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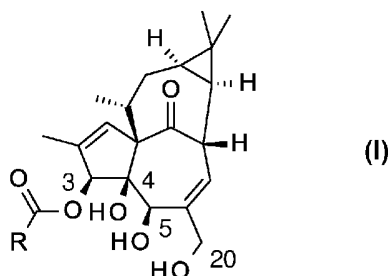
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(54) Title: INGENOL-3-ACYLATES I



(57) Abstract: The invention relates to compounds of general formula (I) wherein R is (C<sub>1</sub>-C<sub>7</sub>)alkyl, (C<sub>2</sub>-C<sub>7</sub>)alkenyl or (C<sub>2</sub>-C<sub>7</sub>)alkynyl; wherein R is substituted with R<sub>1</sub>; and pharmaceutically acceptable salts, hydrates, or solvates thereof, for use -alone or in combination with one or more other pharmaceutically active compounds- in therapy, for preventing, treating or ameliorating diseases or conditions responsive to stimulation of neutrophil oxidative burst, responsive to stimulation of keratinocyte IL-8 release or responsive to induction of necrosis.

## Ingenol-3-acylates I

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### FIELD OF THE INVENTION

This invention relates to novel derivatives of 3-acyl-ingenol and derivatives thereof and their use as a medicament and in therapy. The invention also provides pharmaceutical compositions comprising said compounds and methods of treating diseases with said  
10 compounds.

### BACKGROUND OF THE INVENTION

Ingenol-3-angelate (PEP005, ingenol mebutate) is a diterpene-ester of the ingenol family  
15 which is isolated from various Euphorbia species, particularly from Euphorbia peplus. The compound is presently subject for clinical development for the treatment of actinic keratosis and for non-melanoma skin cancer.

A number of other ingenol-3-acylates, mainly of long-chain saturated and unsaturated  
20 aliphatic fatty acids, have been isolated from various Euphorbia species [H. Gotta, Z. Naturforschung, (1984), 39b, 683-94; K. Abo, Fitoterapia, (1988), 244-46, S. Zayed, J. Cancer Res. Clin. Oncol. (2001), 127, 40-47]. Furthermore, a small number ingenol-3-acylates have been prepared by semi-synthesis (B. Sorg et. al., Z. Naturforsch., (1982), 37b, 748-56). Some of these ingenol derivatives have been described and tested to be  
25 strong irritants and strong tumor-promoting agents. [B. Sorg et. al., Z. Naturforsch., (1982), 37b, 748-56; B. Sorg et. al., Carcinogenesis, (1987), 8, 1-4].

Besides the aliphatic ingenol esters also aromatic esters of ingenol are known. Milliamine C, an ingenol-3-anthraniloate derivative was described (Marston, A. Planta Medica,  
30 (1983), 47, 141-47). Also ingenol-3-benzoate has been described (Sorg, B.; Z Naturforschung , (1982), 37b, 748-56).

Angelic acid and angelic acid esters, as present in ingenol-3-angelate, are prone to isomerisation of the double bond to form the tiglate ester, particularly at basic pH  
35 [Beeby, P., *Tetrahedron Lett.* (1977), 38, 3379-3382, Hoskins, W.M., *J. Chem. Soc. Perkin Trans. 1*, (1977), 538-544, Bohlmann, F. et. al., *Chem. Ber.* (1970), 103, 561-563].

Furthermore, ingenol-3-acylates are known to be unstable as they rearrange to afford the ingenol-5-acylates and ingenol-20-acylates [Sorg, B. et. al, *Z. Naturforsch.*, (1982), 37B, 748-756].

5 WO99/08994 describes isolation of compounds from Euphorbia plant and their use in cancer and other neoplastic diseases hereunder actinic keratosis or solar keratosis. WO01/93883 describes ingenol derivatives different from the present invention for prophylaxis of a PKC-related condition or disorder in a subject. Diseases mentioned in WO01/93883 are: asthma, atherosclerosis, atopic dermatitis, autoimmune disease,  
10 bipolar disorder, blood disorder, cardiac hypertrophy, depression, diabetes, hypertension, hyperplastic dermatosis, multiple sclerosis, myocardial ischemia, osteoarthritis, psoriasis, rheumatoid arthritis, transplantation and latent virus. WO01/93884 discloses ingenol derivatives different from the present invention, and their use in treating inflammatory conditions such as resulting from pathogenic organisms,  
15 virus, yeast, fungus, worms, insects, arachnids, nematodes, aemobe etc. WO01/93885 describes ingenol derivatives different from the present invention for immunopotentialiation. WO08/131491 describes ingenol derivatives different from the present invention for HPV virus infections. WO06/063382 discloses ingenol derivatives different from the present invention for treatment of solid cancers. AU 2006201661  
20 discloses a method for treating acute myeloid leukemia using ingenol-3-angelate. WO02/11743 describes a particular use in prostate and bladder cancer. Ingenol derivatives are described in WO07/059584 for promoting wound healing. WO2010/091472 describes use of ingenols and derivatives in other cosmetic applications.

25 Ingenol-3-angelate is believed to have a dual mode of action: 1) Induction of cell death by direct cytotoxicity or induction of apoptosis and 2) an immunostimulatory effect dominated by neutrophil recruitment and activation (Rosen, R.H., et al., *J Am Acad Derm* (2011), e-published Nov 2011; Ersvaer, E., et al., *Toxins*, (2010), 2, 174-194).  
30 Nanomolar concentrations of the agent cause activation and modulation of protein kinase C (PKC) classical and novel isoforms, with particular importance of PKCdelta. Through activation of PKCdelta the agent induces apoptosis in susceptible cells (Hampson, P., et al., *Blood*, (2005), 106, 1362-1368; Cozzi, S.J., et al., *Cancer Res*, (2006), 66, 10083-10091). Rapid cytotoxicity on cancer cells is observed at high  
35 micromolar concentrations (Ogbourne, S.M., et al., *Cancer Res* (2004), 64, 2833-2839). Through activation of various PKC isoforms the agent also induces pro-inflammatory effects, including release of pro-inflammatory mediators (Challacombe, J.M., et al., *J*

*Immunol* (2006), 177, 8123-8132, activation of vascular endothelium (Hampson, P., et al., *Cancer Immunol Immunother*, (2008), 57, 1241-1251); chemoattraction of neutrophils through induction of interleukin 8 in keratinocytes and development of specific anti-cancer immune responses by CD8+ cells through adjuvant properties in animal models (Le, T.T., et al., *Vaccine*, (2009), 27, 3053-3062).

Compounds exerting dual mode of action by induction of cell death by direct cytotoxicity or induction of apoptosis, and by an immunostimulatory effect involving neutrophil recruitment and activation, may be useful for treatment of conditions associated with hyperplasia or neoplasia. Compounds inducing cell death by primary and / or secondary necrosis and compounds exhibiting a pro-apoptotic effect may reduce unwanted cell growth and remove unwanted cells, and furthermore, stimulation of the innate immune response and adjuvant effects may augment the biological response against aberrant or transformed cells.

Compounds inducing cell death by primary and / or secondary necrosis may be useful for treatment of cosmetic conditions, as these compounds may kill or remove unwanted tissue or cells.

There is a need to find new ingenol derivatives, with a similar or improved biological activity compared to ingenol-3-angelate. Furthermore, there is a need to find new ingenol derivatives which induce cell death by cytotoxicity or apoptosis and / or induce an immunostimulatory effect

The present invention provides branched or substituted 3-O-acyl ingenol derivatives useful for treatment of conditions associated with the use of ingenol-3-angelate or useful for conditions which are affected by induction of cell death by cytotoxicity or induction of apoptosis and / or by an immunostimulatory effect.

Compounds of the present invention stimulate neutrophil oxidative burst, which is part of the innate immune response.

Compounds of the present invention stimulate keratinocyte IL-8 release, thus inducing an immunostimulatory effect.

Some compounds of the present invention induce rapid necrosis.

Compounds of the present invention exhibit suitable stability.

Some compounds of the present invention exhibit improved activity in neutrophil oxidative burst assay compared to ingenol-3-angelate.

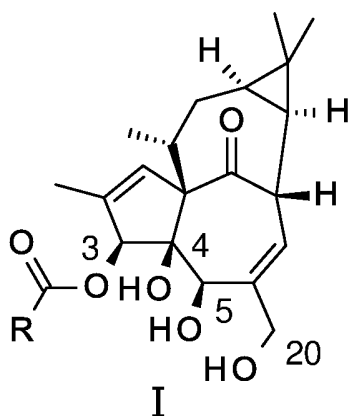
- 5 Some compounds of the present invention exhibit improved activity in IL-8 release assay compared to ingenol-3-angelate.

Some compounds of the present invention exhibit improved activity in necrosis assay compared to ingenol-3-angelate.

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# SUMMARY OF THE INVENTION

In an embodiment the invention provides a compound of the general formula I



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wherein R is (C<sub>1</sub>-C<sub>7</sub>)alkyl, (C<sub>2</sub>-C<sub>7</sub>)alkenyl or (C<sub>2</sub>-C<sub>7</sub>)alkynyl; wherein R is substituted one or more times with substituents independently selected from R<sub>1</sub>; wherein R<sub>1</sub> represents

- (a) Fluoro, cyano or hydroxy; or
- 20 (b) (C<sub>1</sub>-C<sub>4</sub>)alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkylidene each of which may optionally be substituted by one or more substituents independently selected from R<sub>2</sub>, wherein R<sub>2</sub> represents halogen, cyano, hydroxy, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO<sub>2</sub>Rb, -NRaSO<sub>2</sub>NRaRb, -SO<sub>2</sub>NRaRb, -SO<sub>2</sub>Ra, -S(O)Ra, -ORa, -SRa, =N-ORa, =O; or
- 25 (c) -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO<sub>2</sub>Rb, -NRaSO<sub>2</sub>NRaRb, -SO<sub>2</sub>NRaRb, -SO<sub>2</sub>Ra, -S(O)Ra, -ORa, -SRa, =N-ORa, -NRaRb or =O;
- and wherein

Ra and Rb independently represents hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, cyano(C<sub>1</sub>-C<sub>4</sub>)alkyl or aryl;

and wherein

Rc represents (C<sub>1</sub>-C<sub>4</sub>)alkyl, halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl or cyano(C<sub>1</sub>-C<sub>4</sub>)alkyl,

and pharmaceutically acceptable salts, prodrugs, hydrates and solvates thereof;

with the proviso when R<sub>1</sub> represents alkyl or alkenyl the combined length of R and R<sub>1</sub> does not exceed that of a chain of 7 carbon atoms,

and with the proviso that R and R<sub>1</sub> in combination may not be a straight unbranched or unsubstituted alkyl chain or a straight unbranched or unsubstituted alkenyl chain,

and with the proviso that R, or R and R<sub>1</sub> in combination is not *trans*-2-buten-2-yl.

In an embodiment the invention provides a compound of formula I, for use as a medicament in therapy.

In an embodiment the invention provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable stereoisomer, salt or *in vivo* hydrolysable ester thereof together with a pharmaceutically acceptable vehicle or excipient.

In an embodiment the invention provides a pharmaceutical composition suitable for topical administration comprising a compound of formula I or a pharmaceutically acceptable stereoisomer, salt or *in vivo* hydrolysable ester thereof together with a pharmaceutically acceptable vehicle or excipient.

In an embodiment the invention provides a compound of formula I for use in the treatment, prevention, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia or neoplasia.

In an embodiment the invention provides use of a compound of formula I for the manufacture of a medicament for the treatment, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia or neoplasia.

In an embodiment the invention provides a method of preventing, treating, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia or neoplasia by administration to a subject in need thereof a compound of formula I.

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In an embodiment the invention provides a compound of formula I for use in the treatment or amelioration of cosmetic indications.

In an embodiment the invention provides use of compound according to formula I for the manufacture of a medicament for the treatment or amelioration of cosmetic indications.

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In an embodiment the invention provides a method of treatment or amelioration of cosmetic indications by administration to a subject in need thereof a compound of formula I.

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In an embodiment the invention provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable stereoisomer, salt or in vivo hydrolysable ester thereof in combination with one or more other therapeutically active agents.

#### DETAILED DESCRIPTION OF THE INVENTION

In an embodiment the invention provides a compound of the general formula I above, wherein R is a (C<sub>1</sub>-C<sub>7</sub>)alkyl, (C<sub>2</sub>-C<sub>7</sub>)alkenyl or (C<sub>2</sub>-C<sub>7</sub>)alkynyl; wherein R is substituted one or more times with substituents independently selected from R1 wherein R1 represents

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(a) Fluoro, cyano or hydroxy; or

30

(b) (C<sub>1</sub>-C<sub>4</sub>)alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, each of which may optionally be substituted by one or more substituents independently selected from R2, wherein R2 represents halogen, cyano, hydroxy, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO<sub>2</sub>Rb, -NRaSO<sub>2</sub>NRaRb, -SO<sub>2</sub>NRaRb, -SO<sub>2</sub>Ra, -S(O)Ra, -ORa, -SRa, =N-ORa, =O; or

35

(c) -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO<sub>2</sub>Rb, -NRaSO<sub>2</sub>NRaRb, -SO<sub>2</sub>NRaRb, -SO<sub>2</sub>Ra, -S(O)Ra, -ORa, -SRa, =N-ORa and wherein

Ra and Rb represents hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, cyano(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
and wherein

Rc represents (C<sub>1</sub>-C<sub>4</sub>)alkyl, halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, hydroxy(C<sub>1</sub>-  
5 C<sub>4</sub>)alkyl, cyano(C<sub>1</sub>-C<sub>4</sub>)alkyl

with the proviso when R1 represents alkyl or alkenyl the combined length of R and R1  
does not exceed that of a chain of 7 carbon atoms,

10 and with the proviso that R and R1 in combination may not be a straight unbranched or  
unsubstituted alkyl or alkenyl chain,

with the proviso that R, or R and R1 in combination is not *trans*-2-buten-2-yl;

15 In an embodiment the invention provides a compound of formula I wherein R1 is located  
in alpha- or beta-position relative to the carbonyl-group.

In an embodiment the invention provides a compound of formula I wherein R is  
substituted by R1 in the alpha- or beta-position relative to the carbonyl-group.

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In an embodiment the invention provides a compound of formula I wherein R is  
substituted by R1 in the alpha-position relative to the carbonyl-group.

In an embodiment the invention provides a compound of formula I wherein R is (C<sub>1</sub>-C<sub>7</sub>)-  
25 alkyl.

In an embodiment the invention provides a compound of formula I wherein R is ethyl,  
propyl, *tert*-butyl, isopropyl, 2-butyl or 3-pentyl.

30 In an embodiment the invention provides a compound of formula I wherein R is ethyl,  
propyl, *tert*-butyl, isopropyl, 2-butyl, 3-pentyl or isobutyl.

In an embodiment the invention provides a compound of formula I wherein R is (C<sub>2</sub>-C<sub>7</sub>)-  
alkenyl.

35

In an embodiment the invention provides a compound of formula I wherein R is  
propenyl, ethenyl.



In an embodiment the invention provides a compound of formula I wherein R is propenyl or ethenyl.

- 5 In an embodiment the invention provides a compound of formula I wherein R1 is (C<sub>1</sub>-C<sub>4</sub>)-alkyl.

In an embodiment the invention provides a compound of formula I wherein R1 is C<sub>1</sub>-C<sub>4</sub>-alkyl, aryl, cycloalkyl, cycloalkylidene, =N-ORa, =O, -NRaRb, -COORc or cyano.

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In an embodiment the invention provides a compound of formula I wherein R1 is ethyl or methyl.

- 15 In an embodiment the invention provides a compound of formula I wherein R1 is ethyl, methyl, phenyl, cyclohexyl, =N-OCH<sub>3</sub>, -N(CH<sub>3</sub>)(C<sub>6</sub>H<sub>5</sub>), -COOCH<sub>3</sub> or cyclohexylidene.

In an embodiment the invention provides a compound of formula I wherein R1 is methyl.

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In an embodiment the invention provides a compound of formula I wherein R2 is methyl.

In an embodiment the invention provides a compound of formula I said compound being:

- Ingenol 3-(2-methyl-acrylate),  
Ingenol 3-(3-methyl-butenolate),  
25 Ingenol 3-(2,3-dimethyl-butenolate),  
Ingenol 3-(2-methylene-butyrate),  
Ingenol 3-(2-methyl-propanoate),  
Ingenol 3-(3-methyl-butanoate),  
Ingenol 3-(2*RS*-methyl-butanoate),  
30 Ingenol 3-(3,3-dimethyl-butanoate),  
Ingenol 3-(2-ethyl-butanoate),  
Ingenol 3-(2*R*-methyl-butanoate),  
Ingenol 3-tiglate,  
Ingenol 3-(phenyl-acetate),  
35 Ingenol 3-(2*Z*-(methoxycarbonyl)-acrylate),  
Ingenol 3-(2-cyclohexylpropanoate),  
Ingenol 3-((2*Z*)-2-methoxyimino-2-phenyl-acetate),

Ingenol 3-((2E)-2-methoxyimino-2-phenyl-acetate),  
Ingenol 3-((Z)-2-methyl-3-(p-tolyl)prop-2-enoate),  
Ingenol 3-((E)-2-phenylbut-2-enoate),  
Ingenol 3-(2,2-diphenylacetate),  
5 Ingenol 3-(2-cyano-2-cyclohexylidene-acetate) or  
Ingenol 3-(2-(methyl(phenyl)amino)-2-oxo-acetate).

In an embodiment the invention provides a compound of formula I, said compound being Ingenol 3-(2-methylene-butyrate).

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In an embodiment the invention provides a compound of formula I, said compound being Ingenol 3-((Z)-2-methyl-3-(p-tolyl)prop-2-enoate).

In an embodiment the invention provides a compound of formula I, said compound being Ingenol 3-(2,3-dimethyl-butenate).

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In an embodiment the invention provides a compound of formula I, said compound being Ingenol 3-(2-ethyl-butanoate).

In an embodiment the invention provides a compound of formula I, said compound being Ingenol 3-(2-cyclohexylpropanoate).

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In an embodiment the invention provides a compound of formula I, said compound being Ingenol 3-((E)-2-phenylbut-2-enoate).

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#### DEFINITIONS

In the present context, the term "(C<sub>a</sub>-C<sub>b</sub>)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 7, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, isohexyl and heptyl.

30

The term "carbocyclic" refers to a mono-, bi- or tricyclic radical having up to 13 ring atoms, all of which are carbon, and includes aryl, cycloalkyl and cycloalkenyl.

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The term "cycloalkyl" refers to a mono-, bi- or tricyclic saturated cycloalkane radical, comprising 3-13 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptanyl and adamantyl.

- 5 The term "(C<sub>a</sub>-C<sub>b</sub>)alkenyl" wherein a and b are integers refers to a mono-, di- or tri-unsaturated straight or branched chain alkenyl radical having from a to b carbon atoms. Thus when a is 1 and b is 7, for example, the term includes ethenyl, allyl, propenyl; 1-, 2- or 3-butenyl; 1-, 2-, 3- or 4-pentenyl; 1-, 2-, 3-, 4- or 5-hexenyl.
- 10 The term "cycloalkenyl" refers to mono-, di- or triunsaturated non-aromatic cyclic hydrocarbons radicals, including polycyclic radicals, comprising 3-13 carbon atoms and includes, for example, cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

- The term "(C<sub>a</sub>-C<sub>b</sub>)alkynyl" wherein a and b are integers refers to a straight or branched chain hydrocarbon radical having from a to b carbon atoms comprising 1-2 C-C triple bonds. Thus when a is 1 and b is 7, for example, the term includes ethynyl, propynyl, butynyl, pentynyl or hexynyl.
- 15

- The term "heterocyclic" refers to a carbocyclic radical as defined above, comprising 1-4 heteroatoms, selected from O, N, or S, and includes heteroaryl, heterocycloalkyl and heterocycloalkenyl.
- 20

- The term "heterocycloalkyl" refers to a cycloalkyl radical as defined above, including polycyclic radicals, optionally fused with carbocyclic rings, comprising 1-4 heteroatoms, selected from O, N, or S, e.g. tetrahydrofuranyl, pyrrolidinyl, dioxolanyl, morpholinyl, imidazolidinyl, piperidinyl or 5-oxabicyclo[2.2.2]octane.
- 25

- The term "heterocycloalkenyl" refers to a cycloalkenyl radical as defined above, including polycyclic radicals, optionally fused with carbocyclic rings, comprising 1-4 heteroatoms, selected from O, N, or S, e.g. dihydropyranyl.
- 30

- The term "aryl" refers to a radical of aromatic carbocyclic rings comprising 6-10 carbon atoms, in particular phenyl, and optionally fused carbocyclic rings with at least one aromatic ring. Thus the term includes for example phenyl, naphthyl, indenyl or indanyl.
- 35

The term "heteroaryl" refers to radicals of heterocyclic aromatic rings, optionally fused with carbocyclic rings or heterocyclic rings, comprising 1-4 heteroatoms, selected from

O, S and N, and 1- 12 carbon atoms, in particular 5- or 6-membered rings with 1-4 heteroatoms, or optionally fused bicyclic rings with 1-4 heteroatoms, and wherein at least one ring is aromatic. Thus the term includes, for example, pyridyl, quinolyl, isoquinolyl, indolyl, tetrazolyl, furyl, thiazolyl, imidazolyl, imidazo[1,2-a]pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, 1,2,4-triazolyl, thienyl, pyrazinyl, pyrimidinyl, 1,2,3-triazolyl, isothiazolyl, imidazo[2,1-b]thiazolyl, benzimidazolyl, benzofuranyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzooxazolyl, indazolyl.

The term "halogen" is intended to indicate a substituent from the 7th main group of the periodic table, preferably fluoro, chloro and bromo.

The term "alkoxy" is intended to indicate a radical of the formula -OR, wherein R is alkyl as indicated above, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, etc.

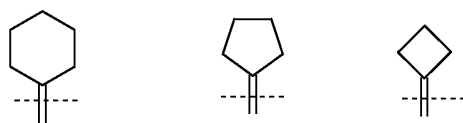
The term hydroxyalkyl is intended to indicate a primary, secondary or tertiary radical of the formula -R-OH, wherein R is alkyl as indicated above, e.g. hydroxymethyl or hydroxyethyl.

The term cyanoalkyl is intended to indicate a primary, secondary or tertiary radical of the formula -R-CN, wherein R is alkyl as indicated above, e.g. cyanomethyl or cyanoethyl.

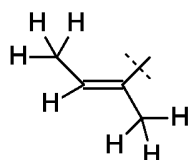
The term haloalkyl is intended to indicate a primary, secondary or tertiary radical of the formula -R-X<sub>(1-3)</sub>, wherein R is alkyl as indicated above, and X is halogen as indicated above, e.g. trifluoromethyl, 2,2,2-trifluoroethyl or difluoromethyl.

The term "alkoxyalkyl" is intended to indicate an alkyl radical as defined above, which is substituted with an alkoxy radical as defined above, i.e. -R-O-R, wherein each R is alkyl, same or different, as indicated above, e.g. methoxymethyl, ethoxymethyl.

In the present context, the term "cycloalkylidene" is intended to indicate a bivalent radical of cycloalkyl, such as cyclohexylidene, cyclopentylidene or cyclobutylidene as indicated below



In the present context, the term "*trans*-2-buten-2-yl" is intended to indicate the radical of the structure indicated below



5

In the present context, a substituted alkyl, a substituted alkenyl, or a substituted alkynyl is intended to mean an alkyl, an alkenyl, or an alkynyl moiety which is substituted with one or more substituent groups attached to the alkyl, alkenyl, or alkynyl moiety.

- 10 The term 'substituted' as applied to any moiety herein is intended to indicate substitution with compatible substituents.

In the present context, a straight unbranched alkyl chain is intended to indicate an unbranched alkyl moiety, such as ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl or *n*-heptyl.

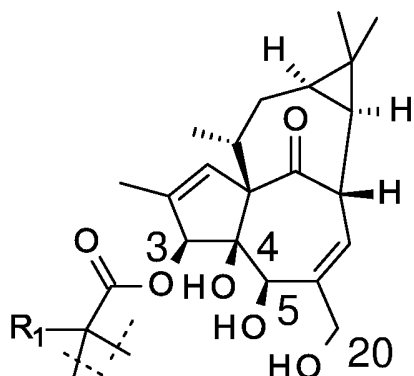
15

In the present context, a straight unbranched alkenyl chain is intended to indicate an unbranched alkenyl moiety, such as ethenyl, allyl, propen-1-yl, buten-1-yl, penten-1, hexen-1-yl or hepten-1-yl.

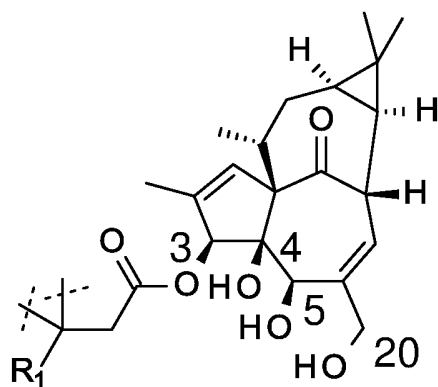
- 20 In the present context, an unsubstituted alkyl chain is intended to indicate a straight alkyl moiety with no substituents attached to the alkyl moiety, such as ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl or *n*-heptyl.

- 25 In the present context, an unsubstituted alkenyl chain is intended to indicate a straight alkenyl moiety with no substituents attached to the alkenyl moiety, such as ethenyl, allyl, propen-1-yl, buten-1-yl, penten-1-yl, hexen-1-yl or hepten-1-yl.

- 30 In the present context, a substituent (R1) in the alpha-position relative to the carbonyl group is intended to indicate a substituent (R1) alpha to the carbonyl moiety as indicated below



In the present context, a substituent (R<sub>1</sub>) in the beta-position relative to the carbonyl group is intended to indicate a substituent (R<sub>1</sub>) beta to the carbonyl moiety as indicated below



5

The term "pharmaceutically acceptable salt" is intended to indicate salts prepared by reacting a compound of formula I comprising a basic moiety with a suitable inorganic or organic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, phosphoric, formic, acetic, 2,2-dichloroacetic, choline, adipic, ascorbic, L-aspartic, L-glutamic, galactaric, lactic, maleic, L-malic, phthalic, citric, propionic, benzoic, glutaric, gluconic, D-glucuronic, methanesulfonic, salicylic, succinic, malonic, tartaric, benzenesulfonic, ethane-1,2-disulfonic, 2-hydroxy ethanesulfonic acid, toluenesulfonic, sulfamic or fumaric acid. Pharmaceutically acceptable salts of compounds of formula I comprising an acidic moiety may also be prepared by reaction with a suitable base such as sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, ammonia, or suitable non-toxic amines, such as lower alkylamines, for example triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis-(2-hydroxyethyl)-

amine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzylethylenediamine, and dibenzylamine, or L-arginine or L-lysine.

5 The present invention further includes prodrugs of compounds of general formula I, such as esters, acetals, ketals, or other derivatives which undergo a biotransformation *in vivo* before exhibiting their pharmacological effects.

10 The term "solvate" is intended to indicate a species formed by interaction between a compound, e.g. a compound of formula I, and a solvent, e.g. alcohol, glycerol or water, wherein said species are in a solid form. When water is the solvent, said species is referred to as a hydrate.

15 The compounds of formula I may be obtained in crystalline form either directly by concentration from an organic solvent or by crystallisation or recrystallisation from an organic solvent or mixture of said solvent and a cosolvent that may be organic or inorganic, such as water. The crystals may be isolated in essentially solvent-free form or as a solvate, such as a hydrate. The invention covers all crystalline modifications and forms and also mixtures thereof.

20 The term "cancer" in the context of the present invention is intended to cover skin cancer such as non-melanoma skin cancer, malignant melanoma, Merkel cell carcinoma, squamous cell carcinoma, basal cell carcinoma. Basal cell carcinomas covers as well superficial basal cell carcinomas as nodular basal cell carcinoma. Squamous cell carcinoma covers squamous cell carcinoma in situ (Bowen's disease), invasive squamous cell carcinoma, cutaneous squamous cell carcinoma, mucosal squamous cell carcinoma, head and neck squamous cell carcinoma. Other cancer types includes haematological cancer such as myeloid cancers in particular such as acute myeloid leukemia and chronic myeloid leukemia; Cancer of the prostate and bladder including benign prostatic hyperplasia, prostatitis intraepithelial carcinoma, carcinoma of the bladder, adenocarcinoma of the prostate and renal cell carcinoma. Other cancer include AIDS related cancer, acoustic neuroma, adenocystic carcinoma, adrenocortical cancer, agnogenic myeloid metaplasia, alopecia, alveolar soft-part sarcoma, anal cancer, angiosarcoma, aplastic anaemia, astrocytoma, ataxia-telangiectasia, basal cell carcinoma (bcc), bladder cancer, bone cancers, bowel cancer, brain stem glioma, brain and CNS cancers, breast cancer, CNS cancers, carcinoid cancers, cervical cancer, childhood brain cancers, childhood cancer, childhood soft tissue sarcoma,

chondrosarcoma, choriocarcinoma, colorectal cancers, cutaneous T-Cell lymphoma, dermatof[ibroma]sarcoma-protuberans, desmoplastic small round cell cancer, ductal carcinoma, endocrine cancers, endometrial cancer, ependymoma, esophageal cancer, Ewing's sarcoma, extra hepatic bile duct cancer, eye cancer, eye: melanoma, retinoblastoma, fallopian tube cancer, fanconi anaemia, fibrosarcoma, gall bladder cancer, gastric cancer, gastrointestinal cancers, gastrointestinal carcinoid cancer, genitourinary cancers, germ cell cancers, gestational trophoblastic disease, glioma, gynecological cancers, hematological malignancies, including acute myeloid leukemia, , head and neck cancer, hepatocellular cancer, hereditary breast cancer, histiocytosis, Hodgkin's disease, human papillomavirus, hydatidiform mole, hypercalcemia, hypopharynx cancer, intra-ocular melanoma, isle T-cell cancer, Kaposi's sarcoma, kidney cancer, Langerhan's cell histiocytosis, laryngeal cancer, leiomyosarcoma, li-fraumeni syndrome, lip cancer, liposarcoma, liver cancer, lung cancer, lymphedema, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, male breast cancer, malignant rhabdoid cancer of kidney, medulloblastoma, mesothelioma, metastatic cancer, mouth cancer, multiple endocrine neoplasia, mycosis fungoides, myelodysplastic syndromes, myeloma, myeloproliferative disorders, nasal cancer, nasopharyngeal cancer, nephroblastoma, neuroblastoma, neurofibromatosis, nijmegen breakage syndrome, non-small cell lung cancer (nsclc), ocular cancers, oesophageal cancer, oral cavity cancer, oropharynx cancer, osteosarcoma, ostomy ovarian cancer, pancreas cancer, paranasal cancer, parathyroid cancer, parotid gland cancer, penile cancer, peripheral neuroectodermal cancers, pituitary cancer, polycythemia vera, prostate cancer, rare cancers and associated disorders, retinoblastoma, rhabdomyosarcoma, rothmund Thomson syndrome, salivary gland cancer, sarcoma, schwannoma, sezary syndrome, small cell lung cancer (sclc), small intestine cancer, soft tissue sarcoma, spinal cord cancers, stomach cancer, synovial sarcoma, testicular cancer, thymus cancer, thyroid cancer, transitional cell cancer (bladder), transitional cell cancer (renal-pelvis/- ureter), trophoblastic cancer, urethral cancer, urinary system cancer, uroplakins, uterine sarcoma, uterus cancer, vaginal Cancer, vulva cancer, Waldenstrom's macroglobulinemia and Wilms' Cancer. The solid cancer which is treated using the methods of the present invention may be a primary lesion or may be the result of metastasis of a primary cancer. Furthermore, if the solid cancer is a metastasis of a primary cancer, the primary cancer may be either a primary solid cancer as described above or may be a dispersed primary cancer.

In an embodiment of the invention "cancer" is skin cancer. In embodiments of the invention, skin cancer is non-melanoma skin cancer, malignant melanoma, Merkel cell



carcinoma, squamous cell carcinoma, squamous cell carcinoma, basal cell carcinoma such as superficial basal cell carcinomas or nodular basal cell carcinoma.

5 The term "photodamaged skin" in the context of the present invention is intended to cover fine lines, wrinkles and UV-ageing. UV ageing is often manifested by an increase in the epidermal thickness or epidermal atrophy and most notably by solar elastosis, the accumulation of elastin containing material just below the dermal-epidermal junction. Collagen and elastic fibres become fragmented and disorganised. At a cosmetic level this can be observed as a reddening and/or thickening of the skin resulting a a lethery  
10 appearance, skin fragility and irregular pigmentation, loss of tone and elasticity, as well as wrinkling, dryness, sunspots and deep furrow formation.

The term "viral infections" in the context of the present invention is intended to cover HPV infections leading to formation of warts on the body, such as the skin, genitals and  
15 mouth. HPV refers to human papilloma virus. Other viruses are selected from adeno-, papova-, herpes- (such as simplex) varicella-zoster, Epstein-Barr-, CMV-, Pox- (such as small pox-) vaccinia-, hepatitis A-, hepatitis B-, hepatitis C-, Rhino-, polio-, rubella-, arbo-, rabies-, influenza- A and B, measles-, mumps-viruses, and HIV, HTLV I and II. In an embodiment of the invention HPV infection refers to common warts or genital warts.

20 The term "bacterial infections" in the context of the present invention is intended to cover prokaryotic and eukaryotic bacterial infections and Gram positive and Gram negative and Gram variable bacteria and intracellular bacteria. Examples of bacteria includes Treponema, Borrelia, Neisseria, Legionella, Bordetella, Escherichia, Salmonella,  
25 Shigella, Klebsiella, Yersinia, Vibrio, Hemophilus, Rickettsia, Chlamydia, Mycoplasma, Staphylococcus, Streptococcus, Bacillus, Clostridium, Corynebacterium, Propionibacterium, Mycobacterium, Ureaplasma and Listeria. In particular the species: Treponema pallidum, Borrelia Burgdorferi, Neisseria gonorrhoea, Legionella pneumophila, Bordetella pertussis, Escherichia coli, Salmonella typhi, salmonella  
30 typhimurium, Shigella dysenteriae, Klebsiella pneumoniae, Yersinia pestis, Vibrio cholerae, Hemophilus influenza, Rickettsia rickettsii, Chlamydia trachomatis, Mycoplasma pneumonia, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Bacillus anthracis, Clostridium botulinum, Clostridium tetani, clostridium perfringens, Corynebacterium diphtheriae, Propionibacterium acne,  
35 Mycobacterium tuberculosis, Mycobacterium leprae and Listeria monocytogenes. Lower eukaryotic organism includes yeast and fungus such as Pneumocystis nterinii, Candida albicans, Aspergillus, Histoplasma capsulatum, Blastomyces dermatitidis, Cryptococcus

neoformans, Trichophyton and Microsporium. Complex eukaryotic organism includes worms, insects, arachnids, nematodes, aemobe, Entamoeba histolytica, Giardia lamblia, Trichomonas vaginalis, Trypanosoma brucei gambiense, Trypanosoma cruzi, Blantidium coli, Toxoplasma gondii, Cryptosporidium or Leishmania.

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The phrase "physiological disorders or diseases associated with hyperplasia or neoplasia" in the context of the present invention is intended to cover disorders or diseases such as Cutaneous warts including common warts (Verruca vulgaris), plantar warts (Verruca plantaris) and flat warts (verruca plana); Genital warts (condyloma acuminatum),

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Pyogenic granuloma, Haemangioma, Scleroderma; Cancers and precancerous lesions such as Actinic keratosis, Squamous cell carcinoma including squamous cell carcinoma in situ (Bowen's disease), invasive squamous cell carcinoma, cutaneous squamous cell carcinoma, mucosal squamous cell carcinoma, head and neck squamous cell carcinoma; Basal cell carcinoma including Superficial basal cell carcinoma and Nodular basal cell carcinoma; Bladder cancer, Lentigo maligna, Cervical dysplasia, Vulva dysplasia and anal dysplasia, Primary melanoma in situ, Head and neck cancer, Cutaneous metastases of any cancer, Kaposi's sarcoma, Keratoacanthoma, Merkel cell tumor, Prostate cancer, Mycosis fungoides, Intraepithelial neoplasias including anal, cervical, ductal, oral, perianal, prostatic, penile, vaginal and vulvar intraepithelial neoplasia.

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The term "cosmetic indications" in the context of the present invention is intended to cover indications such as: Photodamaged skin, Seborrheic keratosis, Scars, Keloids, Melasma, Poikiloderma of Civatte, Tattoo removal, Naevi, Skin tags.

25

In the context of the present invention the term "wound healing" means: reducing or minimizing scar tissue or improving cosmesis or functional outcome in a wound and scar reduction, wherein the wound is cutaneous, chronic or for example diabetes associated, and includes cuts and lacerations, surgical incisions, punctures, grazes, scratches, compression wounds, abrasions, friction wounds, chronic wounds, ulcers, thermal effect wounds, chemical wounds, wounds resulting from pathogenic infections, skin graft/transplant donor and recipient sites, immune response conditions, oral wounds, stomach or intestinal wounds, damaged cartilage or bone, amputation sides and corneal lesions.

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The compounds of the present invention are contemplated in the treatment of cancer, actinic keratosis, seborrheic keratosis, viral infections, bacterial infections, wound healing, and treatment of photodamaged skin.

In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of superficial basal cell carcinoma (BCC), nodular BCC, squamous cell carcinoma or squamous cell carcinoma in situ (SCCIS).

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In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of actinic keratosis.

10 In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of Seborrheic keratosis.

In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of photodamaged skin.

15 In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of or lesions caused by HPV infection.

In an embodiment of the invention the lesions are common warts or genital warts.

20 In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of squamous cell carcinoma in situ or invasive squamous cell carcinoma.

25 In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of cutaneous squamous cell carcinoma, mucosal squamous cell carcinoma or head and neck squamous cell carcinoma.

In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of superficial basal cell carcinoma or nodular basal cell carcinoma.

30 In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of cutaneous warts or genital warts.

In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of common warts, plantar warts and flat warts.

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In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of lentigo maligna.

In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia.

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In an embodiment of the invention the compounds of the invention are contemplated for use in the treatment of acute myeloid leukemia.

10 In an embodiment the invention provides a method of treatment of cancer, actinic keratosis, seborrheic keratosis, viral infections, bacterial infections, wound healing, and treatment of photodamaged skin by administration to a subject in need thereof a compound of formula I.

15 In an embodiment the invention provides a method of treatment actinic keratosis by administration to a subject in need thereof a compound of formula I above.

In an embodiment the invention provides a method of treatment Seborrheic keratosis by administration to a subject in need thereof a compound of formula I above.

20 In an embodiment the invention provides a method of treatment photodamaged skin by administration to a subject in need thereof a compound of formula I above.

25 In an embodiment the invention provides a method of treatment of lesions caused by HPV infection by administration to a subject in need thereof a compound of formula I above.

In an embodiment the invention provides a method of treatment of common warts or genital warts by administration to a subject in need thereof a compound of formula I above.

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In an embodiment the invention provides a method of treatment of cutaneous squamous cell carcinoma, mucosal squamous cell carcinoma or head and neck squamous cell carcinoma by administration to a subject in need thereof a compound of formula I above.

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In an embodiment the invention provides a method of treatment of common warts, plantar warts and flat warts by administration to a subject in need thereof a compound of formula I above.

- 5 In an embodiment the invention provides a method of treatment of lentigo maligna by administration to a subject in need thereof a compound of formula I above.

In an embodiment the invention provides a method of treatment of cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia  
10 by administration to a subject in need thereof a compound of formula I above.

In an embodiment the invention provides a method of treatment of acute myeloid leukemia by administration to a subject in need thereof a compound of formula I above.

- 15 In an embodiment the invention provides use a compound according to formula I above in the manufacture of a pharmaceutical composition for the treatment or amelioration of a disease, disorder or condition responsive to stimulation of neutrophil oxidative burst.

In an embodiment the invention provides use of a compound according to formula I  
20 above in the manufacture of a pharmaceutical composition for the treatment or amelioration of a disease, disorder or condition responsive to stimulation of keratinocyte IL-8 release.

In an embodiment the invention provides use of a compound according to formula I  
25 above in the manufacture of a pharmaceutical composition for the treatment or amelioration of a disease, disorder or condition responsive to induction of necrosis.

In an embodiment the invention provides a method of preventing, treating, amelioration or prophylaxis of physiological disorders or diseases responsive to stimulation of  
30 neutrophil oxidative burst by administration to a subject in need thereof a compound according to formula I above.

In an embodiment the invention provides a method of preventing, treating, amelioration or prophylaxis of physiological disorders or diseases responsive to stimulation of  
35 keratinocyte IL-8 release by administration to a subject in need thereof a compound according to formula I above.

In an embodiment the invention provides a method of preventing, treating, amelioration or prophylaxis of physiological disorders or diseases responsive to responsive to induction of necrosis by administration to a subject in need thereof a compound according to formula I above.

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In an embodiment the invention provides a compound according to formula I above for use in the treatment or amelioration of a disease, disorder or condition responsive to stimulation of neutrophil oxidative burst.

10 In an embodiment the invention provides a compound according to formula I above for use in the treatment or amelioration of a disease, disorder or condition responsive to stimulation of keratinocyte IL-8 release.

15 In an embodiment the invention provides a compound according to formula I above for use in the treatment or amelioration of a disease, disorder or condition responsive to induction of necrosis.

20 In an embodiment the invention provides a method of treatment of acute myeloid leukemia by administration to a subject in need thereof a compound of formula I above.

In an embodiment the invention provides a compound of formula I, for use in the treatment, prevention, amelioration or prophylaxis of physiological disorders or diseases associated with actinic keratosis, seborrheic keratosis, cancer, photodamaged skin or lesions caused by HPV infection.

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In an embodiment the invention provides the use of a compound of formula I, for the manufacture of a medicament for the treatment, amelioration or prophylaxis of physiological disorders or diseases associated with actinic keratosis, Seborrheic keratosis, cancer, photodamaged skin or lesions caused by HPV infection.

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In an embodiment the invention provides a method of preventing, treating, amelioration or prophylaxis of physiological disorders or diseases associated with actinic keratosis, Seborrheic keratosis, cancer, photodamaged skin or lesions caused by HPV infection by administration to a subject in need thereof a compound of formula I.

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Pharmaceutical compositions

For use in therapy, compounds of the present invention are typically in the form of a pharmaceutical composition. The invention therefore relates to a pharmaceutical composition comprising a compound of formula I, together with a pharmaceutically acceptable excipient or vehicle. The excipient must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

Pharmaceutical compositions of the invention may be in unit dosage form such as tablets, pills, capsules, powders, granules, elixirs, syrups, emulsions, ampoules, suppositories or parenteral solutions or suspensions; for oral, parenteral, ophthalmic, transdermal, intra-articular, topical, pulmonal, nasal, buccal or rectal administration or in any other manner appropriate for the formulation of compounds of the invention and in accordance with accepted practices such as those disclosed in *Remington: The Science and Practice of Pharmacy*, 21<sup>st</sup> ed., 2000, Lippincott Williams & Wilkins.

For oral administration in the form of a tablet or capsule, a compound of formula I may suitably be combined with an oral, non-toxic, pharmaceutically acceptable carrier such as ethanol, glycerol, water or the like. Furthermore, suitable binders, lubricants, disintegrating agents, flavouring agents and colourants may be added to the mixture, as appropriate. Suitable binders include, e.g., lactose, glucose, starch, gelatin, acacia gum, tragacanth gum, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes or the like. Lubricants include, e.g., sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride or the like. Disintegrating agents include, e.g., starch, methyl cellulose, agar, bentonite, xanthan gum or the like.

Additional excipients for capsules include macrogols or lipids.

For the preparation of solid compositions such as tablets, the active compound of formula I is mixed with one or more excipients, such as the ones described above, and other pharmaceutical diluents such as water to make a solid preformulation composition containing a homogenous mixture of a compound of formula I. The term "homogenous" is understood to mean that the compound of formula I is dispersed evenly throughout the composition so that the composition may readily be subdivided into equally effective unit dosage forms such as tablets or capsules.

In the form of a dosage unit, the compound may be administered one or more times a day at appropriate intervals, always depending, however, on the condition of the patient, and in accordance with the prescription made by the medical practitioner. Conveniently,

a dosage unit of a formulation contain between 0.01 mg and 200 mg, preferably between 0.01 mg and 20 mg, such as 0.01 - 5 mg of a compound of formula I.

5 A suitable dosage of the compound of the invention will depend, inter alia, on the age and condition of the patient, the severity of the disease to be treated and other factors well known to the practising physician. The compound may be administered either orally, parenterally or topically according to different dosing schedules, e.g. daily or with weekly intervals. In general a single dose will be in the range from 0.01 to 200 mg/kg body weight. The compound may be administered as a bolus (i.e. the entire daily dosis is  
10 administered at once) or in divided doses two or more times a day.

If the treatment involves administration of another therapeutically active compound it is recommended to consult *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9<sup>th</sup> Ed., J.G. Hardman and L.E. Limbird (Eds.), McGraw-Hill 1995, for  
15 useful dosages of said compounds. The administration of a compound of the present invention with one or more other active compounds may be either concomitantly or sequentially.

Liquid formulations for either oral or parenteral administration of the compound of the invention include, e.g., aqueous solutions, syrups, aqueous or oil suspensions and  
20 emulsion with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil. Suitable dispersing or suspending agents for aqueous suspensions include synthetic or natural gums such as tragacanth, alginate, acacia, dextran, sodium carboxymethylcellulose, gelatin, methylcellulose or polyvinylpyrrolidone.

25 For parenteral administration, e.g. intramuscular, intraperitoneal, subcutaneous or intravenous injection or infusion, the pharmaceutical composition preferably comprises a compound of formula I dissolved or solubilised in an appropriate, pharmaceutically acceptable solvent. For parenteral administration, the composition of the invention may include a sterile aqueous or non-aqueous solvent, in particular water, isotonic saline,  
30 isotonic glucose solution, buffer solution or other solvent conventionally used for parenteral administration of therapeutically active substances. The composition may be sterilised by, for instance, filtration through a bacteria-retaining filter, addition of a sterilising agent to the composition, irradiation of the composition, or heating the composition. Alternatively, the compound of the invention may be provided as a sterile,  
35 solid preparation, e.g. a freeze-dried powder, which is dissolved in sterile solvent immediately prior to use. The composition intended for parenteral administration may



additionally comprise conventional additives such as stabilisers, buffers or preservatives, e.g. antioxidants such as methyl hydroxybenzoate or the like.

Compositions for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Compositions suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra-articular and ophthalmic administration.

Compositions suitable for topical administration, including ophthalmic treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Compositions for ophthalmic treatment may preferably additionally contain a cyclodextrin. Compositions suitable for administration to the nasal or buccal cavity or for inhalation include powder, self-propelling and spray formulations, such as aerosols and atomizers.

Human skin, in particular the outer layer, the stratum corneum, provides an effective barrier against penetration of microbial pathogens and toxic chemicals. While this property of skin is generally beneficial, it complicates the dermal administration of pharmaceuticals in that a large quantity, if not most, of the active ingredient applied on the skin of a patient suffering from a dermal disease may not penetrate into the viable layers of the skin where it exerts its activity.

Penetration of the skin is facilitated by addition of penetration enhancers which include isopropyl alcohol, sulphoxides, azones, pyrrolidines, alkanols, and glycols. In embodiments of the invention the penetration enhancers includes DMSO, laurocapram, 2-pyrrolidone, decanol and propylene glycol. In an embodiment of the invention the penetration enhancer is isopropyl alcohol.

In embodiments of the invention the therapeutically active compound is dissolved in a suitable solvent. Suitable solvents are glycols, ketone, acetates and ethers. Ingenol compounds have been shown to have good stability in alcohols such as benzyl alcohol and isopropyl alcohol. In general, ingenol compounds have previously shown to have good stability at low pH. In embodiments of the present invention pH the pharmaceutical

formulation is below 7. In embodiments of the present invention the pH of the pharmaceutical formulation is below 6. In embodiments of the present invention the pH of the pharmaceutical formulation is below 4.5. In embodiments of the present invention the pH of the pharmaceutical formulation is below 4.0. In embodiments of the present invention the pH of the pharmaceutical formulation is below 4.5 and no less than 2.5. In embodiments of the present invention the pH of the pharmaceutical formulation is below 4.0 and no less than 2.5. The preferred pH range can be obtained by including an appropriate buffer. In an embodiment of the invention the buffer is an acetate buffer. In embodiments of the invention a citrate buffer is used. In embodiments of the invention a mixed citrate-phosphate buffer is used.

In one embodiment, the composition is an ointment. According to the current FDA classification, an ointment is a semisolid dosage form which may contain water and volatile substances in an amount of up to 20% by weight and which contains more than 50% by weight of hydrocarbons, waxes or polyols in the vehicle. Thus, according to the invention, the ointment may be a water-in-oil composition in which case the nanosuspension may be added as such to the lipophilic components of the composition, such that the composition contains up to 10% by weight or, preferably, up to 5% by weight of the aqueous phase. Alternatively, the composition may be a non-aqueous ointment which contains less than about 2%, preferably less than 1%, of free water by weight of the composition.

The ointment carrier may suitably contain a paraffin selected from paraffins consisting of hydrocarbons with chain lengths from C<sub>5-60</sub> and mixtures thereof. A frequently used ointment carrier is petrolatum, or white soft paraffin, which is composed of hydrocarbons of different chain lengths, peaking at about C<sub>40-44</sub>, or a mixture of petrolatum and liquid paraffin (consisting of hydrocarbons of different chain lengths peaking at C<sub>28-40</sub>). While petrolatum provides occlusion of the treated skin surface, reducing transdermal loss of water and potentiating the therapeutic effect of the active ingredient in the composition, it tends to have a greasy and/or tacky feel which persists for quite some time after application, and it is not easily spreadable. It may therefore be preferred to employ paraffins consisting of hydrocarbons of a somewhat lower chain length, such as paraffins consisting of hydrocarbons with chain lengths peaking at C<sub>14-16</sub>, C<sub>18-22</sub>, C<sub>20-22</sub>, C<sub>20-26</sub> or mixtures thereof. It has been found that such paraffins are more cosmetically acceptable in that they are less tacky and/or greasy on application and more easily spreadable. They are therefore expected to result in improved patient compliance. Suitable paraffins of this type are manufactured by Sonneborn and marketed under the trade name

Sonnecone, e.g. Sonnecone CM, Sonnecone DM1, Sonnecone DM2 and Sonnecone HV. These paraffins are further disclosed and characterized in WO08/141078 which is incorporated herein by reference. (The hydrocarbon composition of the paraffins has been determined by gas chromatography.)

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To impart a desired viscosity to the composition, it may suitably include a lipophilic viscosity-increasing ingredient such as a wax. The wax may be a mineral wax composed of a mixture of high molecular weight hydrocarbons, e.g. saturated C<sub>35-70</sub> alkanes, such as microcrystalline wax. Alternatively, the wax may be a vegetable or animal wax, e.g. esters of C<sub>14-32</sub> fatty acids and C<sub>14-32</sub> fatty alcohols, such as beeswax. The amount of viscosity-increasing ingredient may vary according to the viscosifying power of the ingredient, but may typically be in the range of about 1-20% by weight of the composition. When the viscosity-increasing ingredient is microcrystalline wax it is typically present in an amount in the range of about 5-15% by weight, e.g. about 10% by weight, of the composition.

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To maintain good physical stability of the composition, in particular to avoid separation of the aqueous and lipid phases therein, it may be advantageous to include a water-in-oil emulsifier with an HLB value of 3-8. Examples of such emulsifiers are polyoxyethylene C<sub>8-22</sub> alkyl ethers, e.g. polyoxyethylene stearyl ether, polyoxyethylene cetyl ether, polyoxyethylene oleyl ether or polyoxyethylene lauryl ether. The amount of emulsifier is typically in the range of 2-10 % w/w of the composition.

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In another embodiment, the composition is a cream which may comprise similar components to the ointment, but which is typically an oil-in-water-emulsion containing a substantial amount of water.

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The composition may also comprise other components commonly used in dermal formulations, e.g. antioxidants (e.g. alpha-tocopherol), preservatives such as benzyl alcohol, sodium edetate, pigments, skin soothing agents, skin healing agents and skin conditioning agents such as urea, allantoin or bisabolol, cf. *CTFA Cosmetic Ingredients Handbook*, 2<sup>nd</sup> Ed., 1992. In an embodiment of the invention the preservative is benzyl alcohol.

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In an embodiment the composition is a gel. Suitable gelling agents include, water soluble cellulose derived polymers, such as hydroxyalkyl cellulose polymers. In embodiments of the invention the polymers are hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose. Other

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gelling agents are celluloses such as carboxymethyl cellulose, methylhydroxyethyl cellulose and methyl cellulose, carbomer such as carbopol and carrageenans. In embodiments of the invention the gelling agent is cellulose derived. In embodiments of the invention the cellulose is a hydroxyalkylcellulose, such as hydroxyethylcellulose.

5

In an embodiment of the invention the composition comprises active compound, penetration enhancer, preservative, gelling agent and buffer at a pH of below 4 and not less than 2.5. For topical administration, the compound of formula I may typically be present in an amount of from 0.001 to 20% by weight of the composition, such as 0.01% to about 10%. In embodiments of the present invention the active compound is present in 0.05-1%. In an embodiment of the present invention the active compound is present in 0.01-0.5%. In an embodiment of the present invention the active compound is present in a concentration of around 0.1%. In an embodiment of the invention the composition comprises 0,005- 0,1% active compound, 20-40% isopropyl alcohol, 0.5-10% benzyl alcohol, 0.5-5 % hydroxyl ethyl cellulose and citrate buffer to 100%.

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Formulation of ingenol derivatives in a gel for topical application has been described in WO07/068963, which is incorporated herein by reference.

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## METHODS OF PREPARATION

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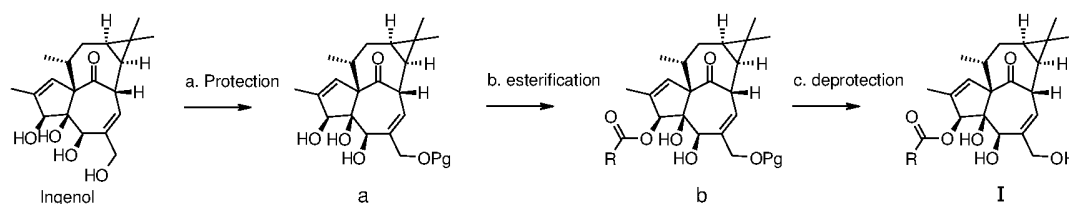
The compounds of formula I may for example be prepared using the reactions and techniques outlined below together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are carried out in solvents appropriate to the reagents and materials employed and suitable for the transformations being effected. Also, in the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognized by one skilled in the art. Not all compounds falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods can be used. The compounds of the present invention or any intermediate may be purified if required using standard methods well known to a synthetic organic chemist, e.g. methods

described in W. Armarego "Purification of Laboratory Chemicals", Butterworth-Heinemann, 6<sup>th</sup> ed. 2009. Starting materials are either known compounds, commercially available, or they may be prepared by routine synthetic methods well known to a person skilled in the art.

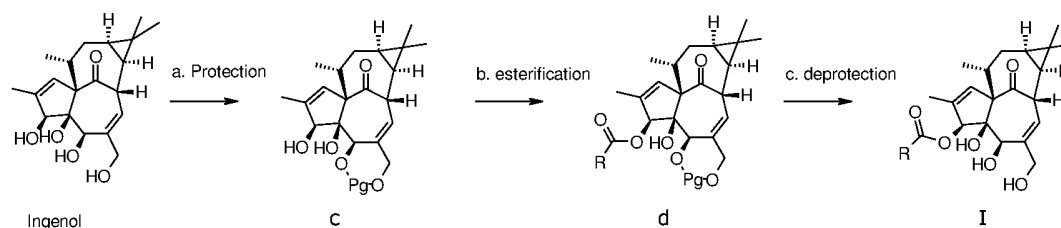
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The compounds of the invention may for example be prepared according to the following non-limiting general methods and examples

Scheme 1



Scheme 2



- 15 The compounds of the general formula I can for example be synthesised according to scheme 1 or 2 by reacting ingenol with a hydroxyl protecting agent or a dihydroxyl protecting agent to afford the protected ingenol derivatives a or c according to methods described in, but not limited to "Protective Groups in Organic Synthesis", 4th ed. P.G.M. Wuts; T.W. Greene, John Wiley, 2007 or in P.J. Kocienski, "Protecting Groups", 3rd ed. G. Thieme, 2003 and references cited therein.
- 20

For example compound a, wherein the protective group (Pg) is triphenylmethyl, can be synthesised by reacting ingenol with a triphenylmethyl reagent such as triphenylmethylpyridinium fluoroborate or triphenylmethyl chloride in a suitable solvent such as pyridine, N,N-dimethylformamide or dichloromethane in the presence or in the absence of base (e.g. Opferkuch et.al., Z. Naturforschung, (1981), 36B, 878).

25

Compound a, wherein the protective group (Pg) is silyl, can for example be synthesised by reacting ingenol with a silyl chloride such as tert-butyldimethylsilyl chloride, tert-butyldiphenylsilyl chloride or triisopropylsilyl chloride in a suitable solvent such as N,N-dimethylformamide, pyridine, dichloromethane, tetrahydrofuran or acetonitrile in the

presence of a suitable base such as imidazole, triethylamine, N,N-diisopropylethylamine or 4-(N,N- dimethylamino)pyridine (e.g. Sorg, B. et. al, Z. Naturforsch., (1982), 37B, 1640-47), or by reacting compound (II) with a silyl triflate such as tert-butyldimethylsilyl trifluoromethanesulfonate in a suitable solvent such as dichloromethane in the presence  
5 of a suitable base such as triethylamine.

Compound a wherein Pg is 2-tetrahydropyranyl, can for example be synthesised by reacting ingenol with dihydropyran in a suitable solvent such as dichloromethane or acetonitrile in the presence of a suitable acid such as p-toluenesulfonic acid.

Compound c wherein the protective group (Pg) represents an acetal such as benzylidene  
10 acetal can for example be prepared by reacting ingenol with benzaldehyde or benzaldehyde dimethyl acetal in a suitable solvent such as dichloromethane or N,N-dimethylformamide in the presence of a suitable acid such as p-toluenesulfonic acid.

Compound c wherein the protective group (Pg) represents a ketal such as isopropylidene  
15 ketal can for example be synthesised by reacting ingenol with a ketone such as acetone or a dimethoxy ketal such as 2,2-dimethoxy propane in a suitable solvent such as dichloromethane or N,N-dimethylformamide in the presence of a suitable acid such as p-toluenesulfonic acid (e.g B. Sorg, Z. Naturforsch. (1982), 37b, 748-756). Acetone and 2,2-dimethoxy propane can also act as solvents.

20 As depicted in scheme 1 and 2 the protected ingenol derivatives a or c may be esterified to give compounds of the general formula b or d according to methods for esterification of hydroxyl groups described in, but not limited to "Esterification" by J. Otera, Wiley-VCH, 2003 and references cited therein. Compound b or d can for example be synthesised by reacting compound a or c with an activated acid derivative such as an  
25 acid halide such as acid chloride. The esterification by reaction with acid chloride can take place in a suitable solvent such as dichloromethane or toluene without an activator, or it can take place in the presence of a base such as pyridine, triethylamine or 4-(N,N-dimethylamino)pyridine (e.g. B. Sorg, Z. Naturforsch. (1982), 37b, 748-756).

Compound b or d can for example be synthesised by reacting compound a or c with  
30 activated acid derivative such as an acid anhydride. The esterification by reaction with an acid anhydride can take place without a catalyst (e.g. Opferkuch et.al., Z. Naturforschung, (1981), 36B, 878), or in the presence of an acidic catalyst using an acid such as perchloric acid or a Lewis acid such as scandium (III) triflate or bismuth (III) triflate, or in the presence of a base such as sodium hydrogencarbonate or  
35 triethylamine.

Compound b or d can for example be synthesised by reacting compound a or c with an activated acid derivative such as a mixed anhydride of an acid such as trichlorobenzoic

acid. The esterification by reaction with a mixed anhydride can take place in a suitable solvent without a catalyst, or in the presence of an acidic catalyst using an acid such as perchloric acid or a Lewis acid such as scandium (III) triflate or bismuth (III) triflate, or in the presence of a base such as sodium hydrogencarbonate or triethylamine.

- 5 Compound b or d can for example be synthesised by reacting compound a or c with an acid in the presence a coupling reagent such as a carbodiimide such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide with or without the presence of a base such as 4-(N,N-dimethylamino)pyridine and with or without catalysts such as 4-(N,N-dimethylamino)pyridine in a suitable solvent such as
- 10 dichloromethane (e.g Appendino et. al., Eur. J. Org. Chem. (1999), 3413). Solid-supported coupling reagents can also be used in the esterification step [Nam, N.-H., Journal of Combinatorial Chemistry, (2003), 5, 479-545, or "Esterification" by J. Otera, Wiley-VCH, 2003].
- 15 The compounds of formula I may be prepared by selective removal of the protective groups Pg from the compounds of the general structure b or d according to methods for deprotection of hydroxyl or dihydroxyl protective groups described, in but not limited to "Protective Groups in Organic Synthesis", 4th ed. P.G.M. Wuts; T.W. Greene, John Wiley, 2007 or in P.J. Kocienski, "Protecting Groups", 3rd ed. G. Thieme, 2003 and references
- 20 cited therein.
- Compounds of general formula I can for example be prepared from compounds of general formula d wherein Pg represents an acetal such as benzylidene acetal or a ketal such as an isopropylidene ketal by cleavage of the protecting group in the presence of a suitable acid such as aqueous hydrogen chloride, acetic acid, trifluoroacetic acid or p-
- 25 toluenesulfonic acid in a suitable solvent such as methanol or aqueous tetrahydrofuran.
- Compounds of general formula I can for example be prepared from compounds of general formula b wherein Pg represents an alkoxyalkyl such as 2-tetrahydropyranyl by cleaving the acetal moiety, for example by acid catalysed cleavage in the presence of a suitable acid such as p-toluenesulfonic acid in a suitable solvent such as methanol.
- 30 Compounds of general formula I can for example be prepared from compounds of general formula b wherein Pg represents silyl such as tert-butyldimethylsilyl by reacting compound b with a suitable acid such as hydrogen chloride in a suitable solvent such as methanol or by reacting with a fluoride source such as tetra n-butylammonium fluoride or tetrafluorosilane in a suitable solvent such as tetrahydrofuran or acetonitrile.
- 35 Compounds of general formula I can for example be prepared from compounds of general formula b wherein Pg represents triphenylmethyl by reacting compound b with a

suitable acid such as formic acid or trifluoroacetic acid in a suitable solvent such as ether, methanol or dichloromethane.

Compounds of formula b, d or I of scheme 1 or 2 above, can for example be synthesised enzymatic esterification by reacting compound a, c or ingenol with an acyl donor such as an acid anhydride, an ester such as vinyl ester or a thioester in the presence of an enzyme such as a lipase or an esterase.

## 10 EXAMPLES

### General

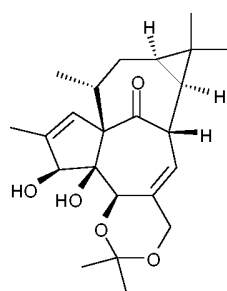
All the starting materials used are commercially available, unless otherwise described.

For  $^1\text{H}$  nuclear magnetic resonance (NMR) spectra, chemical shift values ( $\delta$ ) (in ppm)

are quoted; tetramethylsilane ( $\delta = 0.00$ ) is as standard. The value of a defined doublet (d), triplet (t), quartet (q)) or a range (m) is given. Chemical shifts of exchangeable protons (often broad singlets (bs)) are sometimes difficult to locate in the spectra. All organic solvents used were anhydrous, unless otherwise specified. Flash

chromatography was performed on silica gel. Appropriate mixtures of ethyl acetate and

heptane were used as eluents unless otherwise noted. Compounds were detected on TLC (thin layer chromatography) plates by development with aqueous potassium permanganate solution.



### 25 Ingenol-5,20-acetonide

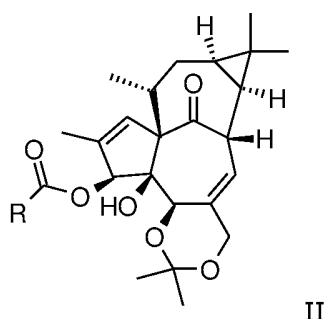
Ingenol (1.00 g, 2.30 mmol) was dissolved in a solution of *p*-toluenesulphonic acid monohydrate in acetone (0.47 mg/mL, 22.5 mL). The solution was stirred at room temperature for 25 min. To this solution was added a saturated aqueous solution of  $\text{NaHCO}_3$  (0.2 mL). The obtained mixture was concentrated in vacuo. The residue was taken up in brine and extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash



chromatography (heptane/ethyl acetate 19:1 → heptane/ethyl acetate 0:1), giving the title compound as a white solid (616 mg, 69%). (See also: Opferkuch, H. J. et.al., *Z. Naturforsch.*, (1981), 86b, 878-887.)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.91 (q,  $J = 1.5$  Hz, 1H), 5.79 (m, 1H), 4.25 (d,  $J = 4.5$  Hz, 1H), 4.20 – 4.07 (m, 3H), 3.93 (s, 1H), 3.51 (s, 1H), 2.57 – 2.41 (m, 2H), 2.25 (ddd,  $J = 15.7, 8.4, 2.9$  Hz, 1H), 1.85 (d,  $J = 1.5$  Hz, 3H), 1.77 (dt,  $J = 15.8, 5.9$  Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.13 (s, 3H), 1.05 (s, 3H), 1.00 – 0.87 (m, 4H), 0.70 (td,  $J = 8.4, 6.4$  Hz, 1H).

## 10 General procedures for the preparation of compounds of general formula II



### Procedure a

A mixture of carboxylic acid (0.100 mmol), dicyclohexylcarbodiimide (0.100 mmol), 4-(N,N-dimethylamino)-pyridine (0.0025 mmol) and ingenol-5,20-acetonide (0.050 mmol) were stirred at room temperature in dichloromethane for 20-24 h. The mixture was mixed with ethyl acetate, filtered and washed with saturated aqueous sodium chloride. The organic phase was dried with sodium sulphate, concentrated in vacuo and purified by flash chromatography (heptane → heptane/ethyl acetate 7:3), giving the title compound as a white solid.

### Procedure b

A mixture of acyl chloride (0.0625 mmol), diisopropylethylamine (0.075 mmol), 4-(N,N-dimethylamino)-pyridine (0.070 mmol) and ingenol-5,20-acetonide (0.050 mmol) were stirred at 55 °C in tetrahydrofuran for 6-20 h. The mixture was mixed with ethyl acetate, filtered and washed with saturated aqueous sodium chloride. The organic phase was dried with sodium sulphate, concentrated in vacuo and purified by flash chromatography (heptane → heptane/ethyl acetate 7:3), giving the title compound as a white solid.

### 30 Procedure c

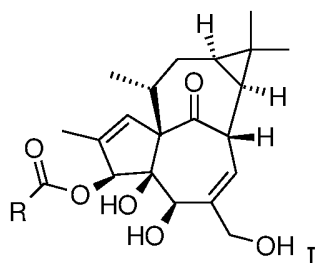
A mixture of carboxylic acid (0.100 mmol), dicyclohexylcarbodiimide (0.100 mmol), 4-(N,N-dimethylamino)-pyridine (0.025 mmol) and ingenol-5,20-acetonide (0.050 mmol) were stirred in a microwave oven at 150 °C in acetonitrile for 5 min. The mixture was mixed with ethyl acetate, filtered and washed with saturated aqueous sodium chloride.

- 5 The organic phase was dried with sodium sulphate, concentrated in vacuo and purified by flash chromatography (heptane → heptane/ethyl acetate 7:3), giving the title compound as a white solid.

#### Procedure d

- 10 A mixture of acyl chloride (0.125 mmol), diisopropylethylamine (0.250 mmol), 4-(N,N-dimethylamino)-pyridine (0.025 mmol) and ingenol-5,20-acetonide (0.050 mmol) were stirred in a microwave oven at 150 °C in acetonitrile for 20 min. The mixture was mixed with ethyl acetate, filtered and washed with saturated aqueous sodium chloride. The organic phase was dried with sodium sulphate, concentrated in vacuo and purified by
- 15 flash chromatography (heptane → heptane/ethyl acetate 7:3), giving the title compound as a white solid.

#### General procedure for the preparation of compounds of general formula I

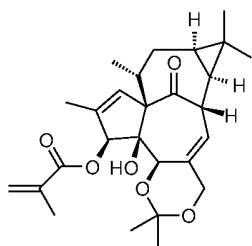


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#### Procedure e

Ingenol-5,20-acetonide-3-acylate (0.10 mmol) was dissolved in tetrahydrofuran (0.47 mL) under argon. An aqueous solution of HCl (4 M, 4.7 µL) was added. The solution was stirred at room temperature for 20-27 h. The solution was concentrated in vacuo. The

25 residue was purified by flash chromatography (heptane/ethyl acetate 5:1 → heptane/ethyl acetate 3:7), giving the title compound.



Preparation 201:

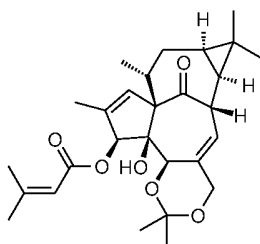
Ingenol-5,20-acetonide-3-(2-methyl-acrylate) (Compound 201)

Compound 201 was prepared according to Procedure a.

- 5 Starting material: 2-Methyl-acrylic acid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.12-6.11 (m, 1H), 6.05 (m, 1H), 5.79-5.77 (m, 1H), 5.62 (s, 1H), 5.60 (m, 1H), 4.25-4.11 (m, 3H), 4.02 (s, 1H), 3.14 (s, 1H), 2.61-2.54 (m, 1H), 2.31-2.22 (m, 1H), 1.97 (m, 3H), 1.81-1.72 (m, 4H), 1.47 (s, 3H), 1.42 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.99 (d, 3H), 0.94-0.88 (m, 1H), 0.73-0.65 (m, 1H).

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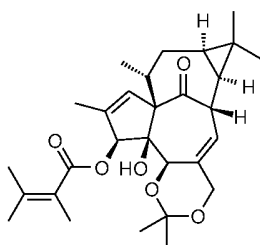


Preparation 202:

Ingenol-5,20-acetonide-3-(3-methyl-butenate) (Compound 202)

Compound 202 was prepared according to Procedure a.

- 15 Starting material: 3-Methyl-butenic acid.

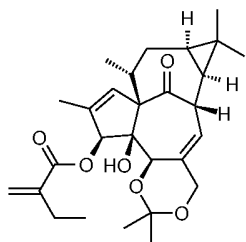


- 20 Preparation 203:

Ingenol-5,20-acetonide-3-(2,3-dimethyl-butenate) (Compound 203)

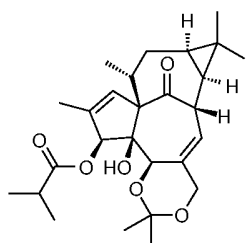
Compound 203 was prepared according to Procedure a.

Starting material: 2,3-Dimethyl-butenic acid.

Preparation 204:Ingenol-5,20-acetonide-3-(2-methylene-butanoate) (Compound 204)

- 5 Compound 204 was prepared according to Procedure a.

Starting material: 2-Methylene-butanoic acid.

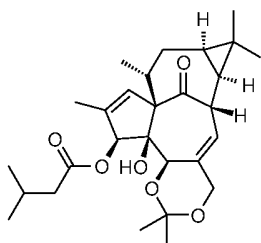
Preparation 205:

- 10 Ingenol-5,20-acetonide-3-(2-methyl-propanoate) (Compound 205)

Compound 205 was prepared according to Procedure a.

Starting material: 2-Methyl-propanoic acid.

- <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.05-6.04 (m, 1H), 5.78-5.76 (m, 1H), 5.54 (s, 1H), 4.24-4.10 (m, 3H), 4.00 (s, 1H), 3.09 (s, 1H), 2.65-2.54 (m, 2H), 2.31-2.22 (m, 1H), 1.80-1.71 (m, 4H), 1.45 (s, 3H), 1.41 (s, 3H), 1.21 (d, 3H), 1.19 (d, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (d, 3H), 0.93-0.87 (m, 1H), 0.73-0.65 (m, 1H).
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Preparation 206:

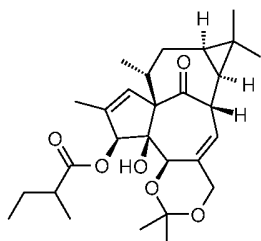
- 20 Ingenol-5,20-acetonide-3-(3-methyl-butanoate) (Compound 206)

Compound 206 was prepared according to Procedure a.

Starting material: 3-Methyl-butanoic acid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.04-6.03 (m, 1H), 5.79-5.77 (m, 1H), 5.55 (s, 1H), 4.24-4.10 (m, 3H), 4.00 (s, 1H), 3.15 (s, 1H), 2.60-2.52 (m, 1H), 2.32-2.04 (m, 4H), 1.80-1.71 (m, 4H), 1.45 (s, 3H), 1.41 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.99 (d, 6H), 0.98 (d, 3H), 0.94-0.87 (m, 1H), 0.73-0.65 (m, 1H).

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#### Preparation 207:

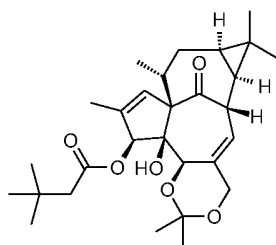
##### Ingenol-5,20-acetonide-3-(2(RS)-methyl-butanoate) (Compound 207a and 207b)

Compound 207a and 207b were prepared according to Procedure a.

10 Starting material: (RS)-2-methyl-butanoic acid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.05-6.03 (m, 1H), 5.79-5.76 (m, 1H), 5.55 (s, 1H), 4.24-4.10 (m, 3H), 4.00 (s, 1H), 3.12 (s, 1H), 2.61-2.53 (m, 1H), 2.48-2.40 (m, 1H), 2.31-2.22 (m, 1H), 1.80-1.66 (m, 5H), 1.56-1.47 (m, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.20-1.16 (2xd, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.99-0.87 (m, 7H), 0.73-0.65 (m, 1H).

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#### Preparation 208:

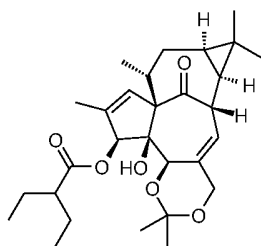
##### Ingenol-5,20-acetonide-3-(3,3-dimethyl-butanoate) (Compound 208)

Compound 208 was prepared according to Procedure a.

20 Starting material: 3,3-Dimethyl-butanoic acid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.04-6.02 (m, 1H), 5.78-5.77 (m, 1H), 5.55 (s, 1H), 4.24-4.10 (m, 3H), 4.00 (s, 1H), 3.15 (s, 1H), 2.62-2.55 (m, 1H), 2.30-2.20 (m, 1H), 2.27 (s, 2H), 1.78-1.69 (m, 4H), 1.45 (s, 3H), 1.41 (s, 3H), 1.10 (s, 3H), 1.06 (s, 9H), 1.05 (s, 3H), 0.97 (d, 3H), 0.93-0.87 (m, 1H), 0.73-0.65 (m, 1H).

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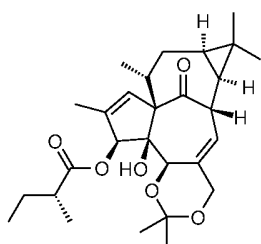
Preparation 209:Ingenol-5,20-acetonide-3-(2-ethyl-butanoate) (Compound 209)

Compound 209 was prepared according to Procedure a.

- 5 Starting material: 2-Ethyl-butanoic acid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.05-6.03 (m, 1H), 5.78-5.76 (m, 1H), 5.56 (s, 1H), 4.25-4.10 (m, 3H), 4.01 (s, 1H), 3.16 (s, 1H), 2.64-2.54 (m, 1H), 2.31-2.21 (m, 2H), 1.78-1.48 (m, 8H), 1.46 (s, 3H), 1.41 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 0.98 (d, 3H), 0.94 (t, 3H), 0.93 (t, 3H), 0.93-0.87 (m, 1H), 0.72-0.65 (m, 1H).

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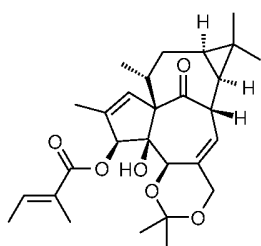
Preparation 210:Ingenol-5,20-acetonide-3-(2R-methyl-butanoate) (Compound 210)

Compound 210 was prepared according to Procedure a.

- 15 Starting material: (R)-2-Methyl-butanoic acid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.05-6.03 (m, 1H), 5.79-5.76 (m, 1H), 5.55 (s, 1H), 4.24-4.10 (m, 3H), 4.00 (s, 1H), 3.12 (s, 1H), 2.61-2.53 (m, 1H), 2.50-2.39 (m, 1H), 2.31-2.22 (m, 1H), 1.79-1.66 (m, 5H), 1.59-1.47 (m, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.19-1.16 (d, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.99-0.87 (m, 7H), 0.73-0.65 (m, 1H).

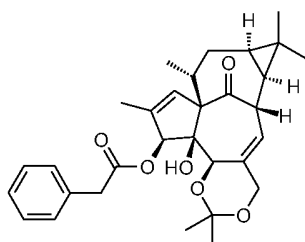
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Preparation 211:Ingenol-5,20-acetonide-3-tiglate (Compound 211)

Compound 211 was prepared according to Procedure a.

Starting material: Tiglic acid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.90-6.82 (m, 1H), 6.05-6.04 (m, 1H), 5.78-5.76 (m, 1H), 5.62 (s, 1H), 4.24-4.11 (m, 3H), 4.01 (s, 1H), 3.17 (s, 1H), 2.61-2.56 (m, 1H), 2.31-2.22 (m, 1H), 1.86-1.72 (m, 10H), 1.45 (s, 3H), 1.42 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 1.00 (d, 3H), 0.94-0.88 (m, 1H), 0.73-0.63 (m, 1H).

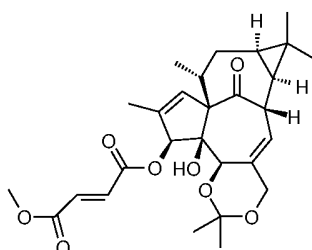


#### Preparation 212:

##### 10 Ingenol-5,20-acetonide-3-(phenyl-acetate) (Compound 212)

Compound 212 was prepared according to Procedure a.

Starting material: Phenyl-acetic acid.



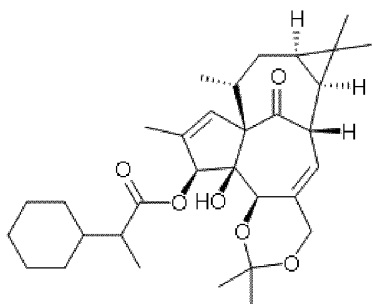
##### 15 Preparation 213:

##### Ingenol-5,20-acetonide-3-(2Z-(methoxycarbonyl)-acrylate) (Compound 213)

Compound 213 was prepared according to Procedure a.

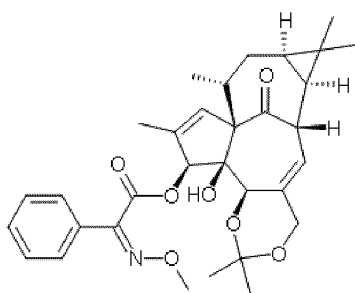
Starting material: Fumaric acid mono-methyl ester.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.93 (d, 1H), 6.85 (d, 1H), 6.09 (m, 1H), 6.80-6.78 (m, 1H), 5.62 (s, 1H), 4.26-4.09 (m, 3H), 4.02 (s, 1H), 3.82 (s, 3H), 3.59-3.53 (m, 1H), 2.29-2.20 (m, 1H), 2.82-2.73 (m, 4H), 1.47 (s, 3H), 1.43 (s, 3H), 1.27 (bs, 1H), 1.09 (s, 3H), 1.05 (s, 3H), 1.00 (d, 3H), 0.94-0.85 (m, 1H), 0.73-0.65 (m, 1H).

**Preparation 214:****Ingenol-5,20-acetonide-3-(2-cyclohexylpropanoate) (Compound 214)**

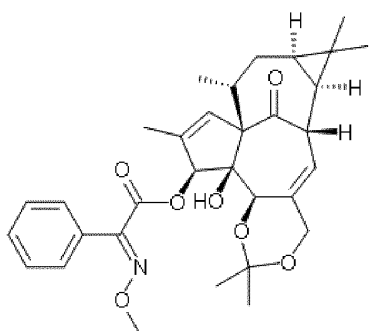
Compound 214 was prepared according to Procedure c.

- 5 Starting material: 2-Cyclohexylpropanoic acid.

**Preparation 215:****Ingenol-5,20-acetonide-3-((2Z)-2-methoxyimino-2-phenyl-acetate) (Compound 215)**

- 10 Compound 215 was prepared according to Procedure c.

Starting material: (2Z)-2-Methoxyimino-2-phenyl-acetic acid.

**Preparation 216:**

- 15 **Ingenol-5,20-acetonide-3-((2E)-2-methoxyimino-2-phenyl-acetate) (Compound 216)**

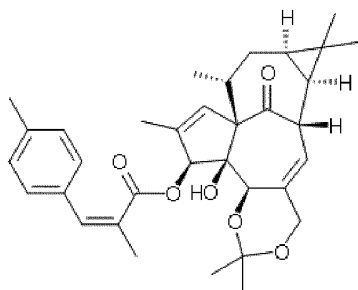
Compound 216 was prepared according to Procedure c.

Starting material: (2E)-2-Methoxyimino-2-phenyl-acetic acid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.47-7.36 (m, 5H), 6.03-6.02 (m, 1H), 5.78-5.76 (m, 1H), 5.70 (s, 1H), 4.23-4.09 (m, 3H), 4.05 (s, 3H), 4.01 (s, 1H), 3.32 (s, 1H), 2.28-2.13 (m,



2H), 1.77 (d, 3H), 1.68-1.57 (m, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.92-0.86 (m, 1H), 0.81 (d, 3H), 0.70-0.62 (m, 1H).

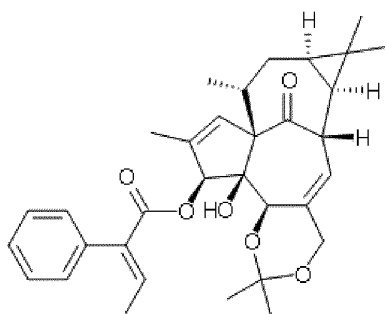


5 Preparation 217:

Ingenol-5,20-acetonide-3-((Z)-2-methyl-3-(p-tolyl)prop-2-enoate) (Compound 217)

Compound 217 was prepared according to Procedure c.

Starting material: (Z)-2-Methyl-3-(p-tolyl)prop-2-enoic acid.



10

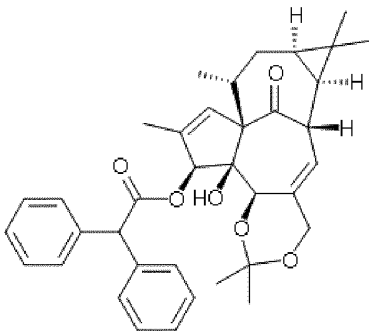
Preparation 218:

Ingenol-5,20-acetonide-3-((E)-2-phenylbut-2-enoate) (Compound 218)

Compound 218 was prepared according to Procedure c.

Starting material: (E)-2-phenylbut-2-enoic acid.

15

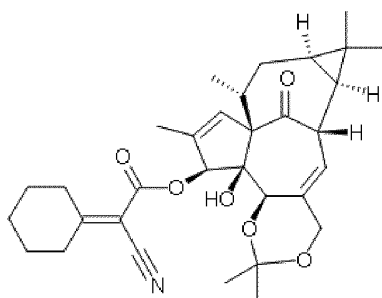


Preparation 219:

Ingenol-5,20-acetonide-3-(2,2-diphenylacetate) (Compound 219)

Compound 219 was prepared according to Procedure c.

Starting material: 2,2-Diphenylacetic acid.

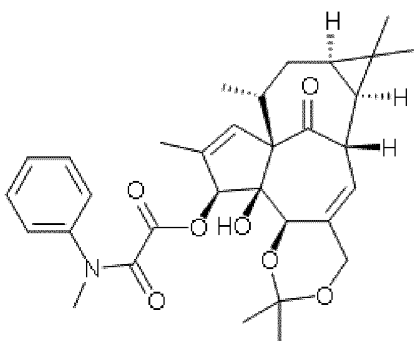


Preparation 220:

5 Ingenol-5,20-acetonide-3-(2-cyano-2-cyclohexylidene-acetate) (Compound 220)

Compound 220 was prepared according to Procedure d, but extending the reaction time to 40 min.

Starting material: 2-cyano-2-cyclohexylidene-acetyl chloride, prepared from 2-cyano-2-cyclohexylidene-acetic acid by reaction with 1.25 eq. oxalyl chloride in dichloromethane and a drop of N,N-dimethylformamide at room temperature for 30 min followed by  
10 evaporation of volatiles in vacuum.



Preparation 221:

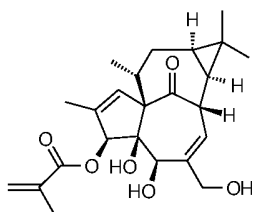
15 Ingenol-5,20-acetonide-3-(2-(methyl(phenyl)amino)-2-oxo-acetate) (Compound 221)

Compound 221 was prepared according to Procedure c.

Starting material: 2-(methyl(phenyl)amino)-2-oxo-acetic acid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.41-7.24 (m, 5H), 5.99-5.98 (m, 1H), 5.76-5.73 (m, 1H), 5.39 (s, 1H), 4.19-4.02 (m, 3H), 3.87-3.86 (m, 1H), 3.36 (s, 3H), 2.75 (s, 1H), 2.46-2.41 (m, 1H), 2.24-2.15 (m, 1H), 1.79-1.67 (m, 1H), 1.51 (d, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 0.94 (d, 3H), 0.91-0.84 (m, 1H), 0.72-0.64 (m, 1H).

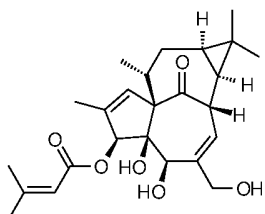
20

**Example 101:****Ingenol 3-(2-methyl-acrylate) (Compound 101)**

Compound 101 was prepared according to Procedure e.

5 Starting material: Compound 201.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.15 (s, 1H), 6.06-6.04 (m, 2H), 5.65-5.64 (m, 1H), 5.56 (s, 1H), 4.20-4.11 (m, 3H), 4.05 (s, 1H), 3.49 (bs, 1H), 2.9-2.7 (bs, 2H), 2.55-2.50 (m, 1H), 2.31-2.22 (m, 1H), 1.99 (s, 3H), 1.79 (d, 3H), 1.80-1.72 (m, 1H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (d, 3H), 0.98-0.91 (m, 1H), 0.74-0.65 (m, 1H).



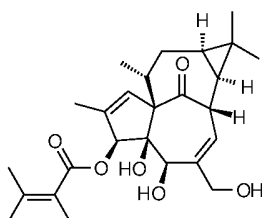
10

**Example 102:****Ingenol 3-(3-methyl-butenate) (Compound 102)**

Compound 102 was prepared according to Procedure e.

Starting material: Compound 202.

15  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.05 (d, 1H), 6.02-6.01 (m, 1H), 5.77-5.76 (m, 1H), 5.51 (s, 1H), 4.15-4.09 (m, 3H), 4.03 (s, 1H), 3.48 (bs, 1H), 2.79 (bs, 2H), 2.54-2.49 (m, 1H), 2.30-2.20 (m, 1H), 2.20 (d, 3H), 1.94 (d, 3H), 1.88-1.72 (m, 1H), 1.78 (d, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98-0.91 (m, 4H), 0.73-0.65 (m, 1H).



20

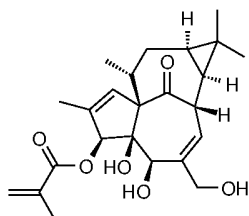
**Example 103****Ingenol 3-(2,3-dimethyl-butenate) (Compound 103)**

Compound 103 was prepared according to Procedure e.

Starting material: Compound 203.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.07-6.05 (d, 1H), 6.03-6.02 (m, 1H), 5.50 (s, 1H), 4.15-4.09 (m, 3H), 4.05 (s, 1H), 3.47 (bs, 1H), 2.55-2.48 (m, 1H), 2.30-2.21 (m, 1H), 2.07 (m, 3H), 1.89 (m, 3H), 1.85 (s, 3H), 1.80 (m, 3H), 1.99-1.55 (m, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.96-0.88 (d, 4H), 0.74-0.65 (m, 1H).

5



Example 104:

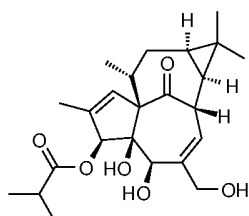
Ingenol 3-(2-methylene-butylate) (Compound 104)

Compound 104 was prepared according to Procedure e.

10 Starting material: Compound 204.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.19 (s, 1H), 6.06-6.04 (m, 2H), 5.61 (m, 1H), 5.57 (s, 1H), 4.20-4.11 (m, 3H), 4.05 (s, 1H), 3.5 (bs, 1H), 2.9 (bs, 2H), 2.55-2.50 (m, 1H), 2.39-2.22 (m, 3H), 1.79 (d, 3H), 1.80-1.72 (m, 1H), 1.11 (t, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (d, 3H), 0.97-0.91 (m, 1H), 0.74-0.65 (m, 1H).

15



Example 105:

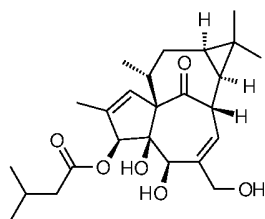
Ingenol 3-(2-methyl-propanoate) (Compound 105)

Compound 105 was prepared according to Procedure e.

20 Starting material: Compound 205.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.05-6.02 (m, 2H), 5.45 (s, 1H), 4.19-4.11 (m, 3H), 4.03 (s, 1H), 3.45 (bs, 1H), 2.65 (m, 1H), 2.54-2.49 (m, 1H), 2.5 (bs, 1H), 2.31-2.22 (m, 1H), 1.81-1.71 (m, 1H), 1.77 (d, 3H), 1.23 (d, 3H), 1.21 (d, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.97 (d, 3H), 0.97-0.86 (m, 2H), 0.73-0.65 (m, 1H).

25

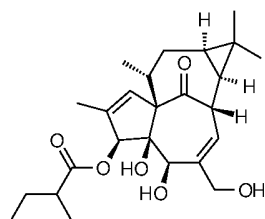
**Example 106:****Ingenol 3-(3-methyl-butanoate) (Compound 106)**

Compound 106 was prepared according to Procedure e.

5 Starting material: Compound 206.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.05-6.02 (m, 2H), 5.43 (s, 1H), 4.19-4.11 (m, 3H), 4.03 (s, 1H), 3.49 (bs, 1H), 2.6-2.4 (bs, 1H), 2.53-2.45 (m, 1H), 2.31-2.23 (m, 3H), 2.17-2.04 (m, 1H), 1.81-1.71 (m, 1H), 1.78 (d, 3H), 1.27 (bs, 1H), 1.09 (s, 3H), 1.05 (s, 3H), 1.00 (d, 6H), 0.97 (d, 3H), 0.97-0.86 (m, 1H), 0.73-0.66 (m, 1H).

10

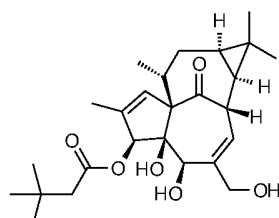
**Example 107:****Ingenol 3-(RS-2-methyl-butanoate) (Compound 107a and Compound 107b)**

Compound 107a and 107b were prepared according to Procedure e.

15 Starting material: Compound 207a and 207b.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.06-6.02 (m, 2H), 5.46 (s, 1H), 4.19-4.11 (m, 3H), 4.03 (s, 1H), 3.45 (bs, 1H), 2.6 (bs, 1H), 2.54-2.41 (m, 2H), 2.31-2.22 (m, 1H), 1.78 (d, 3H), 1.80-1.64 (m, 2H), 1.57-1.47 (m, 1H), 1.28 (bs, 1H), 1.21-1.18 (m, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98-0.85 (m, 7H), 0.73-0.65 (m, 1H).

20

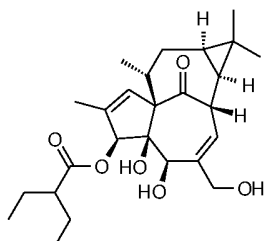
**Example 108:****Ingenol 3-(3,3-dimethyl-butanoate) (Compound 108)**

Compound 108 was prepared according to Procedure e.

25 Starting material: Compound 208.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.06-6.02 (m, 2H), 5.47 (s, 1H), 4.19-4.11 (m, 3H), 4.03 (s, 1H), 3.51 (s, 1H), 2.6-2.4 (bs, 1H), 2.54-2.49 (m, 1H), 2.30 (s, 2H), 2.30-2.21 (m, 1H), 1.78 (d, 3H), 1.77-1.70 (m, 1H), 1.27 (bs, 1H), 1.09 (s, 3H), 1.06 (s, 9H), 1.05 (s, 3H), 0.96 (d, 3H), 0.98-0.88 (m, 1H), 0.73-0.65 (m, 1H).

5



**Example 109:**

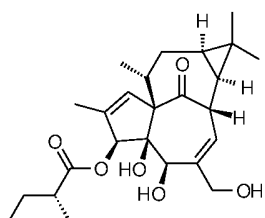
**Ingenol 3-(2-ethyl-butanoate) (Compound 109)**

Compound 109 was prepared according to Procedure e.

10 Starting material: Compound 209.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.06-6.03 (m, 2H), 5.43 (s, 1H), 4.19-4.11 (m, 3H), 4.04 (s, 1H), 3.50 (s, 1H), 2.6-2.4 (bs, 1H), 2.54-2.49 (m, 1H), 2.34-2.22 (m, 2H), 1.78 (d, 3H), 1.79-1.51 (m, 5H), 1.27 (bs, 1H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98-0.89 (m, 10H), 0.73-0.65 (m, 1H).

15



**Example 110:**

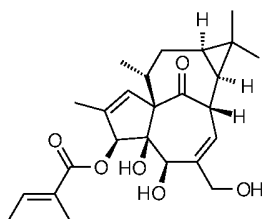
**Ingenol 3-(2R-methyl-butanoate) (Compound 110)**

Compound 110 was prepared according to Procedure e.

20 Starting material: Compound 210.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.06-6.02 (m, 2H), 5.46 (s, 1H), 4.19-4.11 (m, 3H), 4.03 (s, 1H), 3.46 (bs, 1H), 2.6-2.4 (bs, 1H), 2.54-2.44 (m, 2H), 2.31-2.22 (m, 1H), 1.78 (d, 3H), 1.80-1.66 (m, 2H), 1.57-1.48 (m, 1H), 1.27 (bs, 1H), 1.19 (d, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98-0.86 (m, 7H), 0.73-0.65 (m, 1H).

25

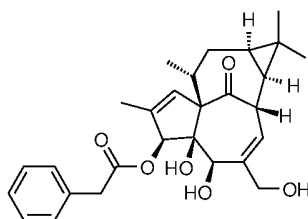
**Example 111:****Ingenol 3-tiglate (Compound 111)**

Compound 111 was prepared according to Procedure e.

5 Starting material: Compound 211.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.95-6.88 (m, 1H), 6.05-6.03 (m, 2H), 5.51 (s, 1H), 4.14-4.11 (m, 3H), 4.05 (s, 1H), 3.47 (bs, 1H), 2.77 (bs, 2H), 2.54-2.49 (m, 1H), 2.30-2.21 (m, 1H), 1.87-1.72 (m, 10H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (d, 3H), 0.98-0.91 (m, 1H), 0.73-0.65 (m, 1H).

10

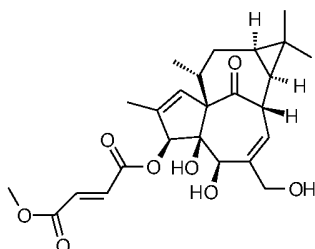
**Example 112:****Ingenol 3-(phenyl-acetate) (Compound 112)**

Compound 112 was prepared according to Procedure e.

15 Starting material: Compound 212.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.25 (m, 5H), 6.00-5.98 (m, 2H), 5.53 (s, 1H), 4.16-4.00 (m, 3H), 3.94 (s, 1H), 3.72 (s, 2H), 3.14 (bs, 1H), 2.3-1.9 (bs, 1H), 2.23-2.18 (m, 1H), 2.09-1.99 (m, 1H), 1.74 (d, 3H), 1.69-1.59 (m, 1H), 1.27 (bs, 1H), 1.05 (s, 6H), 0.93-0.85 (m, 4H), 0.70-0.62 (m, 1H).

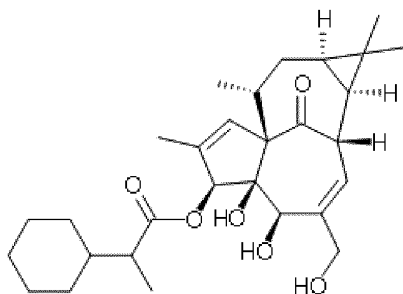
20

**Example 113:****Ingenol 3-(2Z-(methoxycarbonyl))-acrylate (Compound 113)**

Compound 113 was prepared according to Procedure e.

Starting material: Compound 213.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.95 (d, 1H), 6.88 (d, 1H), 6.09 (m, 1H), 6.05 (d, 1H), 5.65 (s, 1H), 4.54 (d, 1H), 4.20-4.13 (m, 3H), 4.05 (d, 1H), 3.83 (s, 3H), 3.57 (s, 1H), 2.54-2.43 (m, 2H), 2.31-2.22 (m, 1H), 1.81-1.72 (m, 4H), 1.07 (s, 3H), 1.05 (s, 3H), 0.97 (d, 3H), 0.95-0.89 (m, 1H), 0.74-0.65 (m, 1H).



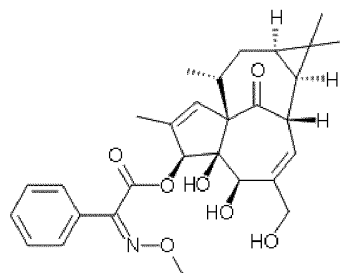
**Example 114:**

**Ingenol 3-(2-cyclohexylpropanoate) (Compound 114)**

Compound 114 was prepared according to Procedure e.

Starting material: Compound 214.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.06-6.02 (m, 2H), 5.46 (d, 1H), 3.32 (t, 1H), 4.19-4.11 (m, 3H), 4.04-4.03 (m, 1H), 3.52 (s, 1H), 2.55-2.47 (m, 1H), 2.39-2.23 (m, 2H), 1.80-1.60 (m, 10H), 1.30-0.86 (m, 19H), 0.73-0.65 (m, 1H).



**Example 115:**

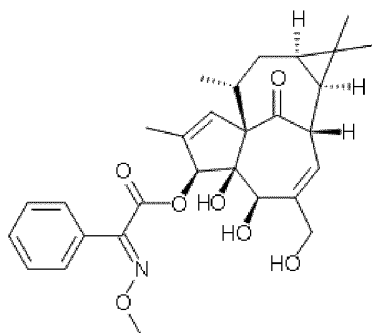
**Ingenol 3-((2Z)-2-methoxyimino-2-phenyl-acetate) (Compound 115)**

Compound 115 was prepared according to Procedure e.

Starting material: Compound 215.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70-7.66 (m, 2H), 7.45-7.38 (m, 3H), 6.12-6.11 (m, 1H), 6.09 (s, 1H), 6.07-6.05 (m, 1H), 4.22-4.12 (m, 4H), 4.07 (s, 3H), 4.00 (d, 1H), 3.58 (d, 1H), 2.41-2.36 (m, 1H), 2.29-2.18 (m, 2H), 1.83 (d, 3H), 1.80-1.73 (m, 1H), 1.12 (s, 3H), 1.07 (s, 3H), 0.96-0.86 (m, 4H), 0.75-0.67 (m, 1H).



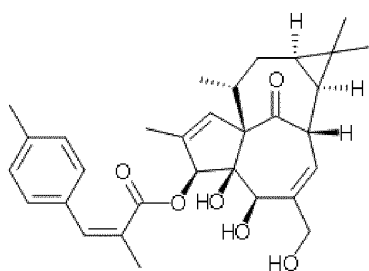
**Example 116:****Ingenol 3-((2E)-2-methoxyimino-2-phenyl-acetate) (Compound 116)**

Compound 116 was prepared according to Procedure e.

5 Starting material: Compound 216.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70-7.66 (m, 2H), 7.45-7.38 (m, 3H), 6.12-6.05 (m, 3H), 4.22-4.09 (m, 4H), 4.07 (s, 3H), 4.00 (d, 1H), 3.60 (d, 1H), 2.41-2.36 (m, 1H), 2.29-2.20 (m, 2H), 1.83 (d, 3H), 1.80-1.73 (m, 1H), 1.12 (s, 3H), 1.07 (s, 3H), 0.99-0.92 (m, 4H), 0.75-0.67 (m, 1H).

10

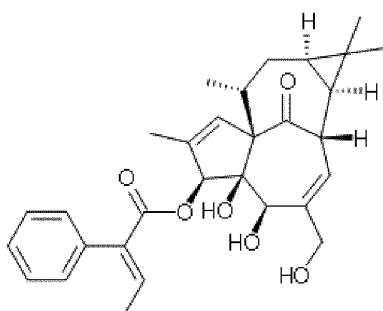
**Example 117:****Ingenol 3-((Z)-2-methyl-3-(p-tolyl)prop-2-enoate) (Compound 117)**

Compound 117 was prepared according to Procedure e.

15 Starting material: Compound 217.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (s, 1H), 7.32 (d, 2H), 7.21 (d, 2H), 6.07-6.05 (m, 2H), 5.60 (s, 1H), 4.44 (d, 1H), 4.17-4.08 (m, 4H), 3.55 (s, 1H), 2.61-2.49 (m, 2H), 2.38 (s, 3H), 2.31-2.23 (m, 1H), 2.15 (d, 3H), 1.83 (d, 3H), 1.80-1.73 (m, 1H), 1.09 (s, 3H), 1.04 (s, 3H), 1.01 (d, 3H), 0.98-0.92 (m, 1H), 0.74-0.66 (m, 1H).

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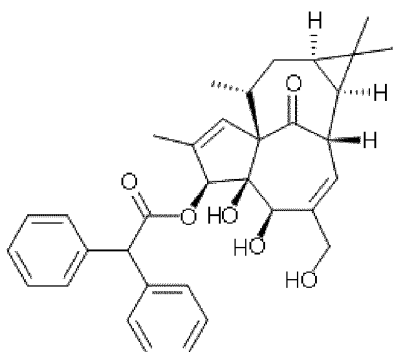
**Example 118:****Ingenol 3-((E)-2-phenylbut-2-enoate) (Compound 118)**

Compound 118 was prepared according to Procedure e.

5 Starting material: Compound 218.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39-7.30 (m, 3H), 7.24 (q, 1H), 7.20-7.15 (m, 2H), 5.99-5.96 (m, 1H), 5.95-5.93 (m, 1H), 5.57 (s, 1H), 4.16-3.93 (m, 4H), 3.80 (d, 1H), 3.19 (s, 1H), 2.34 (t, 1H), 1.95-1.83 (m, 2H), 1.78 (s, 3H), 1.77 (d, 3H), 1.57-1.46 (m, 1H), 1.05 (s, 3H), 1.04 (s, 3H), 0.93-0.85 (m, 1H), 0.76 (d, 3H), 0.65-0.58 (m, 1H).

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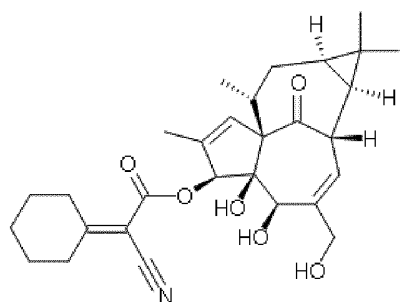
**Example 119:****Ingenol 3-(2,2-diphenylacetate) (Compound 119)**

Compound 119 was prepared according to Procedure e.

15 Starting material: Compound 219.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.25 (m, 10H), 6.01-5.96 (m, 2H), 5.62 (s, 1H), 5.12 (s, 1H), 4.13-3.93 (m, 5H), 3.14 (s, 1H), 2.34 (t, 1H), 2.12-2.05 (m, 1H), 2.04-1.93 (m, 1H), 1.72 (d, 3H), 1.61-1.52 (m, 1H), 1.05 (s, 3H), 1.04 (s, 3H), 0.91-0.83 (m, 4H), 0.67-0.59 (m, 1H).

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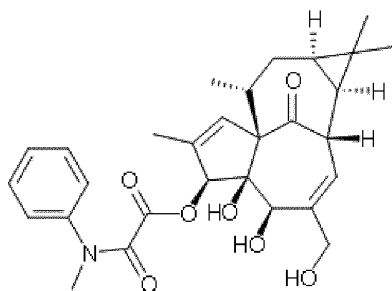
**Example 120:****Ingenol 3-(2-cyano-2-cyclohexylidene-acetate) (Compound 120)**

Compound 120 was prepared according to Procedure e.

5 Starting material: Compound 220.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.12-6.10 (m, 1H), 6.08-6.06 (m, 1H), 5.67 (s, 1H), 4.20-4.02 (m, 5H), 3.56 (s, 1H), 3.02 (t, 2H), 2.71-2.63 (m, 3H), 2.32-2.23 (m, 1H), 2.13-2.08 (m, 1H), 1.85-1.65 (m, 10H), 1.09 (s, 3H), 1.06 (s, 3H), 1.00 (d, 3H), 0.96-0.88 (m, 1H), 0.75-0.67 (m, 1H).

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**Example 121:****Ingenol 3-(2-(methyl(phenyl)amino)-2-oxo-acetate) (Compound 121)**

Compound 121 was prepared according to Procedure e.

15 Starting material: Compound 221.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43-7.33 (m, 3H), 7.28-7.24 (m, 2H), 6.00-5.98 (m, 2H), 5.52 (s, 1H), 4.16-4.02 (m, 3H), 3.84 (s, 2H), 3.37 (s, 3H), 3.29 (s, 1H), 2.38-2.32 (m, 2H), 2.24-2.14 (m, 1H), 1.81-1.69 (m, 1H), 1.50 (d, 3H), 1.08 (s, 3H), 1.06 (s, 3H), 0.96 (d, 3H), 0.93-0.87 (m, 1H), 0.73-0.65 (m, 1H).

20

**Example 1****Neutrophil oxidative burst assay:**

PMN's (polymorphonuclear leukocytes) were isolated and purified from fresh buffy coats by sequential sedimentation, density centrifugation and lysis of contaminating erythrocytes. Buffy coats were incubated with 2% methocel for 30-45 min to

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differentially sediment red blood cells. The leukocyte-rich supernatant was transferred to lymphoprep tubes to remove mononuclear cells by density centrifugation (400×g, 30 min). The pellet was resuspended and any remaining erythrocytes lysed using 0.2% NaCl for 30 sec before restoring isotonicity by the addition of 1.2% NaCl. This step was repeated until the cell pellet appears relatively free of red blood cells. Cells were resuspended in DPBS (Dulbecco's Phosphate Buffered Saline) (w.o.  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ) and the concentration adjusted to  $1.4 \times 10^6$  cells/ml in HBSS (Hanks Balanced Salt solution) (w  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ) containing 0.1% BSA (Bovine Serum Albumin) and 5mM glucose just prior to assay initiation. Titrated reference and test compounds were pre-mixed with HE (Hydroethidine) (10µM final assay concentration) before addition to 96-well plates containing  $2.5 \times 10^5$  cells. Following 40 min incubation at RT, changes in the respiratory burst was estimated by measuring fluorescence at 579 nm (excitation: 485 nm) using an Envision plate reader.

Test compound titration curves were fitted to a four-parameter sigmoidal curve after normalizing the effect of the test compound to the effect of the positive control ( $5 \times 10^{-7}$  M PEP0005). Rel  $\text{EC}_{50}$  denotes the concentration of test compound producing an effect that is midway between the fitted top and bottom. Abs  $\text{EC}_{50}$  is the concentration of test compound that provokes a response corresponding to 50% of the maximal effect associated with the positive control ( $5 \times 10^{-7}$  M PEP0005).

## Example 2

### HeKa cytokine release (IL-8) assay:

Primary human epidermal keratinocytes, HeKa, were seeded (10.000 cells/well) in 96-well plates the day before the assay. Test compounds were diluted in DMSO (dimethyl sulfoxide) and further diluted in assay medium and pipetted into wells of 96 well-plates containing HeKa cells. The plates were incubated for 6h at 37°C in humidified air with 5%  $\text{CO}_2$ . Plates were centrifuged briefly to spin down cells at 4°C, the supernatant was removed and analysed by Meso Scale Discovery (MSD) 4-spot cytokine assay (Pro-inflammatory II Ultra Sensitive kit, MSD, MD, USA). The MSD assay employs a sandwich immunoassay format where capture antibodies are coated in a patterned array on the bottom of the wells of a 4-Spot- Multi-MSD plate. Standard samples were incubated in the MULTI-SPOT plates as well, and the cytokine (IL-8) binds to its corresponding capture antibody spot. The cytokine level was quantitated on a SECTOR™ Imager using a cytokine-specific Detection Antibody labelled with MSD SULFO-TAG™ reagent.

Test compound titration curves were fitted to a four-parameter sigmoidal curve after normalizing the effect of the test compound to the effect of the positive control ( $1.5 \times 10^{-7}$  M PEP0005). Rel EC<sub>50</sub> denotes the concentration of test compound producing an effect that is midway between the fitted top and bottom. Abs EC<sub>50</sub> is the concentration of test compound that provokes a response corresponding to 50% of the maximal effect associated with the positive control ( $1.5 \times 10^{-7}$  M PEP0005).

### Example 3

#### Necrosis Assay

HeLa cells (ATCC CCL-002) were grown in minimal essential medium (Invitrogen catalog no. 42360) containing 10% fetal bovine serum, 100IU/ml penicillin and 100µg/ml streptomycin. 4,000-6,000 cells were seeded into 96-well black ViewPlates-plates, clear bottom, (Perkin Elmer) in 100µl medium and incubated overnight. Compounds were dissolved and pre-diluted in DMSO in 96-well polypropylene plates (Greiner) in a concentration range of 15µM to 600µM. At the time of the experiment cell plates were placed on heating blocks at 37°C, medium was removed and 40µl fresh, pre-warmed medium was added per well. Cells were incubated for 15 min before addition of compounds. In parallel, 3µl of compounds were diluted with 197µl growth medium on a Tecan freedom-EVO pipetting station using 250µl/s pipetting speed, in order to ensure effective mixing of the highly concentrated compound solutions with the aqueous phase. These pre-dilution plates were then equilibrated on heating blocks at 37°C for 10min. 80µl pre-diluted compound were transferred manually to the corresponding wells containing HeLa cells yielding compound concentrations of 10µM to 400µM. Control conditions were 1% DMSO in growth medium (100% viability) and 400µM ingenol mebutate in growth medium (0% viability). Plates were incubated on the heating blocks at 37°C for 30min. At the end of the incubation 10µl PrestoBlue reagent (Invitrogen) were added to each well, plates were sealed with black seal, followed by incubation at 37°C for 10min with gentle shaking (150rpm). Subsequently, plates were placed at room temperature for 20-30min. Plates were read immediately after on an Envision Fluorescence reader (Perkin Elmer) with excitation at 535nm and emission at 630nm. Test compound titration curves were fitted to a four-parameter sigmoidal curve after normalizing the effect of the test compound to the effect of the positive control ( $4 \times 10^{-4}$  M PEP0005/ingenol mebutate). AbsEC<sub>50</sub> denotes the concentration of test compound producing 50% effect.

Compounds of the present invention were tested in the neutrophil oxidative burst assay according to the description in example 1, in the HeKa cytokine release assay according

to the description in example 2 and in the necrosis assay according to the description in example 3.

#### Neutrophil oxidative burst Rel EC<sub>50</sub> ranges

- 5 \* indicates that Rel EC<sub>50</sub> values are  $\geq 100$  nM  
 \*\* indicates that Rel EC<sub>50</sub> values are  $\geq 20$  nM and  $< 100$  nM  
 \*\*\* indicates that Rel EC<sub>50</sub> values are  $< 20$  nM

#### HeKa cytokine release (IL-8) Rel EC<sub>50</sub> ranges

- 10 \* indicates that Rel EC<sub>50</sub> values are  $\geq 100$  nM  
 \*\* indicates that Rel EC<sub>50</sub> values are  $\geq 20$  nM and  $< 100$  nM  
 \*\*\* indicates that Rel EC<sub>50</sub> values are  $< 20$  nM

#### HeLa Necrosis EC<sub>50</sub> ranges

- 15 \* indicates that EC<sub>50</sub> values are  $\geq 350$   $\mu$ M  
 \*\* indicates that EC<sub>50</sub> values are  $\geq 150$   $\mu$ M and  $< 350$   $\mu$ M  
 \*\*\* indicates that EC<sub>50</sub> values are  $< 150$   $\mu$ M

Compound name and number	Neutrophil oxidative burst Rel EC <sub>50</sub> range	HeKa cytokine release (IL-8) Rel EC <sub>50</sub> range	HeLa Necrosis EC <sub>50</sub> range
Ingenol 3-(2-methyl-acrylate) (Compound 101)	***	*	**
Ingenol 3-(3-methyl-butenate) (Compound 102)	***	**	**
Ingenol 3-(2,3-dimethyl-butenate) (Compound 103)	***	***	**
Ingenol 3-(2-methylene-butyrate) (Compound 104)	***	**	**
Ingenol 3-(2-methyl-propanoate) (Compound 105)	***	**	-
Ingenol 3-(3-methyl-butanoate) (Compound 106)	***	**	-
Ingenol 3-( <i>RS</i> -2-methyl-butanoate)	***	**	-

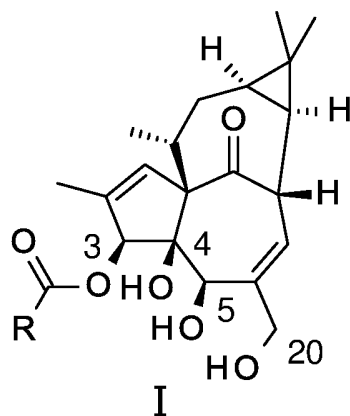
(Compound 107a and Compound 107b)			
Ingenol 3-(3,3-dimethyl-butanoate) (Compound 108)	***	**	**
Ingenol 3-(2-ethyl-butanoate) (Compound 109)	***	***	**
Ingenol 3-(2 <i>R</i> -methyl-butanoate) (Compound 110)	***	**	-
Ingenol 3-tiglate (Compound 111)	***	**	*
Ingenol 3-(phenyl-acetate) (Compound 112)	***	*	**
Ingenol 3-(2 <i>Z</i> -(methoxycarbonyl)- acrylate (Compound 113)	*	-	-
Ingenol 3-(2-cyclohexylpropanoate) (Compound 114)	***	***	**
Ingenol 3-((2 <i>Z</i> )-2-methoxyimino-2- phenyl-acetate) (Compound 115)	**	***	***
Ingenol 3-((2 <i>E</i> )-2-methoxyimino-2- phenyl-acetate) (Compound 116)	**	**	-
Ingenol 3-(( <i>Z</i> )-2-methyl-3-( <i>p</i> - tolyl)prop-2-enoate) (Compound 117)	***	***	***
Ingenol 3-(( <i>E</i> )-2-phenylbut-2- enoate) (Compound 118)	***	***	***
Ingenol 3-(2,2-diphenylacetate) (Compound 119)	***	***	***
Ingenol 3-(2-cyano-2- cyclohexylidene-acetate) (Compound 120)	***	*	-
Ingenol 3-(2- (methyl(phenyl)amino)-2-oxo- acetate) (Compound 121)	**	*	*
PEP005, Ingenol-3-angelate	***	***	**





## CLAIMS

1. A compound of the general formula I



wherein R is (C<sub>1</sub>-C<sub>7</sub>)alkyl, (C<sub>2</sub>-C<sub>7</sub>)alkenyl or (C<sub>2</sub>-C<sub>7</sub>)alkynyl; wherein R is substituted one or more times with substituents independently selected from R<sub>1</sub>; wherein R<sub>1</sub> represents

(a) Fluoro, cyano or hydroxy; or

(b) (C<sub>1</sub>-C<sub>4</sub>)alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkylidene each of which may optionally be substituted by one or more substituents independently selected from R<sub>2</sub>, wherein R<sub>2</sub> represents halogen, cyano, hydroxy, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO<sub>2</sub>Rb, -NRaSO<sub>2</sub>NRaRb, -SO<sub>2</sub>NRaRb, -SO<sub>2</sub>Ra, -S(O)Ra, -ORa, -SRa, =N-ORa, =O; or

(c) -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO<sub>2</sub>Rb, -NRaSO<sub>2</sub>NRaRb, -SO<sub>2</sub>NRaRb, -SO<sub>2</sub>Ra, -S(O)Ra, -ORa, -SRa, =N-ORa, -NRaRb or =O;

and wherein

Ra and Rb independently represents hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, cyano(C<sub>1</sub>-C<sub>4</sub>)alkyl or aryl;

and wherein

Rc represents (C<sub>1</sub>-C<sub>4</sub>)alkyl, halo(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl or cyano(C<sub>1</sub>-C<sub>4</sub>)alkyl,

and pharmaceutically acceptable salts, prodrugs, hydrates and solvates thereof;

with the proviso when R1 represents alkyl or alkenyl the combined length of R and R1 does not exceed that of a chain of 7 carbon atoms,

and with the proviso that R and R1 in combination may not be a straight unbranched or unsubstituted alkyl chain or a straight unbranched or unsubstituted alkenyl chain,  
and with the proviso that R, or R and R1 in combination is not *trans*-2-buten-2-yl.

2. A compound according to claim 1, wherein R is substituted by R1 in the alpha- or beta-position relative to the carbonyl-group.

3. A compound according to claim 1 or 2, wherein R is substituted by R1 in the alpha-position relative to the carbonyl-group.

4. A compound according to any of the above claims, wherein R is C<sub>1</sub>-C<sub>7</sub>-alkyl.

5. A compound according to claim 4, wherein R is ethyl, propyl, *tert*-butyl, isopropyl, 2-butyl, 3-pentyl or isobutyl.

6. A compound according to claim 1, wherein R is C<sub>2</sub>-C<sub>7</sub>-alkenyl.

7. A compound according to claim 6 wherein R is propenyl or ethenyl.

8. A compound according to any of the claims 1-7, wherein R1 is C<sub>1</sub>-C<sub>4</sub>-alkyl, aryl, cycloalkyl, cycloalkylidene, =N-ORa, =O, -NRaRb, -COORc or cyano.

9. A compound according to any of the claims 1-8, wherein R1 is ethyl, methyl, phenyl, cyclohexyl, =N-OCH<sub>3</sub>, -N(CH<sub>3</sub>)(C<sub>6</sub>H<sub>5</sub>), -COOCH<sub>3</sub> or cyclohexylidene.

10. A compound according to any of the claims 1-9, wherein R1 is methyl.

11. A compound according to any of the claims 1-10, wherein R2 is methyl.

12. A compound according to any of the claims 1-10, said compound being:

Ingenol 3-(2-methyl-acrylate),

Ingenol 3-(3-methyl-butenate),

Ingenol 3-(2,3-dimethyl-butenate),

Ingenol 3-(2-methylene-butyrate),

- Ingenol 3-(2-methyl-propanoate),  
Ingenol 3-(3-methyl-butanoate),  
Ingenol 3-(2*RS*-methyl-butanoate),  
Ingenol 3-(3,3-dimethyl-butanoate),  
5 Ingenol 3-(2-ethyl-butanoate),  
Ingenol 3-(2*R*-methyl-butanoate),  
Ingenol 3-tiglate,  
Ingenol 3-(phenyl-acetate),  
Ingenol 3-(2*Z*-(methoxycarbonyl)-acrylate),  
10 Ingenol 3-(2-cyclohexylpropanoate),  
Ingenol 3-((2*Z*)-2-methoxyimino-2-phenyl-acetate),  
Ingenol 3-((2*E*)-2-methoxyimino-2-phenyl-acetate),  
Ingenol 3-((*Z*)-2-methyl-3-(*p*-tolyl)prop-2-enoate),  
Ingenol 3-((*E*)-2-phenylbut-2-enoate),  
15 Ingenol 3-(2,2-diphenylacetate),  
Ingenol 3-(2-cyano-2-cyclohexylidene-acetate) or  
Ingenol 3-(2-(methyl(phenyl)amino)-2-oxo-acetate).

and pharmaceutically acceptable salts thereof.

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13. A compound according to any one of claims 1-12, for use as a medicament in therapy.

14. A compound according to any one of claims 1-12 for use in the treatment,  
25 prevention, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia or neoplasia.

15. A compound according to claim 14 wherein the disorder or disease is selected from cutaneous warts, genital warts, actinic keratosis, squamous cell carcinoma (SCC), basal  
30 cell carcinoma (BCC), lentigo maligna, cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia.

16. Use of a compound according to any one of claims 1-12, for the manufacture of a medicament for the treatment, amelioration or prophylaxis of physiological disorders or  
35 diseases associated with hyperplasia or neoplasia.

17. Use according to claim 16 wherein the disorder or disease is selected from cutaneous warts, genital warts, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), lentigo maligna, cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia,

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18. A method of preventing, treating, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia or neoplasia by administration to a subject in need thereof a compound according to any one of claims 1-12.

10

19. The method according to claim 18 wherein the disorder or disease is selected from cutaneous warts, genital warts, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), lentigo maligna, cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia.

15

20. A compound according to any one of claims 1-12 for use in the treatment or amelioration of cosmetic indications.

21. A compound according to claim 20, wherein the cosmetic indication is selected from photodamaged skin or seborrheic keratosis.

20

22. Use of compound according to any one of claims 1-12 for the manufacture of a medicament for the treatment or amelioration of cosmetic indications.

23. The use according to claim 22, wherein the cosmetic indication is selected from photodamaged skin or seborrheic keratosis.

25

24. A method of treatment or amelioration of cosmetic indications by administration to a subject in need thereof a compound according to any one of claims 1-12.

30

25. The method according to claim 24 wherein the cosmetic indication is selected from photodamaged skin or seborrheic keratosis.

26. Use of a compound according to any one of claims 1-12 in the manufacture of a pharmaceutical composition for the treatment or amelioration of a disease, disorder or condition responsive to stimulation of neutrophil oxidative burst.

35

27. Use of a compound according to any one of claims 1-12 in the manufacture of a pharmaceutical composition for the treatment or amelioration of a disease, disorder or condition responsive to stimulation of keratinocyte IL-8 release.

5 28. Use of a compound according to any one of claims 1-12 in the manufacture of a pharmaceutical composition for the treatment or amelioration of a disease, disorder or condition responsive to induction of necrosis.

10 29. A method of preventing, treating, amelioration or prophylaxis of physiological disorders or diseases responsive to stimulation of neutrophil oxidative burst by administration to a subject in need thereof a compound according to any one of claims 1-12.

15 30. A method of preventing, treating, amelioration or prophylaxis of physiological disorders or diseases responsive to stimulation of of keratinocyte IL-8 release by administration to a subject in need thereof a compound according to any one of claims 1-12.

20 31. A method of preventing, treating, amelioration or prophylaxis of physiological disorders or diseases responsive to responsive to induction of necrosis by administration to a subject in need thereof a compound according to any one of claims 1-12.

25 32. A compound according to any one of claims 1-12 for use in the treatment or amelioration of a disease, disorder or condition responsive to stimulation of neutrophil oxidative burst.

30 33. A compound according to any one of claims 1-12 for use in the treatment or amelioration of a disease, disorder or condition responsive to stimulation of keratinocyte IL-8 release.

34. A compound according to any one of claims 1-12 for use in the treatment or amelioration of a disease, disorder or condition responsive to induction of necrosis.

35 35. A pharmaceutical composition comprising a compound according to any one of claims 1-12 or a pharmaceutically acceptable stereoisomer, salt or in vivo hydrolysable ester thereof together with a pharmaceutically acceptable vehicle or excipient.

36. A pharmaceutical composition according to claim 35, wherein the composition is suitable for topical administration.

5 37. A pharmaceutical composition comprising a compound according to any one of claims 1-12 or a pharmaceutically acceptable stereoisomer, salt or in vivo hydrolysable ester thereof in combination with one or more other therapeutically active agents.

# INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/073759

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> INV. C07C69/54 C07C235/16 C07C251/48 C07C255/23 A61K31/215 A61K31/216 A61K31/22 A61K31/277 A61P35/00 ADD. According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) C07C Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CA 2 541 903 A1 (PEPLIN RESEARCH PTY LTD [AU]) 20 October 2007 (2007-10-20) page 30, lines 20-25; claims 4-8,11-16,18-20 -----	1-37
E	WO 2012/010172 A1 (LEO PHARMA AS [DK]; HOEGBERG THOMAS [SE]; GRUE-SOERENSEN GUNNAR [DK];) 26 January 2012 (2012-01-26) Page 34, line 2; page 39, line 35 to page 40, line 10; the formulae at the top of page 58. -----	1,12
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* 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 document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step 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 11 April 2012		Date of mailing of the international search report 24/04/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Cooper, Simon

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/073759

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CA 2541903	A1	20-10-2007	NONE
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WO 2012010172	A1	26-01-2012	NONE
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