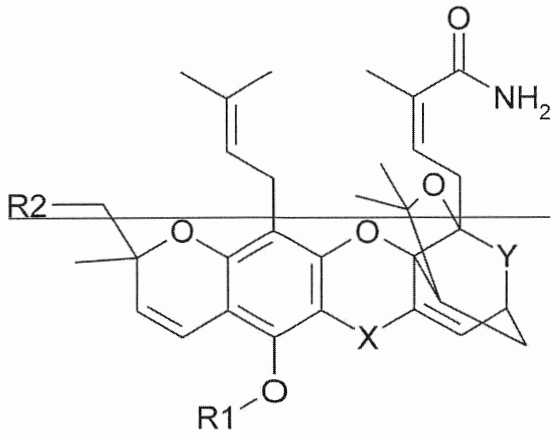
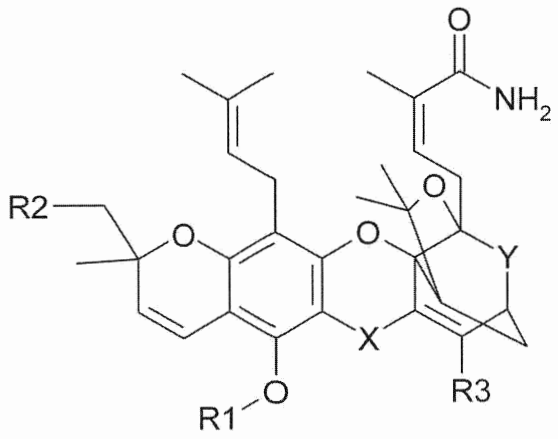
Claims

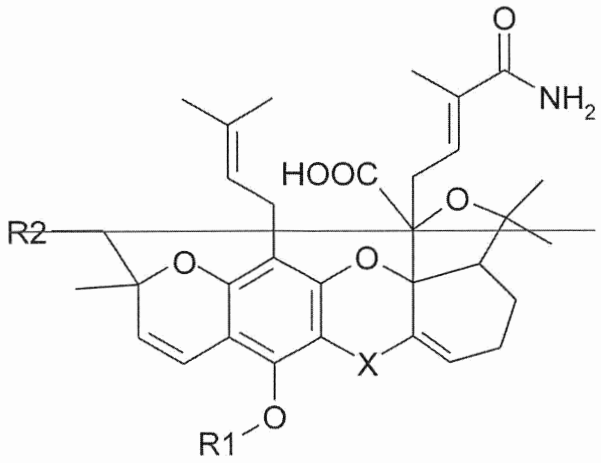
1. A compound according to formula ~~I, II or III~~



~~(I)~~



(II)



~~(III)~~

for use in the treatment of glioblastoma, wherein

X is carbonyl, methylene, hydroxymethinyl, alkoxymethinyl, aminomethinyl, oxime, hydrazone, arylhydrazone or semicarbazone;

Y is carbonyl, methylene, hydroxymethinyl, alkoxymethinyl, aminomethinyl, oxime, a hydrazone, arylhydrazone or semicarbazone;

R_1 is hydrogen, substituted alkyl, acyl (R_aCO-), or carbamyl (R_bR_cNCO); wherein R_a is hydrogen, substituted lower alkyl, substituted aryl, substituted lower aralkyl group or N-succinimidyl; R_b and R_c are independently hydrogen substituted heteroalkyl, substituted lower alkyl, substituted aryl, substituted heteroaryl or substituted lower aralkyl groups;

R_2 is prenyl or hydrogen; and

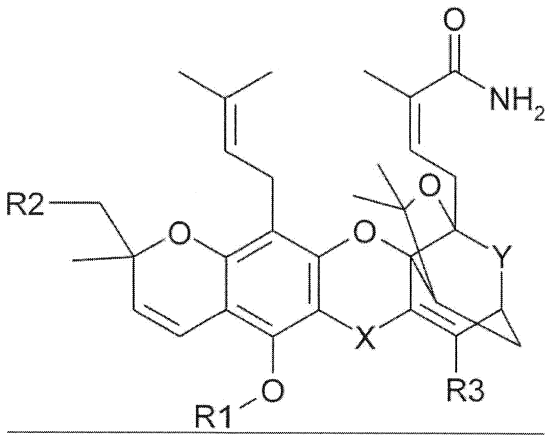
R_3 if present, is hydrogen, halogen, hydroxyl, substituted alkyl, cycloalkyl, alkoxy, alkylthio or amino

or salts thereof.

2. The compound according to claim 1, wherein

(i) the compound is defined by formula II and R_1 is hydrogen, R_2 is prenyl, R_3 is hydrogen X and Y is hydroxymethinyl; or

(ii) the compound is defined by formula I



(I)

or

(iii) the compound is defined by formula I of (ii) and R_1 is hydrogen, R_2 is prenyl, X is carbonyl and Y is carbonyl, or

~~(ii) the compound is defined by formula II and R_1 is hydrogen, R_2 is prenyl, R_3 is hydrogen X and Y is hydroxymethinyl; or~~

(~~iii~~iv) the compound is defined by formula I of (ii) and R_1 is hydrogen, R_2 is prenyl, X is carbonyl and Y is hydroxymethinyl; or

(~~iv~~v) the compound is defined by formula I of (ii) and R_1 is acetyl, R_2 is prenyl, X is carbonyl and Y is carbonyl; or

(vi) the compound is ~~defined by formula III and R_1 is hydrogen, R_2 is prenyl and X is carbonyl~~ gambogic acid amide.

3. The compound of claim 1 or 2, wherein the glioblastoma to be treated is selected from the group consisting of primary glioblastoma, recurrent glioblastoma, glioblastoma with increased methylation of the promoter of the gene O6-Methylguanin-Methyltransferase (MGMT), glioblastoma without increased methylation of the promoter of MGMT, glioblastoma with mutated p53, glioblastoma without mutated p53, glioblastoma with alterations of the gene encoding kappa light polypeptide gene enhancer in B-cells inhibitor (NFKBIA), glioblastoma without alterations of the gene encoding NFKBIA, glioblastoma with alterations of the gene encoding epidermal growth factor receptor (EGFR), glioblastoma without alterations of the gene encoding EGFR, glioblastoma with alterations of the gene encoding platelet-derived growth factor receptor (PDGFRA), glioblastoma without alterations of the gene encoding PDGFRA, glioblastoma with

alterations of the gene encoding isocitrate dehydrogenase 1 (IDHI), glioblastoma without alterations of the gene encoding IDHI, glioblastoma with alterations of the gene encoding neurofibromatosis type 1 (NF1) and glioblastoma without alterations of the gene encoding NF1.

4. The compound of claim 1 or 2, wherein the glioblastoma comprises cells overexpressing or expressing a gene selected from the group consisting of CD133, ATP-binding cassette sub-family G member 2 (ABCG2), aldehyde dehydrogenase 1 (ALDH1A1), musashi homolog 1 (MSI-1), Nestin and sex determining region Y-box 2 (SOX-2).

5. The compound of any of claims 1 to 4, wherein said glioblastoma comprises a subset of stem-like cells.

6. The compound of any of claims 1 to 5, wherein said compound delays cell growth of said glioblastoma cells for up to 10 days after administration.

7. A pharmaceutical composition comprising a compound ~~according to formula I, II or III, wherein X, Y, R_1, R_2 and R_3 have the meaning set out~~as defined in claim 1 or 2, for the treatment of glioblastoma.

~~8. The pharmaceutical composition according to claim 7, wherein~~

~~(i) the compound is defined by formula I and R_1 is hydrogen, R_2 is prenyl, X is carbonyl and Y carbon is carbonyl, or~~

~~(ii) the compound is defined by formula II and R_1 is hydrogen, R_2 is prenyl, R_3 is hydrogen X and Y is hydroxymethinyl; or~~

~~(iii) the compound is defined by formula I and R_1 is hydrogen, R_2 is prenyl, X is carbonyl and Y is hydroxymethinyl; or~~

~~(iv) the compound is defined by formula I and R_1 is acetyl, R_2 is prenyl, X is carbonyl and Y is carbonyl; or~~

~~(v) the compound is defined by formula III and R_1 is hydrogen, R_2 is prenyl and X is carbonyl.~~

~~9~~8. The pharmaceutical composition of claim 7 ~~or 8~~, wherein the glioblastoma to be treated is selected from the group consisting of primary glioblastoma, recurrent glioblastoma,

glioblastoma with increased methylation of the promoter of the gene O6-Methylguanin-Methyltransferase (MGMT), glioblastoma without increased methylation of the promoter of MGMT, glioblastoma with mutated p53, glioblastoma without mutated p53, glioblastoma with alterations of the gene encoding kappa light polypeptide gene enhancer in B-cells inhibitor (NFKBIA), glioblastoma without alterations of the gene encoding NFKBIA, glioblastoma with alterations of the gene encoding epidermal growth factor receptor (EGFR), glioblastoma without alterations of the gene encoding EGFR, glioblastoma with alterations of the gene encoding platelet-derived growth factor receptor (PDGFRA), glioblastoma without alterations of the gene encoding PDGFRA, glioblastoma with alterations of the gene encoding isocitrate dehydrogenase 1 (IDHI), glioblastoma without alterations of the gene encoding IDHI, glioblastoma with alterations of the gene encoding neurofibromatosis type 1 (NF1) and glioblastoma without alterations of the gene encoding NF1.

~~10~~9. The pharmaceutical composition of claim 7 ~~or 8~~, wherein the glioblastoma comprises cells overexpressing or expressing a gene selected from the group consisting of CD133, ATP-binding cassette sub-family G member 2 (ABCG2), aldehyde dehydrogenase 1(ALDH1A1), musashi homolog 1 (MSI-1), Nestin and sex determining region Y-box 2 (SOX-2).

~~11~~10. The pharmaceutical composition of any one of claims 7 to ~~10~~9 further comprising at least one further compound with anti cancer-activity.

~~12~~11. The pharmaceutical composition of claim ~~11~~10, wherein the at least one further compound is temozolomide or a salt thereof.

~~13~~12. An *in vitro* method for determining if treatment with a compound ~~according to formula I, II or III, wherein X, Y, R_1, R_2 and R_3 have the meaning set out~~as defined in claim 1 or 2 is suitable for a patient comprising the steps of

a) determining the expression level of a gene selected from the group consisting of CD133, ATP-binding cassette sub-family G member 2, aldehyde dehydrogenase 1, musashi homolog 1, Nestin and sex determining region Y-box 2 in a sample of tumor tissue or tumor cells of the patient;

b) comparing the expression level determined in step a) with a reference value; and

c) determining whether treatment with ~~a~~ said compound ~~according to formula I, II or III~~ is suitable for a patient based on the result of the comparison of step b), wherein over- expression indicates that said treatment is suitable for the patient.