5 – R_9 are independently a group R, wherein any two adjacent substituents R may together form a 5 or 6-membered ring. In one embodiment, X_1 is CH. In one embodiment, X_1 is O. In one embodiment, X_1 is N. Any position R_5 – R_9 of the phenyl group is hydrogen or independently a group R (*e.g.*, lower alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl, tert-butyl, n-butyl, etc.), halo, hydroxyl, methoxyl, cyano, carboxyl, amino, carbamyl, etc.), and wherein any two adjacent substituents R may together form a 5 or 6-membered ring (optionally containing one, two, or three heteroatoms (O, N, S) in the ring). In one embodiment, X_1 and R_5 together form a five or six-membered heterocyclic ring (*e.g.*, X_1 and R_5 together comprise $-CH-O-$, $-CH-O-CH_2-$, $-CH-CH_2-$, $-CH-CH=CH-$, $-N-CH=CH-$, $-CH-N=CH-$, $-CH-CH=N-$, $-CH-S-$, $-CH-S-CH_2-$, $-CH-NR^*-$, $-CH-NR^*-CH_2-$, $-N-C(=O)-$, $-N-C(=O)-O-$, etc.). In one embodiment, X_1 is O; and R_5 , R_6 , and R_9 are hydrogen, and/or R_7 and R_8 are alkoxyl

groups of the form $-\text{OR}^a$, where R^a is independently a $\text{C}_1\text{-C}_4$ alkyl, or where R_7 and R_8 may together form a substituent $-\text{OR}^a$, where R^a is $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$ such that R_7 and R_8 together form a five or six membered ring. All such embodiments are inclusive of either the thione or enethiol tautomer. For example, the compound may have the structure:



In another embodiment, the composition may have the structure:



[0060] where Z_2 is O, S, CH_2 , NH, NR^* . In one embodiment, Z_2 is O. In one embodiment, Z_2 is S. In one embodiment, Z_2 is CH_2 . In one embodiment, Z_2 is NH or NR^* . $\text{R}_5\text{--R}_8$ are independently hydrogen or a group R (e.g., halogen, hydroxyl, methyl or other lower alkyl, methoxy, cyano, amino, carboxyl, carbamyl, etc.), wherein any two adjacent substituents R may together form a 5 or 6-membered ring. In one embodiment, Z_2 is NR^* , where R^* is lower alkyl. In another embodiment $\text{R}_5\text{--R}_8$ are hydrogen.

[0061] The compounds of Formula I(a)-(e) may be racemic or may comprise and enantiomeric excess of either the R or S enantiomer at any stereocenter.

[0062] The compounds of Formula I(a)-(e) may be formulated in cosmetically acceptable vehicles, which may comprises one or more of a film forming polymer, a thickener, a pH adjuster, a preservative, an emulsifier, a gelling agent, an antioxidant, a fragrance, a colorant, and the like. The vehicle may comprise a water-in-oil, oil-in-water, silicone-in-water, or water-in-silicone emulsion and will typically further comprise an emulsifier.

[0063] The effective amount of the compound of Formulas I(a)-(e) will typically be from about 0.00001% to about 5%, more typically, from 0.0001% to about 2.5% by weight of the composition. In one embodiment the compound of Formulas I(a)-(e) comprises from about 0.001% to about 1% by weight of the composition. In one embodiment the compound of Formulas I(a)-(e) comprises from about 0.01% to about 0.1% by weight of the composition.

[0064] The compositions of the invention may be applied to human skin for depigmentation, including to reduce areas of unwanted pigmentation, such as hyperpigmentation, including age spots and freckles.

[0065] The compounds of Formulas I(a)-(e) can be formulated in cosmetically acceptable vehicles (as described herein) and may include one or more additional agents that combat pigmentation or hyperpigmentation, including tyrosinase inhibitors and/or melanosome transfer inhibitors. Special mention may be made of thiodipropionic acid and esters thereof (notably, di-lauryl esters); hydroquinone and the monobenzyl ether thereof; hydroquinone-beta-D-glucopyranoside; retinoids (e.g., retinoic acid); tretinoin; azelaic acid; Kojic acid (5-hydroxy-4-pyran-4-one-2-methyl); Mequinol (4-hydroxyanisole); Niacinamide; soy protein and other serine protease inhibitors; paper mulberry extract; Glabridin (licorice extract); Arctostaphylos patula and Arctostaphylos viscida extracts; Magnesium-L-ascorbyl-2-phosphate (MAP); 4-Isopropylcatechol; Aleosin; *N*-acetyl-4-S-cysteaminyphenol and *N*-propionyl-4-S-cysteaminyphenol; N-acetyl glucosamine; and Tranexamic acid (*trans*-4-aminomethylcyclohexanecarboxylic acid); to name a few.

[0066] The compositions are applied topically to skin or topically applied to hair or other keratinous substrates. In certain embodiments, the cosmetic compositions described herein can be used to treat and/or prevent hyper-pigmentation of skin and/or that of the hair, for example, to lighten skin or hair. In some

embodiments, the composition is topically applied to the skin or hair, for example to an area of hyper-pigmented skin or hair. Hyper-pigmentation includes any coloration of an individual's skin or hair that is darker than desired by the individual and that is caused by melanocytes. Such unwanted pigmentation may also be called discoloration. Hyper-pigmented areas of the skin include areas of discrete or mottled hyper-pigmentation. Areas of discrete hyper-pigmentation can be distinct, uniform areas of darker color and may appear as brown spots or freckles on the skin, including marks commonly called pigment spots or "age spots." Areas of mottled hyper-pigmentation of the skin can be dark blotches that are larger and more irregular in size and shape than areas of discrete pigmentation. Areas of hyper-pigmentation also include areas of tanned skin, *e.g.*, skin tanned due to UV exposure. Hyper-pigmented hair includes any shade of hair that is darker than desired.

[0067] Skin hyper-pigmentation may be caused by any number of factors, including, for example, genetics, UV or sun exposure, age, scarring, or discoloration due to skin injury, including lacerations, burns, sunburn, acne, or other dermatological conditions, and the like. For example, skin hyper-pigmented areas include melasmic patches. Melasma is a common skin disorder involving facial skin discoloration, including one embodiment prevalent in pregnant women, where it is called chloasma faciei or chloasma. Melasmic (or chloasmic) patches may appear as dark brown, irregular patches on the face, on the upper cheeks, nose, lips, upper lip, and forehead. The patches often develop gradually over time and generally do not itch or otherwise hurt, but may negatively affect an individual's appearance. Skin hyper-pigmentation also refers to areas under the arm, *e.g.*, that have become or are becoming darker than desired.

[0068] Skin hyper-pigmentation may or may not include areas under an individual's eyes that are darker than desired by the individual, commonly referred to as "under eye dark circles" or "dark circles." Dark circles are usually round, uniform areas of pigmentation beneath each eye, which may be caused by heredity, allergies, tiredness, or other causes. In one embodiment, the compositions are topically applied for the treatment of under eye dark circles. However, treatment of hyper-pigmentation, in some embodiments, excludes treating discoloration and/or bagginess in facial skin below the eyes because such pigmentation may entail an unrelated

etiology to other hyperpigmentation conditions. Hyper-pigmented skin may also include skin in the axillary (*i.e.*, underarm) region.

[0069] Treating hyper-pigmentation or hyper-pigmented skin/hair refers to eradicating, reducing, ameliorating, or reversing one or more of the unwanted features associated with hyper-pigmentation, such as producing a perceptible lightening of the skin or hair in the affected area. Lightening hyper-pigmented areas of the skin may be desirable, in one embodiment, in diminishing age spots; lightening a suntan; evening or optimizing skin tones, *e.g.*, in areas of mottled hyper-pigmentation; in treating melasmic and chloasmic patches, freckles, after-burn scars, and post-injury hyper-pigmentation. Preventing hyper-pigmentation or hyper-pigmented skin refers to affording skin, not yet affected by hyper-pigmentation, a benefit that serves to avoid, delay, forestall, or minimize one or more unwanted features associated with skin hyper-pigmentation, such as reducing the darkness or size of hyper-pigmented areas that eventually develop.

[0070] The inventive compositions are capable of treating and/or preventing hyper-pigmented skin and can be referred to as “skin lighteners.” When used for lightening hair, they can be referred to “hair lighteners.” In one embodiment, the compositions of the present invention are usable to lighten hair in a non-bleaching manner; that is, by suppressing the formation and/or transportation of melanin out of follicular melanocytes, rather than by bleaching the hair itself. In one embodiment, the hair lightened by the instant invention includes facial hair (*e.g.*, hair above the upper lip) and body hair (*e.g.*, arms and legs), as opposed to scalp hair. In one embodiment, the hair lightener is applied to facial hair located on the upper lip.

[0071] The compositions are applied to the skin for a period of time sufficient to diminish the appearance of melanin in the skin. The compositions may be applied topically once, twice, or more daily. The treatment may be for a period of one week, two weeks, four weeks, eight weeks, or more. In one embodiment, the compositions of the invention will be applied to the skin in an amount from about 0.001 to about 100 mg/cm², more typically from about 0.01 to about 20 mg/cm², or from about 0.1 to about 10 mg/cm².

[0072] The cosmetic compositions of this invention may further comprise a retinoid. Retinoids may be without limitation retinol (Vitamin A) and esters thereof,

such as retinol palmitate, retinol acetate and retinol propionate, and salts thereof, retinaldehyde, or retinoic acid (*e.g.*, all-trans or 13-cis) and derivatives thereof. The cosmetic compositions of this invention may further comprise alpha-hydroxy acids, such as glycolic acid, or beta hydroxyl acids, such as salicylic acid.

[0073] In practice, the compositions of the invention may be applied, alone or in cosmetically acceptable vehicles, to skin in need of treatment. That is, skin which suffers from a deficiency or loss in any of the foregoing attributes (including skin in need of depigmentation) or which would otherwise benefit from improvement in any of the foregoing skin attributes.

[0074] The compositions may be applied directly to the skin or to a particular area of skin in need of depigmentation such as directly to an age spot or sun spot or dark circle on the skin of the face, neck, lips, chest, arms, legs, and/or hands.

[0075] The cosmetic compositions according to the invention can be formulated in a variety of forms for topical application and will comprise from about 0.00001% to about 90% by weight of a compound of Formula I(a)-(e), and typically will comprise such actives in an amount from about 0.0001% to about 25% by weight, and more typically from about 0.001% to about 10% by weight. In some embodiments, the compounds of Formula I(a)-(e) will individually or collectively comprise from 0.01% to about 5% by weight of the composition. When the cosmetic compositions according to the invention are formulated in a liquid form, they typically will be present at a concentration from about 0.001 μM to about 50 μM , or from about 0.5 μM to about 10 μM , or from about 2.25 μM to about 10 μM .

[0076] The compositions can include a cosmetically acceptable vehicle. Such vehicles may take the form of any known in the art suitable for application to skin and may include, but are not limited to, water; vegetable oils; mineral oils; esters such as octal palmitate, isopropyl myristate and isopropyl palmitate; ethers such as dicapryl ether and dimethyl isosorbide; alcohols such as ethanol and isopropanol; fatty alcohols such as cetyl alcohol, cetaryl alcohol, stearyl alcohol and biphenyl alcohol; isoparaffins such as isooctane, isododecane and is hexadecane; silicone oils such as cyclomethicone, hydrocarbon oils such as mineral oil, petrolatum, isoeicosane and polyisobutene; polyols such as propylene glycol, glycerin, butylene glycol, pentylene

glycol and hexylene glycol; liposomes; waxes; or any combinations or mixtures of the foregoing.

[0077] The vehicle may comprise an aqueous phase, an oil phase, an alcohol, a silicone phase or mixtures thereof and may be in the form of an emulsion. Non-limiting examples of suitable emulsions include water-in-oil emulsions, oil-in-water emulsions, silicone-in-water emulsions, water-in-silicone emulsions, glycerin-in-oil emulsions, wax-in-water emulsions, water-oil-water triple emulsions or the like. The emulsion may include an emulsifier, such as a nonionic, anionic or amphoteric surfactant, or a gelling agent.

[0078] In one embodiment, the topical composition will have a pH range from 1 to 8, with a pH in the range of from 2 to 7 being typical. In some embodiments, the composition will have a pH in the range of from 3.5 to 5.5. Suitable pH adjusters such as citric acid and triethanolamine may be added to bring the pH within the desired range.

[0079] In one embodiment of the invention, the compositions may include additional skin actives, including but not limited to, retinoids, botanicals, keratolytic agents, desquamating agents, keratinocyte proliferation enhancers, collagenase inhibitors, elastase inhibitors, depigmenting agents, anti-inflammatory agents, steroids, anti-acne agents, antioxidants, and advanced glycation end-product (AGE) inhibitors.

[0080] The composition may comprise additional active ingredients having anti-aging benefits, as it is contemplated that synergistic improvements may be obtained with such combinations. Exemplary anti-aging components include, without limitation, botanicals (*e.g.*, *Butea frondosa* extract); phytol; thioldipropionic acid (TDPA) and esters thereof; retinoids (*e.g.*, 9-cis retinoic acid, 13-cis retinoic acid, all-trans retinoic acid and derivatives thereof, phytanic acid, retinol (Vitamin A) and esters thereof, such as retinol palmitate, retinol acetate and retinol propionate, and salts thereof and others); hydroxy acids (including alpha-hydroxy acids and beta-hydroxy acids), salicylic acid and alkyl salicylates; exfoliating agents (*e.g.*, glycolic acid, 3,6,9-trioxaundecanedioic acid, etc.), estrogen synthetase stimulating compounds (*e.g.*, caffeine and derivatives); compounds capable of inhibiting 5 alpha-reductase activity (*e.g.*, linolenic acid, linoleic acid, finasteride, and mixtures thereof);

and barrier function enhancing agents (*e.g.*, ceramides, glycerides, cholesterol and its esters, alpha-hydroxy and omega-hydroxy fatty acids and esters thereof, etc.), to name a few.

[0081] Exemplary retinoids include, without limitation, retinoic acid (*e.g.*, all-trans or 13-cis), and derivatives thereof, retinaldehyde, retinol (Vitamin A) and esters thereof, such as retinol palmitate, retinol acetate and retinol propionate, and salts thereof. Particular mention may be made of retinol. It is contemplated that combinations of the compounds of Formula I(a) or I(b) with any of these retinoids will provide enhanced or synergistic improvements to skin. The retinoids will typically be included in amounts from about 0.0001% to about 5% by weight, more typically from about 0.01% to about 2.5% by weight, or from about 0.1% to about 1.0% by weight. Compositions according to this embodiment will typically include an antioxidant such as ascorbic acid and/or BHT and/or a chelating agent such as EDTA or a salt thereof.

[0082] In another embodiment, the topical compositions of the present invention may also include one or more of the following: a skin penetration enhancer; an emollient, such as isopropyl myristate, petrolatum, volatile or non-volatile silicones oils (*e.g.*, methicone, dimethicone), ester oils, mineral oils, and fatty acid esters; a humectant, such as glycerin, hexylene glycol or caprylyl glycol; a skin plumper, such as palmitoyl oligopeptide, collagen, collagen and/or glycosaminoglycan (GAG) enhancing agents; a sunscreen, such as avobenzone; an exfoliating agent; and an antioxidant.

[0083] Suitable exfoliating agents include, for example, alpha-hydroxy acids, beta-hydroxy acids, oxa-acids, oxadiacids, and their derivatives such as esters, anhydrides and salts thereof. Suitable hydroxy acids include, for example, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, 2-hydroxyalkanoic acid, mandelic acid, salicylic acid and derivatives thereof. One exemplary exfoliating agent is glycolic acid. When present, the exfoliating agent may comprise from about 0.01% to about 20% by weight of the composition.

[0084] Examples of antioxidants that may be used in the present compositions include compounds having phenolic hydroxy functions, such as ascorbic acid and its derivatives/esters; beta-carotene; catechins; curcumin; ferulic acid derivatives (*e.g.*,

ethyl ferulate, sodium ferulate); gallic acid derivatives (*e.g.*, propyl gallate); lycopene; reductic acid; rosmarinic acid; tannic acid; tetrahydrocurcumin; tocopherol and its derivatives; uric acid; or any mixtures thereof. Other suitable antioxidants are those that have one or more thiol functions (-SH), in either reduced or non-reduced form, such as glutathione, lipoic acid, thioglycolic acid, and other sulfhydryl compounds. The antioxidant may be inorganic, such as bisulfites, metabisulfites, sulfites, or other inorganic salts and acids containing sulfur. In one particular embodiment, the inventive compositions will include TDPA or an ester thereof (*e.g.*, dilauryl thiodipropionic acid), and/or an alpha hydroxyl acid (glycolic acid) and/or beta hydroxyl acid (salicylic acid or a derivative). Compositions of the present invention may comprise an antioxidant, which may comprise from about 0.001 wt % to about 10 wt %, or from about 0.01 wt % to about 5 wt %, of the total weight of the composition.

[0085] Other conventional additives include: vitamins, such as tocopherol and ascorbic acid; vitamin derivatives such as ascorbyl monopalmitate; thickeners such as hydroxyalkyl cellulose; gelling agents; structuring agents; metal chelating agents such as EDTA or salts thereof; pigments; colorants; and pH adjusters. The composition may optionally comprise other components known to those skilled in the art including, but not limited to, film formers, moisturizers, minerals, viscosity and/or rheology modifiers, anti-acne agents, insect repellents, skin cooling compounds, skin protectants, lubricants, fragrances, preservatives, stabilizers, and mixtures thereof. In addition to the foregoing, the cosmetic compositions of the invention may contain any other compound for the treatment of skin disorders. The conventional additives, actives, adjuvants, and excipients set forth in the preceding paragraphs are present in the compositions in amounts suitable to obtain their intended purpose and effect, each typically being present in an amount of from 0.01 to 25% by weight of the cosmetic composition, in particular from about 0.1 to 5% by weight of the cosmetic composition.

[0086] The composition may be formulated in a variety of product forms, such as, for example, an emulsion, lotion, cream, serum, spray, aerosol, cake, ointment, essence, gel, paste, patch, pencil, towelette, mask, stick, foam, elixir, concentrate, and the like, particularly for topical administration. The composition is typically formulated as an emulsion, lotion, cream, ointment, serum or gel.

[0087] In another aspect of the invention, the compositions are applied topically to improve the aesthetic appearance of human skin. The method comprises topically applying to an area of the skin in need thereof a composition comprising an effective amount of a compound of Formula I(a)-(e), for a time sufficient to improve the aesthetic appearance of said human skin. The compositions are topically applied to the skin in effective amounts, by which is meant an amount sufficient to achieve a measurable improvement in skin health or reduction in one or more dermatological signs of aging with daily (once, twice, etc.) administration, typically for a period of at least one week or more.

[0088] The aesthetic improvement of human skin may be an improvement of any attribute or characteristic of skin, including without limitation:

- (a) treatment, reduction, and/or prevention of fine lines or wrinkles;
- (b) reduction of skin pore size;
- (c) improvement in skin thickness, plumpness, and/or tautness;
- (d) improvement in skin smoothness, suppleness and/or softness;
- (e) improvement in skin tone, radiance, and/or clarity;
- (f) improvement in procollagen, and/or collagen production;
- (g) improvement in maintenance and remodeling of elastin;
- (h) improvement in skin texture and/or promotion of retexturization;
- (i) improvement in skin barrier repair and/or function;
- (j) improvement in appearance of skin contours;
- (k) restoration of skin luster and/or brightness;
- (l) replenishment of essential nutrients and/or constituents in the skin;
- (m) improvement of skin appearance decreased by aging and/or menopause;
- (n) improvement in skin moisturization;
- (o) increase in skin elasticity and/or resiliency;
- (p) treatment, reduction, and/or prevention of skin sagging;
- (q) improvement in skin firmness; and
- (r) reduction of pigment spots and/or mottled skin; and
- (s) improvement of optical properties of skin by light diffraction or reflection.

[0089] In a related implementation, a method is provided for the treatment of wrinkles and/or fine lines on the skin human skin (typically, skin of the face) comprising topically applying to an area of the skin in need thereof (e.g., applying to a wrinkle or fine line) a composition of Formula I(a)-(e), for a time sufficient to improve the aesthetic appearance of said human skin. The treatment may be a least once or twice daily and may last for a period of at least four weeks, typically at least eight weeks or longer. The composition may optionally further comprise a retinoid (e.g., retinol or retinyl palmitate) and/or an alpha-hydroxy acid (e.g., glycolic acid) and/or a beta-hydroxy acid (e.g., salicylic acid or derivative) in amounts effective to improve the appearance of skin.

[0090] In a related aspect, methods are provided for enhancing the production of collagen or pro-collagen in human skin comprising topically applying to an area of the skin in need thereof (e.g., sagging skin, thinning skin, skin suffering from wrinkles and fine lines, etc.) a topical composition comprising a cosmetically acceptable vehicle, and an effective amount of a compound of Formula I(a)-(e), for a time sufficient to improve the appearance thereof. The treatment may be a least once or twice daily and may last for a period of at least four weeks, typically at least eight weeks or longer. The composition may optionally further comprise a retinoid and/or an alpha-hydroxy acid (e.g., glycolic acid) and/or a beta-hydroxy acid (e.g., salicylic acid or a derivative) in amounts effective to improve the appearance of skin.

[0091] In yet another aspect of the invention, methods are provided for reducing the severity of, reducing the number of, or preventing or forestalling the onset of, wrinkles or fine lines on human skin comprising topically applying to an area of the skin in need thereof (e.g., wrinkled skin), an effective amount (e.g., 0.0001% – 1% by weight, w/w) of a compound of Formula I(a)-(e), in combination with an effective amount (e.g., 0.01% – 5% by weight, w/w) of retinol and/or an effective amount (e.g., 0.001% – 5% by weight, w/w) of an alpha-hydroxy acid (e.g., glycolic acid) and/or a beta-hydroxy acid (e.g., salicylic acid).

[0092] The invention provides a method for treating aging skin by topically applying a composition comprising a compound of Formula I(a) or I(b), typically in a cosmetically acceptable vehicle, over the affected area for a period of time sufficient to remediate, reverse, reduce, ameliorate, or prevent dermatological signs of aging. Generally, the improvement in the condition and/or aesthetic appearance is selected

from the group consisting of: reducing dermatological signs of chronological aging, photo-aging, hormonal aging, and/or actinic aging; preventing and/or reducing the appearance of lines and/or wrinkles; reducing the noticeability of facial lines and wrinkles, facial wrinkles on the cheeks, forehead, perpendicular wrinkles between the eyes, horizontal wrinkles above the eyes, and around the mouth, marionette lines, and particularly deep wrinkles or creases; improving the appearance of suborbital lines and/or periorbital lines; reducing the appearance of crow's feet; rejuvenating and/or revitalizing skin, particularly aging skin; reducing skin fragility; preventing and/or reversing of loss of glycosaminoglycans and/or collagen; ameliorating the effects of estrogen imbalance; preventing skin atrophy; preventing, reducing, and/or treating hyperpigmentation or hypopigmentation; minimizing skin discoloration; improving skin tone, radiance, clarity and/or tautness; preventing, reducing, and/or ameliorating skin sagging; improving skin firmness, plumpness, suppleness and/or softness; improving procollagen and/or collagen production; improving skin texture and/or promoting retexturization; improving skin barrier repair and/or function; improving the appearance of skin contours; restoring skin luster and/or brightness; minimizing dermatological signs of fatigue and/or stress; resisting environmental stress; replenishing ingredients in the skin decreased by aging and/or menopause; improving communication among skin cells; increasing cell proliferation and/or multiplication; increasing skin cell metabolism decreased by aging and/or menopause; retarding cellular aging; improving skin moisturization; enhancing skin thickness; slowing or halting skin thinning; increasing skin elasticity and/or resiliency; enhancing exfoliation; improving microcirculation; decreasing and/or preventing cellulite formation; and any combinations thereof. In some embodiments, each of the foregoing is associated with female skin.

[0093] In some embodiments, the compounds of Formulas I(a)-(e) will be used to reduce the severity of fine lines or wrinkles, often in combination with retinol. The composition will typically be applied to the skin one, two, or three times daily for as long as is necessary to achieve desired results. The treatment regimen may comprise daily application for at least one week, at least two weeks, at least four weeks, at least eight weeks, or at least twelve weeks or more. Chronic treatment regimens are also contemplated. The effect of a composition on the formation or appearance of fine lines and wrinkles can be evaluated qualitatively, *e.g.*, by visual

inspection, or quantitatively, *e.g.*, by microscopic or computer assisted measurements of wrinkle morphology (*e.g.*, the number, depth, length, area, volume and/or width of wrinkles per unit area of skin). In one embodiment, the cosmetic compositions of the invention will be applied to the skin in an amount from about 0.001 to about 100 mg/cm², more typically from about 0.01 to about 20 mg/cm², or from about 0.1 to about 10 mg/cm².

[0094] It is also contemplated that the compositions of the invention will be useful for treating thin skin by topically applying the composition to thin skin of an individual in need thereof. "Thin skin" is intended to include skin that is thinned due to chronological aging, menopause, or photo-damage and skin that is thinning prematurely. In some embodiments, the treatment is for thin skin in men, whereas other embodiments treat thin skin in women, pre-menopausal or post-menopausal, as it is believed that skin thins differently with age in men and women, and in particular in women at different stages of life.

[0095] The method of the invention may be employed prophylactically to forestall aging including in individuals that have not manifested signs of skin aging, most commonly in individuals under 25 years of age. The method may also reverse or treat signs of aging once manifested as is common in individuals over 25 years of age, or to slow the progression of dermatological aging in such individuals.

[0096] In one embodiment, the compositions of the invention are applied to human skin to reduce sebum production or improve the appearance of skin affected by cellulite, and/or reduce unwanted lipogenesis or increase lipolysis. In this embodiment, the compounds of Formulas I(a) or I(b) can be formulated in cosmetically acceptable vehicles (as described herein) and may include one or more additional agents such as anti-acne ingredients (*e.g.*, salicylic acid, benzoyl peroxide and other peroxides, sulfur, retinoids, etc.) in the case of a facial composition, or, in the case of a cellulite treatment, the formulation may comprise any ingredients suitable for treatment of cellulite, including without limitation, perilla oil and other unsaturated fatty oils and omega-3 fatty acids such as alpha-linolenic acid; caffeine; theophylline; xanthines; retinoids (*e.g.*, retinol); and the like. A cellulite treatment according to the invention will typically be applied topically to skin suffering from cellulite, including skin of the buttocks and thighs for a period of time sufficient to improve the appearance thereof, including for example, daily treatment for at least

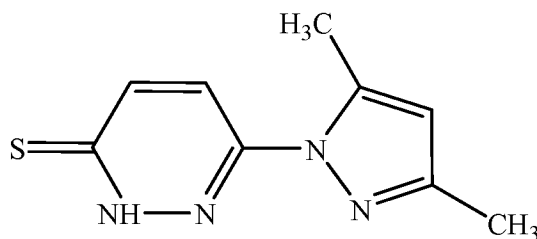
four weeks, at least eight weeks, at least twelve weeks, or longer. In one embodiment, the compositions are topically applied to treat acne.

[0097] In another embodiment, the compounds of Formulas I(a)-(e) are intended for oral use, including for pharmaceutical use. Pharmaceutical formulations will include pharmaceutically acceptable carriers (i.e., diluents and excipients). The pharmaceutical compositions may be included in solid dosage forms, including compressed tablets and capsules, or in liquid or powder forms. Pharmaceutical dosage forms will typically include from about 0.5 mg to about 200 mg, or from about 1 mg to about 100 mg of the compound of Formulas I(a)-(e). The dosage forms may be immediate release, in which case they will typically comprise a water-soluble or dispersible carrier such as microcrystalline cellulose, mannitol, hydroxypropyl methyl cellulose, PVP or the like, or may be delayed, sustained, or modified release, in which case they may comprise water-insoluble polymers such as cellulose ethers (e.g., ethylcellulose), alone or in combination with water soluble or dispersible polymers, to regulate the rate of dissolution of the dosage form in the stomach.

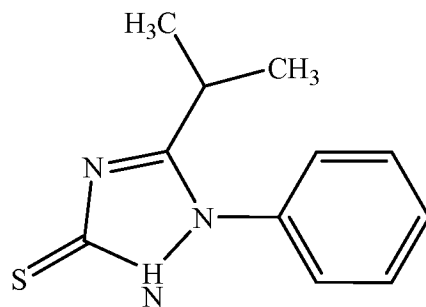
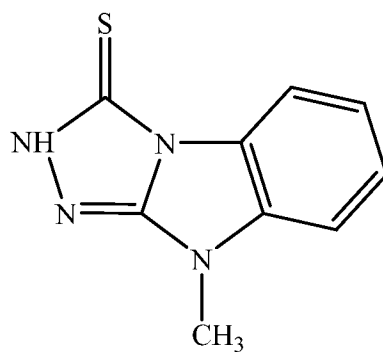
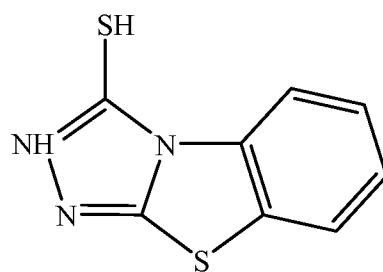
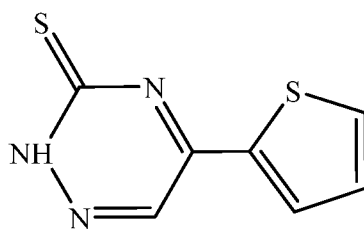
[0098] In one embodiment, the composition is intended for use as a non-therapeutic treatment. In another embodiment, the composition is an article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance, in accordance with the US FD&C Act, §201(i).

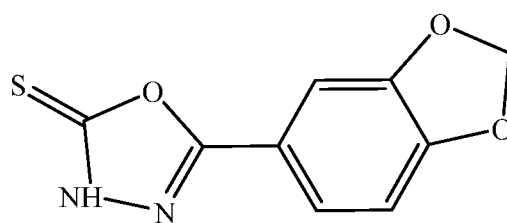
EXAMPLES

[0099] The following example describes specific aspects of the invention to illustrate the invention but should not be construed as limiting the invention, as the example merely provide specific methodology useful in the understanding and practice of the invention and its various aspects. The compounds tested in the following examples are given the following designations.



AV7909

AV1973AV7533AV0442AV4926

AV5828

EXAMPLE 1

[00100] Mushroom Tyrosinase Assay.

[00101] Mushroom tyrosinase and L-Tyrosine were obtained from Sigma-Aldrich, Inc. (St. Louis, Mo.). The enzyme activity was measured in buffer containing 100 mM phosphate buffer pH 6.8, 5% absolute ethanol, 2 micrograms/milliliter mushroom tyrosinase, and 0.2 mg/ml L-Tyrosine. The reaction (conversion of L-Tyrosine to DOPachrome) was conducted in triplicates at 25°C for 30 min, and absorbance was then measured at 492 nm. Kojic Acid was used as a positive control inhibitor in these assays. Percent change in tyrosinase activity relative to vehicle control was calculated.

[00102] Table 1 shows the effect of treatment with each substance on tyrosinase synthesis in the mushroom tyrosinase assay.

TABLE 1.
PERCENT CHANGE IN TYROSINASE ACTIVITY COMPARED TO DMSO
VEHICLE CONTROL MUSHROOM TYROSINASE ASSAY

<u>Test Compound</u>	<u>Concentration</u>	<u>Tyrosinase Activity relative to Vehicle Control</u>
AV7909	0.0100%	-70%
AV7909	0.0010%	-82%
AV1973	0.0100%	-81%
AV7533	0.0100%	-70%
AV7533	0.0010%	-74%
AV0442	0.0100%	-49%
AV0442	0.0010%	-73%
AV4926	0.0100%	-53%
AV4926	0.0010%	-75%

AV5828	0.0100%	-77%
AV5828	0.0010%	-48%

EXAMPLE 2

[00103] Inhibition of Melanin Production.

[00104] The effects of various test compounds on melanin levels were determined by performing assays using B16 melanoma cells. These cells are known to constitutively produce melanin and are a commonly utilized and accepted model system for monitoring the inhibition of melanin synthesis. The B16 mouse melanoma cells were seeded (ATCC, cat. #: CRL-6475) into 96-well tissue culture-treated plates (BD Falcon) and treated with test actives or controls in phenol red free DMEM (Mediatech; cat. #: 17-205-CV) with 2 nanogram / ml of alpha MSH (Fluka; cat #:63605). The cells were examined for their ability to modulate pigment formation. Cells were exposed to diluted test actives or control, where test active had a final concentration of 0.001% or 0.0001%. Tests were performed in 6 replicates each. Following the treatment period (4 days), the level of pigment produced or melanin synthesized was quantified by reading the absorbance at 540 nm using a standard microplate reader (Tecan Group Ltd.).

[00105] After quantifying the amount of melanin, cell viability was determined using the MTT conversion method. The MTT conversion method measures the reduction of the MTT dye from a yellow colored, water-soluble, tetrazolium salt to a bluish-purple colored insoluble formazan precipitate by NAD(P)H-dependent microsomal dehydrogenase enzymes, which only function in viable cells. The intensity of the blue color is indicative of cell viability. After quantifying the amount of melanin pigment produced, the cells were exposed to MTT dye solution (1 mg/ml) for two to three hours. Formazan material was solubilized with reagent alcohol (95% ethanol: 5% isopropanol) and shaken on an orbital shaker for 15 - 30 minutes. MTT dye uptake and conversion by viable cells were determined by measuring the extracted formazan at 570 nm using a microplate reader. Total pigmentation was calculated, normalized to cell viability values and expressed as the average percent change in melanin activity relative to control of the six experiments performed.

[00106] Table 2 shows the effect of treatment with each substance on melanin levels using a B16 melanoma cell assay.

TABLE 2.
PERCENT CHANGE IN MELANIN COMPARED TO DMSO
VEHICLE CONTROL IN B16 CELL ASSAY

<u>Test Compound</u>	<u>Concentration</u>	B16 Assay Percent Change in Melanin Compared to Vehicle
AV7909	0.0010%	-79%
AV7909	0.0001%	-17%
AV1973	0.0010%	-60%
AV1973	0.0001%	-17%
AV7533	0.0010%	-63%
AV7533	0.0001%	-31%
AV0442	0.0010%	-19%
AV4926	0.0010%	-49%
AV5828	0.0010%	-30%
AV5828	0.0001%	-13%

EXAMPLE 3

[00107] Melanin Production in Human Skin Explants.

[00108] The effects of test compound AV7909 on melanin levels in human skin explants were determined relative to a DMSO control and Kojic Acid benchmark. The results are shown below in Table 3.

TABLE 3.
PERCENT CHANGE IN MELANIN COMPARED TO DMSO
VEHICLE CONTROL IN HUMAN SKIN EXPLANT

<u>Test Compound</u>	<u>Concentration</u>	<u>Pigment Production</u>
DMSO	--	--
Kojic Acid	0.1%	-23%
AV7909	0.1%	-17%
AV7909	0.5%	-28%

EXAMPLE

[00109]

4

Inhibition of

Melanin Production in Human Primary Melanocyte

[00110] The effects of various test compounds on melanin productions were determined by performing assays using Human Epidermal Melanocytes, neonatal, darkly pigmented donor (HEMn-DP). The HEMn-DP cells were seeded (Invitrogen; cat. #: C-202-5C) into 6-well tissue culture-treated plates (BD Falcon) and treated with test actives or controls in Medium 254 (Invitrogen; cat. #: M-254-500) supplemented with 1% HMSG (Invitrogen; cat. #: S-002-5) and 1% P/S. The cells were examined for their ability to modulate pigment formation. Cells were exposed to diluted test actives or control, where test active had a final concentration of 0.001% or 0.0001%. Tests were performed in triplicates each. Following the treatment period (5 days), supernatants were aspirated. The melanin was extracted with 0.5 ml of 2N NaOH for 30 minutes at 80°C. The level of melanin synthesized within the cells was quantified by reading the absorbance at 405 nm using a standard microplate reader (Tecan Group Ltd.).

[00111] The cell viability was determined using the MTT conversion method. The MTT conversion method measures the reduction of the MTT dye from a yellow colored, water-soluble, tetrazolium salt to a bluish-purple colored insoluble formazan precipitate by NAD(P)H-dependent microsomal dehydrogenase enzymes, which only function in viable cells. The intensity of the blue color is indicative of cell viability. The cells were exposed to diluted test actives or control, where test active had a final concentration of 0.001% or 0.0001% for 6 days. The cells were then exposed to MTT dye solution (1 mg/ml) for two to three hours. Formazan material was solubilized with reagent alcohol (95% ethanol: 5% isopropanol) and shaken on an orbital shaker for 15 - 30 minutes. MTT dye uptake and conversion by viable cells were determined by measuring the extracted formazan at 570 nm using a microplate reader. Total pigmentation was calculated and normalized to cell viability values. The average percent change in melanin relative to control of the triplicates from the Human Primary Melanocyte Pigmentation Assay (HEMn-DP Pigmentation) is reported in the Table 4 in accordance with the scale: 0: <10% decrease in pigmentation level; +: between 11-30% decrease; ++: between 31-50% decrease; +++: between 51-70% decrease; ++++: >71% decrease; C = cytotoxic.

TABLE 4.
CHANGE IN MELANIN COMPARED TO DMSO
VEHICLE CONTROL IN HUMAN PRIMARY MELANOCYTE PIGMENTATION
ASSAY

<u>Test Compound</u>	<u>Concentration</u>	<u>HUMAN PRIMARY MELANOCYTE PIGMENTATION ASSAY</u>
AV7533	0.0001%	0
AV7533	0.001%	++

EXAMPLE 5

[00112] Inhibition of Melanin Production in 3D Skin Equivalent Tissue

[0098] The effect of the tyrosinase inhibitors on melanin levels was investigated using a MELANODERM™ (MEL-300-B, MatTek Corp., Ashland, MA) human skin model. MELANODERM™ is a viable reconstituted three-dimensional human skin equivalent containing melanocytes derived from African-American donors. Tissues were maintained in culture medium EPI-100-NMM-113 at 37°C as recommended by the manufacturer.

[00113] The compounds were dissolved in either 69% propylene glycol + 30% EtOH + 1% DMSO or 70% propylene glycol + 30% EtOH desired concentration (w/v). 10 µl of the solution was applied topically to the MELANODERM™ tissue while culture medium was added on days 1, 2, 4, 7, and 9. Control tissues were treated with the 10 µl of corresponding vehicle only. On Day 11, tissues were collected and homogenized in a buffer containing 1% SDS, 50 mM EDTA, and 10 mM Tris, pH 6.8. To each homogenate, protease K (5 mg/ml) was added and incubated overnight at 45°C. Additional protease K was added and incubated for 4 hours at 45°C, followed by the addition of 0.5M sodium carbonate and 30% H₂O₂ and incubation at 80°C for 30 minutes. The samples were cooled down to room temperature, and extracted with chloroform/methanol (2:1). After centrifugation at 10,000g for 10 minutes, absorbance of the top phase was measured at 450 nm. Percent change in melanin levels in treated tissue was calculated relative to control. The average percent change in melanin relative to control of the three tissues is reported in the Table 5 in accordance with the scale:

0: <7% decrease in pigmentation level; +: between 8-14% decrease; ++: between 15-20% decrease; +++: between 21-30% decrease; ++++: >31% decrease; C = cytotoxic

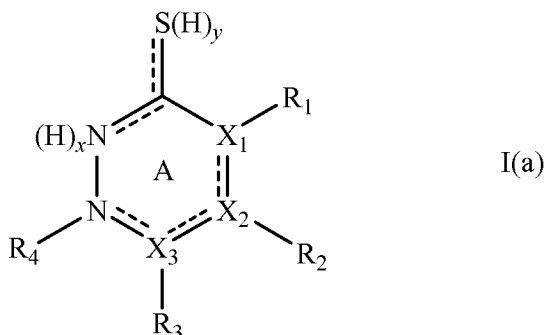
TABLE 5.
CHANGE IN MELANIN COMPARED TO DMSO
VEHICLE CONTROL IN 3D SKIN EQUIVALENT TISSUE PIGMENTATION
ASSAY

<u>Test Compound</u>	<u>Concentration</u>	<u>3D Tissue Pigmentation Assay</u>
AV7909	0.1%	++
AV7909	0.25%	+++
AV7909	0.5%	++++
AV7533	0.05%	+
AV7533	0.1%	+
AV7533	0.25%	++

[00109] All references including patent applications and publications cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

Claims:

1. A cosmetic composition for improving the aesthetic appearance of human skin comprising a cosmetically acceptable vehicle, and an effective amount of a compound according to formula I(a):

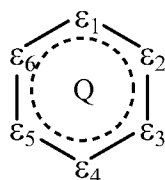


wherein,

“x” is an integer 0 or 1 and “y” is the absolute value of $x-1$ (*i.e.*, $|x-1|$), such that the compound may be in either the thione or enethiol tautomer;

X_1 is $-C-$, $-N-$, $-S-$, or $-O-$; and in the case where X_1 is $-S-$ or $-O-$, then R_1 is absent; X_2 is a bond (*i.e.*, it is absent), $-C-$, $-N-$, $-S-$, or $-O-$; and in the case where X_2 is a bond, $-S-$, or $-O-$, then R_2 is absent; and X_3 is $-C-$ or $-N-$;

at least one of R_1 , R_2 , R_3 and R_4 is a five or six membered ring Q, of the form:



wherein, at least one of $\epsilon_1-\epsilon_6$ is $N-A$, $N-L-A$, $C-A$, or $C-L-A$, where A is ring A of Formula (I) such that one or more of $\epsilon_1-\epsilon_6$ is a point of attachment to ring A, directly or through linker moiety L_1 ; where L_1 is $-X^a-(CH_2)_n-(CH=CH)_m-X^b-$ ($(CH_2)_n-(CH=CH)_m-X^c-$, where X^a , X^b , and X^c are independently a bond (*i.e.*, absent), $-O-$, $-S-$, $-NH-$, $-NR^*-$ and “n” and “m” are independently at each occurrence integers from 0-2, with the proviso that L_1 comprises no more than four atoms in the direct chain between rings A and Q;

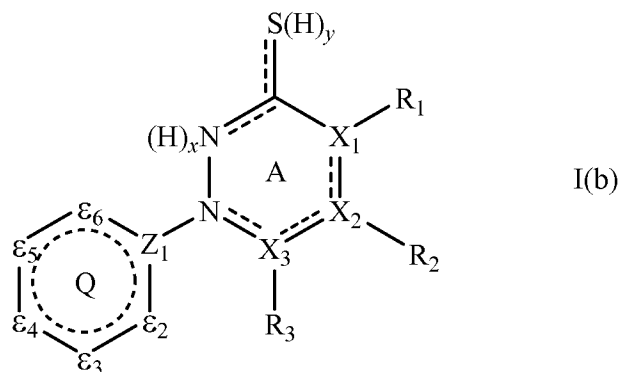
and the remaining ε_1 - ε_6 are independently selected from $-\text{N}-$, $-\text{NH}-$, $-\text{NR}^*-$, $-\text{NL}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{CH}-$, $-\text{CR}-$, $-\text{CR}^*-$, $-\text{CL}_2-$, and in the case where ring B is a five membered ring, one of ε_1 - ε_6 is a bond (*i.e.*, it is absent), and where the dashed circle in ring Q indicates that the ring is aromatic, partially unsaturated, or saturated; and wherein L_2 is a linking moiety that forms an additional linkage between rings A and Q through X_1 , X_2 , or X_3 , where L_2 is group $-\text{X}^a-(\text{CH}_2)_n-(\text{CH}=\text{CH})_m-\text{X}^b-(\text{CH}_2)_n-(\text{CH}=\text{CH})_m-\text{X}^c-$, where X^a , X^b , and X^c are independently a bond (*i.e.*, absent), $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NR}^*-$ and “n” and “m” are independently at each occurrence integers from 0-2, with the proviso that L_2 comprises no more than four atoms in the direct chain between rings A and Q;

any of R_1 , R_2 , R_3 and R_4 that are not connected to ε_1 - ε_6 are independently selected from groups R, wherein R is selected from hydrogen, $-\text{F}$; $-\text{Cl}$; $-\text{Br}$; $-\text{I}$; $-\text{OH}$, $-\text{OR}^*$; $-\text{NH}_2$; $-\text{NHR}^*$; $-\text{N}(\text{R}^*)_2$; $-\text{N}(\text{R}^*)_3^+$; $-\text{N}(\text{R}^*)-\text{OH}$; $-\text{N}(\rightarrow\text{O})(\text{R}^*)_2$; $-\text{O}-\text{N}(\text{R}^*)_2$; $-\text{N}(\text{R}^*)-\text{O}-\text{R}^*$; $-\text{N}(\text{R}^*)-\text{N}(\text{R}^*)_2$; $-\text{C}=\text{N}-\text{R}^*$; $-\text{N}=\text{C}(\text{R}^*)_2$; $-\text{C}=\text{N}-\text{N}(\text{R}^*)_2$; $-\text{C}(\text{=NR}^*)-\text{N}(\text{R}^*)_2$; $-\text{SH}$; $-\text{SR}^*$; $-\text{CN}$; $-\text{NC}$; $-(\text{C}=\text{O})-\text{R}^*$; $-\text{CHO}$; $-\text{CO}_2\text{H}$; $-\text{CO}_2^-$; $-\text{CO}_2\text{R}^*$; $-(\text{C}=\text{O})-\text{S}-\text{R}^*$; $-\text{O}-(\text{C}=\text{O})-\text{H}$; $-\text{O}-(\text{C}=\text{O})-\text{R}^*$; $-\text{S}-(\text{C}=\text{O})-\text{R}^*$; $-(\text{C}=\text{O})-\text{NH}_2$; $-(\text{C}=\text{O})-\text{N}(\text{R}^*)_2$; $-(\text{C}=\text{O})-\text{NHNH}_2$; $-\text{O}-(\text{C}=\text{O})-\text{NHNH}_2$; $-(\text{C}=\text{S})-\text{NH}_2$; $-(\text{C}=\text{S})-\text{N}(\text{R}^*)_2$; $-\text{N}(\text{R}^*)-\text{CHO}$; $-\text{N}(\text{R}^*)-(\text{C}=\text{O})-\text{R}^*$; $-(\text{C}=\text{NR})-\text{O}-\text{R}^*$; $-\text{O}-(\text{C}=\text{NR}^*)-\text{R}^*$; $-\text{SCN}$; $-\text{NCS}$; $-\text{NSO}$; $-\text{SSR}^*$; $-\text{N}(\text{R}^*)-\text{C}(\text{=O})-\text{N}(\text{R}^*)_2$; $-\text{N}(\text{R}^*)-\text{C}(\text{=S})-\text{N}(\text{R}^*)_2$; $-\text{SO}_2-\text{R}^*$; $-\text{O}-\text{S}(\text{=O})_2-\text{R}^*$; $-\text{S}(\text{=O})_2-\text{OR}^*$; $-\text{N}(\text{R}^*)-\text{SO}_2-\text{R}^*$; $-\text{SO}_2-\text{N}(\text{R}^*)_2$; $-\text{O}-\text{SO}_3^-$; $-\text{O}-\text{S}(\text{=O})_2-\text{OR}^*$; $-\text{O}-\text{S}(\text{=O})-\text{OR}^*$; $-\text{O}-\text{S}(\text{=O})-\text{R}^*$; $-\text{S}(\text{=O})-\text{OR}^*$; $-\text{S}(\text{=O})-\text{R}^*$; $-\text{NO}$; $-\text{NO}_2$; $-\text{NO}_3$; $-\text{O}-\text{NO}$; $-\text{O}-\text{NO}_2$; $-\text{N}_3$; $-\text{N}_2-\text{R}^*$; $-\text{N}(\text{C}_2\text{H}_4)$; $-\text{Si}(\text{R}^*)_3$; $-\text{CF}_3$; $-\text{O}-\text{CF}_3$; $-\text{PR}^*_2$; $-\text{O}-\text{P}(\text{=O})(\text{OR}^*)_2$; $-\text{P}(\text{=O})(\text{OR}^*)_2$; C_1 - C_8 perfluoroalkyl; an aliphatic C_1 - C_8 hydrocarbon radical; a C_1 - C_8 aromatic hydrocarbon radical; or a C_1 - C_8 heteroaryl radical;

where R^* is independently at each occurrence hydrogen or a straight chained, branched, or cyclic C_1 - C_{20} hydrocarbon radical, which may be saturated, partially saturated, or aromatic, each of which may be optionally substituted with one or more groups R, or optionally substituted with 1-6 heteroatoms selected from nitrogen, oxygen, sulfur, or halogen;

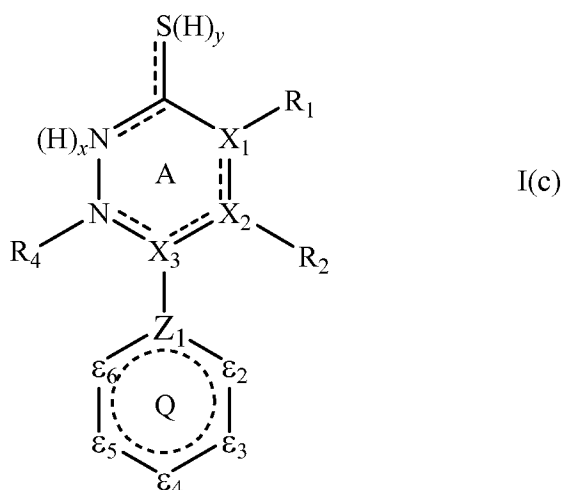
and cosmetically acceptable salts thereof.

2. The composition according to claim 1, wherein the compound has a structure according to Formula I(b):



where Z_1 is selected from $-C-$, $-CH-$, or $-N-$; and cosmetically acceptable salts thereof.

3. The composition according to claim 2, wherein X_1 is $-C-$, $-O-$, or $-N-$; X_2 is $-C-$; and X_3 is $-C-$.
4. The composition according to claims 2, wherein the bond between X_1 and X_2 is a double bond.
5. The composition according to claims 2, wherein the bond between X_1 and X_2 is a single bond.
6. The composition according to claims 2, wherein X_2 is a bond (*i.e.*, absent).
7. The composition according to claims 2-6, wherein ϵ_4 is a bond (*i.e.*, absent).
8. The composition according to claim 1, wherein the compound has a structure according to Formula I(c):



where Z_1 is selected from $-C-$, $-CH-$, or $-N-$; and cosmetically acceptable salts thereof.

9. The composition according to claim 8, wherein X_1 is $-C-$, $-O-$, or $-N-$; X_2 is $-C-$; and X_3 is $-C-$.

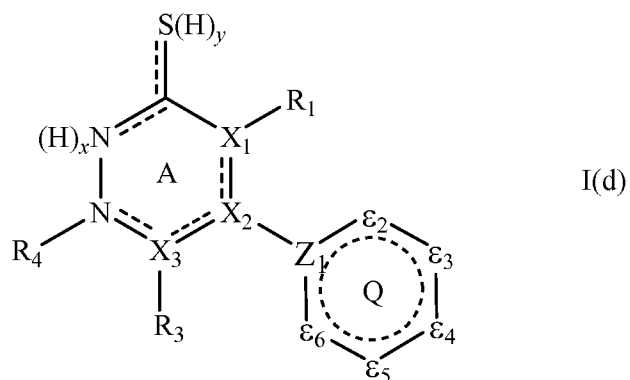
10. The composition according to claims 8, wherein the bond between X_1 and X_2 is a double bond.

11. The composition according to claims 8, wherein the bond between X_1 and X_2 is a single bond.

12. The composition according to claims 8, wherein X_2 is a bond (*i.e.*, absent).

13. The composition according to claims 8-12, wherein ϵ_4 is a bond (*i.e.*, absent).

14. The composition according to claim 1, wherein the compound has a structure according to Formula I(d):



where Z_1 is selected from $-C-$, $-CH-$, or $-N-$; and cosmetically acceptable salts thereof.

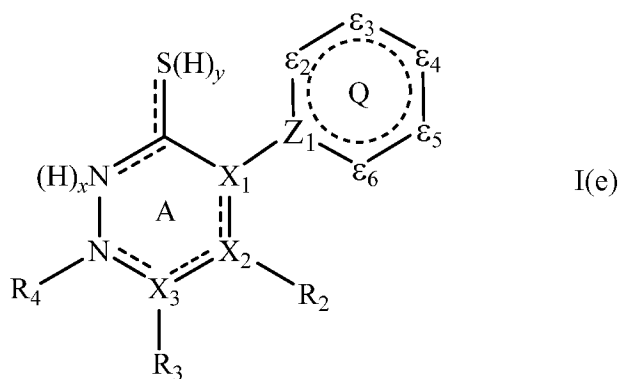
15. The composition according to claim 14, wherein X_1 is $-C-$, $-O-$, or $-N-$; X_2 is $-C-$; and X_3 is $-C-$.

16. The composition according to claims 14, wherein the bond between X_1 and X_2 is a double bond.

17. The composition according to claims 14, wherein the bond between X_1 and X_2 is a single bond.

18. The composition according to claims 14-17, wherein ϵ_4 is a bond (*i.e.*, absent).

19. The composition according to claim 1, wherein the compound has a structure according to Formula I(e):



where Z_1 is selected from $-C-$, $-CH-$, or $-N-$; and cosmetically acceptable salts thereof.

20. The composition according to claim 8, wherein X_1 is $-C-$ or $-N-$; X_2 is $-C-$; and X_3 is $-C-$.

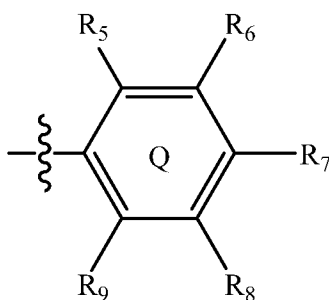
21. The composition according to claims 8, wherein the bond between X_1 and X_2 is a double bond.

22. The composition according to claims 8, wherein the bond between X_1 and X_2 is a single bond.

23. The composition according to claims 8, wherein X_2 is a bond (*i.e.*, absent).

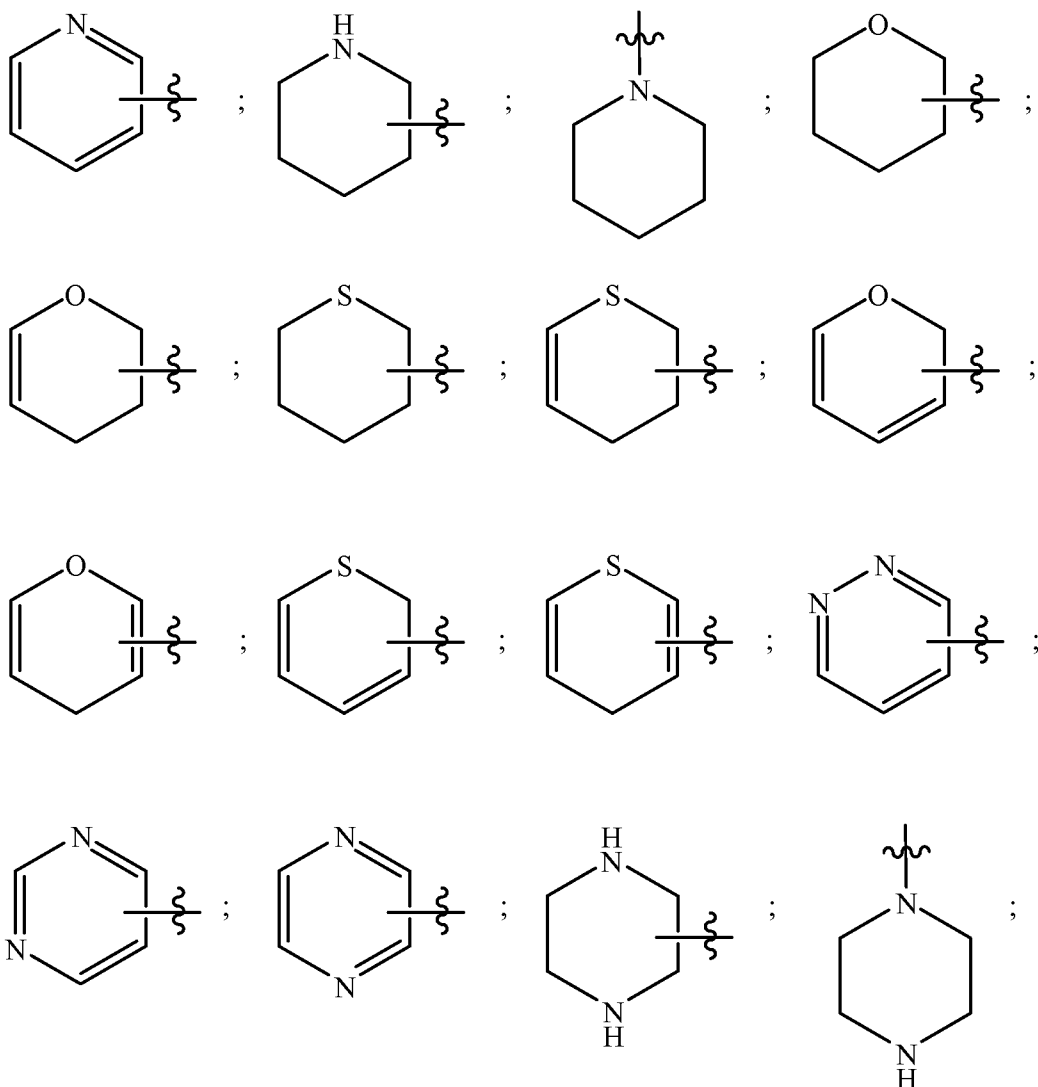
24. The composition according to claims 8-12, wherein ϵ_4 is a bond (*i.e.*, absent).

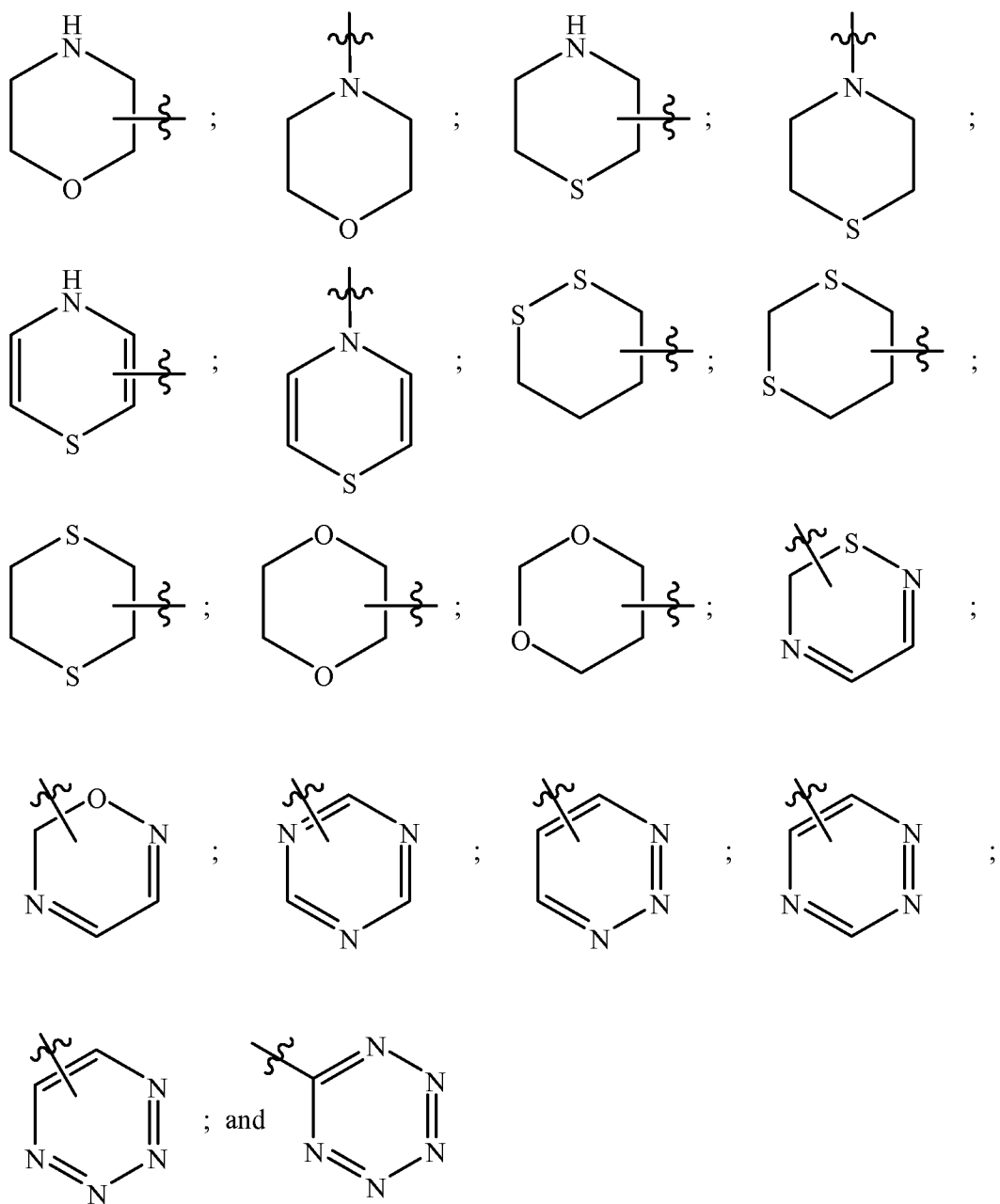
25. The composition according to claim 1, 2, 8, 14, and 19, wherein Z_1 is $-C-$ and Q has the form:



where R_5 - R_9 are independently selected from hydrogen, R, or L_2 .

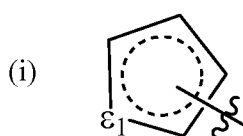
26. The composition according to claim 1, wherein Q is selected from the group consisting of:

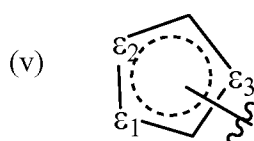
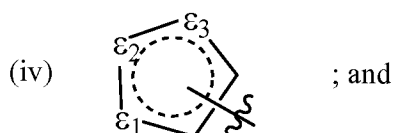
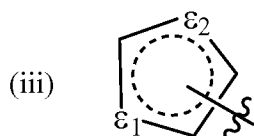
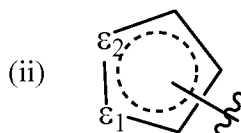




wherein any available site on the ring Q may be optionally substituted with a group R or may optionally connect with X_1 , X_2 , or X_3 through a group L_2 .

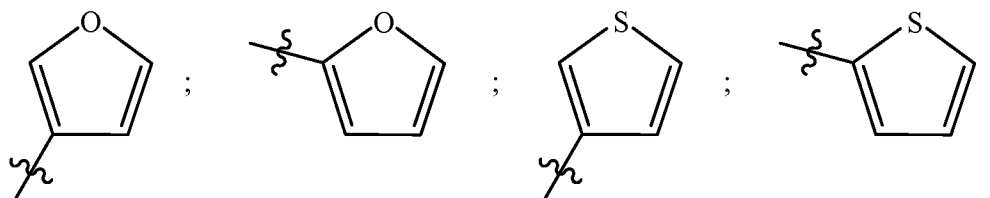
27. The composition according to claim 1, wherein Q represents a five-membered heterocyclic ring selected from the following:

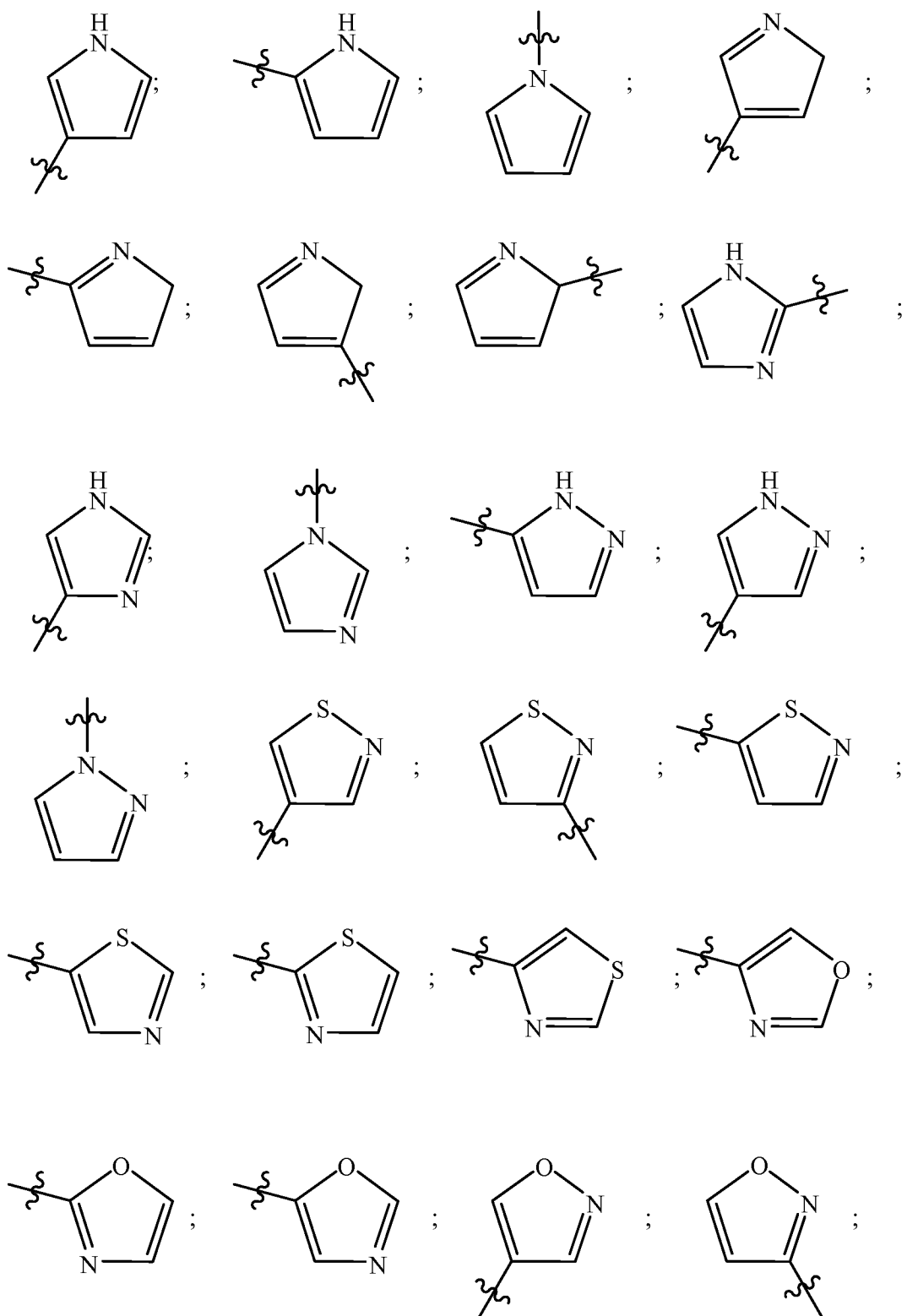


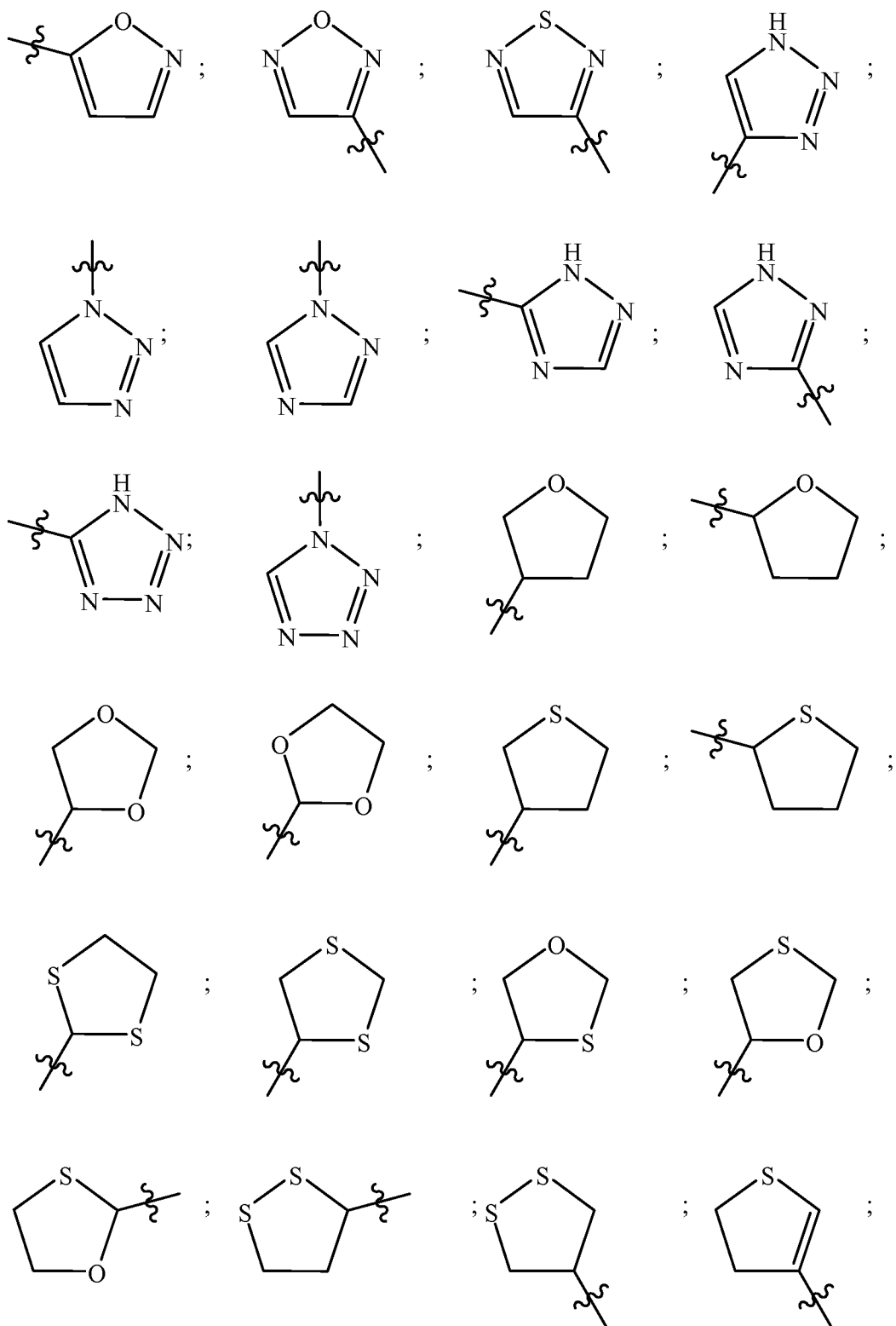


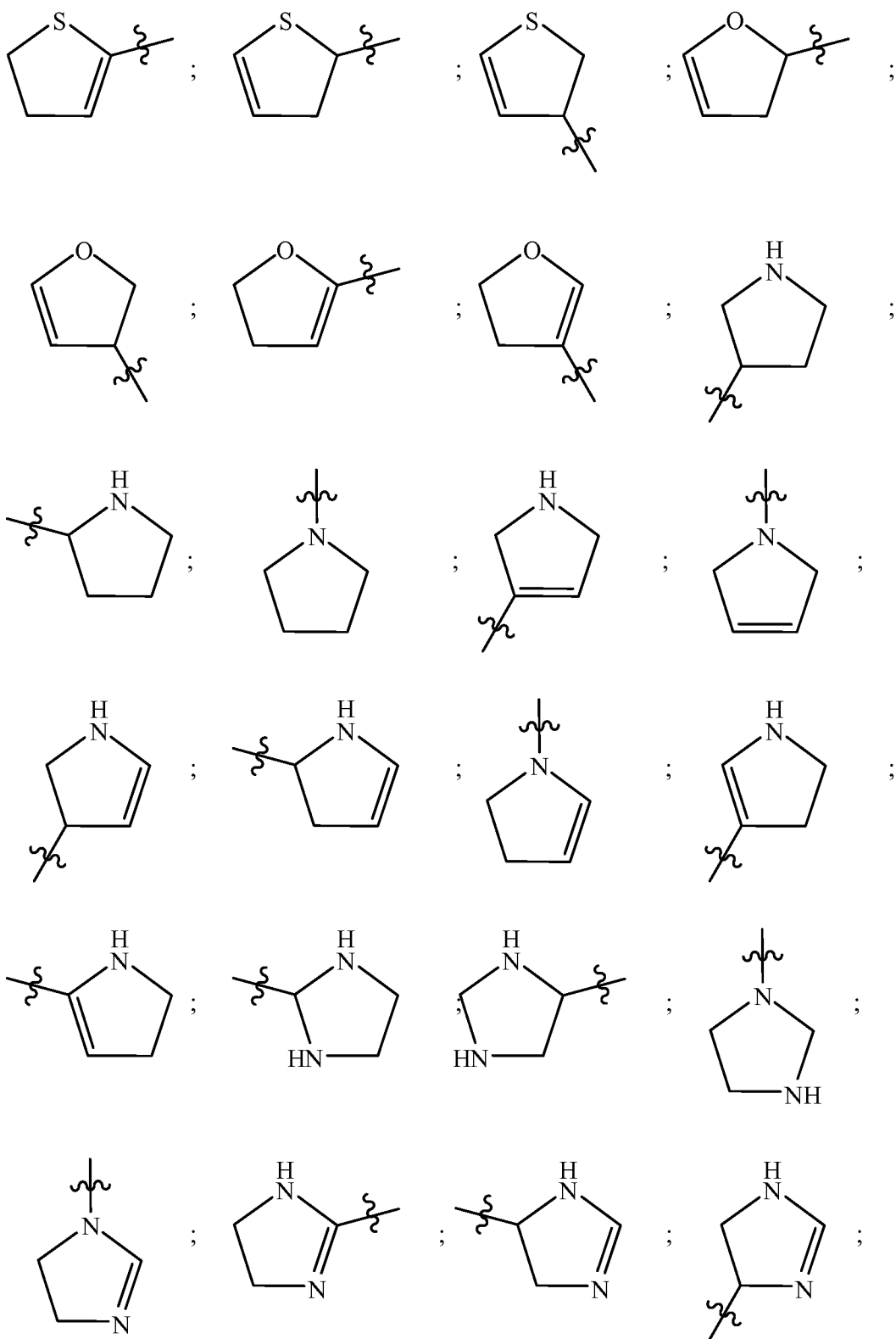
wherein ϵ_1 , ϵ_2 , and ϵ_3 , are independently selected from N, NH, NR^* , NL_2 , S, and O;
with the proviso that where the point of attachment is ϵ_1 , ϵ_2 , or ϵ_3 , then that position represents N; and wherein carbon atoms which are not the point of attachment may be optionally substituted with a group R or L_2 ; and wherein the dashed circles indicate that each ring may comprise zero, one, or two double bonds.

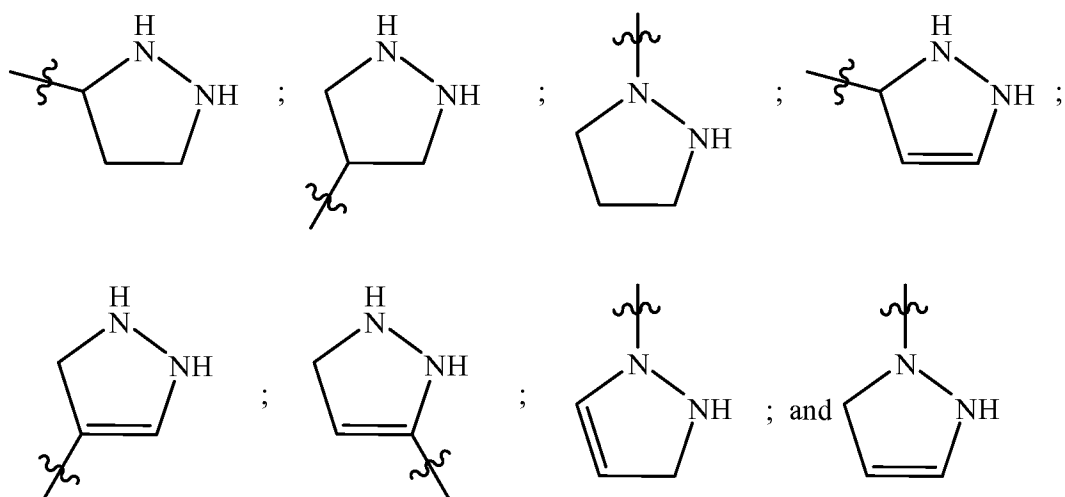
28. The composition according to claim 27, wherein Q is selected from the group consisting of:





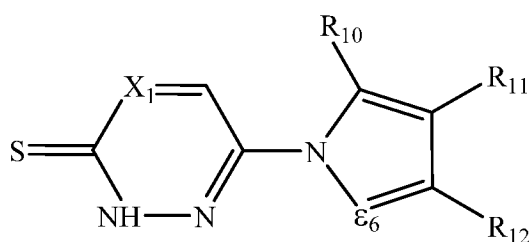






wherein any available site on the ring Q may be optionally substituted with a group R or may optionally connect with X_1 , X_2 , or X_3 through a group L_2 .

29. The composition according to claim 8, wherein the compound has the structure:

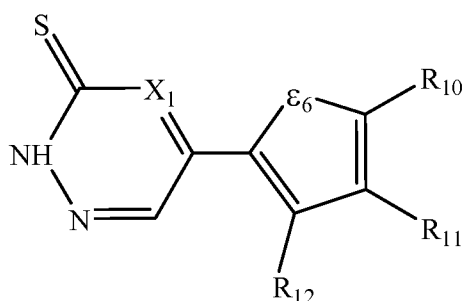


where X_1 is CH or N; ϵ_6 is CH, CR, or N; and R_{10} , R_{11} , and R_{12} are independently a group R.

30. The composition according to claim 29, wherein X_1 is CH; ϵ_6 is N; R_{11} is hydrogen, and R_{10} and/or R_{12} are independently hydrogen or lower alkyl.

31. The composition according to claim 30, wherein R_{10} and R_{12} are methyl.

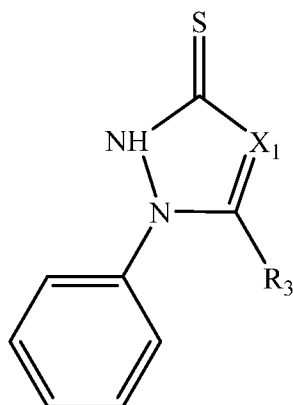
32. The composition according to claim 14, wherein the compound has the structure:



where X_1 is CH or N; ϵ_6 is O, S, or NH; and R_{10} , R_{11} , and R_{12} are independently a group R.

33. The composition according to claim 32, wherein X_1 is N; ϵ_6 is S; R_{10} , R_{11} and R_{12} are hydrogen.

34. The composition according to claim 2, wherein the compound has the structure:

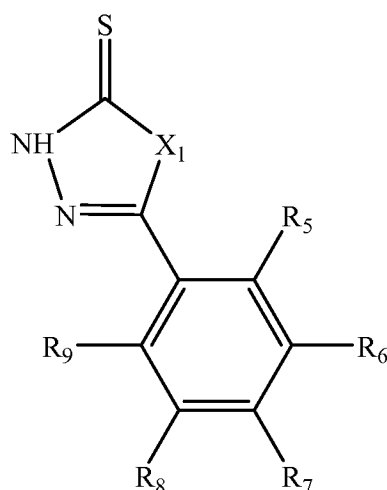


where X_1 is CH or N; and R_3 is a group R, and any position of the phenyl group is optionally and independently substituted with a group R, and wherein any two adjacent substituents R may together form a 5 or 6-membered ring.

35. The composition according to claim 32, wherein X_1 is N; and R_3 is lower alkyl.

36. The composition according to claim 32, wherein R_3 is isopropyl.

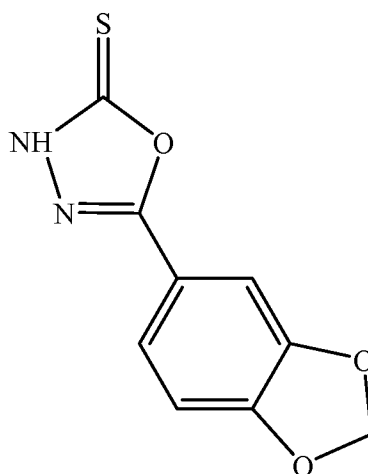
37. The composition according to claim 14, wherein the compound has the structure:



where X_1 is O, S, CH_2 , or NH; and R_5 – R_9 are independently a group R, wherein any two adjacent substituents R may together form a 5 or 6-membered ring.

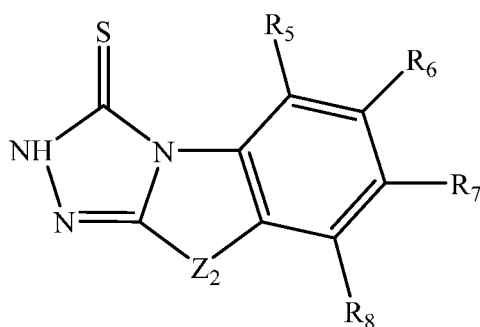
38. The composition according to claim 37, wherein X_1 is O; and R_5 , R_8 , and R_9 are hydrogen, and R_8 and R_9 are alkoxyl groups of the form $-OR^a$, where R^a is a C1–C4 alkyl, or where R_8 and R_9 may together form a substituent $-OR^a$, where R^a is $-CH_2-$ or $-CH_2CH_2-$ such that R_8 and R_9 together form a five or six membered ring.

39. The composition according to claim 38, having the structure:



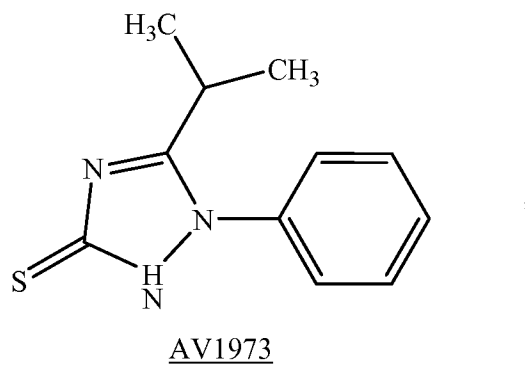
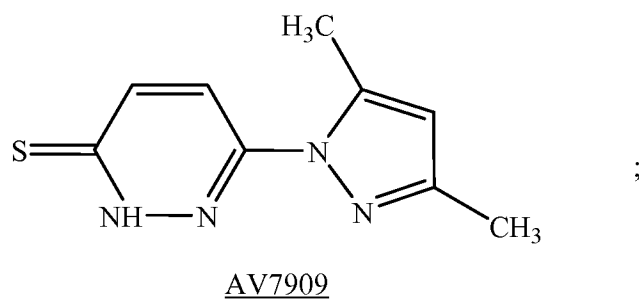
and cosmetically acceptable salts thereof.

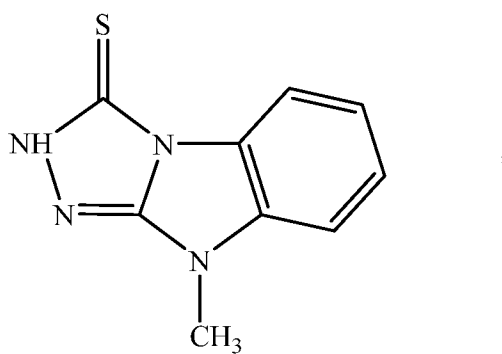
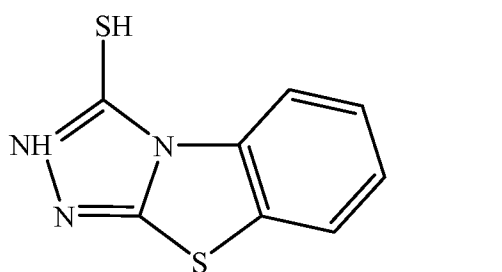
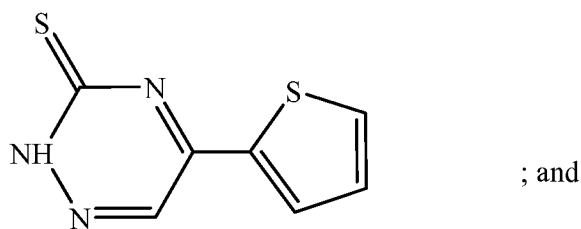
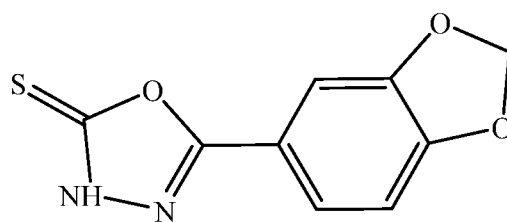
40. A composition according to claim 1, having the structure:



where Z_2 is O, S, CH_2 , NH, NR^* ; and R_5 – R_8 are independently a group R, wherein any two adjacent substituents R may together form a 5 or 6-membered ring.

41. The composition according to claim 40, wherein Z_2 is S.
42. The composition according to claim 40, wherein Z_2 is NR^* , where R^* is lower alkyl.
43. The composition according to claims 40-42 where R_5 – R_8 are hydrogen.
44. A cosmetic composition comprising an effective amount of a compound selected from the group consisting of:



AV7533AV0442AV4926AV5828

and cosmetically acceptable salts thereof, and a cosmetically acceptable vehicle.

45. The cosmetic composition further comprising one or more of a film forming polymer, a thickener, a pH adjuster, a preservative, an emulsifier, a gelling agent, an antioxidant, an emollient, a humectant, a fragrance, and a colorant.

46. The composition according to claim 45, wherein said cosmetically acceptable vehicle comprises a water-in-oil, oil-in-water, silicone-in-water, or water-in-silicone emulsion and further comprises an emulsifier.

47. The composition according to claim 45, wherein said effective amount comprises from about 0.00001% to about 1% by weight of said composition.

48. The composition according to claim 47, further comprising a retinoid selected from the group consisting of retinoic acid, retinol, retinal, retinyl acetate, and retinyl palmitate.

49. A method for reducing unwanted pigmentation in a human keratinous substrate comprising topically applying to said keratinous substrate a composition according to any of claims 1-48, for a time sufficient to reduce pigmentation.

50. The method of claim 49, wherein the unwanted pigmentation is one or more of skin discoloration, freckles, age spots, liver spots, sun damaged skin, tanned skin, pigmented acne marks, scars, pigmented birthmarks, skin hyperpigmentation, post-inflammatory skin hyperpigmentation, post-injury skin hyperpigmentation, melasma, cholasma, after-burn scar, nail stain, yellowing of skin, and dark circles under eyes.

51. A method for lightening human keratinous substrate relative to a baseline comprising topically applying to said keratinous substrate a composition according to any of claims 1-48, for a time sufficient to lighten said keratinous substrate.

52. The method of claim 51, wherein the keratinous substrate is skin.

53. A method for improving the aesthetic appearance of human skin comprising topically applying to an area of the skin in need thereof a composition according to any of claims 1-48, for a time sufficient to improve the aesthetic appearance of said human skin.

54. The method according to claim 53, wherein said aesthetic improvement of said human skin is selected from the group consisting of:

- (a) treatment, reduction, and/or prevention of fine lines or wrinkles;
- (b) reduction of skin pore size;
- (c) improvement in skin thickness, plumpness, and/or tautness;
- (d) improvement in skin smoothness, suppleness and/or softness;

- (e) improvement in skin tone, radiance, and/or clarity;
- (f) improvement in procollagen, and/or collagen production;
- (g) improvement in maintenance and remodeling of elastin;
- (h) improvement in skin texture and/or promotion of retexturization;
- (i) improvement in skin barrier repair and/or function;
- (j) improvement in appearance of skin contours;
- (k) restoration of skin luster and/or brightness;
- (l) replenishment of essential nutrients and/or constituents in the skin;
- (m) improvement of skin appearance decreased by aging and/or menopause;
- (n) improvement in skin moisturization;
- (o) increase in skin elasticity and/or resiliency;
- (p) treatment, reduction, and/or prevention of skin sagging;
- (q) improvement in skin firmness; and
- (r) reduction of pigment spots and/or mottled skin; and
- (s) improvement of optical properties of skin by light diffraction or reflection.

55. The method according to any of claims 49-54, wherein said composition is applied at least once daily for a period of at least four weeks.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US14/21020

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/50, 31/535; C07D 237/02 (2014.01)

USPC - 514/247, 252.01; 544/11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/50, 31/535; C07D 237/02, 413/04, 413/14, 471/04 (2014.01)

USPC - 514/247, 252.01; 544/11, 66, 239, 241

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; PubMed; IP.com; cosmetic composition, appearance, human skin, 4-phenyl-3H-trihydro-1,3,4-oxadiazin-2-thione, 1-phenyl-2,3-dihydro-1H-pyrazole-3-thione, 5-phenyl-1,2,4-triazine-3-thione, 6-(3,5-dimethyl-1H-pyrazol-1-yl)pyridazine-3-thiol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A Y	US 5,086,052 A (BROOKS, DW et al.) February 4, 1992; column 1, lines 30-35, 49-55, 60-65; column 9, lines 39, 44-46; column 10, lines 35-50; column 59, lines 5-20, table 9, 4-phenyl-3H-trihydro-1,3,4-oxadiazin-2-thione	1-3, 5 --- 4
Y	COMMONWEALTH OF PENNSYLVANIA. The Controlled Substances, Drugs, Device, and Cosmetic Act. Act of 1972, P.L. 233, No. 64, pp. 1-32 [online], [retrieved on 2014-05-06]. Retrieved from the Internet <URL: http://www.health.state.pa.us/pdf/ddc/ddcAct.pdf >; page 3, paragraph 16; page 4, paragraph 12	1-3, 5
Y	DEHAVEN, C. Causes of Skin Aging. Science of Skincare, LLC, 2007, pp 1-4 [online], [retrieved on 2014-05-06]. Retrieved from the Internet <URL: http://www.isclinical.com/whitepapers/skin-aging.pdf >; page 1, paragraph 8	1-3, 5
X --- Y --- A	US 2003/0125325 A1 (HEINEMANN, U et al.) July 3, 2003; paragraphs [0124], [0139], [0205], [0270], [0364], [0374]; paragraph [0124], 1-phenyl-2,3-dihydro-1H-pyrazole-3-thione	1-2, 6, 34 --- 35-36 --- 4
X --- Y	WO 2013/007663 A1 (SCHMIDT, B et al.) January 17, 2013, see machine translation; page 14, paragraph 1; page 16, paragraph 1; page 18, paragraphs 6-8; page 19, paragraphs 3, 6, 14; page 20, paragraphs 1-3, 7; page 21, paragraph 4-5; page 23, paragraph 35	1, 8, 37-39, 44-47 --- 48
X --- Y	US 2010/0298562 A1 (DUBREUIL, DM et al.) November 25, 2010; paragraphs [0184], [0223], [0237], [0676]; paragraph [0237], 6-(pyridin-2-yl)-2H-pyridazine-3-thione	1, 8-10, 20-21, 26 --- 11, 22, 27-31



Further documents are listed in the continuation of Box C.



* Special categories of cited documents:

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

"E" earlier application or patent 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 when the document is taken alone

"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

Date of the actual completion of the international search

20 May 2014 (20.05.2014)

Date of mailing of the international search report

02 JUN 2014

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Shane Thomas

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US14/21020

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.:
X — Y	US 4,064,261 A (PAGET, CJ) December 20, 1977; column 11, lines 65-70; column 12, lines 1-5, 45-50; column 13, lines 25-30; column 15, lines 5-15, table 1, s-triazolo(3,4-b)benzothiazole-3-thio; claim 1	1, 8, 12, 19, 23, 40-41 — 42
X — Y	US 4,477,662 A (CORBETT, DF et al.) October 16, 1984; column 1, lines 5-10; column 2, lines 15-20; column 6, lines 10-20, 65-70; column 7, lines 1-2; column 12, lines 35-46, 5-phenyl-1,2,4-triazine-3-thione, compound (5)	1, 14-17 — 32-33
Y	PUBCHEM. CID 20202112. December 5, 2007, pp. 1-4, [online], [retrieved on 2014-05-06]. Retrieved from the Internet <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=20202112 >; page 1, formula, 4,5-Dihydro-6-(5-(2-(pyrrolidin-1-yl)-ethyl)-thien-2-yl)-3(2H)-pyridazinone	11, 22
Y	PUBCHEM. CID 3037083. August 9, 2005, pp. 1-3 [online], [retrieved on 2014-05-06]. Retrieved from the Internet <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3037083&loc=ec_rcs >; page 1, formula, 5-phenyl-as-triazine-3-thiol	16
Y	PUBCHEM. CID 16227230. July 30, 2007, pp. 1-3 [online], [retrieved on 2014-05-06]. Retrieved from the Internet <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=16227230&loc=ec_rcs >; page 1, formula, 6-(3,5-dimethyl-1H-pyrazol-1-yl)pyridazine-3-thiol	27-31
Y	PUBCHEM. BRN 0146267. August 9, 2005; pp. 1-3 [online], [retrieved on 2014-05-06]. Retrieved from the Internet <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3062525&loc=ec_rcs >; page 1, formula, 5-thien-2-yl-1,2,4-triazine-3(2H)-thione	32-33
Y	PUBCHEM. CID 7131297. July 29, 2007, pp. 1-3 [online], [retrieved on 2014-05-06]. Retrieved from the Internet <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=7131297&loc=ec_rcs >; page 1, formula, 5-isopropyl-1-phenyl-1H-1,2,4-triazole-3-thiol	35-36
Y	PUBCHEM. CID 703960. July 8, 2007, pp. 1-3 [online], [retrieved on 2014-05-06]. Retrieved from the Internet <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=703960&loc=ec_rcs >; page 1, formula, 9-methyl-2,9-dihydro-3H-[1,2,4]triazolo[4,3-a]benzimidazole-3-thione	42
Y	US 2010/0286102 A1 (VIELHABER, G) November 11, 2010; abstract; paragraph [0138], 5-pyrazin-2-yl-1,3,4-oxadiazole-2-thiol; paragraph [0300], table	48
A	WO 2008/051808 A2 (BOUNAUD, PY et al.) May 2, 2008; paragraph [0009], formula (I)	4
A	US 4,310,551 A (GULLO, JM et al.) January 12, 1982; entire publication	1-6, 8-12, 14-17, 19-23, 26-42, 44-48
A	EP 0 128 502 A1 (HILBOLL, G et al.) December 19, 1984; page 10, lines 5-10	11-12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US14/21020

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
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, specifically:
3. ☒ Claims Nos.: 7, 13, 18, 24-25, 43, 49-55
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ 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 claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.