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(54) Title: 3-ALKYLAMIDO-3-DEOXY-INGENOLS

(57) Abstract: wherein R1 is selected from the group consisting of hydrogen, methyl and ethyl; wherein R2 and R3 each independently are selected from the group consisting of hydrogen and (C1-C6)alkyl or wherein R2 and R3, together with the carbon atom to which they are attached form a (C1-C6)cycloalkyl or a 4-7 membered heterocycloalkyl, said (C1-C6)cycloalkyl or 4-7 membered heterocycloalkyl optionally being substituted with one or more substituents independently selected from R4; wherein R4 represents the group consisting of (C1-C6)alkyl; wherein X is a bond, -O-, or -(CH2)n, wherein n is 1 or 2; wherein R2 is selected from the group consisting of phenyl or (C1-C6)alkyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from R5; wherein R5 represents the group consisting of halogen, cyano, halo(C1-C6)alkyl, (C1-C6)alkoxy, halo(C1-C6)alkoxy; or pharmaceutically acceptable salts, hydrates, or solvates thereof. The invention relates to said compounds for use in therapy, to pharmaceutical compositions comprising said compounds, to methods of treating diseases with said compounds, and to intermediates for the preparation of said compounds.
3-Alkylamido-3-deoxy-ingenols

FIELD OF THE INVENTION
This invention relates to novel 3-alkylamido-3-deoxy-ingenols and derivatives thereof, to intermediates for the preparation thereof, to said compounds for use in therapy, to pharmaceutical compositions comprising said compounds and to methods of treating diseases with said compounds.

BACKGROUND OF THE INVENTION
Ingenol-3-angelate (PEP005, ingenol mebutate, contained in Picato®) is a diterpene-ester of the ingenol family which is isolated from various Euphorbia species, particularly from Euphorbia peplus. Picato® is marketed for the treatment of actinic keratosis and is subject for clinical development for the treatment of non-melanoma skin cancer, squamous cell carcinoma and genital warts.


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.

WO2012085189 disclose aliphatic ingenol-3-acylates.

WO2012083954 disclose carbocyclic ingenol-3-acylates.

WO2012083953 disclose heterocyclic ingenol-3-acylates and ingenol-3-carbamates.

WO2014001215 disclose 3-O-heteroaryl ingenols.

mebutate analogues.

3-benzoates.

There is a continuous need to find new ingenol derivatives which induce cell death by
cytotoxicity or apoptosis and / or induce an immunostimulatory effect.

SUMMARY OF THE INVENTION
It has surprisingly been found that certain 3-alkylamido-3-deoxy-ingenol derivatives exhibit properties which make them 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.

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

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

Compounds of the present invention induce rapid necrosis.

Compounds of the present invention exhibit favorable stability properties.
Compounds of the present invention may have improved pharmacokinetic and pharmacodynamic properties in comparison with known structurally related compounds.

Accordingly, the present invention relates to a compound according to formula I

![Chemical Structure](image)

wherein R1 is selected from the group consisting of hydrogen, methyl and ethyl;

wherein R2 and R3 each independently are selected from the group consisting of hydrogen and (Cl-C₄)alkyl or wherein R2 and R3 together with the carbon atom to which they are attached form a (C₃-C₆)cycloalkyl or a 4-7 membered heterocycloalkyl, said (C₃-C₆)cycloalkyl or 4-7 membered heterocycloalkyl optionally being substituted with one or more substituents independently selected from R₅;

wherein R₅ represents the group consisting of (Cl-C₄)alkyl;

wherein X is a bond, -0-, or -(CH₂)ₙ- wherein n is 1 or 2;

wherein R₄ is selected from the group consisting of phenyl or (Cl-C₄)alkyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from R₆;

wherein R₆ represents the group consisting of halogen, cyano, halo(Cl-C₄)alkyl, (Cl-C₄)alkoxy, halo(Cl-C₄)alkoxy;

or pharmaceutically acceptable salts, hydrates or solvates thereof;

with the proviso that if one of R₂ or R₃ is hydrogen the other R₂ or R₃ is not hydrogen;

and with the proviso that if R₄ is (Cl-C₄)alkyl both R₂ and R₃ are different from hydrogen.

In another aspect, the invention relates to a compound according to formula I as defined above for use as a medicament.
In yet another aspect, the invention relates to a compound according to formula I as defined above for use in treatment of physiological disorders or diseases associated with hyperplasia or neoplasia.

In yet another aspect, the invention relates to a compound according to formula I as defined above together with a pharmaceutically acceptable vehicle or excipient or pharmaceutically acceptable carrier(s).

In yet another aspect, the invention relates to an intermediate for the preparation of a compound according to formula I as defined above, selected from 5,20-Acetonide-3-(S)-azido-3-deoxy-ingenol; 5,20-Acetonide-3-(S)-amino-3-deoxy-ingenol and 3-(S)-Amino-3-deoxy-ingenol.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "alkyl" is intended to indicate a radical obtained when one hydrogen atom is removed from a branched or linear hydrocarbon. Said alkyl comprises 1-6, preferably 1-4, such as 1-3, such as 2-3 or such as 1-2 carbon atoms. The term includes the subclasses normal alkyl (n-alkyl), secondary and tertiary alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert.-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl and isohexyl.

The terms "alkyloxy" and "alkoxy" are intended to indicate a radical of the formula -OR', wherein R' is alkyl as indicated herein, wherein the alkyl group is appended to the parent molecular moiety through an oxygen atom, e.g. methoxy (-OCH₃), ethoxy (-OCH₂CH₃), n-propoxy, isoproxy, butoxy, tert-butoxy, and the like.

The term "cyano" is intended to indicate a -CN group attached to the parent molecular moiety through the carbon atom.

The term "cycloalkyl" is intended to indicate a saturated cycloalkane hydrocarbon radical, including polycyclic radicals such as bicyclic or tricyclic radicals, comprising 3-10 carbon atoms, preferably 3-8 carbon atoms, such as 3-6 carbon atoms, such as 3-5 carbon atoms or such as 3-4 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.
The term "haloalkyl" is intended to indicate an alkyl group as defined herein substituted
with one or more halogen atoms as defined herein, e.g. fluoro or chloro, such as
difluoromethyl or trifluoromethyl.

The terms "haloalkyloxy" and "haloalkoxy" are intended to indicate a haloalkyl group as
defined herein which is appended to the parent molecular moiety through an oxygen
atom, such as difluoromethoxy or trifluoromethoxy.

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

The term "heterocycloalkyl" is intended to indicate a cycloalkane radical as described
herein, wherein one or more carbon atoms are replaced by heteroatoms, comprising 1-6
carbon atoms, e.g. 2-5 or 2-4 carbon atoms, further comprising 1-6 heteroatoms,
preferrably 1, 2, or 3 heteroatoms, selected from O, N, or S. Representative examples of
heterocycloalkyl groups include, but are not limited to azepanyl, azetidinyl, aziridinyl,
dioxolanyl, dioxynyl, imidazolidinyl, morpholinyl, oxetanyl, piperazinyl, piperidinyl,
pyrrolidinyl, quinoxalinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl,
tetrahydrothiopyranyl, thietylanyl.

The term "4-7 membered heterocycloalkyl" is intended to indicate a "heterocycloalkyl"
as described herein comprising 4-7 ring atoms independently selected from C, O, N or S.

The term "hydrocarbon radical" is intended to indicate a radical containing only hydrogen
and carbon atoms and it may comprise cyclic moieties in combination with branched or
linear moieties. Said hydrocarbon comprises 1-7 carbon atoms, e.g. 3-6, e.g. 1-4, e.g.
1-3, e.g. 1-2 carbon atoms. The term includes alkyl and cycloalkyl as indicated herein.

In some instances, the number of carbon atoms in a hydrocarbon radical is indicated by
the prefix "(C_a-C_b)" in which a is the minimum number and b is the maximum number of
carbons in the hydrocarbon radical. Thus, for example (C_1-C_4)alkyl is intended to indicate
an alkyl radical comprising from 1 to 4 carbon atoms, and (C_3-C_6)cycloalkyl is intended
to indicate a cycloalkyl radical comprising from 3 to 6 carbon ring atoms.

The term "oxo" is intended to indicate an oxygen atom which is connected to the parent
molecular moiety via a double bond (=0).
When two or more of the above defined terms are used in combination, such as aryalkyl, heteroaryalkyl, cycloalkylalkyl and the like, it is to be understood that the first mentioned radical is a substituent on the latter mentioned radical, where the point of attachment to the parent molecular moiety is on the latter radical.

The group C(O) is intended to represent a carbonyl group (C=0).

The term "pharmaceutically acceptable salt" is intended to indicate salts prepared by reacting a compound of formula I, which comprise a basic moiety, with a suitable inorganic or organic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, phosphoric, formic, acetic, 2,2-dichloroacetic, adipic, ascorbic, L-aspartic, L-glutamic, galactaric, lactic, maleic, L-malic, phthalic, citric, propionic, benzoic, glutaric, gluconic, D-glucuronic, methanesulfonylic, 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, silver hydroxide, ammonia or the like, or suitable non-toxic amines, such as lower alkylamines, hydroxy-lower alkylamines, cycloalkylamines, or benzylamines, or L-arginine or L-lysine.

Further examples of pharmaceutical acceptable salts are listed in Berge, S.M.; J. Pharm. Sci.; (1977), 66(1), 1-19, which is incorporated herein by reference.

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 crystalline form. When water is the solvent, said species is referred to as a hydrate.

The term "treatment" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the amelioration, alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The term may also include prevention of the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. Nonetheless, prophylactic (preventive) and therapeutic (curative) treatments are two separate aspects.
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), 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.

Unless otherwise indicated, all exact values provided herein are representative of corresponding approximate values, e.g. exact exemplary values provided with respect to a particular measurement can be considered to also provide a corresponding approximate measurement, modified by "about" where appropriate.

All references, including publications, patent applications and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference, regardless of any separately provided incorporation of particular documents made elsewhere herein.

**Embodiments of the invention**

In one or more embodiments the invention provides a compound of general formula I wherein R₄ is phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from R₆.

In one or more embodiments the invention provides a compound of general formula I wherein X is a bond or -O-.

In one or more embodiments the invention provides a compound of general formula I wherein R₆ represents halogen.
In one or more embodiments the invention provides a compound of general formula I wherein \( R_2 \) and \( R_3 \) each independently are selected from \((C_1-C_4)\)alkyl.

In one or more embodiments the invention provides a compound of general formula I wherein \( R_2 \) and \( R_3 \) together with the carbon atom to which they are attached form a \((C_3-C_6)\)cycloalkyl or a 4-7 membered heterocycloalkyl, said \((C_3-C_6)\)cycloalkyl or 4-7 membered heterocycloalkyl optionally being substituted with one or more substituents independently selected from \( R_5 \).

In one or more embodiments the invention provides a compound of general formula I selected from N-(2-(4-Chlorophenyl)-2-methylpropanoyl)-3-(S)-amino-3-deoxy-ingenol, N-(l-(4-Fluorophenyl)cyclopropanylcarbonyl)-3-(S)-amino-3-deoxy-, N-(2-Methyl-2-phenoxy-propanoyl)-3-(S)-amino-3-deoxy-ingenol, N-(2,2-Dimethylpentanoyl)-3-(S)-amino-3-deoxy-ingenol, N-((2R)-2-Benzyl pyrrolidin-2-yl-carbonyl)-3-(S)-amino-3-deoxy-ingenol, and N-((2R)-2-benzyl-1-methyl-pyrrolidin-2-yl-carbonyl)-3-(S)-amino-3-deoxy-ingenol or pharmaceutically acceptable salts, hydrates or solvates thereof.

In one or more embodiments the invention provides a compound of general formula I wherein \( R_1 \) represents hydrogen or methyl.

In one or more embodiments the invention provides a compound of general formula I wherein \( R_2 \) and \( R_3 \) each represents methyl.

In one or more embodiments the invention provides a compound of general formula I wherein \( R_2 \) represents methyl.

In one or more embodiments the invention provides a compound of general formula I wherein \( R_3 \) represents methyl.

In one or more embodiments the invention provides a compound of general formula I wherein \( R_2 \) and \( R_3 \) together with the carbon atom to which they are attached form cyclopropyl or pyrrolidinyl.
In one or more embodiments the invention provides a compound of general formula I
wherein $R_5$ represents methyl.

In one or more embodiments the invention provides a compound of general formula I
wherein $R_6$ represents fluoro or chloro.

Any combination of two or more embodiments described herein is considered within the
scope of the present invention.

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 forms, such as
polymorphs and pseudopolymorphs, and also mixtures thereof.

Compounds of formula I may or may not comprise asymmetrically substituted (chiral)
carbon atoms besides the ones present in the ingenol-core which give rise to the
existence of isomeric forms, e.g. enantiomers and possibly diastereomers. The present
invention relates to all such isomers, either in optically pure form or as mixtures thereof
(e.g. racemic mixtures or partially purified optical mixtures). Pure stereoisomeric forms
of the compounds and the intermediates of this invention may be obtained by the
application of procedures known in the art. The various isomeric forms may be separated
by physical separation methods such as selective crystallization and chromatographic
techniques, e.g. high pressure liquid chromatography using chiral stationary phases.
Enantiomers may be separated from each other by selective crystallization of their
diastereomeric salts which may be formed with optically active acids. Optically purified
compounds may subsequently be liberated from said purified diastereomeric salts.
Enantiomers may also be resolved by the formation of diastereomeric derivatives.
Alternatively, enantiomers may be separated by chromatographic techniques using chiral
stationary phases. Pure stereoisomeric forms may also be derived from the
 corresponding pure stereoisomeric forms of the appropriate starting materials, provided
that the reaction occur stereoselectively or stereospecifically. Preferably, if a specific
stereoisomer is desired, said compound will be synthesized by stereoselective or
stereospecific methods of preparation. These methods will advantageously employ chiral
pure starting materials.
Furthermore, when a double bond or a fully or partially saturated ring system is present
in the molecule geometric isomers may be formed. It is intended that any geometric
isomer, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention.

In the compounds of general Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of general Formula I. For example, different isotopic forms of hydrogen include \(^1\)H, \(^2\)H and \(^3\)H and different isotopic forms of carbon include \(^12\)C, \(^13\)C and \(^14\)C. Enriching for deuterium (\(^2\)H) may for example increase in-vivo half-life or reduce dosage regimens, or may provide a compound useful as a standard for characterization of biological samples. Isotopically enriched compounds within general formula I can be prepared by conventional techniques well known to a person skilled in the art or by processes analogous to those described in the general procedures and examples herein using appropriate isotopically enriched reagents and/or intermediates.

In one or more embodiments of the present invention, the compounds of formula I as defined above, optionally in combination with other active compounds, may be useful in therapy and in particular useful for treatment of cutaneous warts, genital warts, actinic keratosis, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), lentigo maligna, cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia.

Besides being useful for human treatment, the compounds of the present invention may also be useful for veterinary treatment of animals including mammals such as horses, cattle, sheep, pigs, dogs, and cats.

Pharmaceutical Compositions of the Invention

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, optionally together with one or more other therapeutically active compound(s), together with a pharmaceutically acceptable excipient, vehicle or carrier(s). 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.
Conveniently, the active ingredient comprises from 0.0001-99.9% by weight of the formulation.

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 0.001 mg and 1000 mg, preferably between 0.01 mg and 100 mg, such as 0.1-50 mg of a compound of formula I. 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 parenterally, topically, transdermally or interdermally + other routes according to different dosing schedules, e.g. daily, weekly or with monthly intervals. In general a single dose will be in the range from 0.001 to 1 mg/kg body weight. The compound may be administered as a bolus (i.e. the entire daily dosis is administered at once) or in divided doses two or more times a day.

In the context of topical treatment it may be more appropriate to refer to a "usage unit", which denotes a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid, semisolid or liquid pharmaceutical diluents or carriers.

The term "usage unit" in connection with topical use means a unitary, i.e. a single dose, capable of being administered topically to a patient in an application per square centimetre of the treatment area of from 0.001 microgram to 1 mg and preferably from 0.05 microgram to 0.5 mg of the active ingredient in question.

It is also envisaged that in certain treatment regimes, administration with longer intervals, e.g. every other day, every week, or even with longer intervals may be beneficial.

If the treatment involves administration of another therapeutically active compound it is recommended to consult Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., J.G. Hardman and L.E. Limbird (Eds.), McGraw-Hill 1995, for 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.

The formulations include e.g. those in a form suitable for parenteral, transdermal, intradermal or topical administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by but not restricted to any of the methods well known in the art of pharmacy, e.g. as disclosed in Remington, *The Science and Practice of Pharmacy*, 21ed ed., 2005. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier, semisolid carrier or a finely divided solid carrier or combinations of these, and then, if necessary, shaping the product into the desired formulation.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredients, which is preferably isotonic with the blood of the recipient, e.g. isotonic saline, isotonic glucose solution or buffer solution. Furthermore, the formulation may contain cosolvent, solubilising agent and/or complexation agents. The formulation may be conveniently sterilised by for instance filtration through a bacteria retaining filter, addition of sterilising agent to the formulation, irradiation of the formulation or heating of the formulation. Liposomal formulations as disclosed in e.g. Encyclopedia of Pharmaceutical Technology, vol.9, 1994, are also suitable for parenteral administration.

Alternatively, the compounds of formula I may be presented as a sterile, solid preparation, e.g. a freeze-dried powder, which is readily dissolved in a sterile solvent immediately prior to use.

Transdermal formulations may be in the form of a plaster, patch, microneedles, liposomal or nanoparticulate delivery systems or other cutaneous formulations applied to the skin.

Formulations suitable for topical, such as dermal, intradermal or ophthalmic administration include liquid or semi-solid preparations such as liniments, lotions, gels, applicants, sprays, foams, filmforming systems, microneedles, micro- or nano-emulsions,
oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

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%, but may also be present in an amount of up to about 100% of the composition.

In addition to the aforementioned ingredients, the formulations of a compound of formula I may include one or more additional ingredients such as diluents, buffers, flavouring agents, colourant, surface active agents, thickeners, penetration enhancing agents, solubility enhancing agents preservatives, e.g. methyl hydroxy benzoate (including anti-oxidants), emulsifying agents and the like.

When the active ingredient is administered in the form of salts with pharmaceutically acceptable non-toxic acids or bases, preferred salts are for instance easily water-soluble or slightly soluble in water, in order to obtain a particular and appropriate rate of absorption.

**METHODS OF PREPARATION**

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of synthesis. 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 organist chemist, e.g. methods described in "Purification of Laboratory Chemicals", 6th ed. 2009, W. Amarego and C.
Chai, Butterworth-Heinemann. 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.

5 Synthetic routes

Compounds of formula I may for example be prepared according to the following non-limiting general methods:

10 Schemel

Scheme 2

15
The compounds of the general formula f can for example be synthesised according to Scheme 1, 2 or 3.

As depicted in scheme 1, 2 and 3 the protected 3-amino-3-deoxy-ingenol derivative d, j or the unprotected 3-amino-3-deoxy-ingenol derivative e may be transformed to amide derivatives of the general formula f, g or k according to methods for peptide coupling reaction of Amines described in the review, but not limited to, "N-Acylation Reactions of Amines" by J.E. Taylor and S.D. Bull, Comprehensive Organic Synthesis (2nd Edition) (2014), 6, 427-478 and references cited therein. Compound f or g can for example be synthesised by reacting compound e or d with a carboxylic acid derivative and activate it with a peptide coupling agent such as, but not limited to, HATU or TATU. The peptide coupling reaction can take place in a suitable solvent such as dichloromethane or DMF, typically it can take place in the presence of a base such as triethylamine or DIPEA.

Compound f, g or k can for example be synthesised by reacting compound e, d or j with an activated acid derivative, such as an acid halide, such as acid chloride. The amine reaction with acid chloride can take place in a suitable solvent such as dichloromethane, THF 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.
It may be necessary to use a protecting group in the above schemes. These protecting groups can in general be introduced and removed by standard procedures known to a chemist skilled in the art of organic synthesis (see e.g "Protective Groups in Organic Synthesis", 4th ed., 2007, Greene T.W. and Wuts P.G.M., John Wiley & Sons Inc.).

GENERAL PROCEDURES, PREPARATIONS AND EXAMPLES

1H nuclear magnetic resonance (NMR) spectra were recorded at 600 MHz unless otherwise specified. Chemical shift values (δ, in ppm) are quoted relative to internal tetramethylsilane (δ = 0.00) standards. The value of a multiplet, either defined doublet (d), triplet (t), quartet (q) or not (m) at the approximate midpoint is given unless a range is quoted, (br) indicates a broad peak, whilst (s) indicates a singlet. The organic solvents used were usually anhydrous. Chromatography was performed on Merck silica gel 60 (0.040 - 0.063 mm). The solvent ratios indicated refer to v:v unless otherwise noted. All NMR spectra are recorded in DMSO-d6 unless another solvent is stated.

The following abbreviations have been used throughout:

- DCE: dichloroethane
- DCM: dichloromethane
- DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene
- DMF: N,N'-Dimethylformamide
- DMSO: dimethyl sulfoxide
- Et: ethyl
- HATU: (l-[Bis(dimethylamino)methylene]-lH-l,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
- h: hour(s)
- HPLC: High pressure liquid chromatography
- L: litre
- m: milli
- Me: methyl
- MS: Mass spectrometry
- MTBE: Methyl t-butyl ether
- NMR: nuclear magnetic resonance
- rt: room temperature
- RT: Retention Time
- TATU: 0-(7-Azabenzotriazole-l-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
- TFA: trifluoroacetic acid
- THF: tetrahydrofuran
Preparations and Examples

Preparation 1

5,20-Acetonide-3-O-methanesulfonyl-ingenol (Intermediate 1)

Ingenol-5,20-acetonide (10000 mg, 25.74 mmol) was dissolved in 200 mL DCM. Triethylamine was added (3630 mg, 35.9 mmol) and the reaction was stirred under argon. The clear solution was cooled to 0°C. Methanesulfonyl chloride (3833 mg, 33.46 mmol, 2.59 mL) was added slowly. Internal temperature was kept under 5°C. The reaction was monitored by TLC (eluent heptane/EtOAc 2:1). After 30 min. TLC showed that all starting material was consumed. The reaction mixture was poured into a separation funnel with 500 ml MTBE and 500ml saturated NaHCO₃ aq. The organic layer was washed with 500ml (water/aq. sat. NaHCO₃ 1:1) and then with 500ml brine. The organic layer was dried over sodium sulphate, and concentrated in vacuo.

1H NMR (600 MHz, Chloroform-d) δ 6.10 (q, J = 1.5 Hz, 1H), 5.82 (dq, J = 1.7, 3.4 Hz, 1H), 5.26 (s, 1H), 4.22 (ddt, J = 1.5, 3.0, 14.1 Hz, 1H), 4.14 (ddq, J = 1.6, 4.0, 12.8 Hz, 2H), 3.93 (dp, J = 1.2, 2.1 Hz, 1H), 3.47 (s, 1H), 3.4 (s, 3H), 2.60 - 2.48 (m, 1H), 2.26 (ddd, J = 3.1, 8.5, 15.8 Hz, 1H), 1.85 (d, J = 1.6 Hz, 3H), 1.80 (dt, J = 6.0, 15.9 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H), 0.96 (d, J = 7.1 Hz, 3H), 0.93 (dd, J = 8.4, 11.8 Hz, 1H), 0.71 (td, J = 6.2, 8.4 Hz, 1H).

Preparation 2

5,20-Acetonide-3-(S)-azido-3-deoxy-ingenol (Intermediate 2)
Crude intermediate 1 (25.74 mmol, 12010 mg) was dissolved in 100 ml DMF. Sodium azide (7000 mg, 108 mmol) was added and the suspension was stirred at 60°C. The reaction was kept for 16 h at 5°C. The reaction mixture was cooled on an ice bath and water was added slowly. Precipitation was formed. The precipitate was filtered; the solid was washed with water and dried. The solid was dissolved in MTBE and the solution was extracted with brine. The organic phases were dried over sodium sulfate and concentrated in vacuo. The oil was dissolved in 10 ml of MTBE and 110 ml heptane was added. Crystallization started and the mixture was kept at 5°C for 16 h. The product was filtered to afford the title compound, (5.179 g, 48% over two steps).

\[ \text{1H NMR (600 MHz, Chloroform-d)} \]
\[ \delta \text{ 5.93 (q, } J = 1.6 \text{ Hz, 1H), 5.81 (dq, } J = 1.5, 3.4 \text{ Hz, 1H), 4.23 - 4.11 (m, 4H), 3.94 (t, } J = 1.6 \text{ Hz, 1H), 3.31 (s, 1H), 2.54 (dt, } J = 3.0, 6.0, 6.8, 12.2 \text{ Hz, 1H), 2.26 (ddd, } J = 3.1, 8.8, 15.8 \text{ Hz, 1H), 1.83 (d, } J = 1.6 \text{ Hz, 3H), 1.82 - 1.76 (m, 1H), 1.44 (s, 3H), 1.39 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.96 (d, } J = 7.1 \text{ Hz, 3H), 0.91 (dd, } J = 8.4, 11.8 \text{ Hz, 1H), 0.70 (td, } J = 6.3, 8.6 \text{ Hz, 1H).} \]

Preparation 3
5,20-Acetonide-3-(S)-amino-3-deoxy-inganol (Intermediate 3)
Intermediate 2 (3000 mg, 7.26 mmol) and triphenylphosphine (2090 mg, 7.98 mmol) were dissolved in THF (80 ml) at room temperature. Water (20 ml) was added. The reaction mixture was stirred for 72 h. The reaction mixture was poured into a separation funnel with 500 ml MTBE. 500 ml water containing 4 N HCl aq. (14.5 mmol, 3.63 ml) was added. The acidic water layer was separated and poured directly into 150 ml water containing sodium hydroxide (5N, 21.8 mmol, 4.35 ml). A white precipitate was formed. The precipitate was filtered, washed twice with water and dried on filter to afford the title compound as a white solid (2683 mg, 6.924 mmol, 95.4% Yield).

\[ \text{1H NMR (600 MHz, Chloroform-d)} \]
\[ \delta \text{ 5.82 (q, } J = 1.5 \text{ Hz, 1H), 5.73 (dq, } J = 1.8, 3.8 \text{ Hz, 1H), 5.35 (s, 1H), 4.27 (dq, } J = 2.0, 14.0 \text{ Hz, 1H), 4.14 (ddq, } J = 2.3, 4.5, 11.6 \text{ Hz, 1H), 4.07 (ddt, } J = 1.1, 2.0, 13.9 \text{ Hz, 1H), 3.90 - 3.84 (m, 1H), 3.66 (s, 1H), 2.33 (ddd, } J = 3.1, 9.1, 15.6 \text{ Hz, 1H), 2.13 (th, } J = 3.2, 10.2 \text{ Hz, 1H), 1.83 (d, } J = 1.4 \text{ Hz, 3H), 1.73 (ddd, } J = 4.9, 6.3, 15.7 \text{ Hz, 1H), 1.39 (s, 3H), 1.29 (s, 3H), 1.12 (s, 3H), 1.05 (s, } \]
Preparation 4

3-(S)-Amino-3-deoxy-ingenol (Intermediate 4)

Intermediate 3 (840 mg, 2.168 mmol) was dissolved in MeOH (15 mL) and 4N HCl (2.601 mmol, 0.6503 mL) was added. The reaction mixture was stirred at room temperature for 72h. 1.0g potassium carbonate and 10 mL DCM was added and the mixture was stirred for 5 min before filtration. The solution was concentrated in vacuo. The residue was purified by flash chromatography (DCM/MeOH/TEA 97 : 2.5 : 0.5), giving the title compound as a clear oil which turned into a solid upon storage (745 mg, 1.994 mmol, 92.00% Yield).

1H NMR (300 MHz, Chloroform-d) δ 6.06 - 5.99 (m, 1H), 5.84 (q, J = 1.5 Hz, 1H), 4.21 - 4.04 (m, 3H), 3.79 - 3.70 (m, 1H), 3.61 (s, 1H), 2.38 (ddd, J = 3.1, 9.6, 15.7 Hz, 1H), 2.07 - 1.95 (m, 1H), 1.84 (d, J = 0.6, 1.5 Hz, 3H), 1.72 (ddd, J = 4.3, 6.3, 15.6 Hz, 1H), 1.12 (s, 3H), 1.06 (s, 3H), 0.97 - 0.87 (m, 4H), 0.68 (ddd, J = 6.3, 8.4, 9.7 Hz, 1H).

Preparation 5

5,20-Acetonide-N-methyl-N-(4-nitro-benzenesulfonyl)-3-(S)-amino-3-deoxy-ingenol (Intermediate 5)

Step 1: Intermediate 3 (403 mg, 1.040 mmol) was dissolved in DCM (4 mL) and DIPEA (2.080 mmol, 0.370 mL). 4-Nitrobenzenesulfonyl chloride (276.6 mg, 1.248 mmol) was added and the reaction mixture was stirred at room temperature.
After 1 h the reaction mixture was added to a silica column and purified by flash chromatography. The column was eluted with EtOAc/heptane (0-60% EtOAc). Fractions containing product were concentrated in vacuo giving a white solid.

Step 2: The white solid from step 1 was mixed with triphenylphosphine (409.2 mg, 1.560 mmol) and methanol (49.99 mg, 1.560 mmol) and dissolved in THF (7 mL). Diisopropyl azodicarboxylate (DIAD) was added slowly (1.560 mmol, 0.3072 mL). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography (silica): The crude product was added to column dissolved in DCM and eluted with EtOAc/heptane( 0-60% EtOAc) to afford the title compound as a light yellow solid. (549 mg, 90%)

1H NMR (600 MHz, Chloroform-d) δ 8.42 - 8.36 (m, 2H), 8.13 - 8.06 (m, 2H), 6.02 (s, 1H), 5.82 - 5.76 (m, 1H), 4.80 (s, 1H), 4.27 - 4.11 (m, 2H), 4.10 - 4.04 (m, 1H), 3.94 (s, 1H), 3.22 (s, 1H), 2.80 (s, 3H), 2.50 - 2.36 (m, 1H), 2.22 (ddd, J = 3.1, 10.5, 15.8 Hz, 1H), 1.77 - 1.70 (m, 1H), 1.57 (s, 3H), 1.49 (s, 3H), 1.47 (s, 3H), 1.19 (s, 1H), 1.06 (s, 3H), 1.05 (s, 3H), 1.00 (d, J = 7.3 Hz, 3H), 0.87 - 0.84 (m, 1H), 0.69 (ddd, J = 6.2, 8.2, 10.6 Hz, 1H).

Preparation 6

N-Methyl-3-(S)-amino-3-deoxy-ingenol (Intermediate 6)

Intermediate 5 (686 mg, 1.111 mmol) was dissolved in DMF (5 mL) and DBU (338.2 mg, 2.222 mmol). Thiophenol (146.9 mg, 1.333 mmol) was added and the reaction was stirred at room temperature for 4 h. The reaction mixture was taken up in ethyl acetate and extracted with water (x2) and brine (x1). The organic phases were dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (heptane/ethyl acetate 5:1 to heptane/ethyl acetate 0:1) to afford the title compound as a white solid (281 mg, 47.2% Yield).

1H NMR (300 MHz, Chloroform-d) δ 5.75 (q, J = 1.6 Hz, 1H), 5.73 - 5.68 (m, 1H), 4.36 - 4.20 (m, 1H), 4.15 - 4.01 (m, 2H), 3.89 - 3.77 (m, 1H), 3.36 - 3.26 (m, 1H), 2.60 (s, 3H), 2.28 (ddd, J = 3.1, 8.3, 15.6 Hz, 1H), 2.19 - 2.04 (m, 1H), 1.85 (d, J = 0.6, 1.6 Hz, 3H), 1.71 (dt, J = 6.0, 15.6 Hz, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H), 0.92 (dd, 1H), 0.87 (d, 3H), 0.66 (td, J = 6.3, 8.4 Hz, 1H).
General procedure 1; amide formation

Intermediate 4 (1 eq., ca. 0.14 mmol), carboxylic acid (1.1 eq., ca. 0.16 mmol) and HATU (1.2 eq., ca. 0.17 mmol) were combined in a 4 ml vial. DMF (ca. 0.7 ml, 0.2 M of intermediate 4) and DIPEA (3 eq., ca. 0.43 mmol) was added. The reaction was typically stirred at room temperature for 0.15-4h. The reaction mixture was poured into a separation funnel with EtOAc and washed with 0.01N HCl and with 0.01N NaOH. The organic phases were dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/heptane 0-100% EtOAc) to afford the amide.

Example 1
N-(2-(4-Chlorophenyl)-2-methylpropanoyl)-3-(S)-amino-3-deoxy-ingenol (Compound 1)

The title compound was prepared according to general procedure 1 using 2-(4-chlorophenyl)-2-methylpropanoic acid as starting material.

1H NMR (600 MHz, DMSO-d6) δ 7.38 (s, 4H), 6.30 (d, J = 8.7 Hz, 1H), 5.86 (dt, J = 1.9, 6.0 Hz, 1H), 5.52 (d, J = 5.4 Hz, 1H), 5.41 (s, 1H), 4.79 (s, 1H), 4.76 (t, J = 5.5 Hz, 1H), 4.59 - 4.46 (m, 1H), 4.32 (d, J = 8.6 Hz, 1H), 3.89 - 3.81 (m, 2H), 3.49 (d, J = 5.4 Hz, 1H), 2.41 (s, 1H), 2.03 - 1.93 (m, 1H), 1.62 - 1.52 (m, 4H), 1.50 - 1.45 (m, 6H), 1.13 (s, 3H), 0.99 (s, 3H), 0.92 (dd, J = 8.7, 11.2 Hz, 1H), 0.83 (d, J = 6.8 Hz, 3H), 0.60 - 0.53 (m, 1H).

Example 2
N-(l-(4-Fluorophenyl)cyclopropanylcarbonyl)-3-(S)-amino-3-deoxy-ingenol (Compound 2)
The title compound was prepared according to general procedure 1.
Starting material: l-(4-fluorophenyl)cyclopropanecarboxylic acid.

1H NMR (600 MHz, DMSO-d6) δ 7.51 - 7.40 (m, 2H), 7.25 - 7.12 (m, 2H), 5.85 (dt, J = 1.8, 5.9 Hz, 1H), 5.81 (d, J = 8.8 Hz, 1H), 5.54 (d, J = 6.1 Hz, 1H), 5.39 (s, 1H), 4.91 (s, 1H), 4.42 (d, J = 10.2 Hz, 1H), 4.36 (d, J = 8.8 Hz, 1H), 3.92 - 3.77 (m, 2H), 3.50 (d, J = 6.0 Hz, 1H), 2.11 (s, 1H), 1.98 - 1.90 (m, 1H), 1.65 - 1.56 (m, 3H), 1.52 (ddd, J = 6.5, 8.6, 15.4 Hz, 1H), 1.44 - 1.39 (m, 1H), 1.39 - 1.33 (m, 1H), 1.09 (s, 3H), 1.06 - 1.00 (m, 2H), 0.98 (s, 3H), 0.92 - 0.82 (m, 1H), 0.75 (d, J = 6.8 Hz, 3H), 0.55 (dt, J = 5.8, 8.7 Hz, 1H).

Example 3

N-(2-Methyl-2-phenoxy-propano-3-(S)-amino-3-deoxy-injenol (Compound 3)

The title compound was prepared according to general procedure 1.

Starting material: 2-methyl-2-phenoxy-propanoic acid.

1H NMR (600 MHz, DMSO-d6) δ 7.33 - 7.22 (m, 3H), 7.10 - 6.98 (m, 1H), 6.98 - 6.88 (m, 2H), 5.90 (dt, J = 1.9, 6.0 Hz, 1H), 5.59 (d, J = 5.4 Hz, 1H), 5.50 - 5.37 (m, 1H), 5.02 (s, 1H), 4.81 (t, J = 5.5 Hz, 1H), 4.60 (t, J = 8.5 Hz, 1H), 4.36 (d, J = 9.0 Hz, 1H), 3.93 - 3.80 (m, 2H), 3.58 (d, J = 5.3 Hz, 1H), 2.65 - 2.51 (m, 1H), 1.99 (dt, J = 3.4, 15.9 Hz, 1H), 1.64 - 1.53 (m, 4H), 1.47 (s, 3H), 1.46 (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H), 0.95 (dd, J = 8.8, 11.1 Hz, 1H), 0.85 (d, J = 6.8 Hz, 3H), 0.58 (ddd, J = 4.2, 6.4, 8.8 Hz, 1H).
Example 4

N-(2,2-Dimethylpentanoyl)-3-(S)-amino-3-deoxy-ingenol (compound 4)

The title compound was prepared according to general procedure 1.

Starting material: 2,2-dimethylpentanoic acid.

1H NMR (300 MHz, DMSO-d6) δ 6.70 (d, J = 8.6 Hz, 1H), 5.87 (dt, J = 1.9, 6.2 Hz, 1H), 5.51 (d, J = 5.1 Hz, 1H), 5.48 - 5.39 (m, 1H), 4.80 (s, 1H), 4.73 (t, J = 5.5 Hz, 1H), 4.58 (dd, J = 6.2, 11.2 Hz, 1H), 4.41 - 4.22 (m, 1H), 3.97 - 3.69 (m, 2H), 3.52 (d, J = 5.1 Hz, 1H), 2.78 - 2.56 (m, 1H), 2.02 (dt, J = 3.4, 16.1 Hz, 1H), 1.78 - 1.53 (m, 4H), 1.51 - 1.37 (m, 2H), 1.30 - 1.16 (m, 1H), 1.14 (s, 3H), 1.12 - 1.04 (m, 6H), 0.99 (s, 3H), 0.97 - 0.90 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H), 0.59 (ddd, J = 4.0, 6.2, 9.1 Hz, 1H).

Example 5

N-((2R)-2-Benzylpyrrolidin-2-yl-carbonyl)-3-(S)-amino-3-deoxy-ingenol (Compound 5)

Intermediate 4 (42 mg, 0.1209 mmol), (2R)-2-benzylpyrrolidin-2-yl-carboxylic acid chloride (58.44 mg, 0.2418 mmol) and HATU (59.76 mg, 0.1572 mmol) were mixed in a 4 mL vial. DMF (0.7 mL) and DIPEA (0.2418 mmol, 0.0430 mL) were added. The reaction mixture was stirred at room temperature for 16h. The reaction mixture was poured into a separation funnel with EtOAc and washed with 0.01N NaOH. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/Heptane. 0-100% EtOAc) giving the title compound as an oil (26.7 mg, 41.4% Yield).

1H NMR (600 MHz, DMSO-d6) δ 7.93 (d, J = 9.7 Hz, 1H), 7.32 - 7.25 (m, 2H), 7.25 - 7.17 (m, 3H), 5.89 (dt, J = 2.0, 6.2 Hz, 1H), 5.58 (d, J = 4.7 Hz, 1H), 5.40 (s, 1H), 4.83 (t, J = 5.4 Hz, 1H), 4.55 (d, J = 43.9 Hz, 2H), 4.21 (d, J = 9.5 Hz, 1H), 3.96 - 3.77 (m, 2H), 3.39 (d, J = 4.3 Hz, 1H), 3.27 (d, J = 13.4 Hz, 1H), 2.98 (dq, J = 7.0, 10.1 Hz, 1H), 2.78 - 2.66 (m, 2H), 2.60 - 2.51 (m, 1H), 2.25 (t, J = 6.3 Hz, 1H), 2.04 - 1.88 (m, 2H), 1.72 (dt, J = 7.7, 12.5 Hz, 1H), 1.65 - 1.50 (m, 6H), 1.15 (s, 3H), 1.01 - 0.93 (m, 4H), 0.88 (d, J = 6.7 Hz, 3H), 0.58 (ddd, J = 3.7, 6.4, 8.9 Hz, 1H).
Example 6

N-((2R)-2-benzyl-l-methyl-pyrrolid-2-yl-carbonyl)-3-(S)-amino-3-deoxy-inqenol

(Compound 6)

Compound 5 (22 mg, 0.04114 mmol), sodium triacetoxyborohydride (22 mg, 0.1 mmol) and formaldehyde (1.8 mg, 0.06 mmol) were mixed in a 4 ml test vial. 1,2-Dichloroethane (0.5 ml) was added. The reaction mixture was stirred at room temperature for 4.5 h and was poured into a separation funnel with EtOAc and washed with 0.1 N NaOH. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/heptane, 0-100% EtOAc) to afford the title compound as an oil (12 mg, 53%).

1H NMR (600 MHz, DMSO-d6) δ 7.41 (d, J = 9.5 Hz, 1H), 7.36 - 7.31 (m, 2H), 7.24 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H), 5.91 (dt, J = 1.9, 6.2 Hz, 1H), 5.66 (d, J = 5.1 Hz, 1H), 5.43 (s, 1H), 4.89 (s, 1H), 4.84 (t, J = 5.5 Hz, 1H), 4.68 - 4.59 (m, 1H), 4.32 (d, J = 9.4 Hz, 1H), 4.03 (q, J = 7.1 Hz, 1H), 3.96 - 3.84 (m, 2H), 3.57 (d, J = 5.1 Hz, 1H), 3.33 (s, 7H), 3.13 (d, J = 13.9 Hz, 1H), 2.94 - 2.84 (m, 2H), 2.70 - 2.59 (m, 2H), 2.33 (s, 3H), 2.01 (d, J = 14.4 Hz, 1H), 1.91 - 1.78 (m, 2H), 1.70 - 1.60 (m, 1H), 1.56 (s, 3H), 1.54 - 1.44 (m, 1H), 1.16 (s, 3H), 1.01 - 0.96 (m, 4H), 0.92 (d, J = 6.7 Hz, 3H), 0.63 - 0.57 (m, 1H).

Example 7

N-(2-(4-Chlorophenyl)-2-methylpropanoyl)-N-methyl-3-(S)-amino-3-deoxy-inqenol

(compound 7)
Step 1: 2-(4-Chlorophenyl)-2-methylpropanoic acid (250 mg, 1.2585 mmol) was dissolved in DCM (5 mL). Oxalylchloride (207.664 mg, 1.6361 mmol) and DMF (0.01 mL) were added and the reaction mixture was stirred at room temperature. After 45 min gas production stopped and the reaction mixture was concentrated in vacuo.

Step 2: The residue from step 1 was dissolved in DCM (5 mL). Intermediate 6 (102 mg, 0.2540 mmol) and DIPEA (49.25 mg, 0.3811 mmol, 0.0678 mL) were added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was taken up in MTBE and washed with water (x2) and brine (x1). The MTBE phases were dried over sodium sulfate and concentrated in vacuo.

The residue was purified by flash chromatography (heptane/ethyl acetate 5:0 to heptane/ethyl acetate 1:4).

Step 3: The product from step 2 was mixed with methanol (4 mL), dioxane (3ml) and water (0.5ml). 1,1,1-Trifluoroacetic acid was added to the reaction mixture. The reaction mixture was stirred at 5°C for 16 h. The reaction mixture was taken up in ethyl acetate and washed with saturated sodium carbonate and brine (x1). The organic phases were dried over sodium sulfate and concentrated in vacuo.

The residue was purified by flash chromatography (heptane/ethyl acetate, 5-100% ethyl acetate) to afford the title compound (88mg, 64.0%)

1H NMR (600 MHz, DMSO-d6) δ 7.40 (d, 2H), 7.33 (d, 2H), 5.88 (t, J = 4.8 Hz, 2H), 5.78 (s, 1H), 5.11 (s, 1H), 4.93 (s, 1H), 4.70 (t, J = 5.7 Hz, 1H), 4.15 (dd, J = 5.2, 12.3 Hz, 1H), 4.08 - 3.90 (m, 2H), 3.87 - 3.74 (m, 1H), 3.41 (s, 1H), 2.34 (s, 3H), 2.32 - 2.23 (m, 1H), 2.18 (ddd, J = 2.9, 8.9, 15.7 Hz, 1H), 1.65 (dt, J = 5.9, 15.5 Hz, 1H), 1.58 (s, 3H), 1.53 (s, 3H), 1.45 (s, 3H), 1.07 (s, 3H), 1.02 (s, 3H), 0.86 (d, J = 7.1 Hz, 3H), 0.81 (dd, J = 8.4, 11.9 Hz, 1H), 0.60 (td, J = 6.4, 8.4 Hz, 1H).

Example A
Neutrophil oxidative burst:
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 differentially sediment red blood cells. The leukocyte-rich supernatant was transferred to lymphoprep tubes to remove mononuclear cells by density centrifugation (400xg, 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. Ca²⁺, Mg²⁺) and the concentration adjusted to 1.4x10⁶ cells/ml in HBSS (Hanks Balanced Salt solution) (w Ca²⁺, Mg²⁺) 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 2.5x10^5 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 (5x10^-7 M PEP0005). Rel EC_{50} denotes the concentration of test compound producing an effect that is midway between the fitted top and bottom. Abs EC_{50} is the concentration of test compound that provokes a response corresponding to 50% of the maximal effect associated with the positive control (5x10^-7 M PEP0005).

**Example B**

HeKa cytokine release (IL-8):

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% 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 (1.5x10^-7 M PEP0005). Rel EC_{50} denotes the concentration of test compound producing an effect that is midway between the fitted top and bottom. Abs EC_{50} is the concentration of test compound that provokes a response corresponding to 50% of the maximal effect associated with the positive control (1.5x10^-7 M PEP0005).
Example C

Necrosis Assay

HeLa cells (ATCC CCL-002) were grown in minimal essential medium (Invitrogen catalog no. 42360) containing 10% fetal bovine serum, 100 IU/ml penicillin and 100 μg/ml streptomycin. 4,000-6,000 cells were seeded into 96-well black ViewPlates-plates, clear bottom, (Perkin Elmer) in 100 μl medium and incubated overnight. Compounds were dissolved and pre-diluted in DMSO in 96-well polypropylene plates (Greiner) in a concentration range of 15 μM to 600 μM. At the time of the experiment cell plates were placed on heating blocks at 37°C, medium was removed and 40 μl fresh, pre-warmed medium was added per well. Cells were incubated for 15 min before addition of compounds. In parallel, 3 μl of compounds were diluted with 197 μl growth medium on a Tecan freedom-EVO pipetting station using 250 μl’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 10 min.

80 μl pre-diluted compound were transferred manually to the corresponding wells containing HeLa cells yielding compound concentrations of 10 μM to 400 μM. Control conditions were 1% DMSO in growth medium (100% viability) and 400 μM ingenol mebutate in growth medium (0% viability). Plates were incubated on the heating blocks at 37°C for 30 min. At the end of the incubation 10 μl PrestoBlue reagent (Invitrogen) were added to each well, plates were sealed with black seal, followed by incubation at 37°C for 10 min with gentle shaking (150 rpm). Subsequently, plates were placed at room temperature for 20-30 min. Plates were read immediately after an Envision Fluorescence reader (Perkin Elmer) with excitation at 535 nm and emission at 630 nm. 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 × 10⁻⁴ M PEP0005/ingenol mebutate). AbsEC₅₀ 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 A, in the HeKa cytokine release assay according to the description in example B and in the necrosis assay according to the description in example C.

Example D

Chemical Stability assay at room temperature, buffer pH 7.4

A stock solution was prepared by diluting 50 μl of a ~10 mM DMSO solution of the compound with 1.15 ml acetonitrile (Analytical grade). To 0.75 ml stock solution 2.25 ml Phosphatebuffer (0.067 M) pH 7.4 was added. After filtering (Millipore filter: Millex-LCR
the solution was placed in an HPLC autosampler (room temperature). The solution was repeatedly injected over a period of 16 hours.

**HPLC system:**

Stationary Phase: Chromolith Performance RP18(4.6 x 100mm, 2 µm)

Mobile Phase: A: 25mM Phosphatebuffer  B: Acetonitrile

Based on the decrease of area of the compound signal (UV detection, suitable wavelength) the recovery of the compound over time was assessed.

Data analysis:

Detection: UV: 235 nm

The absolute area under the curve at t=0 hours equals to 100% recovery.

Calculation of the single recovery values at the measured timepoints:

Recovery [%] at tₓ: \[ \frac{\text{Area under the curve (tₓ)}}{\text{Area under the curve (t₀)}} \times 100 \]

Results are shown in the table below.

<table>
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<tr>
<th>Compound no.</th>
<th>Neutrophil oxidative burst Abs EC₅₀ (nM)</th>
<th>HeKa cytokine release (IL-8) Abs EC₅₀ (nM)</th>
<th>HeLa necrosis Abs EC₅₀ (µM)</th>
<th>Chemical stability buffer pH 7.4</th>
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<td>7</td>
<td>n.a.</td>
<td>&gt;400</td>
<td>&gt;95%</td>
</tr>
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</table>
1. A compound according to general formula (I)

\[
\begin{align*}
\text{I} & \\
R_1 & \\
R_2 & \\
R_3 & \\
R_4 & \\
R_5 & \\
R_6 & \\
\end{align*}
\]

wherein R1 is selected from the group consisting of hydrogen, methyl and ethyl;

wherein R2 and R3 each independently are selected from the group consisting of hydrogen and (Ci-C4)alkyl or wherein R2 and R3 together with the carbon atom to which they are attached form a (C3-C6)cycloalkyl or a 4-7 membered heterocycloalkyl, said (C3-C6)cycloalkyl or 4-7 membered heterocycloalkyl optionally being substituted with one or more substituents independently selected from R5;

wherein R5 represents the group consisting of (Ci-C4)alkyl;

wherein X is a bond, -0-, or -(CH₂)n-, wherein n is 1 or 2;

wherein R4 is selected from the group consisting of phenyl or (Ci-C4)alkyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from R6;

wherein R6 represents the group consisting of halogen, cyano, halo(Ci-C4)alkyl, (Ci-C4)alkoxy, halo(Ci-C4)alkoxy;

or pharmaceutically acceptable salts, hydrates or solvates thereof;

with the proviso that if one of R2 or R3 is hydrogen the other R2 or R3 is not hydrogen; and with the proviso that if R4 is (Ci-C4)alkyl both R2 and R3 are different from hydrogen.

2. The compound according to claim 1 wherein R4 is phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from R6.

3. The compound according to any one of claims 1 or 2 wherein X is a bond or -0-.
4. The compound according to any one of claims 1-3 wherein R represents halogen.

5. The compound according to any one of claims 1-4 wherein R₂ and R₃ each independently are selected from (C₁-C₄)alkyl.

6. The compound according to any one of claims 1-4 wherein R₂ and R₃ together with the carbon atom to which they are attached form a (C₃-C₆)cycloalkyl or a 4-7 membered heterocycloalkyl, said (C₃-C₆)cycloalkyl or 4-7 membered heterocycloalkyl optionally being substituted with one or more substituents independently selected from R₅.

7. A compound according to any one of claims 1-6 selected from

N-(2-(4-Chlorophenyl)-2-methyl propionyl)-3-(S)-a mino-3-deoxy-ingenol,
N-(1-(4-Fluorophenyl)cyclopropylcarbonyl)-3-(S)-a mino-3-deoxy-ingenol,
N-(2-Methyl-2-phenoxy-propionyl)-3-(S)-a mino-3-deoxy-ingenol,
N-(2,2-Dimethylpentanoyl)-3-(S)-a mino-3-deoxy-ingenol,
N-((2R)-2-Benzyl pyrrolidin-2-yl-carbonyl)-3-(S)-a mino-3-deoxy-ingenol,
N-((2R)-2-benzyl-1-methyl-pyrrolidin-2-yl-carbonyl)-3-(S)-a mino-3-deoxy-ingenol and
N-(2-(4-Chlorophenyl)-2-methyl propionyl)-N-methyl-3-(S)-a mino-3-deoxy-ingenol

or pharmaceutically acceptable salts, hydrates or solvates thereof.

8. A compound according to any one of claims 1-7 for use as a medicament.

9. A compound according to any one of claims 1-7 for use in treatment of physiological disorders or diseases associated with hyperplasia or neoplasia.

10. A compound according to claim 9 wherein the disorder or disease is selected from cutaneous warts, genital warts, actinic keratosis, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), lentigo maligna, cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia.

11. A pharmaceutical composition comprising a compound according to any one of claims 1-7 together with a pharmaceutically acceptable vehicle or excipient or pharmaceutically acceptable carrier(s).

12. The pharmaceutical composition according to claim 11 together with one or more other therapeutically active compound(s).
13. A compound selected from

5,20-Acetonide-3-(S)-azido-3-deoxy-ingenol,

5,20-Acetonide-3-(S)-amino-3-deoxy-ingenol

and

3-(S)-Amino-3-deoxy-ingenol.
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/EP2016/078316

A. **CLASSIFICATION OF SUBJECT MATTER**

INV. C07C233/32  C07C235/36  A61K31/165  A61P35/00

ADD.

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

B. **FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07C A61K A61P

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

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

EPO-Internal , WPI Data

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C.

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 application or patent but published on or after the international filing date

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

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

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

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

**X** document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

**A** document member of the same patent family

Date of the actual completion of the international search:

15 December 2016

Date of mailing of the international search report:

05/01/2017

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:

Hel ps, Ian

Form PCT/ISA/210 (second sheet) (April 2005)
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