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(54) Title: TAZAROTENE DERIVATIVES

(57) Abstract: The presently described subject matter relates to new derivatives of tazarotene that also exhibit retinoid activity, pharmaceutical compositions comprising the derivatives, method of treating skin disorders with the pharmaceutical compositions, and process of making the derivatives.

TAZAROTENE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to derivatives of tazarotene.

BACKGROUND OF THE INVENTION

Tazarotene has the chemical name: ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl nicotinate. Tazarotene is a retinoid prodrug which is converted to its active form, tazarotenic acid, by rapid de-esterification in most biological systems. Tazarotenic acid binds to all three members of the retinoic acid receptor (RAR) family; RAR_α, RAR_β and RAR_γ, but has relative selectivity for RAR_β and RAR_γ, and may modify gene expression.

Allergan, Inc. market TAZORAC® (tazarotene) cream and TAZORAC® (tazarotene) gel for the treatment of acne and psoriasis.

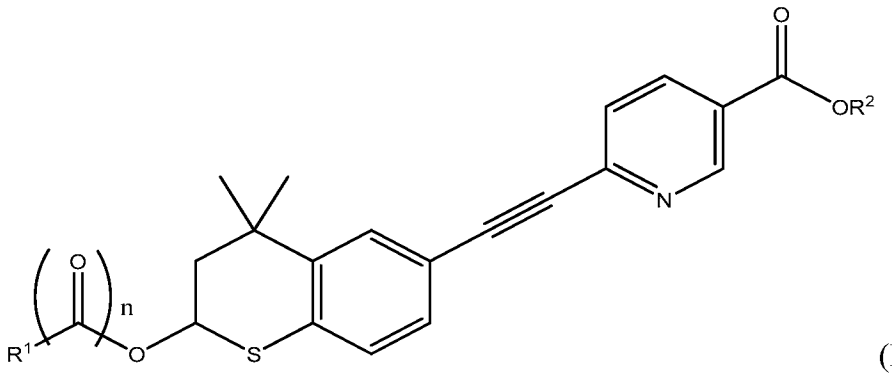
The treatment of skin disorders using a retinoid or an antibiotic in combination with benzoyl peroxide is of great interest to dermatologists. However, this presents challenges to the formulation chemist insofar as retinoids and antibiotics often readily degrade in the presence of benzoyl peroxide. Accordingly, the active ingredients are often not mixed together until immediately before administration to the patient, or are administered at different times of the day. Alternatively, the retinoid or antibiotic might be protected (e.g. by encapsulation) from reaction with the benzoyl peroxide, or the active ingredients may be housed in separate chambers of a dual chamber dispenser.

Thus, there is a need for improved dermatological compositions containing a combination of active ingredients which provide the requisite convenience, efficacy and shelf life. Specifically, a need exists for the identification of stable retinoids that may be combined with benzoyl peroxide in a pharmaceutical composition.

SUMMARY OF THE INVENTION

The present invention is directed to new derivatives of tazarotene that penetrate the skin and exhibit retinoid-like activity.

According to an embodiment, the present invention provides for a compound of general formula (I):



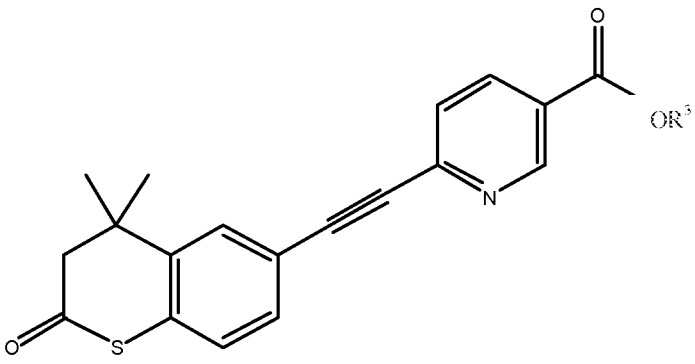
(I)

wherein n is 0 or 1;

R^1 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted cycloalkyl group, or an optionally substituted heteroaryl group; and

R^2 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted cycloalkyl group, or an optionally substituted heteroaryl group; or a pharmaceutically acceptable salt thereof.

According to another embodiment, the present invention provides a compound of formula (II):



(II)

wherein

R^3 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted cycloalkyl group, or an optionally substituted heteroaryl group; or a pharmaceutically acceptable salt thereof.

According to another embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula (I) or (II), or a pharmaceutically

acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

In a further embodiment, the present invention provides a method of treating a skin disorder in a subject, the method comprising administering a composition comprising a therapeutically effective amount of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, to a subject in need thereof.

In an embodiment, the present invention relates to the use of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a skin disorder.

In another embodiment, the present invention relates to the use of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, for the treatment of a skin disorder.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 illustrates the degradation of tazarotene into its degradation products when DUAC® gel and TAZORAC® cream are mixed together. The degradation was observed over 8 hours once "fresh" samples of DUAC gel and TAZORAC cream were mixed.

Figure 2A illustrates the amount of tazarotene sulfoxide and tazarotenic acid in stability samples (at least 4 replicates and 4 donors ($n \geq 17$) ± SEM).

Figure 2B illustrates the amount of tazarotene benzoate in stability samples (at least 4 replicates and 4 donors ($n \geq 17$) ± SEM).

Figure 3A illustrates the amount of tazarotene, tazarotene sulfoxide and tazarotenic acid in the epidermis 2 hours post-application (at least 4 replicates and 4 donors ($n \geq 17$) ± SEM).

Figure 3B illustrates the amount of tazarotene, tazarotene sulfoxide and tazarotenic acid in the dermis 2 hours post-application (at least 4 replicates and 4 donors ($n \geq 17$) ± SEM).

Figure 4A illustrates the amount of tazarotene, tazarotene sulfoxide and tazarotenic acid in the epidermis 6 hours post-application (at least 4 replicates and 4 donors ($n \geq 17$) ± SEM).

Figure 4B illustrates the amount of tazarotene, tazarotene sulfoxide and tazarotenic acid in the dermis 6 hours post-application (at least 4 replicates and 4 donors ($n \geq 17$) ± SEM).

Figure 5A illustrates the amount of tazarotene benzoate in the epidermis and

dermis 2 hours post-application (at least 4 replicates and 4 donors ($n \geq 17$) ± SEM).

Figure 5B illustrates the amount of tazarotene benzoate in the epidermis and dermis 6 hours post-application (at least 4 replicates and 4 donors ($n \geq 17$) ± SEM).

Figure 6 illustrates skin penetration from mixtures of DUAC gel and TAZORAC cream. The data points represent the cumulative amount of tazarotene sulfoxide from at least 4 replicates from 4 donors ($n \geq 18$) ± SEM.

Figure 7 illustrates pro-inflammatory cytokine (IL-1α and IL-8) release from SkinEthic RHE cultures following exposure to various retinoids. Each bar represents the average of duplicate cultures (± Stdev).

Figure 8 illustrates the PMA-induced IL-6 release from A431 cultures following exposure to various retinoids. Each bar represents the average of triplicate cultures (± Stdev).

Figure 9 illustrates the stability of tazarotene, tazarotene sulfoxide and tazarotene benzoate in rat plasma at room temperature.

Figure 10 illustrates the stability of tazarotene, tazarotene sulfoxide and tazarotene benzoate in human plasma at room temperature.

Figure 11 illustrates the peak for tazarotene benzoate measured with a Shimadzu HPLC – Applied Biosystems 4000 QTRAP.

Figure 12 illustrates the peak for hydroxytazarotenic acid measured with a Shimadzu HPLC – Applied Biosystems 4000 QTRAP.

Figure 13 illustrates the mass spectra fragmentation of hydroxytazarotenic acid.

Figure 14 illustrates the mass spectra fragmentation of tazarotenic acid sulfoxide.

Figure 15 illustrates the amount of IL-1α released in the presence of various retinoids.

Figure 16 illustrates the amount of IL-8 released in the presence of various retinoids.

Figure 17 illustrates the biological (retinoid) activity of various metabolites and analogues of tazarotene benzoate i.e. by determining gene expression levels for K4. The respective metabolites and analogues are shown in Table 11 (labeled compounds 1 to 29).

Figure 18 illustrates the biological (retinoid) activity of various metabolites and analogues of tazarotene benzoate i.e. by determining gene expression levels for K10. The respective metabolites and analogues are shown in Table 11.

Figure 19 illustrates the biological (retinoid) activity of various metabolites and analogues of tazarotene benzoate i.e. by determining gene expression levels for K13. The respective metabolites and analogues are shown in Table 11.

Figure 20 illustrates the biological (retinoid) activity of various metabolites and analogues of tazarotene benzoate i.e. by determining gene expression levels for K19. The respective metabolites and analogues are shown in Table 11.

Figure 21 illustrates the biological (retinoid) activity of various metabolites and analogues of tazarotene benzoate i.e. by determining gene expression levels for filaggrin. The respective metabolites and analogues are shown in Table 11.

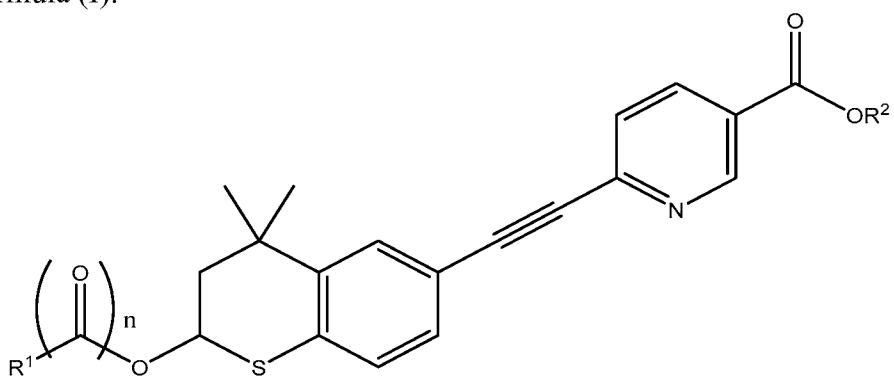
Figure 22 illustrates the proposed metabolism of tazarotene.

Figure 23 illustrates the proposed metabolism of tazarotene benzoate.

Figures 24A, 24B and 24C illustrate the enhanced stability of tazarotene benzoate and tazarotene nicotinate in the presence of benzoyl peroxide, relative to tazarotene and hydroxy tazarotenic acid.

DETAILED DESCRIPTON OF THE INVENTION

According to an embodiment, the present invention provides a compound of general formula (I):



(I)

wherein n is 0 or 1;

R^1 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted C_{3-7} cycloalkyl group, or an optionally substituted heteroaryl group; and

R^2 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted C_{3-7} cycloalkyl group, or an optionally substituted heteroaryl group; or a pharmaceutically acceptable salt thereof.

Suitably, n is 0 or an integer having a value of 1. In one embodiment, n is 1. In another embodiment n is 0. In one embodiment, n is 0, and R^1 is hydrogen.

Suitably, R^1 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted C_{3-7} cycloalkyl group, or an optionally substituted heteroaryl group.

Suitably, R^2 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted C_{3-7} cycloalkyl group, or an optionally substituted heteroaryl group.

When R^1 is an optionally substituted C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocyclic, cycloalkyl or heteroaryl group, the group is optionally substituted one or more times, preferably 1 to 4 times independently by halogen; hydroxy; NR_4R_5; hydroxy substituted C_{1-6} alkyl; C_{1-6} alkoxy, such as methoxy or ethoxy; halosubstituted C_{1-6} alkoxy, halosubstituted C_{1-6} alkyl, such as CF_2CF_2H or CF_3; C_{1-6} alkyl such as methyl, ethyl, isopropyl etc.; $-C(O)OR_6$, or $-OC(O)R_6$. In one embodiment, the optional substituents are selected from hydroxy, NR_4R_5, or hydroxy substituted C_{1-6} alkyl, or $-C(O)OR_6$.

Suitably, R_4 and R_5 are independently selected from hydrogen or C_{1-6} alkyl. In one embodiment both R_4 and R_5 are hydrogen.

Suitably, R_6 is independently selected from hydrogen or C_{1-6} alkyl. In one embodiment R_6 is C_{1-6} alkyl. In another embodiment the C_{1-6} alkyl is methyl.

Suitably, when R^1 or R^2 is an optionally substituted aryl group, the aryl is an aromatic cyclic hydrocarbon group of from 5 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings, such as naphthyl, indene or anthryl. In one embodiment the aryl group is an optionally substituted phenyl, naphthyl or indene. In another embodiment the R^1 aryl group is an optionally substituted phenyl or naphthyl. In another embodiment, R^1 is an optionally substituted phenyl. In another embodiment, R^1 is phenyl or hydroxy substituted phenyl.

Suitably, when R^1 or R^2 is an optionally substituted heteroaryl group, the heteroaryl ring is a monocyclic five- to seven- membered unsaturated aromatic hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Suitable rings include, but are not limited to, furyl, pyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxathiadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or uracil. The heteroaryl group may also include fused aromatic rings comprising at least one heteroatom selected from oxygen, nitrogen and sulfur. Each of the fused rings contains five or six ring atoms. Suitable examples of fused aromatic rings include, but are

not limited to, indolyl, isoindolyl, indazolyl, indolizinyl, azaindolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, purinyl or phthalazinyl.

In one embodiment, when R^1 is an optionally substituted heteroaryl group, the heteroaryl is an optionally substituted 2-, 3- or 4-pyridyl or pyranyl ring. In another embodiment the heteroaryl is an optionally substituted 2-, 3- or 4-pyridyl. In another embodiment R^1 is an optionally substituted pyrid-3-yl.

Suitably, when R^1 or R^2 is an optionally substituted heterocyclic group, the heterocyclic ring is a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom selected from nitrogen, oxygen, sulphur or oxidized sulphur moieties, such as S(O)m, and m is 0 or an integer having a value of 1 or 2. The heterocyclic group may also include fused rings, saturated or partially unsaturated, and wherein one of the rings may be aromatic or heteroaromatic. Each of the fused rings may have from four to seven ring atoms. Suitable examples of heterocyclyl groups include, but are not limited to, the saturated or partially saturated versions of the heteroaryl moieties as defined above, such as tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), azepine, diazepine, aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety).

Suitably, when R^1 is an optionally substituted heterocyclic group, the heterocyclic is an optionally substituted piperidinyl, piperazinyl, tetrahydropyranyl or tetrahydrofuranyl ring. In one embodiment the heterocyclic ring is an optionally substituted 2-, 3- or 4-piperidinyl. In one embodiment the 2-, 3- or 4- piperidinyl is substituted by a C_{1-6} alkyl. In one embodiment, the C_{1-6} alkyl is methyl. In another embodiment R^1 is a 4-methylpiperidin-4-yl group.

In one embodiment, R^1 is an optionally substituted C_{1-18} alkyl. In an embodiment, R^1 is a C_{1-18} alkyl optionally substituted, independently, one or more times by hydroxy, NR_4R_5, C_{1-6} alkoxy, or $-C(O)OR_6$. In another embodiment the C_{1-18} alkyl is unsubstituted. In another embodiment R^1 is a C_{1-3} alkyl or a C_{15} alkyl. In another embodiment R^1 is a C_{1-3} alkyl. In another embodiment the C_{1-18} alkyl is substituted by-$C(O)OR_6$. In another embodiment, R_6 is a C_{1-6} alkyl, preferably methyl.

In one embodiment, R^1 is an optionally substituted C_{2-18} alkenyl.

In another embodiment, R^1 is an optionally substituted aryl, heteroaryl or heterocyclic group.

In another embodiment, R^1 is selected from an optionally substituted C_{1-18} alkyl, a C_{2-18} alkenyl, optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted tetrahydropyranyl, or optionally substituted piperidinyl. In a further embodiment, R^1 is selected from an optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted tetrahydropyranyl, or optionally substituted piperidinyl group.

When R^2 is an optionally substituted C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocyclic, cycloalkyl or heteroaryl group, the group is optionally substituted one or more times, preferably 1 to 4 times, independently by halogen; hydroxy; NR_4R_5; hydroxy substituted C_{1-6} alkyl; C_{1-6} alkoxy, such as methoxy or ethoxy; halosubstituted C_{1-6} alkoxy; halosubstituted C_{1-6} alkyl, such as CF_2CF_2H or CF_3; C_{1-6} alkyl such as methyl, ethyl, isopropyl, etc.; $-C(O)OR_6$ or $-OC(O)R_6$.

In one embodiment R^2 is hydrogen or optionally substituted C_{1-18} alkyl. In an embodiment, R^2 is hydrogen or optionally substituted C_{1-6} alkyl. In another embodiment, R^2 is hydrogen. In another embodiment, R^2 is C_{1-6} alkyl. According to a further embodiment, R^2 is ethyl.

According to one embodiment, n is 1, R^1 is phenyl and R^2 is hydrogen or C_{1-6} alkyl. In another embodiment, n is 1, R^1 is phenyl and R^2 is hydrogen. This compound is known as 6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, and is also described herein as tazarotenic acid benzoate.

In another embodiment, n is 1, R^1 is phenyl and R^2 is C_{1-6} alkyl. In one embodiment, the C_{1-6} alkyl is ethyl. This compound is known as 6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester, and is described herein as tazarotene benzoate.

In another embodiment, the compound is (S)-6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester. In another embodiment, the compound is (R)-6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester.

According to a further embodiment, n is 0, R^1 is hydrogen and R^2 is hydrogen or C_{1-6} alkyl. In an embodiment, R^2 is hydrogen. This compound is 6-((2-hydroxy-4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid, and is also described herein as hydroxy tazarotenic acid.

In another embodiment, n is 0, R^1 is hydrogen and R^2 is C_{1-6} alkyl. According to a further embodiment, C_{1-6} alkyl is ethyl. This compound is ethyl 6-[(2-hydroxy-4,4-

dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethyynyl] pyridine-3-carboxylate, and is also described herein as hydroxy tazarotene.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge *et al.*, J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

According to an embodiment, a compound of Formula (I), is selected from:

(i) 6-[4,4-dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester,

(ii) (S)-6-[4,4-dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester,

(iii) (R)-6-[4,4-dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester,

(iv) Ethyl 6-[2-palmitoyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate,

(v) 6-[2-(2-Hydroxy-acetoxy)-4,4-dimethyl-thiochroman-6-ylethyny1]-nicotinic acid ethyl ester,

(vi) Ethyl 6-[(2-(2-methoxyacetyl)-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate,

(vii) Ethyl 6-[(2-acetyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate,

(viii) Ethyl 6-[(2-n-butyryloxyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate,

(ix) Ethyl 6-[(2-lauroyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate,

(x) Ethyl 6-[(2-isobutyryloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate,

(xi) Ethyl 6-[(2-linoeoyll-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate,

(xii) Ethyl 6-[(2-linleolyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate,

(xiii) Ethyl 6-[(2-(N-methyl-4-piperidinylcarboxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate,

(xiv) Ethyl 6-[(2-propionyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate,

(xv) Ethyl 6-[(2-salicylicyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate,

(xvi) Ethyl 6-[(2-(4-pyranyloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate,

(xvii) Ethyl 6-[(2-monomethyladopyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate,

(xviii) Ethyl 6-[(2-(3-monomethylazelauate-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate, and

(xix) 6-[2-((S)-2-Amino-3-methyl-butyryloxy)-4,4-dimethyl-thiochroman-6-ylethynyl]-nicotinic acid ethyl ester; or

a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is 6-[4,4-dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is (S)-6-[4,4-dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is (R)-6-[4,4-dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[2-palmitoyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is 6-[2-(2-Hydroxy-acetoxy)-4,4-dimethyl-thiochroman-6-ylethyny1]-nicotinic acid ethyl ester, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-(2-methoxyacetyl)-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-acetyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-n-butyryloxyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-lauroyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof. Suitably, the compound of Formula (I) is ethyl 6-[(2-isobutyryloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-linoeoyll-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-linleolyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-(N-methyl-4-piperidinylcarboxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-propionyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-salicylicyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-(4-pyranyloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-monomethyladopyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is ethyl 6-[(2-(3-monomethylazelauate-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate, or a pharmaceutically acceptable salt thereof.

Suitably, the compound of Formula (I) is 6-[2-((S)-2-Amino-3-methyl-butyryloxy)-4,4-dimethyl-thiochroman-6-ylethynyl]-nicotinic acid ethyl ester, or a pharmaceutically acceptable salt thereof.

According to another embodiment, the compound of Formula (I) is selected from the group consisting of:

Ethyl 6-[(2-propionyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-(N-methyl-4-piperidinylcarboxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

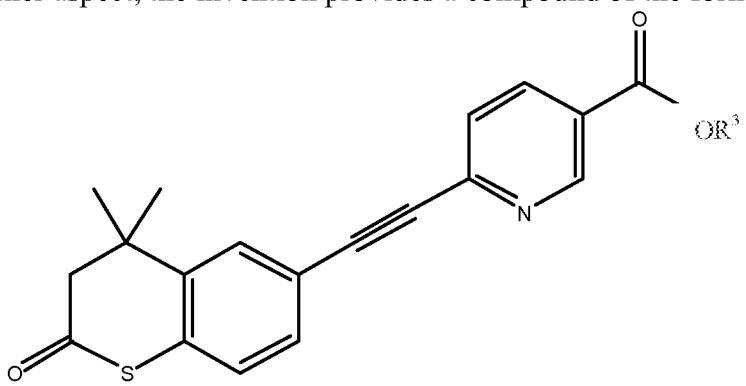
6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinic acid;

6-[2-((S)-2-Amino-3-methyl-butyryloxy)-4,4-dimethyl-thiochroman-6-ylethynyl]-nicotinic acid ethyl ester;

6-[2-(2-Hydroxy-acetoxy)-4,4-dimethyl-thiochroman-6-ylethyny1]-nicotinic acid ethyl ester; and

Ethyl 6-[(2-monomethyladopyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate; or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a compound of the formula:



(II)

wherein

R^3 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted C_{3-7} cycloalkyl group, or an optionally substituted heteroaryl group; or a pharmaceutically acceptable salt thereof.

When R^3 is an optionally substituted C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocyclic, cycloalkyl or heteroaryl group, the group is optionally substituted one or more times, preferably 1 to 4 times independently by halogen; hydroxy; NR_4R_5; hydroxy substituted C_{1-6} alkyl; C_{1-6} alkoxy, such as methoxy or ethoxy; halosubstituted C_{1-6} alkoxy; halosubstituted C_{1-6} alkyl, such as CF_2CF_2H or CF_3; C_{1-6} alkyl such as methyl, ethyl, isopropyl, etc.; $-C(O)OR_6$ or $-OC(O)R_6$.

Suitably, R_4 and R_5 are independently selected from hydrogen or C_{1-6} alkyl. In one embodiment both R_4 and R_5 are hydrogen.

Suitably, R_6 is independently selected from hydrogen or C_{1-6} alkyl. In one embodiment R_6 is C_{1-6} alkyl. In another embodiment the C_{1-6} alkyl is methyl.

When R^3 is an optionally substituted aryl group, it is as defined above for R^1 or R^2 in Formula (I) herein.

When R^3 is an optionally substituted heteroaryl group, it is as defined above for R^1 or R^2 in Formula (I) herein.

When R^3 is an optionally substituted heterocyclic group, it is as defined above for R^1 or R^2 in Formula (I) herein.

In one embodiment, R^3 is hydrogen or an optionally substituted C_{1-6} alkyl.

In one embodiment, R^3 is hydrogen. This compound is 6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinic acid, and is also described herein as keto tazarotenic acid.

According to another embodiment, R^3 is C_{1-6} alkyl. In another embodiment, the C_{1-6} alkyl is ethyl. This compound is ethyl 6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinate, and is also described herein as keto tazarotene.

Tazarotene benzoate

According to a particular embodiment, the compound is 6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester (i.e. tazarotene benzoate). Tazarotene benzoate is formed by combining tazarotene and benzoyl peroxide. This novel compound penetrates the skin and has retinoid-like activity. The S and R enantiomers have been isolated and characterized, and described herein. A range of analogues and metabolites of tazarotene benzoate have also been isolated, synthesized and characterized as is further described.

Active metabolites of tazarotene

Known metabolites of tazarotene i.e. tazarotene sulfoxide and tazarotenic acid, have been shown to penetrate the skin. However, other known metabolites of tazarotene, namely ethyl 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinate (tazarotene sulfone), 6-((4,4-dimethyl-1-oxidothiochroman-6-yl)ethynyl)nicotinic acid (tazarotenic acid sulfoxide), and 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinic acid (tazarotenic acid sulfone), which were previously thought by others to have little or no retinoid activity, have been discovered to exert retinoid like activity (Figure 22 and Example 3).

Accordingly, the present invention also relates to a method of treating a skin disorder in a subject, the method comprising administering a composition comprising a

therapeutically effective amount of a compound selected from the group consisting of ethyl 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinate, 6-((4,4-dimethyl-1-oxidothiochroman-6-yl)ethynyl)nicotinic acid and 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinic acid, or a pharmaceutically acceptable salt thereof, along with one or more pharmaceutically acceptable excipients, to a subject in need thereof.

In an embodiment, the present invention relates to the use of a compound selected from the group consisting of ethyl 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinate, 6-((4,4-dimethyl-1-oxidothiochroman-6-yl)ethynyl)nicotinic acid and 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinic acid, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a skin disorder.

In another embodiment, the invention relates to the use of a compound selected from the group consisting of ethyl 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinate, 6-((4,4-dimethyl-1-oxidothiochroman-6-yl)ethynyl)nicotinic acid and 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinic acid, or a pharmaceutically acceptable salt thereof, for the treatment of a skin disorder.

In yet another embodiment, the invention relates to a pharmaceutical composition comprising a compound selected from the group consisting of ethyl 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinate, 6-((4,4-dimethyl-1-oxidothiochroman-6-yl)ethynyl)nicotinic acid and 6-((4,4-dimethyl-1,1-dioxidothiochroman-6-yl)ethynyl)nicotinic acid, or a pharmaceutically acceptable salt thereof, along with one or more pharmaceutically acceptable excipients.

Pharmaceutical Compositions

According to an embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients.

In one embodiment, the pharmaceutical composition comprises a second pharmaceutically active agent.

In one embodiment, the second pharmaceutically active agent is selected from the group consisting benzoyl peroxide, an antibiotic, a corticosteroid and a vitamin D analogue.

In an embodiment, the second pharmaceutically active agent is benzoyl peroxide.

In another embodiment, the second pharmaceutically active agent is an antibiotic,

such as clindamycin or a pharmaceutically acceptable salt thereof (e.g. clindamycin phosphate).

In another embodiment, the second pharmaceutically active agent is a corticosteroid. Suitable corticosteroids include, but are not limited to, alclometasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, budesonide, clobetasol propionate, clobetasone butyrate, cortisone acetate, desonide, desoximetasone, diflorasone diacetate, diflucortolone valerate, fluclorolone acetonide, flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluprednidene acetate, flurandrenolide, flurandrenolone, fluticasone propionate, halcinonide, halobetasol propionate, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone propionate, hydrocortisone valerate, methylprednisolone acetate, mometasone furoate, pramoxine hydrochloride, prednisone acetate, prednisone valerate, triamcinolone acetonide, prednicarbate, and pharmaceutically acceptable salts thereof.

In another embodiment, the second pharmaceutically active agent is a vitamin D analogue. Suitable vitamin D analogues include, but are not limited to, calcidiol, calcitriol, calcipotriene, paricalcitol, 22-oxacolcitriol, dihydrotachysterol, calciferol, and pharmaceutically acceptable salts thereof.

In an embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof and a second active agent, wherein the stability of the compound of Formula (I) or (II) is superior to the stability of tazarotene in a pharmaceutical composition comprising tazarotene and the second active agent. In an embodiment, the compound of Formula (I) or (II) is tazarotene benzoate or tazarotene nicotinate. According to a particular embodiment, the second active agent is benzoyl peroxide. Suitably, the amounts present in the composition are therapeutically effective amounts for the treatment of skin disorders.

The compounds of the present invention may be formulated as pharmaceutical compositions and administered orally, topically, dermally, parenterally, by injection, by pulmonary or nasal delivery, sublingually, rectally or vaginally. According to a particular embodiment, the pharmaceutical composition is adapted for oral or topical administration. The term "administered by injection" includes intravenous, intraarticular, intramuscular (e.g. by depot injection where the active compounds are released slowly into the blood from the depot and carried from there to the target organs), intraperitoneal, intradermal, subcutaneous, and intrathecal injections, as well as use of infusion techniques. Dermal administration may include topical or transdermal administration. Transdermal

administration can be accomplished by suitable patches, solutions, emulsions, suspensions, ointments, pastes, powders, foams, creams, lotions or gels as generally known in the art, specifically designed for the transdermal delivery of active agents, optionally in the presence of specific permeability enhancers. Similarly, topical administration can be accomplished by a solution, emulsion, suspension, ointment, paste, powder, foam, cream, lotion or gel. In a particular embodiment, topical administration is accomplished with an aerosol foam.

Exemplary pharmaceutically acceptable excipients include abrasives, acidifying agents, adhesives, adsorbents, alkalizing agents, antibacterial agents, anticaking agents, antioxidants, binding agents, buffering agents, bulking agents, chelating agents, coating agents, coloring agents, complexing agents, controlled release agents, cooling agents, detergents, diluents, dispersing agents, dissolution enhancers, emollients, emulsifying agents, emulsion stabilizers, film forming agents, gelling agents, glidants, humectants, lubricants, opacifying agents, penetration enhancers, pH adjusting agents, pigments, plasticizers, preservatives, propellants, sequestering agents, solubilizing agents, solvents, surfactants, suspending agents, thickening agents, viscosity increasing agents and wetting agents.

The pharmaceutical composition may be formulated using methods known in the art as immediate release, sustained release, delayed release, pulsatile release or two step release, for example.

The dosage of the active agent in the pharmaceutical composition will depend upon a variety of factors, including but not limited to, the activity of the active agent, the condition being treated, the nature of the pharmaceutical composition, the mode of administration and the age, body weight, general health and gender of the patient.

Methods of Use

According to an embodiment, the present invention relates to a method of treating a skin disorder. The method comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, along with one or more pharmaceutically acceptable excipients, to a subject in need thereof.

Another to an embodiment, the skin disorder is acne, psoriasis, seborrhea, ichthyosis or keratosis pilaris. According to a particular embodiment, the skin disorder is acne or psoriasis.

Definitions

The term "halo" or "halogens" is used herein to mean the halogens, chloro, fluoro, bromo and iodo.

The term "alkyl" is used herein to mean an aliphatic hydrocarbon group which may be straight or branched chain having about 1 to about 18 carbon atoms in the chain. A preferred embodiment is an alkyl group having from 1 to about 6 carbon atoms. Alkyl as defined herein may be optionally substituted with a designated number of substituents.

The term "unsaturated" refers to the presence of one or more double or triple bonds between carbon atoms of a hydrocarbon chain.

The term "alkenyl" is used herein to mean a hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon double bond, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, vinyl, alkyl or 2-butenyl. Alkenyl as defined herein may be optionally substituted with a designated number of substituents.

The term "alkynyl" is used herein to mean a hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon triple bond, which may occur at any point along the chain. An example of an alkynyl is acetylene. Alkynyl as defined herein may be optionally substituted with a designated number of substituents.

The term “cycloalkyl” is used herein to refer to cyclic radicals, such as a non-aromatic hydrocarbon ring containing a specified number of carbon atoms. For example, C_{3-7} cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Representative examples of “cycloalkyl” as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "aryl" is used herein to mean an aromatic cyclic hydrocarbon group of from 5 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g. naphthyl or anthryl). Preferred aryl groups include phenyl and naphthyl.

The terms “heteroaryl ring”, “heteroaryl moiety”, and “heteroaryl” are used herein to mean a monocyclic five- to seven- membered unsaturated aromatic hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Examples of heteroaryl rings include, but are not limited to, furyl, pyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxathiadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and uracil. The terms “heteroaryl ring”, “heteroaryl moiety”, and “heteroaryl” shall also be used herein to refer to fused aromatic rings comprising at least

one heteroatom selected from oxygen, nitrogen and sulfur. Each of the fused rings may contain five or six ring atoms. Examples of fused aromatic rings include, but are not limited to, indolyl, isoindolyl, indazolyl, indolizinyl, azaindolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, purinyl and phthalazinyl.

The terms “heterocyclic rings”, “heterocyclic moieties” and “heterocyclyl” are used herein to mean a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom selected from nitrogen, oxygen, sulphur or oxidized sulphur moieties, such as S(O)m, and m is 0 or an integer having a value of 1 or 2. The terms “heterocyclic rings”, “heterocyclic moieties”, and “heterocyclyl” shall also refer to fused rings, saturated or partially unsaturated, and wherein one of the rings may be aromatic, or heteroaromatic. Each of the fused rings may have from four to seven ring atoms. Examples of heterocyclyl groups include, but are not limited to, the saturated or partially saturated versions of the heteroaryl moieties as defined above, such as tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), azepine, diazepine, aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety).

The terms "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" are used herein to mean a C_{1-4} alkyl (as defined above) attached to an aryl, heteroaryl or heterocyclic moiety (as also defined above) unless otherwise indicated.

“Heteroatom” refers to a nitrogen, sulfur or oxygen atom, wherein the nitrogen and sulfur atoms may be optionally oxidized.

The phrases an “effective amount" or “an amount effective to” or a “therapeutically effective amount” of a pharmaceutically active agent or ingredient, are used herein to refer to an amount of the pharmaceutically active agent sufficient to have a therapeutic effect upon administration. Effective amounts of the pharmaceutically active agent will vary with the particular condition or conditions being treated, the severity of the condition, the duration of the treatment, and the specific components of the composition being used.

The terms "administering" and “administration” are used herein to mean any method which in sound medical practice delivers the pharmaceutical composition to a subject in such a manner as to provide a therapeutic effect.

The term “prodrug” is used herein to mean a compound which releases an active agent *in vivo* when the prodrug is administered to a subject. Prodrugs of an active agent

are prepared by modifying one or more functional groups present in the active agent in such a way that the modification may be cleaved *in vivo* to release the active compound.

The terms "treatment" or "treating" of a skin disorder encompasses alleviation of at least one symptom thereof, a reduction in the severity thereof, or the delay, prevention or inhibition of the progression thereof. Treatment need not mean that the disorder is totally cured. A useful composition herein need only to reduce the severity of the disorder, reduce the severity of symptoms associated therewith, provide improvement to a patient's quality of life, or delay, prevent or inhibit the onset of the disorder.

The term "pharmaceutically acceptable salt" refers to salts that are pharmaceutically acceptable and that possess the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with acids such as, for example, acetic acid, benzoic acid, citric acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hydrochloric acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, phosphoric acid, propionic acid, sorbic acid, succinic acid, sulfuric acid, tartaric acid, naturally and synthetically derived amino acids, and mixtures thereof; or (2) salts formed when an acidic proton present in the parent compound is either (i) replaced by a metal ion e.g. an alkali metal ion, an alkaline earth metal ion or an aluminum ion; or (ii) protonates an organic base such as, for example, ethanolamine, diethanolamine, triethanolamine, tromethamine and N-methylglucamine.

Any concentration range, percentage range or ratio range recited herein is to be understood to include concentrations, percentages or ratios of any integer within that range and fractions thereof, such as one tenth and one hundredth of an integer, unless otherwise indicated.

It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components. It will be clear to one of ordinary skill in the art that the use of the singular includes the plural unless specifically stated otherwise. Therefore, the terms "a," "an" and "at least one" are used interchangeably in this application.

Throughout the application, descriptions of various embodiments use "comprising" language, however in some specific instances, an embodiment can alternatively be described using the language "consisting essentially of" or "consisting of".

All numbers expressing quantities, percentages or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about."

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

With regard to stereoisomers, the compounds of the Formulas (I) and (II) herein may have one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

Cis (E) and trans (Z) isomerism may also occur. The present invention includes the individual stereoisomers of the compounds of the invention and where appropriate, the individual tautomeric forms thereof, together with mixtures thereof.

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallization, chromatography or HPLC. A stereoisomeric mixture of the agent may also be prepared from a corresponding optically pure intermediate or by resolution, such as HPLC of the corresponding racemate using a suitable chiral support or by fractional crystallization of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

Other terms used herein are intended to be defined by their well known meanings in the art.

EXAMPLES

Example 1 – Degradation of tazarotene in the presence of benzoyl peroxide

DUAC® gel (1% clindamycin and 5% benzoyl peroxide marketed by Stiefel Laboratories, Inc.) and TAZORAC® cream (0.1% tazarotene marketed by Allergan, Inc.) have been successfully used to treat facial acne. However, these topical treatments are not approved for concomitant use. To study whether tazarotene is susceptible to oxidative decomposition by benzoyl peroxide, an *in vitro* laboratory study was conducted wherein a mixture of DUAC gel and TAZORAC cream was prepared.

Samples were prepared by taking equal portions of DUAC gel and TAZORAC cream and mixing them thoroughly at room temperature with a spatula in a suitable container to form a uniform mixture. The initial samples were analyzed immediately by HPLC. The other samples were placed into an oven at 35°C and removed for analysis after one, two, four, six and eight hours. An allowance was made for product evaporation over the course of the study.

Figure 1 and Table 1 illustrate that approximately 22% of tazarotene was lost after four hours. The major degradant product was tazarotene sulfoxide (~16% after 4 hours). A previously unknown derivative was also identified, namely tazarotene benzoate, which

eluted chromatographically after tazarotene and accounted for ~ 6.3% by weight after four hours.

Similar results were obtained when "aged" samples of DUAC gel and TAZORAC cream were used (Table 2). It is believed that the tazarotene sulfoxide and tazarotene benzoate are oxidative reaction products arising from reaction of the benzoyl peroxide in DUAC gel with the tazarotene in TAZORAC cream.

Table 1 – HPLC analysis of mixtures of DUAC gel and TAZORAC cream (using "fresh" samples)

Substance	Time Point (hours)	Preparation	%Label				
			Tazarotene	Tazarotene Sulfoxide	Tazarotene Benzoate	RRT=1.05	RRT=1.15
TAZORAC	0	A	99.0	0.1			0.9
		B	99.0	0.1			0.9
		C	98.3	0.1			1.6
	8	A	99.7	0.1			0.3
		B	99.5	0.1			0.4
		C	99.0	0.1			0.9
Mixture (DUAC / TAZORAC)	0	A	98.6	1.1	0.3		
		B	98.6	1.1	0.3		
		C	98.4	1.3	0.3		
	1	A	93.8	4.5	1.7		
		B	94.5	4.0	1.5		
		C	94.1	4.3	1.6		
	2	A	86.0	10.0	3.7	0.3	
		B	86.9	9.1	3.6	0.3	
		C	87.5	8.8	3.4	0.3	
	4	A	77.3	16.0	6.3	0.4	
		B	77.3	16.0	6.3	0.4	
		C	76.9	16.2	6.5	0.4	
	6	A	67.1	23.3	9.1	0.6	
		B	69.6	21.6	8.3	0.5	
		C	70.6	20.9	8.0	0.5	
	8	A	61.1	27.8	10.5	0.6	
		B	60.2	28.6	10.6	0.6	
		C	59.4	29.4	10.6	0.6	

Table 2 - HPLC analysis of mixtures of DUAC gel and TAZORAC cream (using "aged" samples)

Substance	Time Point	Preparation	%Label				
			Tazarotene	Tazarotene Sulfoxide	Tazarotene Benzoate	RRT=1.05	RRT=1.15
TAZORAC	0	A	99.4	0.1			0.5
		B	99.1	0.1			0.8
		C	99.1	0.1			0.8
	8	A	99.4	0.1			0.5
		B	99.5	0.1			0.4
		C	99.5	0.1			0.4
Mixture (DUAC / TAZORAC)	0	A	99.2	0.8			
		B	99.3	0.7			
		C	99.2	0.8			
	1	A	95.2	3.5	1.3		
		B	95.2	3.4	1.4		
		C	95.3	3.5	1.3		
	2	A	89.1	7.8	3.1		
		B	89.0	7.7	3.0	0.3	
		C	89.1	7.6	3.0	0.3	
	4	A	76.9	16.3	6.5	0.4	
		B	77.0	16.2	6.5	0.4	
		C	77.1	16.0	6.5	0.4	
	6	A	63.4	25.6	10.5	0.5	
		B	63.7	25.5	10.3	0.5	
		C	64.2	25.2	10.1	0.6	
	8	A	54.6	31.9	12.9	0.6	
		B	54.2	32.2	12.9	0.7	
		C	53.6	32.7	13.1	0.7	

Example 2 – further study of tazarotene and its metabolites

An *in vitro* study was conducted to assess the formation of tazarotene degradants following the application of a mixture of DUAC gel and TAZORAC cream to human skin.

Equal portions of DUAC gel and TAZORAC cream were dispensed into a glass vial

and mixed for approximately three minutes with a metal spatula to ensure a homogenous mixture. Samples of European DUAC gel and US DUAC gel were used in separate experiments. The products differ inasmuch as European DUAC gel does not contain paraben preservatives. The test mixtures were then applied to the surface of split-thickness skin (~0.25 mm) at a dose of 15.6 mg/cm^2 and spread evenly using a positive displacement pipette.

After 2 and 6 hours, the skin samples were washed, tape stripped twice, and then the epidermis was peeled from the dermis using a heat block. The skin samples were then extracted with acetonitrile overnight at 4°C. The distribution of tazarotene and its degradants within the epidermis, dermis and surface wash were quantified by LC/MS/MS with a 50 pg/mL LOQ. The experiments were performed under yellow light conditions. For the purposes of comparison, mixtures of DUAC gel and TAZORAC cream were also prepared and retained for stability testing at 0, 2 and 6 hour time points.

As illustrated in Figure 2A, the mixture of DUAC gel and TAZORAC cream in the stability samples resulted in the formation of tazarotene sulfoxide. The quantity of the tazarotene sulfoxide degradant doubled from the 2 hour time point to the 6 hour time point. As shown in Figure 2B, tazarotene benzoate also formed. Again, there was a significant increase in the quantity of tazarotene benzoate present at the 6 hour time point relative to the 2 hour time point.

The study also showed that after 2 hours of application of the DUAC / TAZORAC mixture to the skin, tazarotene sulfoxide was identified in the epidermis and dermis (Figures 3A and 3B). After 6 hours of application, there was a continued loss of tazarotene and resultant formation of tazarotene sulfoxide (Figures 4A and 4B).

Tazarotene benzoate was detectable in all samples including the placebo (Figures 5A and 5B). The presence of tazarotene benzoate in the placebo sample suggests that endogenous benzoic acid may be present.

While tazarotene and tazarotene benzoate could not be detected in the receiving medium of the assay (i.e. did not pass through the skin), tazarotene sulfoxide was detected in the receiving medium, as shown in Figure 6.

Tazarotenic acid was not detected under these experimental conditions.

Example 3 - Retinoid activity of tazarotene, tazarotene benzoate and tazarotene metabolites

A study was conducted to evaluate the retinoid activity of tazarotene, tazarotene benzoate and tazarotene metabolites (tazarotenic acid, tazarotene sulfone, tazarotenic acid sulfone and tazarotenic acid sulfoxide).

SkinEthic RHE cultures were transferred into 6-well plates containing 1.0 mL/well growth media. The cultures were equilibrated at 37°C and the media was changed daily. The cultures were subsequently placed in 60 mm petri dishes containing 3.5 mL growth media. 6 µl aliquots of the Test Articles shown in Table 3 were applied to duplicate cultures. The cultures were incubated at 37°C for 72 hours. At the end of the incubation period, the growth media was collected and stored at -20°C. The tissues were cut in half and one half was placed in 10% NBF for histology, while the other half was placed in RNA*later*™ solution (Ambion). The following analyses were performed: a) IL-1α and IL-8 activity assay; b) HandE staining; c) Immunohistochemistry for K10, K19 and filaggrin; and d) qRT-PCR to quantitate K10, K19 and filaggrin expression.

Table 3

	Test Articles
1	Untreated (negative control)
2	Octyldodecanol (OD) vehicle control
3	TAZORAC® 0.1% cream
4	Retin-A Micro® 0.04% (tretinoin) gel
5	Tretinoin (0.1% in OD)
6	Tazarotene (0.1% in OD)
7	Tazarotenic acid (0.1% in OD)
8	Tazarotene benzoate (0.1% in OD)
9	Tazarotene sulfone (0.1% in OD)
10	Tazarotenic acid sulfoxide (0.1% in OD)
11	Tazarotenic acid sulfone (0.1% in OD)

The study demonstrated that interleukin-1α (IL-1α) (a pro-inflammatory cytokine) activity was only slightly increased in cultures treated with tazarotene, tazarotene benzoate or tazarotene metabolites compared to untreated and vehicle controls (Figures 7 and 15). However, IL-1α activity was significantly increased in cultures treated with TAZORAC cream, and to a lesser extent with Retin-A Micro® tretinoin gel, suggesting that formulation excipients may contribute to the irritation potential of retinoids. Furthermore, interleukin-8 (IL-8) (a pro-inflammatory cytokine specific to retinoids) was significantly increased in all cultures treated with retinoids compared to untreated and vehicle treated controls, suggesting that tazarotene, tazarotene benzoate and the tazarotene metabolites have retinoid activity (Figures 7 and 16).

The histological profiles of cultures treated with TAZORAC cream or Retin-A Micro gel were as expected: namely, there was a decrease in keratohyalin granules

(HandE), a decrease in K10 expression in the suprabasal layers, and an increase in K19 expression in all viable cell layers, compared to untreated controls. Histological profiles for cultures treated with tazarotene, tazarotene benzoate and the tazarotene metabolites were similar to those of TAZORAC cream and Retin-A Micro gel, providing further evidence that they have retinoid activity.

Following the histological profile study, gene expression profiles for K10, K19 and filaggrin in RHE cultures treated with the various retinoids were examined. Gene expression profiles were consistent with histological observations. There was a 3- to 1000-fold down regulation of K10 in all retinoid-treated cultures compared to untreated and vehicle controls, with the possible exception of tazarotene benzoate, which was uninterpretable due to a high standard deviation. In addition, there was a 15- to 1500-fold up regulation of K19 in all retinoid-treated cultures compared to untreated and vehicle controls. There was also a 2- to 15-fold down regulation of filaggrin in all retinoid-treated cultures compared to untreated and vehicle controls. The filaggrin expression after treatment with tazarotene benzoate appeared equivocal due to a high variability in one culture. However, the immunohistochemistry illustrates that filaggrin is down regulated by tazarotene benzoate.

The results of these studies provide strong evidence that tazarotene, tazarotene benzoate and the tazarotene metabolites have retinoid activity in human skin.

Example 4 - Retinoid activity of tazarotene benzoate

A study was conducted to specifically evaluate the retinoid activity of tazarotene benzoate, using a human keratinocyte model (A431).

A431 cells were purchased from ATCC (CRL-1555). Cells were seeded onto 12-well plates at a density of 250,000 cells/well and incubated for 72 hours at 37°C/5% CO_2 to allow cells to grow to confluency. Phorbol-12-myristate 13-acetate (PMA), diluted in DMSO (10 mg/mL stock), was added in a concentration of 10 ng/mL and retinoids were added in concentrations of 0.01 to 1 μg/mL from a 10 mg/mL stock solution in DMSO. Cultures were incubated for 48 hours at 37°C. At the end of the incubation period, growth media was collected and cell viability was determined using a CellTiterGlo assay kit (Promega). Concentrations of IL-6 were determined by ELISA and normalized based on cell viability.

It is known that PMA up regulates IL-6 expression through transactivation of the nuclear transcription factor, AP-1. Retinoids, such as tretinoin, are known to inhibit transactivation of AP-1 via retinoic acid receptors.

The study illustrated that PMA-induced IL-6 release was significantly decreased in

cultures treated with tazarotene benzoate, and was similar to the results obtained for cultures treated with tretinoin, tazarotene and tazarotenic acid (Figure 8).

As such, these results provide further evidence that tazarotene benzoate has retinoid activity in human skin.

Example 5 - Stability of tazarotene benzoate in plasma

To further characterize tazarotene benzoate, the stability of tazarotene benzoate, tazarotene sulfoxide and tazarotene in human and rat plasma was studied.

Tazarotene, tazarotene sulfoxide and tazarotene benzoate were incubated at room temperature with human and rat plasma. The incubation was carried out in duplicate and samples were taken at specific time points for stability analyses (i) rat samples (0 hour, 2 hours and 4 hours) and (ii) human samples (0 hour, 2 hours, 4 hours and 8 hours). Samples were analyzed by LC-MS/MS.

The study demonstrates that in rat plasma, tazarotene, tazarotene sulfoxide and tazarotene benzoate showed rapid degradation, with 75-100% loss in 2 hours (Table 4 and Figure 9). In human plasma, the rate of degradation of tazarotene, tazarotene sulfoxide and tazarotene benzoate was significantly slower, with < 10% loss at 2 hours and < 15% loss by 8 hours (Table 5 and Figure 10). The degradation products were the corresponding ester hydrolysis products of each compound tested.

Table 4

Rat plasma	0 hour	2 hours	4 hours
Tazarotene (ng/mL)	16.4	<LOD	<LOD
Tazarotene sulfoxide (ng/mL)	34.1	<LOD	<LOD
Tazarotene benzoate (ng/mL)	59.8	15.0	2.29

Table 5

Human plasma	0 hour	2 hours	4 hours	8 hours
Tazarotene (ng/mL)	17.1	17.1	16.6	17.5
Tazarotene sulfoxide (ng/mL)	36.2	34.0	32.2	31.9
Tazarotene benzoate (ng/mL)	52.0	52.0	50.0	45.8

Example 6 - Metabolism of tazarotene, tazarotene sulfoxide, tazarotenic acid and tazarotene benzoate in the presence of human liver microsomes

The metabolic stability of tazarotene, tazarotene sulfoxide, tazarotenic acid and tazarotene benzoate in the presence of human liver microsomes was studied.

Hepatic microsomal reactions were carried out in microcentrifuge tubes in the following manner. Human liver microsomes (0.5 or 1.0 mg/ml protein), Test Article (1 or 10 μM), paraoxon (0, 10 or 100 μM), NADPH regenerating system (10 mM glucose-6-phosphate, 1 unit/ml glucose-6-phosphate dehydrogenase, 1 mM $NADP^+$), magnesium chloride (5 mM) in 0.1 M potassium phosphate buffer, pH 7.4 were incubated at 37°C in a shaking water bath. Reactions were initiated with the addition of substrate with the exception of the zero-time incubations. The total reaction volume was 0.2 ml. The reactions were incubated for 15, 30, 45 or 60 minutes, terminated with 0.2 ml ice-cold acetonitrile and then placed on ice. For zero-time incubations, ice cold acetonitrile was added to the mixture containing microsomes, along with NADPH regenerating system, magnesium chloride in phosphate buffer and the Test Article. Each time point was carried out in triplicate.

Disappearance of Test Article and formation of metabolites following *in vitro* metabolism were determined by LC-MS/MS using multiple reaction monitoring. LightSight® software (Applied Biosystems, Foster City, CA) was used to generate the mass spectrometry methods and carry out the data mining.

Control incubations were carried out with the identical incubation procedures as described above with the following exceptions. In negative control reactions, microsomes were not included. Positive control incubations for liver microsomes included an assessment of the microsomal stability of 7-ethoxycoumarin, which is quickly metabolized by CYPs in liver microsomal incubations of laboratory animals and humans. Duplicate reactions with an initial concentration of 10 μM were incubated for 0 or 30 minutes. Microsomal metabolic stability of 7-ethoxycoumarin was determined by LC-MS/MS.

Table 6 - Metabolism of tazarotene, tazarotene sulfoxide, tazarotenic acid and tazarotene benzoate

Compound	Enzyme System	Conc (μM)	Type of reaction	k constant	R-squared	Half-life (min)	CL_{int}*
Tazarotene	HLM	1	Complete	-0.0880	0.977	7.88	176
			Without NADPH	-0.0899	0.981	7.71	180
		10	Complete	-0.0827	0.988	8.38	165
			Without NADPH	-0.0914	0.988	7.58	183
Tazarotene sulfoxide	HLM	1	Complete	-0.0689	0.963	10.1	138
			Without NADPH	-0.0779	0.994	8.90	156
		10	Complete	-0.0647	0.977	10.7	129
			Without NADPH	-0.0763	0.995	9.08	153
Tazarotenic acid	HLM	1	Complete	-0.0064	0.980	108	6.40
			Without NADPH	0.0003	0.124	0.00	0.00
		10	Complete	-0.0047	0.596	147	4.70
			Without NADPH	0.0006	0.037	0.00	0.00
Tazarotene benzoate	HLM	1	Complete	-0.0893	0.967	7.76	179
			Without NADPH	-0.0964	0.954	7.19	193
		10	Complete	-0.0097	0.897	71.4	9.70
			Without NADPH	-0.0146	0.980	47.5	14.6
Tazarotene benzoate	HSkM	1	Complete	-0.0014	0.656	495	0.700
			Without NADPH	-0.0032	0.360	217	1.60
		10	Complete	-0.0017	0.283	408	0.850
			without NADPH	-0.0015	-0.194	462	0.800

* = ml/min/mg

15.4% to 19.8% of tazarotene was converted to tazarotenic acid in complete non-zero minute incubations (with NADPH) (Table 7). In the absence of NADPH, incubations contained higher concentrations of tazarotenic acid (32.4% to 52.7% of tazarotene converted). Tazarotenic acid makes up only a fraction of the metabolism, suggesting the existence of other metabolic pathways such as sulfoxidation to tazarotene sulfoxide or additional metabolism of tazarotenic acid to tazarotenic acid sulfoxide and tazarotenic acid sulfone.

Table 7 – Metabolism of tazarotene to tazarotenic acid

		Percent of initial tazarotene concentration					
		1 μM initial concentration			10μM initial concentration		
Type of Reaction	Incubation time (min)	Tazarotene	Tazarotenic acid	Total	Tazarotene	Tazarotenic acid	Total
Complete (with NADPH)	0	100%	0.00%	100%	100%	0.00%	100%
	15	21.1%	18.0%	39.1%	24.1%	15.4%	39.5%
	30	4.91%	19.6%	24.5%	6.55%	18.4%	24.9%
	45	1.80%	19.6%	21.4%	2.18%	18.3%	20.4%
	60	0.70%	19.8%	20.5%	0.89%	17.4%	18.3%
Without NADPH	0	100%	0.00%	100%	100%	0.00%	100%
	15	22.0%	37.2%	59.2%	21.9%	32.4%	54.3%
	30	4.86%	44.7%	49.6%	4.64%	39.5%	44.1%
	45	1.43%	48.5%	49.9%	1.48%	41.3%	42.8%
	60	0.65%	52.7%	53.4%	0.55%	40.5%	41.1%

Tazarotene sulfoxide was also rapidly metabolized in human liver microsomes (Table 8). Near-quantitative conversion to the tazarotenic acid sulfoxide was observed for 1 μM reactions as shown in the mass balance calculations. In the case of 1 μM reactions without NADPH, the percentage values of tazarotene sulfoxide converted to tazarotenic acid sulfoxide were over 100%. This is an unexpected result which may be due to ion suppression effects between standard and sample injections. For 10 μM substrate reactions, greater than 50% of the Test Article metabolized to tazarotenic acid sulfoxide. In the presence of NADPH, tazarotenic acid sulfoxide was a major metabolite, but its levels were lower than those observed in incubations without NADPH. Only a fraction of NADPH-dependent metabolism is detected as tazarotenic acid sulfoxide. This suggests other metabolic pathways either by oxidation of tazarotene sulfoxide to its sulfone or by additional metabolism of tazarotenic acid sulfoxide to its sulfone.

Table 8 - Metabolism of tazarotene sulfoxide to tazarotenic acid sulfoxide

		Percent of initial tazarotene sulfoxide concentration					
		1 μM initial concentration			10μM initial concentration		
Type of Reaction	Incubation time (min)	Tazarotene sulfoxide	Tazarotenic acid sulfoxide	Total	Tazarotene sulfoxide	Tazarotenic acid sulfoxide	Total
Complete (with NADPH)	0	100%	0.00%	100%	100%	0.00%	100%
	15	25.6%	43.1%	68.7%	30.9%	27.7%	58.6%
	30	8.86%	50.8%	59.7%	11.4%	38.3%	49.7%
	45	4.24%	55.4%	59.7%	4.80%	38.4%	43.2%
	60	2.17%	56.7%	58.9%	2.70%	41.0%	43.7%
Without NADPH	0	100%	0.00%	100%	100%	0.00%	100%
	15	27.9%	87.1%	115%	30.4%	58.4%	88.8%
	30	8.40%	108%	116%	8.96%	74.2%	83.2%
	45	2.72%	112%	115%	2.98%	76.6%	79.6%
	60	1.11%	116%	117%	1.18%	79.1%	80.3%

In the presence of NADPH, tazarotenic acid was slowly metabolized by human liver microsomes to tazarotenic acid sulfoxide (Table 9). Tazarotenic acid was not metabolized in the absence of NADPH. A mass spectrum for tazarotenic acid sulfoxide is shown in Figure 14.

Table 9 – Metabolism of tazarotenic acid to tazarotenic acid sulfoxide

		Percent of initial tazarotenic acid concentration					
		1 μM initial concentration			10 μM initial concentration		
Type of Reaction	Incubation time (min)	tazarotenic acid	tazarotenic acid sulfoxide	Total	tazarotenic acid	tazarotenic acid sulfoxide	Total
Complete (with NADPH)	0	100%	0.00%	100%	100%	0.00%	100%
	15	89.9%	12.6%	103%	93.1%	3.83%	96.9%
	30	82.0%	22.3%	104%	88.6%	7.68%	96.3%
	45	75.8%	30.4%	106%	77.8%	10.3%	88.1%
	60	68.0%	35.9%	104%	77.4%	13.6%	91.0%
Without NADPH	0	100%	0.00%	100%	100%	0.00%	100%
	15	100%	0.00%	100%	102%	0.01%	102%
	30	101%	0.00%	101%	99.0%	0.01%	99.0%
	45	102%	0.00%	102%	106%	0.01%	106%
	60	101%	0.00%	101%	102%	0.02%	102%

31.7% to 47.6% of tazarotene benzoate was converted to hydroxy tazarotenic acid in 1 μM reactions with NADPH. Similarly, greater than 50% of tazarotene benzoate was converted to hydroxy tazarotenic acid in 1 μM reactions without NADPH (Table 10). Since the mass balance is significantly less than 100%, particularly for the 1 μM reactions, it appears that other metabolites are also formed. A HPLC chromatogram and mass spectrum corresponding to hydroxy tazarotenic acid is shown in Figures 12 and 13, respectively.

Table 10 – Metabolism of tazarotene benzoate to hydroxy tazarotenic acid

		Percent of initial tazarotene benzoate concentration					
		1 μM initial concentration			10 μM initial concentration		
Type of Reaction	Incubation time (min)	tazarotene benzoate	hydroxy tazarotenic acid	Total	tazarotene benzoate	hydroxy tazarotenic acid	Total
Complete (with NADPH)	0	100%	0.00%	100%	100%	0.00%	100%
	15	20.3%	31.7%	52.0%	99.3%	6.10%	105%
	30	4.45%	47.6%	52.1%	73.4%	15.6%	89.0%
	45	1.47%	43.8%	45.3%	63.2%	24.3%	87.5%
	60	0.73%	35.2%	35.9%	55.2%	29.2%	84.4%
Without NADPH	0	100%	0.00%	100%	100%	0.00%	100%
	15	17.3%	54.5%	71.8%	87.0%	13.2%	100%
	30	2.97%	71.1%	74.1%	64.0%	32.4%	96.4%
	45	1.07%	63.1%	64.2%	51.0%	43.2%	94.2%
	60	0.53%	53.1%	53.6%	41.0%	51.5%	92.5%

The study demonstrated that tazarotene, tazarotene sulfoxide, tazarotenic acid and tazarotene benzoate were metabolized by human liver microsomes. Ester hydrolysis is believed to be a major metabolic pathway.

To determine the role of esterases in metabolism of tazarotene, tazarotene sulfoxide, tazarotenic acid and tazarotene benzoate, inhibition studies were carried out with paraoxon, a potent inhibitor of all serine esterases including carboxylesterases. Paraoxon inhibited:

(i) tazarotene metabolism to tazarotenic acid in human liver microsomes,

(ii) tazarotene sulfoxide metabolism to tazarotenic acid sulfoxide in human liver microsomes, and

(ii) tazarotene benzoate metabolism to hydroxy tazarotenic acid in human liver and skin microsomes.

Paraoxon did not inhibit the metabolism of tazarotenic acid to tazarotenic acid sulfoxide, which is a CYP- and FMO-mediated reaction.

In all, these results support a conclusion that esterases are responsible for ester hydrolysis of tazarotene, tazarotene sulfoxide and tazarotene benzoate.

Human liver microsomes metabolized 7-ethoxycoumarin as expected, confirming satisfactory incubation conditions for the metabolic stability assay.

Among the metabolites detected, three were identified as tazarotenic acid benzoate

(m/z 444), hydroxy tazarotene (m/z 368), and hydroxy tazarotenic acid (m/z 340). Hydroxy tazarotenic acid was identified as a major metabolite. Metabolites with m/z 338 and 366 were also observed. While not bound by the proposal, it is believed that these are products following enzymatic oxidation of the thiolactol group to the thiolactone i.e. to form keto tazarotene and keto tazarotenic acid (Figure 23). In all, these findings are consistent with cleavage of both ester bonds by esterases.

The proposed metabolism of (i) tazarotene and (ii) tazarotene benzoate is illustrated in Figures 22 and 23, respectively.

Example 7 - Metabolism of tazarotene benzoate in the presence of human skin microsomes

Insofar as several liver microsomal enzymes (including esterases) are found in the human skin, the metabolism of tazarotene benzoate was further studied *in vitro* in the presence of human skin microsomes.

Five time points were chosen, but because of the limitation of human skin microsome supply, each one was carried out in duplicate. Skin microsomal reactions were carried out as described above for hepatic microsomal reactions with the following two exceptions. Firstly, the total reaction volume was 0.1 mL. Secondly, incubations were terminated with 0.1 mL acetonitrile.

Human skin microsomes catalyzed fexofenadine formation from terfenadine (positive control), confirming drug metabolizing activity of human skin microsomes.

The tazarotene benzoate and hydroxy tazarotenic acid metabolite concentrations were quantified by LC-MS/MS.

The results showed that while tazarotene benzoate was metabolized by the human skin microsomes, the compound was metabolized at a slower rate relative to human liver microsomes i.e. after 150 min, 20% of tazarotenic benzoate was metabolized in the presence of 2 mg/ml human skin microsomes. Formation of hydroxy tazarotenic acid was again observed, suggesting esterase metabolism of tazarotene benzoate.

Example 8

The retinoid activity of tazarotene, tazarotene benzoate, hydroxy tazarotenic acid, keto tazarotenic acid, keto tazarotene and a number of analogues of tazarotene benzoate were evaluated using the following methodology. The compounds are set out in Table 11.

Reconstructed human epidermis (RHE) tissues were cultured in-house as previously described by Poumay *et al.* Briefly, polycarbonate culture inserts (12 mm diameter and 0.4 μm pore size, Millipore) were filled with 150 μL of a suspension containing

approximately 5 x 10^5 primary adult human keratinocytes. The inserts received another 500 µL of keratinocyte culture media and were placed in a 6-well plate (1 insert/well) containing 2.5 mL of RHE Growth Media (Epilife media +1.5 mM $CaCl_2$). RHE cultures were incubated at 37°C in a humidified atmosphere containing 5% CO_2, for 24 hours. Subsequently (on Day 0), RHE cultures were exposed to the air-liquid interface by removing the RHE Growth Media from the top of the cultures, and replacing with 1.5 mL/well of RHE Growth Media containing 50 µg/mL vitamin C. Media was changed every other day until the cultures were dosed with Test Articles. A stock solution of 0.1% tazarotene (2.83 mM at 99.5% purity) in OD/10% DMSO was prepared. For tazarotene benzoate, hydroxytazarotenic acid, keto tazarotenic acid, keto tazarotene, and tazarotene nicotinate, a 10 mg/mL stock solution (in DMSO) was already prepared. From this stock solution, a 2.83 mM working solution (in octyldodecanol) was prepared. All other tested compounds were resuspended in DMSO and OD to obtain a final concentration of 2.83 mM in OD/10% DMSO. On Day 12, the cultures were placed in 60 mm petri dishes containing 3 mL of RHE Growth Media (+ VitC). Test articles (6 µl) were applied to triplicate cultures and cultures were incubated at 37°C for 72 hours. Untreated and OD alone served as negative controls. At the end of the incubation period, the growth media was collected and stored at -20°C. The tissues were cut in half: one half was placed in 10% NBF for histology, and the other half was placed in RNA*later*™ solution for RT-qPCR. RNA was isolated and concentrations were determined using a NanoDrop spectrophotometer. In addition to using the same amount of RNA for each sample, data was normalized to internal GAPDH mRNA levels and is expressed as relative quantification (RQ) to untreated controls. RNA extracts from each replicate were amplified using RT-qPCR. The relative gene expression of five biomarkers was determined: Keratin 10, Keratin 19, Filaggrin, Keratin 4, and Keratin 13.

The results of the analyses are shown in Figures 17 to 21. The compounds displayed on the X axes of Figures 17 to 21 correspond to the compounds set out in Table 11. The compounds were ranked for their effect on each biomarker, as set out in Table 12.

Keratin 4 (K4) is not normally expressed in human epidermis but is known to be upregulated upon treatment with retinoids. All tazarotene derivatives caused significant upregulation of K4 (from 11-180-fold) compared to untreated and vehicle controls. Tazarotene, keto tazarotene, compound 17, compound 25 and compound 28 showed the highest increase (from 103 to 180-fold). Compound 21 and compound 19 showed the lowest upregulation with 11 and 19-fold, respectively.

Keratin 10 (K10) is an early differentiation marker that is normally expressed in the suprabasal layers of the viable epidermis, but is known to be downregulated upon

treatment with retinoids. With the exception of the S enantiomer of tazarotene benzoate, compound 19 and compound 21, all other tazarotene derivatives caused a significant downregulation of K10 (approximately 7±4-fold) compared to untreated and vehicle controls. The highest K10 downregulation was observed with tazarotene nicotinate, keto tazarotenic acid, and compound 24 (14 to 17-fold).

Keratin 13 (K13) is not normally expressed in human epidermis but is known to be upregulated upon treatment with retinoids. With the exception of compound 19 and compound 21, all tazarotene derivatives caused a significant upregulation of K13 (approximately 13±5-fold) compared to untreated and vehicle controls. The highest K13 upregulation was observed with compound 24 (23-fold), keto tazarotenic acid, and hydroxy tazarotene (20-fold), compound 23 and compound 27 (19-fold), compound 28 (18-fold), and compound 25 (17-fold).

Keratin 19 (K19) is not normally expressed in human epidermis but is known to be upregulated in all the viable layers of the epidermis upon treatment with retinoids. With the exception of compound 19 and compound 21, all other tazarotene derivatives caused a significant upregulation of K19 (approximately 23±11-fold) compared to untreated and vehicle controls. Tazarotene, compound 15, compound 23, compound 24 and compound 27 showed the highest increase (33 to 43-fold).

Filaggrin is a late-stage differentiation marker that is normally expressed in the stratum granulosum and is known to be downregulated upon treatment with retinoids. With the exception of the S enantiomer of tazarotene benzoate, keto tazarotene, compound 13, compound 17, compound 19, and compound 21, all other tazarotene derivatives caused a significant (3-100-fold) downregulation of filaggrin. The highest level of filaggrin downregulation was observed with tazarotene nicotinate (100-fold), compound 24 (56-fold), keto tazarotenic acid (36-fold) and compound 27 (23-fold).

Based on a qualitative assessment of gene expression profiles (Table 12), the top 5 tazarotene derivatives are: compound 24, compound 23, compound 11, compound 29 and compound 15.

In summary, the retinoid activity of a variety of tazarotene metabolites and derivatives were assessed by 5 biomarkers (Keratins 4, 10, 13, 19 and Filaggrin). The respective compounds had unique expression profiles. In ranking the compounds tested, 13 derivatives were found to be more active than tazarotene.

Example 9 – Stability of tazarotene benzoate and tazarotene nicotinate in the presence of benzoyl peroxide

The reaction of (i) tazarotene, tazarotene benzoate, hydroxy tazarotenic acid and tazarotene nicotinate with (ii) benzoyl peroxide (BPO) in 30% aqueous solutions was monitored at 35°C, room temperature and 5°C.

Individual solutions of each compound were prepared at approximately 0.25 mg/mL in acetonitrile: water (6:4 by volume). Reactions were initiated by mixing equal volumes of the test solution with an approximately 12 mg/mL solution of benzoyl peroxide (BPO) in acetonitrile:water (4:1 by volume). Therefore, the reaction solution contained approximately 0.125 mg/mL of the test compound and the BPO was at a 50-fold excess by weight (i.e. at the same ratio as a product containing 0.1% tazarotene and 5% BPO). Aliquots of the reaction solutions were stored at various temperatures protected from light.

Reactions were quenched by diluting 30 µL of the reaction solution to 50 mL with a diluent (acetonitrile: water in a ratio of 1:1 by volume) and storing the sample at 10°C in the LC/MS sample tray or at 5°C for storage. Duplicate samples were prepared at each time point (three at the start of the reaction) and the results were averaged together to generate a single value.

Samples were analyzed on a Waters Acquity UPLC with a Waters Xevo TQMS using an ESI source in the positive mode controlled by MassLynx V4.1 software. Separations were performed using an Acquity BEH C8 UPLC column (1.7 µm particle size, 2.1 x 50 mm) at 45°C. The mobile phase consisted of water and acetonitrile, each containing 0.1% formic acid. A flow rate of 0.4 mL/min was used.

The results are set out in Figures 24A, 24B and 24C.

Significantly, at all three temperatures, tazarotene benzoate and tazarotene nicotinate were in the order of 25 times less reactive than tazarotene and hydroxy tazarotenic acid (with BPO). The rate of reaction of each of the test compounds with BPO was found to be a function of temperature. The rate of reaction increased roughly by a factor of 5 at room temperature compared to 5°C and increased a further factor of approximately 3 when the reaction temperature was increased to 35°C. The reaction rates of tazarotene benzoate and tazarotene nicotinate appear to be similar at all temperatures.

Example 10 – Synthesis of tazarotene derivatives

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anhydrous conditions in an Ar atmosphere where necessary.

List of Abbreviations

DMAP: 4-(Dimethylamino)pyridine	SPE: Solid phase extraction
DCM: Dichloromethane	m-CPBA: 3-Chlorobenzene-carboperoxoic acid
DMF: *N,N*-Dimethylformamide	Fmoc: Fluorenylmethyloxycarbonyl
dppf: 1,1'-Bis(diphenylphosphino)-ferrocene	NIS: *N*-Iodosuccinimide
DMSO: Dimethylsulfoxide	HATU: *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
DIPEA: *N,N*-Diisopropylethylamine	HBTU: *O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
DSC: differential scanning calorimetry	HOBT: 1-Hydoxybenzotriazole hydrate
EtOAc: Ethyl acetate	IPA: isopropyl alcohol
EDC: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride	THF: Tetrahydrofuran
TFA: Trifluoroacetic anhydride	mol: moles
TEA: Triethylamine	VCD: Vibrational Circular Dichroism analysis
M: molar	mmol: millimoles

L: liters	satd: saturated
mL: milliliters	eq: equivalents
g: grams	min: minutes
mg: milligrams	mp: melting point
h: hours	rt: room temperature
Aq: aqueous	NMP = 1-methyl-2-pyrrolidinone

General procedure for the preparation of acid chlorides

Oxalyl chloride (4.0 equivalents) was added to a solution of carboxylic acid (1.0 equivalent) in dichloromethane (DCM) while stirring, along with a catalytic amount of anhydrous dimethyl formamide (DMF). The resultant solution was refluxed at 40°C for 2 hours. The solution was cooled, the solvent removed under vacuum, the excess oxalyl chloride removed using toluene, and the resultant acid chloride was redissolved in DCM and subsequently used for ester formation.

General procedure for the preparation of esters from acid chlorides

The acid chloride (1.6 mmol) was added to a solution of compound 14 (0.5 mmol) in DCM (5 mL) while stirring. Triethylamine (TEA) (2.7 mmol) was subsequently added and the reaction mixture was stirred overnight. The progress of the reaction was monitored by LC/MS. Upon completion of reaction, the reaction mixture was poured into water, extracted with DCM (2 x 5 mL aliquots). The organic extracts were combined and washed with water/brine and dried over anhydrous Na_2SO_4. The organic extract was concentrated and the crude ester was purified with an ISCO cartridge in a Companion system using an ethylacetate/heptanes solvent system (0-40%).

General procedure for the preparation of esters from the coupling of a carboxylic acid and an alcohol (using EDC and HOBt)

N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC.HCl) (2.7 mmol) and HOBt (2.7 mmol) was added to a solution of the carboxylic acid (2.7 mmol) in DCM (10mL), while stirring. TEA (5.4 mmol) was added, followed by compound 14 (an alcohol). The reaction mixture was stirred overnight at room temperature. Upon completion of the reaction (determined by LC/MS), the mixture was poured into water (20 mL), the organic phase removed and the aqueous phase extracted with DCM (10 mL).

The organic (DCM) phase was washed with brine and dried over anhydrous Na_2SO_4 to give the crude ester.

The molecular weight of the metabolites and analogues as determined by mass spectrometry is listed in Table 11.

Analysis of the metabolites and analogues was also conducted using ^1H NMR spectroscopy at 400 MHz (Varian), with the samples dissolved in deuterated chloroform or deuterated DMSO.

Compound 4 - 6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester (tazarotene benzoate)

Triethylamine (0.75mL) was added to a cooled (0°C) solution of compound 14 (0.551 g, 1.5 mmol) in DCM (15mL) under nitrogen, followed by the addition of benzoyl chloride (0.281 g, 2.0 mmol) in DCM (3 mL). The mixture was stirred for 1 hour at room temperature and then diluted with DCM (50 mL) and then treated with saturated $NaHCO_3$ solution, followed by water (30 mL) and brine (30 mL). The organic phase was extracted, dried over anhydrous Na2SO4, concentrated and purified using column chromatography (20% EtOAc/Heptanes) to obtain a colorless solid. Yield: 0.700g (99%).

1H NMR (400 MHz, CHLOROFORM-d) d 1.43 (t, J=7.08 Hz, 3H), 1.49 (s, 3 H), 1.56 (s, 3H), 2.32 (br. s., 1H), 2.33 (d, J=1.66 Hz, 1H), 4.44 (q, J=7.13 Hz, 2H), 6.49 (t, J=5.52 Hz, 1H), 7.13 (d, J=8.10 Hz, 1H), 7.35 (d, J=0.88 Hz, 1H), 7.46 (t, J=7.71 Hz, 2H), 7.59 (d, J=7.91 Hz, 2H), 7.69 (s, 1H), 8.05 (d, J=7.52 Hz, 2H), 8.29 (dd, J=8.15, 1.81 Hz, 1H), 9.21 (s, 1H)

Compounds 5 and 6 – (S)-6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester and (R)-6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester (enantiomers of tazarotene benzoate)

The S and R enantiomers of compound 4 (100 mg) were separated by HPLC using a chiral ADH column with a 10-50% gradient of isopropyl alcohol / water. UV absorbance was monitored at 340 nm. 33 mg and 27 mg of the respective enantiomers were obtained in > 97% purity.

The stereochemistry of the enantiomers was determined using *Ab Initio* Vibrational Circular Dichroism (VCD) analysis.

Compound 7 - 6-[4,4-Dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester (tazarotene nicotinate)

A solution of compound 14 (1.00 g, 2.72 mmol) in DCM (100 mL) was chilled in an ice water bath to 0°C, then charged with TEA (1.38 g, 1.90 mL, 13.6 mmol), and then nicotinoyl chloride hydrochloride (605 mg, 3.40 mmol) was added. The reaction was then allowed to warm to room temperature and stirred for 18 hours. The reaction was diluted with DCM (200 mL) and washed with water (2 x 200 mL aliquots). The aqueous washes were then pooled and back-extracted with DCM (2 x 100 mL). The organic fractions were then pooled, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was chromatographed on a silica column using a heptane:EtOAc solvent system. Yield: 968 mg (75%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.43 (t, *J* = 7.1 Hz, 3 H), 1.49 (s, 3 H), 1.56 (s, 3 H), 2.33 (d, *J* = 5.6 Hz, 2 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 6.51 (t, *J* = 5.6 Hz, 1 H), 7.13 (d, *J* = 8.2 Hz, 1 H), 7.37 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.41 (ddd, *J* = 8.0, 4.9, 0.8 Hz, 1 H), 7.59 (dd, *J* = 8.2, 0.8 Hz, 1 H), 7.69 (d, *J* = 1.7 Hz, 1 H), 8.22 - 8.36 (m, 2 H) 8.81 (dd, *J* = 4.9, 1.7 Hz, 1 H), 9.22 (ddd, *J* = 9.3, 2.1, 0.8 Hz, 2 H).

Compounds 8 and 9 - 6-[4,4-Dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester (tazarotene nicotinate – S and R enantiomers)

The S and R enantiomers of compound 7 were separated by supercritical fluid chromatography using an OJH column (10 x 250 mm at 10 ml/min) using 15% ethanol as a modifier. UV absorbance was monitored at 254 nm. The respective enantiomers were obtained in a purity of about 96%.

The stereochemistry of the enantiomers was determined using *Ab Initio* Vibrational Circular Dichroism (VCD) analysis.

Compound 10 - 6-((2-hydroxy-4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid (hydroxytazarotenic acid)

6-(4,4-Dimethyl-1-oxo-1λ^4-thiochroman-6-ylethynyl)nicotinic acid ethyl ester

A suspension of tazarotene (10.0 g, 28.5 mmol) in methanol (300 mL) was chilled in an ice water bath to < 10°C, and then charged with the dropwise addition of a solution of $NaIO_4$ (9.13 g, 42.7 mmol) in water (100 mL) over 30 minutes. The reaction was allowed to warm to room temperature while stirring for 18 hours, and was then concentrated under reduced pressure to remove as much methanol as possible. The reaction was then diluted with DCM (500 mL) and water (150 mL). The two layers were

then separated, and the aqueous layer was extracted with DCM (2 x 100 mL aliquots). The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude sulfoxide product was then chromatographed using a DCM:EtOAc solvent system. Yield: 9.00 g (86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.34 (s, 3 H), 1.43 (t, *J* = 7.1 Hz, 3 H), 1.47 (s, 3 H), 1.91 (ddd, *J* = 15.1, 8.9, 2.3 Hz, 1 H), 2.45 (ddd, *J* = 15.1, 10.3, 2.4 Hz, 1 H), 3.04 - 3.29 (m, 2 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 7.58 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.63 (dd, *J* = 8.2, 0.7 Hz, 1 H), 7.71 (d, *J* = 1.6 Hz, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 8.32 (dd, *J* = 8.2, 2.2 Hz, 1 H), 9.22 (dd, *J* = 2.1, 0.7 Hz, 1 H). MS (ESI+) 368.0.

6-(2-Acetoxy-4,4-dimethylthiochroman-6-ylethynyl)nicotinic acid ethyl ester

A solution of the above sulfoxide (9.00 g, 24.5 mmol) in acetic anhydride (185 mL) was heated to 130°C for 5 hours, then concentrated under reduced pressure, with toluene added to aid evaporation of the acetic anhydride. The crude acetate was then chromatographed on a silica plug using a heptane:EtOAc solvent system. Yield: 8.47 g (84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.46 (s, 3 H), 2.10 - 2.22 (m, 2 H), 2.11 (s, 3 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 6.22 (dd, *J* = 6.9, 5.2 Hz, 1 H), 7.11 (d, *J* = 8.1 Hz, 1 H), 7.34 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.58 (dd, *J* = 8.2, 0.8 Hz, 1 H), 7.64 (d, *J* = 1.7 Hz, 1 H), 8.29 (dd, *J* = 8.2, 2.2 Hz, 1 H), 9.20 (dd, *J* = 2.2, 0.8 Hz, 1 H). MS (ESI+) 410.0.

6-((2-hydroxy-4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid

A suspension of the above acetate (3.00 g, 7.33 mmol) in ethanol (90 mL) was charged with the dropwise addition of a solution of KOH (2.47 g, 44.0 mmol) in water (15 mL). Within 30 minutes the reaction became homogenous, and was then allowed to stir at room temperature for 18 hours. The reaction was then concentrated under reduced pressure, diluted with water (40 mL), and then treated with the dropwise addition of 1.0 N HCl (33 mL) until a pH of ~5 was reached. The resulting yellow precipitate was filtered, and the filter cake was then washed with water (40 mL) and heptane (40 mL), and then dried under vacuum at 50°C for 18 hours. Yield: 1.95 g (78%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (s, 3 H), 1.42 (s, 3 H), 1.90 (dd, *J* = 13.5, 9.8 Hz, 1 H), 2.11 (dd, *J* = 13.5, 4.2 Hz, 1 H), 5.43 (dd, *J* = 9.8, 4.2 Hz, 1 H), 7.11 (d, *J* = 8.2 Hz, 1 H), 7.32 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.62 (d, *J* = 1.8 Hz, 1 H), 7.72 (dd, *J* = 8.1, 0.7

Hz, 1 H), 8.26 (dd, *J* = 8.1, 2.2 Hz, 1 H), 9.04 (dd, *J* = 2.2, 0.8 Hz, 1 H). MS (ESI+) 340.0.

Compound 11 - 6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinic acid (keto tazarotenic acid)

A suspension of compound 12 (1.28 g, 3.50 mmol) in ethanol (30 mL) was charged with the dropwise addition of a solution of KOH (2.47 g, 44.0 mmol) in water (15 mL), and the reaction was allowed to stir at room temperature for 18 hours. The reaction was then concentrated under reduced pressure, diluted with water (20 mL), and then treated with the dropwise addition of 1.0 N HCl until a pH of ~5 was reached. The resulting yellow precipitate was filtered, and the filter cake was then washed with water (10 mL) and heptane (10 mL), and then dried under vacuum at 50°C for 18 hours. Crude product (1.12 g) was then dissolved in DMSO and purified by reversed-phase HPLC using a methanol:water gradient with 0.1% HCO_2H present in both solvents. Yield: 26 mg (2.2%).

^{1}H NMR (400 MHz, DMSO-D_6) δ ppm 1.35 (s, 6 H), 2.80 (s, 2 H), 7.37 (br. d, *J* = 7.8 Hz, 1 H), 7.52 (br. d, *J* = 7.8 Hz, 1 H), 7.65 – 7.80 (m, 2 H), 8.23 (br. d, *J* = 7.2 Hz, 1 H), 9.01 (br. s, 1 H).

Compound 12 - ethyl 6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinate (keto tazarotene)

6-(4,4-Dimethyl-1-oxo-1λ^4-thiochroman-6-ylethynyl)nicotinic acid ethyl ester

A suspension of tazarotene (10.0 g, 28.5 mmol) in methanol (300 mL) was chilled in an ice water bath to < 10°C, and then charged with the dropwise addition of a solution of $NaIO_4$ (9.13 g, 42.7 mmol) in water (100 mL) over 30 minutes. The reaction was allowed to warm to room temperature while stirring for 18 hours, and was then concentrated under reduced pressure to remove as much methanol as possible. The reaction was then diluted with DCM (500 mL) and water (150 mL). The two layers were then separated, and the aqueous layer was extracted with DCM (2 x 100 mL aliquots). The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude sulfoxide product was then chromatographed using a DCM:EtOAc solvent system. Yield: 9.00 g (86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.34 (s, 3 H), 1.43 (t, *J* = 7.1 Hz, 3 H), 1.47 (s, 3 H), 1.91 (ddd, *J* = 15.1, 8.9, 2.3 Hz, 1 H), 2.45 (ddd, *J* = 15.1, 10.3, 2.4 Hz, 1 H), 3.04 - 3.29

(m, 2 H), 4.44 (q, J = 7.1 Hz, 2 H), 7.58 (dd, J = 8.1, 1.6 Hz, 1 H), 7.63 (dd, J = 8.2, 0.7 Hz, 1 H), 7.71 (d, J = 1.6 Hz, 1 H), 7.78 (d, J = 8.1 Hz, 1 H), 8.32 (dd, J = 8.2, 2.2 Hz, 1 H), 9.22 (dd, J = 2.1, 0.7 Hz, 1 H). MS (ESI+) 368.0.

6-(2-Acetoxy-4,4-dimethylthiochroman-6-ylethynyl)nicotinic acid ethyl ester

A solution of the above sulfoxide (9.00 g, 24.5 mmol) in acetic anhydride (185 mL) was heated to 130°C for 5 hours, then concentrated under reduced procedure, with toluene added to aid evaporation of the acetic anhydride. The crude acetate was then chromatographed on a silica plug using a heptane:EtOAc solvent system. Yield: 8.47 g (84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (s, 3 H), 1.43 (t, J = 7.2 Hz, 3 H), 1.46 (s, 3 H), 2.10 - 2.22 (m, 2 H), 2.11 (s, 3 H), 4.43 (q, J = 7.1 Hz, 2 H), 6.22 (dd, J = 6.9, 5.2 Hz, 1 H), 7.11 (d, J = 8.1 Hz, 1 H), 7.34 (dd, J = 8.2, 1.8 Hz, 1 H), 7.58 (dd, J = 8.2, 0.8 Hz, 1 H), 7.64 (d, J = 1.7 Hz, 1 H), 8.29 (dd, J = 8.2, 2.2 Hz, 1 H), 9.20 (dd, J = 2.2, 0.8 Hz, 1 H). MS (ESI+) 410.0.

6-(2-Hydroxy-4,4-dimethylthiochroman-6-ylethynyl)nicotinic acid ethyl ester

A solution of the above acetate (3.29 g, 8.03 mmol) in THF (50 mL) was charged with NaOEt (2.18 g, 32.1 mmol), and the reaction was heated to 75°C for 12 hours. The reaction was then diluted with EtOAc (250 mL) and washed with water (2 x 100 mL aliquots). The aqueous washes were then pooled and back-extracted with EtOAc (2 x 100 mL aliquots). The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the thiolactol. Yield: 2.31 g (78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.31 (s, 3 H), 1.43 (t, J = 7.1 Hz, 3 H), 1.48 (s, 3 H), 1.95 - 2.07 (m, 1 H), 2.26 (dd, J = 13.5, 4.5 Hz, 1 H), 2.54 (d, J = 8.5 Hz, 1 H), 4.43 (q, J = 7.2 Hz, 2 H), 5.50 (td, J = 8.8, 4.5 Hz, 1 H), 7.09 (d, J = 8.2 Hz, 1 H), 7.32 (dd, J = 8.1, 1.8 Hz, 1 H), 7.58 (dd, J = 8.2, 0.8 Hz, 1 H), 7.62 (d, J = 1.7 Hz, 1 H), 8.28 (dd, J = 8.2, 2.2 Hz, 1 H), 9.20 (dd, J = 2.2, 0.8 Hz, 1 H).

ethyl 6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinate

A solution of the above thiolactol (2.31 g, 6.29 mmol) in DCM (500 mL) was charged with Dess-Martin periodinane (2.80 g, 6.60 mmol), and the reaction stirred at room temperature for 1 hour. The reaction was then concentrated under reduced pressure, then diluted with EtOAc (250 mL) and washed with a saturated aqueous $NaHCO_3$ solution (2 x 100 mL aliquots). The aqueous washes were then pooled and back-extracted with

EtOAc (2 x 200 mL). The organic fractions were then pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was then chromatographed on a silica plug using a heptane:EtOAc solvent system. Yield: 1.28 g (56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.44 (t, *J* = 7.2 Hz, 3 H), 1.44 (s, 6 H), 2.71 (s, 2 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 7.23 (d, *J* = 8.1 Hz, 1 H), 7.48 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.62 (dd, *J* = 8.1, 0.8 Hz, 1 H), 7.73 (d, *J* = 1.7 Hz, 1 H), 8.31 (dd, *J* = 8.2, 2.2 Hz, 1 H), 9.22 (dd, *J* = 2.2, 0.8 Hz, 1 H).

Compound 13 - Ethyl 6-[2-palmitoyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with palmitoyl chloride in DCM and TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 0.85 (d, *J*=13.57 Hz, 2H), 0.85 (s, 2H), 1.22 (s, 26H), 1.29 (br. s, 6H), 1.35 - 1.50 (m, 11H), 1.56 (s, 2H), 1.63 (br. s, 1H), 1.60 (d, *J*=7.42 Hz, 2H), 2.03 - 2.20 (m, 2H), 2.31 (d, *J*=15.03 Hz, 1H), 2.31 (s, 1H), 4.40 (q, *J*=7.13 Hz, 2H), 6.19 (dd, *J*=6.49, 5.32 Hz, 1H) 7.07 (d, *J*=8.10 Hz, 1H), 7.31 (dd, *J*=8.15, 1.61 Hz, 1H), 7.55 (d, *J*=8.10 Hz, 1H), 7.61 (d, *J*=1.56 Hz, 1H), 8.25 (dd, *J*=8.15, 2.10 Hz, 1H), 9.17 (d, *J*=1.56 Hz, 1H)

Compound 14 - Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene)

Hydrolysis of compound 17 with sodium ethoxide in refluxing THF gave a mixture of the title compound, along with compound 10. The title compound was obtained (51%) by column chromatographic purification to remove the non-polar impurities and compound 10 (the hydroxy acid).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.25 (s, 3H), 1.38 (t, *J*=7.13 Hz, 3H), 1.42 (s, 3H), 1.98 (dd, *J*=13.42, 9.32 Hz, 1H), 2.21 (dd, *J*=13.47, 4.49 Hz, 1H), 3.21 (d, *J*=8.10 Hz, 1H), 4.39 (q, *J*=7.13 Hz, 2H), 5.48 (dt, *J*=13.03, 4.47 Hz, 1H), 7.02 (d, *J*=8.10 Hz, 1H), 7.26 (dd, *J*=8.10, 1.56 Hz, 1H), 7.53 (d, *J*=8.20 Hz, 1H), 7.57 (d, *J*=1.46 Hz, 1H), 8.24 (dd, *J*=8.15, 2.10 Hz, 1H), 9.15 (d, *J*=1.56 Hz, 1H)

Compound 15 - 6-[2-(2-Hydroxy-acetoxy)-4,4-dimethyl-thiochroman-6-ylethynyl]-nicotinic acid ethyl ester

Glycolic acid (4.2 g, 0.05 mole) and *tert*-butyldimethylchlorosilane (17.7 g, 0.012 mole) were stirred in 40 mL of dry DMF. Imidazole (15.62 g, 0.23 mol) was added to the mixture and stirred under nitrogen for 18 hours. The mixture was poured into deionized water (approximately 250 mL) and extracted with diethyl ether (3 x 100 mL aliquots). The organic fractions were combined, washed with saturated $NaHCO_3$, dried over MgSO4, and concentrated in vacuo to give an oil. Further drying under high vacuum provided 10.7 g (91%) of the bis-silylated glycolic acid as a white solid.

The bis-silylated glycolic acid was dissolved in 125 mL of dry DCM containing several drops of DMF. A solution of 13.4 mL oxalyl chloride (148 mmoles, 4.5 equivalents) was added drop wise under nitrogen for 20 minutes. The mixture was stirred for 4 hours at ambient temperature, then concentrated under vacuum to remove the volatiles (unreacted oxalyl chloride) to give the crude acid chloride (*tert*-butyldimethyl-silyloxy glycolic acid chloride) as a yellow oil.

A solution of Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) (400 mg, 1 mmole)) in DCM / TEA at room temperature was prepared. The mixture was placed under a nitrogen atmosphere and the above acid chloride (340 mg, 1.5 mmoles, 1.5 equivalents) was added slowly at room temperature. The mixture was stirred at ambient temperature for 17 hours after which time, LCMS analysis showed complete conversion. The mixture was diluted with DCM (50 mL) and washed with H_2O (15 mL) followed by saturated $NaHCO_3$ (15 mL) and brine solution. The organic layer was dried over Na_2SO_4, filtered and concentrated to an oil - a silylated intermediate. Chromatography on silica gel eluting with an ethyl acetate-heptanes gradient gave 300 mg of purified product.

The silylated intermediate was dissolved in THF (4 mL) and acetic acid (0.5 mL). The stirring mixture was treated with 1M TBAF (1mL, 1mmole) and stirred for 1 hour at ambient temperature. The crude reaction mixture was concentrated to an oil. The oil was treated with heptanes (5 mL) and kept cold (~ 4 ^{o}C) overnight. The resulting solid was filtered and washed with heptanes to give 130 mg (29%) of compound 15 as a white translucent solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.36 - 1.51 (m, 11H), 2.10 - 2.29 (m, 2H), 2.35 (t, *J*=5.66 Hz, 1H), 4.21 (d, *J*=5.66 Hz, 2H), 4.37 - 4.50 (m, 2H), 6.36 (dd, *J*=6.59, 5.32 Hz, 1H), 7.11 (d, *J*=8.10 Hz, 1H), 7.36 (dd, *J*=8.10, 1.56 Hz, 1H), 7.59 (d, *J*=8.20

Hz, 1H), 7.65 (d, *J*=1.46 Hz, 1H), 8.29 (dd, *J*=8.15, 2.10 Hz, 1H), 9.21 (d, *J*=1.46 Hz, 1H)

Compound 16 - Ethyl 6-[(2-(2-methoxyacetyl)-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with methoxyacetyl chloride in DCM / TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.43 (d, *J*=14.45 Hz, 7H), 1.43 (s, 2H), 2.09 - 2.34 (m, 2H), 3.46 (s, 3H), 4.07 (s, 2H), 4.43 (q, *J*=7.19 Hz, 2H), 6.33 (dd, *J*=6.64, 5.27 Hz, 1H), 7.11 (d, *J*=8.20 Hz, 1H), 7.35 (dd, *J*=8.15, 1.61 Hz, 1H), 7.58 (d, *J*=8.10 Hz, 1H), 7.64 (d, *J*=1.46 Hz, 1H), 8.28 (dd, *J*=8.15, 2.10 Hz, 1H), 9.20 (d, *J*=1.46 Hz, 1H)

Compound 17 - Ethyl 6-[(2-acetyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate

Tazarotene was oxidized with sodium periodate in methanol/water to give the corresponding sulfoxide. After column purification it yielded 47g (90%) of the sulfoxide, which was subjected to Pummerer rearrangement with acetic anhydride as the solvent and acylating agent to yield the desired product (42g).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.39 (s, 4H), 1.41 (s, 2H) 1.43 - 1.49 (m, 4H), 2.10 (s, 3H), 2.11 - 2.18 (m, 2H), 4.42 (q, *J*=7.13 Hz, 2H), 6.20 (dd, *J*=6.69, 5.42 Hz, 1H), 7.09 (d, *J*=8.10 Hz, 1H), 7.33 (dd, *J*=8.10, 1.37 Hz, 1H), 7.57 (d, *J*=8.10 Hz, 1H), 7.63 (d, *J*=1.27 Hz, 1H), 8.27 (dd, *J*=8.15, 2.00 Hz, 1H), 9.19 (d, *J*=1.37 Hz, 1 H)

Compound 18 - Ethyl 6-[(2-n-butyryloxyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with butyryl chloride in DCM / TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 0.97 (t, *J*=7.42 Hz, 4H), 1.38 - 1.50 (m, 11H), 1.63 - 1.74 (m, 3H), 2.15 (d, *J*=6.83 Hz, 1H), 2.17 (d, *J*=5.27 Hz, 1H), 2.33 (d, *J*=15.13

Hz, 1H), 2.34 (s, 1H), 4.43 (q, *J*=7.13 Hz, 2H), 6.23 (dd, *J*=6.49, 5.42 Hz, 1H), 7.11 (d, *J*=8.10 Hz, 1H), 7.34 (dd, *J*=8.10, 1.56 Hz, 1H), 7.58 (d, *J*=8.10 Hz, 1H), 7.64 (d, *J*=1.37 Hz, 1H), 8.29 (dd, *J*=8.15, 2.10 Hz, 1H), 9.21 (d, *J*=1.56 Hz, 1H)

Compound 19 - Ethyl 6-[(2-lauroyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with lauroyl chloride in DCM / TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 0.88 (d, *J*=13.71 Hz, 2H), 0.88 (s, 2H), 1.20 - 1.38 (m, 4H), 1.26 (s, 18H), 1.41 (s, 4H), 1.43 (s, 2H), 1.44 - 1.49 (m, 4H), 1.57 - 1.73 (m, 4H), 2.14 (d, *J*=6.74 Hz, 1H), 2.17 (d, *J*=5.22 Hz, 1H), 2.31 - 2.39 (m, 2H), 4.43 (q, *J*=7.11 Hz, 2H), 6.22 (dd, *J*=6.64, 5.22 Hz, 1H), 7.10 (d, *J*=8.15 Hz, 1H), 7.34 (dd, *J*=8.13, 1.73 Hz, 1H), 7.58 (dd, *J*=8.15, 0.83 Hz, 1H), 7.64 (d, *J*=1.71 Hz, 1H), 8.28 (dd, *J*=8.15, 2.15 Hz, 1H), 9.20 (dd, *J*=2.15, 0.78 Hz, 1H)

Compound 20 - Ethyl 6-[(2-isobutyryloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with isobutyryl chloride in DCM / TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 0.74 - 0.98 (m, 4H), 1.20 (d, *J*=7.03 Hz, 7 H), 1.44 (d, *J*=14.15 Hz, 6H), 1.43 (t, *J*=7.13 Hz, 5H), 2.17 (d, *J*=4.39 Hz, 2H), 2.15 (s, 1 H) 2.49 - 2.66 (m, 1H), 4.44 (q, *J*=7.13 Hz, 2H) 6.16 - 6.26 (m, 1H), 7.11 (d, *J*=8.10 Hz, 1H), 7.34 (dd, *J*=8.10, 1.46 Hz, 1H), 7.59 (d, *J*=8.20 Hz, 1H), 7.65 (d, *J*=1.37 Hz, 1H), 8.29 (dd, *J*=8.10, 2.05 Hz, 1H), 9.21 (d, *J*=1.46 Hz, 1H)

Compound 21- Ethyl 6-[(2-linoeoyll-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with linoleoyl chloride in DCM /

TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 0.76 - 0.97 (m, 9H), 1.19 - 1.39 (m, 26H), 1.40 - 1.50 (m, 15H), 1.67 (br. s, 1H), 1.64 (d, *J*=7.32 Hz, 2H), 2.03 (br. s, 1H), 2.05 (d, *J*=6.74 Hz, 5H), 2.15 (d, *J*=6.83 Hz, 2H), 2.17 (d, *J*=5.27 Hz, 1H), 2.35 (d, *J*=14.93 Hz, 2H), 2.35 (s, 1H), 2.78 (d, *J*=12.49 Hz, 1H), 2.78 (s, 1H), 4.44 (q, *J*=7.13 Hz, 3H), 5.27 - 5.45 (m, 6H), 6.23 (dd, *J*=6.54, 5.37 Hz, 1H), 7.11 (d, *J*=8.10 Hz, 1H) 7.34 (dd, *J*=8.10, 1.56 Hz, 1H), 7.59 (d, *J*=8.20 Hz, 1H), 7.64 (d, *J*=1.46 Hz, 1H), 8.29 (dd, *J*=8.15, 2.10 Hz, 1H)

Compound 22 - Ethyl 6-[(2-linleolyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with linolenoyl chloride in DCM / TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 0.98 (t, *J*=7.52 Hz, 4H), 1.22 - 1.38 (m, 14H), 1.38 - 1.50 (m, 13H), 1.66 (br. s, 1H), 1.64 (d, *J*=7.22 Hz, 2H), 2.01 - 2.22 (m, 9H), 2.35 (t, *J*=7.52 Hz, 3H), 2.69 - 2.93 (m, 6H), 4.44 (q, *J*=7.13 Hz, 3H), 5.28 - 5.45 (m, 9H), 6.23 (dd, *J*=6.54, 5.37 Hz, 1H), 7.11 (d, *J*=8.10 Hz, 1H), 7.34 (dd, *J*=8.10, 1.56 Hz, 1H), 7.59 (d, *J*=8.20 Hz, 1H), 7.64 (d, *J*=1.56 Hz, 1H), 8.29 (dd, *J*=8.15, 2.10 Hz, 1H)

Compound 23 - Ethyl 6-[(2-(N-methyl-4-piperidinylcarboxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with 1-methyl piperidine carbonyl chloride in DCM / TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.35 - 1.50 (m, 11H), 1.70 - 1.85 (m, 1H), 1.78 (dd, *J*=11.23, 1.46 Hz, 2H), 1.85 - 2.06 (m, 5H), 2.14 (d, *J*=11.81 Hz, 1H), 2.14 (s, 1H), 2.21 - 2.36 (m, 1H), 2.25 (s, 4H), 2.79 (d, *J*=11.23 Hz, 2H), 4.42 (q, *J*=7.13 Hz, 2H), 6.15 - 6.26 (m, 1H), 7.09 (d, *J*=8.10 Hz, 1H), 7.33 (dd, *J*=8.10, 1.56 Hz, 1H), 7.57

(d, *J*=8.20 Hz, 1H), 7.63 (d, *J*=1.37 Hz, 1H), 8.27 (dd, *J*=8.15, 2.10 Hz, 1H), 9.19 (d, *J*=1.46 Hz, 1H)

Compound 24 - Ethyl 6-[(2-propionyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with propionyl chloride in DCM with TEA as a base at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.17 (t, *J*=7.56 Hz, 4H), 1.34 - 1.51 (m, 11H), 2.15 (d, *J*=6.74 Hz, 1H), 2.17 (d, *J*=5.27 Hz, 1H), 2.38 (q, *J*=7.58 Hz, 2H), 4.43 (q, *J*=7.13 Hz, 2H), 6.23 (dd, *J*=6.59, 5.32 Hz, 1H), 7.11 (d, *J*=8.10 Hz, 1H), 7.34 (dd, *J*=8.10, 1.56 Hz, 1H), 7.59 (d, *J*=8.10 Hz, 1H), 7.64 (d, *J*=1.46 Hz, 1H), 8.29 (dd, *J*=8.20, 2.15 Hz, 1H), 9.21 (d, *J*=1.56 Hz, 1H)

Compound 25 - Ethyl 6-[(2-salicylicyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with salicylic acid using EDC and HOBt. The reaction afforded the desired compound, along with a self coupled impurity. The desired product was obtained via column chromatography.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.40 (t, *J*=7.13 Hz, 7H), 1.47 (s, 7H), 1.52 (s, 8H), 2.29 (d, *J*=1.56 Hz, 2H), 2.31 (d, *J*=2.44 Hz, 2H), 4.41 (q, *J*=7.06 Hz, 4H), 6.47 (t, *J*=5.51 Hz, 2H), 6.79 - 6.92 (m, 2H), 6.98 (d, *J*=8.30 Hz, 2H), 7.10 (d, *J*=8.10 Hz, 2H), 7.34 (dd, *J*=8.10, 1.37 Hz, 2H), 7.46 (s, 2H), 7.57 (d, *J*=8.10 Hz, 2H), 7.66 (d, *J*=1.17 Hz, 2H), 7.76 (dd, *J*=7.96, 1.32 Hz, 2H), 8.26 (dd, *J*=8.10, 2.05 Hz, 2H), 9.18 (d, *J*=1.37 Hz, 2H), 10.53 (s, 1 H)

Compound 26 - Ethyl 6-[(2-(4-tetrahydropyranyloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with tetrahydropyran-4-carbonyl chloride in DCM / TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.31 - 1.50 (m, 11H), 1.69 - 1.92 (m, 5H), 2.04 - 2.26 (m, 2H), 2.55 (t, *J*=10.54 Hz, 1H), 3.32 - 3.48 (m, 2H), 3.94 (dd, *J*=11.47, 2.88 Hz, 2H), 4.41 (q, *J*=7.13 Hz, 2H), 6.14 - 6.28 (m, 1H), 7.08 (d, *J*=8.10 Hz, 1H), 7.32 (dd, *J*=8.10, 1.46 Hz, 1H), 7.56 (d, *J*=8.10 Hz, 1H), 7.62 (d, *J*=1.27 Hz, 1H), 8.26 (dd, *J*=8.20, 2.05 Hz, 1H), 9.18 (d, *J*=1.37 Hz, 1H)

Compound 27 - Ethyl 6-[(2-monomethyladopyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with monomethyl adipoyl chloride in DCM / TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.40 (d, *J*=16.40 Hz, 8H), 1.40 (s, 3H), 1.66 (d, *J*=14.06 Hz, 1H), 1.66 (t, *J*=3.42 Hz, 3H), 2.05 - 2.21 (m, 2H), 2.25 - 2.42 (m, 4H), 3.64 (s, 3H), 4.40 (q, *J*=7.13 Hz, 2H), 6.19 (dd, *J*=6.59, 5.32 Hz, 1H), 7.07 (d, *J*=8.10 Hz, 1H), 7.31 (dd, *J*=8.10, 1.56 Hz, 1H), 7.55 (d, *J*=8.20 Hz, 1H), 7.61 (d, *J*=1.46 Hz, 1H), 8.26 (dd, *J*=8.10, 2.15 Hz, 1H), 9.17 (d, *J*=1.46 Hz, 1H)

Compound 28 - Ethyl 6-[(2-(3-monomethylazelauate-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate

Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with monomethyl azelate chloride in DCM / TEA at room temperature. The crude product was purified by column chromatography to give the desired compound.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 1.32 (br. s., 11H), 1.39 - 1.50 (m, 11H), 1.53 - 1.73 (m, 7H), 2.15 (d, *J*=6.74 Hz, 2H), 2.17 (d, *J*=5.17 Hz, 1H), 2.26 - 2.46 (m, 7H), 3.58 - 3.77 (m, 5H), 4.44 (q, *J*=7.13 Hz, 2H), 6.22 (dd, *J*=6.54, 5.37 Hz, 1H), 7.11 (d, *J*=8.20 Hz, 1H), 7.34 (dd, *J*=8.10, 1.56 Hz, 1H), 7.59 (d, *J*=8.20 Hz, 1H), 7.64 (d, *J*=1.46 Hz, 1H), 8.29 (dd, *J*=8.15, 2.10 Hz, 1H), 9.21 (d, *J*=1.46 Hz, 1H)

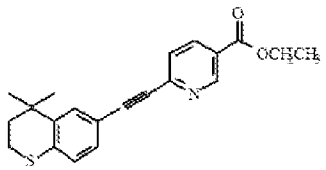
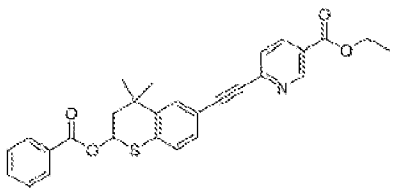
Compound 29 - 6-[2-((S)-2-Amino-3-methyl-butyryloxy)-4,4-dimethyl-thiochroman-6-ylethynyl]-nicotinic acid ethyl ester

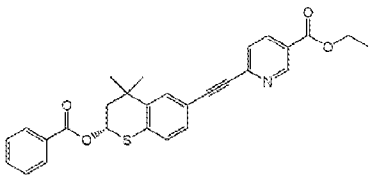
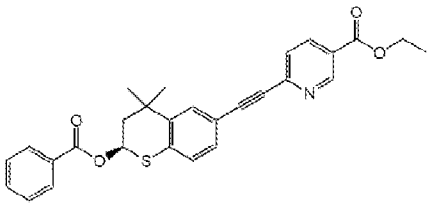
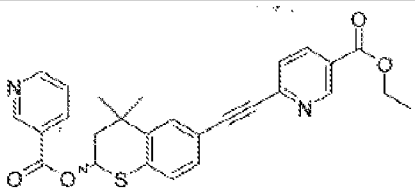
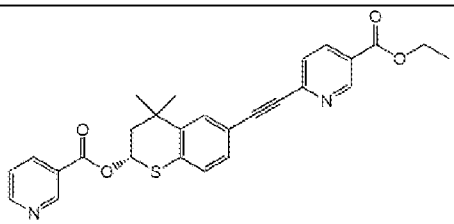
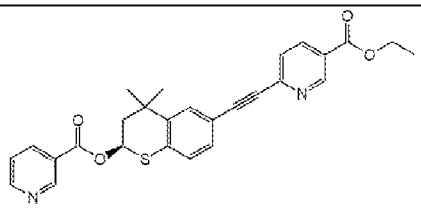
Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethynyl] pyridine-3-carboxylate (hydroxy tazarotene) was reacted with Fmoc protected amino acid chloride (from Valine) to give the Fmoc protected amino ester. Fmoc deprotection was facilitated with dilute piperidine in THF at room temperature, as follows:

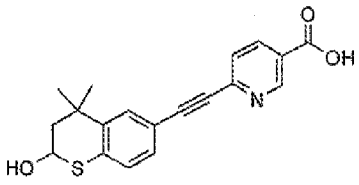
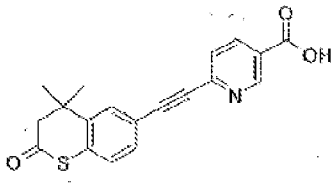
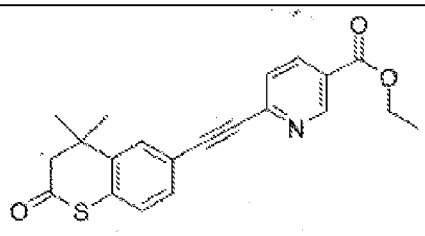
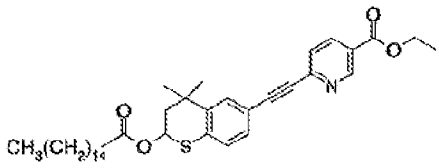
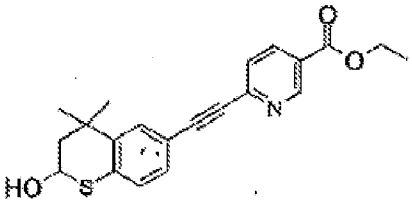
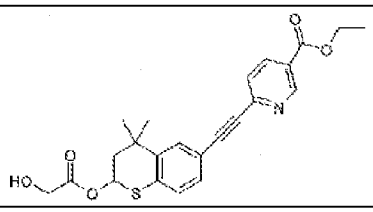
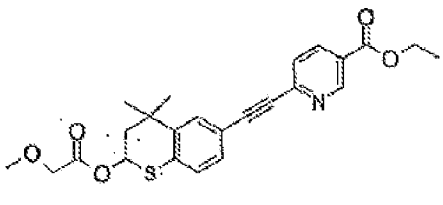
20% Piperidine (5 equivalents) in THF was added to a solution of the Fmoc-protected amino ester in THF, while stirring. The reaction mixture was stirred for 5 hours and progress of the reaction was periodically monitored by LC/MS. At completion of the reaction, the reaction mixture was poured into water and extracted with EtOAc (2 x 20mL aliquots). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified in a Companion purification system using a 12.0g cartridge.

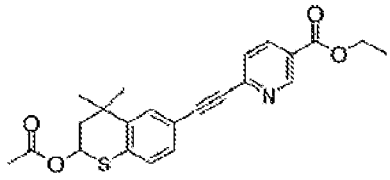
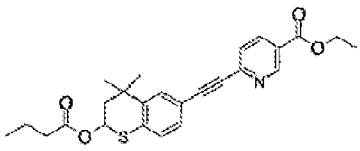
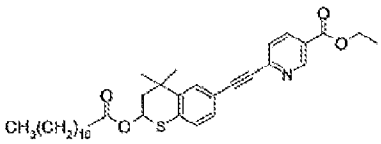
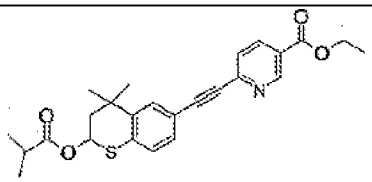
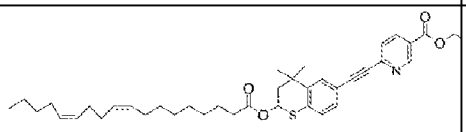
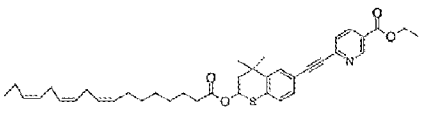
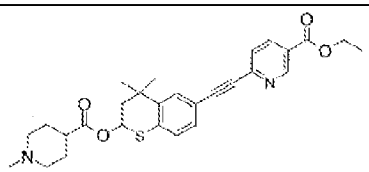
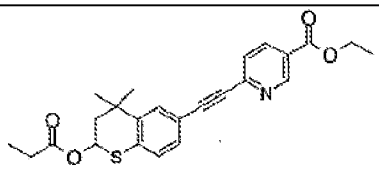
^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 0.92 (t, *J*=6.78 Hz, 3H), 0.99 (d, *J*=6.74 Hz, 3H), 1.35 - 1.59 (m, 12H), 1.97 - 2.09 (m, 1H), 2.09 - 2.26 (m, 2H), 3.31 (d, *J*=5.17 Hz, 1H), 4.43 (q, *J*=7.06 Hz, 2H), 6.20 - 6.34 (m, 1H), 7.10 (d, *J*=8.10 Hz, 1H), 7.34 (d, *J*=8.10 Hz, 1H), 7.58 (d, *J*=8.20 Hz, 1H), 7.64 (d, *J*=1.27 Hz, 1H), 8.28 (dd, *J*=8.10, 2.05 Hz, 1H), 9.20 (d, *J*=1.56 Hz, 1H)

Table 11

	Description	Structure	Notes
1	Untreated (negative) control	NA	None
2	OD (vehicle) control	NA	None
3	Tazarotene (0.1% in OD)		MW 351.46 Purity 99.5%
4	Tazarotene benzoate 6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester		MW 471.58 Purity 98.0%

	Description	Structure	Notes
5	Tazarotene benzoate (S isomer) (S) - 6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester		MW 471.58 Purity >97.0%
6	Tazarotene benzoate (R isomer) (R) - 6-(2-(2-benzoyloxy-4,4-dimethylthiochroman-6-yl) ethynyl) nicotinic acid, ethyl ester		MW 471.58 Purity >97.0%
7	Tazarotene nicotinate 6-[4,4-Dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester		MW 472.57 Purity 94.0%
8	Tazarotene nicotinate (S isomer) S-6-[4,4-Dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester		MW 472.56 Purity 95.0%
9	Tazarotene nicotinate (R isomer) R-6-[4,4-Dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester		MW 472.56 Purity 95.0%

	Description	Structure	Notes
10	Hydroxy tazarotenic acid 6-((2-hydroxy-4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid		MW 339.42 Purity 99.3%
11	Keto tazarotenic acid 6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinic acid		MW 337.40 Purity 87.0%
12	Keto tazarotene Ethyl 6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinate		MW 406.00 Purity 99.0%
13	Ethyl 6-[2-palmitoyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate		MW 605.89 Purity 94.8%
14	Hydroxy Tazarotene Ethyl 6-[(2-hydroxy-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl)ethyynyl] pyridine-3-carboxylate		MW 367.47 Purity 98.4%
15	6-[2-(2-Hydroxy-acetoxy)-4,4-dimethyl-thiochroman-6-ylethyny1]-nicotinic acid ethyl ester		MW 425.50 Purity >99.5%
16	Ethyl 6-[(2-(2-methoxyacetyl)-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate		MW 439.53 Purity 96.3%

	Description	Structure	Notes
17	Ethyl 6-[(2-acetyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate		MW 409.51 Purity 95.4%
18	Ethyl 6-[(2-n-butyryloxyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate		MW 437.56 Purity 98.4%
19	Ethyl 6-[(2-lauroyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate		MW 549.78 Purity 98.5%
20	Ethyl 6-[(2-isobutyryloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate		MW 437.56 Purity 98.4%
21	Ethyl 6-[(2-linoeoyll-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate		MW 629.91 Purity 98.3%
22	Ethyl 6-[(2-linleolyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate		MW 627.89 Purity 96.1%
23	Ethyl 6-[(2-(N-methyl-4-piperidinylcarboxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate		MW 492.64 Purity 94.9%
24	Ethyl 6-[(2-propionyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate		MW 423.54 Purity 98.7%

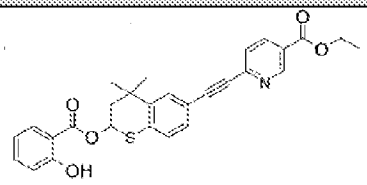
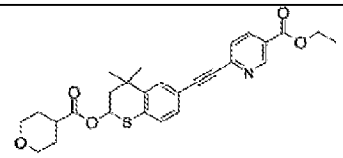
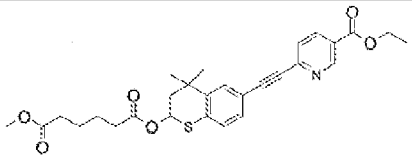
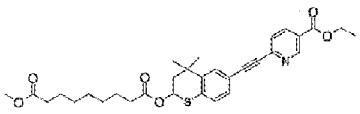
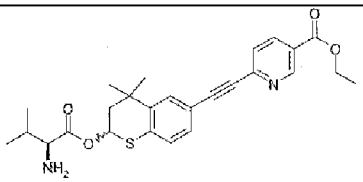
	Description	Structure	Notes
25	Ethyl 6-[(2-salicylicyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate		MW 487.58 Purity 98.7%
26	Ethyl 6-[(2-(4-tetrahydropyranyloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate		MW 479.60 Purity 98.3%
27	Ethyl 6-[(2-monomethyladopyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate		MW 509.63 Purity 99.5%
28	Ethyl 6-[(2-(3-monomethylazelauate-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine3-carboxylate		MW 551.71 Purity 95.3%
29	6-[2-((S)-2-Amino-3-methyl-butyryloxy)-4,4-dimethyl-thiochroman-6-ylethynyl]-nicotinic acid ethyl ester		MW 466.60 Purity 97.8%

Table 12. Qualitative summary of gene expression data from RHE cultures treated with tazarotene derivatives.

Rank	Compound	Fold Change vs Untreated/OD controls Upregulation / Downregulation					Ranking Score
		K10	K19	Filaggrin	K4	K13	
1	24	14	33	56	74	23	*20*
2	23	9	43	18	73	19	*23*
3	11	17	21	36	52	20	*27*
4	29	9	29	11	71	13	*31*
5	15	7	36	8	64	12	*33*
6	27	10	41	23	70	19	*40*
7	28	6	30	7	77	18	*43*
8	14	7	29	11	87	20	*44*
9	8	7	18	9	35	7	*47*
10	18	4	22	7	60	9	*48*
11	10	6	25	6	65	11	*48*
12	22	7	12	11	38	10	*49*
13	25	3	23	4	103	17	*52*
14	Tazarotene (3)	3	41	3	119	12	*52*
15	9	6	17	10	32	5	*55*
16	7	19	17	100	23	8	*57*
17	12	2	27	1	173	15	*59*
18	16	7	20	7	69	9	*63*

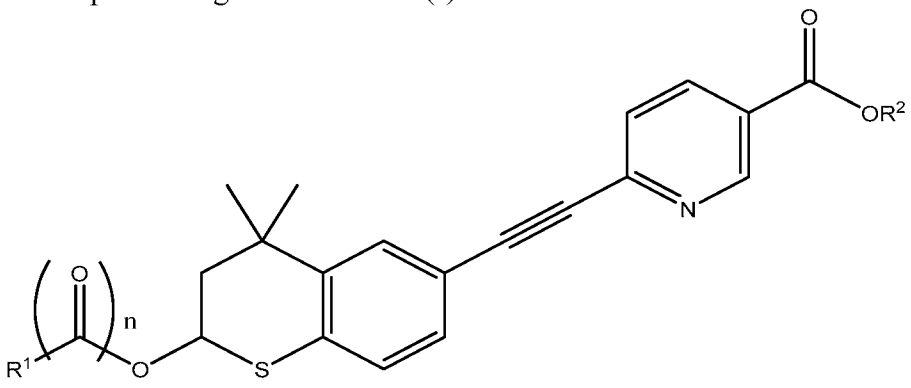
Rank	Compound	Fold Change vs Untreated/OD controls Upregulation / Downregulation					Ranking Score
19	17	3	24	2	180	15	*64*
20	6	8	8	16	20	7	*64*
21	20	10	15	12	22	6	*65*
22	26	4	20	4	90	10	*68*
23	5	1	8	1	45	7	*76*
24	21	1	2	1	11	3	*80*
25	4	2	8	3	29	7	*84*
26	13	2	4	1	38	6	*89*
27	19	2	2	2	19	2	*90*

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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

What is Claimed Is:

1. A compound of general formula (I):



(I)

wherein n is 0 or 1;

R^1 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted cycloalkyl group, or a optionally substituted heteroaryl group; and

R^2 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted cycloalkyl group, or a optionally substituted heteroaryl group; or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein n is 1.

3. The compound according to claim 1 or 2, wherein R^1 is an optionally substituted C_{1-18} alkyl.

4. The compound according to claim 1 or 2, wherein R^1 is an optionally substituted aryl, heteroaryl or heterocyclic group.

5. The compound according to claim 1 or 2, wherein R^1 is an optionally substituted C_{2-18} alkenyl.

6. The compound according to any of the preceding claims, wherein when R^1 is an optionally substituted C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocyclic, C_{3-7} cycloalkyl or heteroaryl group, the group is optionally substituted one or more times,

independently by halogen; hydroxy; NR_4R_5; hydroxy substituted C_{1-6} alkyl; C_{1-6} alkoxy; halosubstituted C_{1-6} alkoxy; halosubstituted C_{1-6} alkyl; C_{1-6} alkyl; $-C(O)OR_6$, or $-OC(O)R_6$;

R_4 and R_5 are independently selected from hydrogen or C_{1-6} alkyl; and

R_6 is independently selected from hydrogen or C_{1-6} alkyl.

7. The compound according to claim 6, wherein R^1 is C_{1-18} alkyl or C_{1-18} alkyl substituted one or more times by hydroxy, NR_4R_5, C_{1-6} alkoxy or $-C(O)OR_6$.

8. The compound according to claim 4, wherein R^1 is an optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted tetrahydropyranyl, or optionally substituted piperidinyl.

9. The compound according to any of the preceding claims, wherein R^2 is hydrogen or C_{1-6} alkyl.

10. The compound according to claim 8, wherein R^1 is phenyl.

11. The compound according to claim 1, 3, 4, 5 or 10, wherein R^2 is C_{1-6} alkyl.

12. The compound according to claim 11, wherein R^2 is ethyl.

13. The compound according to claim 1, wherein n is 0.

14. The compound according to claim 13, wherein R^1 is H and R^2 is H.

15. The compound according to claim 1 which is:

6-[4,4-dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester;

(S)-6-[4,4-dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester;

(R)-6-[4,4-dimethyl-2-(pyridine-3-carbonyloxy) thiochroman-6-ylethynyl] nicotinic acid ethyl ester;

Ethyl 6-[2-palmitoyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate;

6-[2-(2-Hydroxy-acetoxy)-4,4-dimethyl-thiochroman-6-ylethyny1]-nicotinic acid ethyl ester;

Ethyl 6-[(2-(2-methoxyacetyl)-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-acetyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-n-butyryloxyl-4,4-dimethyl-3,4-dihydro-2-thiochromen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-lauroyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-isobutyryloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-linoeoyll-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-linleolyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-(N-methyl-4-piperidinylcarboxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-propionyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-salicylicyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-(4-pyranyloxy-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-monomethyladopyl-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate;

Ethyl 6-[(2-(3-monomethylazelauate-4,4-dimethyl-3,4-dihydro-2-thiochrornen-6-yl) ethynyl] pyridine-3-carboxylate; or

6-[2-((S)-2-Amino-3-methyl-butyryloxy)-4,4-dimethyl-thiochroman-6-yl-ethynyl]-nicotinic acid ethyl ester; or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15, and one or more pharmaceutically acceptable carriers or excipients.

17. The pharmaceutical composition according to claim 16, comprising a second pharmaceutically active agent.

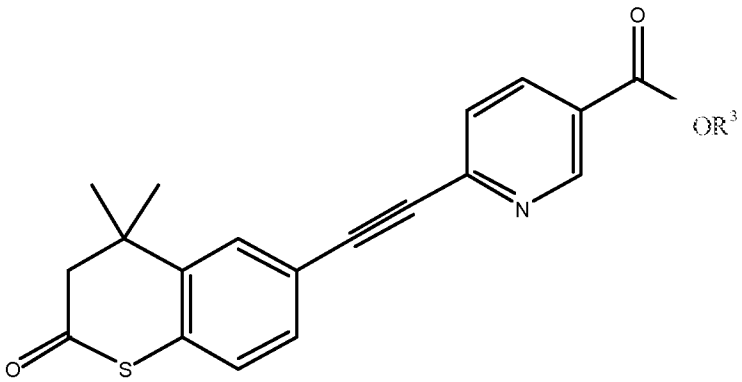
18. The pharmaceutical composition according to claim 17, wherein the second pharmaceutically active agent is benzoyl peroxide.

19. Use of a compound according to any one of claims 1 to 15 for the treatment of a skin disorder.

20. A method of treating a skin disorder in a human in need thereof, said method comprising administering to said human an effective amount of a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1 to 15.

(II)

21. A compound of general formula (II):



wherein

R^3 is hydrogen, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl group, optionally substituted heterocyclic group, optionally substituted C_{3-7} cycloalkyl group, or a optionally substituted heteroaryl group; or a pharmaceutically acceptable salt thereof.

22. The compound according to claim 21, wherein R^3 is hydrogen or C_{1-6} alkyl.

23. The compound according to claim 22, wherein R^3 is hydrogen.

24. The compound according to claim 22, wherein R^3 is C_{1-6} alkyl.

25. The compound according to claim 24, wherein C_{1-6} alkyl is ethyl.

26. The compound according to claim 21 which is:
6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinic acid; or
Ethyl 6-((4,4-dimethyl-2-oxothiochroman-6-yl)ethynyl)nicotinate; or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising a compound according to any one of claims 21 to 26, and one or more pharmaceutically acceptable carriers or excipients.

28. The pharmaceutical composition according to claim 27, comprising a second pharmaceutically active agent.

29. The pharmaceutical composition according to claim 28, wherein the second pharmaceutically active agent is selected from the group consisting benzoyl peroxide, an antibiotic, a corticosteroid and a vitamin D analogue.

30. Use of a compound according to any one of claims 21 to 26 for the treatment of a skin disorder.

31. A method of treating a skin disorder in a human in need thereof, said method comprising administering to said human an effective amount of a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 21 to 26.

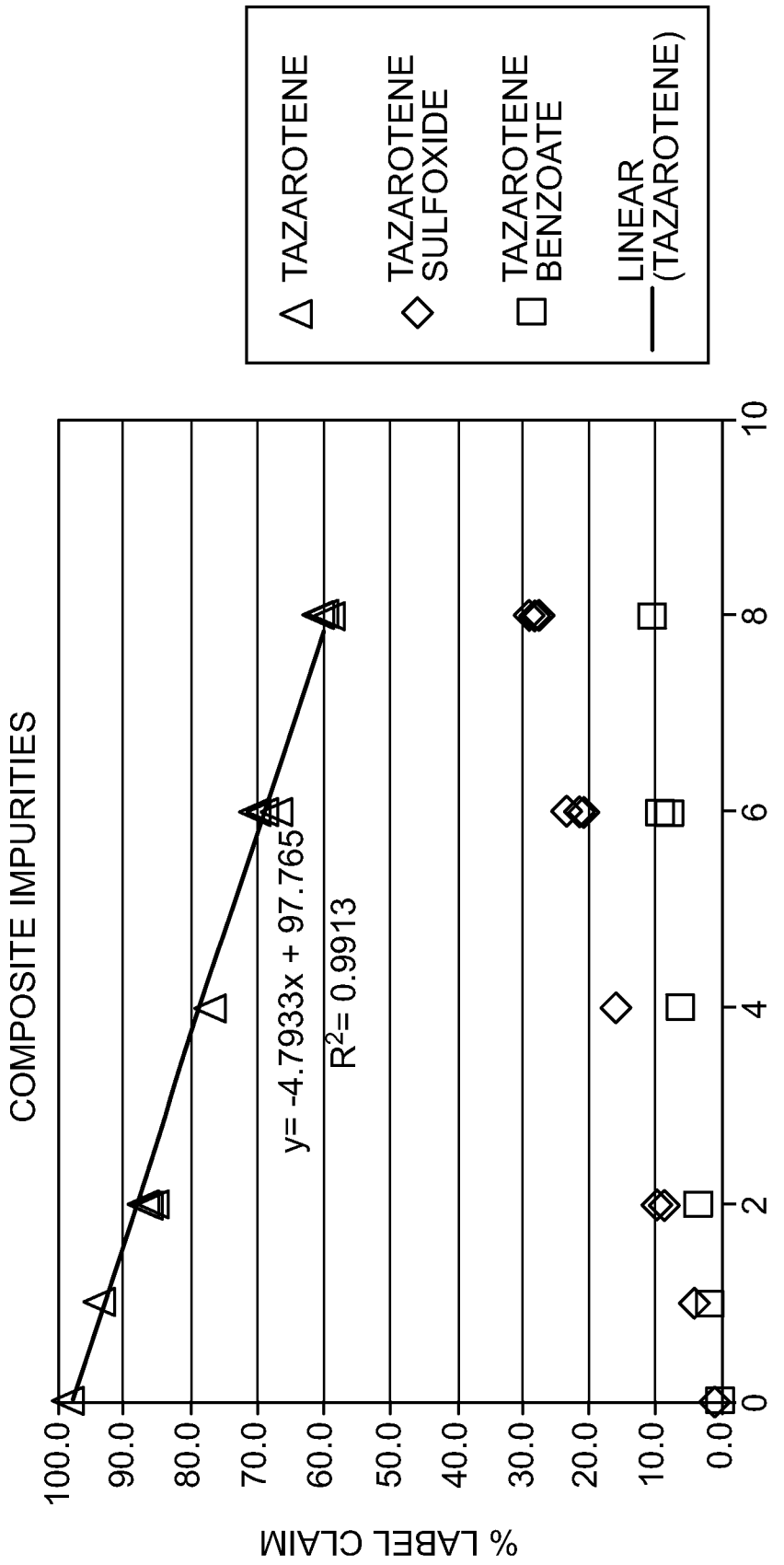

COMPOSITE IMPURITIES
% LABEL CLAIM
TIME (HOURS)
y= -4.7933x + 97.765
R2= 0.9913
TAZAROTENE
TAZAROTENE SULFOXIDE
TAZAROTENE BENZOATE
LINEAR (TAZAROTENE)
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
2
4
6
8
10

FIG. 1

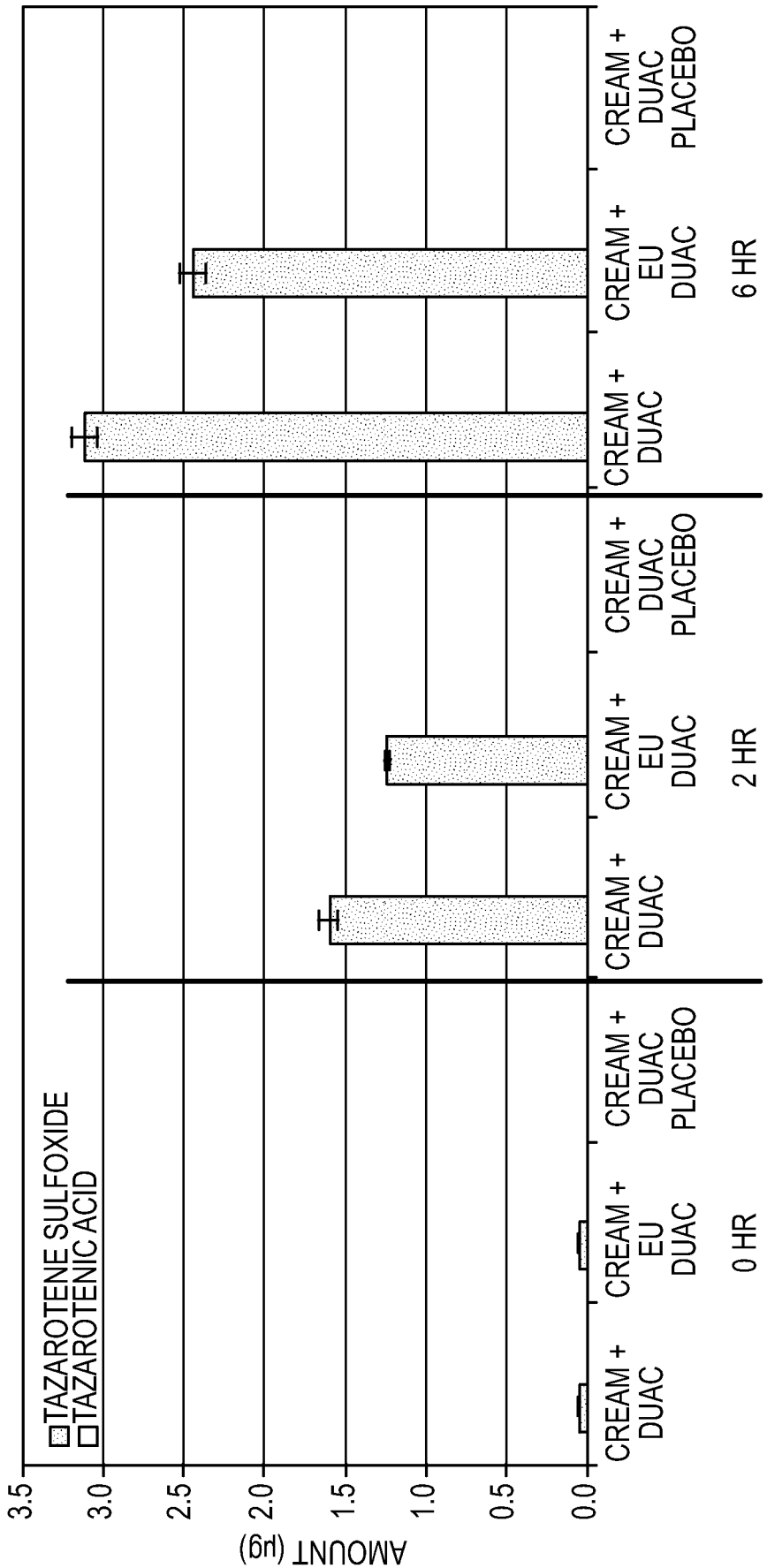

TAZAROTENE SULFOXIDE
TAZAROTENIC ACID
AMOUNT (µg)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
CREAM + DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO
0 HR
2 HR
6 HR

FIG. 2A

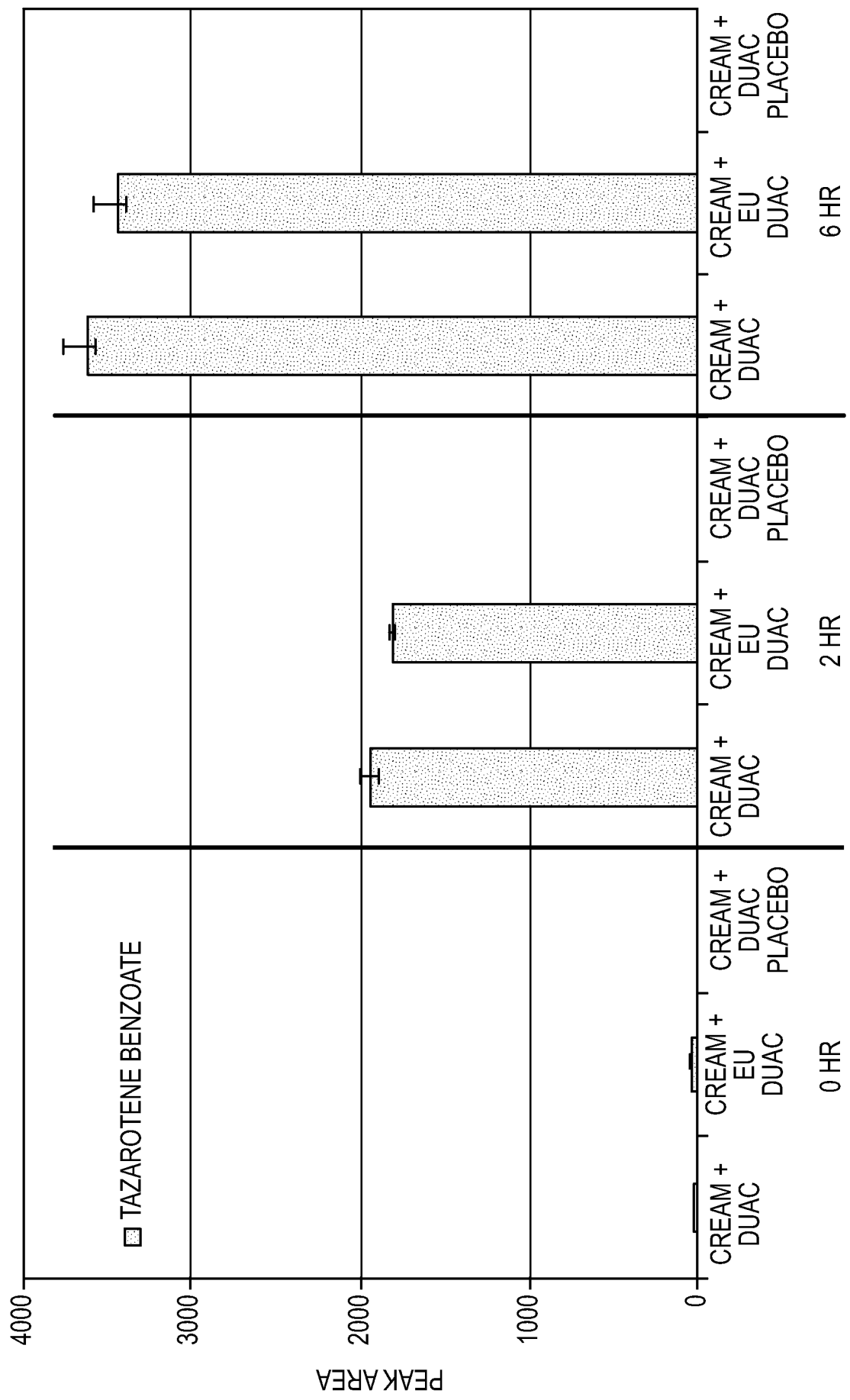

PEAK AREA
4000
3000
2000
1000
0
TAZAROTENE BENZOATE
CREAM + DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO
0 HR
CREAM + DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO
2 HR
CREAM + DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO
6 HR

FIG. 2B

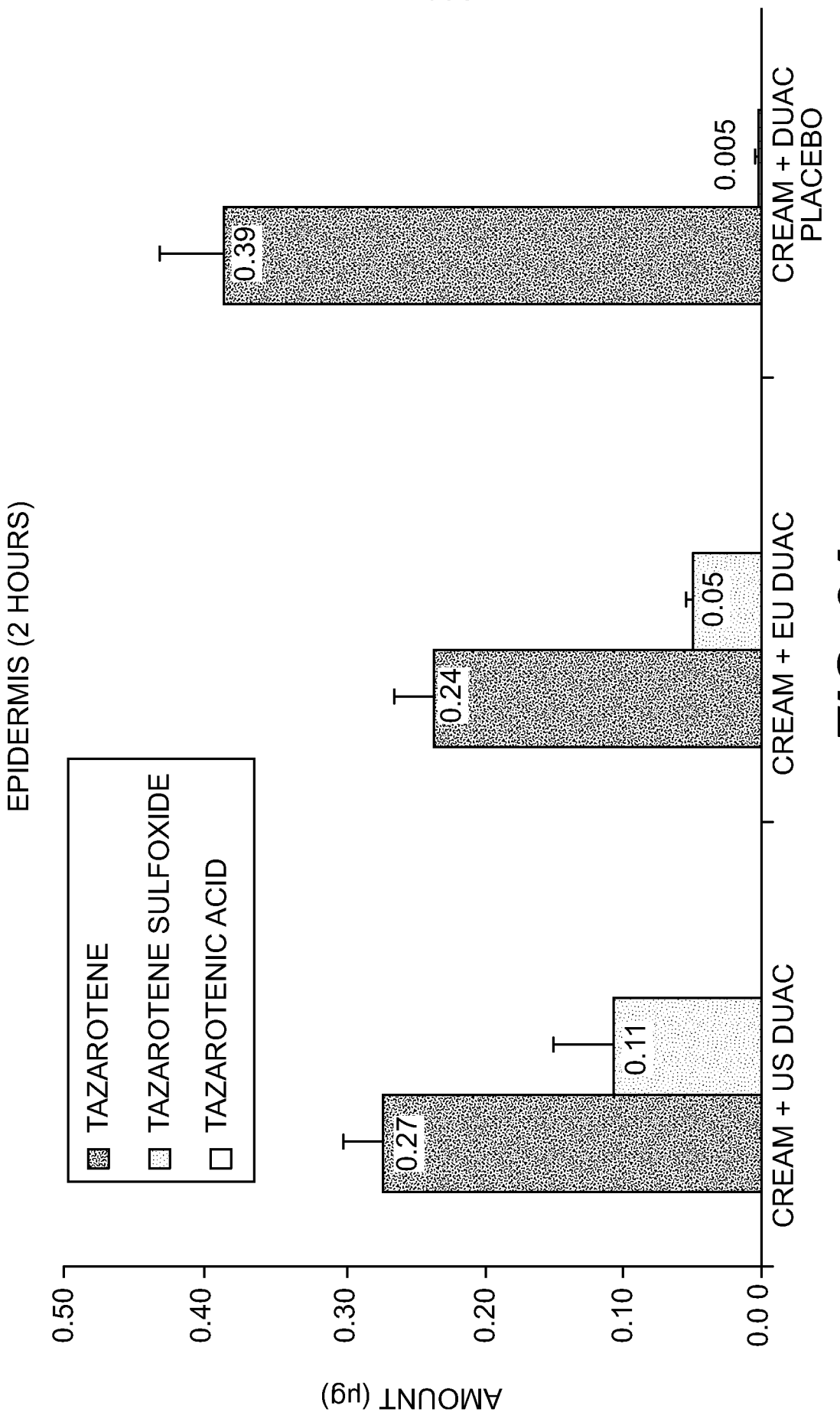

EPIDERMIS (2 HOURS)
TAZAROTENE
TAZAROTENE SULFOXIDE
TAZAROTENIC ACID
AMOUNT (µg)
0.50
0.40
0.30
0.20
0.10
0.0 0
0.27
0.11
0.24
0.05
0.39
0.005
CREAM + US DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO

FIG. 3A

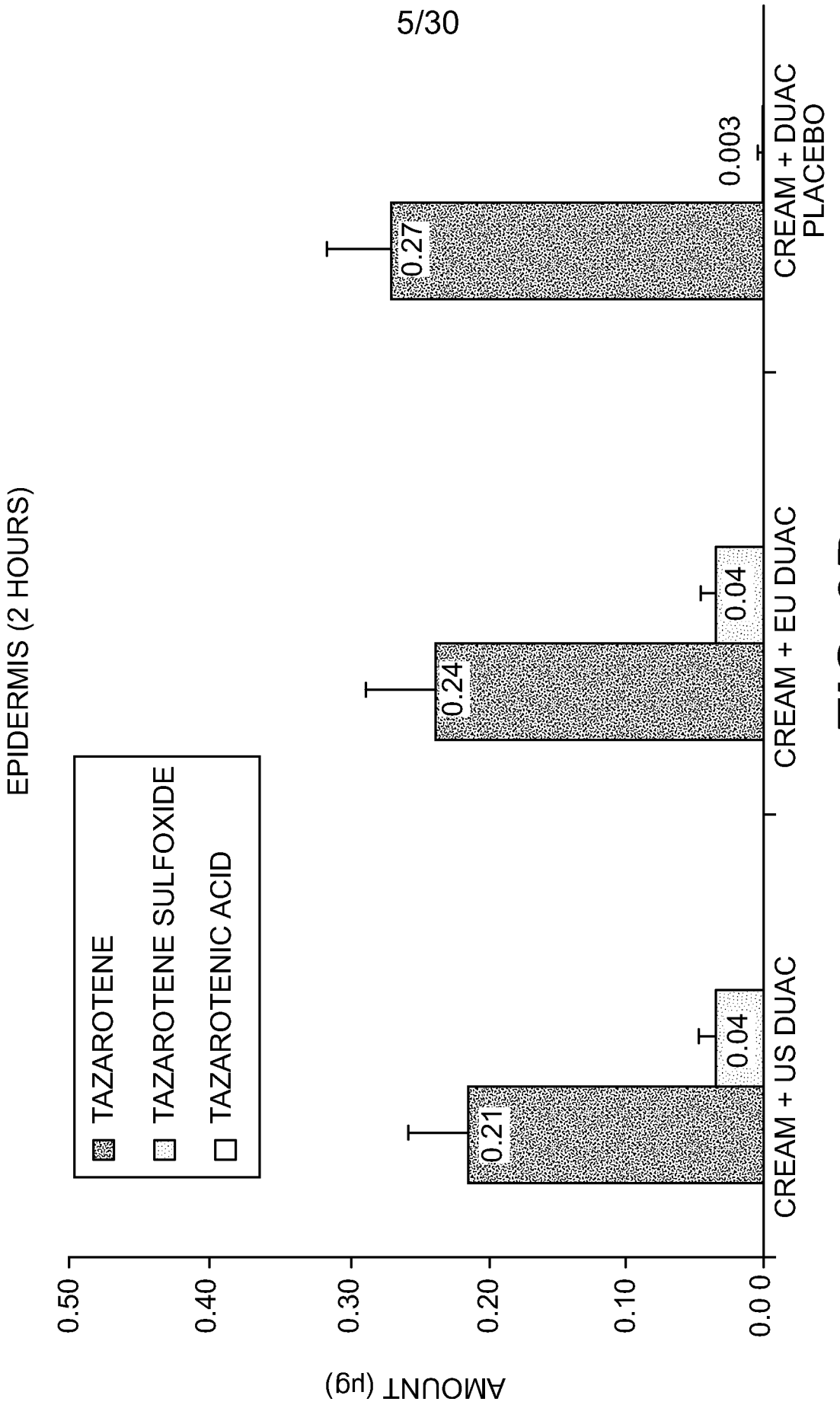

EPIDERMIS (2 HOURS)
TAZAROTENE
TAZAROTENE SULFOXIDE
TAZAROTENIC ACID
AMOUNT (µg)
0.50
0.40
0.30
0.20
0.10
0.0 0
0.21
0.04
0.24
0.04
0.27
0.003
CREAM + US DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO

FIG. 3B

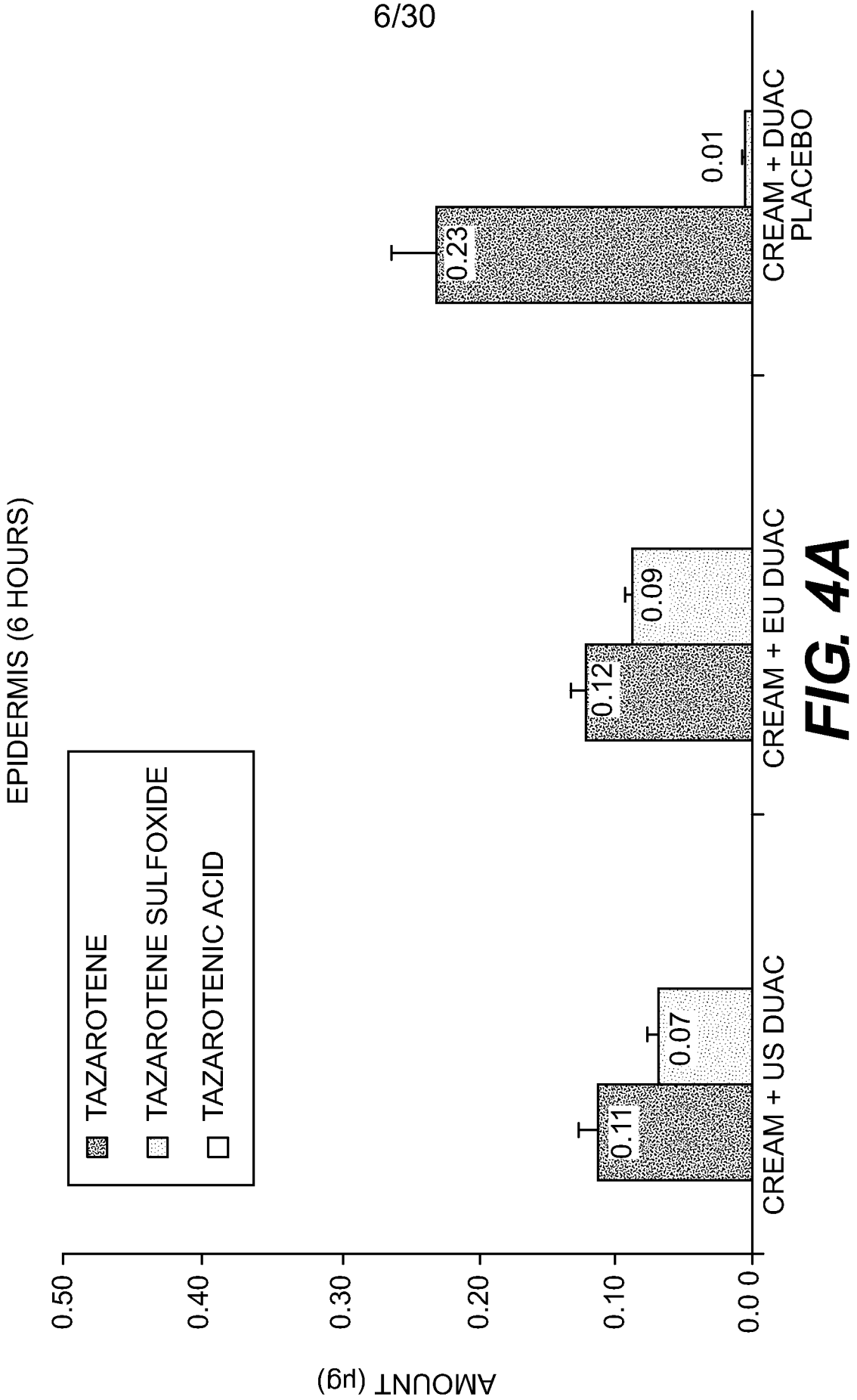

EPIDERMIS (6 HOURS)
TAZAROTENE
TAZAROTENE SULFOXIDE
TAZAROTENIC ACID
AMOUNT (µg)
0.50
0.40
0.30
0.20
0.10
0.0 0
0.11
0.07
0.12
0.09
0.23
0.01
CREAM + US DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO

FIG. 4A

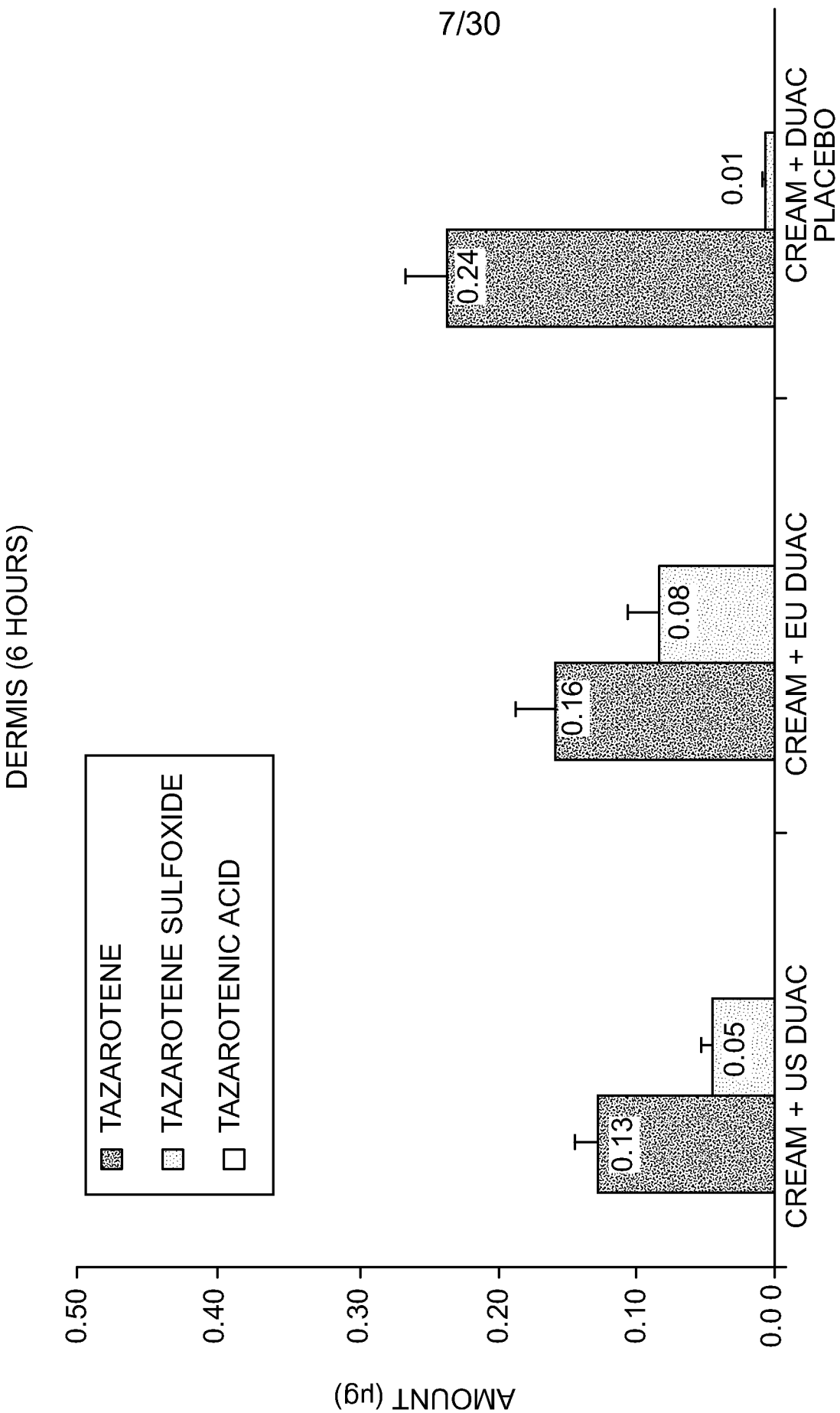

DERMIS (6 HOURS)
TAZAROTENE
TAZAROTENE SULFOXIDE
TAZAROTENIC ACID
AMOUNT (µg)
0.50
0.40
0.30
0.20
0.10
0.0 0
0.13
0.05
0.16
0.08
0.24
0.01
CREAM + US DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO

FIG. 4B

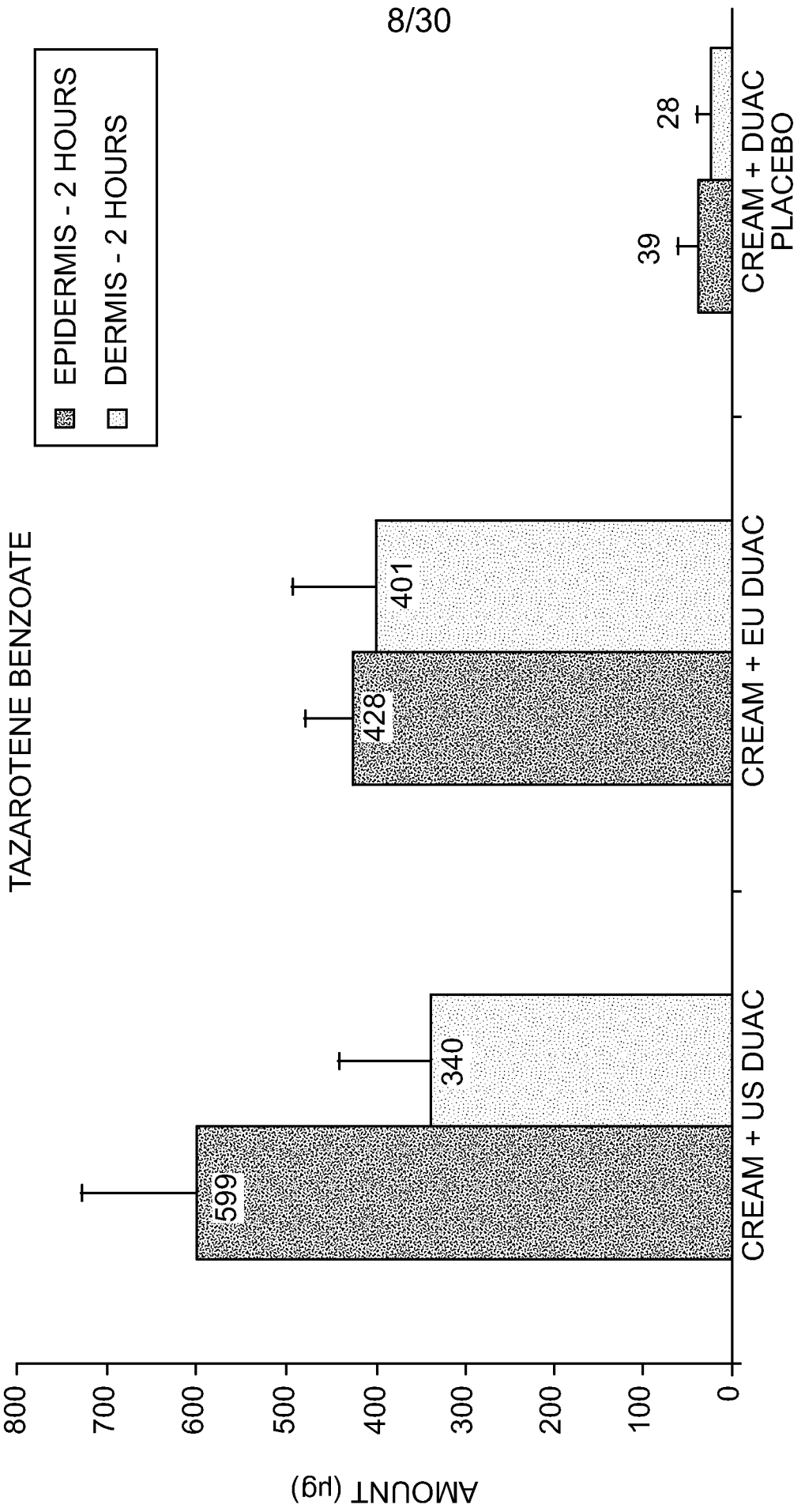

TAZAROTENE BENZOATE
EPIDERMIS - 2 HOURS
DERMIS - 2 HOURS
AMOUNT (µg)
800
700
600
500
400
300
200
100
0
599
340
428
401
39
28
CREAM + US DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO

FIG. 5A

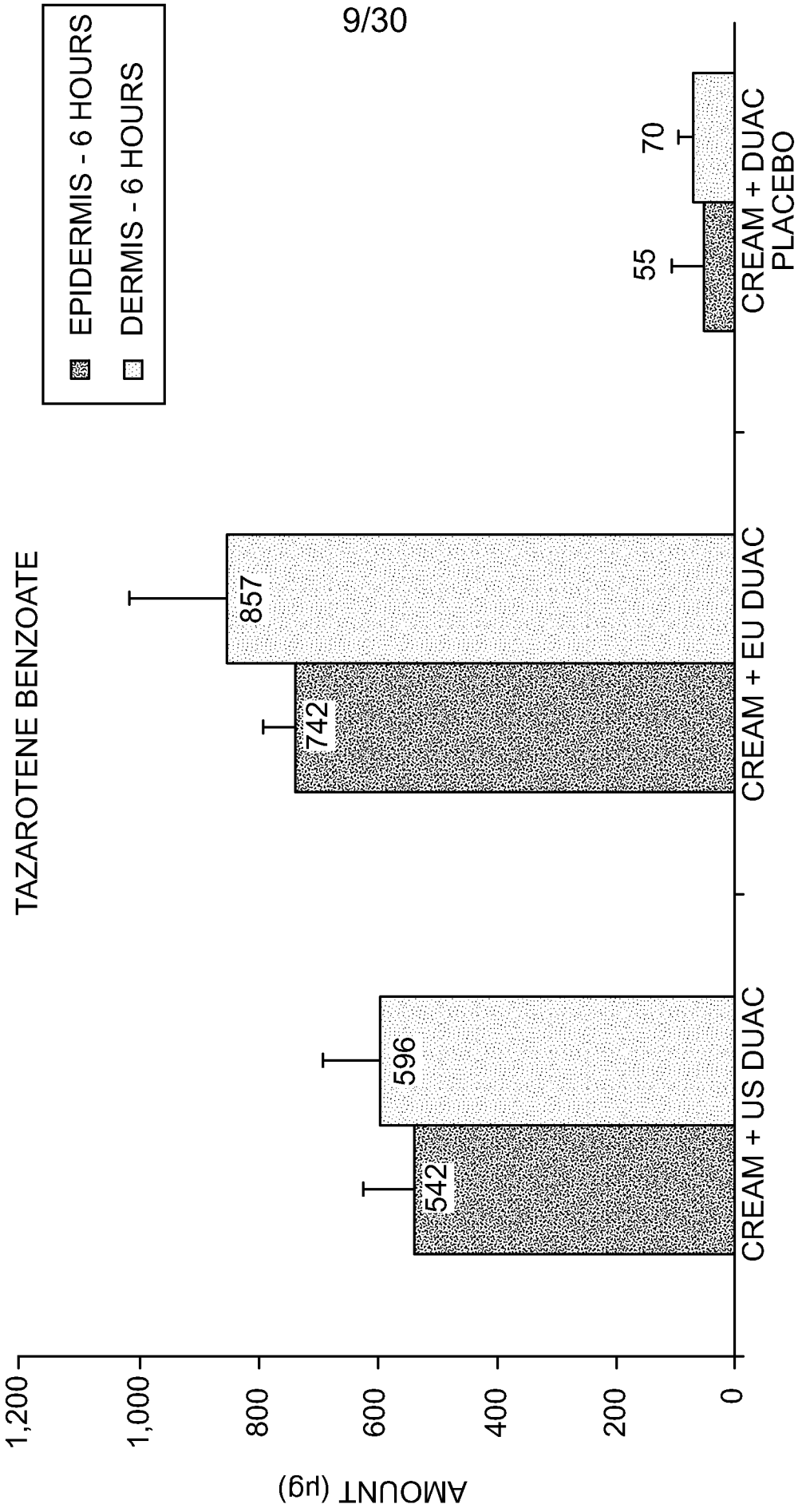

EPIDERMIS - 6 HOURS
DERMIS - 6 HOURS
TAZAROTENE BENZOATE
AMOUNT (pg)
1,200
1,000
800
600
400
200
0
542
596
742
857
55
70
CREAM + US DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO

FIG. 5B

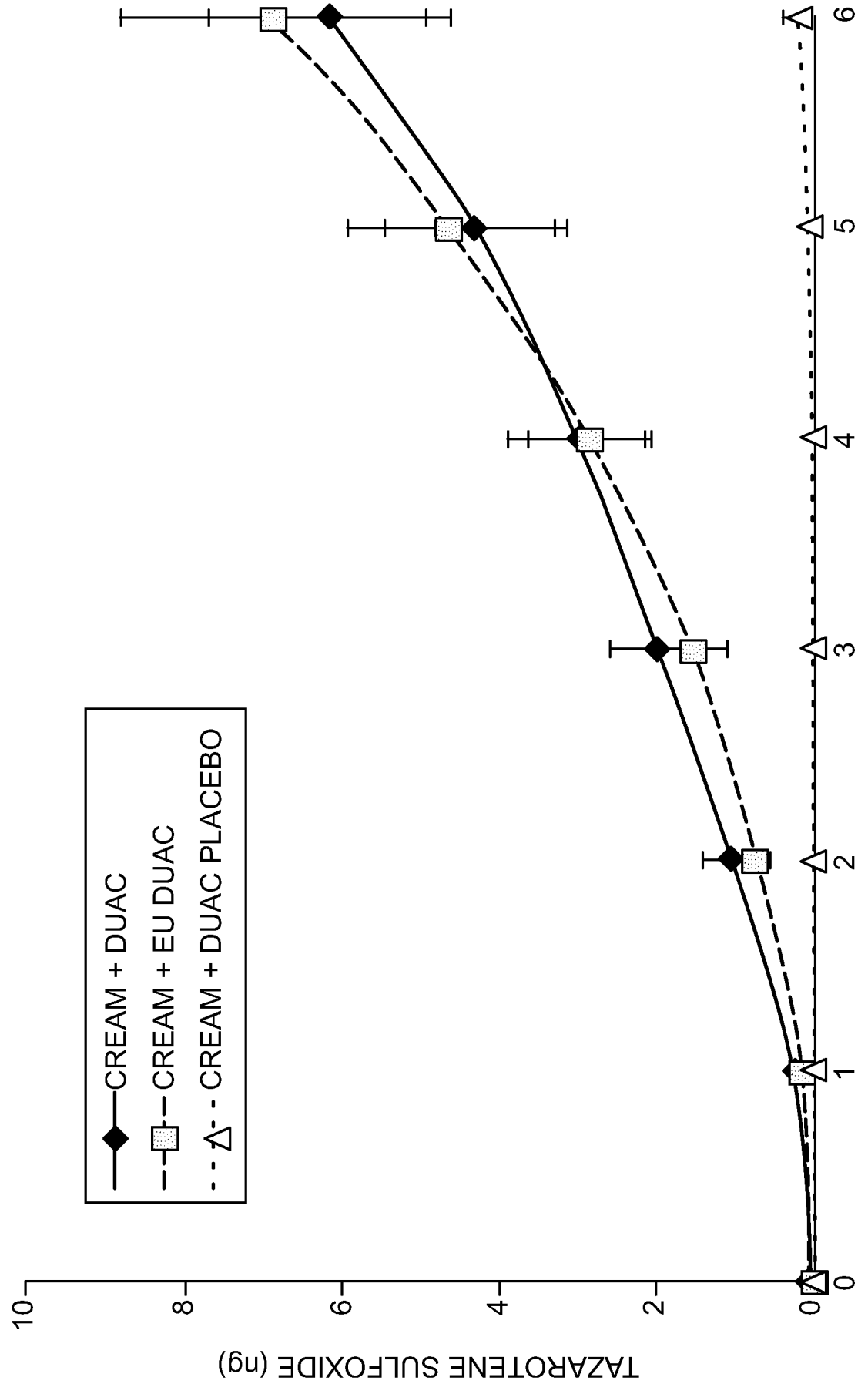

CREAM + DUAC
CREAM + EU DUAC
CREAM + DUAC PLACEBO
TAZAROTENE SULFOXIDE (ng)
TIME (HR)
0
2
4
6
8
10
0
1
2
3
4
5
6

FIG. 6

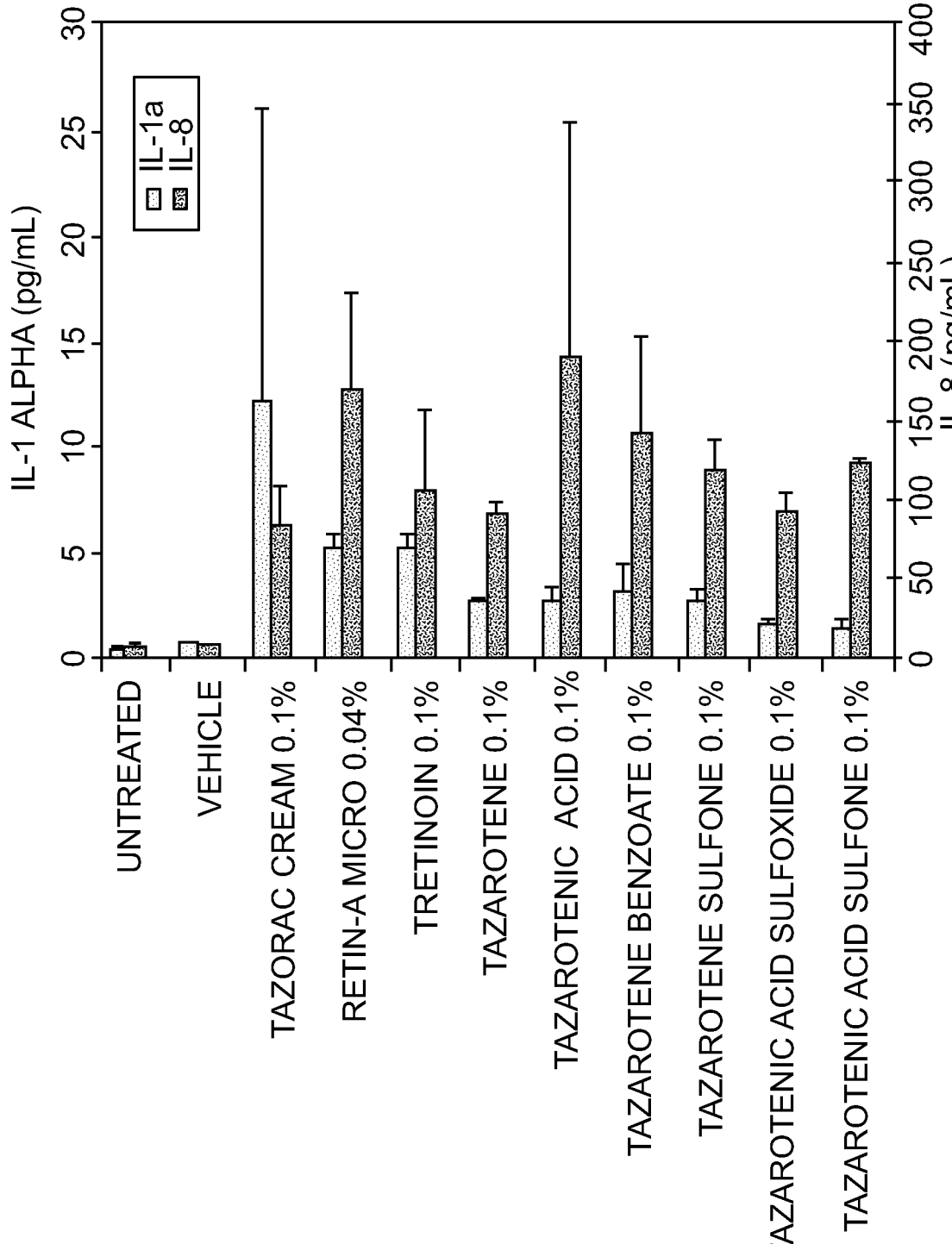

IL-1 ALPHA (pg/mL)
IL-8 (pg/mL)
IL-1a
IL-8
0
5
10
15
20
25
30
0
50
100
150
200
250
300
350
400
UNTREATED
VEHICLE
TAZORAC CREAM 0.1%
RETIN-A MICRO 0.04%
TRETINOIN 0.1%
TAZAROTENE 0.1%
TAZAROTENIC ACID 0.1%
TAZAROTENE BENZOATE 0.1%
TAZAROTENE SULFONE 0.1%
TAZAROTENIC ACID SULFOXIDE 0.1%
TAZAROTENIC ACID SULFONE 0.1%

FIG. 7

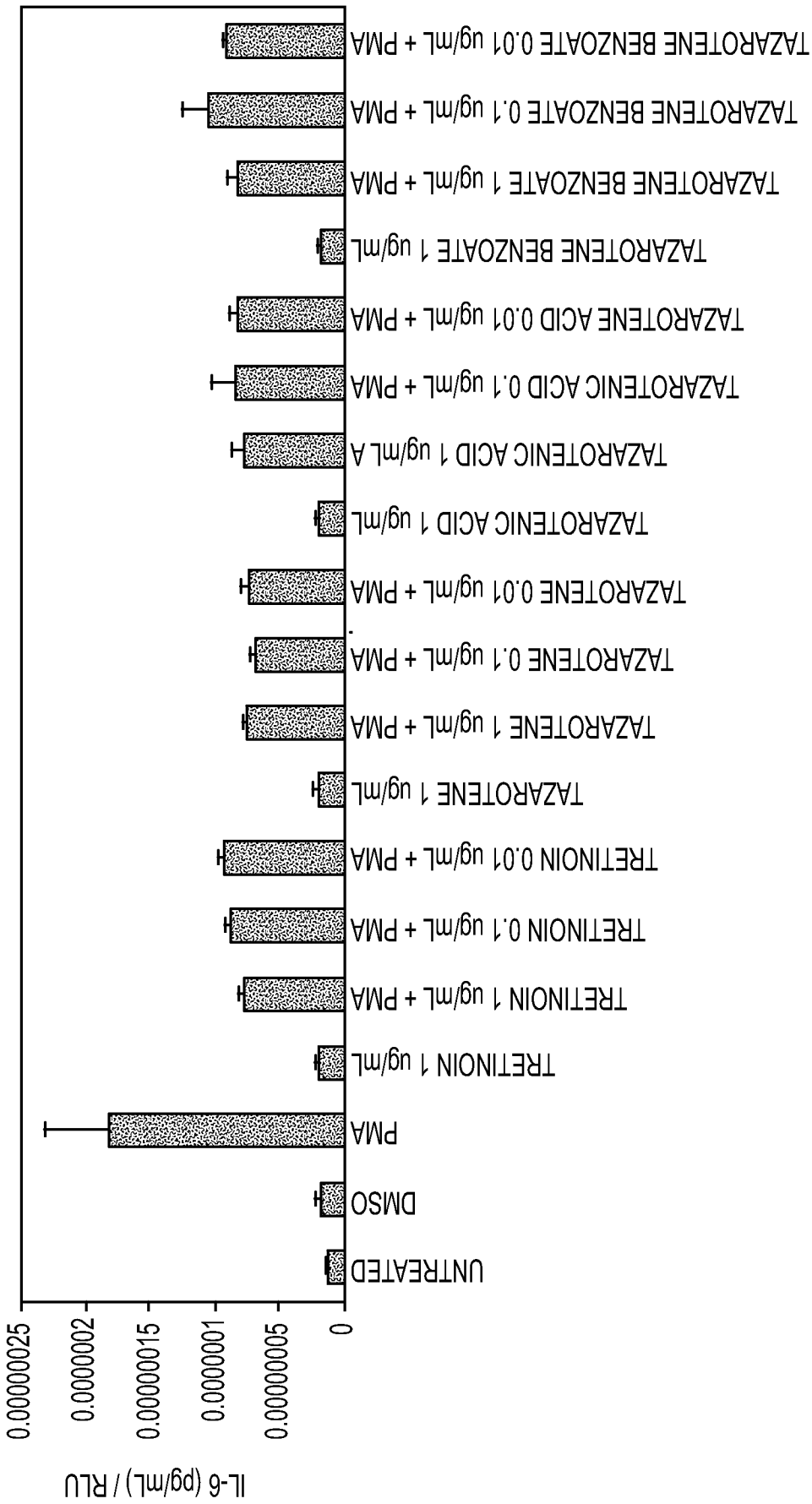

IL-6 (pg/mL) / RLU
0.00000025
0.0000002
0.00000015
0.0000001
0.00000005
0
UNTREATED
DMSO
PMA
TRETINOIN 1 ug/mL
TRETINOIN 1 ug/mL + PMA
TRETINOIN 0.1 ug/mL + PMA
TRETINOIN 0.01 ug/mL + PMA
TAZAROTENE 1 ug/mL
TAZAROTENE 1 ug/mL + PMA
TAZAROTENE 0.1 ug/mL + PMA
TAZAROTENE 0.01 ug/mL + PMA
TAZAROTENIC ACID 1 ug/mL
TAZAROTENIC ACID 1 ug/mL A
TAZAROTENIC ACID 0.1 ug/mL + PMA
TAZAROTENE ACID 0.01 ug/mL + PMA
TAZAROTENE BENZOATE 1 ug/mL
TAZAROTENE BENZOATE 1 ug/mL + PMA
TAZAROTENE BENZOATE 0.1 ug/mL + PMA
TAZAROTENE BENZOATE 0.01 ug/mL + PMA

FIG. 8

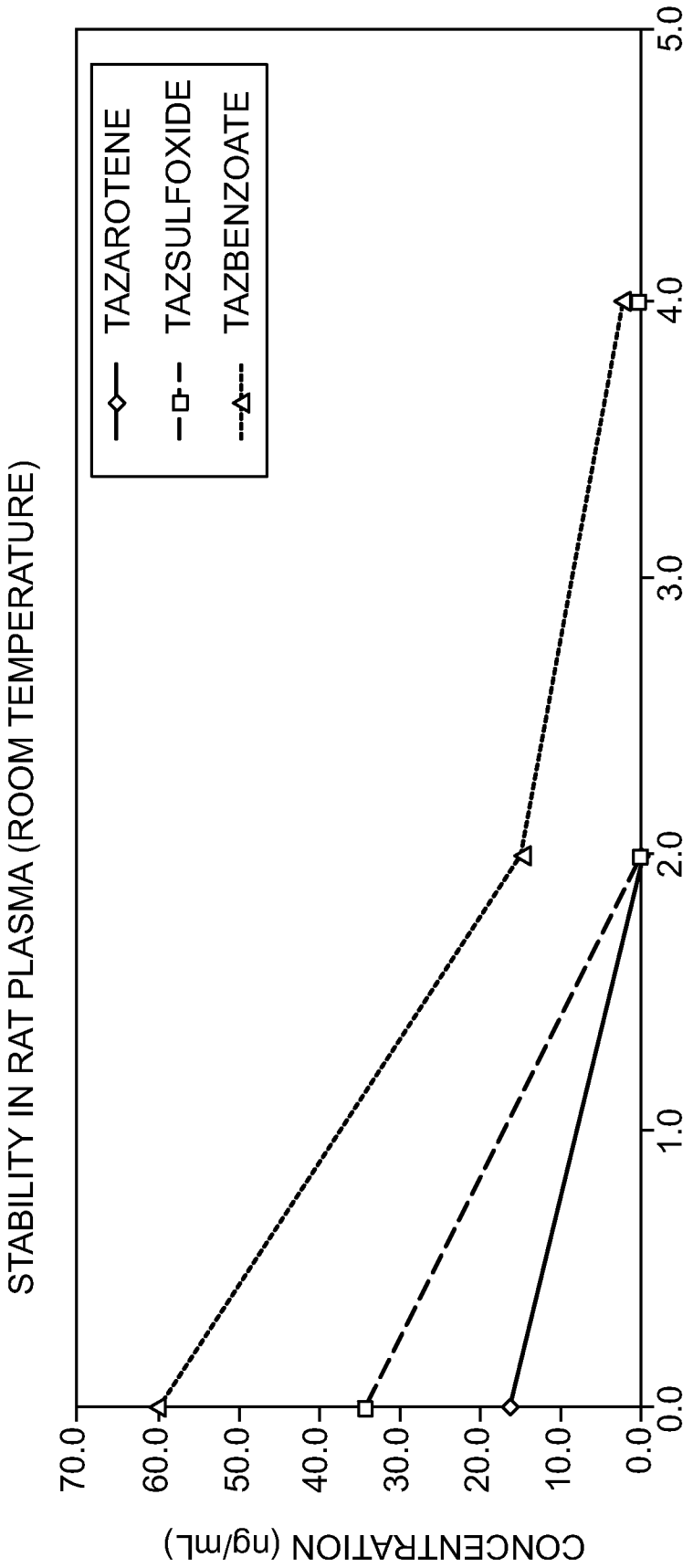

STABILITY IN RAT PLASMA (ROOM TEMPERATURE)
TAZAROTENE
TAZSULFOXIDE
TAZBENZOATE
CONCENTRATION (ng/mL)
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0.0
1.0
2.0
3.0
4.0
5.0
TIME (hs)

FIG. 9

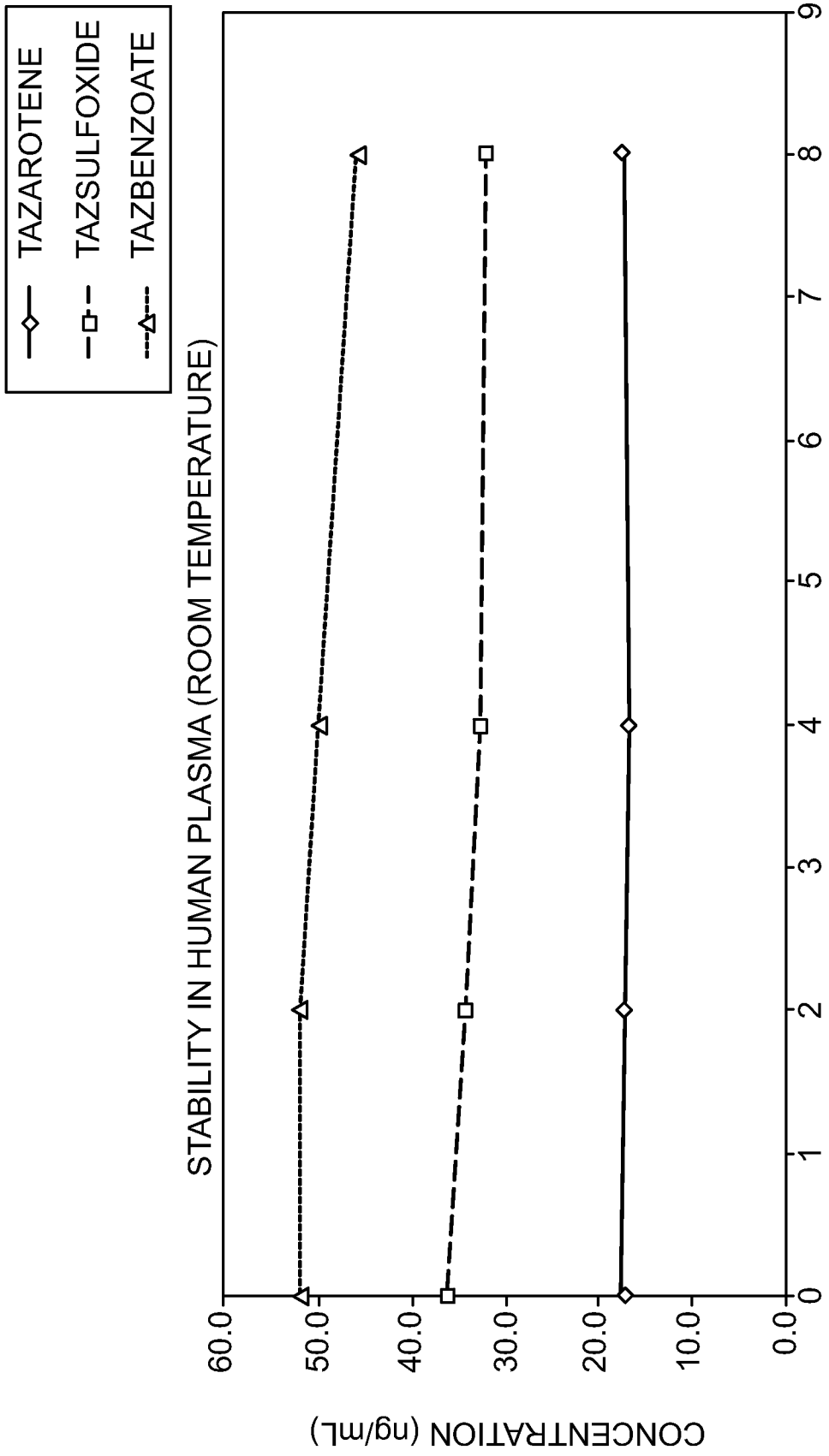

TAZAROTENE
TAZSULFOXIDE
TAZBENZOATE
STABILITY IN HUMAN PLASMA (ROOM TEMPERATURE)
CONCENTRATION (ng/mL)
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
1
2
3
4
5
6
7
8
9
TIME (hs)

FIG. 10

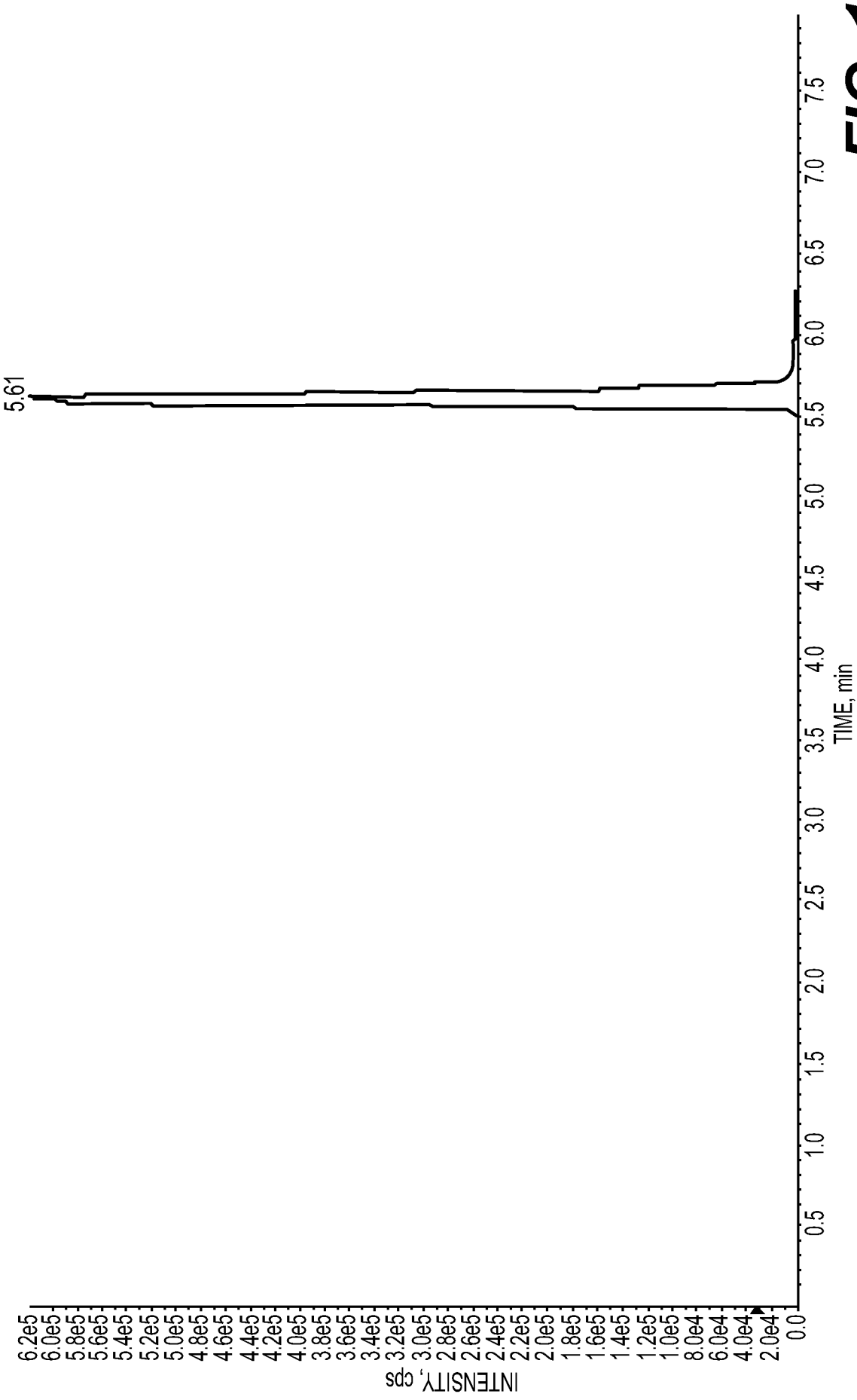
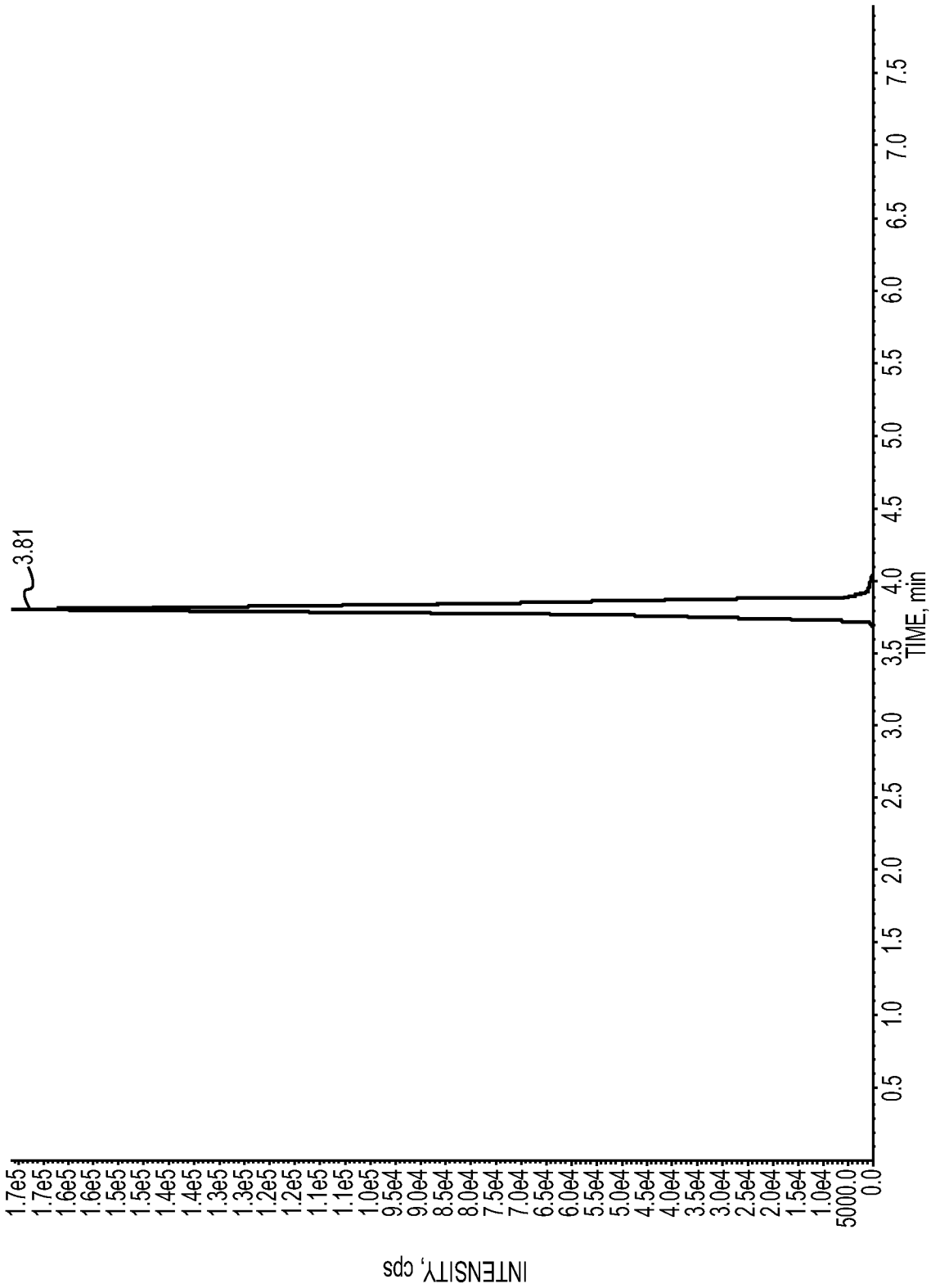

5.61
INTENSITY, cps
TIME, min
6.2e5
6.0e5
5.8e5
5.6e5
5.4e5
5.2e5
5.0e5
4.8e5
4.6e5
4.4e5
4.2e5
4.0e5
3.8e5
3.6e5
3.4e5
3.2e5
3.0e5
2.8e5
2.6e5
2.4e5
2.2e5
2.0e5
1.8e5
1.6e5
1.4e5
1.2e5
1.0e5
8.0e4
6.0e4
4.0e4
2.0e4
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

FIG. 11

FIG. 12



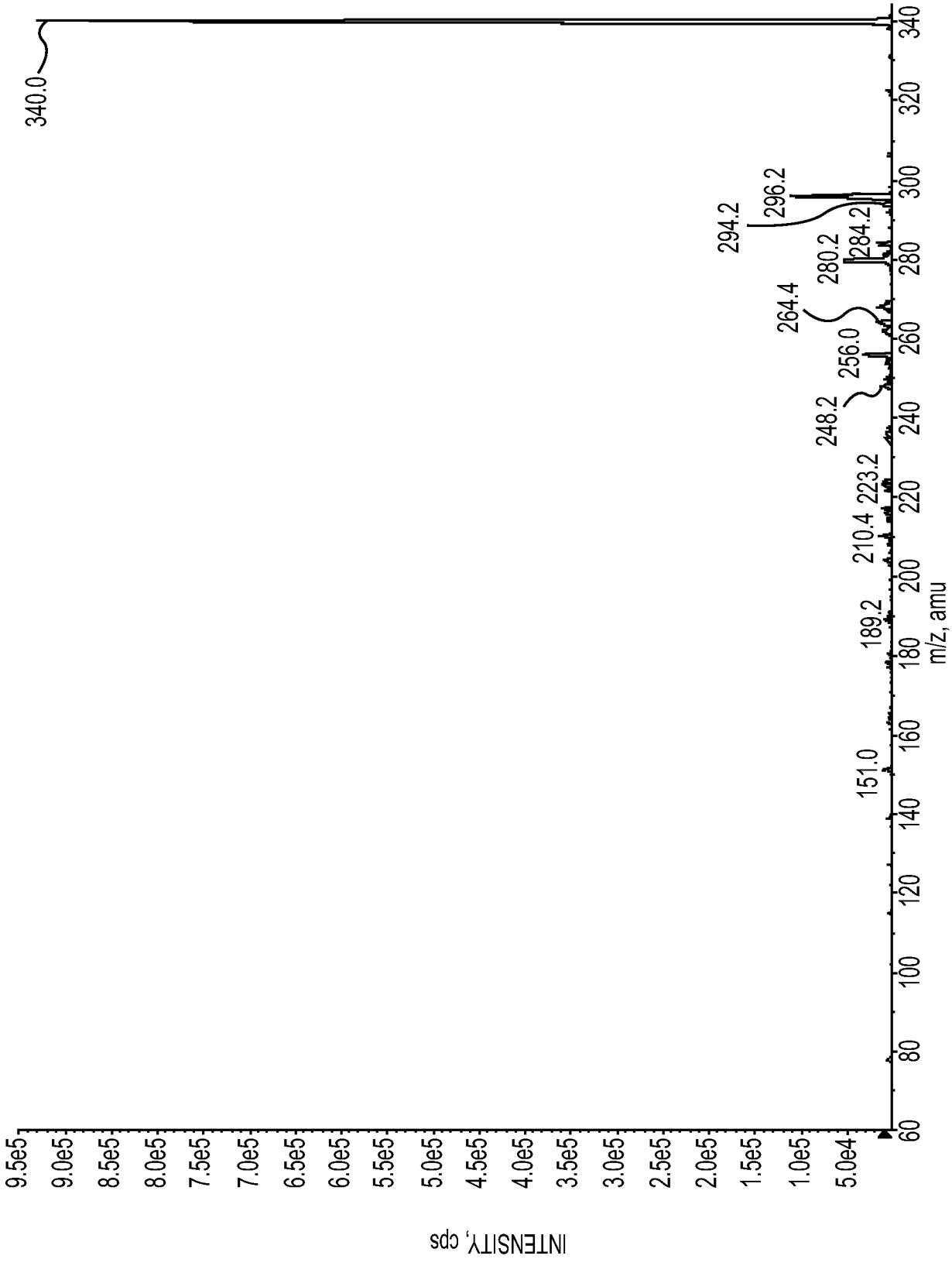

INTENSITY, cps
9.5e5
9.0e5
8.5e5
8.0e5
7.5e5
7.0e5
6.5e5
6.0e5
5.5e5
5.0e5
4.5e5
4.0e5
3.5e5
3.0e5
2.5e5
2.0e5
1.5e5
1.0e5
5.0e4
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
m/z, amu
340.0
296.2
294.2
284.2
280.2
264.4
256.0
248.2
223.2
210.4
189.2
151.0

FIG. 13

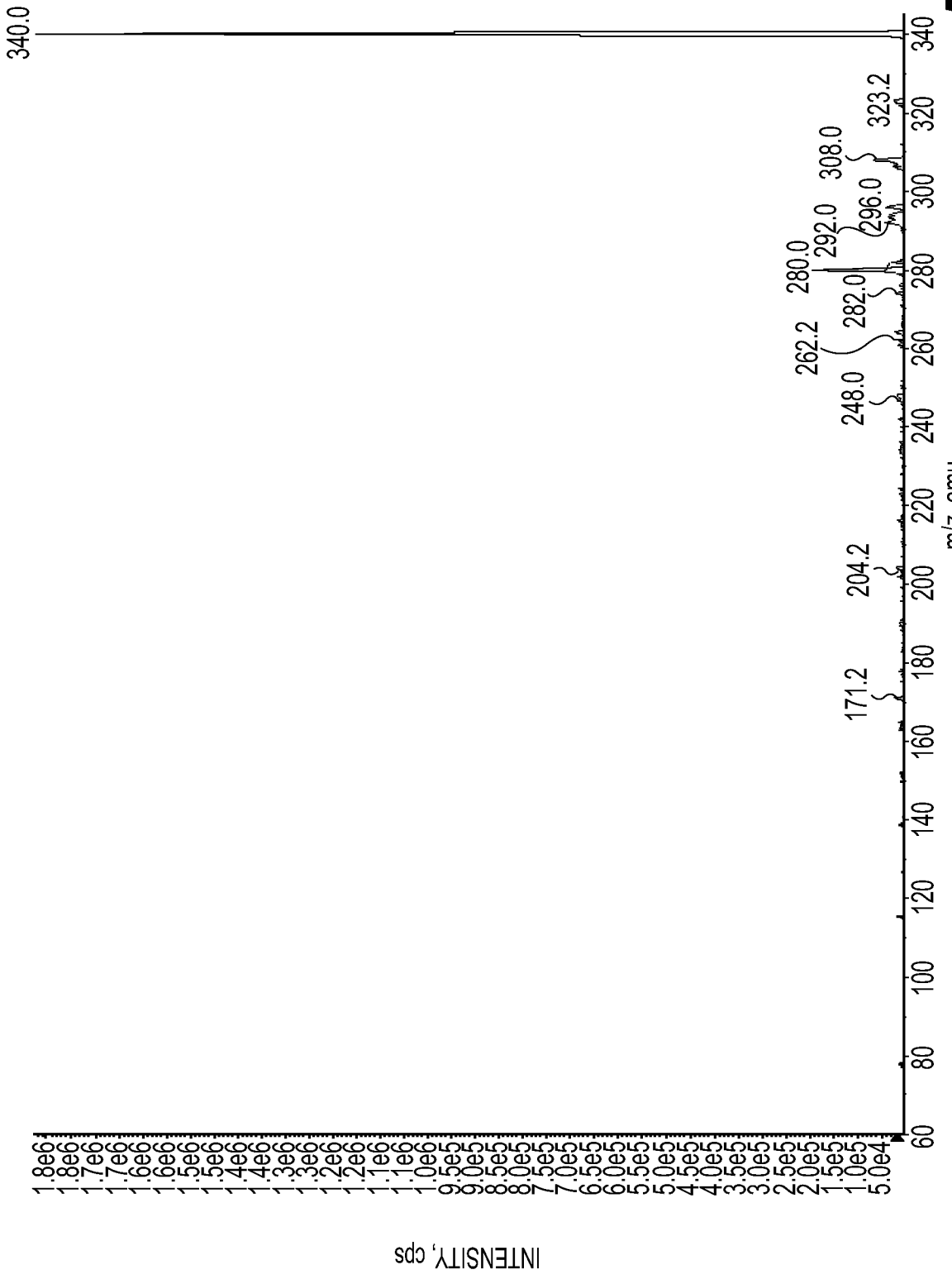

340.0
323.2
308.0
296.0
292.0
280.0
282.0
262.2
248.0
204.2
171.2
m/z, amu
INTENSITY, cps

FIG. 14

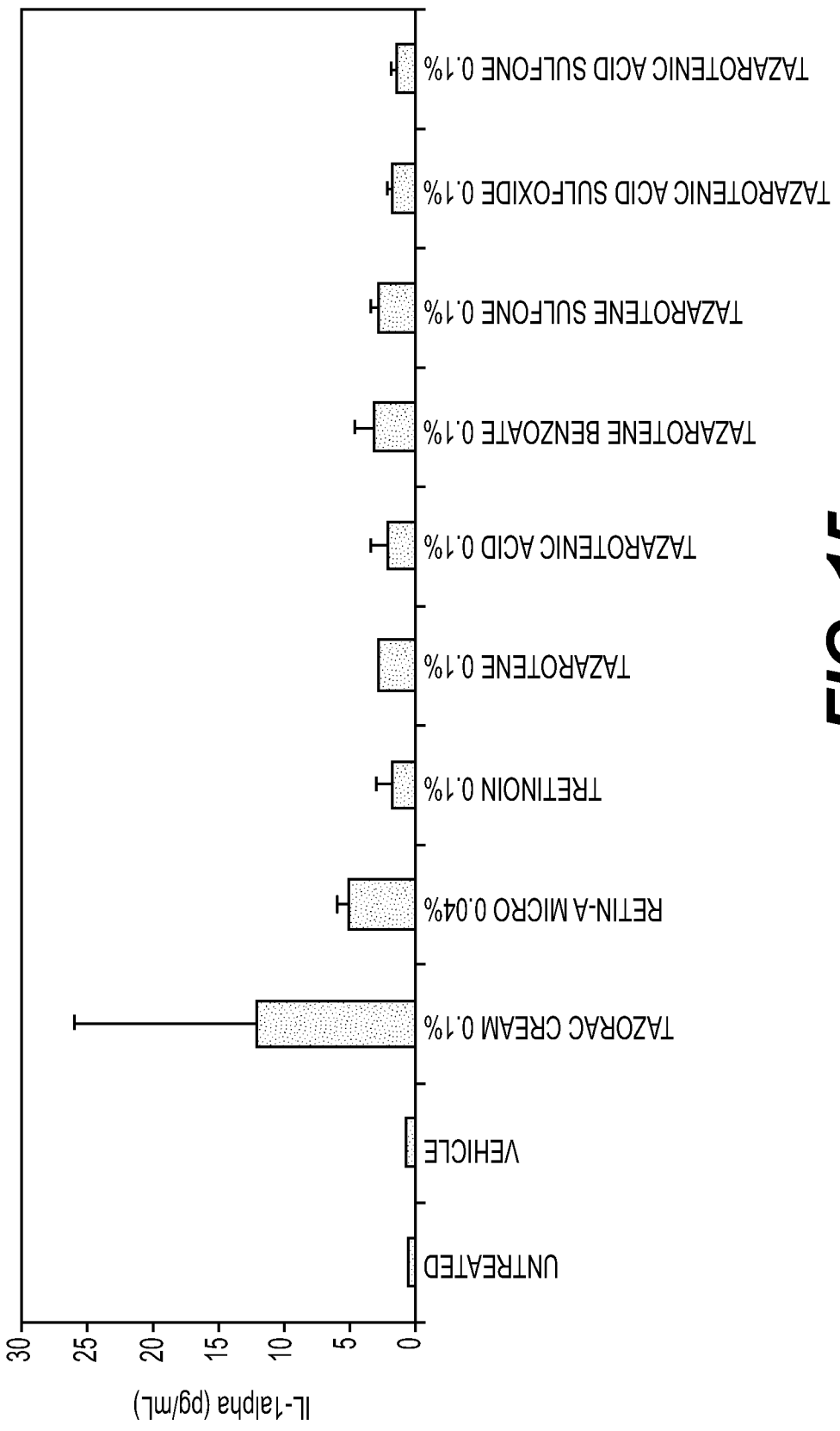

IL-1alpha (pg/mL)
0
5
10
15
20
25
30
UNTREATED
VEHICLE
TAZORAC CREAM 0.1%
RETIN-A MICRO 0.04%
TRETINOIN 0.1%
TAZAROTENE 0.1%
TAZAROTENIC ACID 0.1%
TAZAROTENE BENZOATE 0.1%
TAZAROTENE SULFONE 0.1%
TAZAROTENIC ACID SULFOXIDE 0.1%
TAZAROTENIC ACID SULFONE 0.1%

FIG. 15

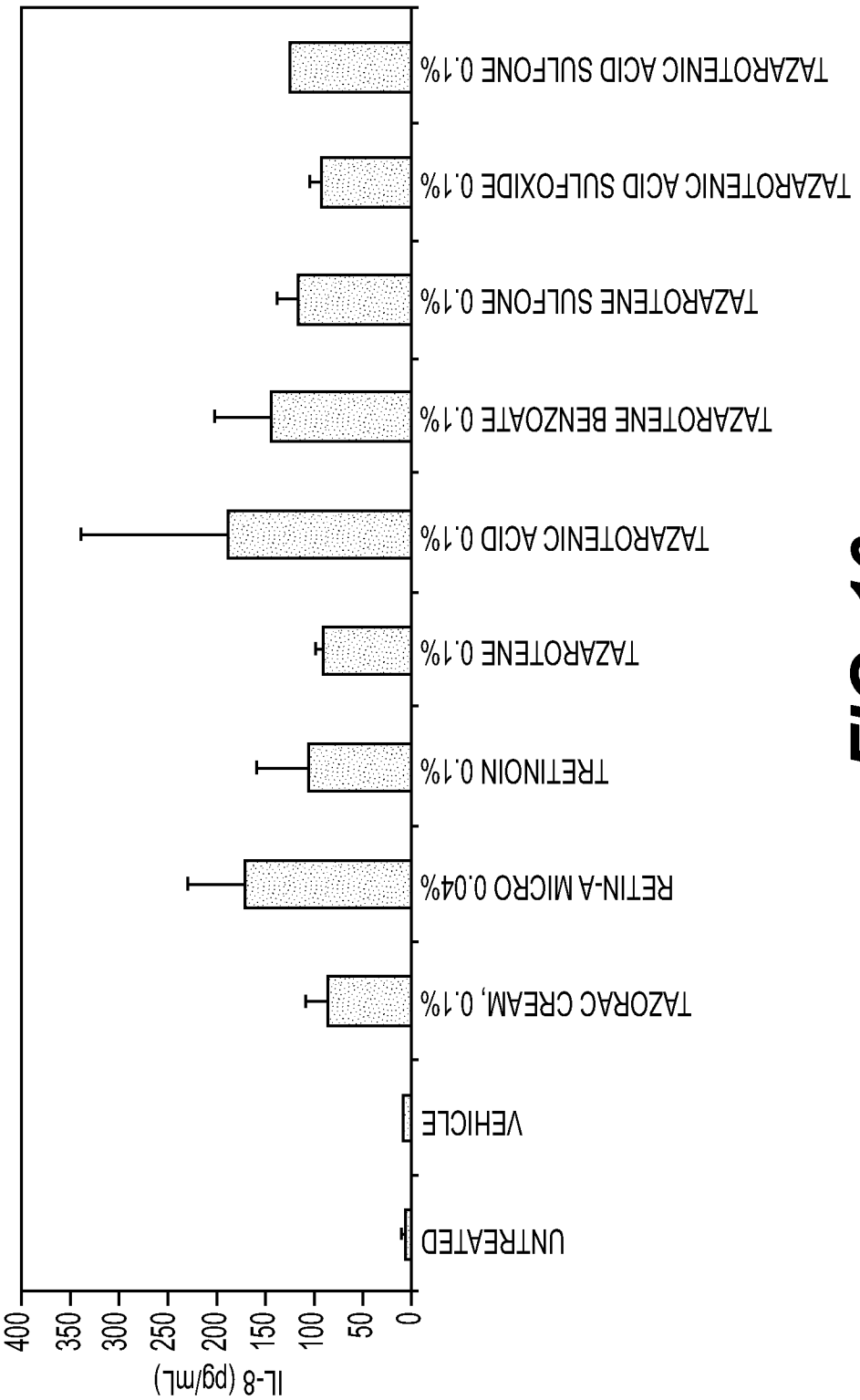

IL-8 (pg/mL)
0
50
100
150
200
250
300
350
400
UNTREATED
VEHICLE
TAZORAC CREAM, 0.1%
RETIN-A MICRO 0.04%
TRETINOIN 0.1%
TAZAROTENE 0.1%
TAZAROTENIC ACID 0.1%
TAZAROTENE BENZOATE 0.1%
TAZAROTENE SULFONE 0.1%
TAZAROTENIC ACID SULFOXIDE 0.1%
TAZAROTENIC ACID SULFONE 0.1%

FIG. 16

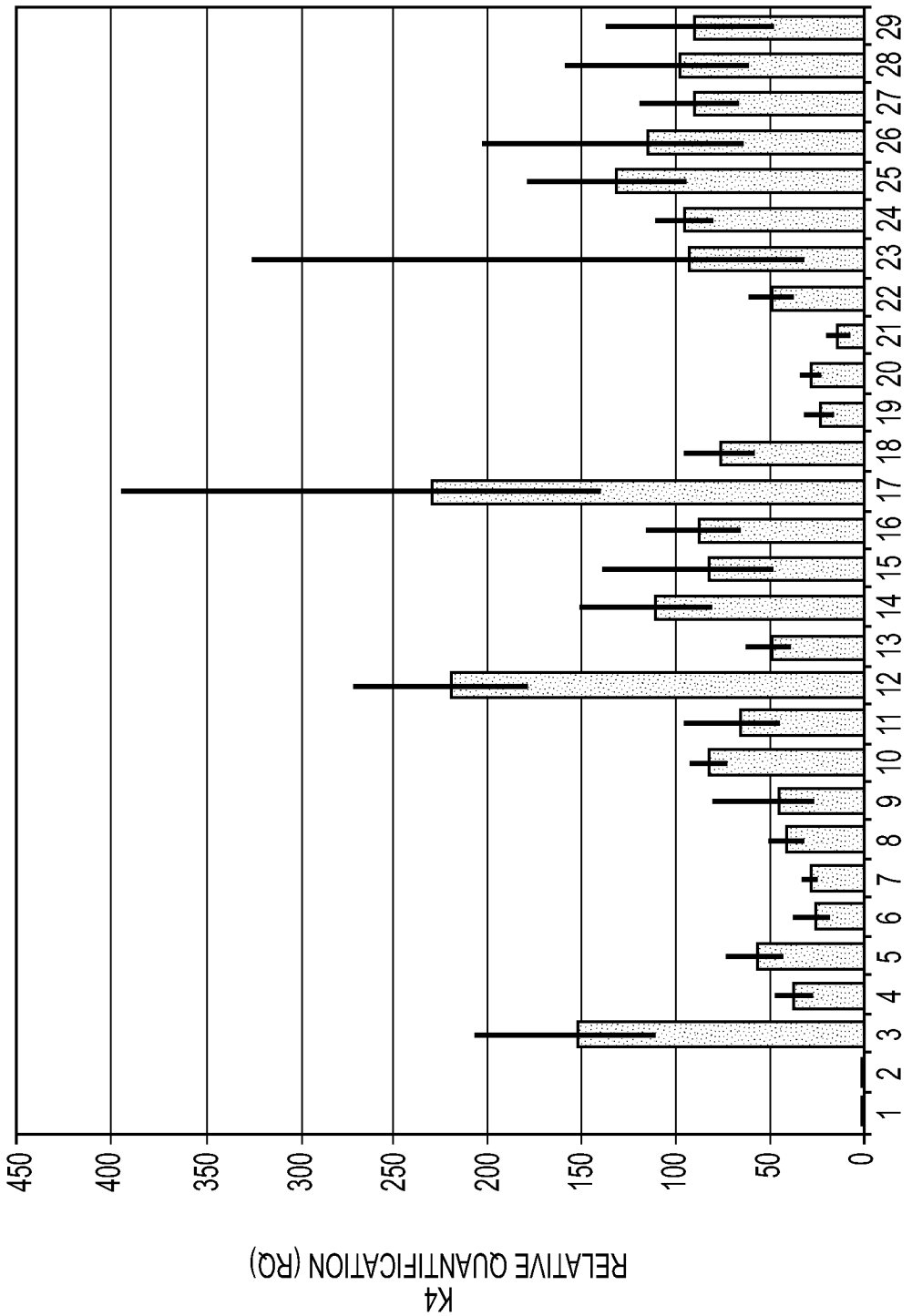

K4
RELATIVE QUANTIFICATION (RQ)
450
400
350
300
250
200
150
100
50
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

FIG. 17

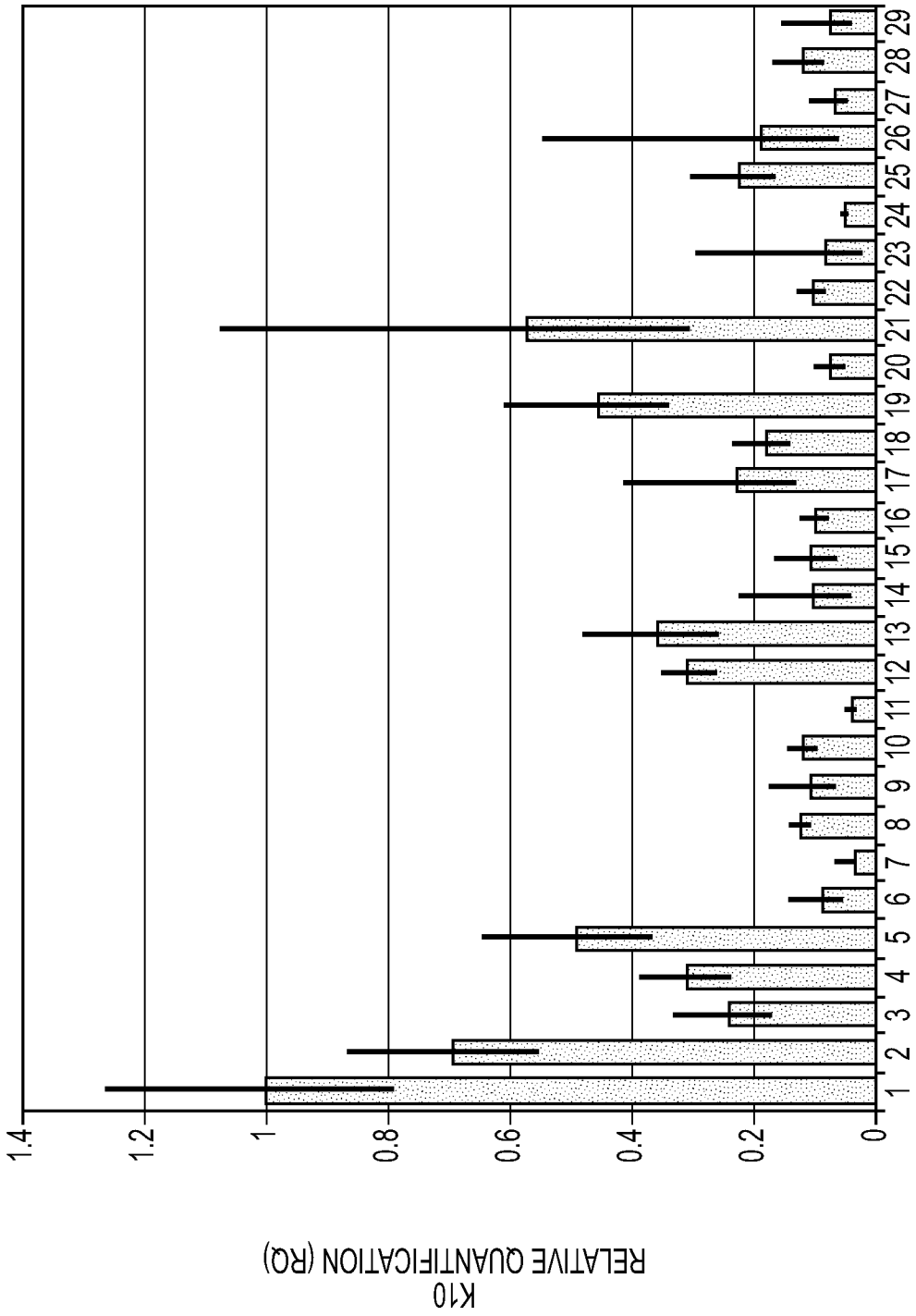

RELATIVE QUANTIFICATION (RQ)
K10
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

FIG. 18

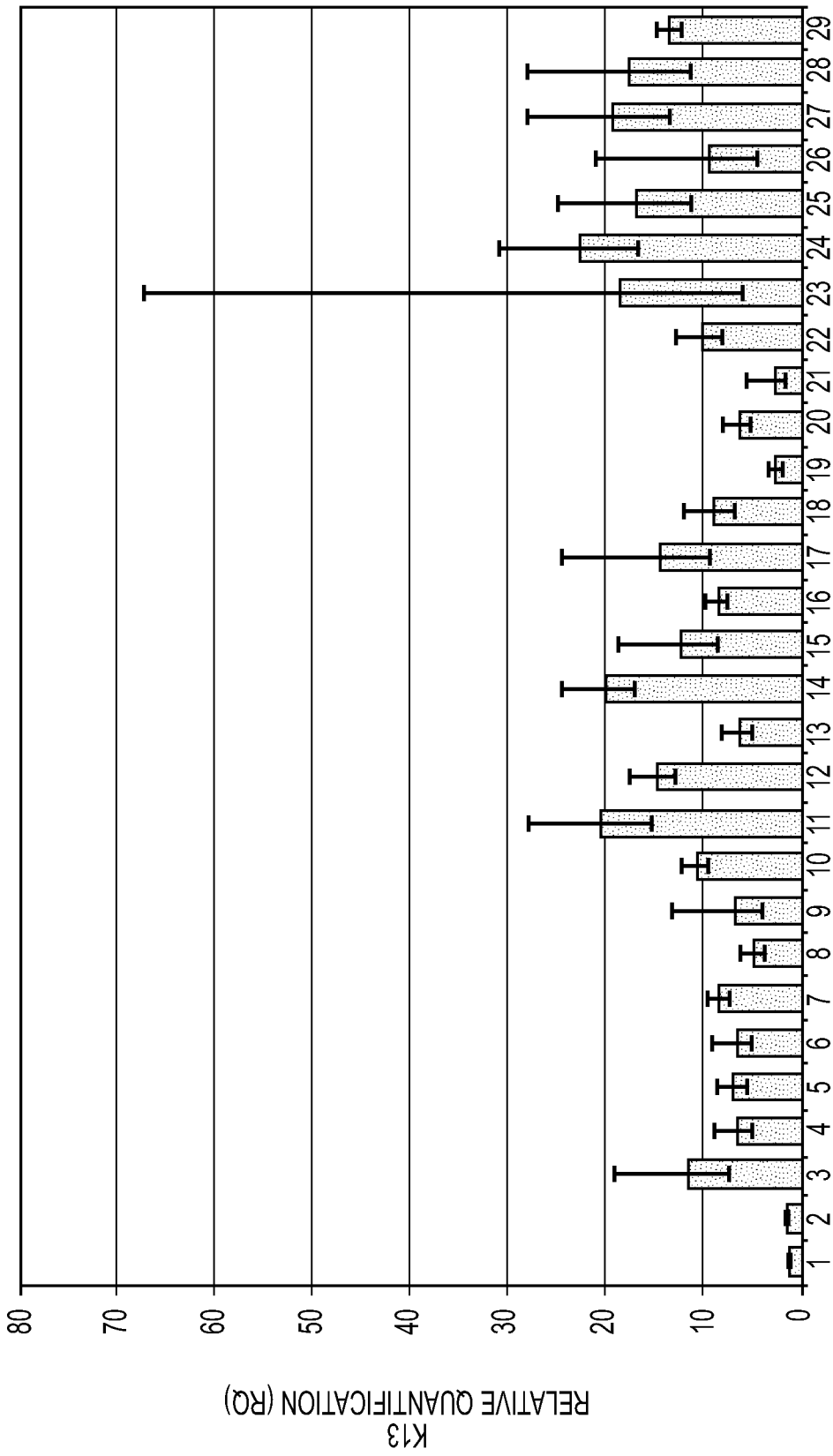
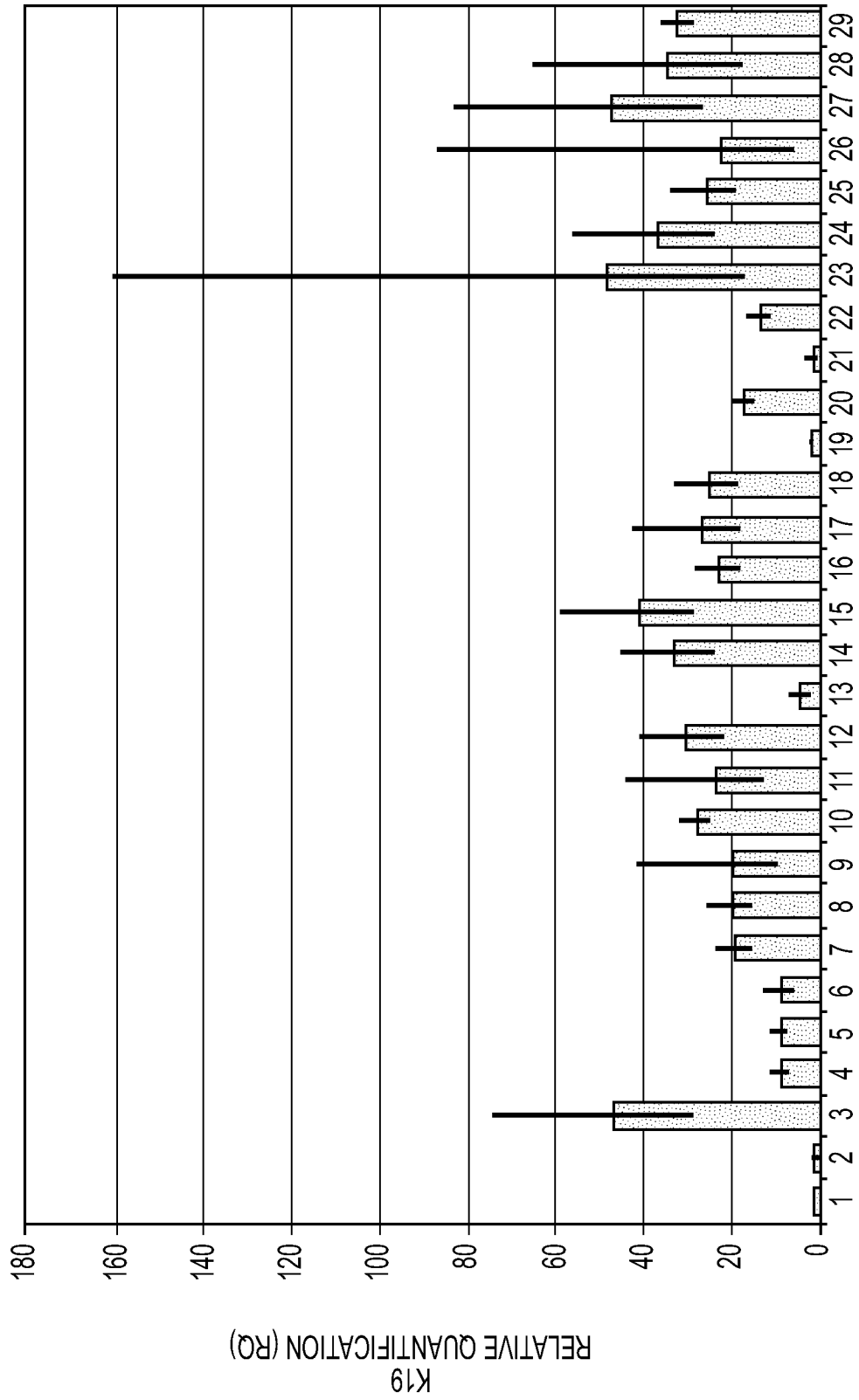

K13
RELATIVE QUANTIFICATION (RQ)
0
10
20
30
40
50
60
70
80
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

FIG. 19


K19
RELATIVE QUANTIFICATION (RQ)
0
20
40
60
80
100
120
140
160
180
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
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19
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21
22
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28
29

FIG. 20

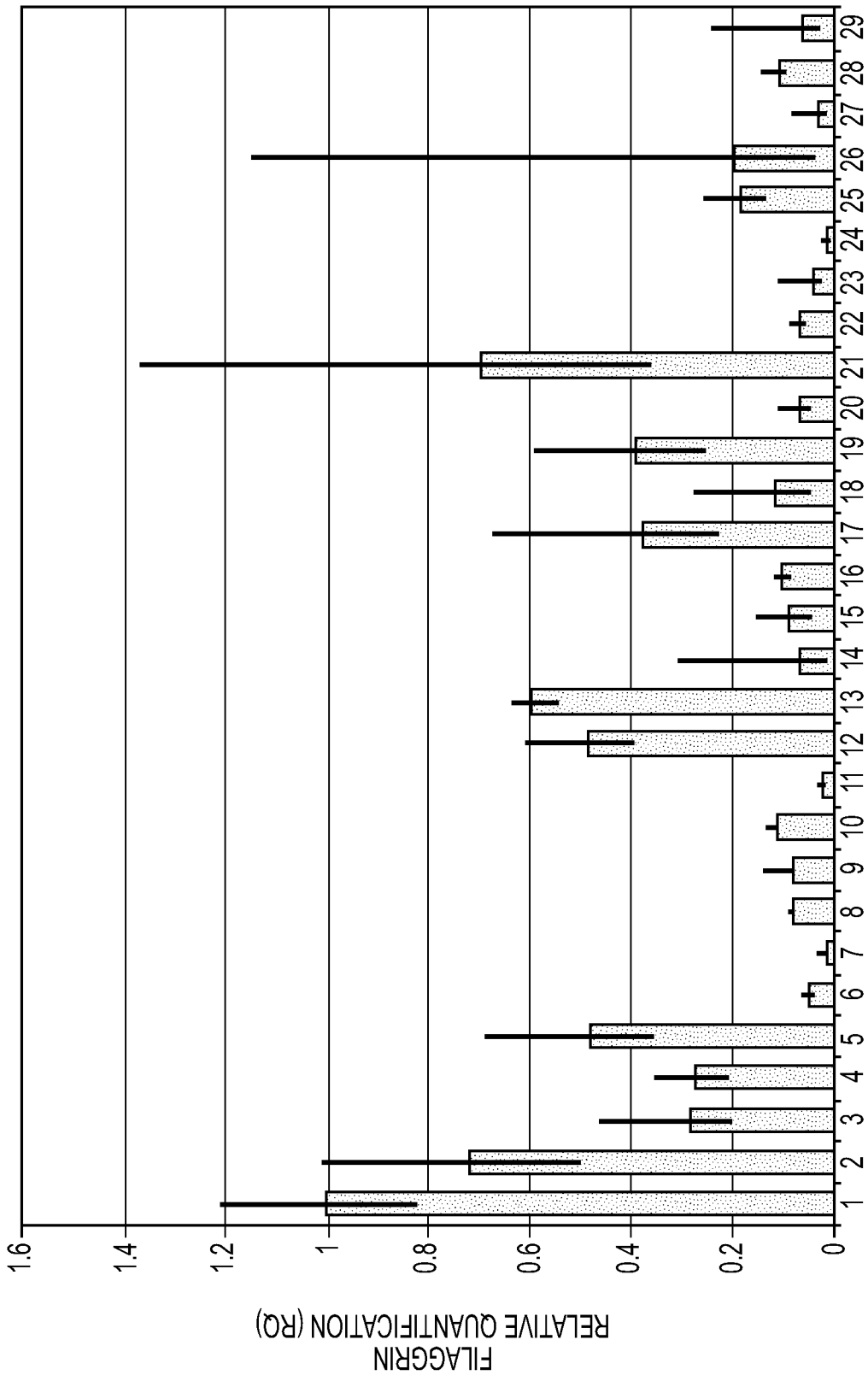
FILAGGRIN
RELATIVE QUANTIFICATION (RQ)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

FIG. 21

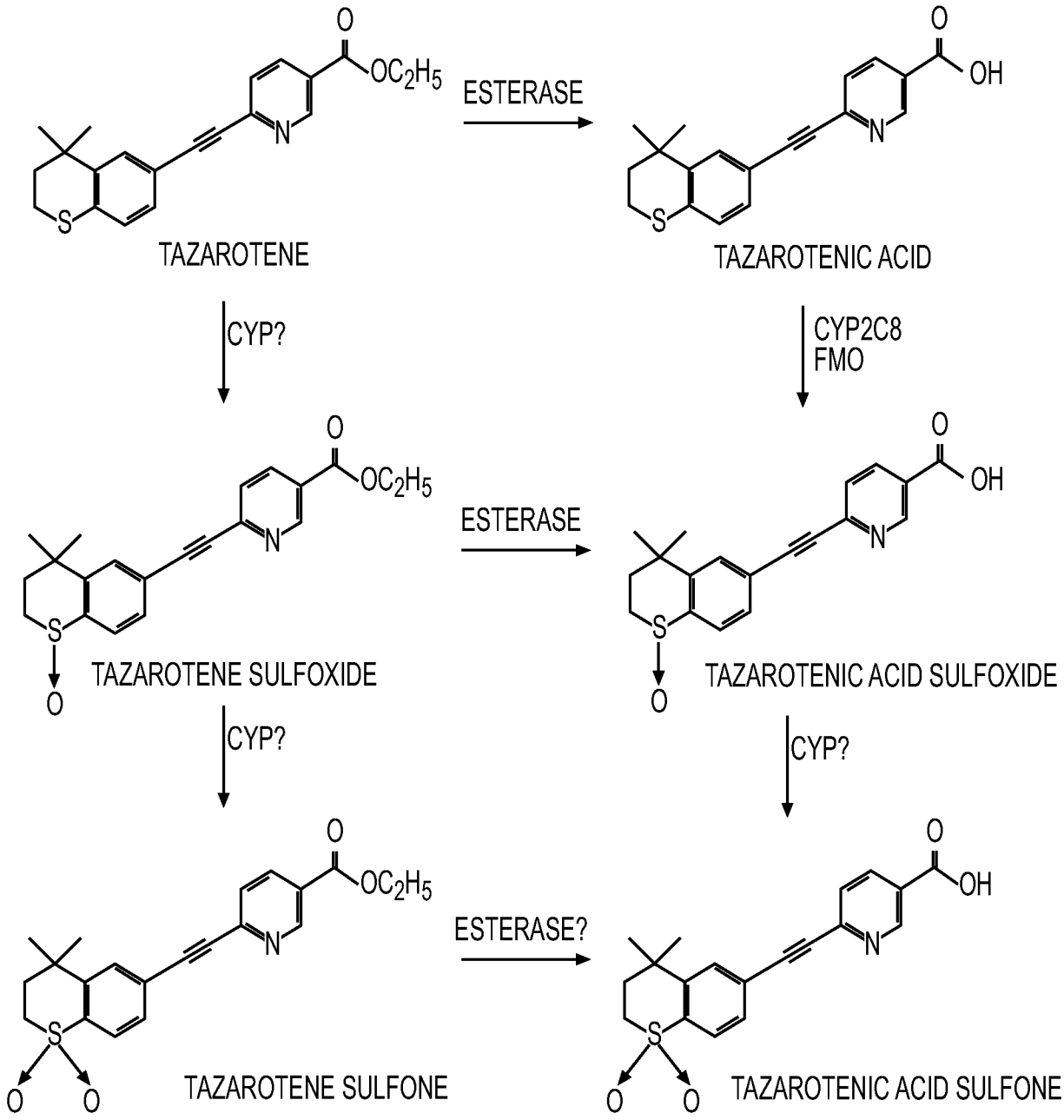
TAZAROTENE
ESTERASE
TAZAROTENIC ACID
CYP?
CYP2C8
FMO
TAZAROTENE SULFOXIDE
ESTERASE
TAZAROTENIC ACID SULFOXIDE
CYP?
CYP?
TAZAROTENE SULFONE
ESTERASE?
TAZAROTENIC ACID SULFONE

FIG. 22

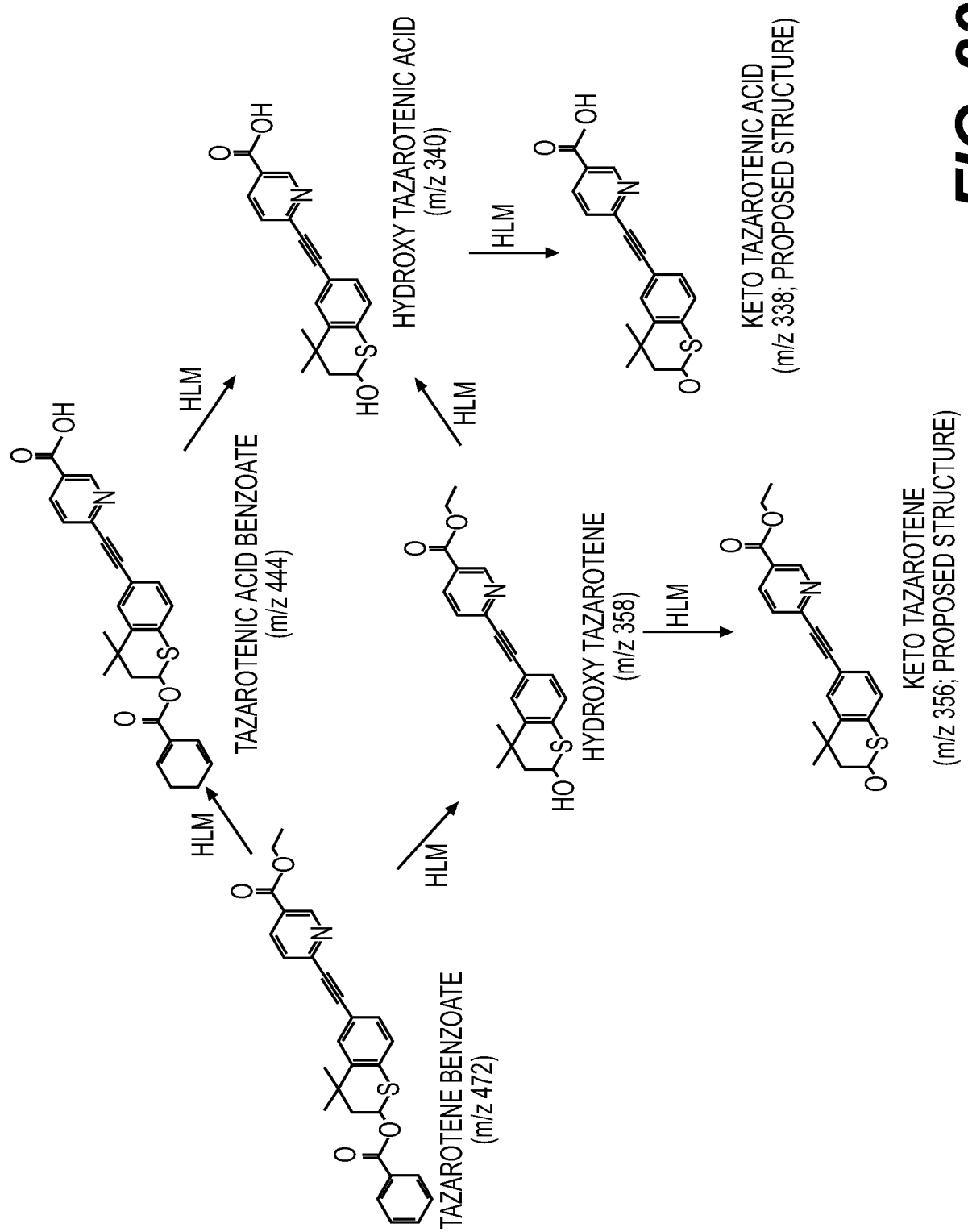
TAZAROTENE BENZOATE
(m/z 472)
HLM
TAZAROTENIC ACID BENZOATE
(m/z 444)
HLM
HYDROXY TAZAROTENIC ACID
(m/z 340)
HLM
KETO TAZAROTENIC ACID
(m/z 338; PROPOSED STRUCTURE)
HLM
HYDROXY TAZAROTENE
(m/z 358)
HLM
KETO TAZAROTENE
(m/z 356; PROPOSED STRUCTURE)

FIG. 23

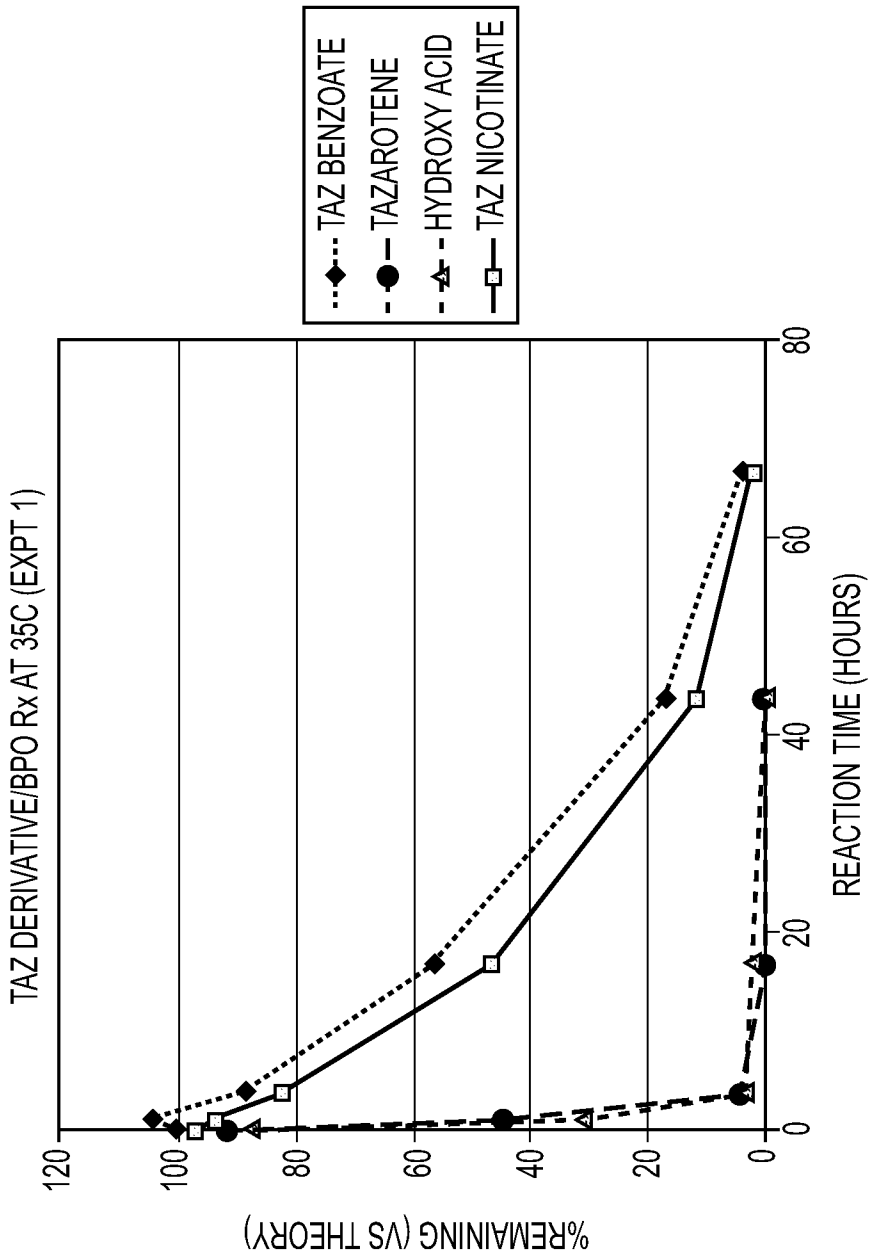
TAZ BENZOATE
TAZAROTENE
HYDROXY ACID
TAZ NICOTINATE
TAZ DERIVATIVE/BPO Rx AT 35C (EXPT 1)
%REMAINING (VS THEORY)
REACTION TIME (HOURS)
120
100
80
60
40
20
0
0
20
40
60
80

FIG. 24A

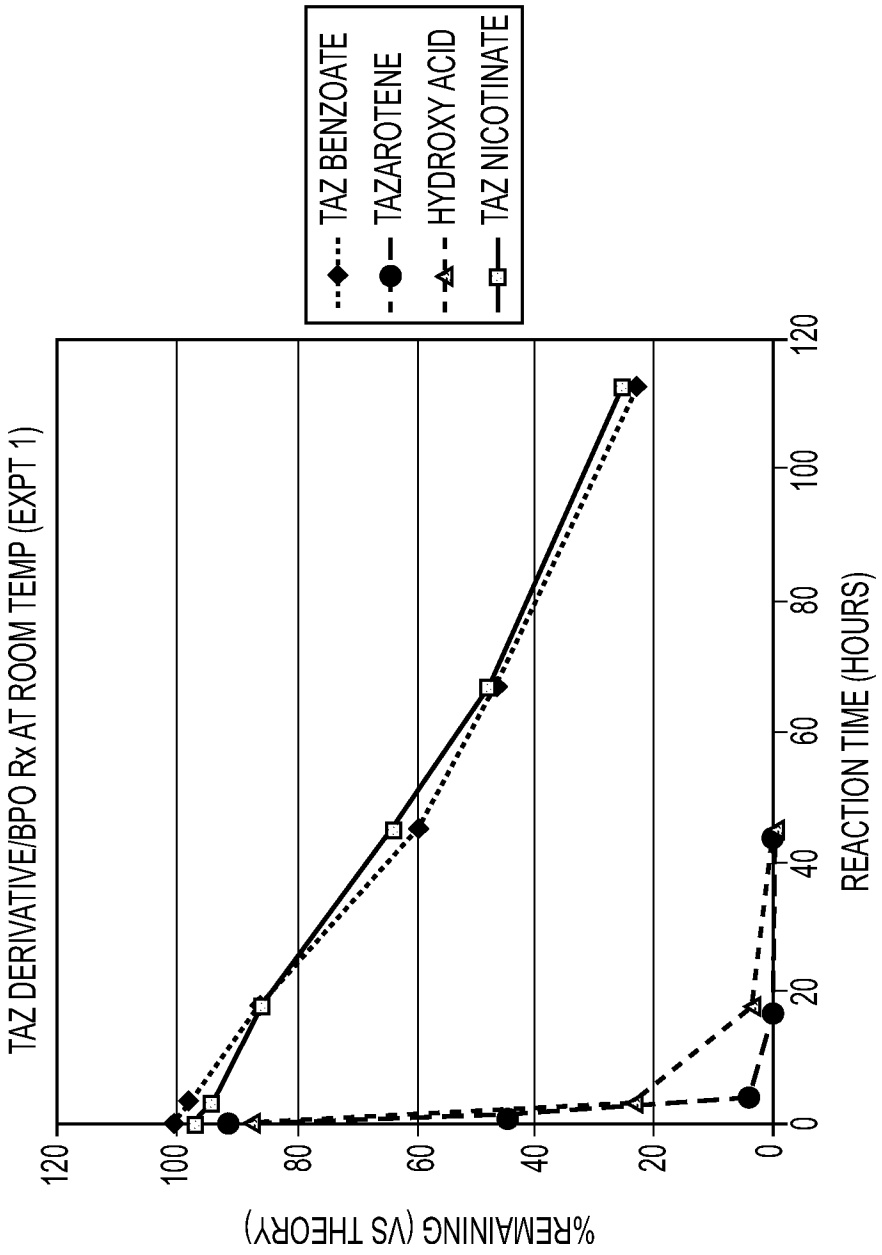
TAZ BENZOATE
TAZAROTENE
HYDROXY ACID
TAZ NICOTINATE
TAZ DERIVATIVE/BPO Rx AT ROOM TEMP (EXPT 1)
%REMAINING (VS THEORY)
REACTION TIME (HOURS)
0
20
40
60
80
100
120

FIG. 24B

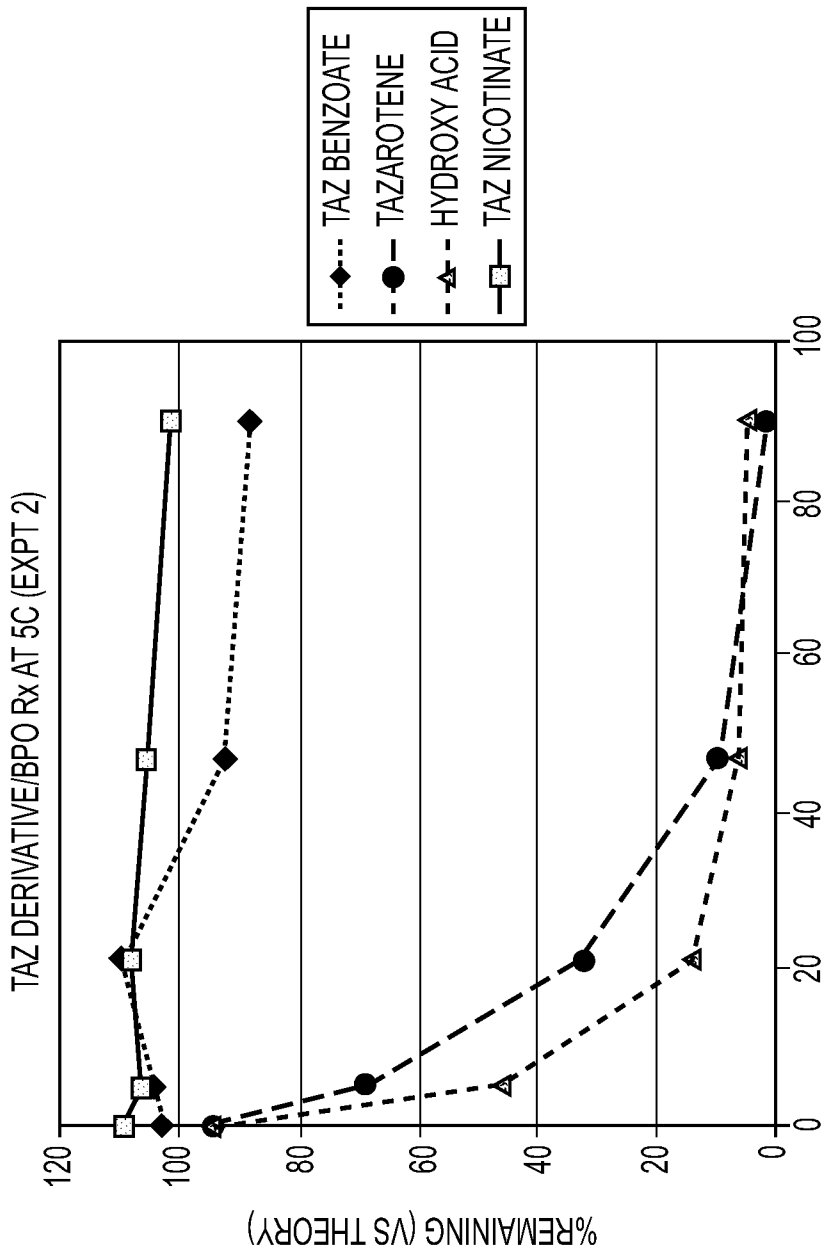
TAZ BENZOATE
TAZAROTENE
HYDROXY ACID
TAZ NICOTINATE
TAZ DERIVATIVE/BPO Rx AT 5C (EXPT 2)
%REMAINING (VS THEORY)
120
100
80
60
40
20
0
0
20
40
60
80
100
REACTION TIME (HOURS)

FIG. 24C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/42225

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/06, 43/12; A61K 31/38 (2010.01)
USPC - 514/443-445
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)
USPC - 514/443-445

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/95-96, 396, 430, 432, 434, 441; 504/282; 548/365.7 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Database Searched: PubWest (PGPB,USPT,USOC,EPAB,JPAB), Google. Search Terms Used Tazarotene, skin disorder benzoyl peroxide, antibiotic, corticosteroid, oxothiochroman$, ethynyl near4 nicotinate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,399,561 A (Chandraratna) 21 March 1995 (21.03.1995) entire document especially abstract; col 2, ln 35 to col 3, ln 07; claim 32	21-27 and 30-31 ---------- 28-29
Y	US 2005/0002878 A1 (Lefrancois et al.) 06 January 2005 (06.01.2005) especially para [0011]	1-5, 8, 10 and 13-15
Y	US 5,677,323 A (Chandraratna) 14 October 1997 (14.10.1997) especially col 1, ln 50-60	1-5, 8, 10 and 13-15
Y	US 6,448,233 B1 (Lefevre et al.) 10 September 2002 (10.09.2002) especially abstract; col 3, ln 34-37	28-29
Y	US 4,801,593 A (Hodson et al.) 31 January 1989 (31.01.1989) especially col 1, ln 41-66	4, 8 and 10
A	US 7,273,937 B2 (Frigoli et al.) 25 September 2007 (25.09.2007) entire document	1-5, 8, 10, 13-15, 21-31

☐ 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	Date of mailing of the international search report
07 September 2010 (07.09.2010)	16 SEP 2010

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/42225

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.: 6-7, 9, 11-12 and 16-20
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.