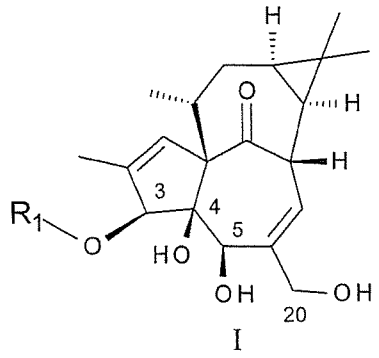
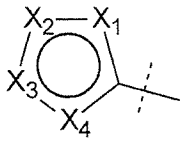
CLAIMS

1. A compound according to the general formula I

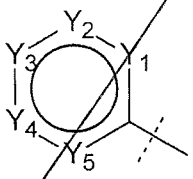


I

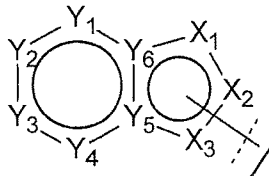
wherein R_1 represents heteroaryl, said heteroaryl optionally being substituted with one or more substituents independently selected from R_2; wherein said heteroaryl is selected from the group consisting of



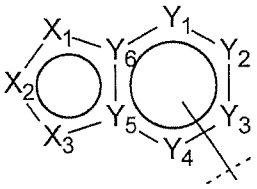
G1



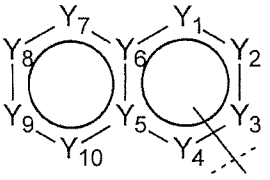
G2



G3



G4



G5

wherein X_1, X_2, X_3 and X_4 are each independently selected from the group consisting of C, CH, N, NH, S and O;

and wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9 and Y_{10} are each independently selected from the group consisting of C, CH and N;

wherein

R_1 represents G_1 and at least one of X_1 or X_4 is selected from the group consisting of N, NH, S and O;

or

R_1 represents G_2 and at least one of Y_1 or Y_5 represents N;

or

R_1 represents G_3 and the point of attachment to 3-O-ingenol occurs through X_1 or X_3, and X_2 is selected from the group consisting of N, NH, S and O;

or

R_1 represents G_3 and the point of attachment to 3-O-ingenol occurs through X_2, and at least one of X_1 and X_3 is selected from the group consisting of N, NH, S and O;

or

R_1 represents G_4 and the point of attachment to 3-O-ingenol occurs through Y_1, and Y_2 represents N;

or

R_1 represents G_4 and the point of attachment to 3-O-ingenol occurs through Y_2, and at least one of Y_1 and Y_3 represents N;

or

R_1 represents G_5 and the point of attachment to 3-O-ingenol occurs through Y_1, and Y_2 represents N;

or

R_1 represents G_5 and the point of attachment to 3-O-ingenol occurs through Y_2, and at least one of Y_1 and Y_3 represents N;

R_2 represents halogen, cyano, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_1$-$C_6)$alkoxy or $(C_3$-$C_6)$cycloalkyl;

and pharmaceutically acceptable salts, hydrates or solvates thereof.

2. The compound according to claim 1, wherein
R_1 represents G_1 and wherein one X_1 or X_4 is selected from the group consisting of N, NH, S and O and wherein the other X_1 or X_4 is substituted with R_2;
or
R_1 represents G_2 and wherein one Y_1 or Y_5 represents N, and wherein the other Y_1 or Y_5 is substituted with R_2;
or
R_1 represents G_3 and wherein the point of attachment to 3-O-ingenol occurs through X_1 or X_3 and wherein X_2 is selected from the group consisting of N, NH, S and O;
or
R_1 represents G_4 and wherein the point of attachment to 3-O-ingenol occurs through Y_1 and wherein Y_2 represents N;
or
R_1 represents G_5 and wherein the point of attachment to 3-O-ingenol occurs through Y_1 and wherein Y_2 represents N.

3. The compound according to claims 1-2 wherein R_1 represents oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, isoquinolinyl, benzoxazolyl, indazolyl, thienopyridyl, furopyridyl or oxadiazolyl.

4. The compound according to claims 1-3 wherein R_2 represents methyl, trifluoromethyl, trifluoroethyl, propenyl, bromo, chloro, fluoro, cyano, methoxy, isopropyl, cyclopentyl, difluoroethyl or fluoroethyl.

5. The compound according to claims 1-4 selected from the group consisting of
3-O-(6-Chloro-5-methyl-pyrimidin-4-yl)-ingenol,
3-O-(1,2-Benzoxazol-3-yl)-ingenol,
3-O-(5-(Trifluoromethyl)-2-pyridyl)-ingenol,
3-O-(5-Allyl-6-chloro-pyrimidin-4-yl)-ingenol,
3-O-(3-Formyl-2-pyridyl)-ingenol,
3-O-(2-Pyridyl)-ingenol,

3-O-(1-Methylindazol-3-yl)-ingenol,
3-O-(1-Methylimidazol-2-yl)-ingenol,
3-O-(1-Allylimidazol-2-yl)-ingenol,
3-O-(5-(Trifluoromethyl)-pyrimidin-2-yl)-ingenol,
3-O-(4-Bromo-2-pyridyl)-ingenol,
3-O-(3-Fluoro-2-pyridyl)-ingenol,
3-O-(4-(Trifluoromethyl)-2-pyridyl)-ingenol,
3-O-(4-(Trifluoromethyl)-pyrimidin-2-yl)-ingenol,
3-O-(3-Chloro-2-pyridyl)-ingenol,
3-O-(3-Cyano-2-pyridyl)-ingenol,
3-O-(6-(Trifluoromethyl)-2-pyridyl)-ingenol,
3-O-(3-(Trifluoromethyl)-2-pyridyl)-ingenol,
3-O-(1-Isoquinolyl)-ingenol,
3-O-(1-Cyclopentylimidazol-2-yl)-ingenol,
3-O-(1-(2,2-Difluoroethyl)imidazol-2-yl)-ingenol,
3-O-(1-(2-Fluoroethyl)imidazol-2-yl)-ingenol,
3-O-(Thieno[2,3-c]pyridine-7-yl)-ingenol,
3-O-(3-Methyl-2-pyridyl)-ingenol,
3-O-(6-Chloro-1,2-benzoxazol-3-yl)-ingenol,
3-O-(Furo[3,2-c]pyridine-4-yl)-ingenol,
3-O-(Thieno[3,2-c]pyridine-4-yl)-ingenol,
3-O-(4-Fluoro-1,2-benzoxazol-3-yl)-ingenol,
3-O-(3-Methoxy-pyridin-2-yl)-ingenol,
3-O-(5-Methoxy-1,2-benzoxazol-3-yl)-ingenol,
3-O-(5-Chloro-1,2-benzoxazol-3-yl)-ingenol,
3-O-(6-Methoxy-1,2-benzoxazol-3-yl)-ingenol,
3-O-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-ingenol
and pharmaceutically acceptable salts, hydrates or solvates thereof.

6. A compound according to any one of claims 1-5, for use as a medicament in therapy.

7. A compound according to any one of claims 1-5 for use in the treatment, prevention, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia, neoplasia or dysplasia.

8. The compound according to claim 10 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.

9. A use of a compound according to any of claims 1-5, in the manufacture of a pharmaceutical medicament.

10. Use of a compound according to claim 9 in the manufacture of a medicament for the treatment, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia, neoplasia or dysplasia.

11. Use according to claim 10 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.

12. Use according to claim 11 wherein the disorder or disease is actinic keratosis.

13. A compound according to any one of claims 1-5 for use in the treatment or amelioration of cosmetic indications.

14. A pharmaceutical composition comprising a compound according to any one of claims 1-5 or a pharmaceutically acceptable stereoisomer or salt thereof together with a pharmaceutically acceptable vehicle or excipient.

15. The pharmaceutical composition according to claim 14, wherein the composition is suitable for topical administration.

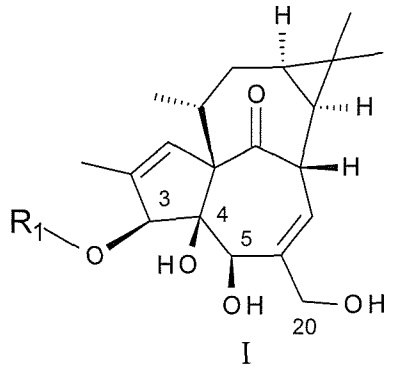
16. A pharmaceutical composition comprising a compound according to any one of claims 1-5 or a pharmaceutically acceptable stereoisomer or salt thereof in combination with one or more other therapeutically active agents.

17. A compound selected from the group consisting of
3-O-(6-Chloro-5-methyl-pyrimidin-4-yl)-ingenol-5,20-acetonide,
3-O-(1,2-Benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(5-(Trifluoromethyl)-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(5-Allyl-6-chloro-pyrimidin-4-yl)-ingenol-5,20-acetonide,
3-O-(3-Formyl-2-pyridyl)-ingenol-5,20-acetonide,

3-O-(2-Pyridyl)-ingenol-5,20-acetonide,
3-O-(1-Methylindazol-3-yl)-ingenol-5,20-acetonide,
3-O-(1-Methylimidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(1-Allylimidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(5-(Trifluoromethyl)-pyrimidin-2-yl)-ingenol-5,20-acetonide,
3-O-(4-Bromo-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(3-Fluoro-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(4-(Trifluoromethyl)-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(4-(Trifluoromethyl)-pyrimidin-2-yl)-ingenol-5,20-acetonide,
3-O-(3-Chloro-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(3-Cyano-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(6-(Trifluoromethyl)-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(3-(Trifluoromethyl)-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(1-Isoquinolyl)-ingenol-5,20-acetonide,
3-O-(1-Cyclopentylimidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(1-(2,2-Difluoroethyl)imidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(1-(2-Fluoroethyl)imidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(Thieno[2,3-c]pyridine-7-yl)-ingenol-5,20-acetonide,
3-O-(3-Methyl-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(6-Chloro-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(Furo[3,2-c]pyridine-4-yl)-ingenol-5,20-acetonide,
3-O-(Thieno[3,2-c]pyridine-4-yl)-ingenol-5,20-acetonide,
3-O-(4-Fluoro-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(3-Methoxy-pyridin-2-yl)-ingenol-5,20-acetonide,
3-O-(5-Methoxy-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(5-Chloro-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(6-Methoxy-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-ingenol-5,20-acetonide.

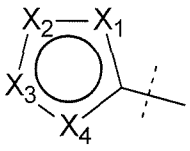
CLAIMS

1. A compound according to the general formula I

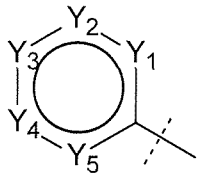


I

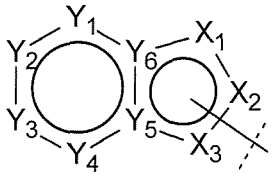
wherein R_1 represents heteroaryl, said heteroaryl optionally being substituted with one or more substituents independently selected from R_2; wherein said heteroaryl is selected from the group consisting of



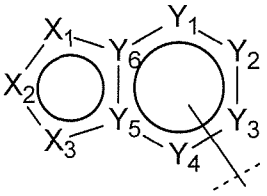
G1



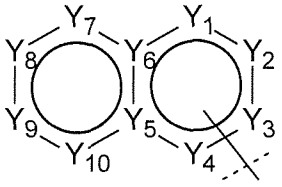
G2



G3



G4



G5

wherein X_1, X_2, X_3 and X_4 are each independently selected from the group consisting of C, CH, N, NH, S and O;

and wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9 and Y_{10} are each independently selected from the group consisting of C, CH and N;

wherein

R_1 represents G_1 and at least one of X_1 or X_4 is selected from the group consisting of N, NH, S and O;

or

R_1 represents G_2 and at least one of Y_1 or Y_5 represents N;

or

R_1 represents G_3 and the point of attachment to 3-O-ingenol occurs through X_1 or X_3, and X_2 is selected from the group consisting of N, NH, S and O;

or

R_1 represents G_3 and the point of attachment to 3-O-ingenol occurs through X_2, and at least one of X_1 and X_3 is selected from the group consisting of N, NH, S and O;

or

R_1 represents G_4 and the point of attachment to 3-O-ingenol occurs through Y_1, and Y_2 represents N;

or

R_1 represents G_4 and the point of attachment to 3-O-ingenol occurs through Y_2, and at least one of Y_1 and Y_3 represents N;

or

R_1 represents G_5 and the point of attachment to 3-O-ingenol occurs through Y_1, and Y_2 represents N;

or

R_1 represents G_5 and the point of attachment to 3-O-ingenol occurs through Y_2, and at least one of Y_1 and Y_3 represents N;

R_2 represents halogen, cyano, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkoxy or $(C_3\text{-}C_6)$cycloalkyl;

and pharmaceutically acceptable salts, hydrates or solvates thereof.

2. The compound according to claim 1, wherein

R_1 represents G_1 and wherein one X_1 or X_4 is selected from the group consisting of N, NH, S and O and wherein the other X_1 or X_4 is substituted with R_2;

or

R_1 represents G_2 and wherein one Y_1 or Y_5 represents N, and wherein the other Y_1 or Y_5 is substituted with R_2;

or

R_1 represents G_3 and wherein the point of attachment to 3-O-ingenol occurs through X_1 or X_3 and wherein X_2 is selected from the group consisting of N, NH, S and O;

or

R_1 represents G_4 and wherein the point of attachment to 3-O-ingenol occurs through Y_1 and wherein Y_2 represents N;

or

R_1 represents G_5 and wherein the point of attachment to 3-O-ingenol occurs through Y_1 and wherein Y_2 represents N.

3. The compound according to claims 1-2 wherein R_1 represents oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, isoquinolinyl, benzoxazolyl, indazolyl, thienopyridyl, furopyridyl or oxadiazolyl.

4. The compound according to claims 1-3 wherein R_2 represents methyl, trifluoromethyl, trifluoroethyl, propenyl, bromo, chloro, fluoro, cyano, methoxy, isopropyl, cyclopentyl, difluoroethyl or fluoroethyl.

5. The compound according to claims 1-4 selected from the group consisting of
3-O-(6-Chloro-5-methyl-pyrimidin-4-yl)-ingenol,
3-O-(1,2-Benzoxazol-3-yl)-ingenol,
3-O-(5-(Trifluoromethyl)-2-pyridyl)-ingenol,
3-O-(5-Allyl-6-chloro-pyrimidin-4-yl)-ingenol,
3-O-(3-Formyl-2-pyridyl)-ingenol,
3-O-(2-Pyridyl)-ingenol,
3-O-(1-Methylindazol-3-yl)-ingenol,
3-O-(1-Methylimidazol-2-yl)-ingenol,
3-O-(1-Allylimidazol-2-yl)-ingenol,
3-O-(5-(Trifluoromethyl)-pyrimidin-2-yl)-ingenol,
3-O-(4-Bromo-2-pyridyl)-ingenol,
3-O-(3-Fluoro-2-pyridyl)-ingenol,
3-O-(4-(Trifluoromethyl)-2-pyridyl)-ingenol,
3-O-(4-(Trifluoromethyl)-pyrimidin-2-yl)-ingenol,
3-O-(3-Chloro-2-pyridyl)-ingenol,
3-O-(3-Cyano-2-pyridyl)-ingenol,
3-O-(6-(Trifluoromethyl)-2-pyridyl)-ingenol,
3-O-(3-(Trifluoromethyl)-2-pyridyl)-ingenol,
3-O-(1-Isoquinolyl)-ingenol,
3-O-(1-Cyclopentylimidazol-2-yl)-ingenol,
3-O-(1-(2,2-Difluoroethyl)imidazol-2-yl)-ingenol,
3-O-(1-(2-Fluoroethyl)imidazol-2-yl)-ingenol,
3-O-(Thieno[2,3-c]pyridine-7-yl)-ingenol,
3-O-(3-Methyl-2-pyridyl)-ingenol,
3-O-(6-Chloro-1,2-benzoxazol-3-yl)-ingenol,
3-O-(Furo[3,2-c]pyridine-4-yl)-ingenol,
3-O-(Thieno[3,2-c]pyridine-4-yl)-ingenol,
3-O-(4-Fluoro-1,2-benzoxazol-3-yl)-ingenol,
3-O-(3-Methoxy-pyridin-2-yl)-ingenol,
3-O-(5-Methoxy-1,2-benzoxazol-3-yl)-ingenol,
3-O-(5-Chloro-1,2-benzoxazol-3-yl)-ingenol,
3-O-(6-Methoxy-1,2-benzoxazol-3-yl)-ingenol,
3-O-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-ingenol

and pharmaceutically acceptable salts, hydrates or solvates thereof.

6. A compound according to any one of claims 1-5, for use as a medicament in therapy.

7. A compound according to any one of claims 1-5 for use in the treatment, prevention, amelioration or prophylaxis of physiological disorders or diseases associated with hyperplasia, neoplasia or dysplasia.

8. The compound according to claim 7 wherein the disorder or disease is selected from actinic keratosis, squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and lentigo maligna.

9. A use of a compound according to any of claims 1-5, in the manufacture of a pharmaceutical medicament for the treatment of the disorder or disease selected from actinic keratosis, squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and lentigo maligna.

10. Use according to claim 9 wherein the disorder or disease is actinic keratosis.

11. A pharmaceutical composition comprising a compound according to any one of claims 1-5 or a pharmaceutically acceptable stereoisomer or salt thereof together with a pharmaceutically acceptable vehicle or excipient.

12. The pharmaceutical composition according to claim 11, wherein the composition is suitable for topical administration.

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

14. A compound selected from the group consisting of
3-O-(6-Chloro-5-methyl-pyrimidin-4-yl)-ingenol-5,20-acetonide,
3-O-(1,2-Benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(5-(Trifluoromethyl)-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(5-Allyl-6-chloro-pyrimidin-4-yl)-ingenol-5,20-acetonide,
3-O-(3-Formyl-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(2-Pyridyl)-ingenol-5,20-acetonide,
3-O-(1-Methylindazol-3-yl)-ingenol-5,20-acetonide,
3-O-(1-Methylimidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(1-Allylimidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(5-(Trifluoromethyl)-pyrimidin-2-yl)-ingenol-5,20-acetonide,
3-O-(4-Bromo-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(3-Fluoro-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(4-(Trifluoromethyl)-2-pyridyl)-ingenol-5,20-acetonide,

3-O-(4-(Trifluoromethyl)-pyrimidin-2-yl)-ingenol-5,20-acetonide,
3-O-(3-Chloro-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(3-Cyano-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(6-(Trifluoromethyl)-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(3-(Trifluoromethyl)-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(1-Isoquinolyl)-ingenol-5,20-acetonide,
3-O-(1-Cyclopentylimidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(1-(2,2-Difluoroethyl)imidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(1-(2-Fluoroethyl)imidazol-2-yl)-ingenol-5,20-acetonide,
3-O-(Thieno[2,3-c]pyridine-7-yl)-ingenol-5,20-acetonide,
3-O-(3-Methyl-2-pyridyl)-ingenol-5,20-acetonide,
3-O-(6-Chloro-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(Furo[3,2-c]pyridine-4-yl)-ingenol-5,20-acetonide,
3-O-(Thieno[3,2-c]pyridine-4-yl)-ingenol-5,20-acetonide,
3-O-(4-Fluoro-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(3-Methoxy-pyridin-2-yl)-ingenol-5,20-acetonide,
3-O-(5-Methoxy-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(5-Chloro-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(6-Methoxy-1,2-benzoxazol-3-yl)-ingenol-5,20-acetonide,
3-O-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-ingenol-5,20-acetonide.