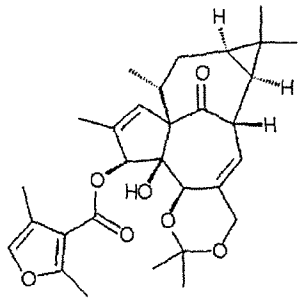
Compound 628 was prepared according to Procedure c.

Starting material: 2,5-Dimethyloxazole-4-carboxylic acid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10-6.09 (m, 1H), 5.80-5.78 (m, 1H), 5.73 (s, 1H), 4.27-4.12 (m, 3H), 4.04 (bs, 1H), 3.37 (s, 1H), 2.67-2.62 (m, 1H), 2.55 (s, 3H), 2.48 (s, 3H), 2.31-2.22 (m, 1H), 1.82 (d, 3H), 1.79-1.71 (m, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 1.01 (d, 3H), 0.94-0.87 (m, 1H), 0.73-0.65 (m, 1H).



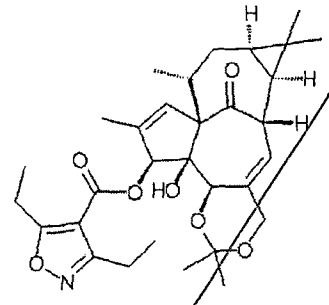
Preparation 629:

Ingenol-5,20-acetonide-3-(2,4-dimethylfuran-3-carboxylate) (Compound 629)

Compound 629 was prepared according to Procedure d.

Starting material: 2,4-Dimethylfuran-3-carbonyl chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (q, 1H), 6.09-6.08 (m, 1H), 6.80-6.78 (m, 1H), 5.73 (s, 1H), 4.26-4.12 (m, 3H), 4.05 (s, 1H), 3.34 (s, 1H), 2.69-2.62 (m, 1H), 2.54 (s, 3H), 2.33-2.24 (m, 1H), 2.13 (d, 3H), 1.81 (d, 3H), 1.78-1.69 (m, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 1.00 (d, 3H), 0.91-0.86 (m, 1H), 0.74-0.65 (m, 1H).



Preparation 630:

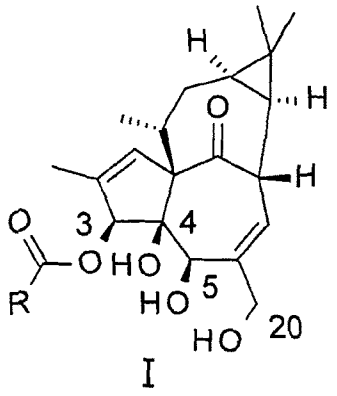
Ingenol-5,20-acetonide-3-(3,5-diethylisoxazole-4-carboxylate) (Compound 630)

Compound 630 was prepared according to Procedure d.

Starting material: 2,4-Diethylfuran-3-carbonyl chloride, prepared from 2,4-diethylfuran-3-carboxylic acid by reaction with 1.25 eq. oxalyl chloride in dichloromethane and a drop

CLAIMS

1. A compound of the general formula I



I

wherein R is heteroaryl which may optionally be substituted by one or more substituents independently selected from R7;
or R is heterocycloalkyl or heterocycloalkenyl, wherein said heterocycloalkyl or heterocycloalkenyl are optionally substituted by one or more substituents independently selected from R8;
or R is X;

R7 represents halogen, cyano or hydroxyl;
or R7 represents $(C_1$-$C_4)$alkyl,$(C_2$-$C_4)$-alkenyl, $(C_3$-$C_7)$-cycloalkyl, heterocycloalkyl, aryl, heteroaryl arylalkyl, heterocycloalkylalkyl or $(C_3$-$C_7)$-cycloalkylalkyl, wherein said $(C_1$-$C_4)$alkyl,$(C_2$-$C_4)$-alkenyl, $(C_3$-$C_7)$-cycloalkyl, heterocycloalkyl, aryl, heteroaryl arylalkyl, heterocycloalkylalkyl or $(C_3$-$C_7)$-cycloalkylalkyl are optionally substituted by one or more substituents independently selected from R9;
or R7 represents -NRaCORb, -CONRaRb, -COORc, -OCORa, -ORa, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -SRa or -NRaRb;

R9 represents halogen, cyano, hydroxy, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -ORa, -SRa or =O;

R8 represents halogen, cyano or hydroxyl;

or R8 represents (C_1-C_4)alkyl, (C_2-C_4)alkenyl, aryl, heteroaryl, (C_3-C_7)-cycloalkyl or heterocycloalkyl, wherein said C_1-C_4)alkyl, (C_2-C_4)alkenyl, aryl, heteroaryl, (C_3-C_7)-cycloalkyl or heterocycloalkyl are optionally substituted by one or more substituents independently selected from R10;

or R8 represents -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -ORa, -SRa, =O, =N-ORa, -O-N=CRaRb, NRaRb or -C(O)N(Ra)O-Rb;

R10 represents halogen, cyano, hydroxy, (C_1-C_4)-alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkyl, halo(C_1-C_4)alkoxy, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -ORa, -SRa or =O;

Ra and Rb represents hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl;

Rc represents hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_x)alkyl, cyano(C_1-C_x)alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl;

X represents –NR11R12;

wherein R11 and R12 independently represent hydrogen,

or

wherein R11 and R12 independently represents (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, heterocycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkylaryl, alkylheteroaryl or alkylheterocycloalkyl, wherein said (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, heterocycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkylaryl, alkylheteroaryl or alkylheterocycloalkyl are optionally substituted by one or more substituents independently selected from R13;

R13 represents halogen, cyano or hydroxyl,

or R13 represents (C_1-C_4)alkyl, (C_2-C_4)alkenyl, aryl, (C_3-C_7)cycloalkyl, heteroaryl or heterocycloalkyl, wherein said (C_1-C_4)alkyl, (C_2-C_4)alkenyl, aryl, (C_3-C_7)cycloalkyl, heteroaryl or heterocycloalkyl are optionally substituted by one or more substituents selected from R14,

or R13 represents -NRdCORe, -COORf, -OCORd, -CONRdRe, -OCONRdRe, -NRdCOORe, -NRdCONRdRe, -NRdSO2Re, -NRdSO2NRdRe, -SO2NRdRe, -SO2Rd, -S(O)Rd, -ORd, -SRd, =O, =N-ORd, -O-N=CRdRe, -NRdRe or -C(O)N(Rd)-ORe,

wherein Rd and Re independently represents hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl;

Rf represents hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxyl(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl;

R14 represents halogen, hydroxyl, cyano, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkyl, halo(C_1-C_4)alkoxy, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -NRdCORe, -COORf, -OCORd, -CONRdRe, -OCONRdRe, -NRdCOORe, -NRdCONRdRe, -NRdSO2Re, -NRdSO2NRdRe, -SO2NRdRe, -SO2Rd, -S(O)Rd, -ORd, -SRd or =O;

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

2. A compound according to claim 1;
wherein R is heteroaryl which may optionally be substituted by one or more substituents independently selected from R7,
or R is heterocycloalkyl or heterocycloalkenyl, each of which may optionally be substituted by one or more substituents independently selected from R8;

R7 represents halogen, cyano, hydroxyl;
or R7 represents (C_1-C_4)alkyl,(C_2-C_4)-alkenyl, (C_3-C_7)-cycloalkyl, heterocycloalkyl, aryl, heteroaryl, each of which is optionally substituted by one or more substituents independently selected from R9;

or R7 represents -NRaCORb, -CONRaRb, -COORc, -OCORa, -ORa, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -SRa;

R9 represents halogen, cyano, hydroxy, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -ORa, -SRa, =O;

R8 represents halogen, cyano, hydroxyl;
or R8 represents (C_1-C_4)-alkyl, (C_2-C_4)alkenyl, aryl, heteroaryl, (C_3-C_7)-cycloalkyl, heterocycloalkyl, each of which is optionally substituted by one or more substituents independently selected from R10,
or R8 represents -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -ORa, -SRa, =O;

R10 represents halogen, cyano, hydroxy, (C_1-C_4)-alkyl, halo(C_1-C_4)alkyl, -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -ORa, -SRa, =O;

Ra and Rb represents hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl;
Rc represents (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl.

3. A compound according to claim 1-2, wherein R is heteroaryl.

4. A compound according to claims 1-3, wherein heteroaryl is isoxazolyl, pyridyl, quinolyl, isoquinolyl, indolyl, furyl, thiazolyl, imidazolyl, pyrazolyl, oxazolyl, thienyl, pyrimidinyl, 1,2,3-triazolyl, indazolyl, cinnolyl, 1,2-benzoxazolyl, imidazothiazolyl, imidazopyridinyl, pyrrolyl, isothiazolyl, tetrahydroindazolyl or oxadiazolyl,

5. A compound according to any of the claims above, wherein R7 is independently selected one or more times from the group of (C_1-C_4)alkyl, (C_2-C_4)alkenyl, aryl, arylalkyl, heterocycloalkylalkyl, (C_3-C_7)-cycloalkylalkyl, (C_3-C_7)-cycloalkyl –COORc, -ORa or halogen.

6. A compound according to claim 5, wherein R7 is selected from phenyl, methyl, ethyl, isopropyl, *t*-butyl, piperidyl, tert-butyloxycarbonyl, benzyl, tetrahydropyranylmethyl, -OCH_3, cyclopropyl, allyl, cyclopropylmethyl, Cl, Br or I.

7. A compound according to any of the claims above, wherein R9 is halogen, -ORa, (C_1-C_4)alkyl or -SO2Ra.

8. A compound according to claim 7, wherein R9 is Cl, F, -OCH_3, methyl or methylsulfonyl.

9. A compound according to claim 1-2, wherein R is heterocycloalkyl or heterocycloalkenyl.

10. A compound according to claims 1, 2 or 9, wherein heterocycloalkyl or heterocycloalkenyl is pyrrolidinyl, piperidinyl, morpholinyl, 5-oxabicyclo[2.2.2]octanyl, oxaspiro[4.5]dec-1-enyl, oxo-thiazolyl, dihydrothiazolyl, oxo-pyranyl, azepanyl, azabicyclo[3.2.2]nonanyl, benzoxazinyl, quinoxalinyl, isoindolinyl, dihydroquinolinyl, indolinyl or dihydroquinoxalinyl.

11. A compound according to claims 1, 2 or 9, wherein R8 is (C_1-C_4)alkyl, aryl or =O.

12. A compound according to claim 11, wherein R8 is methyl, phenyl or =O.

13. A compound according to claim 1,2 or 9, wherein R10 represents halogen.

14. A compound according to claim 1, wherein R is –NR11R12.

15. A compound according to claim 1 or 14, wherein R11 and R12 independently represents hydrogen, (C_1-C_6)alkyl, aryl, cycloalkyl, arylalkyl, heteroaryl, cycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, (C_2-C_6)alkenyl or(C_2-C_6)alkynyl .

16. A compound according to claim 1, 14 or 15 wherein R11 and R12 independently represents hydrogen, methyl, ethyl, isopropyl, phenyl, benzyl, cyclohexyl, indanyl, tetralinyl, phenylethyl, cyclopropylmethyl, pyrazolyl, isoxazolylmethyl, cyclopentyl, cyclopropyl, pyridyl, piperidyl, tetrahydropyranylmethyl, tetrahydropyranyl, cyclobutyl, allyl, propynyl or thiazolyl.

17. A compound according to claim 1, 14 or 15, wherein R13 represents (C_1-C_4)alkyl, cyano, halogen, , =O, -ORa or -COORf.

18. A compound according to claim 17, wherein R13 represents methyl, cyano, F, =O, -OCH_3 or -$COOC(CH_3)_3$.

19. A compound according to claim 1, 14, 15 or 16 wherein R11 or R12 independently represent hydrogen.

20. A compound according to any of the claims above, said compound being selected from the group consisting of:
Ingenol 3-(5-methyl-3-phenyl-isoxazole-4-carboxylate),
Ingenol 3-(5-methyl-3-(2-chloro-6-fluoro-phenyl)-isoxazole-4-carboxylate),
Ingenol 3-(1S-camphanate),
Ingenol 3-(3-phenyltriazole-4-carboxylate,
Ingenol 3-(2-phenylpyrazole-3-carboxylate,
Ingenol 3-(1-methylindazole-3-carboxylate),
Ingenol 3-(3-ethyl-5-methyl-isoxazole-4-carboxylate),
Ingenol 3-(3-methyl-5-methyl-isoxazole-4-carboxylate),
Ingenol 3-(1-methylindole-3-carboxylate),
Ingenol 3-(3-phenylthiophene-2-carboxylate),
Ingenol 3-(5-phenylisoxazole-3-carboxylate),
Ingenol 3-(N-ethyl-carbamate),
Ingenol 3-(N,N-dimethyl-carbamate),
Ingenol 3-(morpholine-4-carboxylate),
Ingenol 3-(pyrrolidine-1-carboxylate),
Ingenol 3-(N-methtyl-N-phenyl-carbamate),
Ingenol 3-(N,N-diethyl-carbamate),
Ingenol 3-(piperidine-1-carboxylate),
Ingenol 3-(N-benzyl-N-methyl-carbamate),
Ingenol 3-(N-cyclohexyl-N-methyl-carbamate),
Ingenol 3-(N-cyclohexyl-carbamate),
Ingenol 3-(N-phenyl-carbamate),
Ingenol 3-(N-(indan-1-yl)-carbamate),
Ingenol 3-(3,3-dimethyl-piperidine-1-carboxylate),
Ingenol 3-(N-Methyl-N-tetralin-1-yl-carbamate),
Ingenol 3-(N-(2-cyano-1-methyl-ethyl)-N-methyl-carbamate),

Ingenol 3-(N-methyl-N-((S)-1-phenethyl)-carbamate),
Ingenol 3-(N-methyl-N-(cyclopropylmethyl)-carbamate,
Ingenol 3-(isoquinoline-1-carboxylate),
Ingenol 3-(quinoline-4-carboxylate),
Ingenol 3- (cinnoline-4-carboxylate),
Ingenol 3-(3-phenylimidazole-4-carboxylate),
Ingenol 3-(5-phenyloxazole-4-carboxylate),
Ingenol 3-(1,2-benzoxazole-3-carboxylate),
Ingenol 3-(3-isopropyl-5-methyl-isoxazole-4-carboxylate),
Ingenol 3-(3-(2-methoxyphenyl)-5-methyl-isoxazole-4-carboxylate),
Ingenol 3-(4-bromo-2-methyl-pyrazole-3-carboxylate),
Ingenol 3-(4-bromo-2-ethyl-pyrazole-3-carboxylate),
Ingenol 3-(4-chloro-2-methyl-pyrazole-3-carboxylate),
Ingenol 3-(5-bromopyrimidine-4-carboxylate),
Ingenol 3-(3-bromopyridine-2-carboxylate),
Ingenol 3-(5-methylthiazole-4-carboxylate),
Ingenol 3-(4-chloro-1-methyl-pyrazole-3-carboxylate),
Ingenol 3-(2,4-dimethylthiazole-5-carboxylate),
Ingenol 3-(2,5-dimethyloxazole-4-carboxylate),
Ingenol 3-(2,4-dimethylfuran-3-carboxylate),
Ingenol 3-(3,5-diethylisoxazole-4-carboxylate),
Ingenol 3-(N-(3-fluoro-phenyl)-N-methyl-carbamate),
Ingenol 3-(N-(2,5-dimethylpyrazol-3-yl)-N-methyl-carbamate),
Ingenol 3-(1H-indole-7-carboxylate),
Ingenol 3-(2-*tert*-butyl-5-methyl-pyrazole-3-carboxylate),
Ingenol 3-(5-*tert*-butyl-2-methyl-pyrazole-3-carboxylate),
Ingenol 3-(6-methylimidazo[2,1-b]thiazole-5-carboxylate),
Ingenol 3-(2-methylimidazo[1,2-a]pyridine-3-carboxylate),
Ingenol 3-(2,4,5-trimethylfuran-3-carboxylate),
Ingenol 3-(3-methylthiophene-2-carboxylate),
Ingenol 3-(2-methyl-4-(1-piperidyl)pyrazole-3-carboxylate),
Ingenol 3-(2-chloro-5-isopropyl-thiazole-4-carboxylate),
Ingenol 3-(4-chloro-2,5-dimethyl-pyrazole-3-carboxylate),
Ingenol 3-(1,2,4-trimethylpyrrole-3-carboxylate),
Ingenol 3-(1,3,5-trimethylpyrrole-2-carboxylate),
Ingenol 3-(1-ethyl-3,5-dimethylpyrrole-2-carboxylate),
Ingenol 3-(1-*tert*-butyloxycarbonyl-3,3-dimethylpyrrolidine-2-carboxylate),

Ingenol 3-((*2S*)-1-phenylpyrrolidine-2-carboxylate),
Ingenol 3-(1-isopropyl-3,5-dimethyl-pyrazole-4-carboxylate),
Ingenol 3-(5-ethyl-3-isopropyl-isoxazole-4-carboxylate),
Ingenol 3-(2-methylindazole-3-carboxylate),
Ingenol 3-(5-methyl-3-*tert*-butyl-isoxazole-4-carboxylate),
Ingenol 3-(2-methyl-3-oxo-4-oxaspiro[4.5]dec-1-ene-1-carboxylate),
Ingenol 3-(1-*tert*-butyl-3,5-dimethyl-pyrazole-4-carboxylate),
Ingenol 3-(3,5-dimethylisothiazole-4-carboxylate),
Ingenol 3-(5-iodo-3-methyl-isothiazole-4-carboxylate),
Ingenol 3-(4-(4-methoxyphenyl)-2-methyl-pyrazole-3-carboxylate),
Ingenol 3-(4-(2-methylphenyl)-2-methyl-pyrazole-3-carboxylate),
Ingenol 3-(2-methyl-4-(4-methylsulfonylphenyl)pyrazole-3-carboxylate),
Ingenol 3-(2-methyl-4-phenyl-pyrazole-3-carboxylate),
Ingenol 3-(3,5-dimethyl-1-phenyl-pyrazole-4-carboxylate),
Ingenol 3-(1,5-dimethyl-3-phenyl-pyrazole-4-carboxylate),
Ingenol 3-(1-benzyl-3,5-dimethyl-pyrazole-4-carboxylate),
Ingenol 3-(3,5-dimethyl-1-(tetrahydropyran-4-ylmethyl)pyrazole-4-carboxylate),
Ingenol 3-(4-methyl-2-oxo-3H-thiazole-5-carboxylate),
Ingenol 3-(2-methyl-4,5,6,7-tetrahydroindazole-3-carboxylate),
Ingenol 3-(1,2-dimethylindole-3-carboxylate),
Ingenol 3-(5-methoxy-1,2-dimethyl-indole-3-carboxylate),
Ingenol 3-(1,3,5-trimethylpyrazole-4-carboxylate),
Ingenol 3-(4-methyl-1,2,5-oxadiazole-3-carboxylate),
Ingenol 3-(2-methoxy-4-methyl-thiazole-5-carboxylate),
Ingenol 3-(4,5-dimethylisoxazole-3-carboxylate),
Ingenol 3-(4-bromo-1-methyl-pyrazole-3-carboxylate),
Ingenol 3-(1,3-dimethylindole-2-carboxylate),
Ingenol 3-(5-methoxy-1,3-dimethyl-indole-2-carboxylate),
Ingenol 3-(2,4-dimethyl-6-oxo-pyran-3-carboxylate),
Ingenol 3-(1-methyl-3-phenyl-indole-2-carboxylate),
Ingenol 3-(3-methyl-5-(trifluoromethyl)isoxazole-4-carboxylate),
Ingenol 3-(1,3-dimethylpyrrole-2-carboxylate),
Ingenol 3-(3,5-dimethyl-1-(2,2,2-trifluoroethyl)pyrazole-4-carboxylate),
Ingenol 3-(1-cyclopropyl-2,5-dimethyl-pyrrole-3-carboxylate),
Ingenol 3-(1,2,5-trimethylpyrrole-3-carboxylate),
Ingenol 3-(2,4-dimethyl-1H-pyrrole-3-carboxylate),
Ingenol 3-(1-methylpyrrole-2-carboxylate),

Ingenol 3-(4-methyl-1H-pyrrole-2-carboxylate),
Ingenol 3-(1,5-dimethylpyrrole-2-carboxylate),
Ingenol 3-(3-methyl-1H-pyrrole-2-carboxylate),
Ingenol 3-(1-cyclopropylpyrrole-2-carboxylate),
Ingenol 3-(1-ethyl-2,4-dimethyl-pyrrole-3-carboxylate),
Ingenol 3-(1-allyl-2,4-dimethyl-pyrrole-3-carboxylate),
Ingenol 3-(1-(cyclopropylmethyl)-2,4-dimethyl-pyrrole-3-carboxylate),
Ingenol 3-(1-(2-methoxyethyl)-2,4-dimethyl-pyrrole-3-carboxylate),
Ingenol 3-(N-(3,5-dimethylisoxazol-4-yl)-N-methyl-carbamate),
Ingenol 3-(N-(1,5-dimethylpyrazol-3-yl)-N-methyl-carbamate),
Ingenol 3-(N-cyclopentyl-N-methyl-carbamate),
Ingenol 3-(N-cyclopropyl-N-methyl-carbamate),
Ingenol 3-(N-methyl-N-(2-pyridyl)-carbamate),
Ingenol 3-(4-oxo-2,3-dihydroquinoline-1-carboxylate),
Ingenol 3-(3,4-dihydro-2H-quinoline-1-carboxylate),
Ingenol 3-(indoline-1-carboxylate),
Ingenol 3-(azepane-1-carboxylate),
Ingenol 3-(N-(4-chloro-phenyl)-N-methyl-carbamate),
Ingenol 3-(N-(4-fluoro-phenyl)-N-methyl-carbamate),
Ingenol 3-(N-methyl-N-(2-methoxy-phenyl)-carbamate),
Ingenol 3-(N-methyl-N-(2-methyl-phenyl)-carbamate),
Ingenol 3-(3-oxo-2,4-dihydroquinoxaline-1-carboxylate),
Ingenol 3-(N-ethyl-N-phenyl-carbamate),
Ingenol 3-(2-trifluoromethyl-pyrrolidine-1-carboxylate),
Ingenol 3-(3-azabicyclo[3.2.2]nonane-3-carboxylate),
Ingenol 3-(2,3-dihydro-1,4-benzoxazine-4-carboxylate),
Ingenol 3-(N-(2-fluoro-phenyl)-N-methyl-carbamate),
Ingenol 3-(3-methyl-2,3-dihydro-1,4-benzoxazine-4-carboxylate),
Ingenol 3-(2-trifluoromethyl-pyrrolidine-1-carboxylate) (ISOMER A),
Ingenol 3-(2-trifluoromethyl-pyrrolidine-1-carboxylate) (ISOMER B),
Ingenol 3-(N-methyl-N-(N-(*tert*-butyloxycarbonyl)-4-piperidyl)-carbamate),
Ingenol 3-(N-methyl-N-(3-methyl-phenyl)-carbamate),
Ingenol 3-(3,4-dihydro-2H-quinoxaline-1-carboxylate),
Ingenol 3-(isoindoline-2-carboxylate),
Ingenol 3-(N-methyl-N-(tetrahydropyran-4-ylmethyl)-carbamate),
Ingenol 3-(N-methyl-N-(tetrahydropyran-4-yl)-carbamate),
Ingenol 3-(N-methyl-N-(3-methoxy-phenyl)-carbamate),

Ingenol 3-(N-cyclobutyl-N-methyl-carbamate),
Ingenol 3-(N-allyl-N-methyl-carbamate),
Ingenol 3-(N-methyl-N-prop-2-ynyl-carbamate),
Ingenol 3-(N-methyl-N-(4-methylthiazol-2-yl)-carbamate) or
Ingenol 3-(N-(4-cyano-phenyl)-N-methyl-carbamate).

21. A compound according to any one of claims 1-20, for use as a medicament in therapy.

22. A compound according to any one of claims 1-20 for use in the treatment, prevention, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia or neoplasia.

23. A compound according to claim 22 wherein the disorder or disease is selected from cutaneous warts, genitial warts, actinic keratosis, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), lentigo maligna, cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia.

24. A use of a compound according to any of claims 1-20, for the manufacture of a pharmaceutical medicament.

25. Use of a compound according to claim 24 for the manufacture of a medicament for the treatment, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia or neoplasia.

26. Use according to claim 25 wherein the disorder or disease is selected from cutaneous warts, genitial warts, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), lentigo maligna, cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia,

27. 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 1-20.

28. The method according to claim 27 wherein the disorder or disease is selected from cutaneous warts, genitial warts, squamous cell carcinoma (SCC), basal cell carcinoma

(BCC), lentigo maligna, cervical intraepithelial neoplasia, anal intraepithelial neoplasia or vulva intraepithelial neoplasia.

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

30. A compound according to claim 29, wherein the cosmetic indication is selected from photodamaged skin or seborrheic keratosis.

31. Use of compound according to claim 24 for the manufacture of a medicament for the treatment or amelioration of cosmetic indications.

32. The use according to claim 31, wherein the cosmetic indication is selected from photodamaged skin or seborrheic keratosis.

33. 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 1-20.

34. The method according to claim 33 wherein the cosmetic indication is selected from photodamaged skin or seborrheic keratosis.

35. Use of a compound according to claim 24 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.

36. Use of a compound according to claim 24 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.

37. Use of a compound according to claim 24 in the manufacture of a pharmaceutical composition for the treatment or amelioration of a disease, disorder or condition responsive to induction of necrosis.

38. 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 1-20.

39.. 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 1-20.

40. 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 1-20.

41. A compound according to any one of claims 1-20 for use in the treatment or amelioration of a disease, disorder or condition responsive to stimulation of neutrophil oxidative burst.

42. A compound according to any one of claims 1-20 for use in the treatment or amelioration of a disease, disorder or condition responsive to stimulation of keratinocyte IL-8 release.

43. A compound according to any one of claims 1-20 for use in the treatment or amelioration of a disease, disorder or condition responsive to induction of necrosis.

44. A pharmaceutical composition comprising a compound according to any one of claims 1-20 or a pharmaceutically acceptable stereoisomer, salt or in vivo hydrolysable ester thereof together with a pharmaceutically acceptable vehicle or excipient.

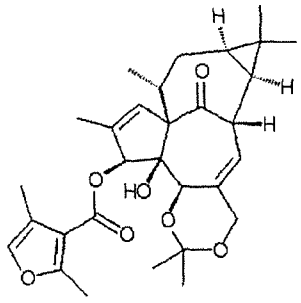
45. A pharmaceutical composition according to claim 44, wherein the composition is suitable for topical administration.

46. A pharmaceutical composition comprising a compound according to any one of claims 1-20 or a pharmaceutically acceptable stereoisomer, salt or in vivo hydrolysable ester thereof in combination with one or more other therapeutically active agents.

Compound 628 was prepared according to Procedure c.

Starting material: 2,5-Dimethyloxazole-4-carboxylic acid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10-6.09 (m, 1H), 5.80-5.78 (m, 1H), 5.73 (s, 1H), 4.27-4.12 (m, 3H), 4.04 (bs, 1H), 3.37 (s, 1H), 2.67-2.62 (m, 1H), 2.55 (s, 3H), 2.43 (s, 3H), 2.31-2.22 (m, 1H), 1.82 (d, 3H), 1.79-1.71 (m, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 1.01 (d, 3H), 0.94-0.87 (m, 1H), 0.73-0.65 (m, 1H).



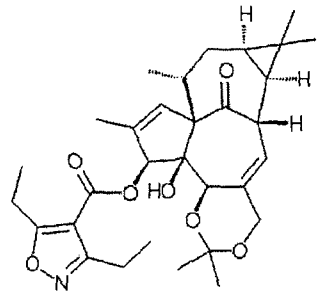
Preparation 629:

Ingenol-5,20-acetonide-3-(2,4-dimethylfuran-3-carboxylate) (Compound 629)

Compound 629 was prepared according to Procedure d.

Starting material: 2,4-Dimethylfuran-3-carbonyl chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (q, 1H), 6.09-6.08 (m, 1H), 6.80-6.78 (m, 1H), 5.73 (s, 1H), 4.26-4.12 (m, 3H), 4.05 (s, 1H), 3.34 (s, 1H), 2.69-2.62 (m, 1H), 2.54 (s, 3H), 2.33-2.24 (m, 1H), 2.13 (d, 3H), 1.81 (d, 3H), 1.78-1.69 (m, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 1.00 (d, 3H), 0.91-0.86 (m, 1H), 0.74-0.65 (m, 1H).



Preparation 630:

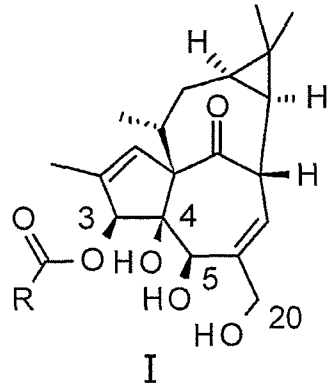
Ingenol-5,20-acetonide-3-(3,5-diethylisoxazole-4-carboxylate) (Compound 630)

Compound 630 was prepared according to Procedure d.

Starting material: 3,5-diethylisoxazole-4-carbonyl chloride, prepared from 3,5-diethylisoxazole-4-carboxylic acid by reaction with 1.25 eq. oxalyl chloride in dichloromethane and a drop

CLAIMS

1. A compound of the general formula I



I

wherein

R is heteroaryl which may optionally be substituted by one or more substituents independently selected from R7;

R7 represents halogen, cyano or hydroxyl;

or R7 represents (C_1-C_4)alkyl,(C_2-C_4)-alkenyl, (C_3-C_7)-cycloalkyl, heterocycloalkyl, aryl, heteroaryl arylalkyl, heterocycloalkylalkyl or (C_3-C_7)-cycloalkylalkyl, wherein said (C_1-C_4)alkyl,(C_2-C_4)-alkenyl, (C_3-C_7)-cycloalkyl, heterocycloalkyl, aryl, heteroaryl arylalkyl, heterocycloalkylalkyl or (C_3-C_7)-cycloalkylalkyl are optionally substituted by one or more substituents independently selected from R9;

or R7 represents -NRaCORb, -CONRaRb, -COORc, -OCORa, -ORa, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -SRa or -NRaRb;

R9 represents halogen, cyano, hydroxy, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -ORa, -SRa or =O;

Ra and Rb represents hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl; and

Rc represents hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_x)alkyl, cyano(C_1-C_x)alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein

R is heteroaryl which may optionally be substituted by one or more substituents independently selected from R7;

R7 represents halogen, cyano, hydroxyl;

or R7 represents (C_1-C_4)alkyl,(C_2-C_4)-alkenyl, (C_3-C_7)-cycloalkyl, heterocycloalkyl, aryl, heteroaryl, each of which is optionally substituted by one or more substituents independently selected from R9;

or R7 represents -NRaCORb, -CONRaRb, -COORc, -OCORa, -ORa, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -SRa;

R9 represents halogen, cyano, hydroxy, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, -NRaCORb, -COORc, -OCORa, -CONRaRb, -OCONRaRb, -NRaCOORb, -NRaCONRaRb, -NRaSO2NRaRb, -NRaSO2Rb, -SO2NRaRb, -SO2Ra, -S(O)Ra, -ORa, -SRa, =O;

Ra and Rb represents hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl; and

Rc represents (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, cyano(C_1-C_4)alkyl.

3. A compound according to claim 1, wherein heteroaryl is isoxazolyl, pyridyl, quinolyl, isoquinolyl, indolyl, furyl, thiazolyl, imidazolyl, pyrazolyl, oxazolyl, thienyl, pyrimidinyl, 1,2,3-triazolyl, indazolyl, cinnolyl, 1,2-benzoxazolyl, imidazothiazolyl, imidazopyridinyl, pyrrolyl, isothiazolyl, tetrahydroindazolyl or oxadiazolyl.

4. A compound according to claim 1, wherein R7 is independently selected one or more times from the group of (C_1-C_4)alkyl, (C_2-C_4)alkenyl, aryl, arylalkyl, heterocycloalkylalkyl, (C_3-C_7)-cycloalkylalkyl, (C_3-C_7)-cycloalkyl –COORc, -ORa or halogen.

5. A compound according to claim 4, wherein R7 is selected from phenyl, methyl, ethyl, isopropyl, *t*-butyl, piperidyl, tert-butyloxycarbonyl, benzyl, tetrahydropyranylmethyl, $-OCH_3$, cyclopropyl, allyl, cyclopropylmethyl, Cl, Br or I.

6. A compound according to claim 1, wherein R9 is halogen, -ORa, (C_1-C_4)alkyl or -SO2Ra.

7. A compound according to claim 6, wherein R9 is Cl, F, $-OCH_3$, methyl or methylsulfonyl.

8. A compound according to claim 1, said compound being selected from the group consisting of:

Ingenol 3-(5-methyl-3-phenyl-isoxazole-4-carboxylate),

Ingenol 3-(5-methyl-3-(2-chloro-6-fluoro-phenyl)-isoxazole-4-carboxylate),

Ingenol 3-(3-phenyltriazole-4-carboxylate,

Ingenol 3-(2-phenylpyrazole-3-carboxylate,

Ingenol 3-(1-methylindazole-3-carboxylate),

Ingenol 3-(3-ethyl-5-methyl-isoxazole-4-carboxylate),

Ingenol 3-(3-methyl-5-methyl-isoxazole-4-carboxylate),

Ingenol 3-(1-methylindole-3-carboxylate),

Ingenol 3-(3-phenylthiophene-2-carboxylate),

Ingenol 3-(5-phenylisoxazole-3-carboxylate),

Ingenol 3-(isoquinoline-1-carboxylate),

Ingenol 3-(quinoline-4-carboxylate),

Ingenol 3- (cinnoline-4-carboxylate),

Ingenol 3-(3-phenylimidazole-4-carboxylate),

Ingenol 3-(5-phenyloxazole-4-carboxylate),

Ingenol 3-(1,2-benzoxazole-3-carboxylate),

Ingenol 3-(3-isopropyl-5-methyl-isoxazole-4-carboxylate),

Ingenol 3-(3-(2-methoxyphenyl)-5-methyl-isoxazole-4-carboxylate),

Ingenol 3-(4-bromo-2-methyl-pyrazole-3-carboxylate),

Ingenol 3-(4-bromo-2-ethyl-pyrazole-3-carboxylate),

Ingenol 3-(4-chloro-2-methyl-pyrazole-3-carboxylate),

Ingenol 3-(5-bromopyrimidine-4-carboxylate),

Ingenol 3-(3-bromopyridine-2-carboxylate),

Ingenol 3-(5-methylthiazole-4-carboxylate),

Ingenol 3-(4-chloro-1-methyl-pyrazole-3-carboxylate),

Ingenol 3-(2,4-dimethylthiazole-5-carboxylate),

Ingenol 3-(2,5-dimethyloxazole-4-carboxylate),

Ingenol 3-(2,4-dimethylfuran-3-carboxylate),

Ingenol 3-(3,5-diethylisoxazole-4-carboxylate),

Ingenol 3-(1H-indole-7-carboxylate),

Ingenol 3-(2-*tert*-butyl-5-methyl-pyrazole-3-carboxylate),

Ingenol 3-(5-*tert*-butyl-2-methyl-pyrazole-3-carboxylate),

Ingenol 3-(6-methylimidazo[2,1-b]thiazole-5-carboxylate),

Ingenol 3-(2-methylimidazo[1,2-a]pyridine-3-carboxylate),

Ingenol 3-(2,4,5-trimethylfuran-3-carboxylate),

Ingenol 3-(3-methylthiophene-2-carboxylate),

Ingenol 3-(2-methyl-4-(1-piperidyl)pyrazole-3-carboxylate),

Ingenol 3-(2-chloro-5-isopropyl-thiazole-4-carboxylate),

Ingenol 3-(4-chloro-2,5-dimethyl-pyrazole-3-carboxylate),

Ingenol 3-(1,2,4-trimethylpyrrole-3-carboxylate),

Ingenol 3-(1,3,5-trimethylpyrrole-2-carboxylate),

Ingenol 3-(1-ethyl-3,5-dimethylpyrrole-2-carboxylate),

Ingenol 3-(1-isopropyl-3,5-dimethyl-pyrazole-4-carboxylate),

Ingenol 3-(5-ethyl-3-isopropyl-isoxazole-4-carboxylate),

Ingenol 3-(2-methylindazole-3-carboxylate),

Ingenol 3-(5-methyl-3-*tert*-butyl-isoxazole-4-carboxylate),

Ingenol 3-(1-*tert*-butyl-3,5-dimethyl-pyrazole-4-carboxylate),

Ingenol 3-(3,5-dimethylisothiazole-4-carboxylate),

Ingenol 3-(5-iodo-3-methyl-isothiazole-4-carboxylate),

Ingenol 3-(4-(4-methoxyphenyl)-2-methyl-pyrazole-3-carboxylate),

Ingenol 3-(4-(2-methylphenyl)-2-methyl-pyrazole-3-carboxylate),

Ingenol 3-(2-methyl-4-(4-methylsulfonylphenyl)pyrazole-3-carboxylate),

Ingenol 3-(2-methyl-4-phenyl-pyrazole-3-carboxylate),

Ingenol 3-(3,5-dimethyl-1-phenyl-pyrazole-4-carboxylate),

Ingenol 3-(1,5-dimethyl-3-phenyl-pyrazole-4-carboxylate),

Ingenol 3-(1-benzyl-3,5-dimethyl-pyrazole-4-carboxylate),

Ingenol 3-(3,5-dimethyl-1-(tetrahydropyran-4-ylmethyl)pyrazole-4-carboxylate),

Ingenol 3-(2-methyl-4,5,6,7-tetrahydroindazole-3-carboxylate),

Ingenol 3-(1,2-dimethylindole-3-carboxylate),

Ingenol 3-(5-methoxy-1,2-dimethyl-indole-3-carboxylate),

Ingenol 3-(1,3,5-trimethylpyrazole-4-carboxylate),

Ingenol 3-(4-methyl-1,2,5-oxadiazole-3-carboxylate),

Ingenol 3-(2-methoxy-4-methyl-thiazole-5-carboxylate),

Ingenol 3-(4,5-dimethylisoxazole-3-carboxylate),

Ingenol 3-(4-bromo-1-methyl-pyrazole-3-carboxylate),

Ingenol 3-(1,3-dimethylindole-2-carboxylate),

Ingenol 3-(5-methoxy-1,3-dimethyl-indole-2-carboxylate),

Ingenol 3-(2,4-dimethyl-6-oxo-pyran-3-carboxylate),

Ingenol 3-(1-methyl-3-phenyl-indole-2-carboxylate),

Ingenol 3-(3-methyl-5-(trifluoromethyl)isoxazole-4-carboxylate),

Ingenol 3-(1,3-dimethylpyrrole-2-carboxylate),

Ingenol 3-(3,5-dimethyl-1-(2,2,2-trifluoroethyl)pyrazole-4-carboxylate),

Ingenol 3-(1-cyclopropyl-2,5-dimethyl-pyrrole-3-carboxylate),

Ingenol 3-(1,2,5-trimethylpyrrole-3-carboxylate),

Ingenol 3-(2,4-dimethyl-1H-pyrrole-3-carboxylate),
Ingenol 3-(1-methylpyrrole-2-carboxylate),
Ingenol 3-(4-methyl-1H-pyrrole-2-carboxylate),
Ingenol 3-(1,5-dimethylpyrrole-2-carboxylate),
Ingenol 3-(3-methyl-1H-pyrrole-2-carboxylate),
Ingenol 3-(1-cyclopropylpyrrole-2-carboxylate),
Ingenol 3-(1-ethyl-2,4-dimethyl-pyrrole-3-carboxylate),
Ingenol 3-(1-allyl-2,4-dimethyl-pyrrole-3-carboxylate),
Ingenol 3-(1-(cyclopropylmethyl)-2,4-dimethyl-pyrrole-3-carboxylate), and
Ingenol 3-(1-(2-methoxyethyl)-2,4-dimethyl-pyrrole-3-carboxylate).

9. A pharmaceutical composition comprising a compound according to claim 1 or a pharmaceutically acceptable stereoisomer, or salt thereof together with a pharmaceutically acceptable vehicle or excipient.

10. A pharmaceutical composition according to claim 9, wherein the composition is suitable for topical administration.

11. A compound according to claim 1 which is Ingenol 3-(3-ethyl-5-methyl-isoxazole-4-carboxylate).

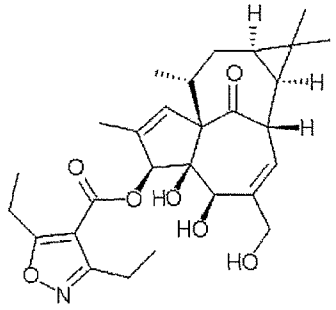
12. A compound according to claim 1 which is Ingenol 3-(2,4-dimethylfuran-3-carboxylate).

13. A compound which is Ingenol 3-(3,5-diethylisoxazole-4-carboxylate).

14. A compound according to claim 1 which is Ingenol 3-(2,4,5-trimethylfuran-3-carboxylate).

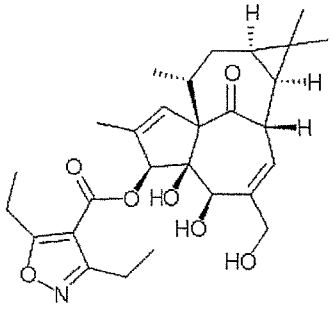
15. A compound according to claim 1 which is Ingenol 3-(5-methyl-3-phenyl-isoxazole-4-carboxylate).

16. A compound of the formula:



17. A pharmaceutical composition comprising a compound which is Ingenol 3-(3,5-diethylisoxazole-4-carboxylate) together with a pharmaceutically acceptable vehicle or excipient.

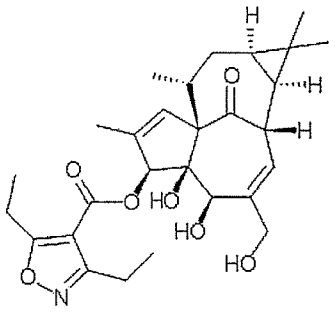
18. A pharmaceutical composition comprising a compound of the formula:



together with a pharmaceutically acceptable vehicle or excipient.

19. A pharmaceutical composition comprising a compound which is Ingenol 3-(3,5-diethylisoxazole-4-carboxylate) together with a pharmaceutically acceptable vehicle or excipient, wherein the composition is suitable for topical administration.

20. A pharmaceutical composition comprising a compound of the formula:



together with a pharmaceutically acceptable vehicle or excipient, wherein the composition is suitable for topical administration.