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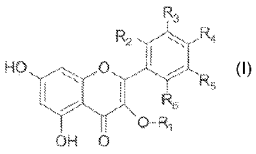

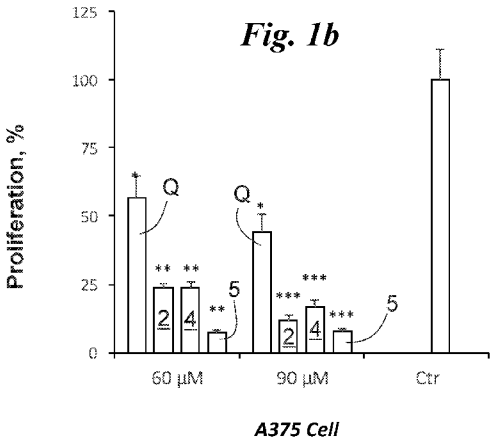

(57) Abstract: There is provided a medical compound comprising a synthetic flavone derivative, according to the formula (I) with allotment in position C-3 of a group as shown below: Formula (I) wherein at least two of R_2-R_6 a re H, and the remaining are independently selected from: H, OH, R_1, OR_1, NO_2, NH_2, NHR_1, F, CI, Br, I, where R_1 is a radical. Also provided are dimeric, trimeric and tetrameric compounds, where two or more quercetin units are linked through position 3 and a spacer to a central linker (scaffold). The medical compounds may be used for the treatment of malignant tumours, in particular malignant epithelial tumours, such as colon carcinoma, melanoma and/or skin squamous carcinoma, lung carcinoma, mammary carcinoma, basal cell carcinoma (basalioma).

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[Continued on next page]

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DESCRIPTION

MEDICAL COMPOUND

The present invention relates to a medical compound, particularly for the treatment of malignant tumours, more particularly malignant epithelial tumours and lung carcinoma, colon carcinoma, melanoma and skin squamous carcinoma, or for anti-inflammatory and analgesic activities of the type specified in the preamble of the first claim.

In recent decades, neoplastic disease is emerging as one of the biggest challenges for medicine as well as one of the major causes of mortality, in both developing and industrialised countries. Every year, about 1.6 million new cases of neoplasia are diagnosed and to date more than 100 different types of neoplasia are known, including a huge variety of epithelial tumours, especially breast, lung, colorectal, prostate, liver and skin carcinomas.

Despite the progress made in the treatment of neoplastic disease, further advances are undoubtedly required, mainly due to the severe side effects associated with the most common anti-cancer therapies, such as chemo- and radio-therapy.

In the effort to find new drugs, several studies have attempted to investigate the anti-tumour potential of substances derived from fruit and vegetables, called plant protection products. Among the plant protection products known to date, flavones and flavonoids, particularly quercetin, in many studies have shown anti-neoplastic properties against different tumour cell lines, such as leukaemia HL-60, colon carcinoma SW-480, murine mammary carcinoma 4T1 and epidermoid carcinoma A431.

Quercetin (3,3',4',5,7-pentahydroxyl flavone) is a natural flavonoid characterized by the presence of 5 hydroxyl groups responsible for its biological activity. It occurs in

a wide variety of plants, in particular broccoli, tea leaves, onion, carrots. In nature, its activity allows the bilateral growth of embryos in plants to be inhibited. The most representative quercetin derivatives are glycosides and esters. Numerous studies have shown the antioxidant power of quercetin, which is attributable to the presence of the hydroxyl group in ring A and the catechol group in ring B. These characteristics allow quercetin to remove the oxygen free radicals, by transferring hydrogen or electrons or chelating metal ions, thus inhibiting the pro-inflammatory enzymatic activities.

Flavonoid compounds inhibit lipid peroxidase activity, by preventing LDL (low density lipoprotein) oxidation and cell membrane damage. In addition, flavonoids raise glutathione levels and prevent the formation of free radicals.

The therapeutic efficacy of quercetin is closely related to its bioavailability after oral administration. After ingestion, quercetin is hydrolyzed by intestinal glycosidase enzymes and absorbed as an aglycone through the stomach or the gut. Subsequent enzymatic modifications of the molecule transform it into pharmacologically active forms, such as quercetin-3-glycoside, quercetin-3-sulphate, quercetin-3-glucuronide, quercetin-3-methyl ether.

Quercetin metabolic process in the human body is very fast, therefore its availability in the active form is limited. Moreover, quercetin is poorly water-soluble, further affecting its therapeutic potential. It is therefore necessary to increase the water-solubility and delay the metabolism of quercetin in order to obtain extended blood and tissue levels of the molecule.

The anti-neoplastic effects of quercetin involve multiple aspects:

1) Cell growth inhibition: quercetin has shown anti-proliferative effects in different types of neoplasia, both in vitro and in vivo. In vitro, it inhibited cell growth

in L1210 and P388 leukemia cell lines, mammary tumour, COLO 20DM colon carcinoma, OVCA 43 ovarian carcinoma, and A431 epidermoid carcinoma. The molecular mechanisms involved appear to be the modulation of pro-proliferative intracellular cascades such as PI3K/akt, Her-2/neu, Wnt/beta-catenin, and EGFR. Quercetin appears to inhibit the activity of mammalian Target Of Rapamycin (mTOR), which is hyperactive in neoplastic cells and essential in controlling intracellular growth signals, in apoptosis mechanisms, protein synthesis and PI3K/Akt activation. In addition to suppressing the activation of PI3K/Akt, quercetin down-regulates Her-2/neu (human epidermal growth factor receptor 2) over-expressed in some mammary neoplasms and allows for inhibition of the Wn/beta-catenin signalling pathway, resulting in reduced cell growth. In addition to modulating the pro-proliferative intracellular signalling pathways described above, quercetin interferes with normal cell cycle progression, leading to reduced cell growth.

2) Inhibition of the metastatic process: the metastatic process is closely linked to the production of metalloproteinases (MMPs), which are enzymes responsible for extracellular matrix degradation and invasion of surrounding tissues by tumour cells. Several studies have analysed the potential of quercetin in the inhibition of MMPs.

3) Induction of apoptosis: apoptosis, or programmed cell death, is essential in the homeostasis of the human body. Dysregulation and defects in apoptotic processes lead to the development of neoplasms. Quercetin has been shown to increase the synthesis of pro-apoptotic factors in mammary and colorectal carcinoma cell lines.

Despite these promising aspects of flavones and flavonoids, their current use as potential candidates for the treatment of malignant tumours suffers from some

limitations. In fact, as previously mentioned, these molecules exhibit low solubility in H_2O (1 mcg/mL), low intrinsic activity, low absorption (<10%), a fast metabolism (<1 hr), a fast clearance from the body (>40%), multiple inactive metabolic products.

These features indicate that it is strictly necessary to identify quercetin derivatives having greater bioavailability and greater biological activity in order to use these plant protection products in the treatment of malignant neoplasms.

In this context, the technical task underlying the present invention is to devise a medical compound, particularly for the treatment of malignant, particularly epithelial tumours, or for anti-inflammatory activity, or the like, which is capable of substantially obviating at least some of the above-mentioned drawbacks.

Within the scope of said technical task, a major object of the invention is to obtain a medical compound for the treatment of malignant tumours in general, and in particular lung carcinoma, colon carcinoma, melanoma, skin squamous carcinoma, and basal cell carcinoma (basalioma).

The technical task and the specified objects are achieved by means of a medical compound as claimed in the appended claim 1.

The features and advantages of the invention will be apparent from the detailed description of preferred embodiments of the invention, with reference to the accompanying drawings, in which:

Figs. 1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 5a, 5b, 6a, 6b, 7a, 7b, 8a, 8b, 9a, 9b, 10a, 10b, 11a, 11b, 12, 13a, 13b, 14, 15, 16, 17, 18, 19, 20, 21, 22a, 22b show the results of tests carried out following treatments performed with standard compounds and with the medical compound according to the invention.

Preferred embodiments are described in the dependent claims.

In the present document, the measures, values, shapes and geometric references

(such as perpendicularity and parallelism), when associated with terms like “about” or other similar terms such as “almost” or “substantially”, are to be understood as unless measurement errors or inaccuracies due to production and/or manufacturing defects and, especially, unless a slight difference from the value, measure, shape, or geometric reference with which it is associated. For example, these terms, if associated with a value, preferably indicate a difference not exceeding 10% of the value itself.

Furthermore, when used, terms such as "first", "second", "higher", "lower", "main" and "secondary" do not necessarily identify an order, a priority relationship or a relative position, but can simply be used to distinguish more clearly the different components from each other.

The measurements and the data reported in this text are to be considered, unless otherwise indicated, as carried out in the International Standard Atmosphere ICAO (ISO 2533).

The medical compound according to the invention is particularly used for the treatment of malignant tumours, in particular malignant epithelial tumours. The term “epithelial tumours” is intended to mean malignant neoplasms derived from epithelial tissue (skin, mucosa, glandular system). Neoplastic transformation changes the numerical homeostasis of cells in the tissue, causing uncontrolled growth and genomic instability.

In particular, the compound according to the invention is used for one or more of the following malignant tumours, in particular malignant epithelial tumours: colon carcinoma, melanoma and/or skin squamous carcinoma, lung carcinoma, mammary carcinoma, basal cell carcinoma (basalioma).

In addition, the compound according to the invention is preferably used to stem the

proliferation of the aforementioned tumours, since it affects the tumours' proliferative ability and apoptosis. It can also be used both to induce cell death and apoptosis, for example by increasing ROS (reactive oxygen species), disrupting the mitochondrial activity, damaging the DNA or activating caspases 3, 8 and 9, and to cause cell cycle arrest.

Furthermore, the compound according to the invention is used for one or more of the following malignant tumours: head and neck cancer, stomach cancer, liver cancer, pancreatic cancer, breast cancer, prostate cancer, bladder cancer, kidney cancer, mesothelioma, and ovarian cancer.

The compound according to the invention does not apply to the treatment of hepatitis C and the consequent malignant liver tumours or hepatocellular carcinoma induced by hepatitis C virus infection.

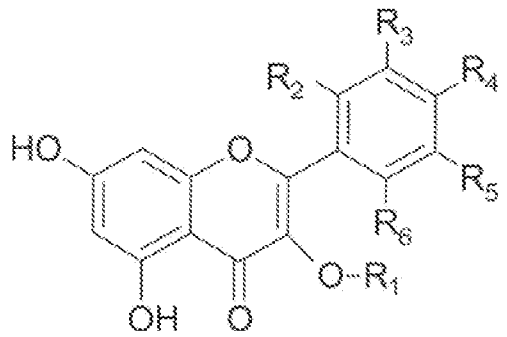
Still further, the compound according to the invention is used for one or more of the following malignant tumours: salivary gland tumours, esophageal cancer, small intestine tumours, gall bladder and extrahepatic biliary tract cancer, soft tissue sarcoma, cervical cancer, uterine cancer, testicular cancer, urinary tract tumours, choroidal melanoma, thyroid cancer, endometrial cancer, retinal tumour, uveal melanoma, anal canal cancer and anal cancer, bone and joint cancer.

Finally, the compound according to the invention is used for non-tumour therapeutic uses of our compounds, namely for:

- anti-inflammatory activity,
- analgesic activity,
- antimicrobial activity (bacteria, viruses, fungi),
- immunomodulatory activities,
- antioxidant activity,

- cytoprotective and nourishing activity,
- anti-degenerative and anti-ageing activities,
- in idiopathic chronic inflammatory diseases (Crohn's disease, ulcerative rectocolitis, irritable colon syndrome, fibromyalgia, arthritis, myopathy),
- in neurodegenerative diseases (Alzheimer's disease, Huntington's disease, ALS, Parkinson's disease, senile dementia, glaucoma),
- in syndromes from long-term toxicity of chemotherapy and radiotherapy (central and peripheral neurotoxicity, inflammation, oxidative stress, fatigue, vomiting, nausea, diarrhea, constipation, impotence, hearing loss, heart disease).

The compound according to the invention is preferably a synthetic flavone derivative, according to the formula (I) with allotment in position C-3 of a group as shown below.



(I)

wherein at least two of R_2-R_6 are H, and the remaining are independently selected from: H, OH, R_1, OR_1, NO_2, NH_2, NHR_1, F, Cl, Br, I, and more particularly R_2, R_3, R_6 are H, and R_4 and R_5 are OH,

where R_1 is a radical preferably selected from:

- H;
- C_{1-24} alkyl or heteroalkyl, C_{1-24} alkenyl or heteroalkenyl; C_{1-24} alkynyl or heteroalkynyl
- an acyl residue of a fatty acid. Said fatty acid can be saturated, unsaturated,

polyunsaturated, of either synthetic or natural origin.

Preferably, R_1 is:

where R'_1 is selected from the same compounds as R_1,

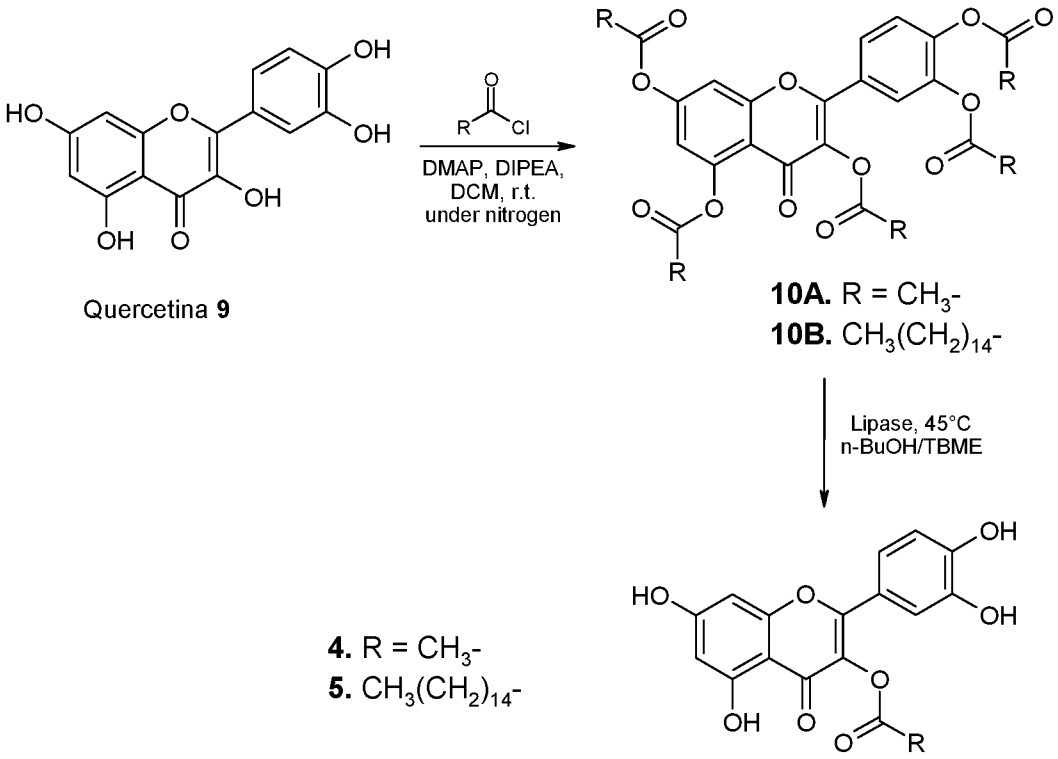
where a, b, and c each range from 0 to 12,

where X, Y, and Z are each independently selected from: CH2, O, N(R1), S, NH, SO, SO_2, OC(O), CO, NHC(O), C(O)NH, NH-C(O)-NH, NH-C(S)-NH.

As regards the synthesis of quercetin ethers 1, 2 and 3, the synthetic strategy provides an orthogonal protection of quercetin as reported by Rolando et al. (Tetrahedron Letters, 2011, 52, 4738). The synthesis of quercetin ethers 1, 2 and 3, starting from commercial rutin 6, provides extensive benzylation of the free hydroxyl groups, followed by selective hydrolysis of the disaccharide in position 3 and consequent alkylation with the appropriate alkyl bromide, and finally, removal of the benzyl groups through Pd/C-catalysed hydrogenation. The strategy is simplified below:

Rutin

The synthesis of quercetin esters 4 and 5 is carried out by means of the enzymatic strategy reported by D. Lambusta et al. (J. Mol. Catal. B-Enzymatic, 2003, 22, 271). The strategy comprises the esterification of quercetin 9 on all five hydroxyl groups, followed by selective alcoholysis mediated by the appropriate selection of lipases from Candida antarctica (CAL) and Mucor miehei (MML), as shown in the following scheme.

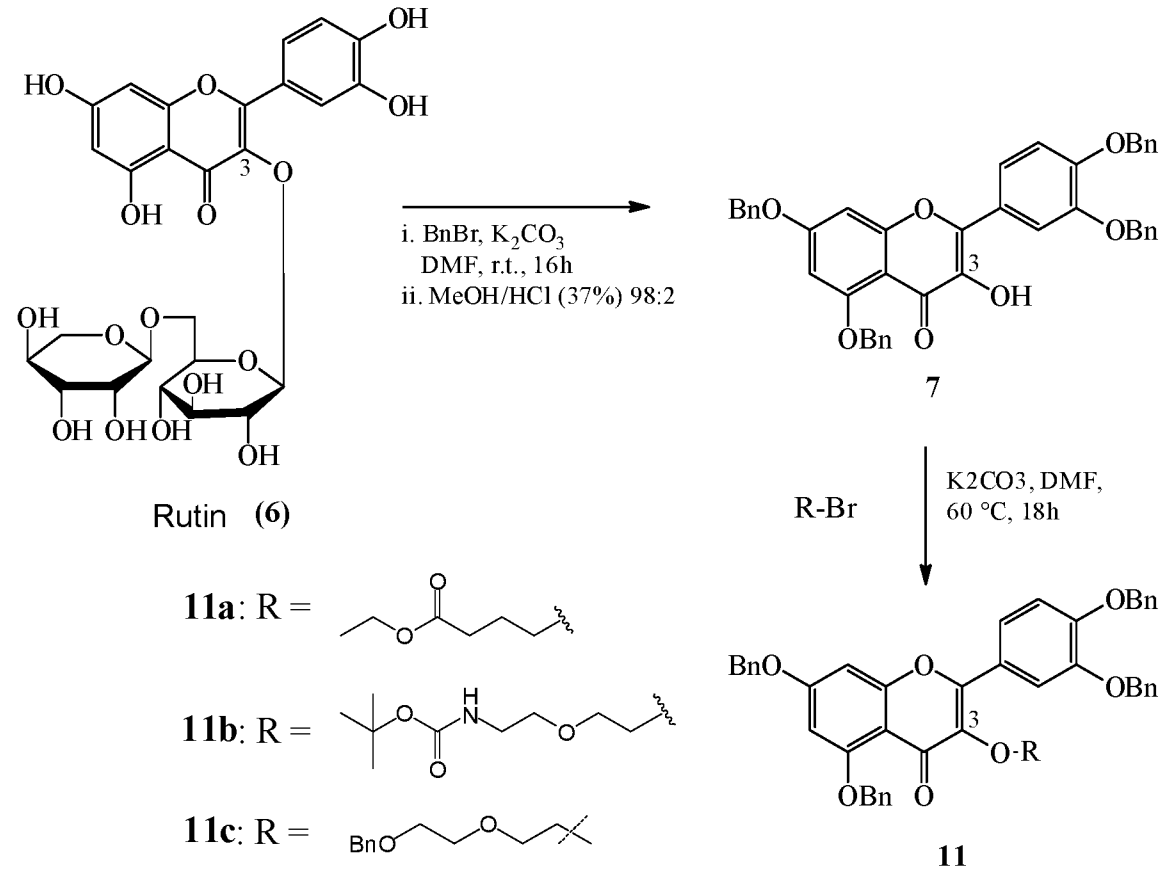


Quercetina **9**

10A. R = CH_3-
10B. $CH_3(CH_2)_{14}$-

4. R = CH_3-
5. $CH_3(CH_2)_{14}$-

Similarly as described for the synthesis of products 8, shown below is the synthesis of products of the series 11, as set forth in the following scheme.



Rutin **(6)**

7

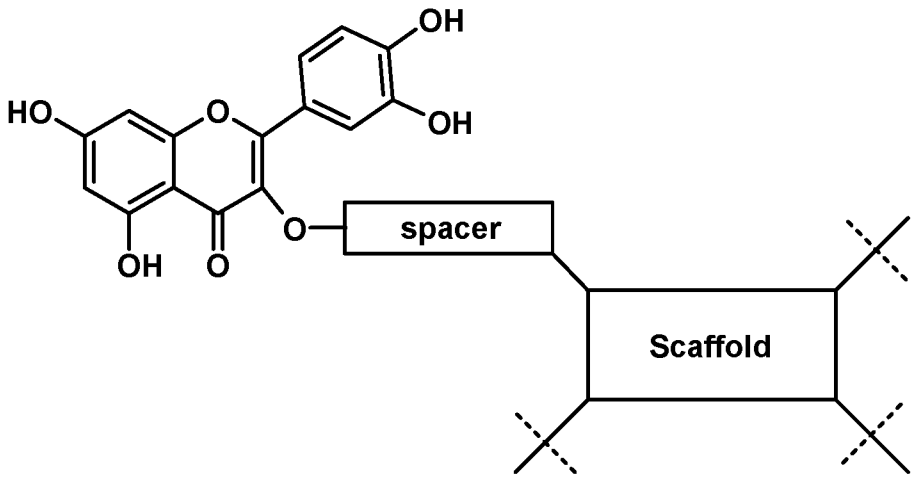
11a: R =

11b: R =

11c: R =

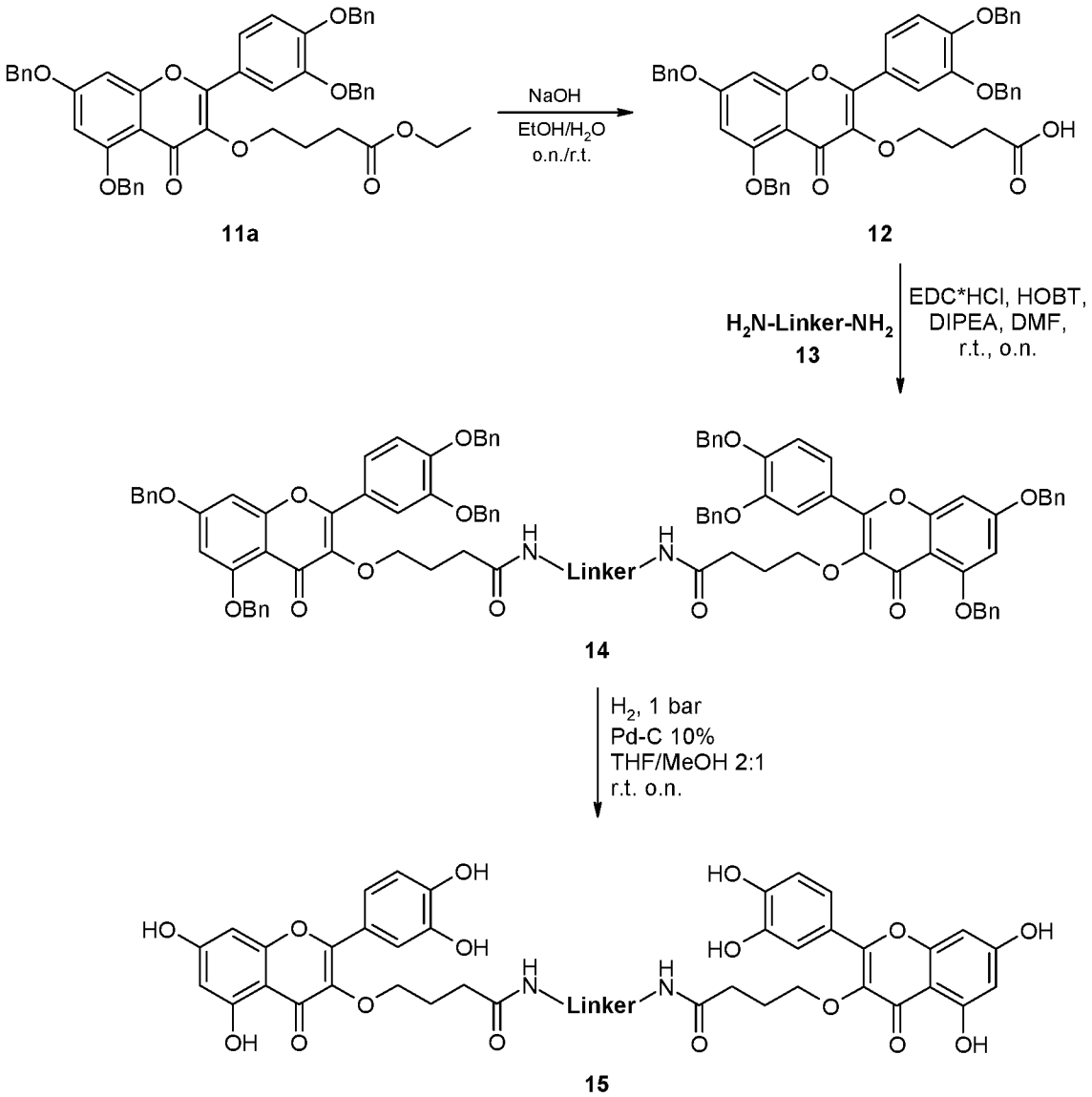
11

The compounds according to the invention also include di-, tri- and tetra-meric molecules, where two or more quercetin units are linked, through position 3 and a spacer, to a suitable central linker (scaffold), as reported below.

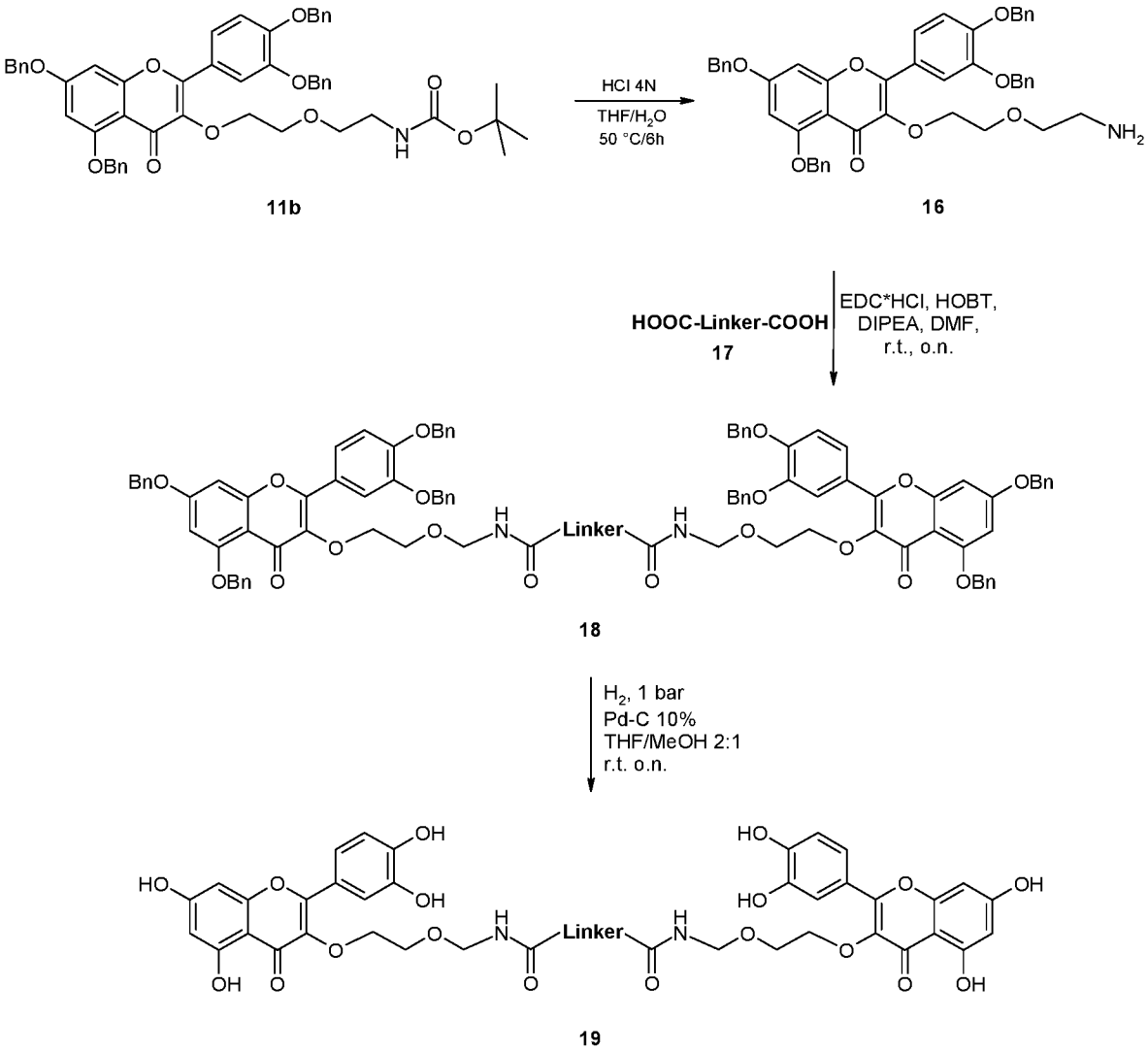


The selection of both the spacer and the central scaffold was made attempting to investigate the effect due to the flexibility and the distance between the quercetin units.

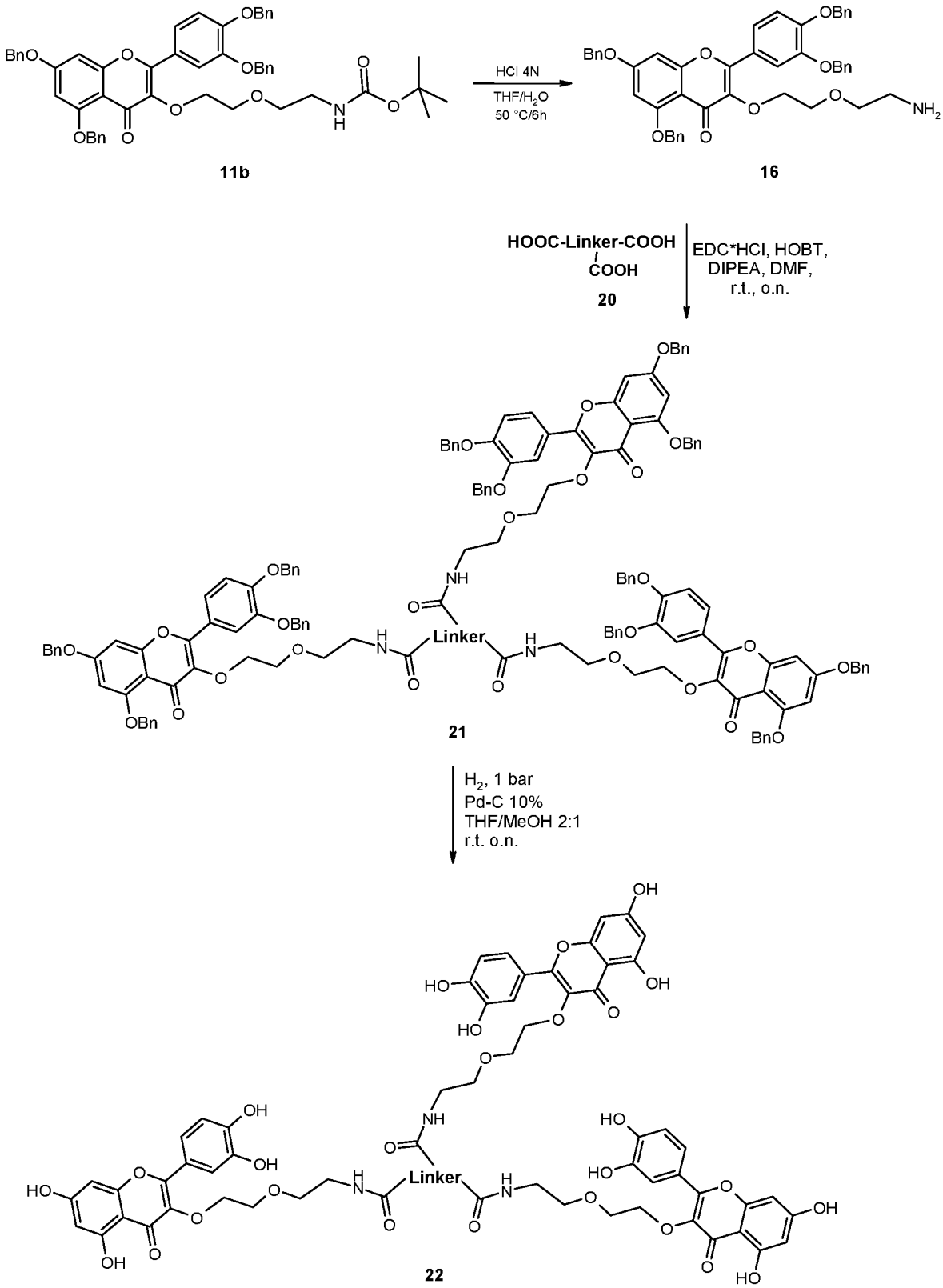
A first group of dimeric molecules was synthesized by the strategy shown in the following scheme, where the ethylester of the intermediate 11a is hydrolyzed by treatment with sodium hydroxide in THF/H2O and the corresponding carboxylic acid 12, activated with EDC/HOBt, is condensed with the suitable diamine (H2N-linker-NH2) 13. Lastly, the final products 15 were obtained by extensive debenzylation of the intermediates 14 carried out by a classical catalytic hydrogenation.



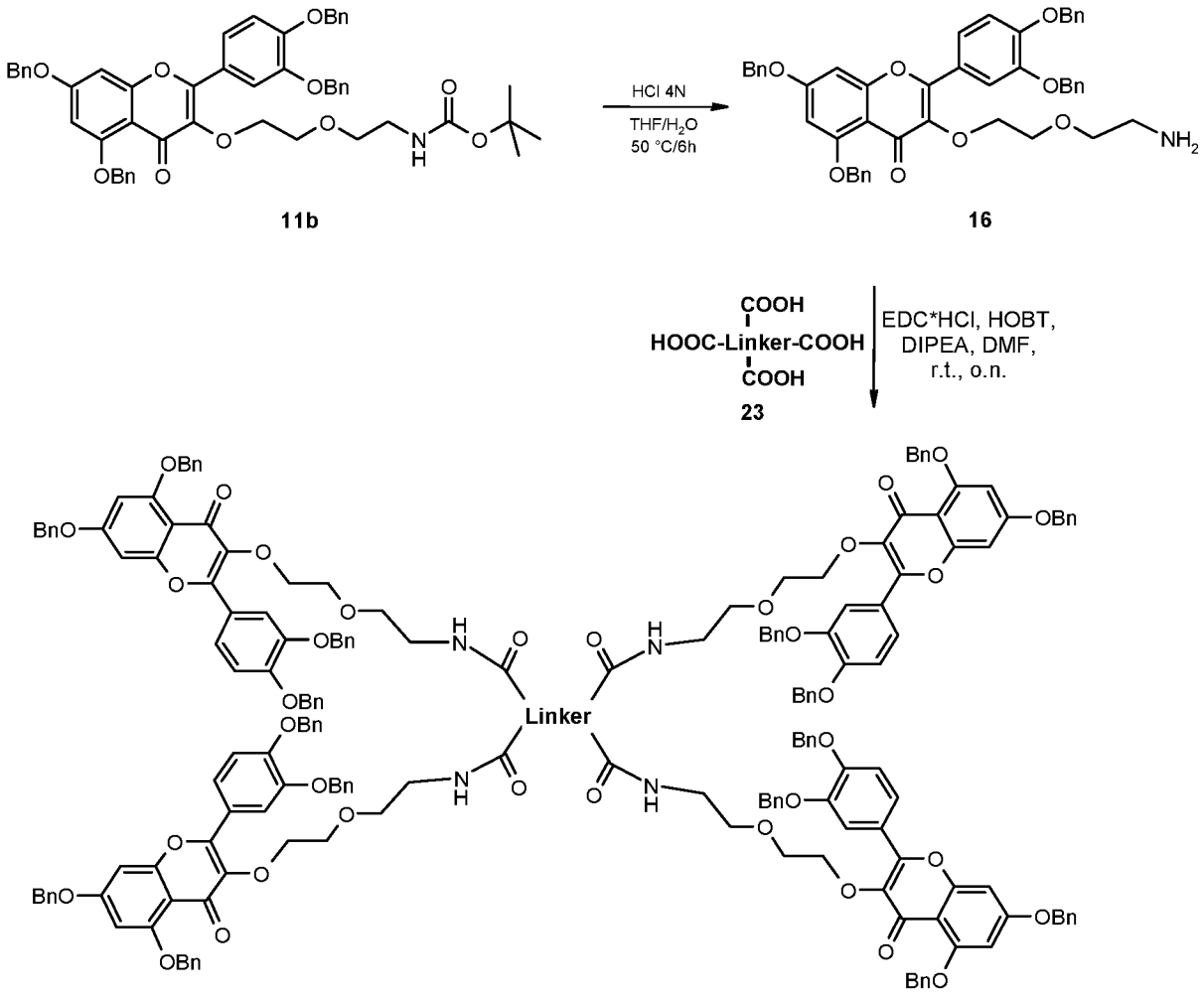
A second group of dimeric molecules was synthesized by the strategy shown in the following scheme, which comprises the removal of the protective group (BOC) from the amine 11b by treatment with 4N HCl in THF/H2O. The corresponding amine 16 is then condensed with the suitable dicarboxylic molecule 17, upon activation with EDC/HOBt. Lastly, the final products 19 were obtained by extensive debenzylation of the intermediates 18 carried out by catalytic hydrogenation.



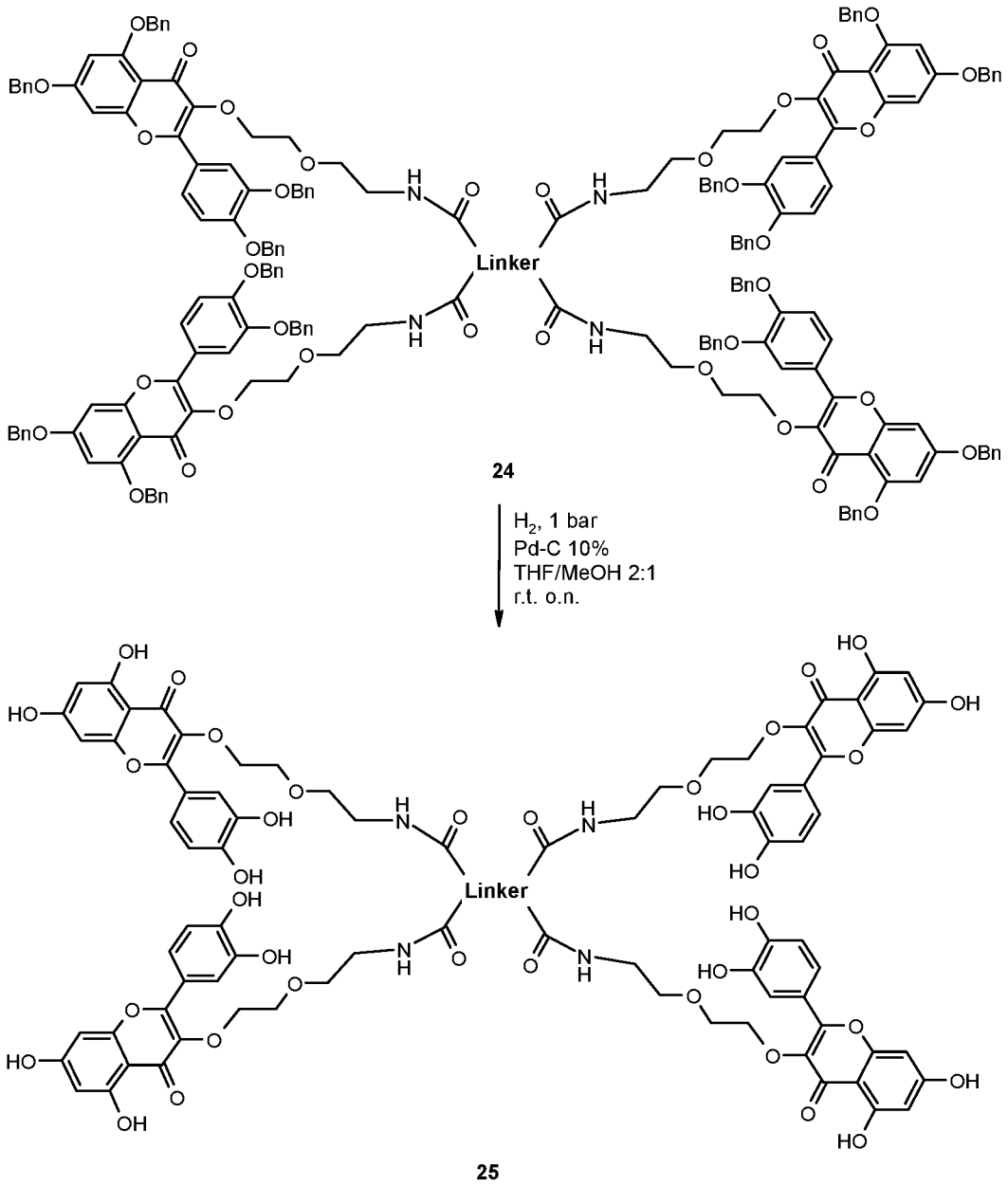
Similarly, the trimeric molecules were synthesized starting from intermediate 16 by condensation with the appropriately selected tricarboxylic molecule 20, upon activation with EDC/HOBt (scheme below). The final products 22 were obtained by extensive debenzylation of the intermediates 21 carried out by a classical catalytic hydrogenation.



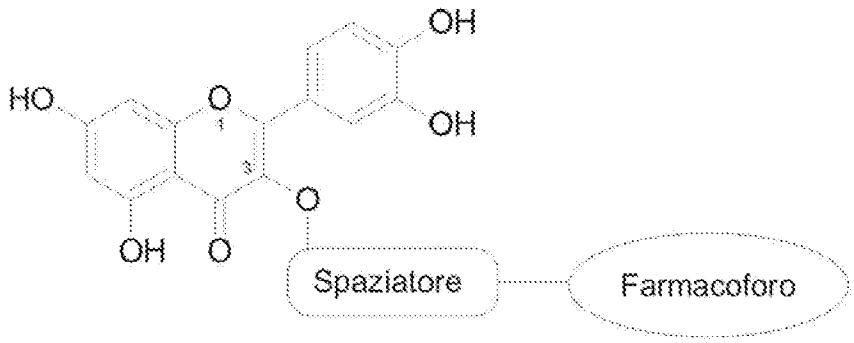
The tetrameric molecules are synthesized starting from intermediate 16 by condensation with the appropriately selected tetracarboxylic molecule 23, upon activation with EDC/HOBt (scheme below).



Lastly, the final products 25 were obtained by extensive debenzylation of the intermediates 24 carried out by a classical catalytic hydrogenation (scheme below).



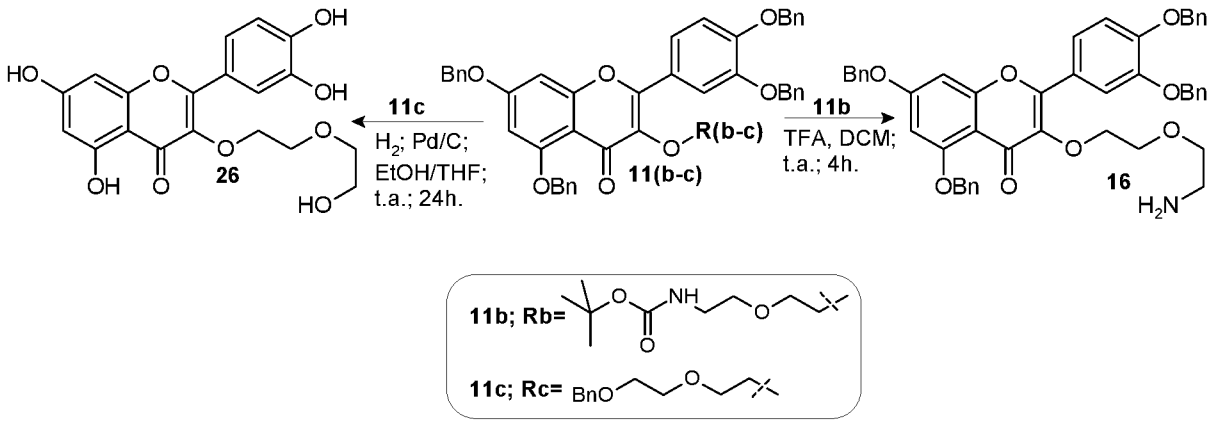
Other compounds according to the invention include molecules in which a pharmacophore appendage is linked, through an appropriate spacer bridge, to the oxygen in position 3 of quercetin (Figure below).



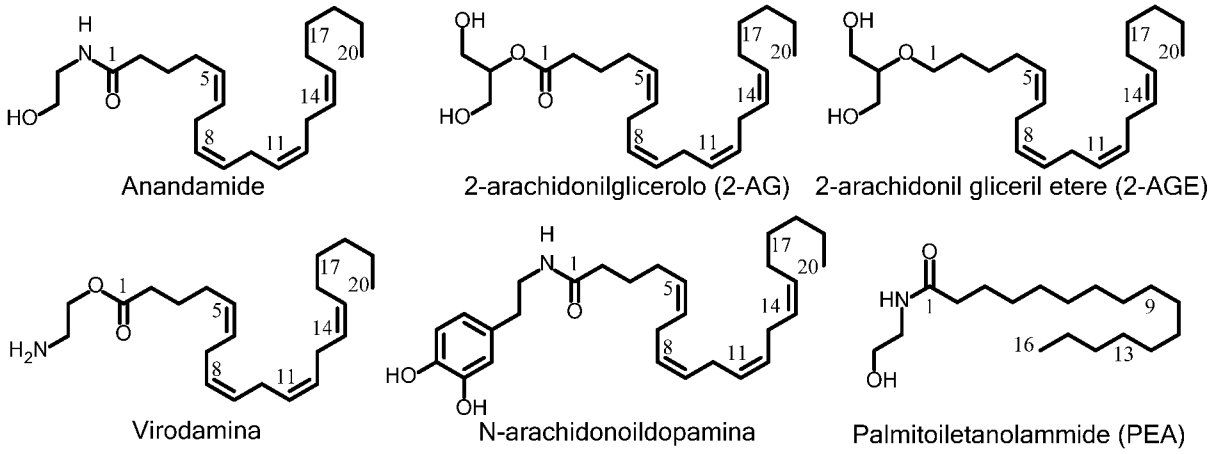
["Spaziatore" = Spacer;

"Farmacoforo" = Pharmacophore]

These molecules were synthesized starting from compounds 11(b-c), thereby obtaining quercetin derivatives 26 (obtained by complete debenzylation of 11c) and 16 (obtained by removing the protecting group Boc from 11b in an acidic environment), according to the following scheme.



Some of the compounds according to the invention exhibit, as the pharmacophore group, a chemical structure relatable to endocannabinoids and N-acylethanolamines (NAEs; the structures of biological compounds relevant to humans are shown in the following figure).



["2-arachidonilglicerolo" = 2-arachidonylglycerol;

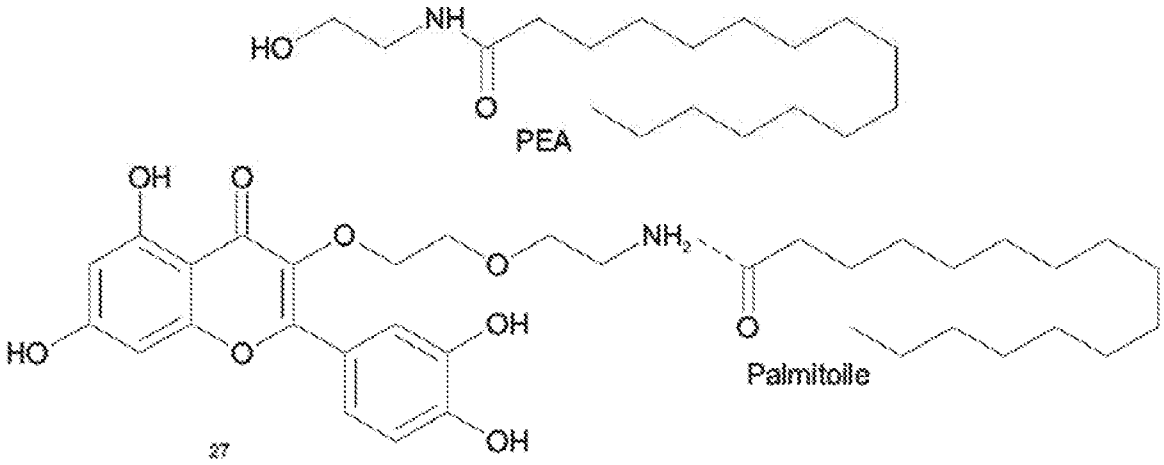
"2-arachidonil gliceril etere" = 2-arachidonyl glyceryl ether;

"Virodamina" = Virodamine;

"N-arachidonoildopamina" = N-arachidonoyl dopamine;

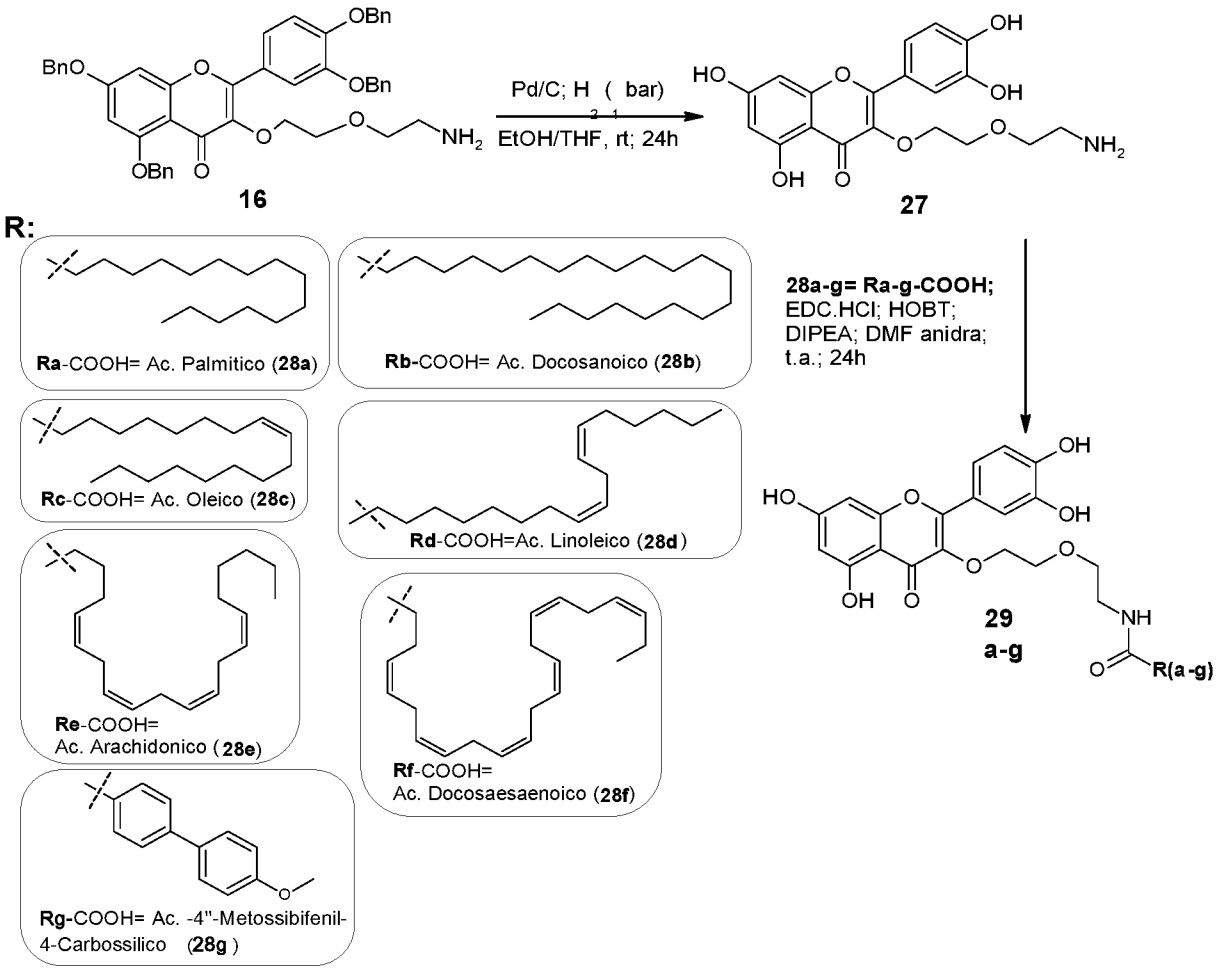
"Palmitoiletanolammide" = Palmitoylethanolamide]

As an example, palmitic acid ethanolamide (PEA), arachidonic acid (anandamide) ethanolamide, and dopamine amide with arachidonic acid (N-arachidonoyl dopamine) can be mentioned among the main structures listed in the figure above. By comparing these structures with that of quercetin derivative 27 (scheme below), it appears that in the latter the chain linked to the oxygen in position 3 can mimic, in its final aminoethanol portion, the ethanolamine portion of endocannabinoids and NAEs, while the innermost ethylene portion acts as a spacer between quercetin and the pharmacophore (e.g. in the following figure, which shows PEA at the top, the formation of the compound according to the invention containing the PEA structure, by joining the quercetin derivative 27 with a suitable acyl group, the ethylene bridge between the two oxygens separating the two structures, at the bottom).



["Palmitoile" = Palmitoyl]

Therefore, by binding the appropriate acyl portion to the quercetin derivative 27, quercetin molecules are obtained, whose oxygen in position 3 is joined, through an ethylene spacer, to an endocannabinoid or a NAE. Quercetin derivative 27, obtained by debenzylation of compound 16, through its amine function, has thus been channelled into a parallel synthesis process for obtaining amides, wherein each time it was reacted with a different acid (28(a-g)) previously activated with EDC and HOBt to obtain amides 29(a-g) (scheme below).



["Ac. Palmitico" = Palmitic acid;

"Ac. Docosanoico" = Docosanoic acid;

"DMF anidra" = Anhydrous DMF;

"t.a." = r.t.;

"Ac. Oleico" = Oleic acid;

"Ac. Linoleico" = Linoleic acid;

"Ac. Arachidonico" = Arachidonic acid;

"Ac. Docosaesaenoico" = Docosahexaenoic acid;

"Ac. 4"-Metossibifenil-4-Carbossilico" = 4"-Methoxybiphenyl-4-carboxylic acid]

Compounds according to the invention with different, unique and new acyl residues (compounds 29b, 29c, 29d, 29f) were therefore synthesized in addition to those

containing PEA (29a) and anandamide (29e), so as to also obtain information about the importance of the type of fatty acid present in the molecule. A molecule (29g) was also made in which the acyl substituent was no longer a long chain fatty acid but a diphenyl derivative, in order to obtain information and assessment about the effects and the biological activity associated with the transition from a linear polyunsaturated system to an aromatic one.

Furthermore, the compounds according to the invention include quercetin-NAE hybrid structures, such as heterotrimeric molecules of the Q2E type, i.e. containing two quercetin units (Q) and one endocannabinoid or NAE unit (E). For this purpose, the endocannabinoid arachidonoyl dopamine (Figure 3), in which the two dopamine phenolic groups allow attachment of two quercetin units, was taken as a model. The molecule 36, in which arachidonic acid (present in the reference template, i.e. the endocannabinoid arachidonoyl dopamine) is replaced by palmitic acid and each

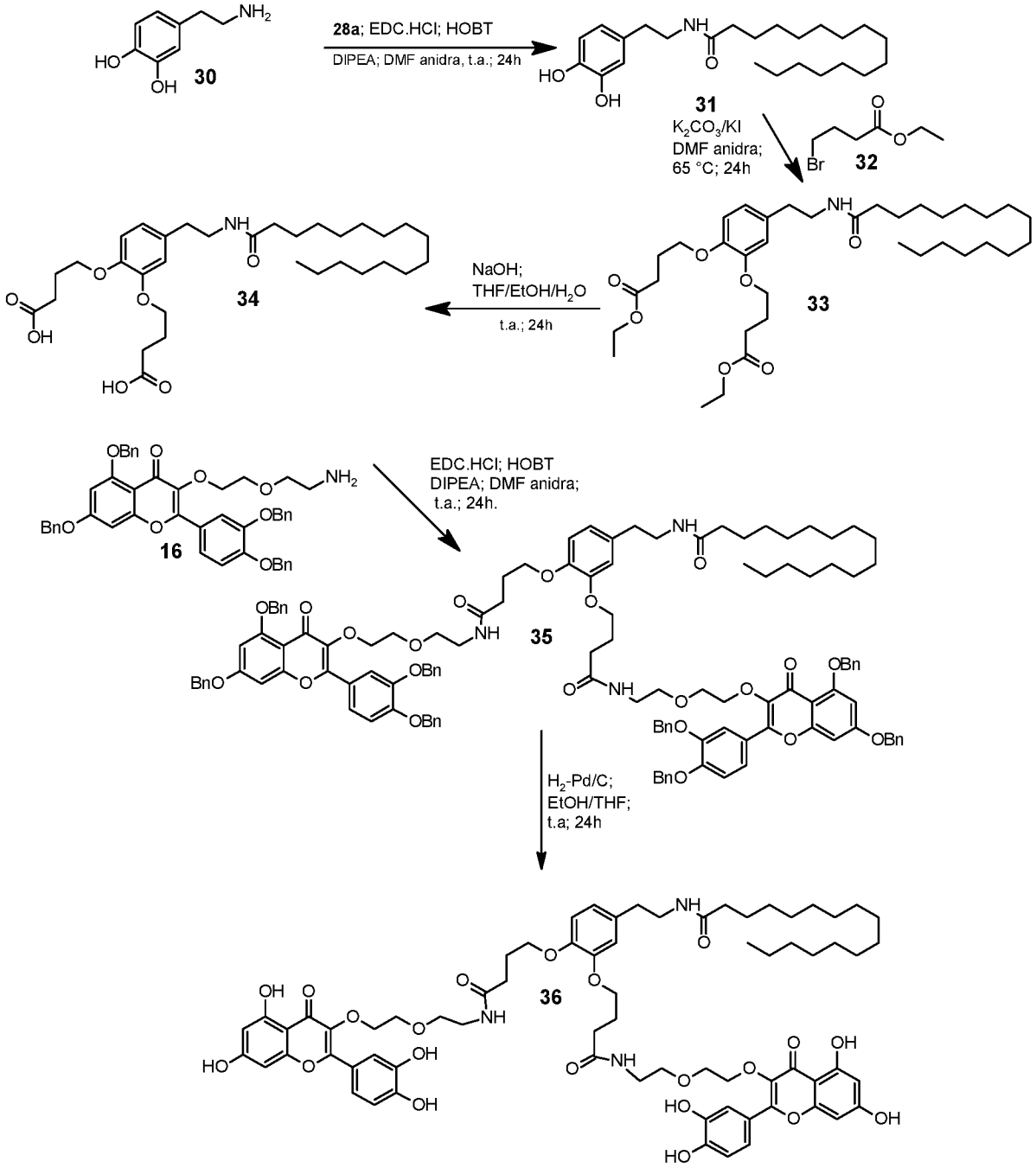
Q2E quercetin is bridged to a different dopamine hydroxyl group (scheme below), was prepared as the first representative of this class of compounds.

In short, the dopamine 30 was reacted with EDC/HOBt-activated palmitic acid to yield the amide 31, which in turn was converted into the diester 33 by reaction with

["DMF anidra" = Anhydrous DMF;

"t.a." = r.t.]

the bromide 32. The basic hydrolysis of the diester afforded the diacid 34, which,



upon activation with EDC and HOBt, was reacted with an excess of quercetin tetrabenzylate 16 to obtain the compound 35, which by hydrogenation in the presence of Pd/C was completely debenzylated to yield the target molecule 36. A molecule was thus obtained, in which an artificial analogue of the endocannabinoid arachidonoyl dopamine, i.e. palmitoyl dopamine, is linked to two quercetin units, thereby forming a heterotrimer of the Q_2E type.

Examples of synthesis of the various components are set out below. All chemical reagents used were of analytical grade and were used as received.

^1H and ^{13}C-NMR experiments were recorded in deuterated solvents indicated in a Bruker Avance 400™ spectrometer at 400.13 and 100.62 MHz, respectively. Coupling constants are reported in Hertz and rounded off to the nearest 0.1 Hz. Where required, chromatographic purifications were performed on silica gel by flash chromatography (70-230 mesh) using the eluants specified.

Where specified, reactions were carried out using a CEM Discover microwave reactor.

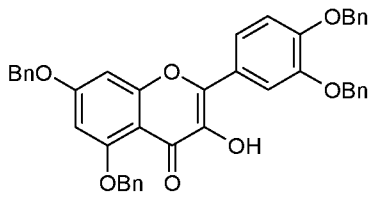
Example of synthesis of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-hydroxy-4*H*-chromen-4-one: 7.

Anhydrous K_2CO_3 (1.81 g; 13.1 mmol) and benzyl bromide (2.24 g; 13.1 mmol) were added sequentially to a solution of 2-(3,4-dihydroxyphenyl)-4,5-dihydroxy-3-[3,4,5-trihydroxy-6-[(3,4,5-trihydroxy-6-methyl-oxan-2-yl)oxymethyl]oxan-2-yl]oxy-chromen-7-one **6** (1 g; 1.6 mmol) in DMF (12 ml). The reaction mixture is allowed to stir under argon atmosphere at room temperature. Upon completion (about 24 hours), the reaction mixture was diluted with EtOAc (40 ml) and washed with H_2O (2 × 30 ml). The organic phase was dried with anhydrous Na_2SO_4, filtered, and the

solvent was removed under reduced pressure. The residue is added with a mixture of HCl (37 %)/MeOH = 2/98 v/v, and heated to reflux (T°= 65°C) for 2 hours.

Upon completion, the mixture is allowed to cool to room temperature, then filtered through a Buchner funnel, and finally the orange solid is washed with cold methanol.

The final product **7** thus obtained does not require a further final purification (450 mg; 42.45 %).



7

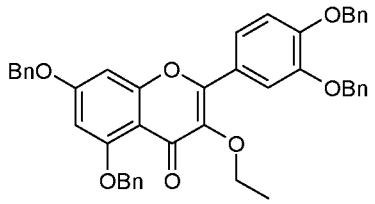
^{1}H NMR (400 MHz, $CDCl_3$): 7.88 (s, 1H), 7.75 (d, 1H, *J* = 6.5 Hz), 7.65-7.25 (m, 21H, Ph), 7.01 (d, 2H), 6.56 (s, 1H, *J* = 8.7 Hz), 6.45 (s, 1H), 5.26 (s, 2H, C*H*$_2$Ph), 5.23 (s, 2H, C*H*$_2$Ph), 5.21 (s, 2H, C*H*$_2$Ph), 5.11 (s, 2H, C*H*$_2$Ph);

^{13}C NMR (100 MHz, $CDCl_3$): 171.70, 163.19, 159.33, 158.63, 150.14, 148.58, 141.83, 137.68, 137.13, 136.82, 136.15, 135.59, 128.74, 128.62, 128.53, 128.45, 127.89, 127.85, 127.77, 127.62, 127.53, 127.18, 126.63, 124.26, 121.20, 114.17, 106.68, 97.52, 93.66, 71.52, 70.93, 70.67, 70.53.

Example of synthesis of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-ethoxy-4H-chromon-4-one: 8a.

Ethyl iodide (0.072 ml; 0.0009 mol) and anhydrous K2CO3 (0.104 g; 0.0007 mol) were added sequentially to a solution of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-hydroxy-4H-chromen-4-one 7 (0.2 g; 0.0003 mol) in anhydrous DMF (2.14 ml). The reaction mixture is stirred at a temperature of 65°C for 12 hours. Upon completion, the reaction was partitioned between water (10 ml)

and EtOAc/DCM (1/1; 30 ml). The organic phase was washed with a saturated aqueous solution of NaCl and the aqueous phase extracted with 10 ml of EtOAc/DCM (1/1). The combined organic phases were dried over anhydrous sodium sulphate, the solvent was removed under reduced pressure, and the residue as a yellow solid (290 mg) was purified by flash column chromatography (SiO2; EtOAc/n-hexane 25%). The product 8a was isolated as a white solid (120 mg, 60%).



8a

^{1}H NMR (400 MHz, $CDCl_3$): 7.83 (d, 2H), 7.68 (dd, 1H), 7.61 (d, 2H), 7.54-7.27 (m; 19H), 7.02 (d, 1H), 6.53 (d, 1H), 6.45 (d, 1H), 5.24 (d, 6H), 5.09 (s, 1H), 4.06 (q, 2H), 1.26 (t, 3H);

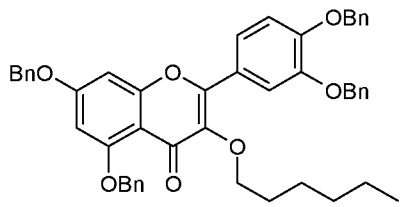
^{13}C NMR (100 MHz, $CDCl_3$): 173.95, 162.66, 159.77, 158.65, 152.70, 150.65, 148.27, 140.23, 137.05, 136.77, 136.40, 135.71, 128.74, 128.57, 128.53, 128.41, 127.95, 127.87, 127.61, 127.58, 127.31, 127.19, 126.66, 124.15, 122.20, 115.26, 113.81, 98.01, 93.86, 71.43, 70.93, 70.79, 70.45, 68.15, 15.60.

Example of synthesis of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-hexyloxy-4H-chromon-4-one: 8b.

Hexyl bromide (0.084 ml; 0.0006 mol), anhydrous K2CO3 (0.104 g; 0.0007 mol) and KI (0.015 g; 0.00009 mol) were added sequentially to a solution of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-hydroxy-4H-chromen-4-one 7 (0.2 g; 0.0003 mol) in anhydrous DMF (2.14 ml). The reaction mixture is stirred at a temperature of 65°C for 12 hours. Upon completion, the mixture was partitioned

between water (10 ml) and EtOAc/DCM (1/1; 30 ml). The organic phase was washed with a saturated aqueous solution of NaCl and the aqueous phase extracted with 10 ml of EtOAc/DCM (1/1). The combined organic phases were dried over anhydrous Na2SO4 and the solvent was removed under reduced pressure. The residue obtained as a yellow oil (173 mg) was purified by cold precipitation from a solution of EtOAc/hexane. The white solid product corresponding to 8b was separated from the liquid by centrifugation and the traces of solvent were removed under reduced pressure.

The white solid 8b (67.5 mg; 30 %).



8b

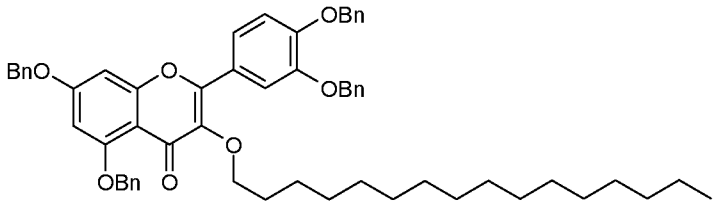
^{1}H NMR (400 MHz, $CDCl_3$): 7.82 (d, 2H, *J* = 1.8 Hz), 7.68 (dd, 1H, J_1 = 8.6 Hz; J_2 = 1.8, Hz), 7.62 (d, 2H, *J* = 7.6 Hz, CH_2Ph), 7.55-7.27 (m, 18H, CH_2Ph), 7.02 (d, 1H, *J* = 8.6 Hz), 6.53 (d,1H, *J* = 2.0 Hz), 6.45 (d, 1H, *J* = 2.0 Hz), 4.02 (t, 2H, *J* = 7.1 Hz), 1.56-1.53 (m, 2H), 1.40-1.20 (m, 6H), 0.87 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 173.82, 162.56, 159.68, 152.53, 150.60, 148.24, 140.43, 136.73, 136.40, 128.66, 128.45, 127.87, 127.80, 127.53, 127.28, 127.12, 126.59, 124.07, 122.28, 115.23, 113.72, 110.01, 97.96, 93.79, 72.67, 71.40, 70.85, 70.68, 70.37, 31.59, 30.08, 25.52, 22.54, 13.98.

Example of synthesis of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-hexadecyloxy-4H-chromon-4-one: 8c.

Hexyl decyl bromide (0.2 g; 0.0007 mol), anhydrous K_2CO_3 (0.121 g; 0.0009 mol)

and KI (0.017 g; 0.0001 mol) were added sequentially to a solution of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-hydroxy-4H-chromen-4-one 7 (0.2 g; 0.0003 mol) in anhydrous DMF (3ml). The reaction mixture is stirred at a temperature of 65°C for 2 hours. Upon completion, the reaction mixture was partitioned between H2O (10 ml) and EtOAc/DCM (1/1; 30 ml). The organic phase was washed with a saturated aqueous solution of NaCl and the aqueous phase extracted with 10 ml EtOAc/DCM (1/1). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The obtained residue (490 mg) was purified by flash column chromatography (SiO_2; EtOAc/n-hexane 15%) and the desired product 8c was isolated as a white solid (250 mg, 73.5%).



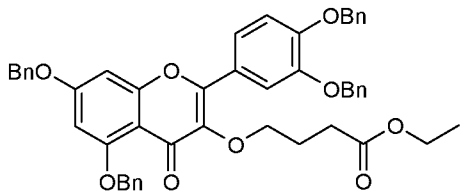
8c

^{1}H NMR (400 MHz, $CDCl_3$): 7.79 (d, 1H, *J* = 1.8 Hz), 7.66 (dd, 1H, J_1 = 8.6 Hz, J_2 = 1.8 Hz), 7.59 (d, 2H, *J* = 7.4 Hz, CH_2*Ph*), 7.53-7.28 (m, 18H, CH_2*Ph*), 7.01 (d, 1H, *J* = 8.6 Hz), 6.52 (d, 1H, *J* = 1.8 Hz), 6.44 (d, 1H, *J* = 1.8 Hz), 5.254 (s, 3H, CH_2*Ph*), 5.248 (s, 3H, CH_2*Ph*), 5.23 (s, 3H, CH_2*Ph*), 5.09 (s, 3H, CH_2*Ph*), 3.98 (t, 2H, *J* = 7.1 Hz), 1.67 (t, 2H), 1.30-1.19 (m, 29H), 0.38 (q, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): 173.76, 162.54, 159.65, 158.52, 152.44, 150.60, 148.25, 137.00, 136.71, 136.40, 135.70, 128.61, 128.45, 128.40, 128.26, 127.83, 127.48, 127.26, 127.10, 126.57, 122.23, 115.22, 113.71, 109.99, 97.91, 93.79, 72.65, 71.37, 70.84, 70.65, 70.32, 31.82, 30.13, 29.61, 29.55, 29.42, 29.26, 25.87, 22.59, 14.02.

Example of synthesis of compound 11a.

Ethyl 4-bromobutyrate (218 µl; 1.508 mmol), anhydrous K2CO3 (250 mg; 1.810 mmol) and KI (36 mg; 0.226 mmol) were added sequentially to a solution of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-hydroxy-4H-chromen-4-one 7 (0.5 g; 0.754 mmol) in anhydrous DMF (4 ml). The reaction mixture is stirred at a temperature of 65°C for 12 hours. Upon completion, the reaction was partitioned between H2O (20 ml) and EtOAc (20 ml). The organic phase was washed with a saturated aqueous solution of NaCl and the aqueous phase extracted with 10 ml EtOAc. The combined organic phases were dried over anhydrous sodium sulphate, the solvent was removed under reduced pressure, and the residue as a light yellow solid was purified by flash column chromatography (SiO2; EtOAc/n-hexane 25%). The product 11a was isolated as a white oil (440 mg, 75%).



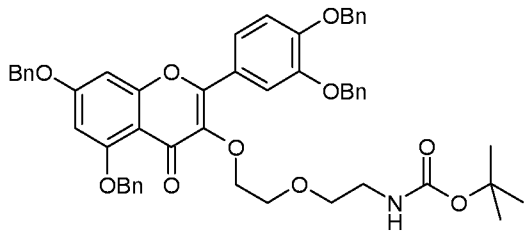
11a

^{1}H NMR (400 MHz, DMSO-*d6*): 7.76 (s, 1H), 7.66 (d, 1H, *J* = 8.0 Hz), 7.61 (d, 2H, *J* = 7.9 Hz), 7.49 (m, 6H), 7.38 (m, 12H), 7.36 (d, 1H, *J* = 4.8 Hz), 6.91 (d, 1H, *J* = 2.0 Hz), 6.69 (d, 1H, *J* = 2.0 Hz), 5.23 (m, 8H), 4.01 (q, 2H, *J* = 6.8 Hz), 3.91 (t, 2H, *J* = 6.4 Hz), 2.38 (t, 2H, *J* = 7.2 Hz), 1.85 (t, 2H, *J* = 6.8Hz), 1.12 (t, 3H, *J* = 7.2Hz).

^{13}C NMR (100 MHz, DMSO-*d6*): 173.4, 173.1, 163.5, 160.0, 159.0, 152.8, 151.2, 148.7, 140.4, 138.0, 137.8, 137.7, 137.0, 129.5, 129.4, 129.1, 129.0, 128.9, 128.5, 128.4, 127.9, 124.0, 122.9, 115.1, 114.7, 109.9, 98.7, 95.1, 71.6, 71.4, 71.0, 70.9, 30.9, 25.9, 15.0.

Example of synthesis of compound 11b.

2-[2-(Boc-amino)ethoxy]ethyl bromide (404 mg; 1.508 mmol), anhydrous K2CO3 (250 mg; 1.810 mmol) and KI (36 mg; 0.226 mmol) were added sequentially to a solution of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-hydroxy-4H-chromen-4-one 7 (500 mg; 0.754 mmol) in anhydrous DMF (4 ml). The reaction mixture is stirred at a temperature of 65°C for 12 hours. Upon completion, the mixture was partitioned between H2O (10 ml) and EtOAc (20 ml). The organic phase was washed with a saturated aqueous solution of NaCl and the aqueous phase extracted with EtOAc (20 ml). The combined organic phases were dried over anhydrous Na2SO4 and the solvent was removed under reduced pressure. The residue obtained as a yellow oil was purified by flash column chromatography (SiO2; EtOAc/n-hexane 25%). The product 11b was isolated as a white oil (460 mg, 72%).



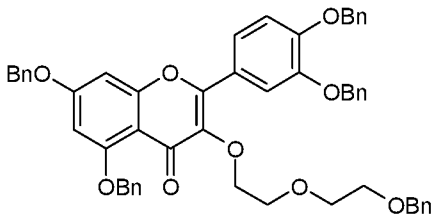
11b

1H NMR (400 MHz, DMSO-d6): 7.83 (bs, 1H), 7.63 (d, 1H, J = 4.0 Hz), 7.46-7.18 (m, 21H), 6.95 (d, 1H, J = 2.0 Hz), 6.76 (bt, 1H, J = 8.0 Hz), 6.70 (d, 1H, J = 2.0 Hz), 5.25 (m, 8H), 4.12 (m, 2H), 3.60 (m, 2H), 3.32 (m, 2H), 3.03 (m, 2H), 1.35 (s, 9H).

13C NMR (100 MHz, DMSO-d6): 173.2, 163.6, 159.0, 156.5, 152.5, 151.2, 148.6, 140.3, 138.1, 137.8, 137.7, 137.0, 129.5, 129.4, 129.3, 129.2, 129.0, 128.9, 128.8, 128.6, 128.5, 127.8, 123.9, 123.3, 115.1, 114.6, 109.8, 98.7, 95.1, 78.6, 71.6, 71.4, 71.0, 70.9, 70.3, 70.0, 29.1.

Example of synthesis of compound 11c.

2-[2-(Benzyloxy)ethoxy]ethyl bromide (390 mg; 1.508 mmol), anhydrous K2CO3 (250 mg; 1.810 mmol) and KI (36 mg; 0.226 mmol) were added sequentially to a solution of 5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-hydroxy-4H-chromen-4-one 7 (0.5 g; 0.754 mmol) in anhydrous DCM (4 ml). The reaction mixture is stirred at a temperature of 65°C for 12 hours. Upon completion, the reaction was partitioned between H2O (20 ml) and EtOAc (20 ml). The organic phase was washed with a saturated aqueous solution of NaCl and the aqueous phase extracted with EtOAc (10 ml). The combined organic phases were dried over anhydrous Na2SO4, the solvent was removed under reduced pressure, and the residue as a light yellow solid was purified by flash column chromatography (SiO2; EtOAc/n-hexane 25%). The product 11a was isolated as a white oil (539 mg, 85%).



11c

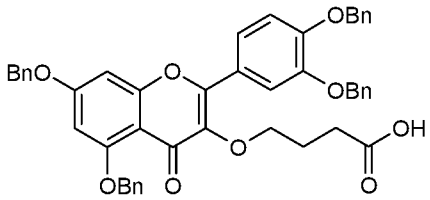
^{1}H NMR (400 MHz, DMSO-*d6*): 7.63 (d, 1H, *J* = 7.6 Hz), 7.50 (d, 4H, *J* = 7.6 Hz), 7.47-7.28 (m, 22H), 7.20 (d, 1H, *J* = 8.4 Hz), 6.93 (d, 1H, *J* = 1.2 Hz), 6.72 (d, 1H, *J* = 1.2 Hz), 5.25 (m, 6H), 5.04 (m, 2H), 4.95 (m, 2H).

^{13}C NMR (100 MHz, DMSO-*d6*): 172.9, 163.2, 159.6, 158.6, 158.4, 152.6, 150.5, 148.0, 139.6, 137.5, 136.7, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.3, 123.3, 122.2, 114.6, 114.1, 109.3, 98.3, 94.6, 73.3, 70.6, 70.4, 70.3, 70.2.

Example of synthesis of compound 12.

An aqueous solution of 2N NaOH (2 ml) was added to a solution of 11a (440 mg;

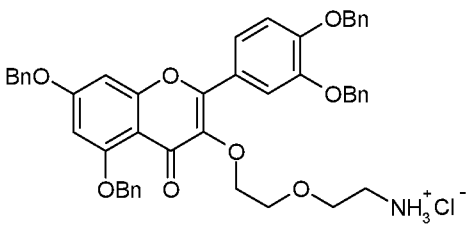
0.567 mmol) in ethanol (6 ml). The reaction mixture is stirred at room temperature for 12 hours. Upon completion, the reaction mixture was added with an aqueous solution of 2N HCl (~2.5 ml) to pH ~ 3 and then extracted with DCM (3 x 10 ml). The combined organic phases were dried over anhydrous Na2SO4, the solvent was removed under reduced pressure, and the residue as a white solid was used in the subsequent reaction without further chromatographic purification, 12 (quantitative).



12

Example of synthesis of compound 16.

An aqueous solution of 4N HCl (4 ml) was added to a solution of 11a (460 mg; 0.541 mmol) in THF (6 ml). The reaction mixture is stirred at 50°C for 6 hours. Upon completion, the reaction mixture was brought to dryness under reduced pressure, and the residue as a white solid was used in the subsequent reaction without further chromatographic purification, 16 (quantitative).

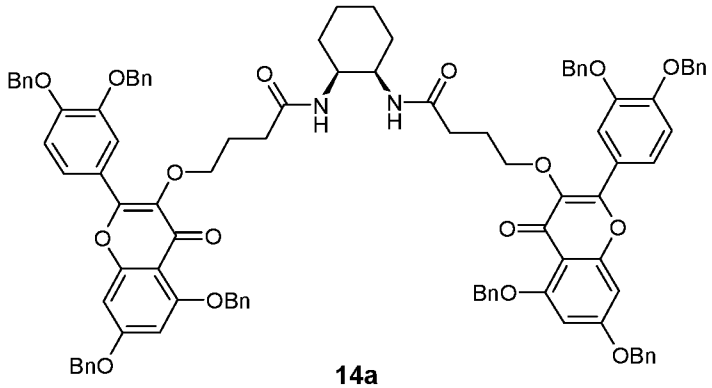


16

^{1}H NMR (400 MHz, CD_3OD): 7.66-7.30 (m, 22H), 7.05 (d, 1H, *J* = 8.4 Hz), 6.57 (d, 1H, *J* = 2.0 Hz), 6.51 (d, 1H, *J* = 2.0 Hz), 5.27 (s, 2H), 5.25 (s, 2H), 5.17 (s, 2H), 5.12 (2H), 3.83-3.74 (m, 2H, 3.72-3.64 (m, 2H), 3.60-3.53 (m, 2H), 3.22-3.12 (m, 2H).

Example of a general procedure for the synthesis of the products 14.

HOBt (32 mg, 0.24 mmol), EDC*HCl (46 mg; 0.24 mmol) and DIPEA (140 µl; 0.8 mmol) were added sequentially to a solution of 12 (158 mg; 0.2 mmol) in anhydrous DCM (6 ml). The reaction mixture is stirred at room temperature for 15-30 min. and then added to a solution of the selected diamine 13 (0.08 mmol) in anhydrous DCM (6 ml) and a catalytic amount of DMAP (~1mg, 0.008 mmol). The reaction mixture is stirred at room temperature for 12 hours. Upon completion, the reaction mixture was diluted with DCM (10 ml) and washed sequentially with a saturated aqueous solution of NH_4Cl (3 x 10 ml), a saturated aqueous solution of $NaHCO_3$ (3 x 10 ml), and finally a saturated aqueous solution of NaCl (1 x 10 ml). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography.



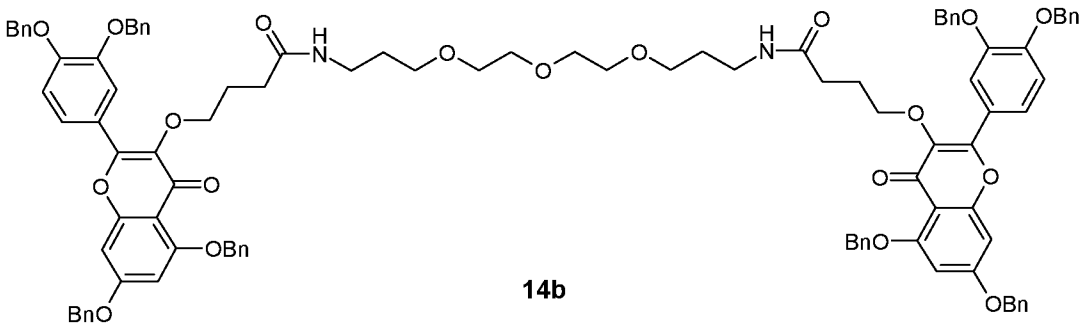
14a

Compound 14a was isolated as a white oil (274 mg, 87.5%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.79 (bd, 2H, J = 7.6 Hz), 7.65 (d, 2H, J = 2.0 Hz), 7.58-7.50 (m, 6H), 7.47-7.25 (m, 36H), 6.83 (d, 2H, J = 8.8 Hz), 6.31 (dd, 4H, J_1 = 7.1 Hz, J_2 = 2.1 Hz), 5.29 (s, 4H), 5.14 (s, 4H), 5.05 (s, 4H), 4.87 (d, 2H, J = 11.3 Hz), 4.77 (d, 2H, J = 11.3 Hz), 4.23 (m, 2H), 3.95 (m, 2H), 3.85 (m, 2H), 2.53 (m, 4H), 2.02 (m, 4H), 1.94 (m, 2H), 1.58 (m, 2H), 1.36 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.7, 172.7, 162.6, 159.5, 158.4, 152.5, 150.9, 148.3,

139.9, 137.0, 136.6, 136.4, 135.5, 128.6, 128.5, 128.2, 127.9, 127.8, 127.7, 127.3, 127.2, 127.1, 126.5, 123.5, 122.2, 114.8, 113.4, 109.6, 97.9, 93.5, 71.5, 70.6, 70.5, 70.1, 49.0, 33.1, 28.4, 27.0.

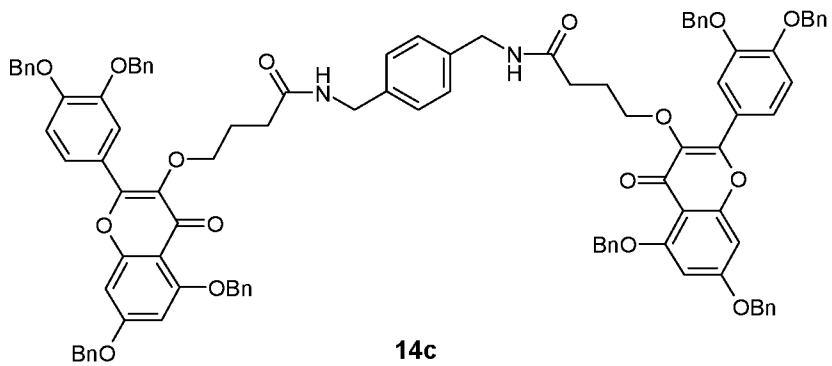


14b

Compound 14b was isolated as a white oil (312 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.75 (d, 2H, J = 2.0 Hz), 7.68 (dd, 2H, J_1 = 10.4 Hz, J_2 = 2.0 Hz), 7.59 (d, 4H, J = 8.0 Hz), 7.48 (t, 8H, J = 6.4 Hz), 7.45-7.30 (m, 28H), 7.16 (bt, 2H, J = 5.6 Hz), 7.03 (d, 2H, J = 8.0 Hz), 6.52 (d, 2H, J = 2.0 Hz), 6.54 (d, 2H, J = 2.0 Hz), 5.19 (s, 8H), 5.15 (s, 4H), 5.03 (s, 4H), 3.88 (t, 4H, J = 5.6 Hz), 3.53 (m, 4H), 3.47 (m, 4H), 3.41 (t, 4H, J = 6.4 Hz), 3.27 (q, 4H, J = 12.4, 6.4 Hz), 2.46 (t, 4H, J = 6.8 Hz), 1.97 (m, 4H), 1.73 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.9, 173.0, 162.8, 159.7, 158.6, 153.6, 150.9, 148.4, 140.0, 137.0, 136.6, 136.3, 135.6, 128.7, 128.5, 128.4, 128.0, 127.9, 127.7, 127.5, 127.3, 127.2, 126.7, 123.6, 122.4, 115.1, 113.8, 109.8, 97.9, 93.8, 71.6, 70.8, 70.7, 70.4, 70.0, 69.3, 37.1, 33.1, 29.3, 26.7.

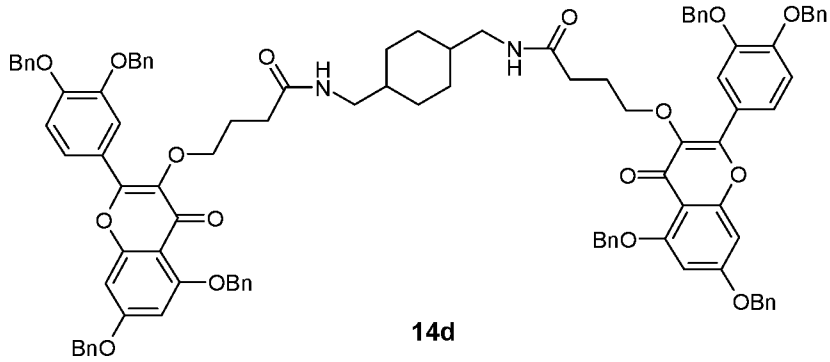


14c

Compound 14c was isolated as a white oil (298 mg, 93.2%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.72 (d, 2H, J = 2.0 Hz), 7.63 (dd, 2H, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 7.55-7-20 (m, 44H), 7.01 (d, 2H, J = 8.8 Hz), 6.56 (d, 2H, J = 2.4 Hz), 6.45 (d, 2H, J = 2.0 Hz), 5.23 (s, 4H) 5.22 (s, 4H), 5.14 (s, 4H), 5.12 (s, 4H), 4.22 (d, 4H, J = 5.6 Hz), 3.82 (t, 4H, J = 5.2 Hz), 2.52 (t, 4H, J = 6.4 Hz), 1.96 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.9, 173.1, 162.9, 159.7, 158.6, 153.1, 150.9, 148.3, 139.9, 137.5, 137.0, 136.6, 136.2, 135.6, 128.7, 128.6, 128.5, 128.4, 128.0, 127.9, 127.7, 127.6, 127.3, 127.2, 126.6, 123.6, 122.3, 115.1, 113.8, 109.8, 98.0, 93.8, 71.5, 70.8, 70.6, 70.5, 43.0, 33.4, 26.7.



14d

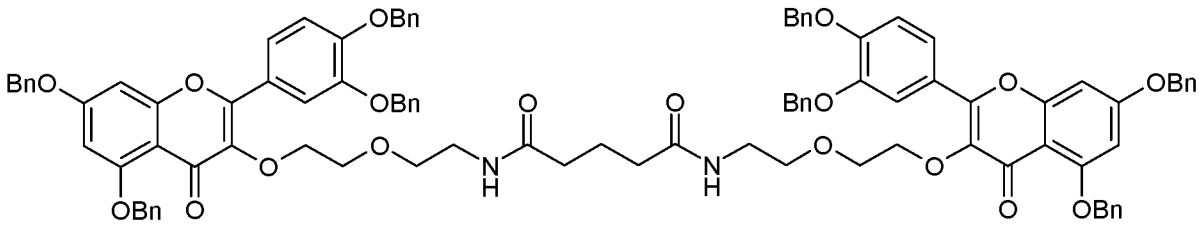
Compound 14d was isolated as a white oil (294 mg, 91.6%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.75 (bs, 2H), 7.67 (dd, 2H, J_1 = 8.8 Hz, J_2 = 1.6 Hz), 7.58 (d, 4H, J = 7.6 Hz), 7.55-7.25 (m, 38 H), 7.04 (d, 2H, J = 8.4 Hz), 6.91 (bs, 2H), 6.54 (d, 2H, J = 1.8 Hz), 6.47 (d, 2H, J = 1.6 Hz), 5.26 (s, 4H), 5.25 (s, 4H), 5.21 (s, 4H), 5.11 (s, 4H), 3.82 (t, 4H, J = 5.2 Hz), 2.93 (t, 4H, J = 6.0 Hz), 1.96 (m, 4H), 1.51 (m, 4H), 1.23 (bs, 2H), 0.65 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 174.2, 173.9, 162.9, 159.7, 158.7, 153.2, 151.0, 140.0, 136.9, 136.6, 136.3, 135.6, 128.7,128.6,128.5,128.4, 128.0, 127.7, 127.9, 127.7, 127.6, 127.3, 127.2, 126.6, 123.6, 122.3, 115.2, 113.8, 109.8, 98.0, 93.9, 71.6, 70.9, 70.7, 70.5, 45.6, 37.6, 33.3, 30.0, 26.8.

Example of a general procedure for the synthesis of the products 18, 21, and 24.

HOBt (38 mg, 0.28 mmol), EDC*HCl (54 mg; 0.28 mmol) and DIPEA (175 µl, 1.0 mmol) were added sequentially to a solution of the appropriate dicarboxylic linker 17 (0.10 mmol) or tricarboxylic linker 20 (0.062 mmol) or tetracarboxylic linker 23 (0.050 mmol) in anhydrous DCM (6 ml). The reaction mixture is stirred at room temperature for 15-30 min. and then added to a solution of 16 (196 mg; 0.25 mmol) in anhydrous DCM (6 ml) and a catalytic amount of DMAP (~1mg, 0.008 mmol). The reaction mixture is stirred at room temperature for 12 hours. Upon completion, the reaction mixture was diluted with DCM (10 ml) and washed sequentially with a saturated aqueous solution of NH_4Cl (3 x 10 ml), a saturated aqueous solution of $NaHCO_3$ (3 x 10 ml), and finally a saturated aqueous solution of NaCl (1 x 10 ml). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography.



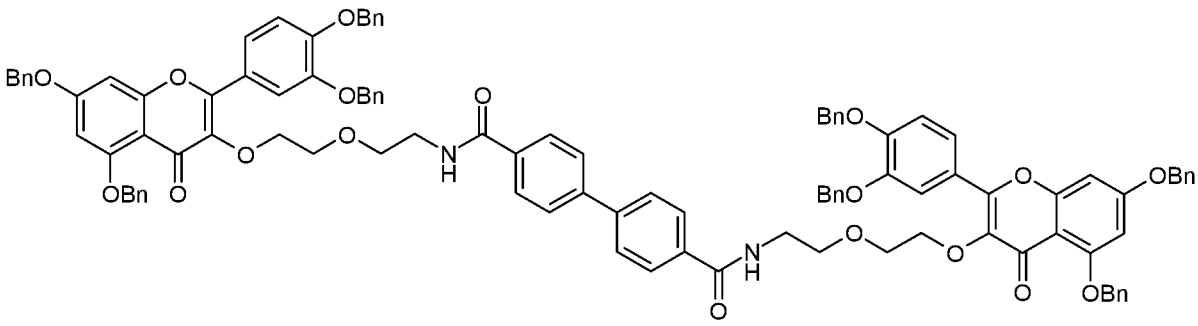
18a

Compound 18a was isolated as a white oil (298 mg, 93.4%).

^{1}H NMR (400 MHz, DMSO-*d6*): 7.83 (bs, 4H), 7.62 (d, 2H, *J* = 7.6 Hz), 7.55-7.20 (m, 40H), 6.94 (s, 2H), 6.71 (s, 2H), 5.25 (bs, 16 H), 4.13 (bs, 4H), 3.60 (bs, 4H), 3.44 (m, 4H), 3.14 (d, 4H, *J* = 5.2 Hz), 2.17 (t, 4H, *J* = 7.6 Hz), 2.07 (m, 4H), 1.68 (t, 2H, *J* = 7.6 Hz).

^{13}C NMR (100 MHz, DMSO-*d6*): 175.2, 173.2, 172.7, 163.6, 160.0, 159.0, 152.5, 151.2, 148.6, 140.3, 138.1, 137.8, 137.7, 137.0, 129.5, 129.4, 129.3, 129.2, 129.0, 128.9, 128.6, 128.5, 127.9, 123.9, 123.3, 115.1, 114.6, 109.8, 98.0, 95.1, 71.6, 71.4,

71.0, 70.9, 70.4, 70.0, 35.3, 19.5.

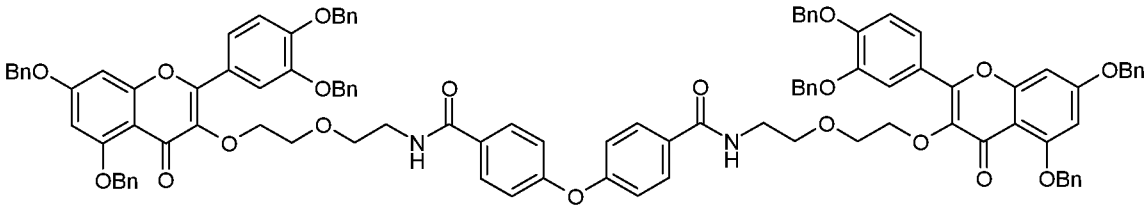


18b

Compound 18b was isolated as a white oil (264 mg, 77.4%).

^{1}H NMR (400 MHz, DMSO-*d6*): 8.54 (bt, 2H, *J* = 5.4 Hz), 7.92 (d, 4H, *J* = 8.4 Hz), 7.84 (m, 4H), 7.43 (d, 4H, *J* = 8.4Hz), 7.61 (d, 4H, *J* = 7.2 Hz) 7.55-7.15 (m, 38H), 7,93 (d, 2H, *J* = 1.6 Hz), 7.70 (d, 2H, *J* = 2.0 Hz), 5.24 (s, 16H), 4.15 (bm, 4H), 3.67 (bm, 4H), 3.52 (bm, 4H), 3.42 (bm, 4H).

^{13}C NMR (100 MHz, DMSO-*d6*): 173.4, 166.4, 163.8, 160.1, 157.9, 152.3, 151.2, 148.4, 142.2, 140.2, 138.3, 137.8, 137.7, 137.0, 134.5, 129.5, 129.4, 129.3, 129.0, 128.8, 128.6, 127.8, 127.4, 124.3, 123.5, 115.2, 114.8, 110.4, 98.9, 95.7, 71.5, 71.4, 71.2, 71.0, 70.9, 70.6, 70.0.



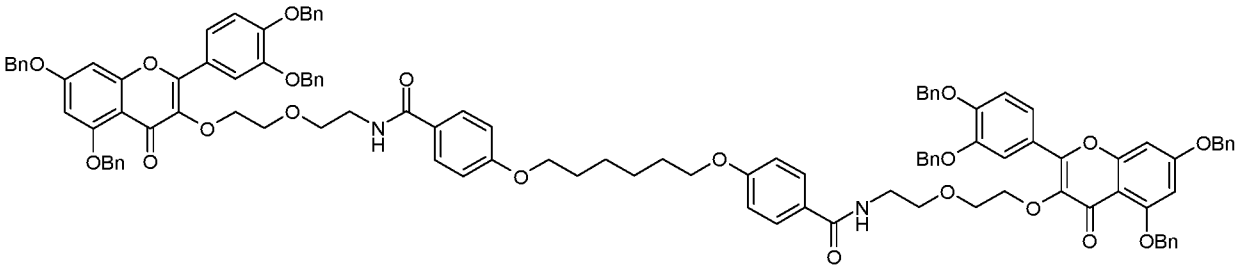
18c

Compound 18c was isolated as a white oil (236 mg, 68.5%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.84 (d, 2H, *J* = 2.0 Hz), 7.76 (d, 4H, *J* = 8.8 Hz), 7.69 (dd, 2H, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 7.53 (d, 4H, *J* = 7.6 Hz), 7.50-7.20 (m, 44H), 6.97 (d, 2H, *J* = 8.8 Hz), 6.78 (d, 4H, *J* = 8.8 Hz), 6.51 (d, 2H, *J* = 2.0 Hz), 6.41 (d, 2H, *J* = 2 Hz), 5.25 (s, 4H), 5.21 (s, 4H), 5.11 (s, 4H), 5.07 (s, 4H), 4.15 (bm, 4H), 3.72

(bm, 4H), 3.61 (bm, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.8, 166.7, 162.9, 159.6, 158.7, 158.6, 152.7, 151.0, 148.2, 140.0, 136.9, 136.5, 136.2, 135.6, 129.8, 129.3, 128.7, 128.6, 128.5, 128.4, 128.0, 127.9, 127.7, 127.6, 127.4, 127.2, 126.6, 123.6, 122.5, 118.3, 115.7, 113.6, 109.7, 98.0, 93.8, 71.7, 71.2, 70.8, 70.6, 70.5, 70.2, 69.5.

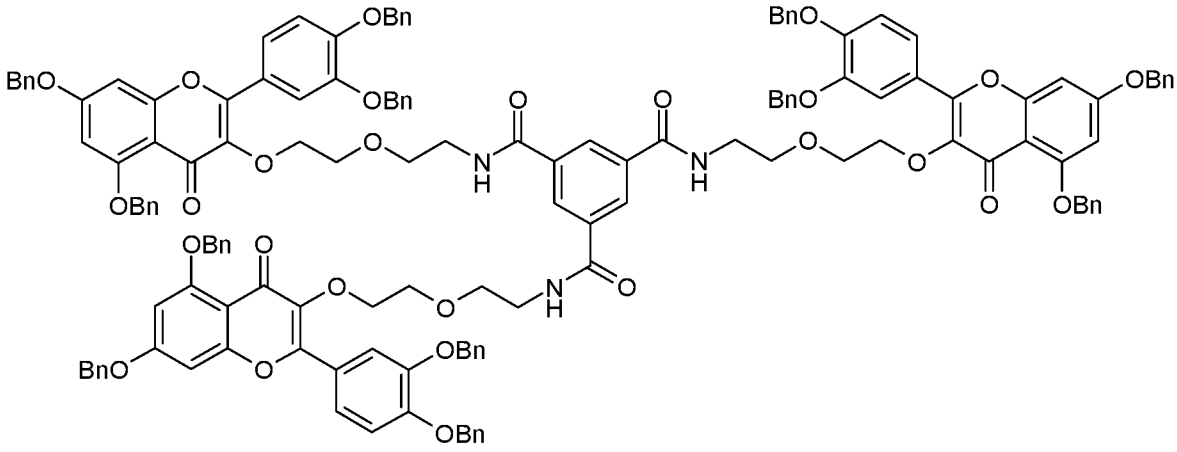


18d

Compound 18d was isolated as a white oil (242 mg, 66.4%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.82 (d, 2H, *J* = 1.6 Hz), 7.74 (d, 4H, *J* = 3.2 Hz), 7.56 (d, 4H, *J* = 7.2 Hz), 7.50-7.25 (m, 38H), 7.01 (bs, 2H), 6.98 (d, 2H, *J* = 8.8 Hz), 6.75 (d, *J* = 8.8 Hz), 6.53 (d, 2H, *J* = 2.0 Hz), 6.44 (d, 2H, *J* = 2.0 Hz), 5.23 (s, 4H), 5.18 (s, 8H), 5.08 (s, 4H), .4.18 (m, 2H), 3.85 (t, 4H, *J* = 6.4 Hz), 3.71 (m, 4H), 3.58 (bm, 8H), 1.74 (bt, 4H), 1.46 (bt, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.7, 167.0, 162.8, 161.4, 159.7, 158.6, 152.7, 151.0, 148.2, 148.2, 140.0, 137.0, 136.6, 136.2, 135.6, 128.9, 128.7, 128.5, 128.4, 128.0, 127.9, 127.7, 127.6, 127.4, 1272, 126.6, 123.7, 122.6, 115.7, 113.9, 113.6, 109.9, 98.0, 93.8, 71.7, 71.2, 70.8, 70.7, 70.5, 70.3, 69.7, 67.8, 39.8, 37.0, 29.0, 25.8.

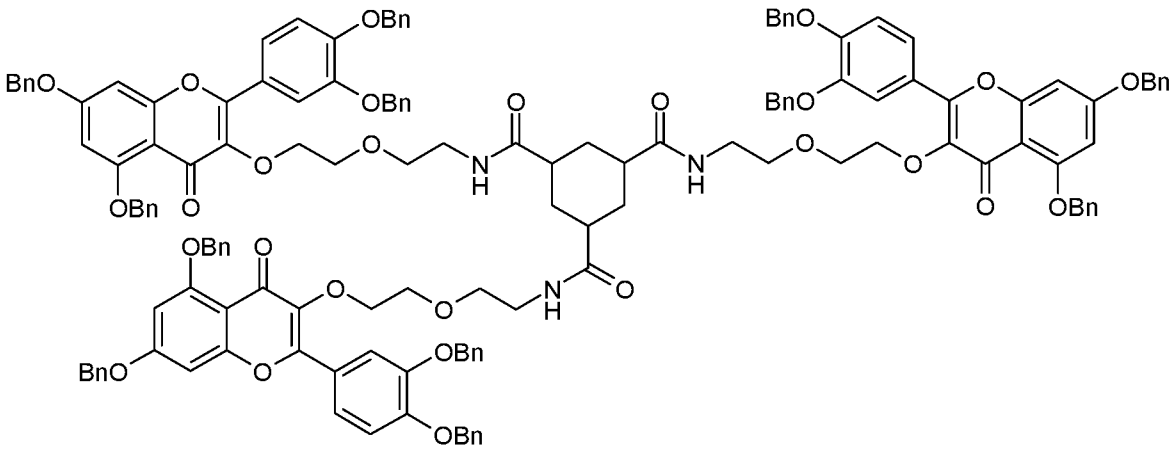


21a

Compound 21a was isolated as a white oil (283 mg, 58.8%).

^{1}H NMR (400 MHz, $CDCl_3$ - CD_3OD 80:20): 8.32 (s, 3H) 7.96 (bt, 3H, *J* = 5.2 Hz), 7.65 (d, 6H, *J* = 8.8 Hz), 7.45-7.15 (m, 60H); 6.91 (d, 3H, *J* = 8.8 Hz), 6.46 (d, 3H, *J* = 1.6 Hz), 6.38 (d, 3H, *J* = 1.6 Hz), 5.10 (sm 6H), 5.07 (s, 6H), 5.06 (s, 6H), 4.99 (s, 6H), 4.38 (bs, 3H), 3.96 (bm, 6H), 3.54 (bm, 6H), 3.44 (m, 6H), 3.39 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$ - CD_3OD 80:20): 174.3, 166.6, 163.0, 159.5, 158.5, 153.1, 150.9, 148.0, 139.8, 136.8, 136.4, 136.0, 135.6, 134.5, 128.8, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.4, 127.3, 127.2, 126.7, 123.2, 122.7, 115.1, 113.5, 109.4, 97.9, 93.9, 71.4, 71.3, 70.7, 70.6, 70.4, 70.0, 69.3, 39.9.



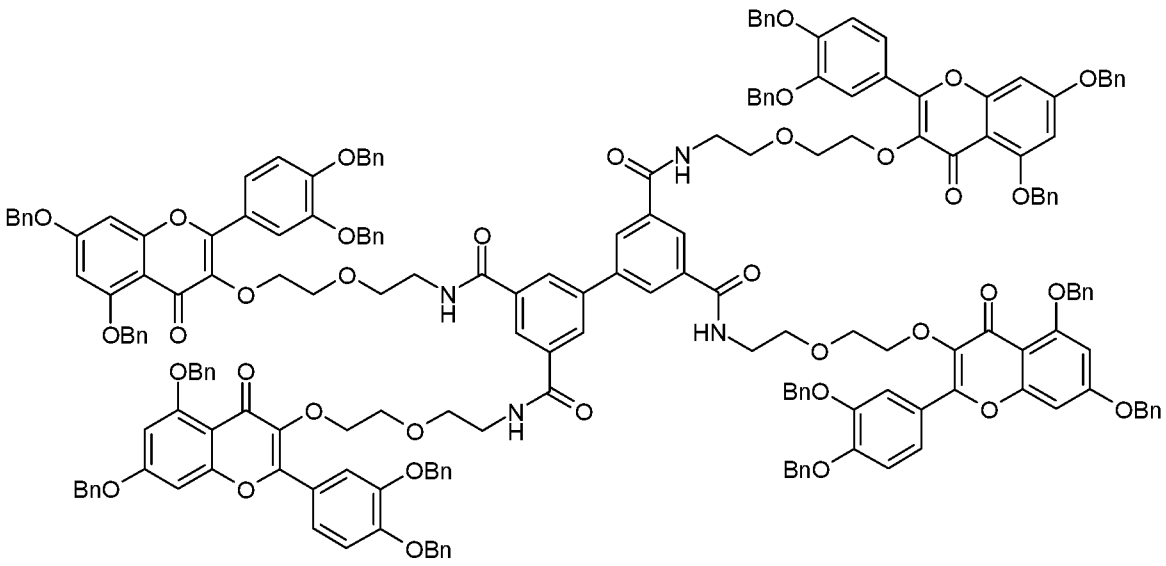
21b

Compound 21b was isolated as a white oil (293 mg, 60.7%).

^{1}H NMR (400 MHz, $CDCl_3$ - CD_3OD 80:20): 7.79 (bs, 3H), 7.71 (d, 3H, *J* = 8.4 Hz),

7.57 (d, 6H, *J* = 7.6 Hz), 7.50 – 7.25 (m, 54H), 6.98 (d, 3H, *J* = 8.8 Hz), 6.53 (d, 3H, *J* = 1.8 Hz), 6.44 (d, 3H, *J* = 1.8 Hz), 6.22 (bt, 3H), 5.21 (s, 8H), 5.20 (s, 16H), 5.06 (s, 8H), 4.13 (bs, 6H), 3.60 (bs, 6H), 3.34 (t, 6H, *J* = 4.8 Hz), 3.23 (t, 6H, *J* = 4.8 Hz), 1.98 (bs, 3H), 1.88 (t, 3H, *J* = 12 Hz), 1.78 (d, 3H, *J* = 12 Hz), 1.42 (q, 3H, *J* = 12.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$ - CD_3OD 80:20): 174.3, 173.6, 162.8, 159.7, 158.6, 152.7, 150.9, 148.2, 140.0, 137.0, 136.6, 136.3, 135.6, 128.7, 128.5, 128.4, 128.0, 127.9, 127.7, 127.6, 127.4, 127.2, 126.6, 123.6, 122.7, 115.6, 113.7, 109.8, 98.0, 93.9, 71.6, 71.2, 70.8, 70.7, 70.4, 70.1, 69.7, 43.5, 39.1, 31.5.



24a

Compound 24a was isolated as a white oil (385 mg, 59.1%).

^{1}H NMR (400 MHz, $CDCl_3$ - CD_3OD 80:20): 8.17 (s, 2H), 8.09 (s, 4H), 7.69 (d, 4H, *J* = 1.6 Hz), 7.65 (dd, 4H, J_1 = 10.4 Hz, J_2 = 2.0 Hz), 7.45-7.22 (m, 80H), 7.18 (m, 4H), 6.92 (d, 4H, *J* = 8.8 Hz), 6.46 (d, 4H, *J* = 1.6 Hz), 6.36 (d, 4H, *J* = 1.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$ - CD_3OD 80:20): 171.5, 164.1, 158.8, 154.0, 151.7, 148.7, 143.8, 139.1, 136.8, 136.4, 135.8, 135.0, 134.3, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.2, 126.9, 126.6, 124.0, 122.8, 114.7, 111.9, 105.2, 95.4, 93.3, 72.8, 71.4, 71.3, 71.0, 70.7, 70.6, 70.5, 70.4, 70.2, 69.7,

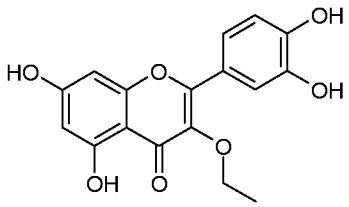
37.6.

Example of a general procedure of debenzylation of 3-*O*-alkylated quercetins: 2-(3,4-Dihydroxyphenyl)-3-ethoxy-5,7-dihydroxy-4*H*-chromen-4-one 1; 2-(3,4-Dihydroxyphenyl)-3-hexyloxy-5,7-dihydroxy-4*H*-chromen-4-one 2; 2-(3,4-Dihydroxyphenyl)-3-hexadecyloxy-5,7-dihydroxy-4*H*-chromen-4-one 3.

A solution of the product of interest dissolved in a mixture of EtOH/THF (1:2 % v/v) was transferred into a hydrogenation flask. The catalyst Pd/C (10%) was added to the mixture. The reaction mixture was subjected three times to a vacuum - nitrogen cycle in order to remove the air from the system; after being vacuumed one last time, the flask was filled with hydrogen up to a pressure of 1.2 bar. Lastly, the reaction mixture was stirred at room temperature until complete debenzylation of the desired product (approximately 18 hours). Upon completion, the catalyst was removed from the reaction mixture by filtration, and the solvent was removed under reduced pressure. The final residue corresponding to the desired product does not require a further final purification.

SUBSTRATE (g; mol)	SOLVENT THF/EtOH=1/2	CATALYST Pd/C (10 %)	PRODUCT (mg; mol)
8a (0.105 g; 0,00013 mol)	4.5 ml	0.105 g	1 (10 mg, 30%)
8b (0.07 g; 0.00008 mol)	5 ml	0.07 g	2 (51 mg, 95%)
8c (0.07 g; 0.00008 mol)	9 ml	0.07 g	3 (54 mg, 78%)

2-(3,4-Dihydroxyphenyl)-3-ethoxy-5,7-dihydroxy-4*H*-chromen-4-one 1:

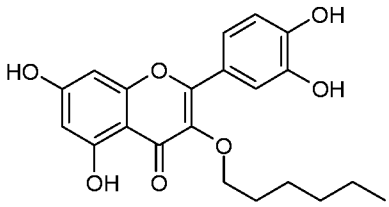


1

^{1}H NMR (400 MHz, $CDCl_3$): 7.62 (d, 1H, *J* = 2.1 Hz), 7.54 (dd, 1H, J_1 = 8.5 Hz, J_2= 2.1 Hz), 6.89 (d, 1H, *J* = 8.5 Hz), 6.37 (d, 1H, *J* = 2.1 Hz), 6.18 (d, 1H, *J* = 2.1 Hz), 3.89 (q, 2H, *J* = 7.1 Hz), 1.32 (t, 1H, *J* = 7.1 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): 180.29, 166.85, 163.22, 158.66, 158.39, 150.07, 146.56, 138.53, 123.34, 122.55, 122.26, 116.71, 116.46, 116.42, 116.16, 105.78, 100.15, 99.86, 95.02, 94.73, 69.77, 69.49, 15.82, 15.55.

2-(3,4-Dihydroxyphenyl)-3-hexyloxy-5,7-dihydroxy-4*H*-chromen-4-one 2:

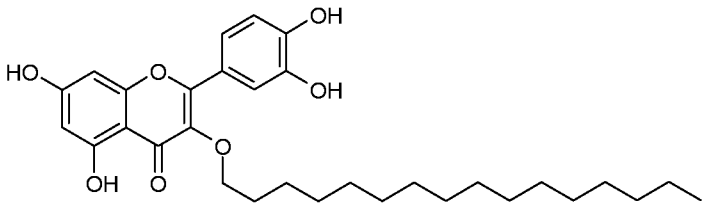


2

^{1}H NMR (400 MHz, $CDCl_3$): 7.55 (s, 1H); 7.47 (d, 1H, *J* = 8.2 Hz), 6.86 (d, 1H, *J* = 8.2 Hz), 6.35 (s, 1H), 6.17 (s, 1H), 3.88 (t, 1H, *J* = 6.0 Hz), 1.75-1.60 (m, 2H), 1.50-1.10 (m, 6H), 0.87 (t, 3H, *J* = 6.0 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): 180.27, 165.90, 163.22, 158.54, 149.87, 146.44, 138.79, 123.31, 122.68, 116.87, 116.31, 106.06, 99.84, 94.80, 74.18, 32.86, 31.11, 26.89, 23.78, 14.52.

2-(3,4-Dihydroxyphenyl)-3-hexadecyloxy-5,7-dihydroxy-4*H*-chromen-4-one 3:



3

^{1}H NMR (400 MHz, $CDCl_3$): 7.49 (d, 1H, *J* = 2.1 Hz), 7.45 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.1 Hz), 6.81 (d, 1H, *J* = 8.5 Hz), 6.27 (d, 1H, *J* = 2.1 Hz), 6.15 (d, 1H, *J* = 2.1 Hz), 3.78 (t, 3H, *J* = 7.1 Hz), 1.68-1.55 (m, 2H), 1.26-1.09 (m, 30H), 0,76 (t, 3H, *J*= 7.1 Hz);

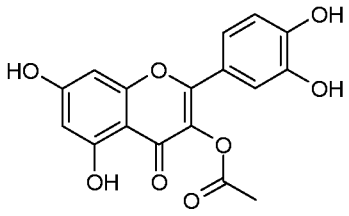
^{13}C NMR (100 MHz, $CDCl_3$): 178.72, 163.64, 161.26, 156.80, 156.58, 147.52, 144.25, 137.42, 122.11, 121.52, 115.18, 114.82, 104.91, 98.60, 93.75, 49.16, 48.95, 48.74, 48.52, 48.30, 31.67, 29.68, 29.44, 29.40, 29.36, 29.32, 29.17, 29.10, 25.60, 22.41, 13.75.

Example of synthesis of 2-(3,4-bis(palmitoyloxy)phenyl)-4-oxo-4*H*-chromene-3,5,7-triyl acetate: 10a.

Acetyl chloride (0.850 ml; 0.012 mol), DIPEA (3.09 ml; 0.018 mol) and DMAP (0.36 g; 0.003 mol) were added sequentially to a solution of 3,3',4',5,7-pentahydroxy flavone 9 (0.56 g; 0.0016 mol) in anhydrous DCM (50 ml). The reaction mixture was stirred at room temperature. Upon completion (after 24 hours), a white precipitate forms. The reaction mixture was partitioned between H_2O and DCM and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The solid residue was recrystallized from MTBE (*tert*-butyl methyl ether) from which a yellow solid product corresponding to 10a (74.7 %) is obtained.

Example of synthesis of 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl acetate: 4

Lypozime® (2 g) and butanol (1 ml; 0.01 mol) were added sequentially to a suspension of 2-(3,4-bis(palmitoyloxy)phenyl)-4-oxo-4*H*-chromene-3,5,7-triyl acetate 10a (0.512 g; 0.001 mol) in MTBE. The reaction was placed inside an orbital shaker (300 rpm/min) at a temperature of 45°C until complete conversion to the desired product. The course of the reaction is monitored by TLC (DCM and DCM/MeOH = 9/1). Upon completion (approximately 9 days), the solution was filtered, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica Diol: DCM/MeOH=9/1). The product 4 was thus isolated as a yellow solid (260 mg, 76.3%).



4

^{1}H NMR (400 MHz, $CDCl_3$): 7.45 (d, 1H, *J*= 2.1 Hz), 7.37 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.1 Hz), 6.99 (d, 1H, *J*= 8.5 Hz), 6.53 (d, 1H, *J*= 2.1 Hz), 6.30 (d, 1H, *J*= 2.1 Hz), 2.63 (t, 2H, *J*= 7.4 Hz), 1.79-1.62 (m, 2H), 0.87 (t, 3H, *J*= 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 176.58, 171.22, 165.31, 162.79, 158.12, 157.32, 149.55, 146.05, 131.46, 122.00, 121.95, 116.36, 115.95, 105.12, 99.86, 23.31, 14.34.

Example of synthesis of 2-(3,4-bis(palmitoyloxy)phenyl)-4-oxo-4*H*-chromene-3,5,7-triyl tripalmitate: 10b.

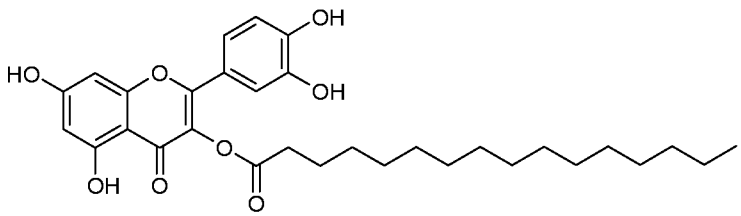
Palmitoyl chloride (3.51 ml; 0.012 mol), DIPEA (3.09 ml; 0.018 mol) and DMAP (0.36 g; 0.003 mol) were added sequentially to a solution of 3,3',4',5,7-pentahydroxy

flavone 9 (0.56 g; 0.0016 mol) in anhydrous DCM (50 ml). The reaction mixture is stirred at room temperature. Upon completion (after 24 hours), a white precipitate forms.

The reaction mixture was partitioned between H_2O and DCM and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The solid residue was recrystallized from MTBE from which a yellow solid product corresponding to 10b (64.7 %) is obtained.

Example of synthesis of 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl palmitate: 5

Lypozime® (2 g) and butanol (1 ml; 0.01 mol) were added sequentially to a suspension of 2-(3,4-bis(palmitoyloxy)phenyl)-4-oxo-4*H*-chromene-3,5,7-triyl tripalmitate 10b (1.3 g; 0.001 mol) in MTBE. The reaction was placed inside an orbital shaker (300 rpm/min) at a temperature of 45°C until complete conversion to the desired product. The course of the reaction is monitored by TLC (DCM and DCM/MeOH = 9/1). Upon completion (approximately 9 days), the solution was filtered, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica Diol: DCM/MeOH=9/1). The product 5 was thus isolated as a yellow solid (250 mg, 46.3%).



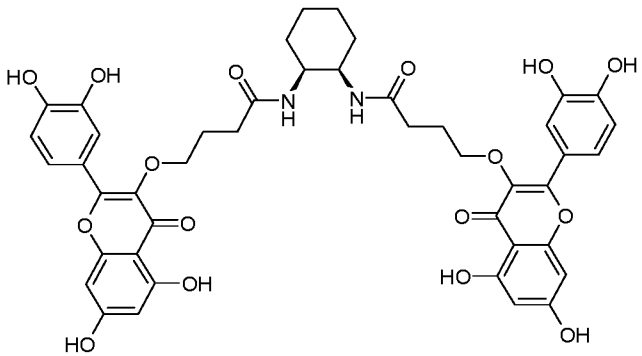
5

^{1}H NMR (400 MHz, $CDCl_3$): 7.45 (d, 1H, *J*= 2.1 Hz), 7.37 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.1 Hz), 6.99 (d, 1H, *J*= 8.5 Hz), 6.53 (d, 1H, *J*= 2.1 Hz), 6.30 (d, 1H, *J*= 2.1 Hz),

2.63 (t, 2H, *J*= 7.4 Hz), 1.79-1.62 (m, 2H), 1.47-1.36 (m, 2H), 1.28 (s, 22H), 0.87 (t, 3H, *J*= 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 176.58, 171.22, 165.31, 162.79, 158.12, 157.32, 149.55, 146.05, 131.46, 122.00, 121.95, 116.36, 115.95, 105.12, 99.81, 99.76, 94.89, 34.28, 32.63, 30.42, 30.29, 30.22, 30.10, 30.03, 29.90, 29.84, 29.65, 29.46, 29.26, 25.55, 23.31, 14.34.

Example of a general debenzylation procedure.

A solution of the product of interest (0.01 mmol) in a mixture of EtOH/THF (1:2 % v/v) is transferred into a hydrogenation flask. The catalyst Pd/C (10%) was added to the mixture. The reaction mixture was subjected three times to a vacuum - nitrogen cycle in order to remove the air from the system; after being vacuumed one last time, the flask was filled with hydrogen up to a pressure of 1.2 bar. Lastly, the reaction mixture was stirred at room temperature until complete debenzylation of the desired product (approximately 12 hours). Upon completion, the catalyst was removed from the reaction mixture by filtration, and the solvent was removed under reduced pressure. The residue was washed with a mixture of n-hexane/Et_2O 70:30 (3 x 10 ml). Unless otherwise indicated, the final residue corresponding to the desired product did not require a final chromatographic purification.

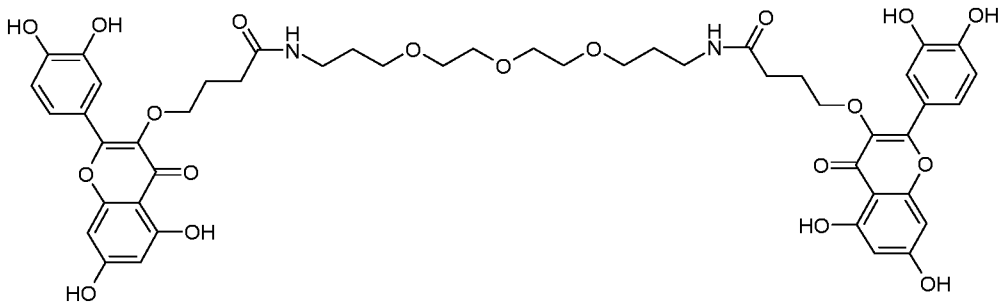


15a

The product 15a was isolated as a yellow amorphous solid (65 mg, 76%).

^{1}H NMR (400 MHz, DMSO-*d6*): 12.70 (s, 2H), 10.85 (s, 2H), 9.73 (bs, 2H), 9.39 (bs, 2H), 7.55 (bs, 2H), 7.45 (d, 2H, J = 8.4 Hz), 7.39 (d, 2H, J = 8.0 Hz), 6.89 (d, 2H, J = 8.4 Hz), 6.40 (s, 2H), 6.18 (s, 2H), 3.89 (m, 6H), 2.22 (q, 4H, J = 6.8 Hz), 1.87 (t, 4H, J = 6.8 Hz), 1.55 (m, 4H), 1.43 (m, 4H), 1.35 (m, 2H), 1.23 (m, 2H).

^{13}C NMR (100 MHz, CD_3OD): 178.5, 176.3, 174.6, 171.6, 164.0, 163.6, 161.2, 158.5, 156.8, 148.1, 145.4, 144.5, 137.0, 136.8, 125.7, 124.6, 121.6, 121.4, 121.1, 116.5, 115.4, 115.2, 108.9, 107.0, 104.8, 98.8, 96.2, 93.9, 67.4, 33.9, 30.0, 27.8, 25.7, 19.6, 17.6.

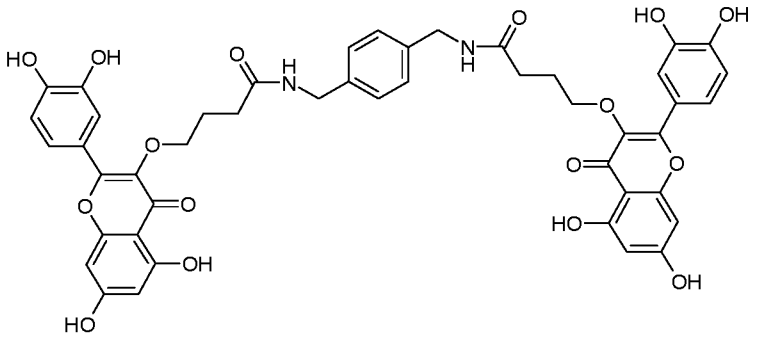


15b

The product 15b was isolated as a yellow amorphous solid (70 mg, 72.8%).

^{1}H NMR (400 MHz, CD_3OD): 7.57 (s, 2H, J = 2.4 Hz), 7.45 (dd, 2H, J = 8.4, 2.0 Hz), 6.88 (d, 2H, J = 8.4 Hz), 6.31 (dd, 2H, J = 2.0 Hz), 6.14 (d, 2H, J = 2.0 Hz), 3.89 (t, 4H, J = 6.0 Hz), 3.58 (m, 4H), 3.52 (m, 4H), 3.48 (t, 4H, J = 6.4 Hz), 3.27 (t, 4H, J = 6.8 Hz), 2.40 (t, 4H, J = 7.2 Hz), 2.01 (t, 4H, J = 6.4 Hz), 1.74 (t, 4H, J = 6.4 Hz).

^{13}C NMR (100 MHz, CD_3OD): 178.5, 176.3, 164.0, 163.6, 161.2, 158.5, 156.8, 148.1, 145.4, 137.0, 124.7, 121.6, 115.0, 104.8, 98.4, 93.3, 71.3, 68.5, 57.0, 36.6, 33.9, 32.2, 28.8, 27.4, 26.0, 16.9.

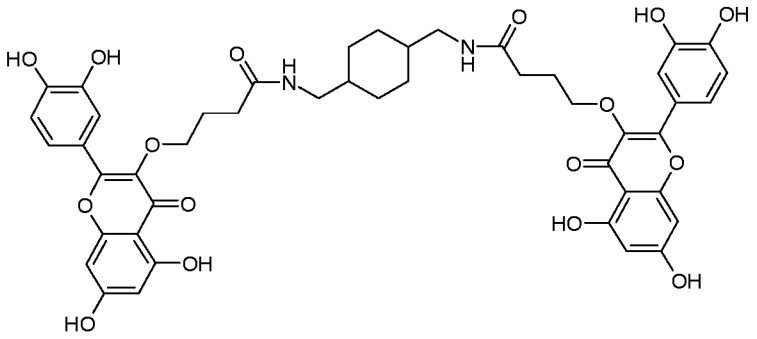


15c

The product 15c was isolated as a yellow amorphous solid (82 mg, 93.5%).

^{1}H NMR (400 MHz, CD_3OD): 7.52 (d, 2H, J = 2.0 Hz), 7.41 (dd, 4H, J = 8.4, 2.0 Hz), 7.09 (s, 4H); 6.83 (d, 2H, J = 8.8 Hz), 6.26 (d, 2H, J = 1.6 Hz), 6.09 (d, 2H, J = 2.0 Hz), 4.25 (s, 4H), 3.83 (t, 4H, J = 6.0 Hz), 2.42 (t, 4H, J = 6.8 Hz), 1.99 (t, 4H, J = 6.4 Hz).

^{13}C NMR (100 MHz, CD_3OD): 178.3, 176.4, 164.17, 161.4, 156.7, 156.6, 148.3, 144.8, 137.2, 136.8, 127.4, 121.5, 121.0, 115.16, 114.9, 104.4, 98.3, 93.3, 71.2, 65.4, 42.6, 32.4, 26.0.



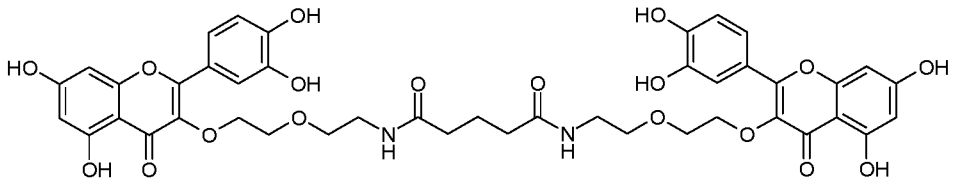
15d

The product 15d was isolated as a yellow amorphous solid (74 mg, 83.8%).

^{1}H NMR (400 MHz, CD_3OD): 7.57 (bs, 1H), 7.47 (d, 2H, J = 8.0 Hz), 6.87 (d, 2H, J = 8.0 Hz), 6.31 (bs, 2H), 6.13 (m, 2H), 3.89 (m, 4H), 2.99 (m, 4H), 2.39 (m, 4H), 2.00 (m, 4H), 1.70 (m, 4H), 1.36 (m, 2H), 0.86 (m, 4H).

^{13}C NMR (100 MHz, CD_3OD): 178.5, 174.3, 164.3, 161.5, 156.9, 156.7, 148.4,

144.8, 136.9, 121.6, 121.0, 115.2, 114.9, 104.4, 98.3, 93.3, 71.3, 37.7, 32.3, 29.9, 26.0.

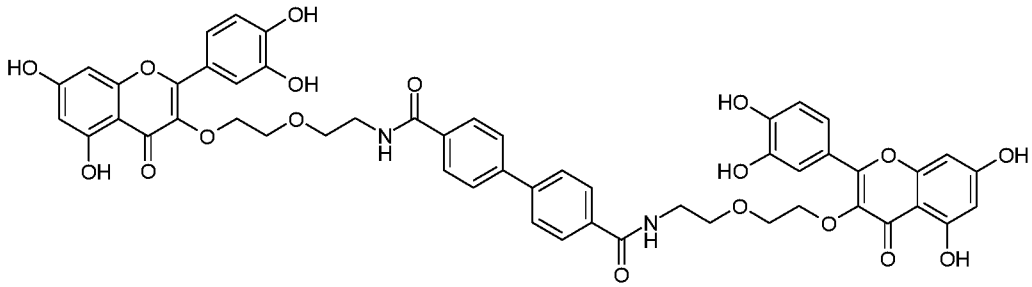


19a

The product 19a was isolated as a yellow amorphous solid (85 mg, 97.2%).

^{1}H NMR (400 MHz, DMSO-*d6*): 7.82 (s, 2H), 7.56 (m, 2H), 6.88 (d, 2H, J = 8.4 Hz), 6.40 (s, 2H), 6.18 (s, 2H), 4.26 (m, 4H), 3.64 (m, 4H), 3.63 (t, 4H, J = 5.6 Hz), 3.18 (m, 4H), 2.17 (t, 4H, J = 6.8 Hz), 2.09 (t, 4H, J = 7.2 Hz), 1.69 (m, 4H).

^{13}C NMR (100 MHz, DMSO-*d6*): 178.8, 175.4, 172.8, 165.5, 162.2, 157.3, 156.6, 149.9, 146.2, 137.5, 122.0, 121.7, 116.6, 104.9, 99.6, 94.5, 72.0, 70.3, 70.0, 35.4, 34.3, 31.4, 21.8.



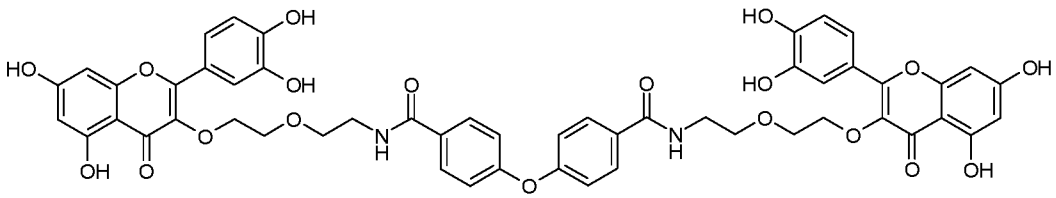
19b

The product 19b was isolated as a yellow amorphous solid (95 mg, 96.4%).

^{1}H NMR (400 MHz, DMSO-*d6*): 12.70 (s, 2H), 10.92 (s, 2H), 9.81 (s, 2H), 9.38 (s, 2H), 8.57 (bt, 2H), 7.95 (d, 4H, J = 8.0 Hz), 7.79 (d, 4H, J = 8.0 Hz), 7.57 (m, 2H), 6.92 (d, 2H, J = 8.4 Hz), 6.43 (d, 2H, J = 1.6 Hz), 6.20 (d, 2H, J = 1.6 Hz), 4.15 (m, 4H), 3.71 (m, 4H), 3.53 (m, 4H), 3.43 (m, 4H).

^{13}C NMR (100 MHz, DMSO-*d6*): 178.8, 166.9, 165.1, 162.2, 157.2, 156.7, 149.6, 146.6, 146.1, 142.6, 140.1, 137.6, 134.6, 129.2, 128.9, 127.60, 125.9, 122.1, 121.9,

116.6, 105.1, 99.5, 72.0, 70.3, 69.8, 69.2.

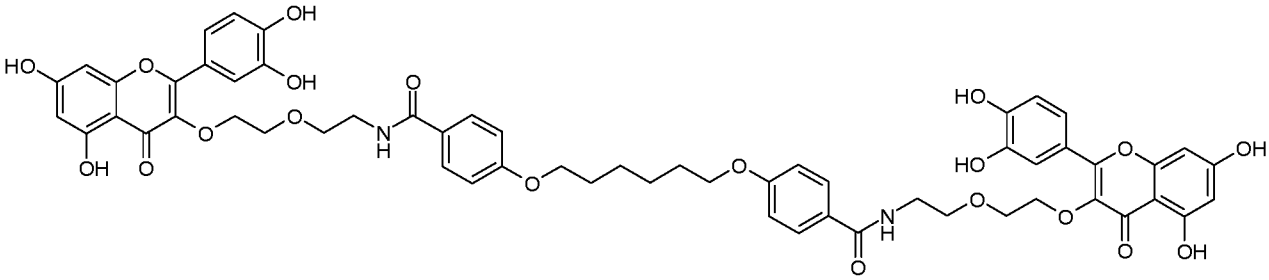


19c

The product 19c was isolated as a yellow amorphous solid (87 mg, 86.9%).

^{1}H NMR (400 MHz, CD_3OD): 7.74 (d, 4H, J = 8.0 Hz), 7.63 (bs, 2H), 7.48 (d, 2H, J = 8.4 Hz), 6.91 (d, 4H, J = 8.0 Hz), 6.82 (d, 2H, J = 8.4 Hz), 6.26 (s, 2H), 6.08 (s, 2H), 4.05 (m, 4H), 3.72 (m, 4H), 3.60 (m, 4H), 3.56 (m, 4H).

^{13}C NMR (100 MHz, CD_3OD): 178.3, 168.2, 164.2, 161.5, 159.1, 156.8, 156.5, 148.4, 144.7, 136.8, 129.5, 129.1, 121.5, 121.2, 118.2, 115.5, 114.8, 104.4, 98.3, 93.3, 71.3, 69.7, 69.1, 39.7.

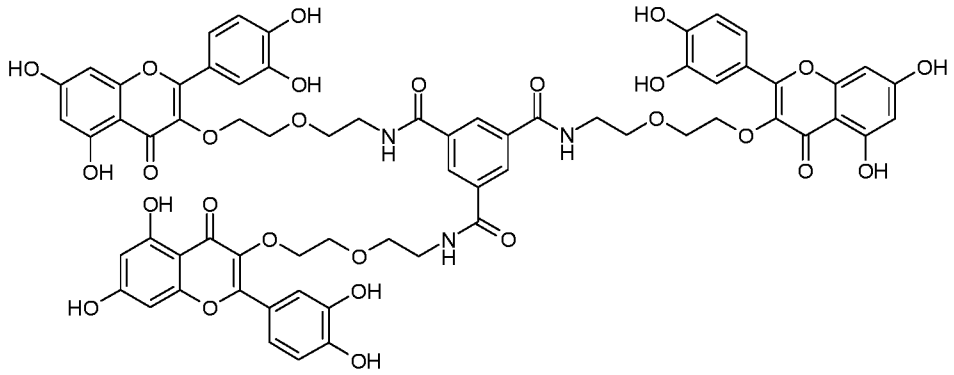


19d

The product 19d was isolated as a yellow amorphous solid (93 mg, 84.5%).

^{1}H NMR (400 MHz, CD_3OD): 7.68 (m, 6H), 7.53 (dd, 2H, J = 8.4, 2.0 Hz), 6.87 (d, 2H, J = 8.4 Hz), 6.81 (d, 4H, J = 8.8 Hz), 6.33 (d, 2H, J = 1.6 Hz), 6.17 (d, 2H, J = 1,6 Hz), 4.08 (m, 4H), 3.92 (t, 4H, J = 6.0 Hz), 3.74 (m, 4H), 3.63 (m, 4H), 3.57 (t, 4H, J = 4.4 Hz), 1.75 (m, 4H), 1.48 (m, 4H).

^{13}C NMR (100 MHz, CD_3OD): 178.4, 168.7, 164.2, 161.8, 161.5, 156.9, 156.7, 148.4, 144.7, 136.9, 128.7, 126.0, 121.6, 121.3, 115.7, 114.9, 113.8, 104.6, 98.5, 93.5, 71.4, 69.8, 69.3, 67.6, 39.6, 28.7, 25.4

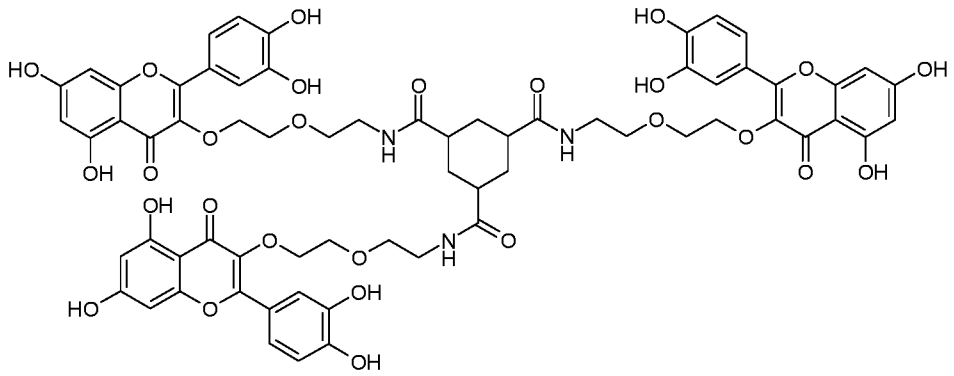


22a

The product 22a was isolated as a yellow amorphous solid (132 mg, 99.7%).

^{1}H NMR (400 MHz, CD_3OD): 8.32 (s, 3H), 7.60 (d, 3H, J = 2.0 Hz), 7.47 (dd, 3H, J = 8.4, 2.0 Hz), 6.82 (d, 3H, J = 8.4 Hz), 6.27 (d, 3H, J = 2.4Hz), 6.09 (d, 3H, J = 2.0 Hz), 4.02 (m, 6H), 3.70 (m, 6H), 3.65 (m, 6H), 3.58 (m, 6H), 3.53 (m, 6H).

^{13}C NMR (100 MHz, CD_3OD): 181.8, 178.1, 172.6, 167.3, 166.0, 161.4, 159.4, 156.9, 156.4, 148.6, 144.8, 136.6, 134.9, 128.5, 121.4, 121.2, 115.4, 114.9, 103.9, 98.9, 93.7, 71.3, 69.7, 69.0, 39.8.



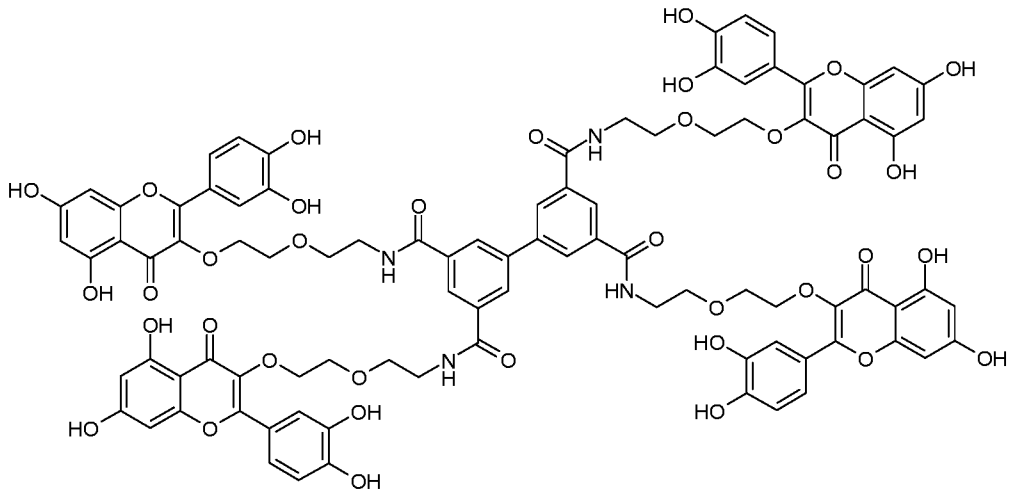
22b

The product 22b was isolated as a yellow amorphous solid (126 mg, 94.7%).

^{1}H NMR (400 MHz, CD_3OD): 7.61 (bs, 3H), 7.49 (d, 3H, J = 6.8 Hz), 6.84 (bs, 3H), 6.25 (m, 3H), 6.12 (m, 3H), 3.98 (bs, 6H), 3.65 (bs, 6H), 3.46 (m, 6H), 3.35 (m, 3H), 2.32 (bs, 3H), 1.88 (m, 3H), 1.59 (m, 3H).

^{13}C NMR (100 MHz, CD_3OD): 178.3, 176.0, 164.2, 161.4, 156.7, 156.5, 148.3,

144.7, 136.8, 121.5, 121.2, 115.5, 114.8, 104.3, 98.3, 93.3, 71.3, 69.6, 68.9, 43.2, 39.0, 31.3.

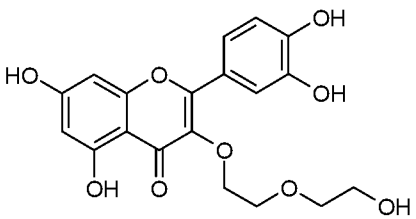


25a

The product 25a was isolated as a yellow amorphous solid (142 mg, 78.2%).

^{1}H NMR (400 MHz, CD_3OD): 8.09 (s, 2H), 7.94 (d, 4H, J = 1.2 Hz), 7.53 (d, 4H, J = 1.2 Hz), 7.42 (dd, 4H, J = 8.4, 2.4 Hz), 6.75 (dd, 4H, J = 8.4, 1.6 Hz), 6.22 (s, 4H), 6.04 (s, 4H), 4.06 (bs, 8H), 3.74 (m, 8H), 3.61 (bt, 8H, J = 4.8 Hz), 5.52 (bt, 8H, J = 4.8 Hz).

^{13}C NMR (100 MHz, CD_3OD): 178.2, 167.6, 164.2, 161.4, 156.9, 156.2, 148.2, 144.6, 139.5, 136.8, 134.9, 128.2, 125.5, 121.5, 121.2, 115.4, 114.8, 104.3, 98.2, 93.3, 71.1, 69.7, 68.8, 39.8.

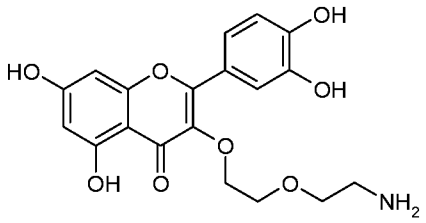


26

The product 26 was isolated as a yellow amorphous solid (74 mg, 95.0%).

^{1}H NMR (400 MHz, DMSO-*d6*): 12.47 (bs, 1H), 9.36 (bs, 1H), 7.67 (bs, 1H), 7.53 (d, 1H, J = 8.4 Hz), 6.87 (m, 1H), 6.41 (bs, 1H), 6.18 (bs, 1H), 3.45-3.20 (m, 8H).

^{13}C NMR (100 MHz, DMSO-*d6*): 175.9, 164.0, 160.8, 156.2, 147.8, 146.9, 145.1, 135.8, 125.0, 122.0, 120.1, 115.7, 115.1, 103.1, 98.2, 93.4.



27

The product 27 was isolated as a yellow amorphous solid (74 mg, 95.0%).

^{1}H NMR (400 MHz, CD_3OD): 7,67 (d, 1H, *J*= 2.0 Hz), 7.52 (dd, 1H, J_1= 8.4 Hz, J_2= 2.0 Hz), 6.39 (d, 1H, *J*= 1.6 Hz), 6.19 (d, 1H, *J*= 2.0 Hz), 4.10-4.01 (m, 2H), 3.83-3.75 (2H, m), 3.74-3.67 (2H, m), 3.19-3.10 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): 179.9, 166.0, 163.0, 158.5, 158.4, 150.0, 146.3, 138.3, 122.8, 122.5, 117.0, 116.4, 105.8, 99.9, 94.8, 72.9, 71.2, 67.8, 40.6.

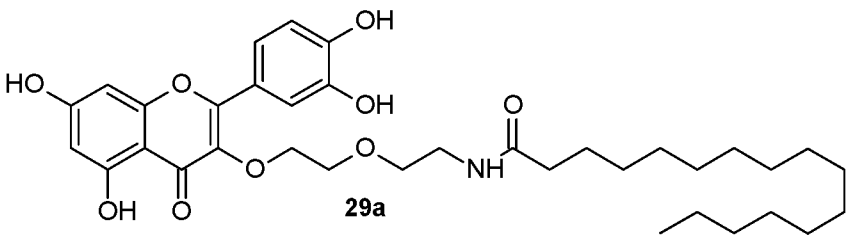
Example of synthesis of compounds 29 (a-g)

Procedure performed in the dark. EDC•HCl (1.5 eq.), followed 30 minutes later by HOBt (1.2 eq.) were added to a solution of the acid 28 (a-g) (approximately 0.025 M) in anhydrous DMF, under argon atmosphere and magnetic stirring. After a further 30 minutes, the solution obtained as above was added dropwise over 5 minutes via a syringe to a solution of compound 27 (1.1 eq. 0.029 M approx.) and DIPEA (6-8 eq.) in anhydrous DMF, under stirring, kept at 0°C and under argon atmosphere. The reaction thus obtained was brought to room temperature and maintained under stirring and argon atmosphere for 24 hours. After the 24 hours, the reaction mixture was diluted with EtOAc (5 times the reaction volume) and extracted with water (twice) and a saturated NaCl solution (once). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to dryness to yield a crude product, which was purified by flash column chromatography (SiO_2;

DCM/MeOH= 2->4%) to afford the final compound, that is 29(a-g).

Examples of synthesis conditions for individual compounds:

- 29a: 27 (15 mg; 0.028 mmol), DIPEA (40 µl;0.23 mmol); anhydrous DMF (1 ml); 28a (6.5 mg; 0.025 mmol); EDC•HCl (7.5 mg; 0.038 mmol); HOBt (3.8



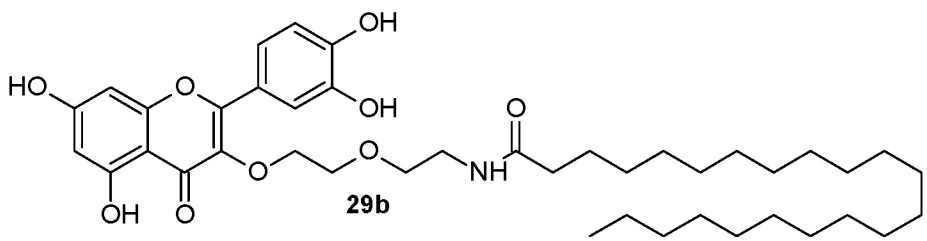
29a

mg; 0.028 mmol); anhydrous DMF (1.5 ml). Compound 29a was obtained as a yellow solid (5 mg, 30%).

^{1}H NMR (400 MHz, CD_3OD): 7.68 (d, 1H, *J*= 2.0 Hz), 7.52 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 6.86 (d, 1H, *J* = 8.4 Hz), 6.35 (d, 1H, *J* = 2.0 Hz), 6.21 (d, 1H, *J* = 2.0 Hz), 4.06-4,00 (m, 2H), 3.72-3.66 (m, 2H), 3.49 (t, 2H, *J* = 4.8 Hz), 3.36 (t, 2H, *J* = 4.8 Hz), 2.12 (t, 2H, *J* = 8 Hz), 1.58-1.46 (m, 2H), 1.30-1.10 (m, 24H), 0.81 (t, 3H, J= 7.2 Hz);

^{13}C NMR (100 MHz, CD_3OD): 178.8, 175.2, 164.3, 161.6, 157.2, 157.0, 148.3, 144.8, 137.3, 122.0, 121.7, 115.9, 115.3, 105.1, 99.1, 94.2, 71.7, 70.1, 69.8, 39.4, 32.0, 29.8, 29.76, 29.6, 29.5, 29.47, 29.41, 26.0, 22.8, 14.1.

- 29b: 27 (15 mg; 0.028 mmol), DIPEA (40 µl;0.23 mmol); anhydrous DMF (1 ml); 28b (8.7 mg; 0.025 mmol); EDC•HCl (7.5 mg; 0.038 mmol); HOBt (3.8



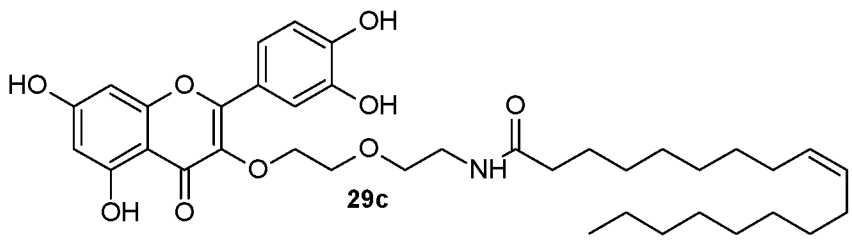
29b

mg; 0.028 mmol); anhydrous DMF (1.5 ml). Compound 29b was obtained as a yellow solid (4.5 mg, 25%).

^{1}H NMR (400 MHz, CD_3OD): 7.70 (d, 1H, J = 2.0 Hz), 7.54 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 6.88 (d, 1H, J = 8.4 Hz), 6.37 (d, 1H, J = 2.4 Hz), 6.23 (d, 1H, J = 2.4 Hz), 4.08-4.02 (m, 2H), 3.75-3.68 (m, 2H), 3.52 (t, 2H, J = 5.2 Hz), 3.38 (t, 2H, J = 5.2 Hz), 2.15 (t, 2H, J = 7.6 Hz), 1.62-1.48 (m, 2H), 1.31-1.11 (m, 36H), 0.84 (t, 3H, J= 6.8 Hz);

^{13}C NMR (100 MHz, CD_3OD): 179.0, 175.5, 164.6, 161.9, 157.4, 157.3, 148.6, 145.1, 137.5, 122.2, 121.9, 116.2, 115.5, 105.3, 99.3, 94.3, 71.9, 70.3, 70.0, 39.6, 36.7, 32.2, 30.9, 30.0, 29.8, 29.69, 29.65, 29.60, 26.2, 23.0, 14.2.

- 29c: 27 (21 mg; 0.042 mmol), DIPEA (44 µl;0.25 mmol); anhydrous DMF (1 ml); 28c (10.6 mg; 0.038 mmol); EDC•HCl (11 mg; 0.057 mmol); HOBt (5.6



29c

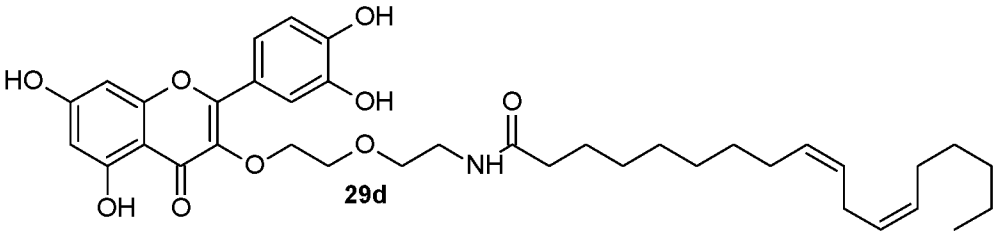
mg; 0.042 mmol); anhydrous DMF (1.5 ml). Compound 29c was obtained as a yellow solid (2 mg, 8%).

^{1}H NMR (400 MHz, CD_3OD): 7.68 (d, 1H, J = 1.6 Hz), 7.53 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 6.86 (d, 1H, J = 8,4 Hz), 6.35 (d, 1H, J = 2.0 Hz), 6.21 (d, 1H, J = 2.0 Hz), 5.29-5.22 (m, 2H), 3.72-3.65 (m, 2H), 3.49 (t, 2H, J = 5.2 Hz), 3.36 (t, 2H, J = 5.2 Hz), 2.12 (t, 2H, J = 7.6 Hz), 1.98-1.85 (m, 4H), 1.70-1.40 (m, 2H), 11.35-1.10 (m, 20 H), 0,81 (t, 3H, J = 7.6 Hz);

^{13}C NMR (100 MHz, CD_3OD): 178.8, 175.1, 164.3, 161.6, 157.2, 157.0, 148.3,

144.8, 137.3, 130.0, 129.9, 122.0, 121.7, 115.9, 115.2, 105.1, 99.1, 94.2, 71.7, 70.1, 69.8, 39.4, 36.6, 32.0, 29.9, 29.8, 29.6, 29.4, 29.3, 27.3, 26.0, 22.8, 14.1.

- 29d: 27 (15 mg; 0.028 mmol), DIPEA (40 µl;0.23 mmol); anhydrous DMF (1 ml); 28d (7.1 mg; 0.025 mmol); EDC•HCl (7.5 mg; 0.038 mol); HOBt (3.8 mg; 0.028 mmol); anhydrous DMF (1.5 ml). Compound 29d was obtained as a



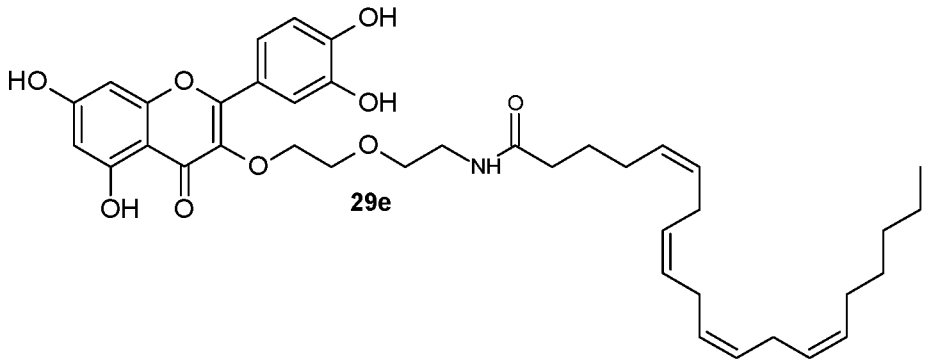
29d

yellow solid (5 mg, 30%).

^{1}H NMR (400 MHz, CD_3OD): 7.69 (d, 1H, 2.4 Hz), 7.54 (dd, 1H, J_1 = 8.4 Hz J_2 = 2.0 Hz), 6.88 (d, 1H, J = 8.4 Hz), 6.37 (d, 1H, J = 2.0 Hz), 6.22 (d, 1H, J = 2.0 Hz), 5.37-5.20 (m, 4H), 4.08-4.01 (m, 2H), 3.73-3.67 (m, 4H), 3.51 (t, 2H, J = 5.2 Hz), 3.38 (t, 2H, J = 5.2 Hz), 2.70 (t, 2H, J = 6.4 Hz), 21.47 (t, 2H, J = 7.6 Hz), 2.04-1.92 (m, 4H), 1.61-1.50 (m, 2H), 1.35-1.13 (m, 14H), 0.84 (t, 3H, J = 7.2 Hz);

^{13}C NMR (100 MHz, CD_3OD): 178.9, 175.3, 164.5, 161.8, 157.3, 157.1, 148.5, 145.0, 137.4, 130.4, 130.3, 128.21, 128.15, 122.1, 121.8, 116.0, 115.4, 105.2, 99.2, 94.3, 71.9, 70.2, 69.9, 39.5, 36.6, 31.7, 29.9, 29.8, 29.6, 29.5, 29.4, 27.4, 26.1, 25.8, 22.8, 14.1

- 29e: 27 (14 mg; 0.026 mmol), DIPEA (27 µl;0.16 mmol); anhydrous DMF (1 ml); 28e (7.2 mg; 0.024 mmol); EDC•HCl (6.8 mg; 0.036 mmol); HOBt (3.5



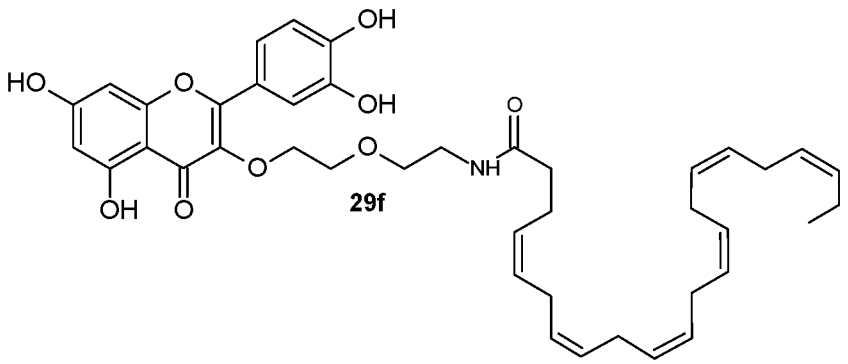
29e

mg; 0.026 mmol); anhydrous DMF (1.5 ml). Compound 29e was obtained as a yellow solid (5 mg, 31%).

^{1}H NMR (400 MHz, CD_3OD): 7.69 (d, 1H, *J* = 2.0 Hz), 7.54 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 6.88 (d, 1H, *J* = 8.4 Hz), 6.37 (d, 1H, *J* = 1.6 Hz), 6.22 (d, 1H *J* = 1.6 Hz), 5.38-5.21 (m, 8H), 4.08-4.00 (m, 2H), 3.74-3.66 (m, 2H), 3.51 (t, 2H, *J* = 5.2 Hz), 3.38 (t, 2H, *J* = 5.2 Hz), 2.82-2.68 (m, 6H), 2.17 (t, 2H, *J* = 8,0 Hz) 2.1-1.94 (m, 4H), 1.70-1.58 (m, 2H), 1.35-1.15 (m, 6H), 0.831 (t, 3H, *J* = 6.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): 178.7, 175.5, 163.1, 161.93, 156.9, 156.7, 148.2, 144.2, 137.4, 130.7, 129.1, 128.9, 128.8, 128.4, 128.2, 128.0, 127.6, 122.3, 121.6, 116.1, 115.1, 105.6, 99.4, 94.3, 71.6, 70.1, 69.7, 39.6, 36.2, 31.6, 29.8, 29.4, 27.3, 26.7, 25.8, 25.7, 22.7, 14.2.

- 29f: 27 (25 mg; 0.05 mmol), DIPEA (63 µl; 0.36 mmol); anhydrous DMF (1.5 ml), 28f (15 mg; 0.046 mmol), EDC•HCl (13 mg; 0.069 mmol), HOBt (8 mg;



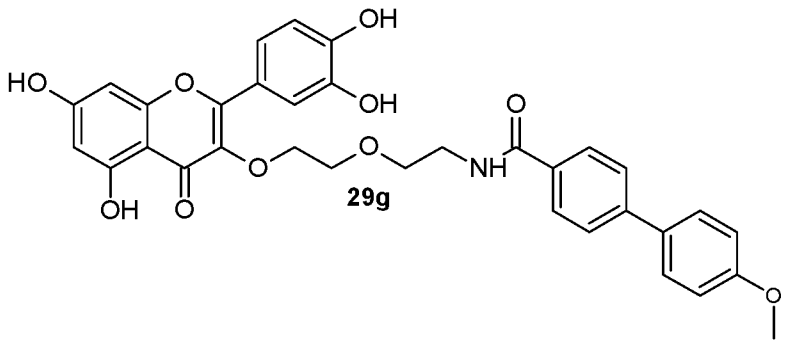
29f

0.06 mmol), anhydrous DMF (2.5 ml). Compound 29f was obtained as a yellow solid (14 mg, 44%).

^{1}H NMR (400 MHz, CD_3OD: 7.69 (d, 1H, *J*= 2.0), 7.54 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 6.88 (d, 1H, *J* = 8.8 Hz), 6.37 (d, 1H, *J* = 2.0 Hz), 6.22 (d, 1H, *J* = 2.0), 5.38-5.23 (m, 12H), 4.08-4.01 (m, 2H), 3.74-3.66 (m, 2H), 3.51 (t, 2H, *J* = 5.2 Hz), 3.38 (t, 2H, *J* = 5.2 Hz), 2.85-2.70 (m, 10 H), 2.39-2.30 (m, 2H), 2.22 (t, 2H, *J* = 6.8 Hz), 2.08-1.97 (m, 2H), 0.92 (t, 3H, *J* = 7.2 Hz);

^{13}C NMR (100 MHz, CD_3OD): 178.9, 174.4, 164.5, 161.8, 157.3, 157.2, 148.5, 145.0, 137.4, 132.2, 129.4, 128.8, 128.5, 128.43, 128.37, 128.33, 128.13, 127.3, 122.2, 121.8, 116.1, 115.4, 105.3, 99.2, 94.3, 71.9, 70.2, 69.9, 39.6, 36.3, 25.83, 25.81, 25.74, 23.8, 20.8, 14.3.

- 29g: 27 (32 mg; 0.063 mmol), DIPEA (100 µl;0.57 mmol), anhydrous DMF (2 ml), 28g (15.8 mg; 0.069 mmol), EDC•HCl (19.8 mg; 0.10 mmol); HOBt (11.2



29g

mg; 0.083 mmol), anhydrous DMF (3 ml). Compound 29g was obtained as a yellow solid (9 mg, 22%).

^{1}H NMR (400 MHz, CD_3OD): 7.82-7.77 (m, 2H), 7.68 (d, 1H, *J* = 2.4 Hz), 7.59-7.47 (m, 5H), 6,99-6.93 (m, 2H), 6.89 (d, 1H, *J* = 8.4 Hz), 6.34 (d, 1H, *J* = 1.6Hz), 6.16 (d, 1H, *J* = 1.6 Hz), 4.15-4.09 (m, 2H), 3.81 (s, 3H), 3.79-3.73 (m, 2H), 3.66-3.61 (m, 2H), 3.61-3.55 (m, 2H);

^{13}C NMR (100 MHz, CD_3OD): 179.9, 170.3, 165.8, 163.0, 161.2, 158.3, 158.0, 149.9, 146.3, 145.2, 138.3, 133.52, 133.48, 129.1, 128.8, 127.3, 123.0, 122.6, 117.0, 116.3, 115.3, 105.8, 99.8, 94.7, 72.8, 71.3, 70.6, 55.7, 41.1.

Examples of significant reactions and syntheses, also associated with obtaining the heterotrimer Q_2E 36

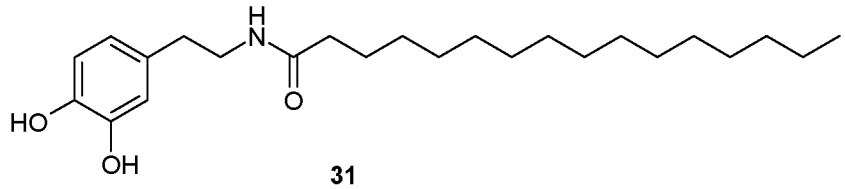
Example of synthesis of intermediate 31.

EDC•HCl (379 mg; 1.98 mmol), followed approximately 30 minutes later by HOBt (214 mg; 1.58 mmol) were added to a solution of palmitic acid (372 mg; 1.45 mmol) in anhydrous DMF (2 ml) under magnetic stirring and argon atmosphere. The

reaction mixture thus obtained was stirred for about thirty minutes and then added dropwise over 5 minutes via a syringe to a solution of dopamine•HCl (30; 250 mg; 1.32 mmol) and DIPEA (1.38 ml; 7.9 mmol) in anhydrous DMF (10 ml) kept at 0°C (in an ice bath).

When the addition was complete, the reaction mixture was slowly allowed to reach room temperature and then kept stirring under argon atmosphere for further 24 hours before being diluted with AcOEt (30 ml) and washed sequentially with H2O (2 × 30 ml) and a saturated NaCl solution (20 ml).

The organic phase was dried over anhydrous Na2SO4 , filtered, and concentrated under vacuum to dryness to yield a crude product, which was purified by flash column chromatography (SiO2, EtOAc/n-hexane= 30->45%) to afford intermediate 31 as a white solid (190 mg, 37%).



31

1H NMR (400 MHz, CD3OD): 6.67 (d, 1H, J = 7.6 Hz), 6.64 (d, 1H, J = 2.0 Hz), 6.51 (dd, 1H, J1 = 7.6 Hz, J2 = 2.0 Hz), 3.33 (t, 2H, J = 7.2 Hz), 2.62 (t, 2H, J = 7.2 Hz), 2.14 (t, 2H, J = 7.6 Hz), 1.62-1.51 (m, 2H), 1.37-1.22 (m, 24H), 0.90 (t, 3H, J= 6.8 Hz);

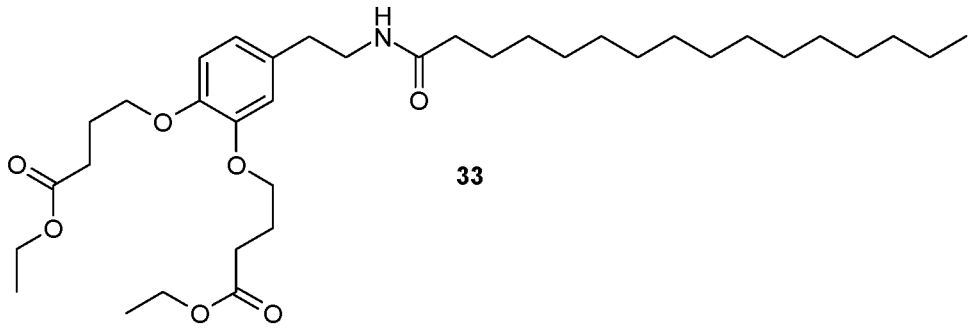
13C NMR (100 MHz, CD3OD): 178.3, 146.3, 144.8, 132.0, 121.0, 116.8, 116.3, 42.2, 37.2, 36.0, 33.1, 30.79, 30.76, 30.6, 30.5, 30.4, 30.3, 27.1, 23.7, 14.4.

Example of synthesis of intermediate 33.

K2CO3 (230 mg) and KI (43 mg) were added sequentially to a solution of amide 31 (170 mg; 0.43 mmol) and ethyl 4-bromobutanoate (32) (319 mg; 1.91 mmol) in

anhydrous DMF (10 ml), under argon atmosphere. The reaction thus obtained was magnetically stirred for 24 hours before being diluted with EtOAc (40 ml) and washed with H2O (2 × 30 ml) and a saturated aqueous solution of NaCl (20 ml).

The final organic phase was dried over anhydrous Na2SO4 , filtered, and concentrated under vacuum to dryness to yield a crude product from which intermediate 33 was obtained as a white solid (192 mg, 72%) after purification by flash column chromatography.



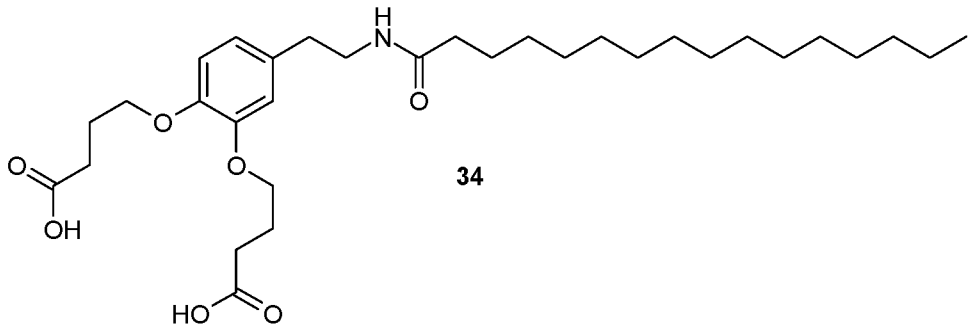
33

1H NMR (400 MHz, CDCl3):6.81 (d, 1H, J= 5.6Hz), 6.75-6.65 (m, 2H), 5.47 (bt, 1H), 4.13 (q, 4H, J= 7.2 Hz), 4.013 (t, 2H, J= 6.0 Hz), 4.007 (t, 2H, J= 6.0 Hz), 4.04-3.98 (m, 4H), 3.51-3.42 (m, 2H), 2.72 (t, 2H, J= 6.8 Hz), 2.53 (t, 4H, J= 7.6 Hz), 2.16-2.06 (m, 6 H), 1.64-1.53 (m, 2H), 1.34-1.19 (m, 30H), 0.87 (t, 3H, J= 7.2 Hz); 13C NMR (100 MHz CDCl3): 173.22, 173.19, 173.10, 149.0, 147.5, 132.1, 121.3, 114.9, 114.5, 68.3, 68.1, 60.4, 40.5, 36.8, 35.2, 30.70, 30.68, 29.7, 29.62, 29.59, 29.5, 29.34, 29.32, 29.29, 25.7, 24.73, 24.70, 22.7, 14.2, 14.1.

Example of synthesis of intermediate 34

NaOH (66 mg) was added to a solution of ester 33 (58 mg; 0.095 mmol) in THF/MeOH/H2O= 2/2/1 (5 ml): the reaction thus obtained was stirred for 18 hours before being cautiously adjusted to approximately pH 5 with successive additions of

small amounts of 2N HCl (780 µl total). The reaction was then diluted with AcOEt (10 ml) and washed with H2O (2 × 6 ml) and a saturated aqueous solution of NaCl (6 ml). Lastly, the organic phase was dried over anhydrous Na2SO4 , filtered, and concentrated under vacuum to dryness to yield diacid 34 as a white solid (49 mg, 91%). This appeared to be pure by NMR analysis, requiring no further purification in order to be used in the subsequent step.



34

1H NMR (400 MHz, CD3OD): 6.82 (d, 1H, J= 8.4 Hz), 6.78 (d, 1H, J= 1.6 Hz), 6.71 (dd, 1H, J1= 8.4 Hz, J2= 2.0 Hz), 4.07-3.97 (m, 4H), 3.36 (t, 2H, J= 7.2 Hz), 2.70 (t, 2H, J= 7.6 Hz), 2.52 (t, 2H, J= 7.6 Hz), 2.51 (t, 2H, 7.2 Hz), 2.16-2.01 (m, 6H), 1.60-1.50 (m, 2H), 1.32-1.17 (m, 24H), 0.86 (t, 3H, J= 6.8 Hz); 13C NMR (100 MHz, CD3OD): 176.6, 175.7, 149.7, 148.2, 133.3, 122.2, 115.84, 115.48, 69.22, 68.98, 41.5, 36.9, 35.6, 32.5, 31.1, 30.28, 30.26, 30.1, 29,995, 29,968, 29,863, 26.6, 25.4, 23.2, 14.3.

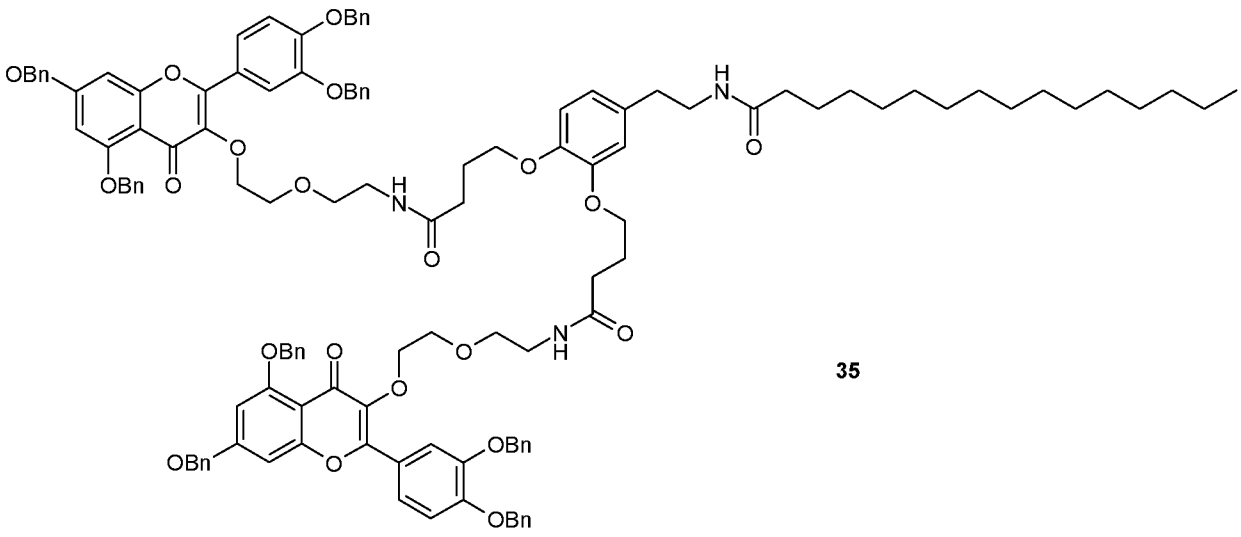
Example of synthesis of intermediate 35

EDC•HCl (51 mg; 0.27 mmol) first and 30 minutes later HOBt (26 mg; 0.31 mmol) were added to a solution of 34 (50 mg; 0.089 mmol) in anhydrous DMF (3 ml) under stirring and argon atmosphere. The reaction mixture was stirred for thirty minutes and then added dropwise via a syringe (over 5 minutes) to a solution of 16 (0.23 mol) and DIPEA (247 µl; 1.42 mmol) in anhydrous DMF (2 ml), kept under stirring

at 0°C (using an ice bath) under argon atmosphere.

The reaction mixture thus obtained was slowly allowed to warm to room temperature and then kept stirring for 24 hours before being diluted with EtOAc (20 ml) and washed sequentially with H_2O (2 × 10 ml) and a saturated aqueous solution of NaCl (10 ml).

The organic phase is finally dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum to dryness to yield a crude product, which was purified by flash column chromatography (DCM/MeOH= 1->3%) to afford intermediate 35 as a white solid (40 mg, 22%).



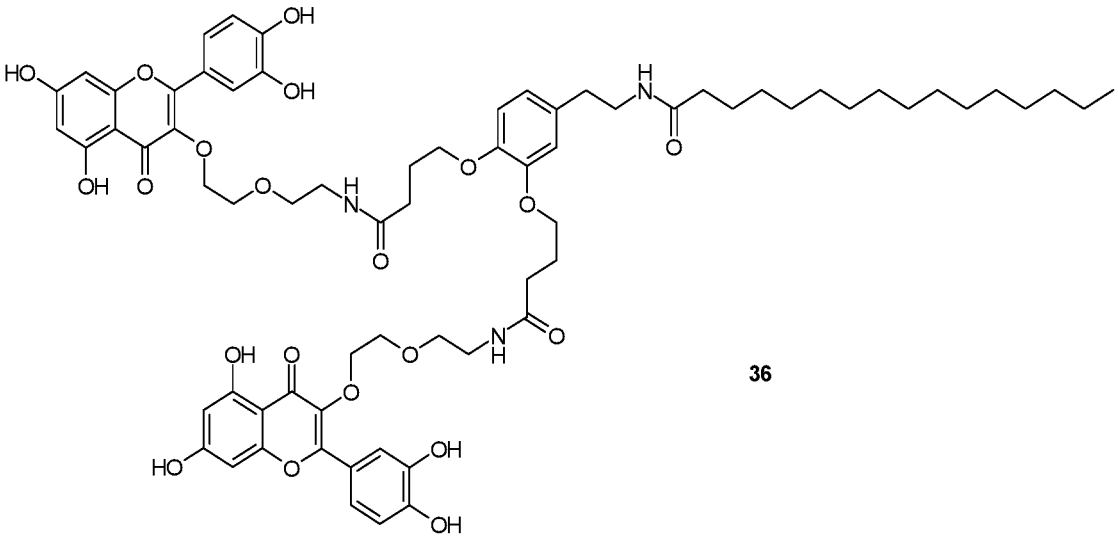
35

^{1}H NMR (400 MHz, CD_3OD, TMS): 7.78, (m, 2H), 7.73 (dd, 2H, J_1= 8.8 Hz, J_2= 2.4 Hz), 7.56-7.51 (m, 4H), 7.49-7.24 (m, 36 H), 7.03 (d, 2H, J= 8.8), 6.74-6.60 (m, 3H), 6.56 (d, 2H, J= 1.6 Hz), 6.45 (d, 2H, J= 2.0 Hz), 5.24-5.17 (m, 12H), 5.09 (s, 4H), 4.07-4.0 (m, 4H), 3.89 (t, 2H, J= 6.4 Hz), 3.86 (t, 2H, J= 6.4 Hz), 3.63-3.57 (m, 4H), 3.44 (t, 4H, J= 3.2 Hz), 3.39-3.34 (m, 2H), 3.34-3.28 (m, 4H), 2.65 (t, 2H, J= 7.2 Hz), 2.36-2.27 (m, 4H), 2.09 (t, 2H, J= 7.6 Hz), 2,03-1.93 (m, 4H), 1.61-1.50 (m, 2H),

1.33-1.18 (m, 24H), 0.87 (t, 3H, *J*= 6.8); ^{13}C NMR (100 MHz, CD_3OD): 174.7, 174.5, 174.0, 163.4, 159.9, 160.0, 159.0, 153.6, 151.4, 149.0, 148.5, 147.6, 140.2, 137. 2, 136.9, 136.5, 135.9, 132.5, 129.0, 128.81, 128.79, 128.67, 128.29, 128.23, 128.05, 127.8, 127.7, 127.6, 127.0, 123.7, 123.2, 121.6, 116.0, 115.2, 114.8, 114.1, 109.9, 98.4, 94.3, 72.0, 71.5, 71.2, 71.0, 70.8, 70.2, 69.7, 68.8, 68.6, 40.9, 39.5, 36.7, 35.2, 32.70, 32.65, 32.1, 29.9, 29.7, 29.60, 29.56, 29.53, 26.1, 25.63, 25.58, 22.9, 14.2.

Example of synthesis of compound 36

Pd/C (18 mg) and a solution of compound 35 (33 mg; 0.016 mmol) in EtOH/THF=2/1 (4 ml) were added in this order to a 100 ml hydrogenation flask under argon atmosphere. The reaction mixture was subjected to four nitrogen/vacuum cycles before introducing an atmosphere of hydrogen (1 bar) into the flask. The reaction was kept under stirring at room temperature for 24 hours before being degassed under vacuum and filtered through 0.45 µm PTFE. The solution thus obtained was dried under vacuum to dryness: the crude product obtained as above was washed with an Et_2O/ *n*-hexane= 2.5/7.5 (2 × 5 ml) mixture and finally dried again in vacuo to yield 36 as a yellow solid (13 mg, 60%).



36

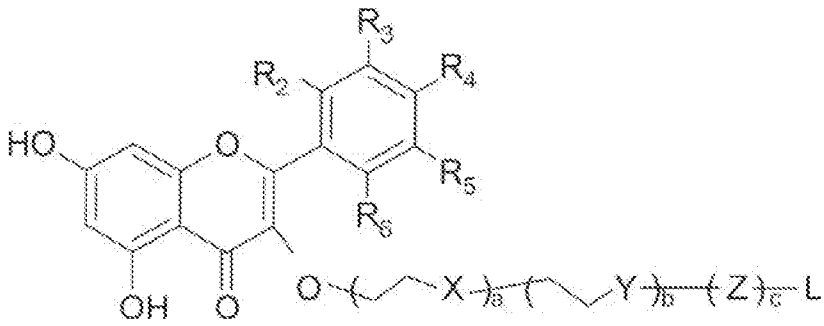
^{1}H NMR (400 MHz, CD_3OD/MeOH=4/1, TMS): 7.74 (d, 2H, *J* = 1.6 Hz), 7.54 (dd, 2H, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 6.96-6.88 (m, 2H) 6.75-6.67 (m, 2H), 6.62 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.2 Hz), 6.39 (d, 2H, *J* = 1.2 Hz), 6.25 (dd, 2H, J_1 = 4.4 Hz, J_2 = 1.6 Hz), 4.08-4.01 (m, 4H), 3.98-3.88 (m, 4H), 3.73-3.67 (m, 4H), 3.57-3.49 (m, 4H), 3.46-3.39 (m, 4H), 3.39-3.35 (m, 2H), 2.65 (t, 2H, *J* = 7.2 Hz), 2.41 (t, 4H, *J* = 7.2 Hz), 2.15 (t, 2H, *J* = 8.0 Hz), 2.11-2.01 (m, 4H), 1.64-1.52 (m, 2H), 1.37-1.20 (m, 24H), 0.89, (t, 3H, *J*= 7.2 Hz);

^{13}C NMR (100 MHz, CD_3OD/MeOH=4/1, TMS): 178.9, 175.2, 174.6, 164.5, 161.8, 157.3, 157.1, 149.0, 148.6, 147.6, 145.0, 137.4, 132.6, 125.7, 122.2, 121.8, 121.7, 116.3, 115.5, 115.2, 114.8, 105.3, 99.3, 94.3, 71.8, 70.2, 69.9, 68.8, 68.7, 57.9, 41.1, 39.7, 36.8, 35.3, 33.0, 30.5, 30.0, 29.9, 29.8, 29.7, 29.62, 29.57, 26.2, 25.8, 22.9, 18.0, 14.2.

The compound comprises molecules (I) which may be connected to each other resulting, in particular, in homo- or hetero- dimers, trimers and tetramers according to formula (I), as described above with the exception of R1 or R1' which consists of

a Linker L.

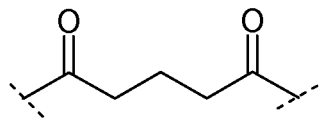
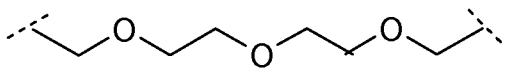
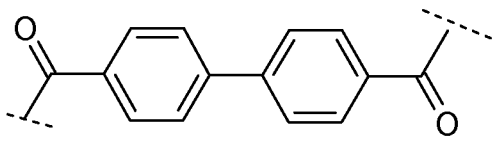
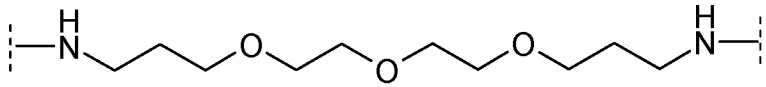
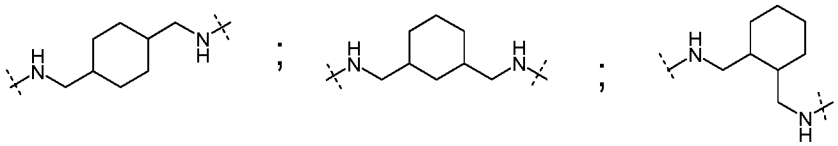
The formula (I) thus modified is designated as formula (II), and is preferably as follows:

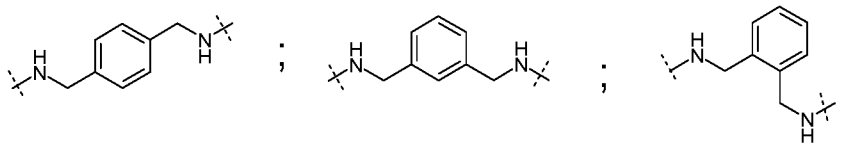
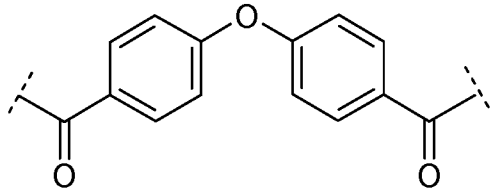
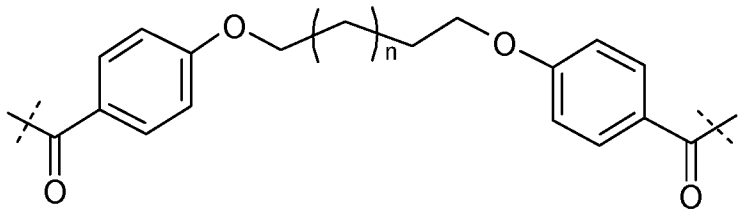
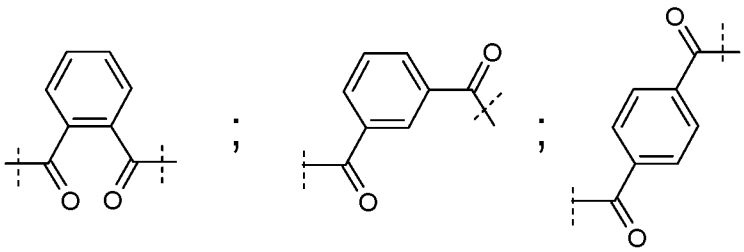
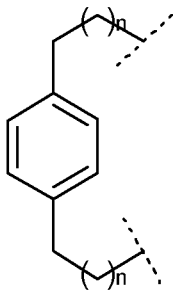


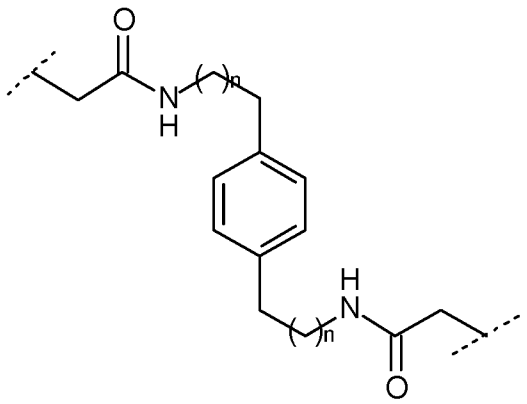
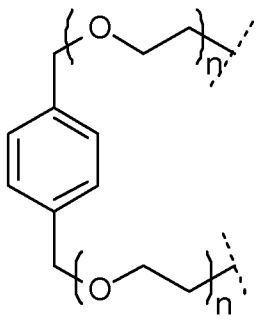
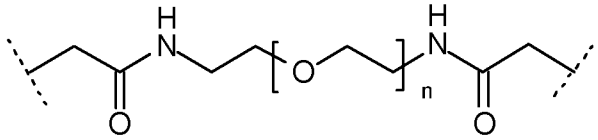
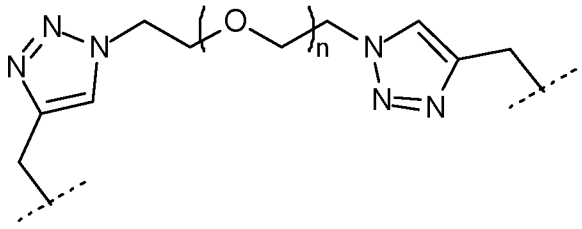
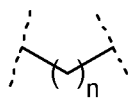
(II)

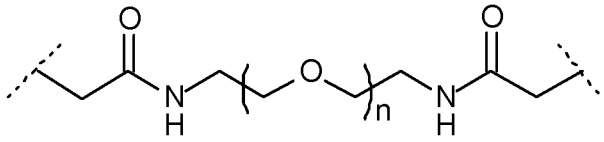
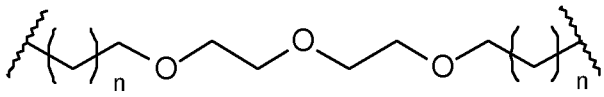
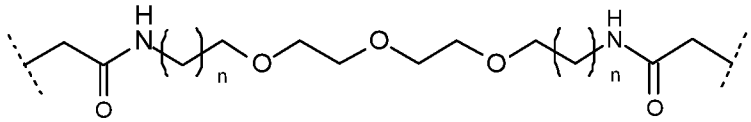
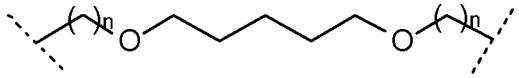
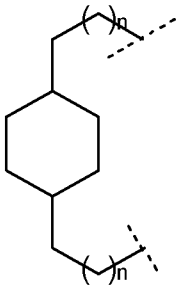
X, Y, Z and a, b, c are as previously defined.

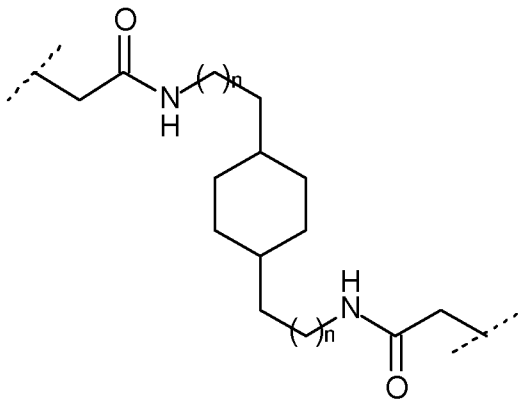
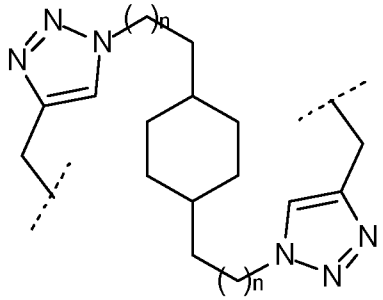
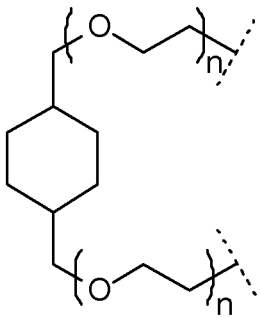
The Linker L is more preferably selected from the compounds listed below.

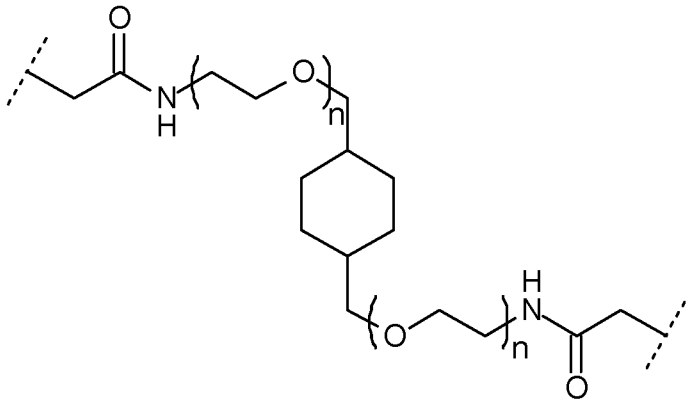
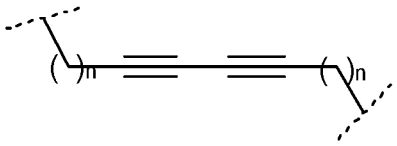
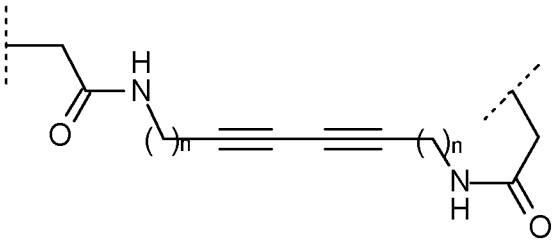
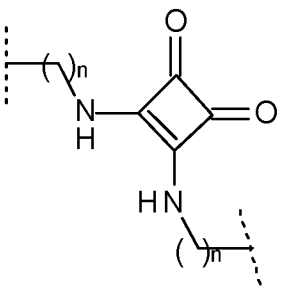
LINKER L	
L1	
L2	
L3	
L4	
L5	

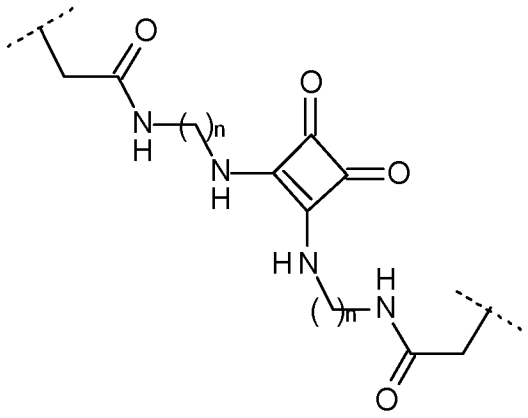
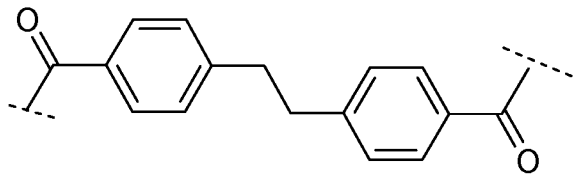
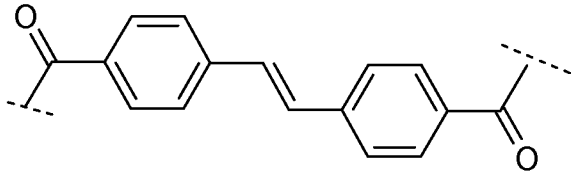
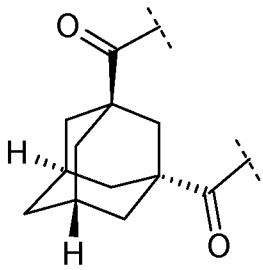
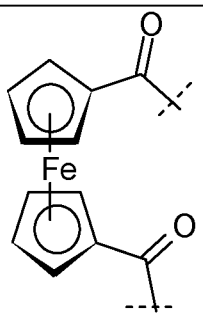
L6	
L7	
L8	 n = 0 - 8
L9	
L11	 n = 1-6, each independently

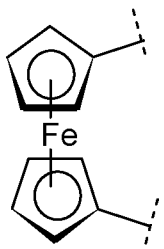
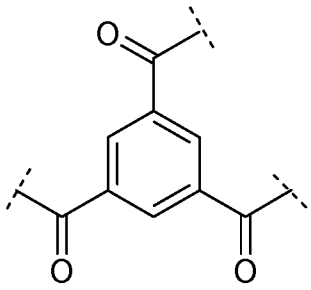
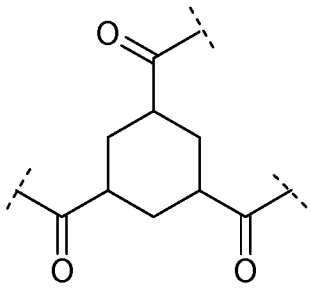
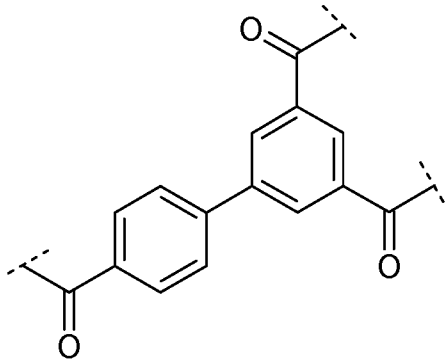
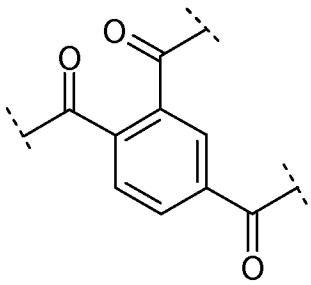
L12	 n = 1-6
L13	 n = 1-3, each independently
L14	 n = 1-4
L15	 n = 1-4, each independently
L16	

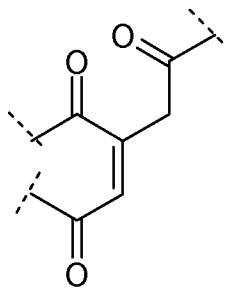
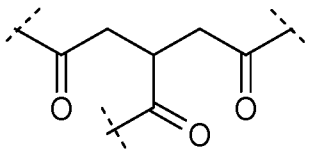
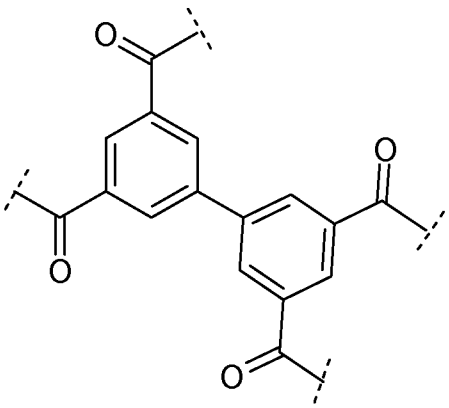
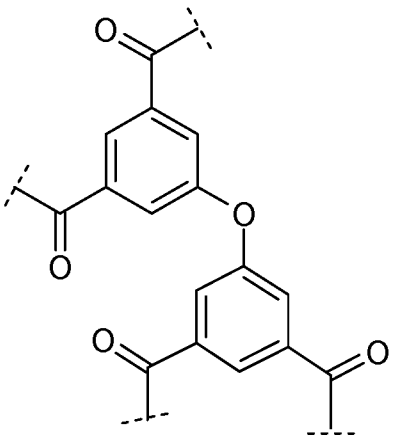
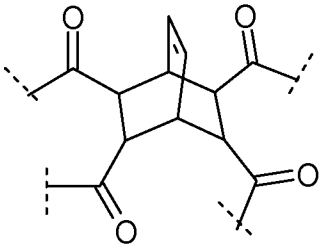
	n = 2-12
L17	 n = 1-5
L18	 n = 1-3
L19	 n = 1-3
L20	 n = 1-3
L21	 n = 1-6

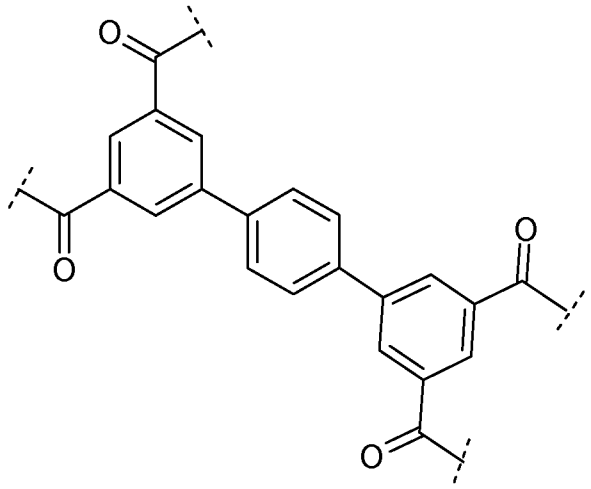
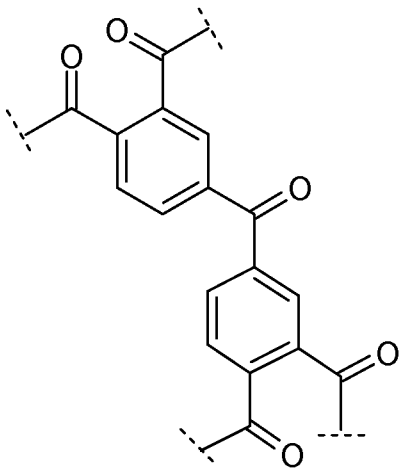
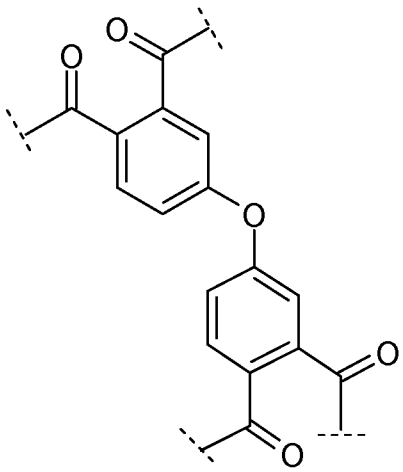
L22	 n = 1-6
L23	 n = 1-6, each independently
L24	 n = 1-3, each independently

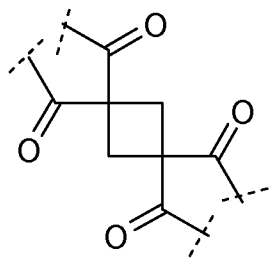
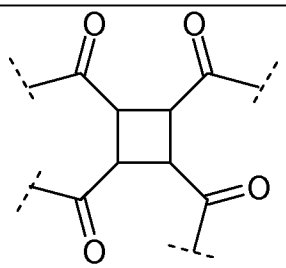
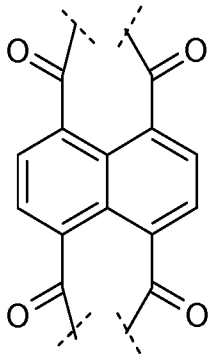
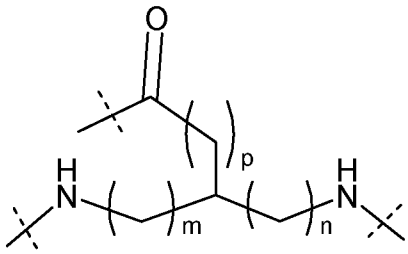
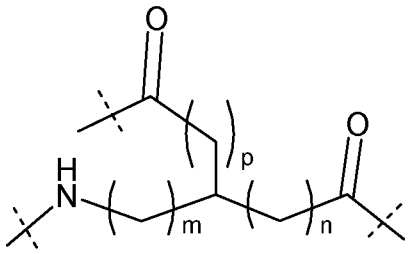
L25	 n = 1-3, each independently
L26	 n = 1-6, each independently
L27	 n = 1-6, each independently
L28	 n = 1-6, each independently

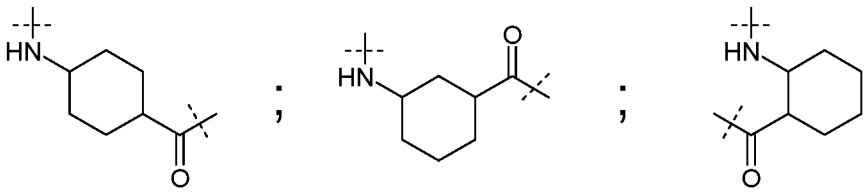
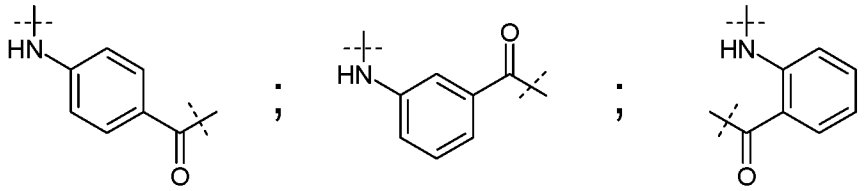
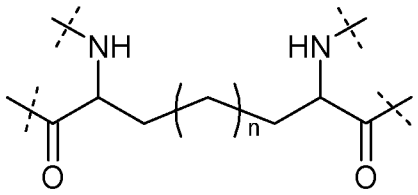
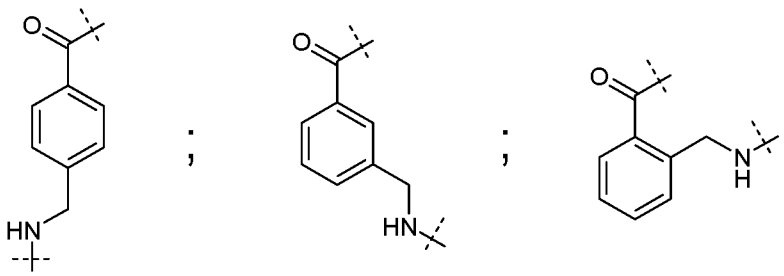
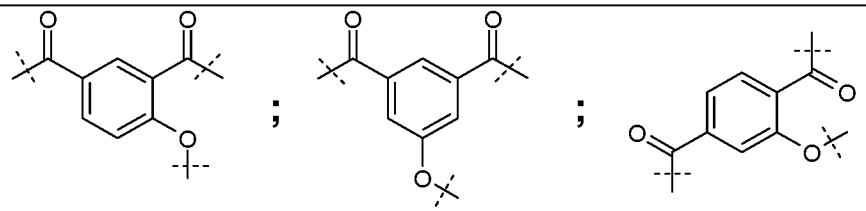
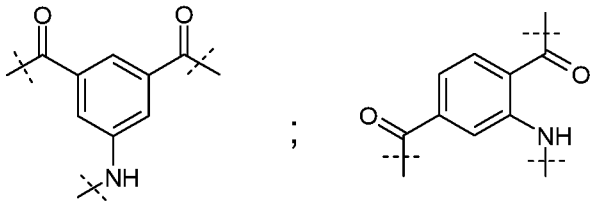
L29	 n = 1-6, each independently
L30	
L31	
L32	
L33	

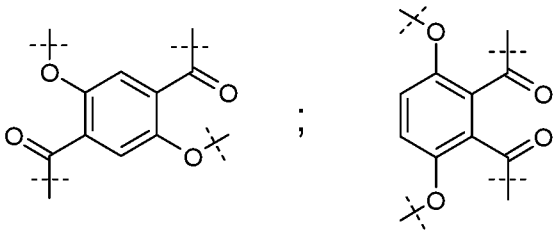
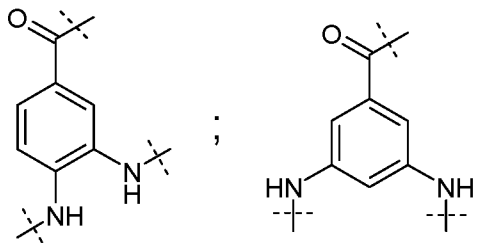
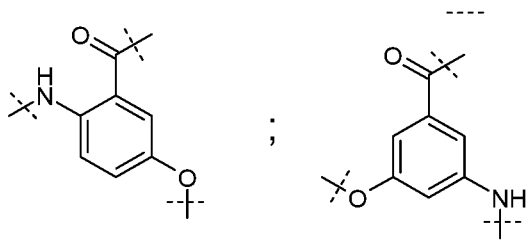
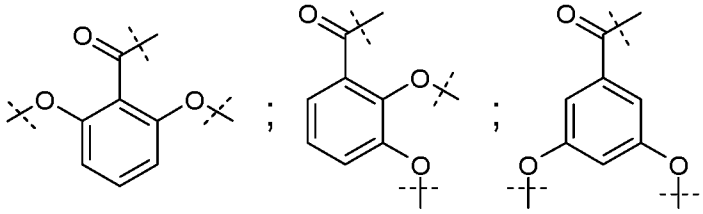
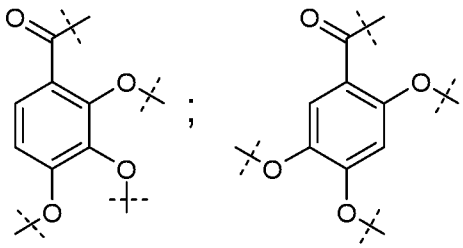
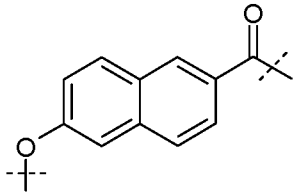
L34	
L35	
L36	
L37	
L38	

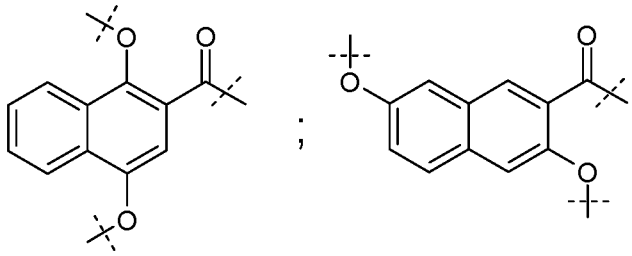
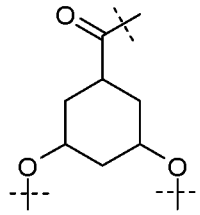
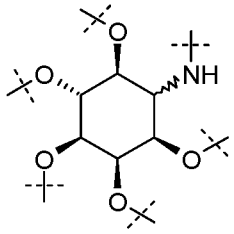
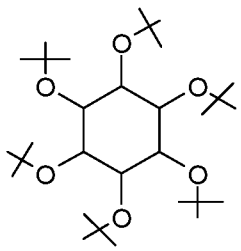
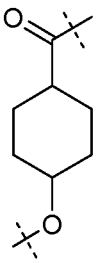
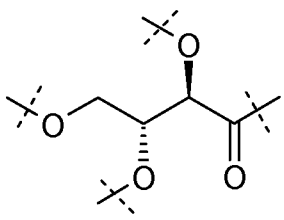
L39	
L40	
L41	
L42	
L43	

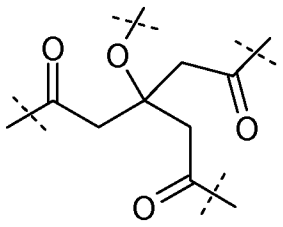
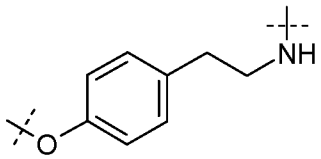
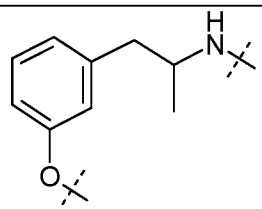
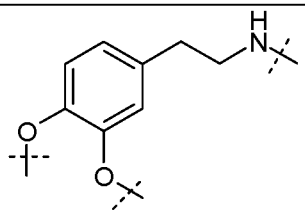
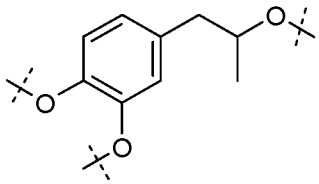
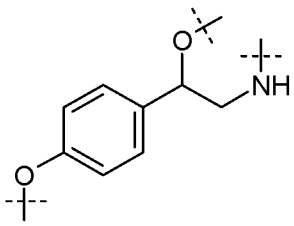
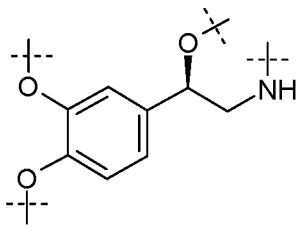
L44	
L45	
L46	

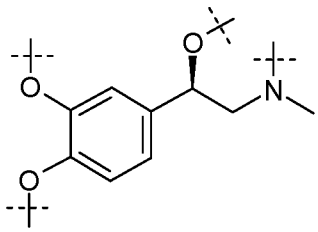
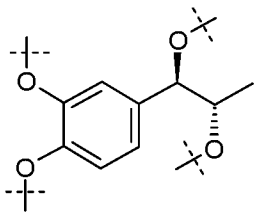
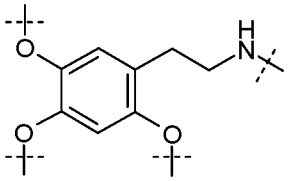
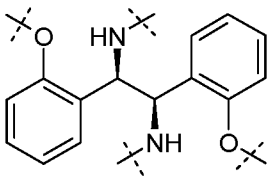
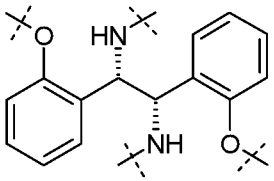
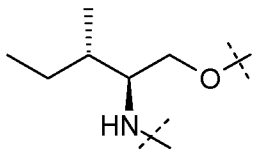
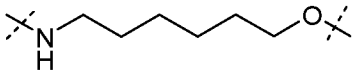
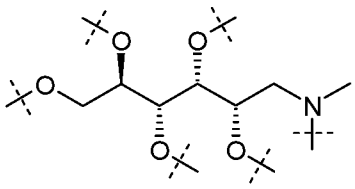
L47	
L48	
L49	
L50	 n, m, p = 0-6; each independently
L51	 n, m, p = 0-6; each independently

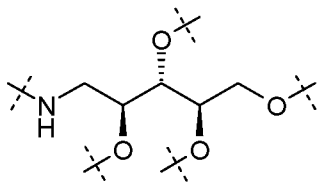
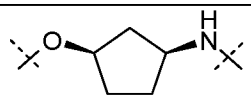
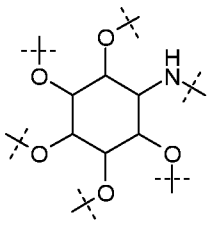
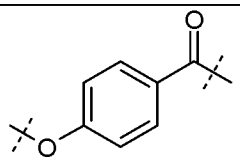
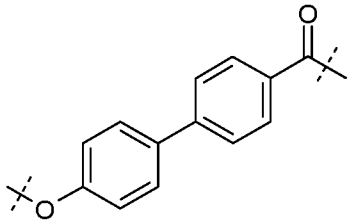
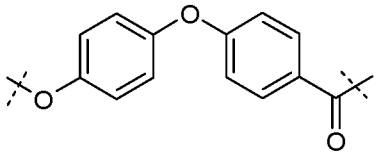
L52	
L53	
L54	 n = 0, 5
L55	
L56	
L57	

L58	
L59	
L60	
L61	
L62	
L63	

L64	
L65	
L66	
L67	
L68	
L69	

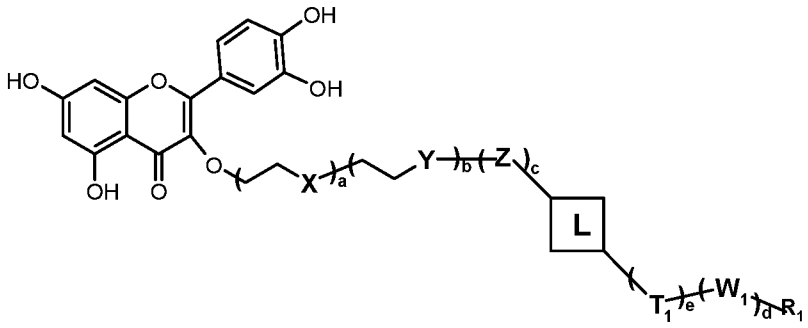
L70	
L71	
L72	
L73	
L74	
L75	
L76	

L77	
L78	
L79	
L80	
L81	
L82	
L83	
L84	

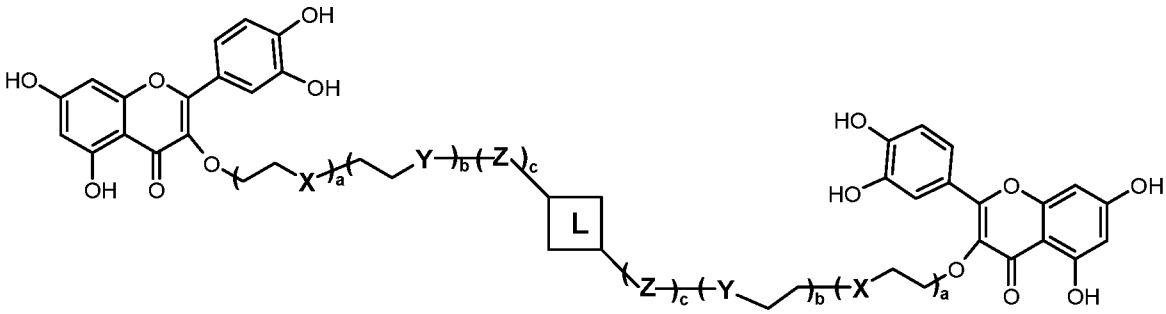
L85	
L86	
L87	
L88	
L89	
L90	

Most of the linkers shown in the table are known and commercially available. Any other linker can be easily prepared according to known methods.

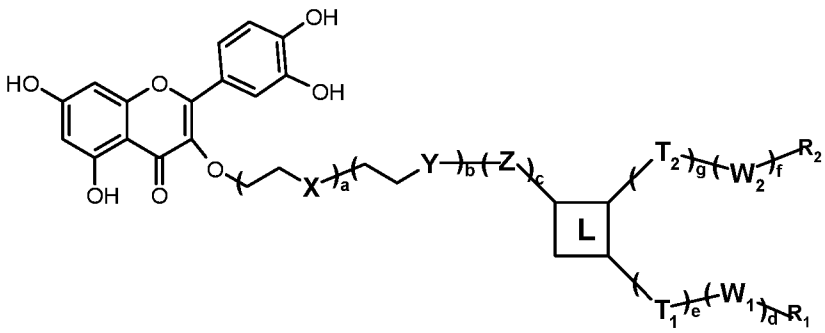
1. According to the general formula (I) or (II), the compound may have the following general structures (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) and (XI):



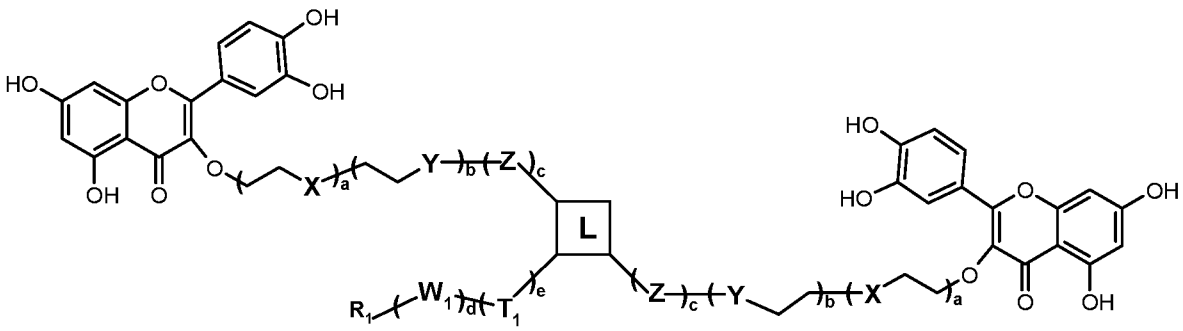
(III)



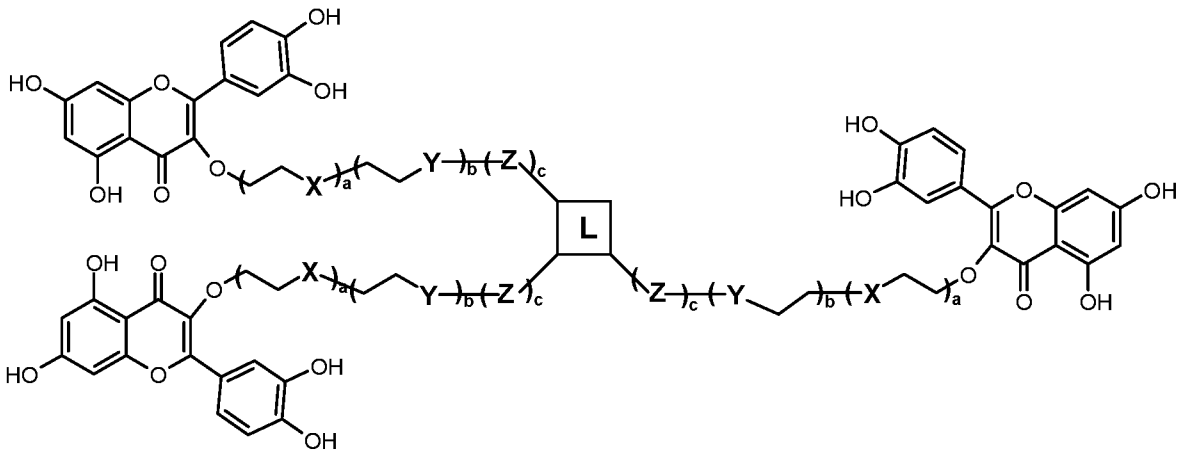
(IV)



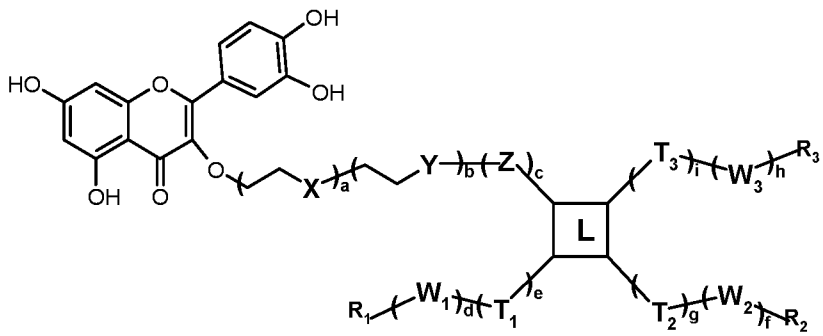
(V)



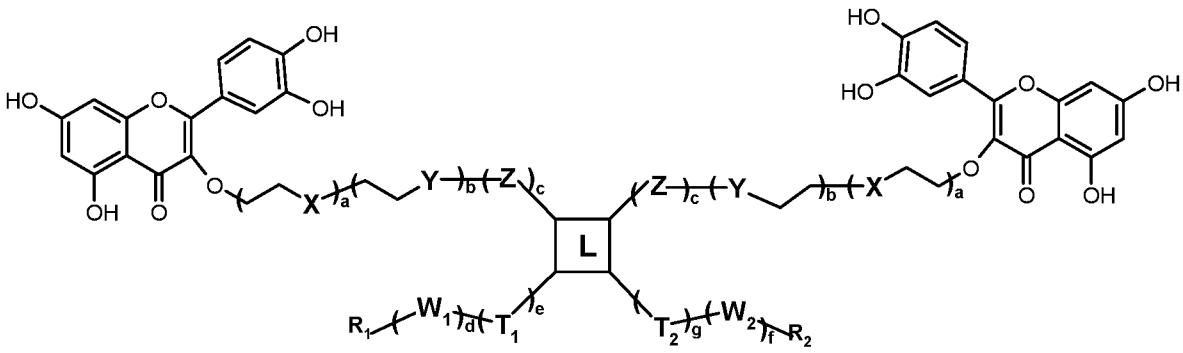
(VI)



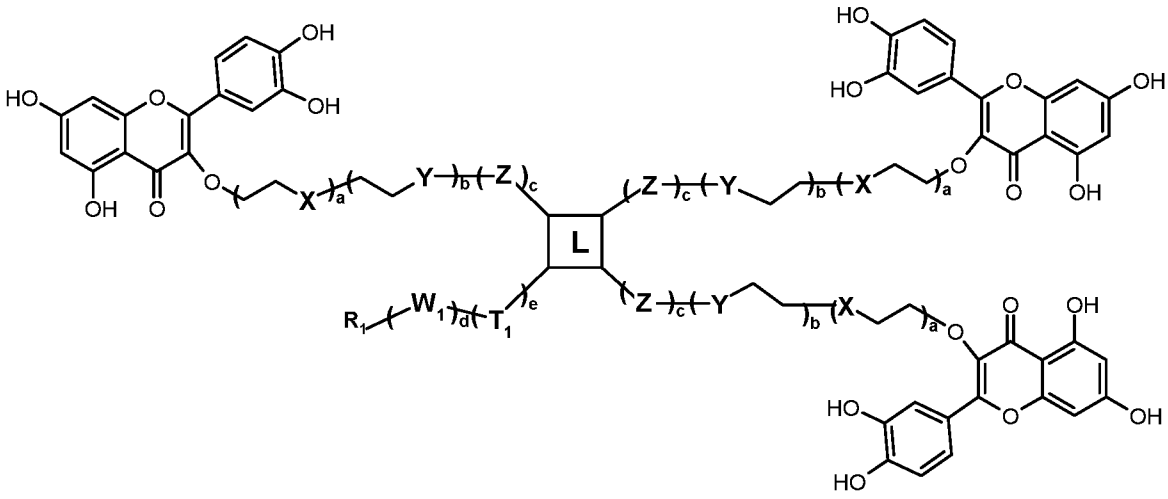
(VII)



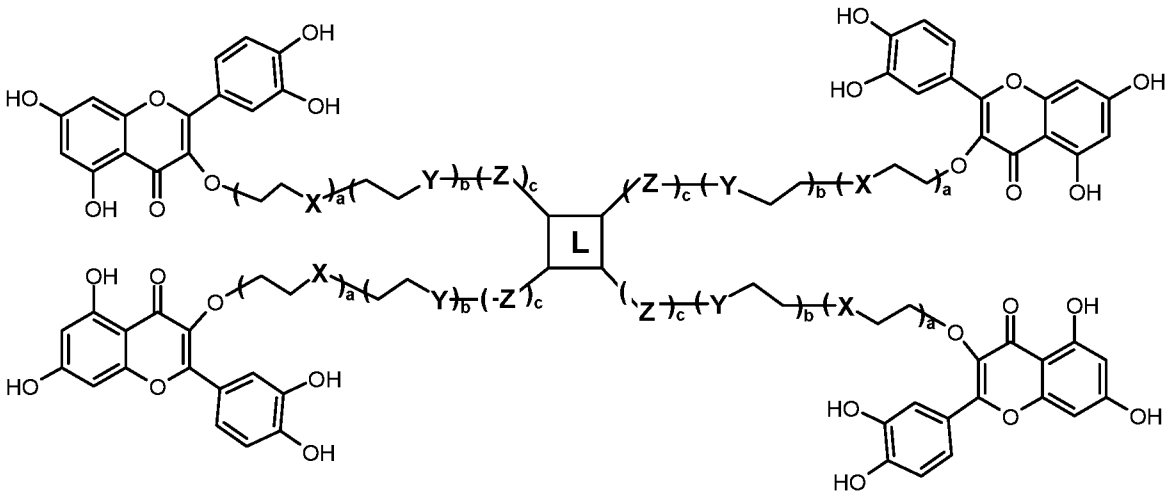
(VIII)



(IX)



(X)

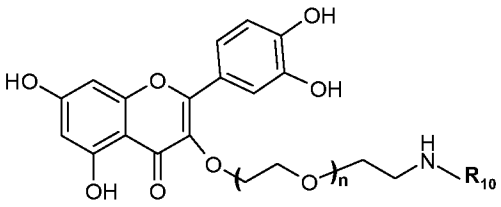


(XI)

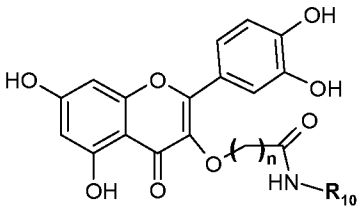
where d, e, f, g, h, i each range from 0 to 12,

where T_1-T_3, W_1-W_3 are each independently selected from: CH2, O, N(R1), S, NH, SO, SO_2, OC(O), CO, NHC(O), C(O)NH, NH-C(O)-NH, NH-C(S)-NH.

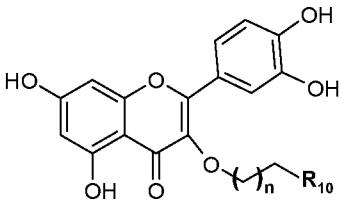
2. According to the general formula (I), the compound may have the following general structures (XII), (XIII), (XIV) and (XV):



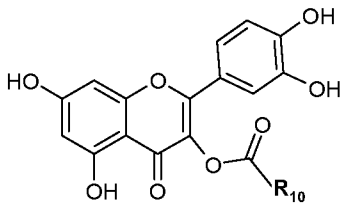
(XII)



(XIII)



(XIV)

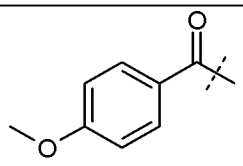
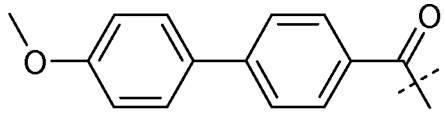
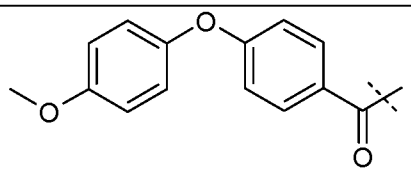


(XV)

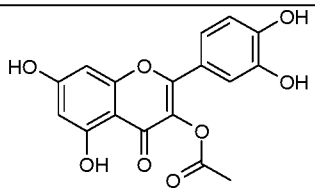
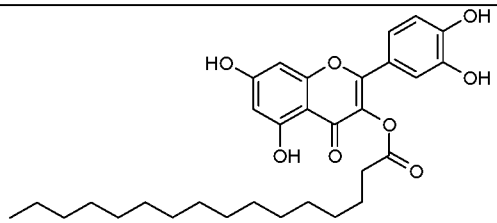
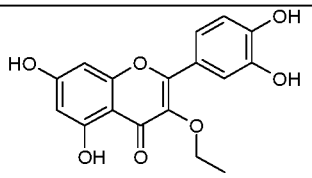
where n can independently take a value between 0 and 12.

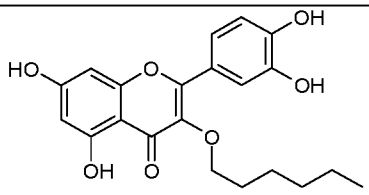
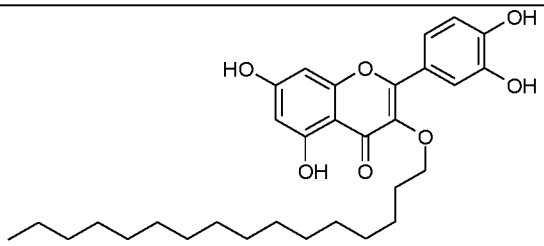
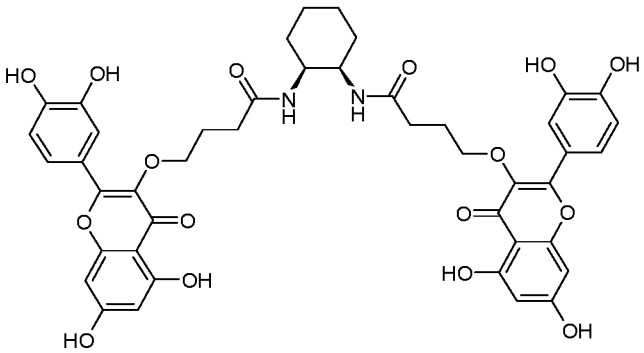
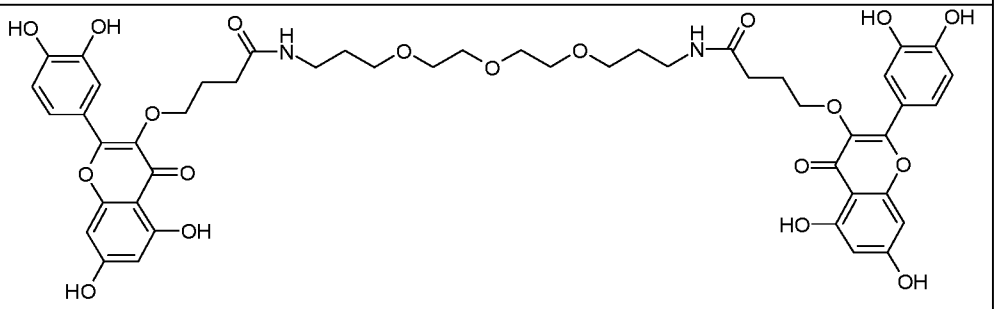
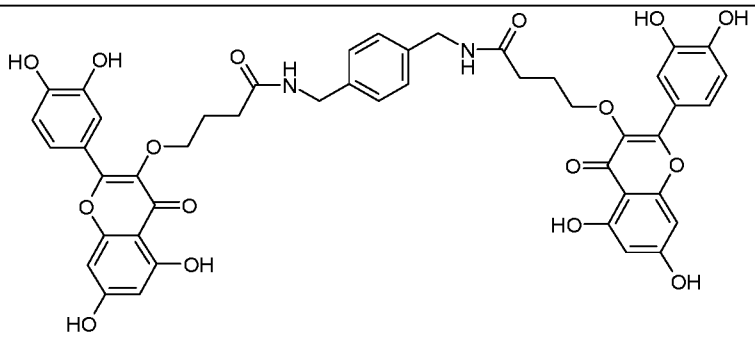
R_{10}, could be independently, but not exclusively and in possible combinations of the following:

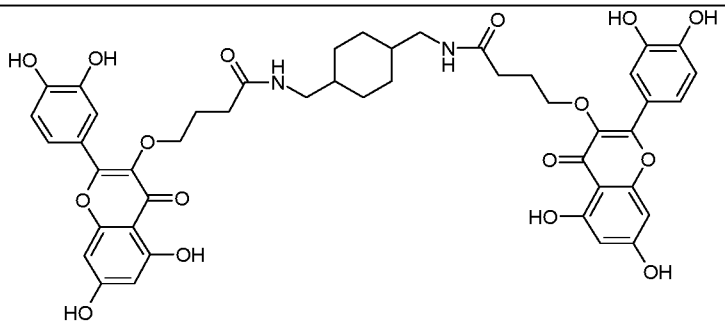
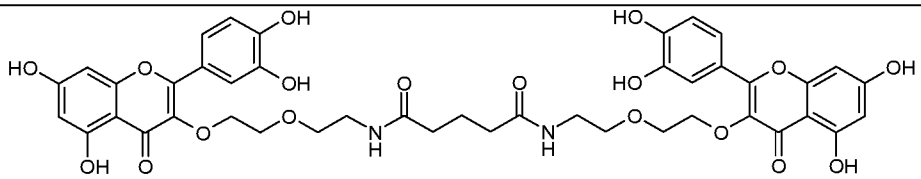
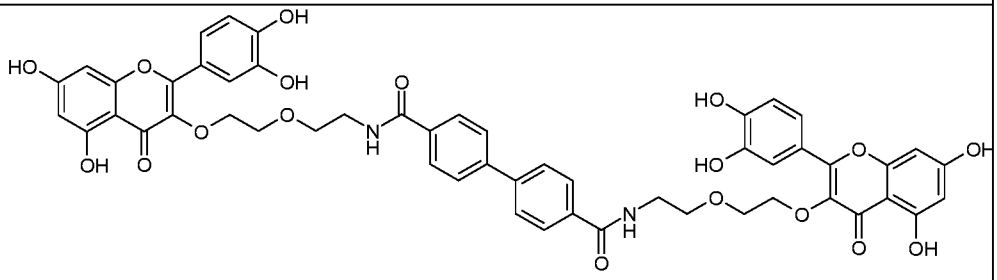
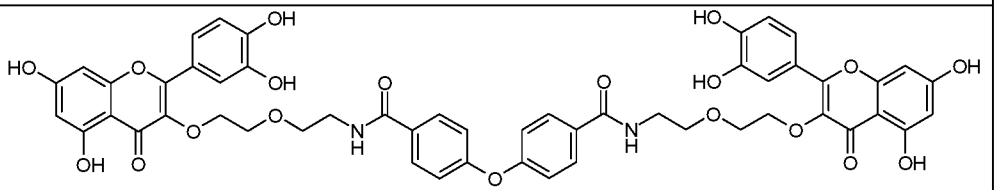
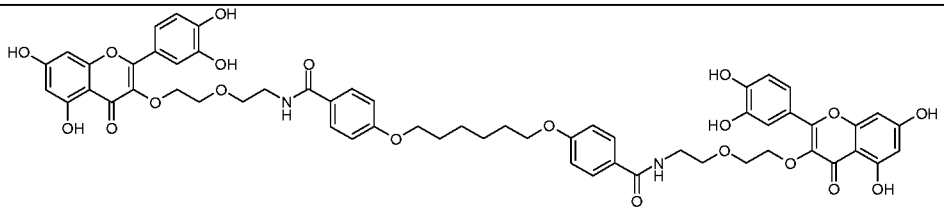
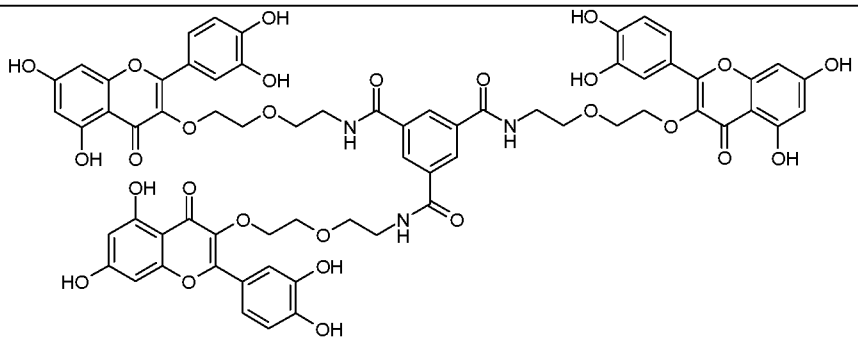
- Hydrogen;
- C_{1-24} alkyl or heteroalkyl, C_{1-24} alkenyl or heteroalkenyl; C_{1-24} alkynyl or heteroalkynyl
- An acyl residue of a saturated/unsaturated/polyunsaturated fatty acid, of either synthetic or natural origin
- A residue that may be preferably, but not exclusively selected from those shown in the table below:

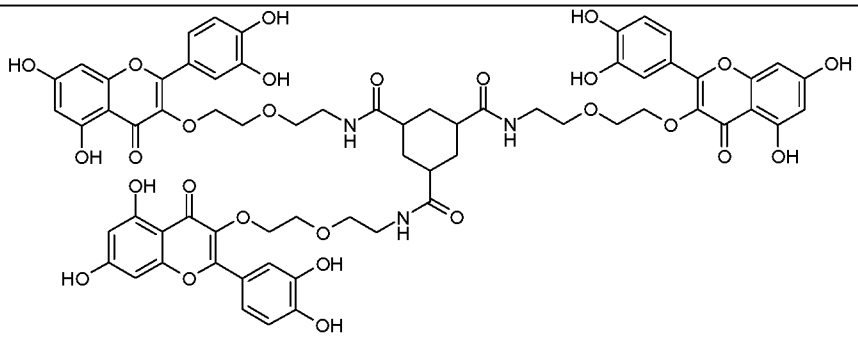
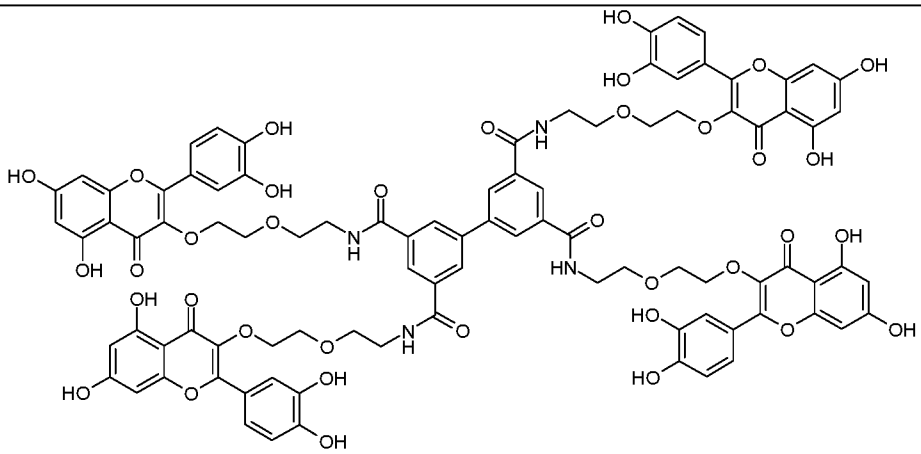
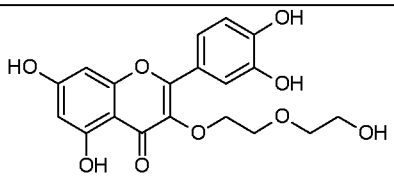
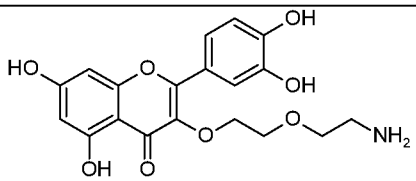
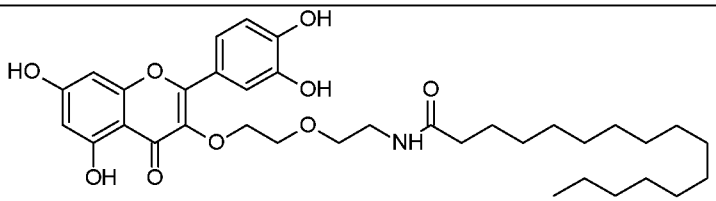
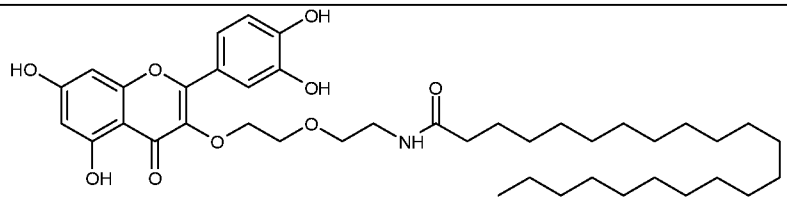
L91	
L92	
L93	

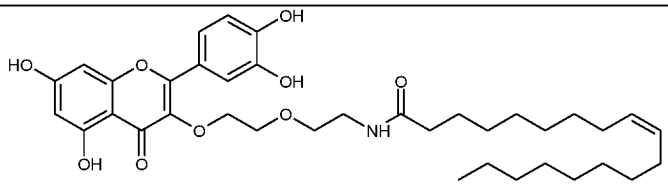
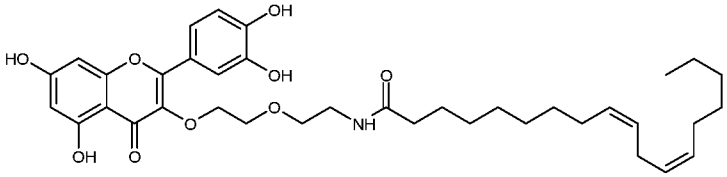
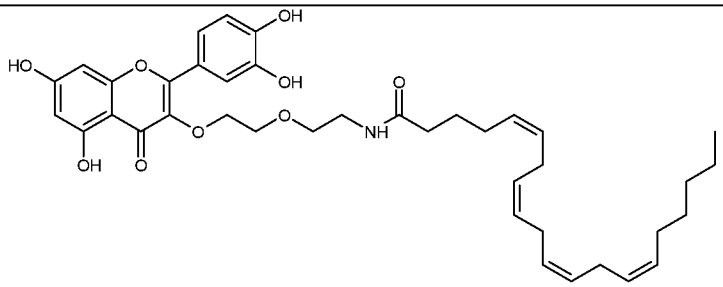
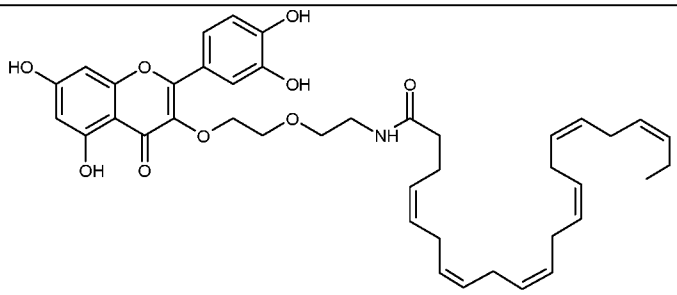
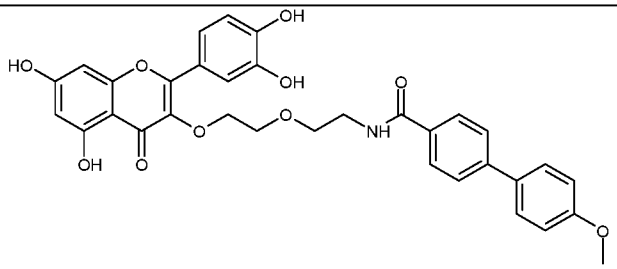
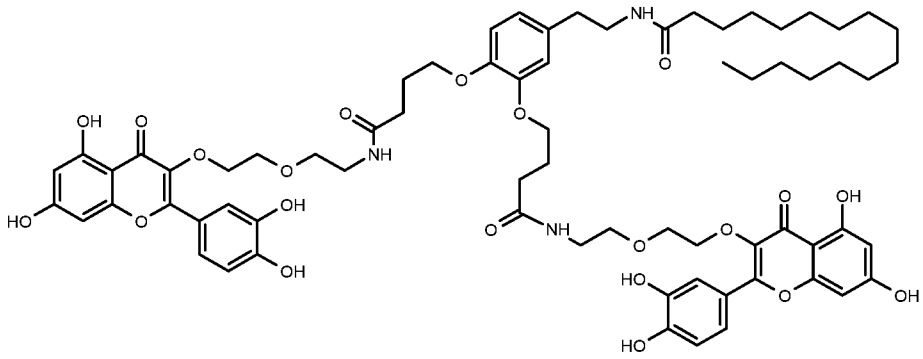
Below are some examples of the compounds according to the invention, whose technical effect has been proved.

Compound	Structure
1	
2	
3	

4	
5	
15a	
15b	
15c	

15d	
19a	
19b	
19c	
19d	
22a	

22b	
25a	
26	
27	
29a	
29b	

29c	
29d	
29e	
29f	
29g	
36	

Said compound can also be made by a method described in patent application WO-A-99/66062 by the National Research Council and Felice Rao's Rao-Erbe. In this patent it is described from page 3 line 8 to page 9 line 22, which are incorporated herein by reference. However, other similar methods may be used.

The invention therefore also defines a new method for treating the aforementioned tumours with the aforementioned compound and a new method for manufacturing drugs for treating the aforementioned tumours.

The compound according to the invention, and in particular the synthetic quercetin derivatives described and illustrated herein were investigated in vitro by using human tumour cells and assessing their impact on the tumour proliferative capacity, with regard to the tumours described above. In particular, the following human tumour cell lines were assessed experimentally: 1) HCT116, colon adenocarcinoma cells; 2) H1299, lung adenocarcinoma cells; 3) A375, melanoma cells, and 4) A431, squamous skin cell carcinoma; 5) 786-O, renal carcinoma cells; 6) PC3, prostate carcinoma cells; 7) BT549, mammary carcinoma cells; 8) CAL27, tongue carcinoma cells (belonging to the head-and-neck carcinomas); 9) HepG2, hepatocellular carcinoma cells; 10) PANC-1, pancreas carcinoma cells; 11) T24, bladder carcinoma cells; 12) OVCAR-3, ovarian carcinoma cells. In addition, a normal human cell line, WS1 (skin fibroblasts) was also treated with the novel synthetic compounds.

Cell proliferation was quantified by the crystal violet method with a spectrophotometer. In short, after acquiring serial images (0, 24 and 48 hrs) with the EVOS XL Cell Imaging System microscope (Thermo Fisher Scientific), the cells imaged at 48 hrs were fixed with paraformaldehyde (4%) and stained with Crystal Violet (1%). Then, the specific absorbance (λ=590 nm) at 48 hrs was measured with

a spectrophotometer (Infinite® 200 PRO, Tecan). Data analysis was carried out by using ad-hoc Excel files for graphical representation and statistical processing (t-test). Moreover, the results obtained with Crystal Violet were confirmed by using another cell proliferation assessment method based on the real time cellular analyzer XCELLigence RTCA DP (ACEA Biosciences, Inc.). This tool allows cell growth to be monitored from electrical impedance-derived quantitative values (the so-called Cell Index) measured by tiny electrodes located at the base of the culture wells. Proliferation is monitored for several days (5-7) by setting a Cell Index per minute measure on the instrument. The data are analysed by processing various parameters calculated by the dedicated software, such as the cell duplication time, the slope and the Max Cell Index.

The results show that, compared to the controls (treated with the solvent-vehicle alone), the compounds according to the invention, and in particular the various compounds described and illustrated herein significantly inhibit the proliferation of the colon (HCT116) and lung (H1299) adenocarcinoma cells, the melanoma cells (A375), and the skin squamous carcinoma (A431), renal carcinoma (786-O), prostate carcinoma (PC3), mammary carcinoma (BT549), tongue carcinoma (CAL27), hepatocellular carcinoma (HepG2), pancreas carcinoma (PANC-1), bladder carcinoma (T24) and ovarian carcinoma (OVCAR-3) cells.

Tumour cell apoptosis was quantified by the acridine orange/ethidium bromide (AO/EB) method and by using a fluorescence microscope and image-J. In short, after treatment with the test compounds (2 hrs), the tumour cells were placed in contact with an AO/EB solution (in sterile H_2O) and photographed with a fluorescence microscope (Leica) by using the ≥20X objective (so as to distinguish the morphology of cell nuclei). In this way, the living cells are labelled with AO and

emit fluorescence in the green channel, while the necrotic cells, which have undergone the rupture of the plasma membrane, are permeable to EB and emit fluorescence in the red channel. In contrast, apoptotic cells are permeable to both AO and EB, and as a consequence of the colocalization of the two fluorescences appear yellow-orange when the two individual microscope-acquired fluorescences are superimposed by using the editing program Image J. The objective quantification of the colocalization areas (apoptotic cells) and the non-colocalization areas (living or necrotic cells) was carried out on a number of cells ≥300/condition through the use of Apoptosis Correlator (ImageJ plug-in) and shown as the percentage of living (green), necrotic (red) or apoptotic (yellow-orange) tumour cells. Data analysis was carried out by using GraphPad Prism 6 for graphical representation and statistical processing (2-way ANOVA test).

The compounds according to the invention were compared with the simple quercetin. In these comparisons, the dose-response curves showed that the compounds according to the invention are significantly more powerful and effective in inhibiting proliferation and inducing apoptosis of all tested tumour cells of the type described above.

In addition, compared to the controls (treated with the solvent-vehicle alone), the compounds according to the invention induce cell death and apoptosis of colon adenocarcinoma (HCT116) and melanoma (A375) cells in a very short time (<2 hrs). Highly importantly, the compounds according to the invention, and in particular all the compounds described and illustrated herein were shown to be significantly less effective in inhibiting proliferation and incapable of inducing apoptosis in normal human cells (WS1 skin fibroblasts), compared to tumour cells, indicating the possibility of a clinical selectivity of the toxic action of the compounds object of this

patent, which may only be focused on the tumour while preserving the healthy cells of the patient.

Progression through the tumour cell cycle was assessed by the propidium iodide method and quantification of the cell DNA content with a cytofluorimeter. Briefly, after treatment (in duplicate) with the test compounds (24 hrs), the tumour cells were washed (with PBS), detached with trypsin-EDTA and pelleted by centrifugation (125 g for 6 min). The cells were then fixed in ethanol (70%) and stored in the freezer (-20°C) for 1-3 days. After further washing (PBS) and treatment with RNAse (50 ug/ml), the cells were contacted (on ice in the dark; 30 min) with propidium iodide (50 µg/ml). FL2 and FL3 cytofluorimeter readings analysed approximately 50,000 cells (1 µl/second) per sample. Statistical analysis and graphical representation were performed by using t-tests and preset Excel property files.

Intracellular ROS levels were measured in tumour cells by using the probe 2,7-dichlorodihydrofluorescein diacetate (DCFH2-DA) and a fluorescence spectrophotometer. DCFH2-DA diffuses readily through the cell membrane into the cytosolic space of the cell where it is hydrolyzed by intracellular esterases into the non-permeable DCFH2 product. DCFH2 oxidation by intracellular ROS (mainly H2O2, HO•, ROO•, NO• and ONOO) results in the production of intracellular fluorescent DCF, whose concentration is directly proportional to the levels of ROS in the cell. Once the treatment with the test compounds was ended (1 hr), the tumour cells were washed (with PBS), the probe DCFH2-DA (10 µM) was added over 30 min, and after further washing in PBS, intracellular DCF fluorescence was quantified with a spectrophotometer (Synergy; emission at 498 nm and emission at 530 nm). All the experiments were repeated at least 3 times. Data analysis was carried out with GraphPad Prism 6 for graphical representation and statistical processing (1-

way ANOVA test).

The results demonstrate that the compounds according to the invention halt the replicative tumour cell cycle. In fact, compared to the control treated with the solvent-vehicle, the tumour cells (in particular the colon carcinoma and melanoma cells) treated with the compounds according to the invention accumulate significantly in the S and G2 phases of the cell cycle. This effect on the cell cycle is partly mediated by ROS, as also confirmed by the fact that the compounds according to the invention promote a fast (≤1 h) increase in the intracellular ROS levels in malignant tumour cells. Therefore, the synthetic flavone derivatives object of this invention selectively inhibit the growth and proliferation of malignant epithelial tumours at least through: promoting the cell death and apoptosis processes, halting the cell cycle and producing intracellular ROS.

In detail, the medical compounds according to the invention were shown to exhibit greater anti-proliferative effects than the parent chemical scaffold in melanoma. The proliferation of human melanoma cells (A375) was quantitated by using the crystal violet method and a spectrophotometer, as illustrated in Fig. 1a. Quercetin (Que) and synthetic derivatives thereof (Compound 2, Compound 4, and Compound 5) were compared (Fig. 1a; 60, 60 μM). Compounds 2, 4, and 5 significantly inhibit the growth of melanoma cells, with a higher efficiency than that of quercetin (Fig. 1b). Ctr, control (treated with the vehicle). *, $p<0.05$ **, $p<0.01$ and ***, $p<0.001$ compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in skin squamous carcinoma (SCC). The proliferation of SCC cells (A431) was quantitated by using the crystal violet method and a spectrophotometer. Quercetin (Que) and synthetic derivatives thereof (Compound 2, Compound 4, and

Compound 5) were compared (Fig. 2a; 90, 90 μM). While quercetin has no effect, compounds 2, 4, and 5 significantly inhibit A431 cell growth (Fig. 2b). Ctr, control (treated with the vehicle). **, $p<0.01$ compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in colorectal carcinoma. The proliferation of human colon carcinoma cells (HCT116) was quantitated by using the crystal violet method and a spectrophotometer. Quercetin (Que) and synthetic derivatives thereof (Compound 2, Compound 3, Compound 4, and Compound 5) were compared (Fig. 3a; 100, 100 μM). Compounds 2, 3, 4, and 5 significantly inhibit HCT116 cell growth (Fig. 3b). Ctr, control (treated with the vehicle). *, $p<0.05$ **, $p<0.01$ compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in renal carcinoma. The proliferation of human renal carcinoma cells (786-O) was quantitated by using the crystal violet method and a spectrophotometer. Quercetin (Que) and synthetic derivatives thereof (Compound 1, Compound 2, Compound 3, Compound 4, and Compound 5) were compared (Fig. 4a; 80, 80 μM). While quercetin has no effect, compounds 1, 2, 3, 4, and 5 significantly inhibit 786-O cell growth (Fig. 4b). Ctr, control (treated with the vehicle). *, $p<0.05$ **, $p<0.01$ and ***, $p<0.001$ compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in prostate carcinoma. The proliferation of human prostate carcinoma cells (PC3) was quantitated spectrophotometrically by using the crystal violet method. Quercetin (Que) and synthetic derivatives thereof (Compound 1, Compound 2, Compound 3, Compound 4, and Compound 5) were compared (Fig. 5a; 80, 80 μM). While quercetin exhibits modest anti-proliferative effects,

compounds 1, 3, 4, and 5 are superior and significantly inhibit PC3 cell growth (Fig. 5b). Ctr, control (treated with the vehicle). *, $p<0.05$ and **, $p<0.01$ compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in mammary carcinoma. The proliferation of human mammary carcinoma cells (BT549) was quantitated spectrophotometrically by using the crystal violet method. Quercetin (Que) and synthetic derivatives thereof (Compound 1, Compound 2, Compound 3, Compound 4, and Compound 5) were compared (Fig. 6a; 80, 80 μM). Compounds 1, 2, 3, 4, and 5 significantly inhibit BT549 cell growth (Fig. 6b). Ctr, control (treated with the vehicle). *, $p<0.05$ and **, $p<0.01$ compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in tongue carcinoma (belonging to the head-and-neck carcinomas, HNC). The proliferation of human tongue carcinoma cells (Cal27) was quantitated spectrophotometrically by using the crystal violet method. Quercetin (Que) and synthetic derivatives thereof (Compound 1, Compound 2, Compound 3, Compound 4, and Compound 5) were compared (Fig. 7a; 80, 80 μM). All synthetic compounds significantly inhibit tumour growth, with Compound 5 showing an anti-proliferative effect superior to that of quercetin (Fig. 7b). Ctr, control (treated with the vehicle). *, $p<0.05$ **, $p<0.01$ and ***, $p<0.001$ compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in liver carcinoma. The proliferation of human hepatocellular carcinoma cells (HepG2) was quantitated spectrophotometrically by using the crystal violet method. Quercetin (Que) and synthetic derivatives thereof (Compound

1, Compound 2, Compound 3, Compound 4, and Compound 5) were compared (Fig. 8a; 80, 80 μM). All synthetic compounds significantly inhibit tumour growth, with compounds 3, 4, and 5 showing an anti-proliferative effect superior to that of quercetin (Fig. 8b). HepG2. Ctr, control (treated with the vehicle). *, $p<0.05$ **, $p<0.01$, compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in pancreatic carcinoma. The proliferation of human pancreatic carcinoma cells (PANC-1) was quantitated spectrophotometrically by using the crystal violet method. Quercetin (Que) and synthetic derivatives thereof (Compound 1, Compound 2, Compound 3, Compound 4, and Compound 5) were compared (Fig. 9a; 80, 80 μM). While quercetin has no effect, compounds 2, 3, 4, and 5 significantly inhibit PANC-1 cell growth (Fig. 9b). Ctr, control (treated with the vehicle). *, $p<0.05$ **, $p<0.01$, compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in bladder carcinoma. The proliferation of human bladder carcinoma cells (T24) was quantitated spectrophotometrically by using the crystal violet method. Quercetin (Que) and synthetic derivatives thereof (Compound 1, Compound 2, Compound 3, Compound 4, and Compound 5) were compared (Fig. 10a; 80, 80 μM). While quercetin has no effect, compounds 2, 3, 4, and 5 significantly inhibit T24 cell growth (Fig. 10b). Ctr, control (treated with the vehicle). *, $p<0.05$ **, $p<0.01$ and ***, $p<0.001$ compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit greater anti-proliferative effects than the parent chemical scaffold in ovarian carcinoma. The proliferation of human ovarian carcinoma cells (OVCAR-3) was quantitated spectrophotometrically by using the crystal violet method. Quercetin (Que) and synthetic derivatives thereof (Compound

5, Compound 19c, Compound 19d, Compound 29e, and Compound 29f) were compared (Fig. 11a; 60, 60 μM). While quercetin has no effect, compounds 5, 19c, 19d, 29e, and 29f significantly inhibit OVCAR-3 cell growth (Fig. 11b). Ctr, control (treated with the vehicle). *, $p<0.05$ **; $p<0.01$, and ***, $p<0.001$ compared to the control, by Student's t-test.

Synthetic flavone derivative Compound 26 exhibits greater anti-proliferative effects than the parent chemical scaffold in melanoma. The proliferation of human melanoma cells (A375) was quantitated spectrophotometrically by using the crystal violet method. Compound 26 significantly inhibits A375 cell proliferation with greater effectiveness compared to quercetin. Ctr, control (treated with the vehicle). *, $p<0.05$ and **, $p<0.01$ compared to the control, by Student's t-test (Fig. 12).

Synthetic flavone derivatives Compound 26 and Compound 27 exhibit greater anti-proliferative effects than the parent chemical scaffold in colorectal carcinoma. The proliferation of human colon carcinoma cells (HCT116) was quantitated by using the crystal violet method and a spectrophotometer. Quercetin (Que) and synthetic derivatives thereof (Compound 26 and Compound 27) were compared (Fig. 13a; 100, 100 μM). Compound 26 significantly inhibits HCT116 cell growth with greater effectiveness compared to quercetin (Fig. 13b). Ctr, control (treated with the vehicle). *, $p<0.05$ and **, $p<0.01$ compared to the control, by Student's t-test.

Synthetic flavone derivatives exhibit significant anti-proliferative effects in melanoma. The proliferation of human melanoma cells (A375) was quantitated spectrophotometrically by using the crystal violet method. The synthetic compounds used at 10 μM and 30 μM concentrations significantly inhibited A375 cell growth with high potency. Ctr, control (treated with the vehicle). 15a, Compound 15a; 15b, Compound 15b; 15c, Compound 15c; 15d, Compound 15d; 19b, Compound 19b;

19c, Compound 19c; 19d, Compound 19d; 29a, Compound 29a; 29c, Compound 29c; 29d, Compound 29d; 29e, Compound 29e; 29f, Compound 29f, and 29g, Compound 29g. *, $p<0.05$ **; $p<0.01$, and ***, $p<0.001$ compared to the control, by Student's t-test (Fig. 14).

Synthetic flavone derivatives exhibit significant anti-proliferative effects in colorectal carcinoma. The proliferation of human colon carcinoma cells (HCT116) was quantitated by using the crystal violet method and a spectrophotometer. The synthetic compounds used at 10 μM and 30 μM concentrations significantly inhibited HCT116 cell growth with high potency. Ctr, control (treated with the vehicle). 15a, Compound 15a; 15b, Compound 15b; 15c, Compound 15c; 15d, Compound 15d; 19b, Compound 19b; 19c, Compound 19c; 19d, Compound 19d; 29a, Compound 29a; 29c, Compound 29c; 29d, Compound 29d; 29e, Compound 29e; 29f, Compound 29f, and 29g, Compound 29g. *, $p<0.05$ **; $p<0.01$, and ***, $p<0.001$ compared to the control, by Student's t-test (Fig. 15).

Synthetic trimeric flavone derivatives exhibit anti-proliferative effects in colorectal carcinoma and melanoma. The proliferation of human colon carcinoma (HCT116) and melanoma (A375) cells was quantitated spectrophotometrically by using the crystal violet method. Synthetic trimeric compounds (Compound 22a and Compound 36), used at 30 μM and 100 μM concentrations, inhibit HCT116 and A375 cell growth. Ctr, control (treated with the vehicle). 22a, Compound 22a; 36, Compound 36. *, $p<0.05$ compared to the control, by Student's t-test (Fig. 16).

Synthetic flavone derivatives do not disrupt normal human cell proliferation. The proliferation of human skin fibroblasts (WS1) was studied with crystal violet and a spectrophotometer. Quercetin (Que), a synthetic derivative thereof (Compound 2), and apigenin (API) were examined at the indicated concentrations. While apigenin

significantly inhibits the proliferation of normal human skin cells, quercetin and Compound 2 do not disrupt their growth. Ctr, control (treated with the vehicle). *, $p<0.05$ and ***, $p<0.005$ compared to the control, by Student's t-test (Fig. 17).

Synthetic flavone derivatives selectively induce apoptosis in tumour cells. The percentage of cells that have launched the cell death program (apoptosis) was quantified by the acridine orange/ethidium bromide method and using a fluorescence microscope and Image-J. All synthetic quercetin derivatives (Compound 2, Compound 5, Compound 4, Compound 3, and Compound 1) induced apoptosis (at 2 hrs) in human colon (HCT116) and skin (melanoma, A375) tumour lines, but not in normal cells (human skin fibroblasts, WS1). The substances were used at the following concentrations (with regard to the respective anti-proliferative IC50s): Compound 2, 50 µM (HCT116) or 40 µM (A375; WS1); Compound 5, 40 µM; Compound 4, 40 µM; Compound 3, 60 µM; Compound 1, 60 µM (HCT116) or 80 µM (A375; WS1). Ctr, control (treated with the vehicle). *, $p<0.05$; **, $p<0.01$; ***, $p<0.005$ and ****, $p<0.001$ compared to the control, by the 2-way ANOVA test (Fig. 18).

Synthetic flavone derivatives halt the cell cycle in melanoma. Progression of human melanoma cells (A375) through the cell cycle was quantified by using the propidium iodide (PI) method and a cytofluorimeter. Quercetin (Que) and synthetic derivatives thereof (Compound 1, Compound 2, Compound 3, Compound 4, and Compound 5) were used at the respective anti-proliferative IC50s. With the exception of Compound 3, all compounds investigated significantly halt the tumour cells in S and/or G2. Ctr, control (treated with the vehicle). H_2O_2, hydrogen peroxide (positive control; 200 µM). *, $p<0.05$ **; $p<0.01$, and ***, $p<0.001$ compared to the control, by Student's t-test (Fig. 19).

Synthetic flavone derivatives halt the cell cycle in colorectal carcinoma. Progression of human colon carcinoma cells (HCT116) through the cell cycle was quantified by using the propidium iodide (PI) method and a cytofluorimeter. Quercetin (Que) and synthetic derivatives thereof (Compound 1, Compound 2, Compound 3, Compound 4, and Compound 5) were used at the respective anti-proliferative IC50s. Compounds 1, 3, and 4 significantly halt the tumour cells in S. Ctr, control (treated with the vehicle). H_2O_2, hydrogen peroxide (positive control; 200 μM). *, $p<0.05$; **, $p<0.01$ and ***, $p<0.001$ compared to the control, by Student's t-test (Fig. 20).

The effects of Compound 1 on the tumour cell cycle are partly mediated by ROS. The cell cycle of human colon carcinoma (HCT116) and melanoma (A375) cells was examined by using the propidium iodide method and a cytofluorimeter. A reactive oxygen species (ROS) scavenger, i.e. N-Acetyl Cysteine (NAC; 10 mM), prevents - at least in part - the effect on the cell cycle induced by Compound 1 (used at its anti-proliferative IC50) in HCT116 (left) and A375 (right) cells. Ctr, control (treated with the vehicle). *, $p<0.05$; **, $p<0.01$ and ***, $p<0.001$ compared to the respective control (Compound 1 for Compound 1+NAC), by Student's t-test (Fig. 21).

Synthetic flavone derivatives cause an increase in intracellular ROS levels in colorectal carcinoma. Intracellular levels of reactive oxygen species (ROS) after 2 hrs of treatment of the human colon carcinoma cells (HCT116) were quantified by using the fluorescent DCFH2-DA probe. Fluorescence data were measured with a spectrophotometer and expressed in Arbitrary Units (A.U.). Quercetin (QUE) and synthetic derivatives thereof (Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, and Compound 19b) were used at the respective anti-proliferative IC50s. While quercetin has no effect, Compound 1, Compound 2, Compound 3, and Compound 19b significantly raise ROS levels in HCT116 cells (left panel). The effect

of Compound 1 is blocked by pretreatment with N-Acetyl-L-Cysteine (NAC; 10 mM), a ROS scavenger (right panel). H_2O_2, hydrogen peroxide (positive control; 500 µM). CTR, control (treated with the vehicle). *, $p<0.05$; **, $p<0.01$ and ***, $p<0.001$ compared to the control, by the 1-way ANOVA test (Fig. 22).

The following table, divided into two parts, shows the inhibitory concentrations representing 50% of the maximum anti-proliferative effect (IC_{50}), expressed in µM, corresponding to individual compounds according to the invention (no. indicated in the first column on the left) for each human malignant tumour cell line tested (top row, from column 2 onwards). Cell proliferation was quantitated spectrophotometrically by the crystal violet method.

Compound	CRC (HCT116)	Melanoma (A375)	LC (H1299)	SCC (A431)	PCC (PANC-1)	BC (T24)
1	165.90	67.07	100.40	N.D.	>1000	>1000
2	42.82	19.26	50.68	40.32	95.37	66.79
3	59.78	48.15	34.89	N.D.	155.5	44.91
4	22.89	20.10	15.89	30.99	69.58	45.49
5	28.83	16.38	50.45	25.50	69.39	50.45
15a	13.27	23.00	N.D.	N.D.	N.D.	N.D.
15b	18.63	24.55	N.D.	N.D.	N.D.	N.D.
15c	15.78	15.47	N.D.	N.D.	N.D.	N.D.
15d	12.08	7.16	N.D.	N.D.	N.D.	N.D.
19a	>1000	N.D.	N.D.	N.D.	N.D.	N.D.

19b	5.51	9.48	N.D.	N.D.	N.D.	N.D.
19c	1.28	3.95	N.D.	N.D.	N.D.	N.D.
19d	0.74	1.62	N.D.	N.D.	N.D.	N.D.
Compound	**CRC (HCT116)**	**Melanoma (A375)**	**LC (H1299)**	**SCC (A431)**	**PCC (PANC-1)**	**BC (T24)**
22a	49.87	136.10	N.D.	N.D.	N.D.	N.D.
22b	407.31	>1000	N.D.	N.D.	N.D.	N.D.
25a	303.84	>1000	N.D.	N.D.	N.D.	N.D.
26	81.19	52.28	N.D.	N.D.	N.D.	N.D.
27	378	N.D.	N.D.	N.D.	N.D.	N.D.
29a	15.74	5.21	N.D.	N.D.	N.D.	N.D.
29b	>1000	>1000	N.D.	N.D.	N.D.	N.D.
29c	3.64	7.03	N.D.	N.D.	N.D.	N.D.
29d	2.89	7.73	N.D.	N.D.	N.D.	N.D.
29e	4.36	5.89	N.D.	N.D.	N.D.	N.D.
29f	3.08	5.17	N.D.	N.D.	N.D.	N.D.
29g	5.93	7.84	N.D.	N.D.	N.D.	N.D.
36	112.11	89.79	N.D.	N.D.	N.D.	N.D.

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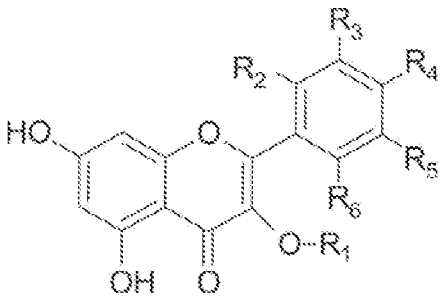
Compound	RCC -(786-O)	PC - (PC3)	BRC - (BT549)	HNC - (Cal27)	HCC - HepG2)	OCC - (OVCAR)
1	148.90	79.34	190.80	15.57	144.00	N.D.
2	72.50	309.10	156.30	63.21	264.9	N.D.
3	65.37	46.16	119.4	36.72	50.21	N.D.
4	41.22	34.91	48.55	22.86	54.44	N.D.
5	32.6	56.86	46.45	19.7	105.7	79.20
15a	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
15b	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
15c	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
15d	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
19a	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
19b	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
19c	N.D.	N.D.	N.D.	N.D.	N.D.	7.44
19d	N.D.	N.D.	N.D.	N.D.	N.D.	5.01
22a	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
22b	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
25a	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
26	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
27	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

29a	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
29b	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Compound	**RCC -(786-O)**	**PC - (PC3)**	**BRC - (BT549)**	**HNC - (Cal27)**	**HCC - HepG2)**	**OCC - (OVCAR)**
29c	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
29d	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
29e	N.D.	N.D.	N.D.	N.D.	N.D.	16.09
29f	N.D.	N.D.	N.D.	N.D.	N.D.	11.84
29g	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
36	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

Legend: CRC, Colon-Rectal Cancer; LC, Lung Cancer; SCC, Squamous Cell Carcinoma; PCC, Pancreatic Cancer Cell; RCC, Renal Cell Carcinoma; PC, Prostate Cancer; BC, Bladder Carcinoma; BRC, Breast Cancer; HNC, Head and Neck Cancer; HCC, Hepatocellular Carcinoma; OCC, Ovarian Cell Carcinoma; N.D., not determined.

CLAIMS

1. A medical compound characterised in that it comprises a synthetic flavone derivative, according to the formula (I) with allotment in position C-3 of a group as shown below:



(I)

wherein at least two of R_2-R_6 are H, and the remaining are independently selected from: H, OH, R_1, OR_1, NO_2, NH_2, NHR_1, F, Cl, Br, I,

where R_1 is a radical.

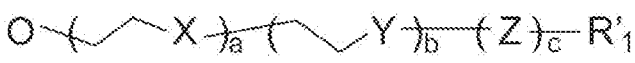
2. The medical compound according to claim 1, wherein R_1 is selected from:

- H;
- $C_{1\text{-}24}$ alkyl or heteroalkyl, $C_{1\text{-}24}$ alkenyl or heteroalkenyl; $C_{1\text{-}24}$ alkynyl or heteroalkynyl
- an acyl residue of a fatty acid.

3. The medical compound according to claim 1, wherein:

- R_4 and R_5 are OH,
- R_2, R_3, R_6, are H.

4. The medical compound according to at least one of the preceding claims, wherein: R_1 is:

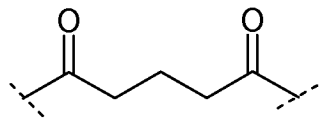
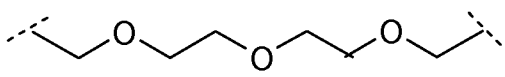
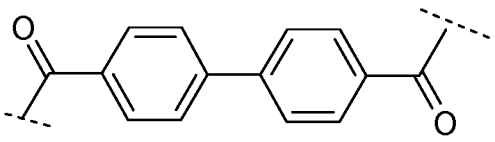
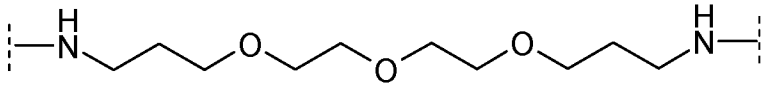
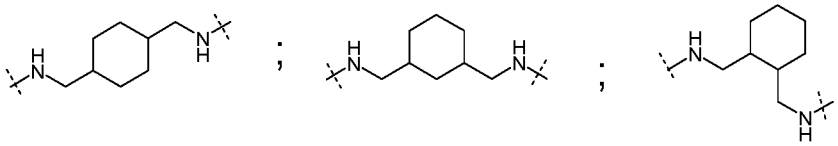
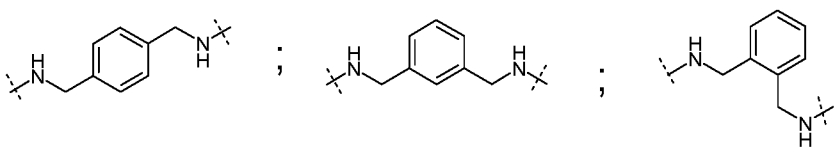


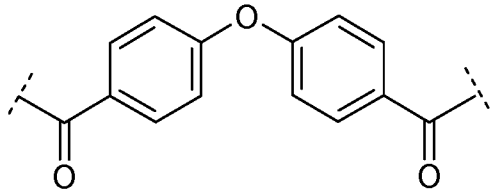
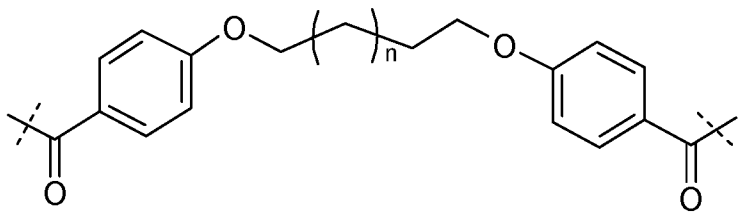
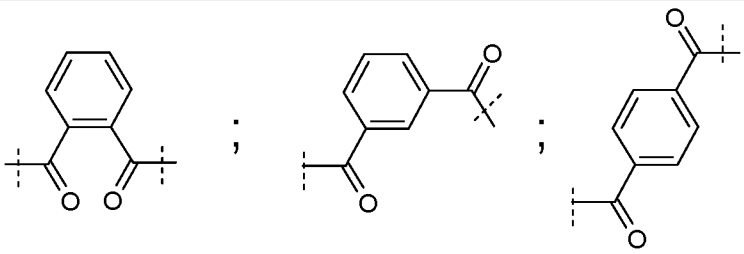
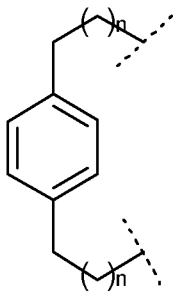
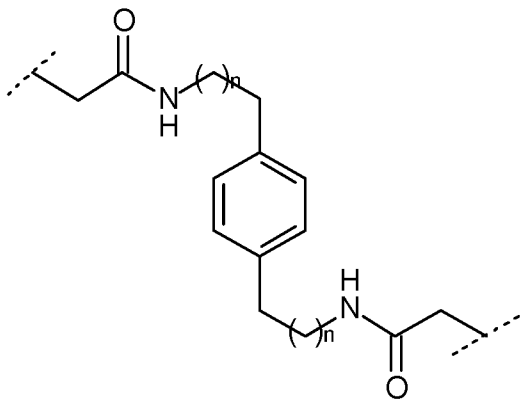
- where R'_1 is selected from:
  - H;

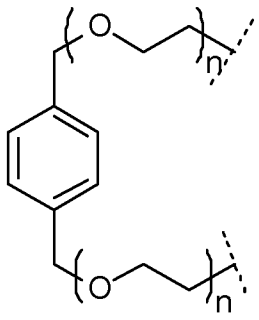
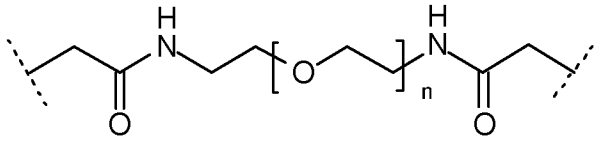
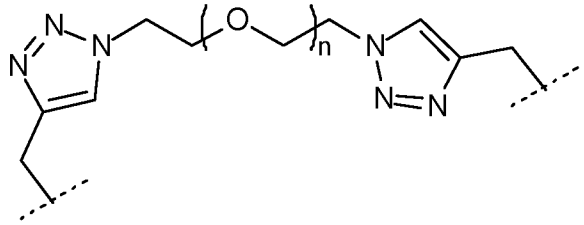
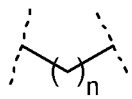
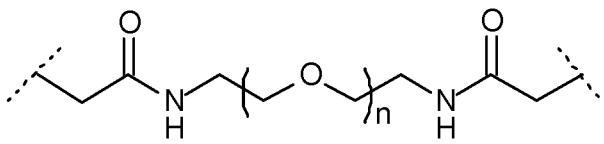
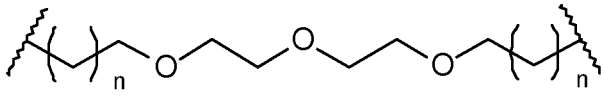
- C_{1-24} alkyl or heteroalkyl, C_{1-24} alkenyl or heteroalkenyl; C_{1-24} alkynyl or heteroalkynyl
- an acyl residue of a fatty acid,
- a linker L,

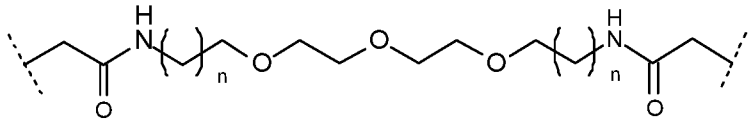
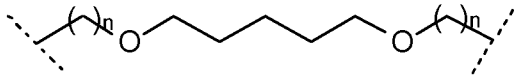
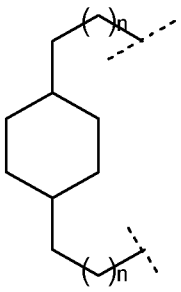
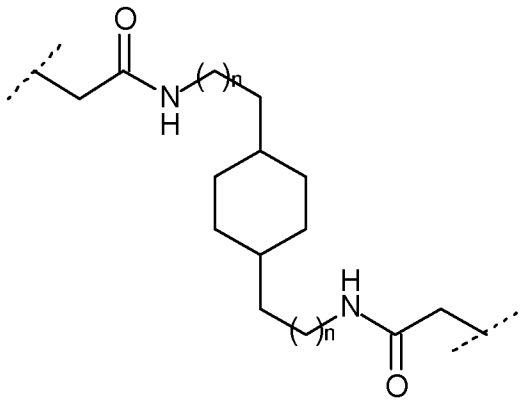
- where a, b, and c each range from 0 to 12,
- where X, Y, and Z are each independently selected from: CH2, O, N(R1), S, NH, SO, SO2, OC(O), CO, NHC(O), C(O)NH, NH-C(O)-NH, NH-C(S)-NH.

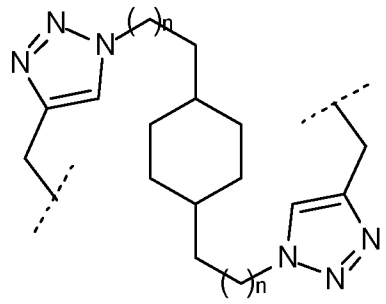
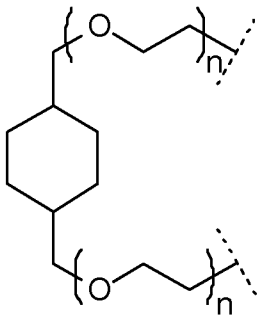
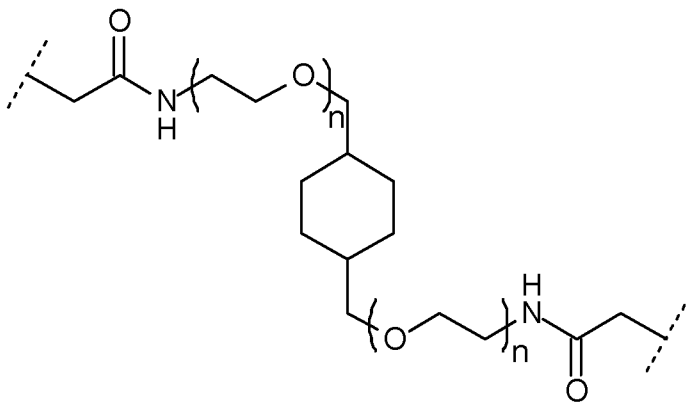
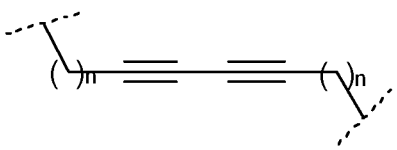
5. The medical compound according to the preceding claim, wherein R'$_1$ is a Linker L and said linker is selected from the following compounds:

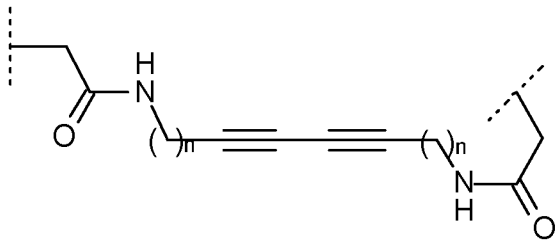
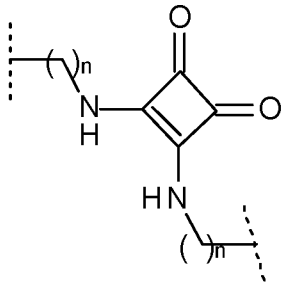
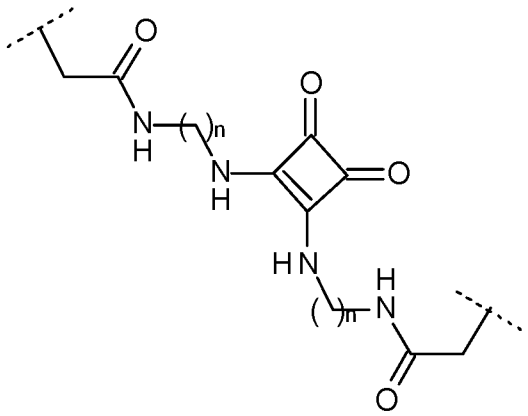
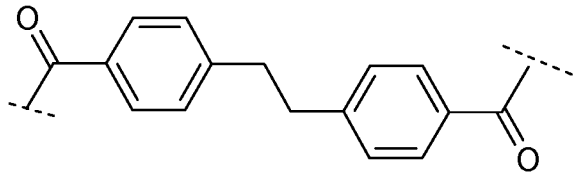
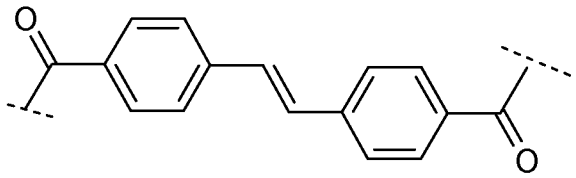
LINKER L	
L1	
L2	
L3	
L4	
L5	
L6	

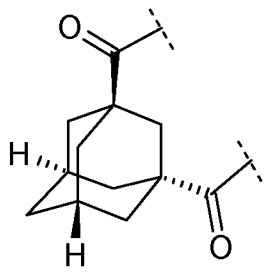
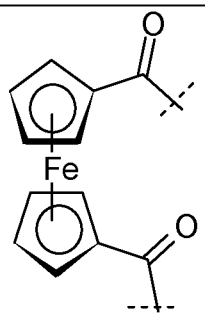
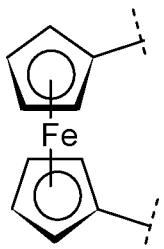
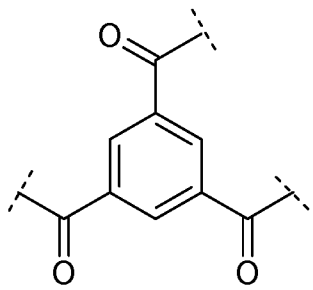
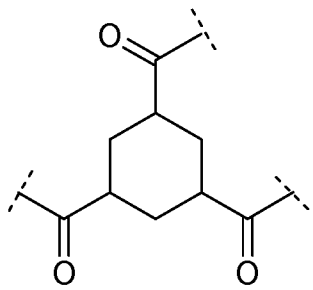
L7	
L8	 n = 0 - 8
L9	
L11	 n = 1-6, each independently
L12	

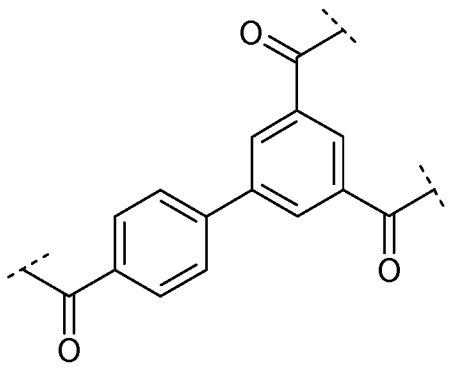
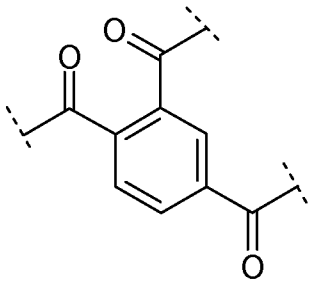
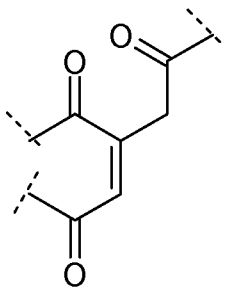
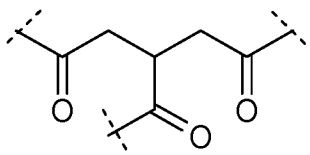
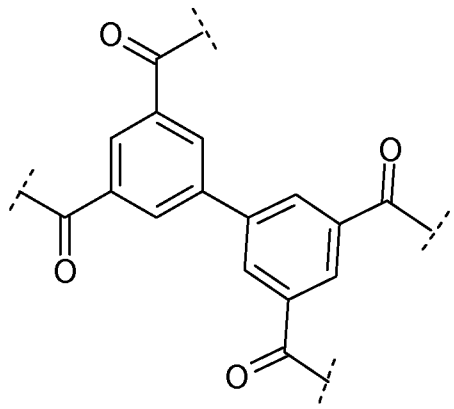
	n = 1-6
L13	 n = 1-3, each independently
L14	 n = 1-4
L15	 n = 1-4, each independently
L16	 n = 2-12
L17	 n = 1-5
L18	

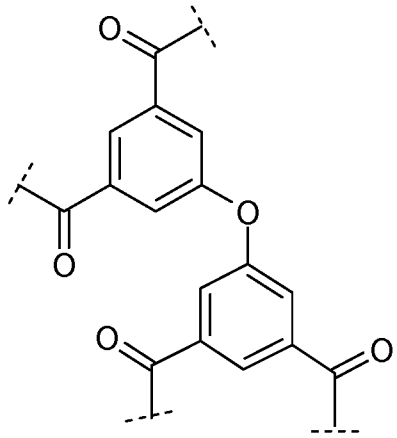
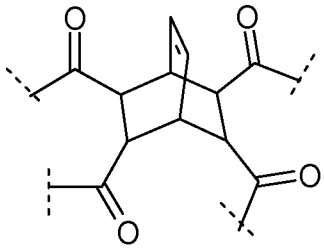
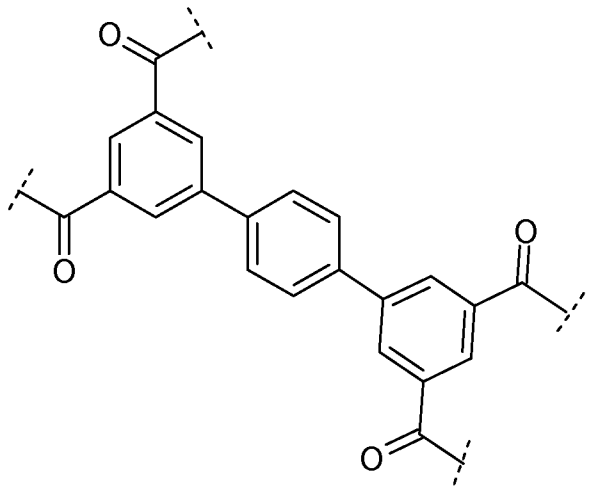
	n = 1-3
L19	 n = 1-3
L20	 n = 1-3
L21	 n = 1-6
L22	 n = 1-6

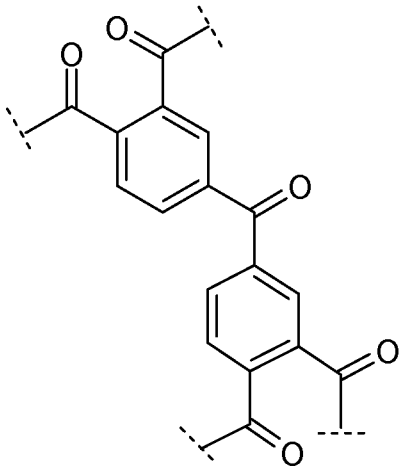
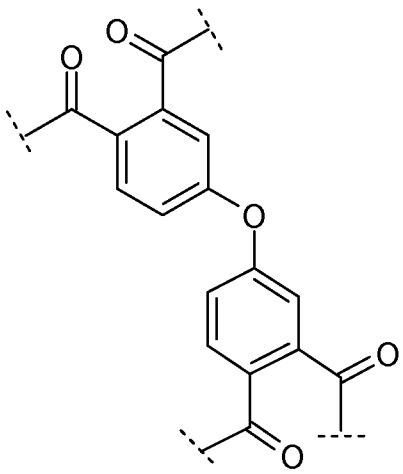
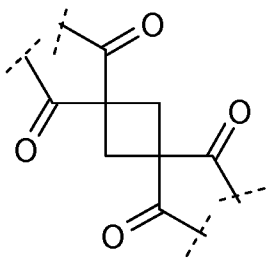
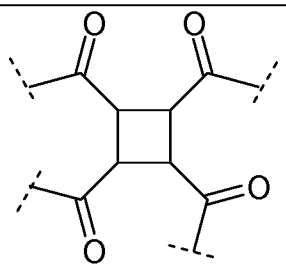
L23	 n = 1-6, each independently
L24	 n = 1-3, each independently
L25	 n = 1-3, each independently
L26	 n = 1-6, each independently

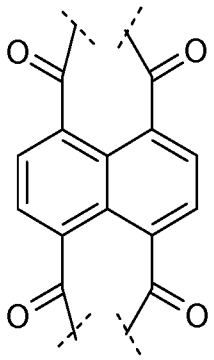
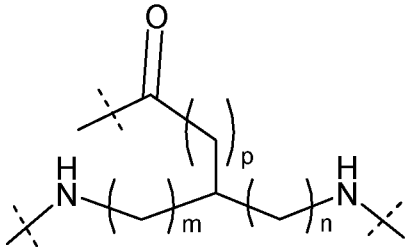
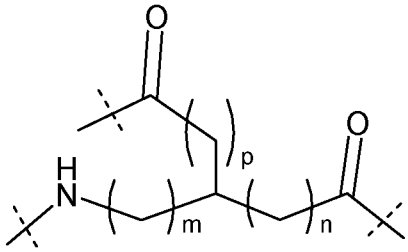
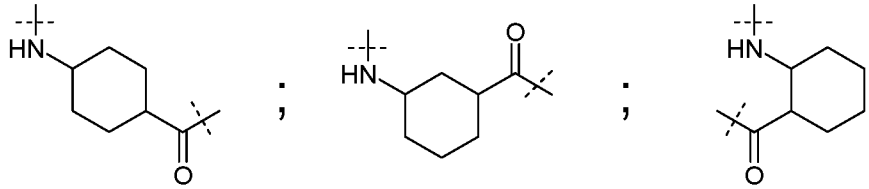
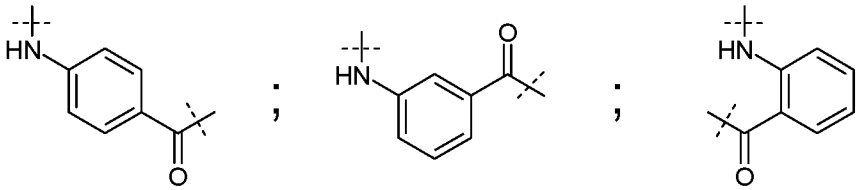
L27	 n = 1-6, each independently
L28	 n = 1-6, each independently
L29	 n = 1-6, each independently
L30	
L31	

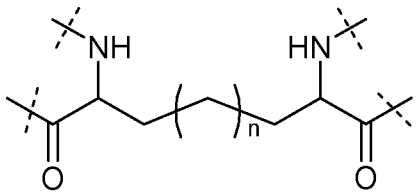
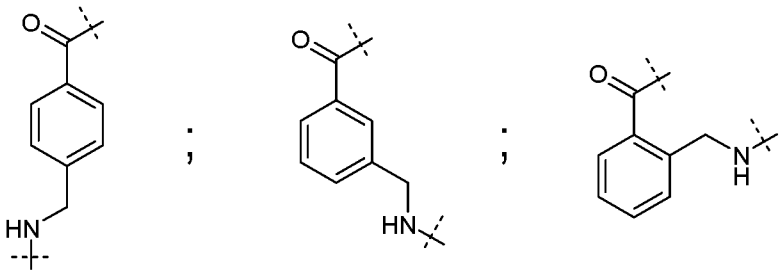
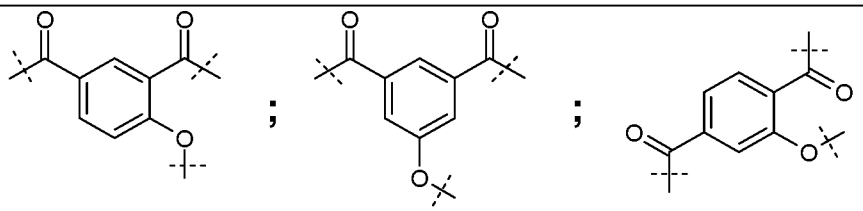
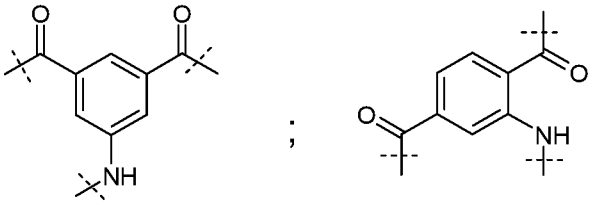
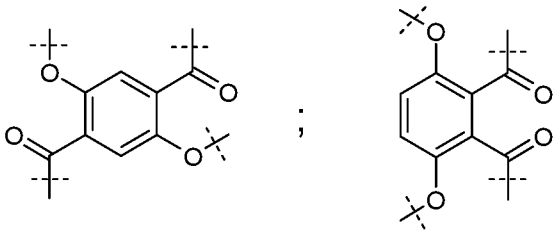
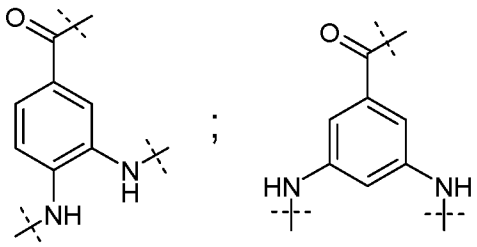
L32	
L33	
L34	
L35	
L36	

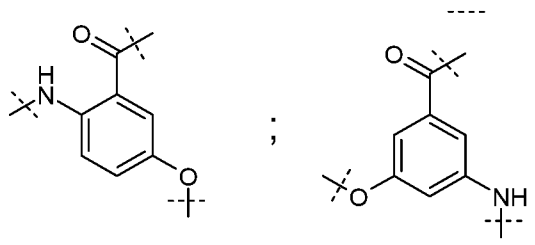
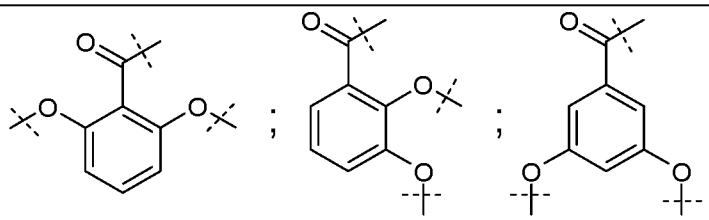
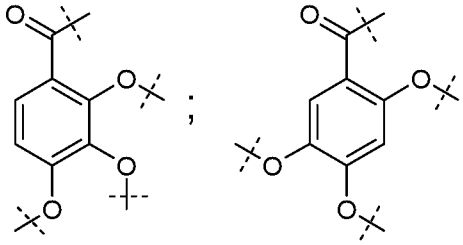
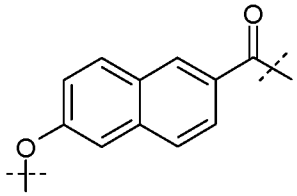
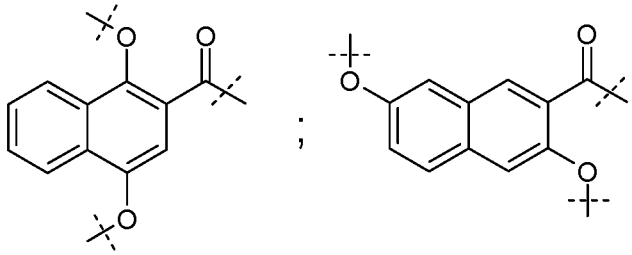
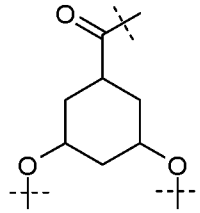
L37	
L38	
L39	
L40	
L41	

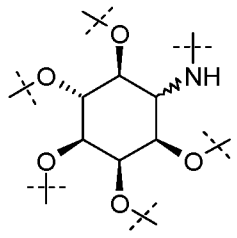
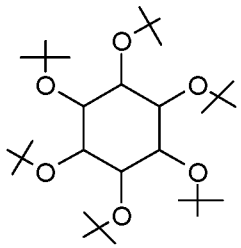
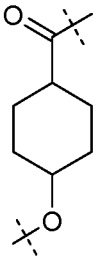
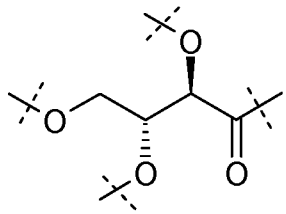
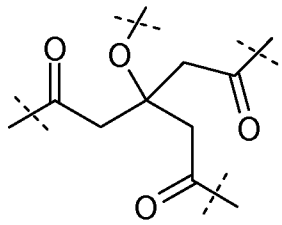
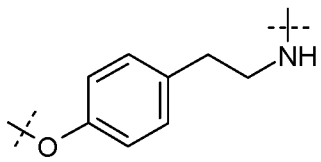
L42	
L43	
L44	

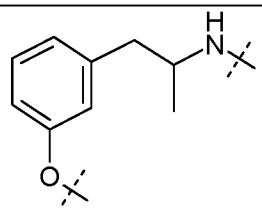
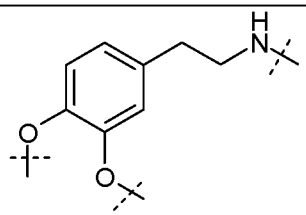
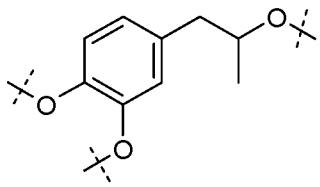
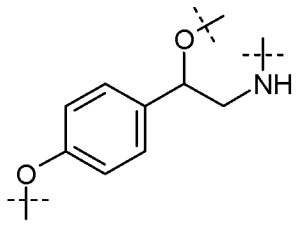
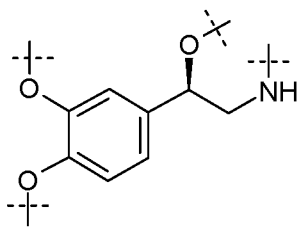
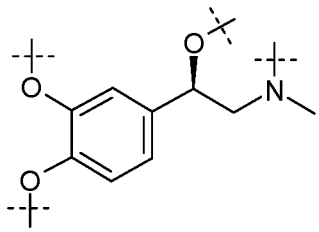
L45	
L46	
L47	
L48	

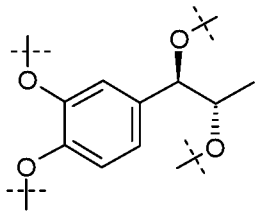
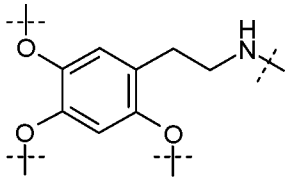
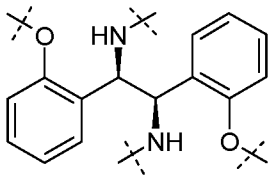
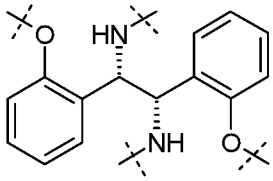
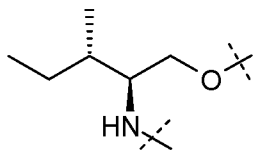
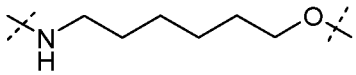
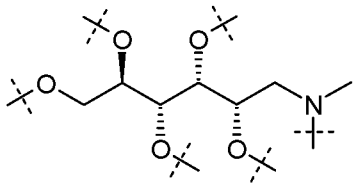
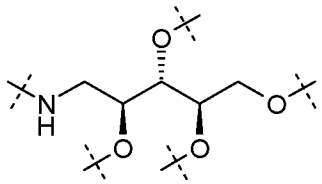
L49	
L50	 n, m, p = 0-6; each independently
L51	 n, m, p = 0-6; each independently
L52	
L53	

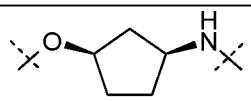
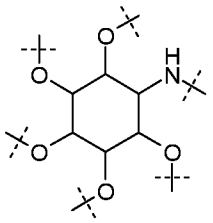
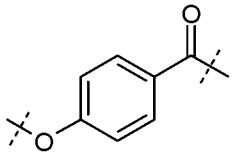
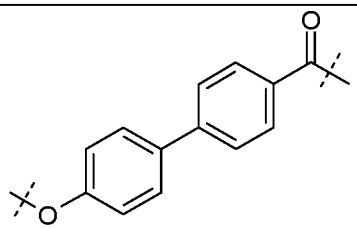
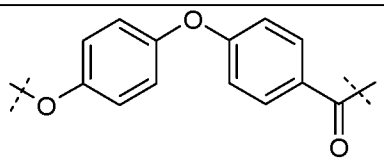
L54	 n = 0, 5
L55	
L56	
L57	
L58	
L59	

L60	
L61	
L62	
L63	
L64	
L65	

L66	
L67	
L68	
L69	
L70	
L71	

L72	
L73	
L74	
L75	
L76	
L77	

L78	
L79	
L80	
L81	
L82	
L83	
L84	
L85	

L86	
L87	
L88	
L89	
L90	

6. The compound according to at least one of the preceding claims, for the treatment of lung carcinoma.

7. The compound according to at least one of claims 1-5, for the treatment of colon carcinoma.

8. The compound according to at least one of claims 1-5, for the treatment of melanoma.

9. The compound according to at least one of claims 1-5, for the treatment of malignant epithelial tumours.

10. The compound according to at least one of claims 1-5, for the

treatment of skin squamous carcinoma.

11. The compound according to at least one of claims 1-5, for the treatment of basal cell carcinoma (basalioma).

12. The compound according to at least one of claims 1-5, used for one or more of the following malignant tumours: head and neck cancer, stomach cancer, liver cancer, pancreatic cancer, breast cancer, prostate cancer, bladder cancer, kidney cancer, mesothelioma, and ovarian cancer.

13. The compound according to at least one of claims 1-5, used for one or more of the following malignant tumours: salivary gland tumours, esophageal cancer, small intestine tumours, gall bladder and extrahepatic biliary tract cancer, soft tissue sarcoma, cervical cancer, uterine cancer, testicular cancer, urinary tract tumours, choroidal melanoma, thyroid cancer, endometrial cancer, retinal tumour, uveal melanoma, anal canal cancer and anal cancer, bone and joint cancer.

14. The compound according to at least one of claims 1-5 for the treatment of a cancer patient, as a monotherapy or in combination with radiotherapy, chemotherapy, hormone therapy, biological therapy, immunotherapy and/or gene therapy.

15. The compound according to at least one of claims 1-5, for anti-inflammatory activity.

16. The compound according to at least one of claims 1-5, for analgesic activity.

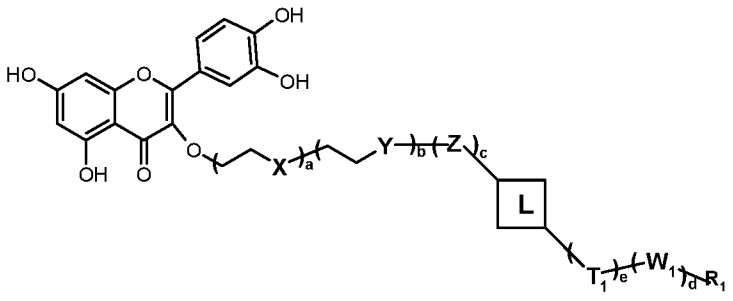
17. The compound according to at least one of claims 1-5, for anti-degenerative and anti-ageing activities.

18. A dimer characterised in that it comprises at least one medical compound according to claim 4 or 5, and wherein R'_1 is a linker L.

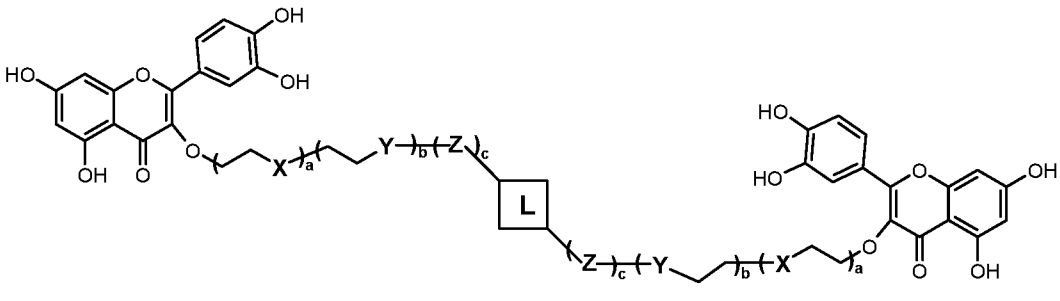
19. A trimer characterised in that it comprises at least one medical compound according to claim 4 or 5, and wherein R'$_1$ is a linker L.

20. A tetramer characterised in that it comprises at least one medical compound according to claim 4 or 5, and wherein R'$_1$ is a linker L.

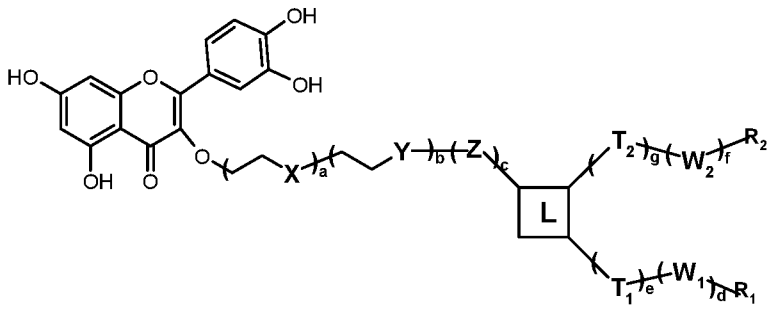
21. The medical compound according to at least one of claims 4-5, wherein the overall structure is selected from the following structures (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI):



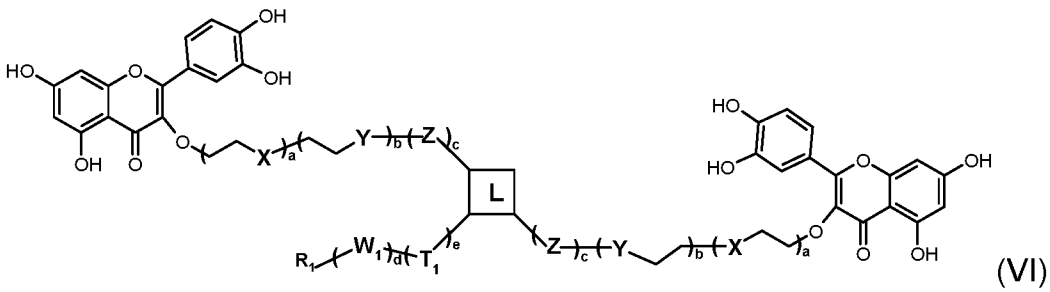
(III)



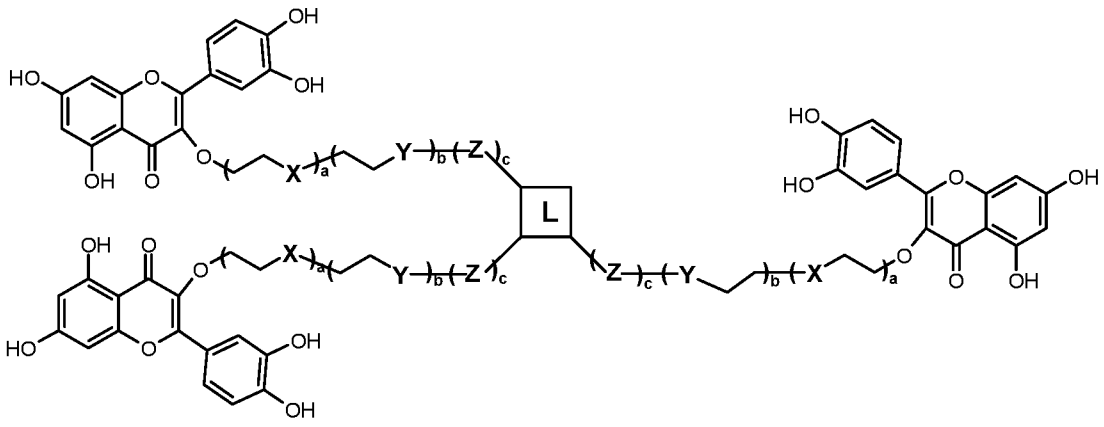
(IV)



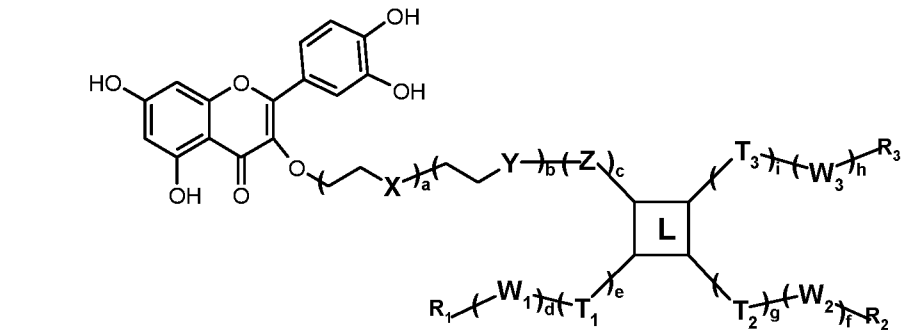
(V)



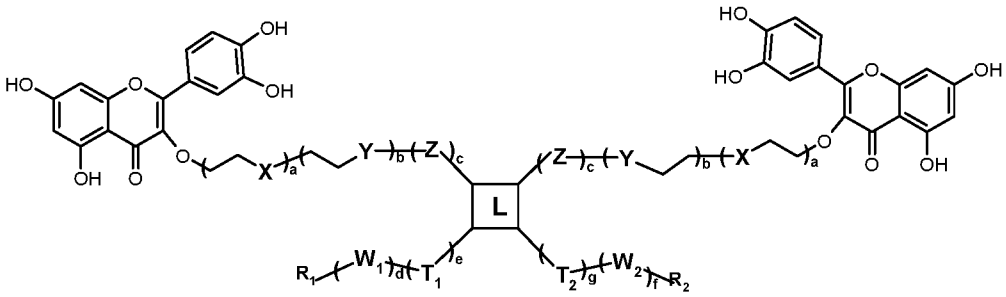
(VI)



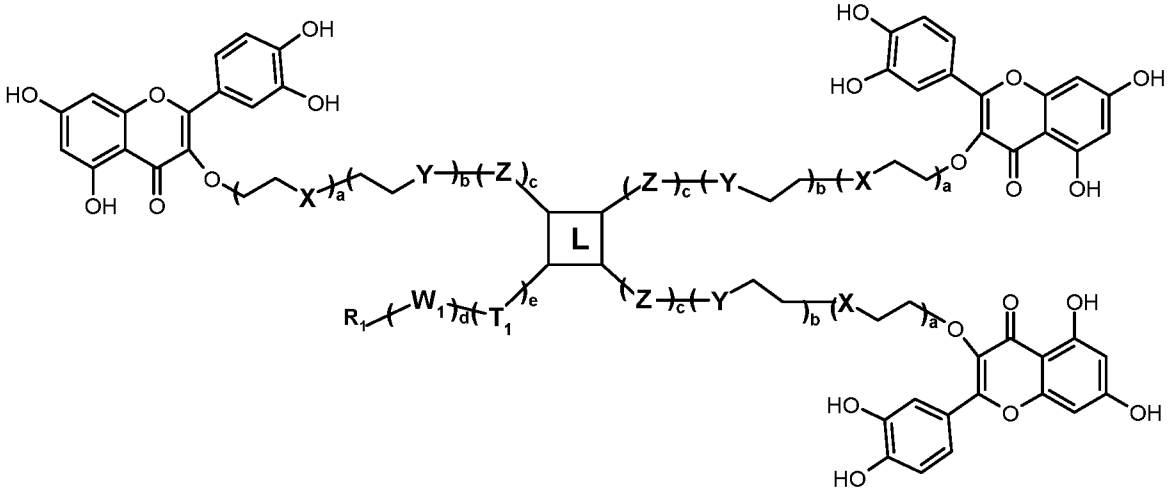
(VII)



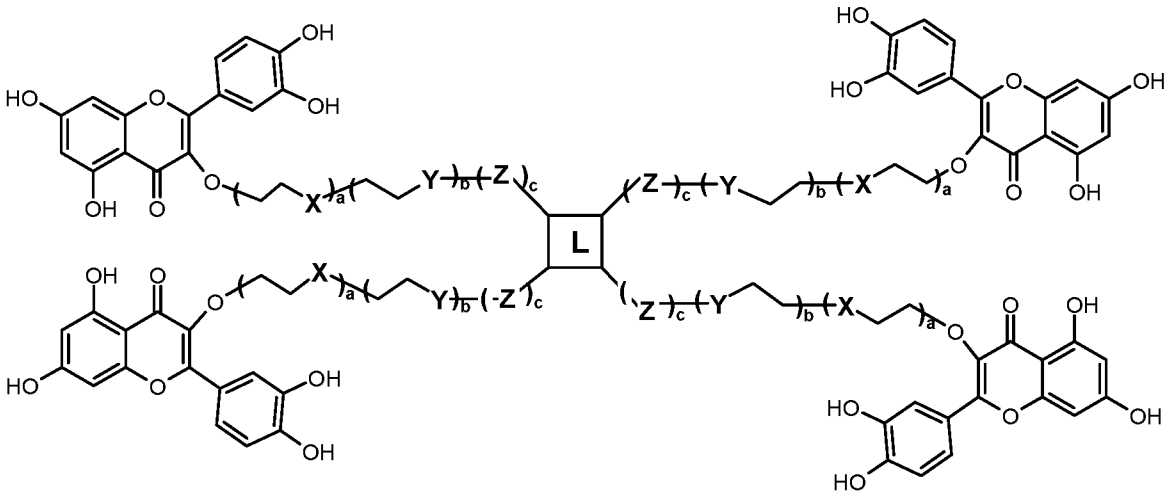
(VIII)



(IX)



(X)

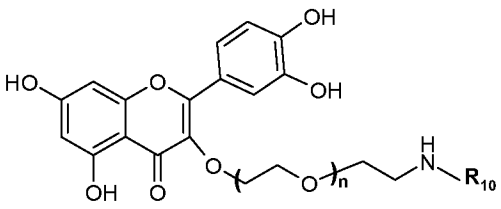


(XI)

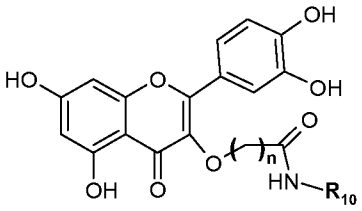
where d, e, f, g, h, i each range from 0 to 12,

where T_1-T_3, W_1-W_3 are each independently selected from: CH2, O, N(R1), S, NH, SO, SO_2, OC(O), CO, NHC(O), C(O)NH, NH-C(O)-NH, NH-C(S)-NH.

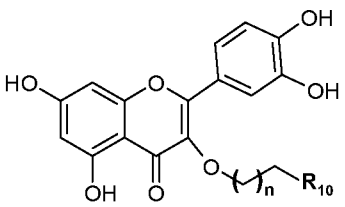
22. The medical compound according to at least one of claims 1-5, wherein the overall structure is selected from the following structures (XII), (XIII), (XIV) and (XV):



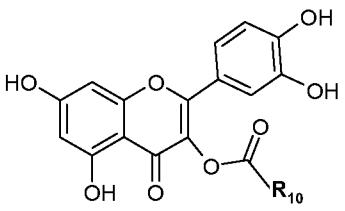
(XII)



(XIII)



(XIV)



(XV)

where n can independently take a value between 0 and 12.

R_{10}, could be independently, but not exclusively and in possible combinations of the following:

- Hydrogen;
- C_{1-24} alkyl or heteroalkyl, C_{1-24} alkenyl or heteroalkenyl; C_{1-24} alkynyl or heteroalkynyl
- An acyl residue of a saturated/unsaturated/polyunsaturated fatty acid, of either synthetic or natural origin
- A residue that may be preferably, but not exclusively selected from those shown in the table below:

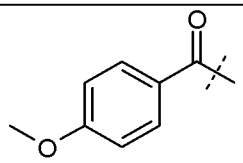
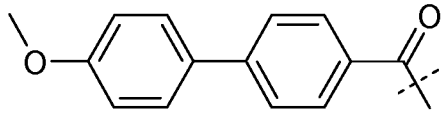
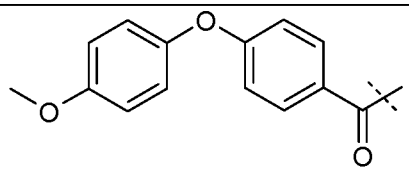
L91	
L92	
L93	

Fig. 1a

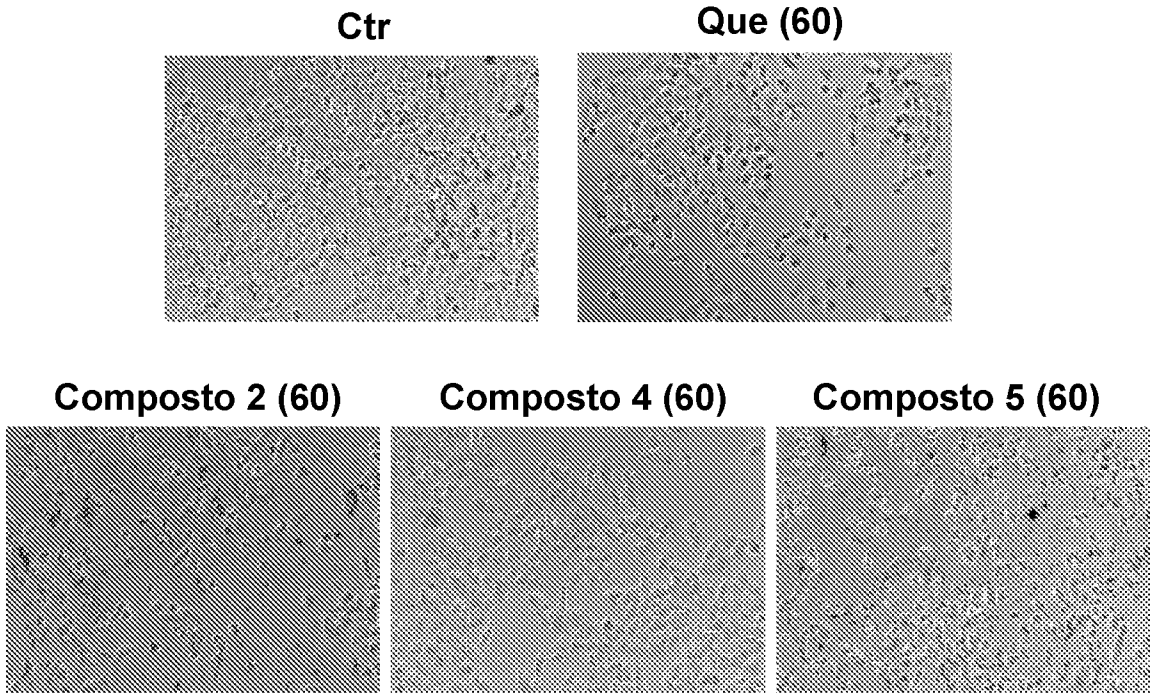
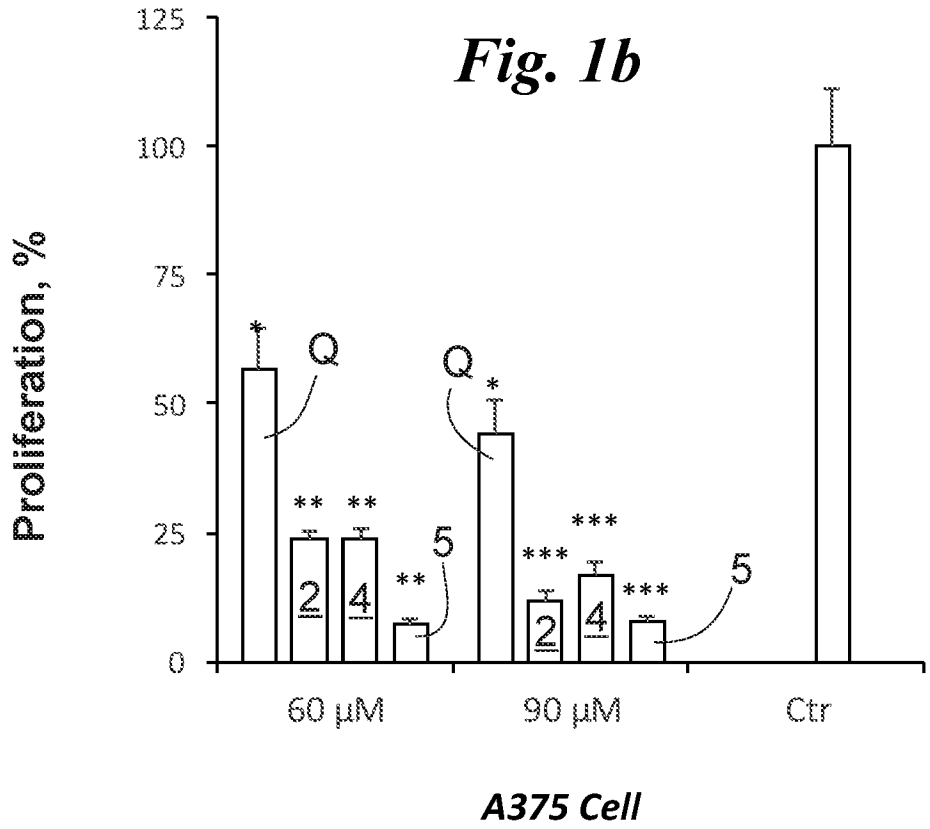

Melanoma
Ctr
Que (60)
Composto 2 (60)
Composto 4 (60)
Composto 5 (60)

Fig. 1b


Proliferation, %
125
100
75
50
25
0
Q
Q
2
4
5
2
4
5
60 µM
90 µM
Ctr
A375 Cell

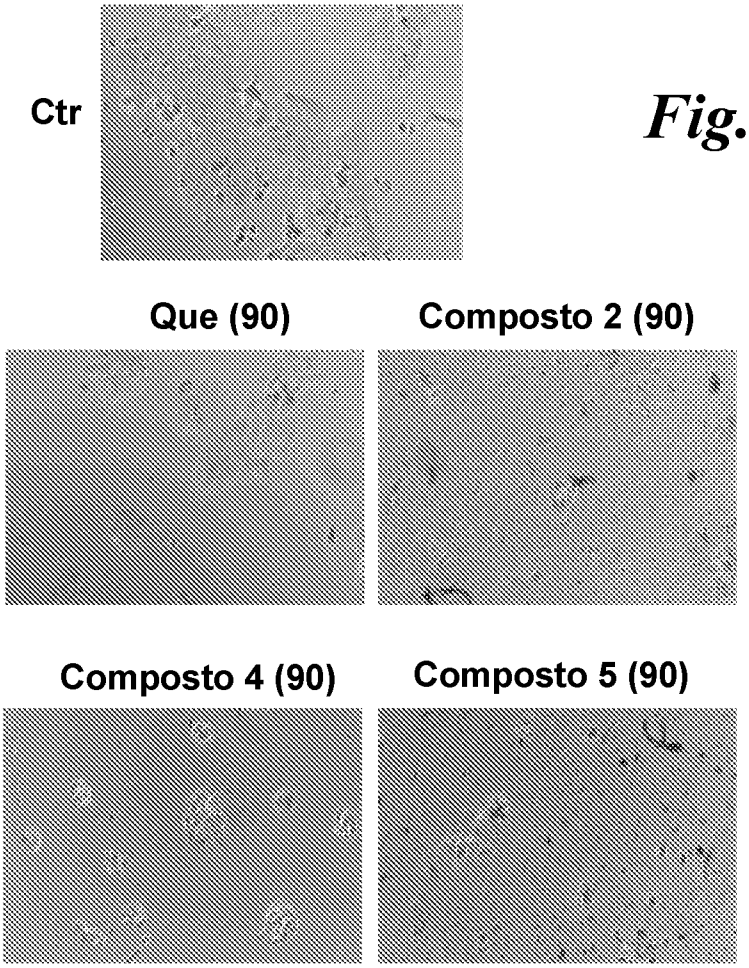

Ctr
Que (90)
Composto 2 (90)
Composto 4 (90)
Composto 5 (90)

Fig. 2a

Fig. 2b

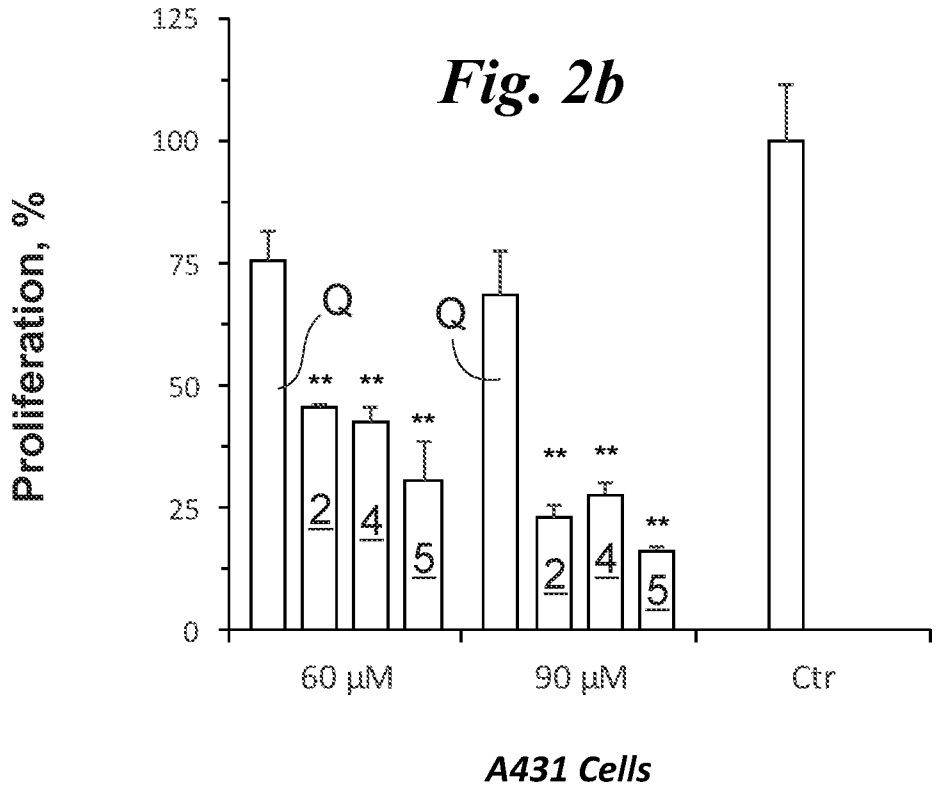

Proliferation, %
125
100
75
50
25
0
Q
Q
**
**
**
**
**
**
2
4
5
2
4
5
60 µM
90 µM
Ctr
A431 Cells

Fig. 3a

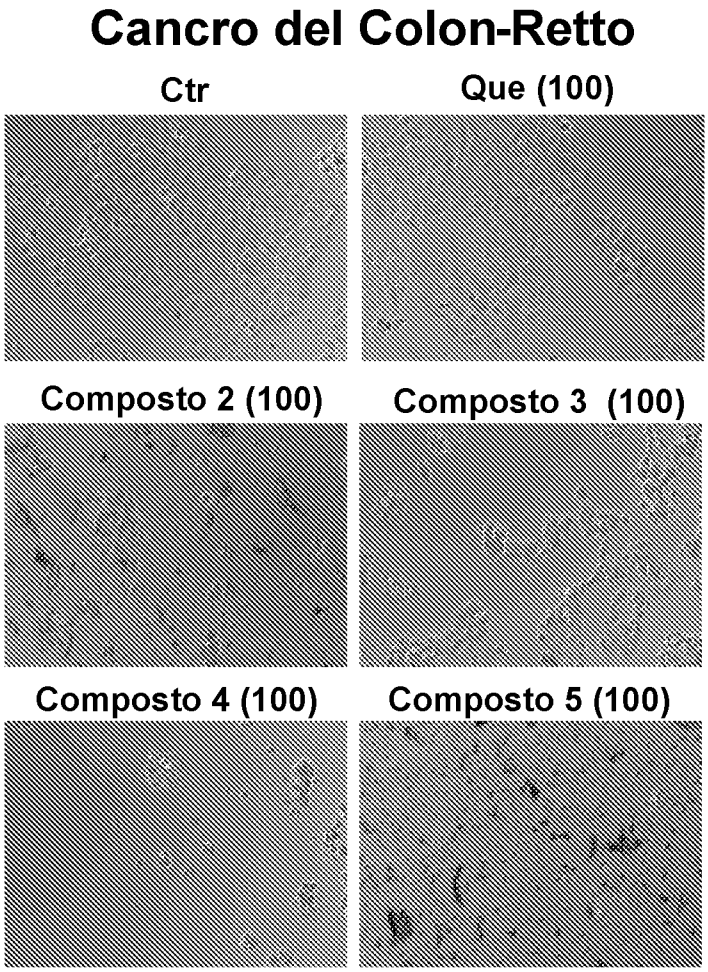

Cancro del Colon-Retto
Ctr
Que (100)
Composto 2 (100)
Composto 3 (100)
Composto 4 (100)
Composto 5 (100)

Fig. 3b

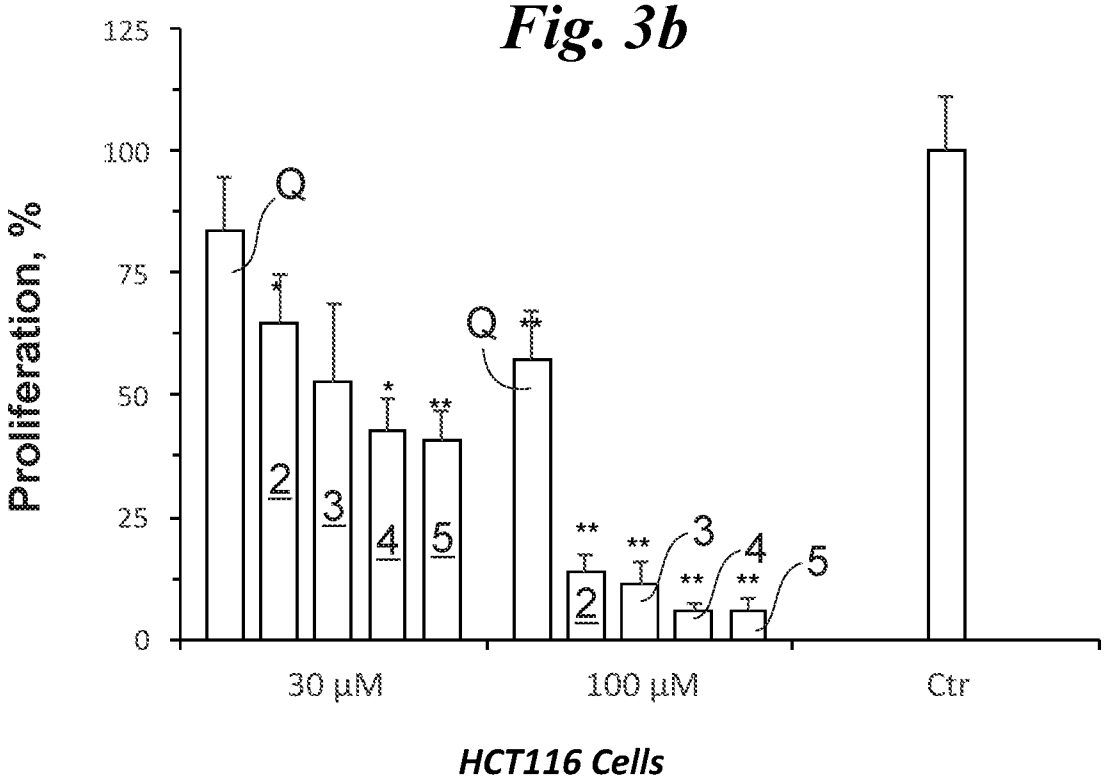

Proliferation, %
125
100
75
50
25
0
Q
2
3
4
5
30 µM
100 µM
Ctr
HCT116 Cells

Fig. 4a

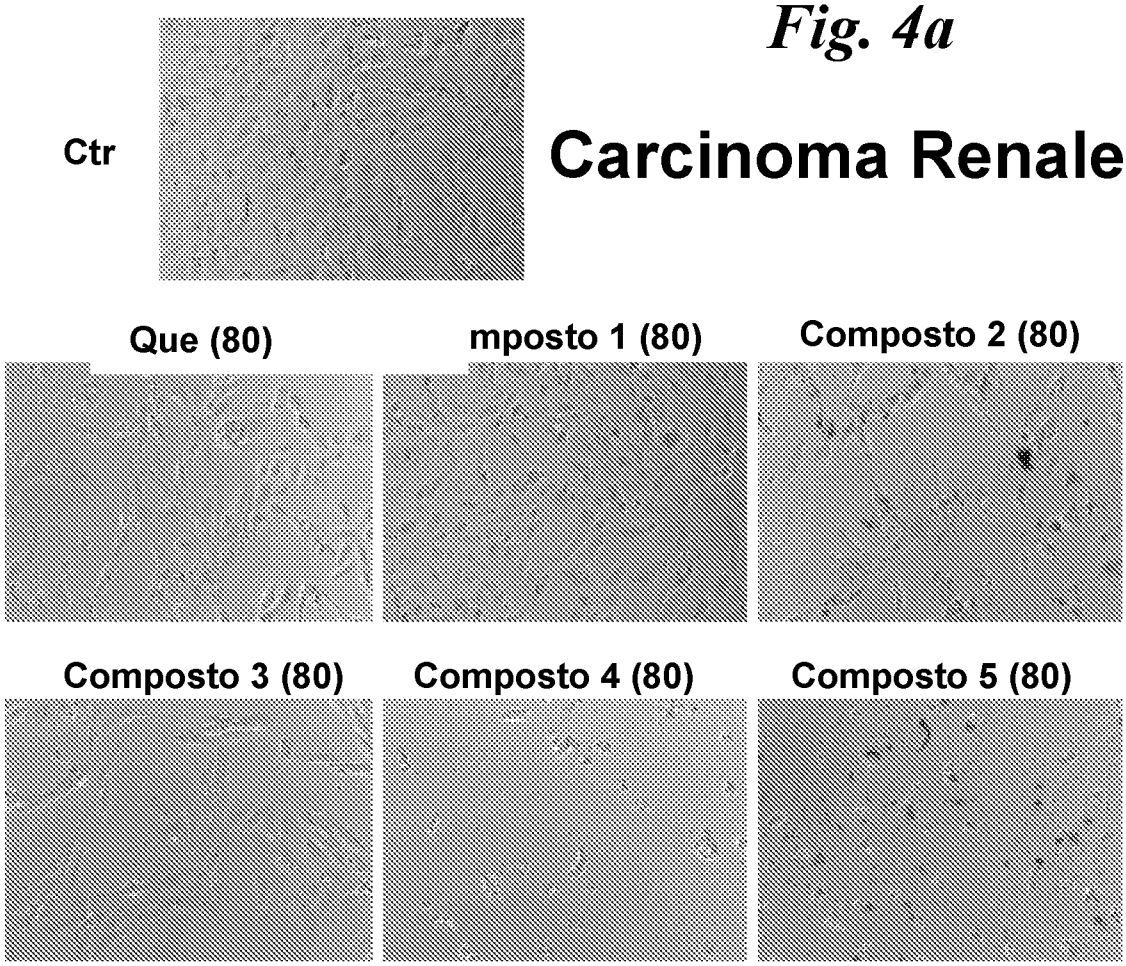
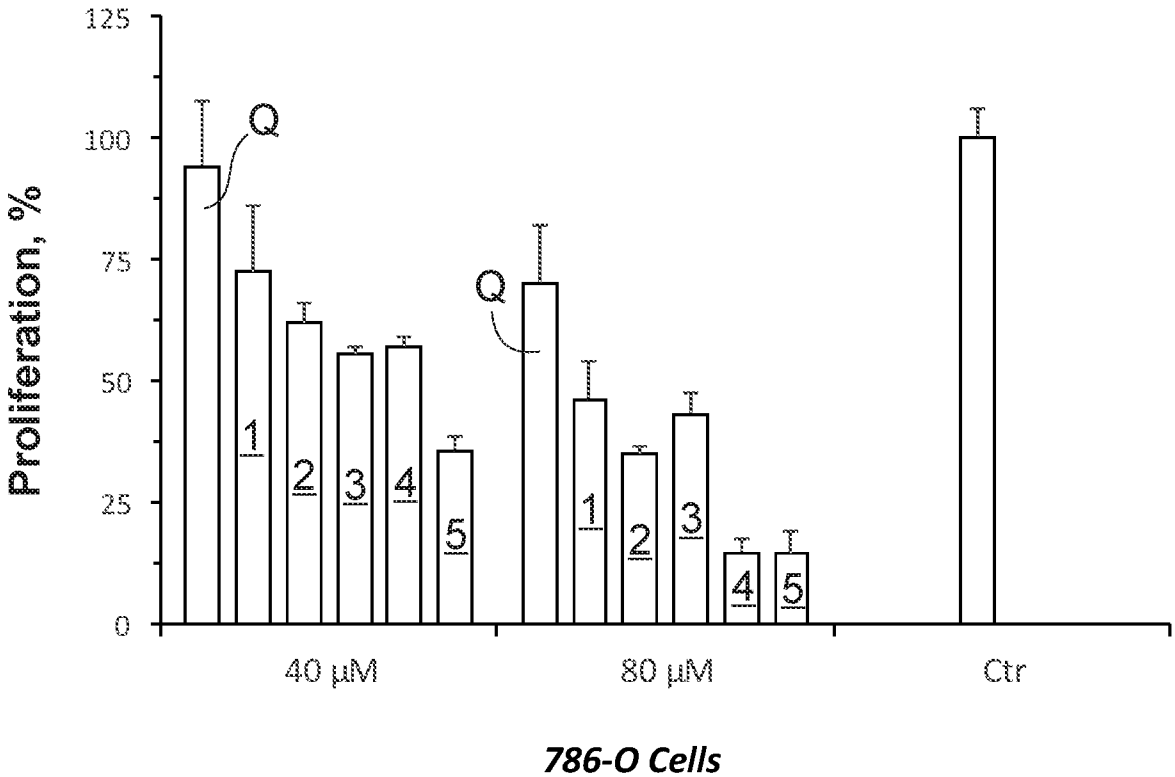


Fig. 4b



786-O Cells

Fig. 5a

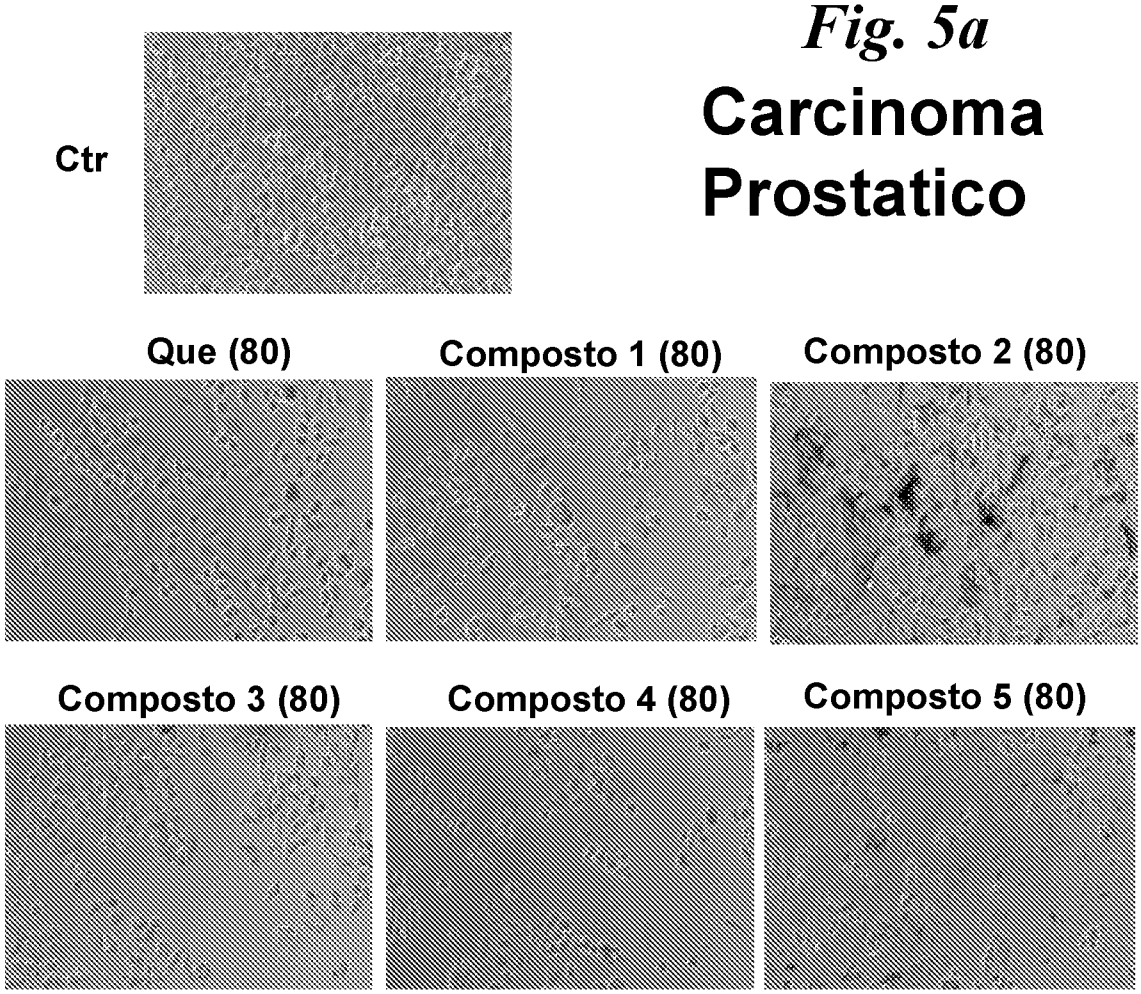

Ctr
Carcinoma Prostatico
Que (80)
Composto 1 (80)
Composto 2 (80)
Composto 3 (80)
Composto 4 (80)
Composto 5 (80)

Fig. 5b

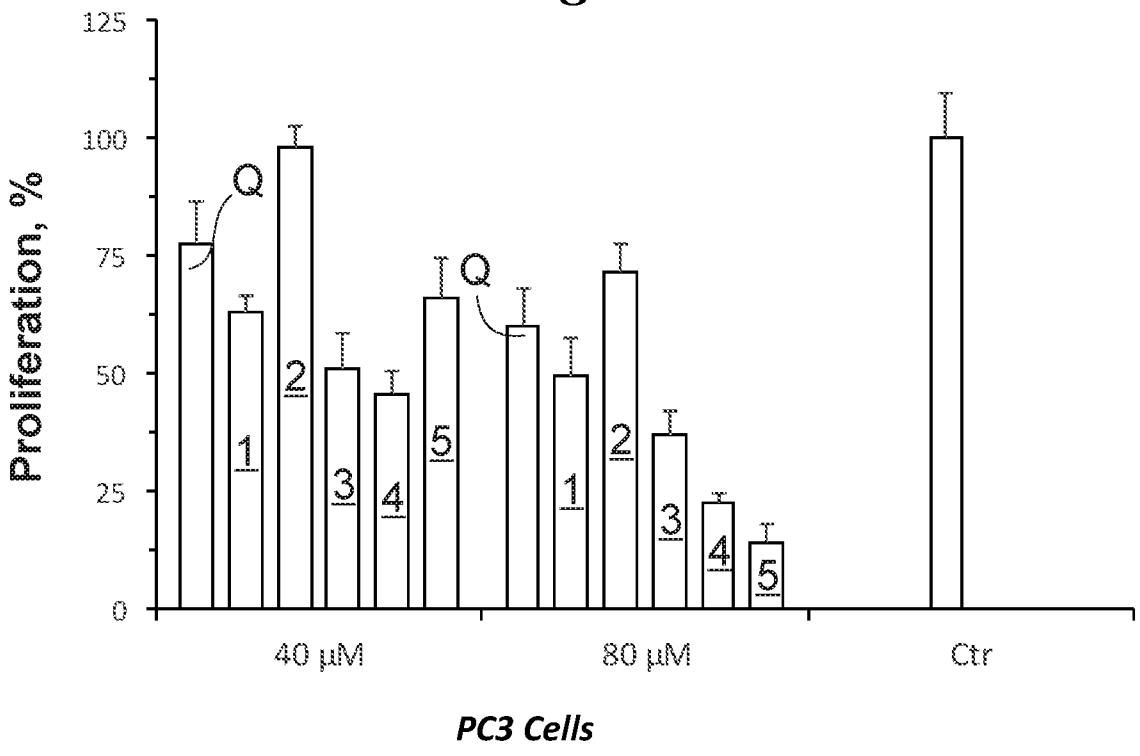

Proliferation, %
125
100
75
50
25
0
Q
Q
1
2
3
4
5
1
2
3
4
5
40 µM
80 µM
Ctr
PC3 Cells

Fig. 6a

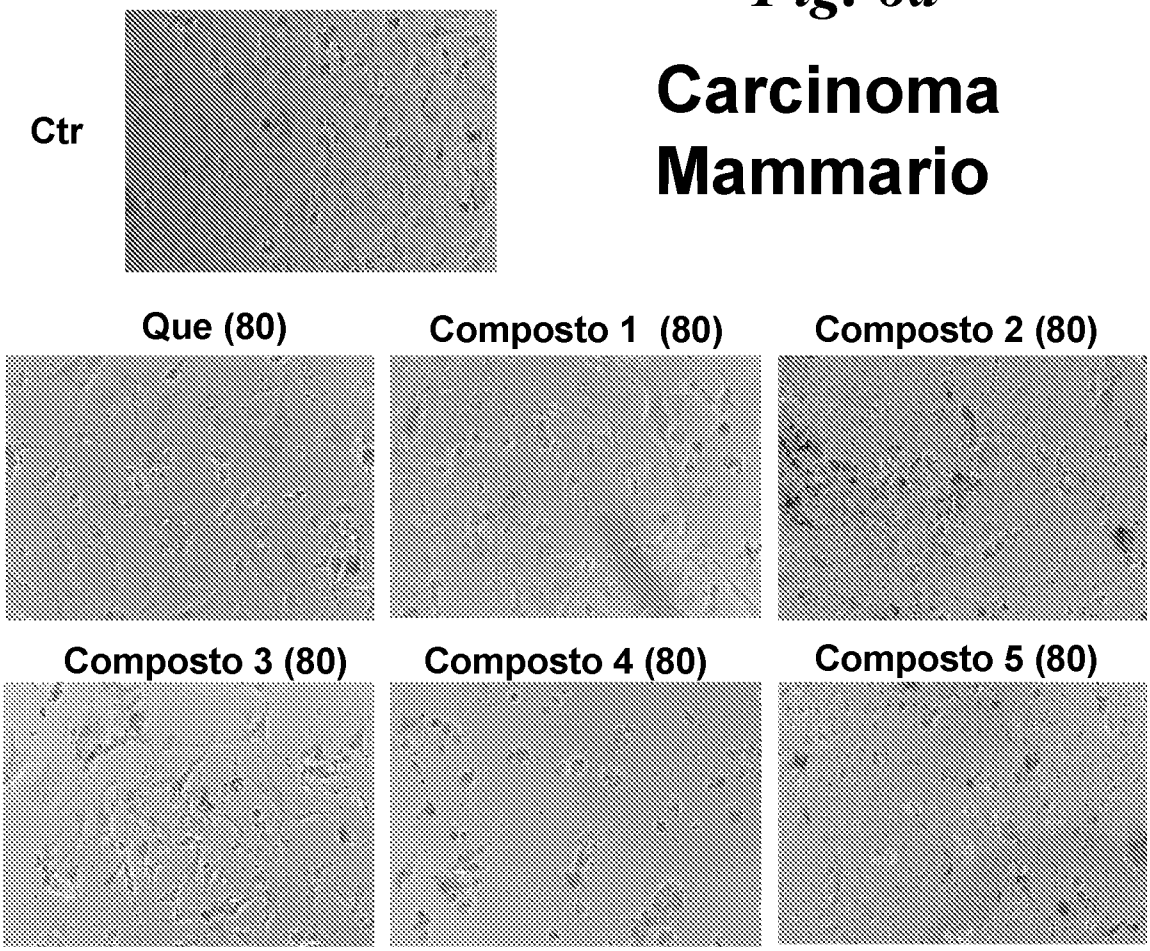
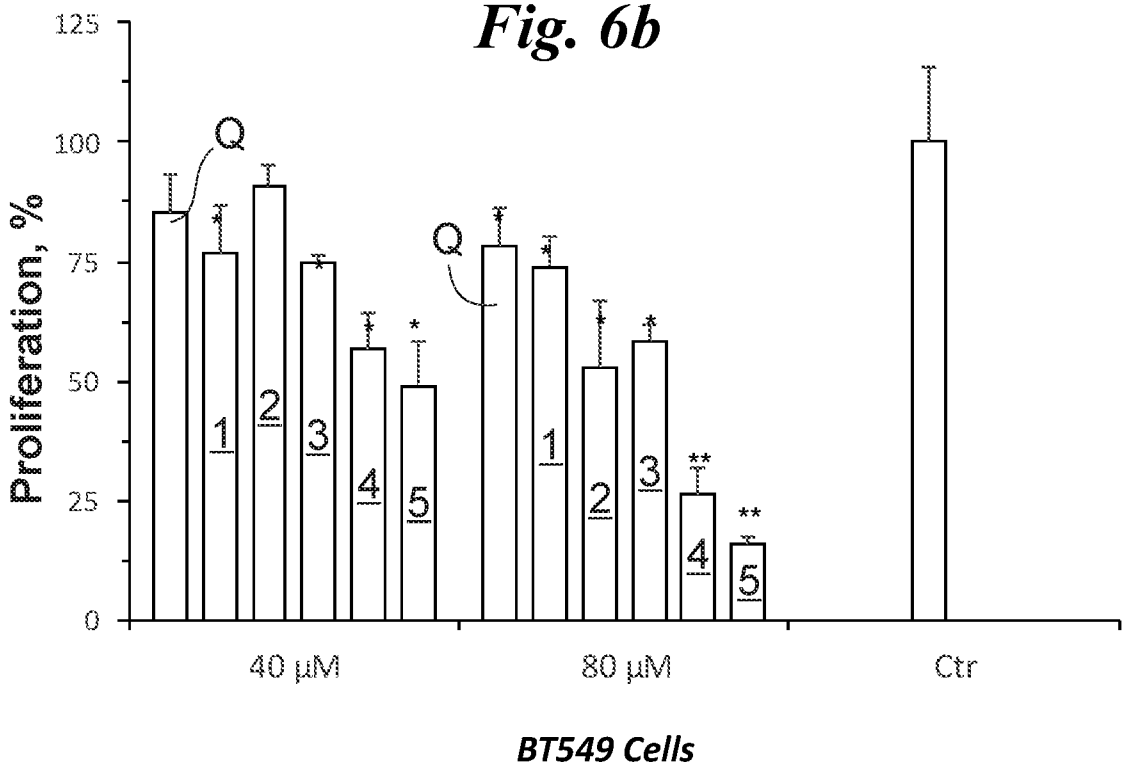


Fig. 6b



BT549 Cells

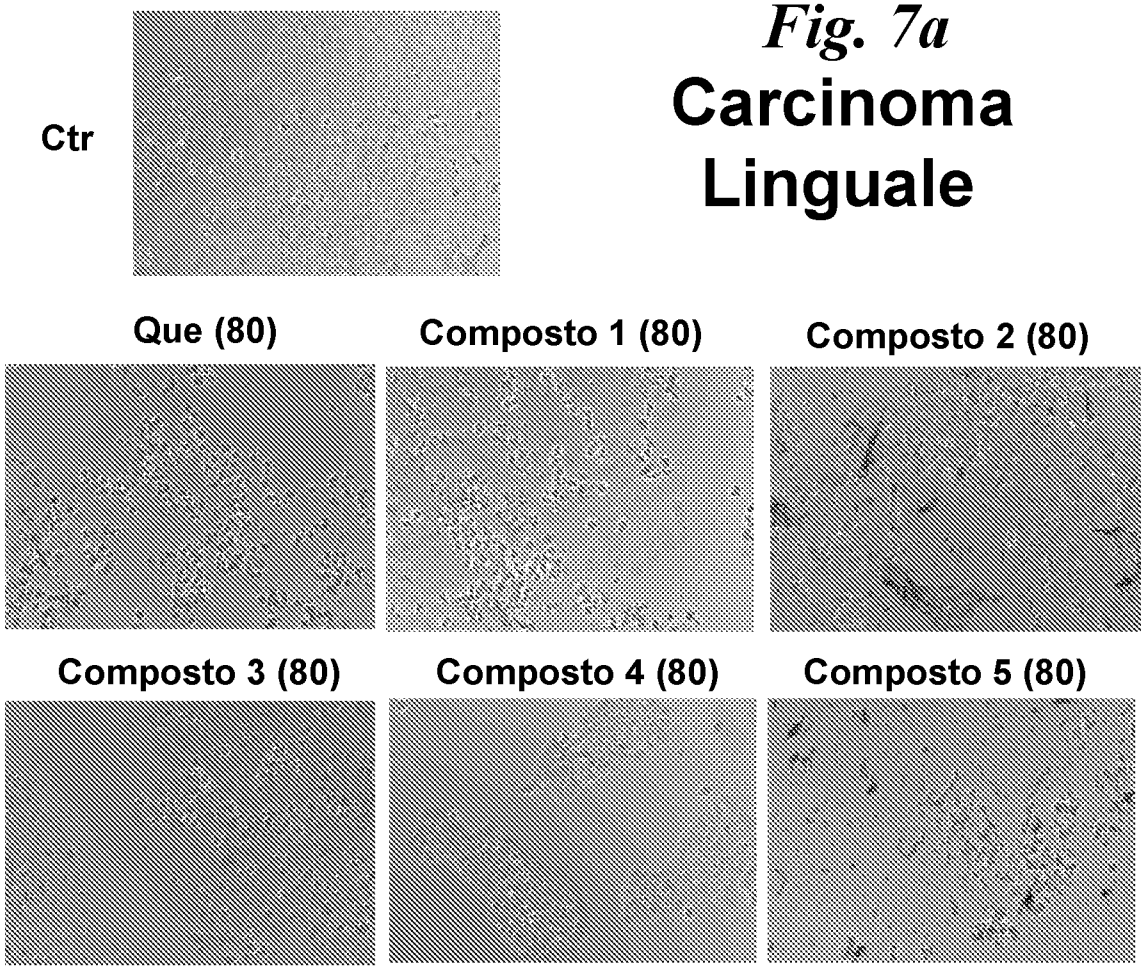


Fig. 7a
Carcinoma Linguale

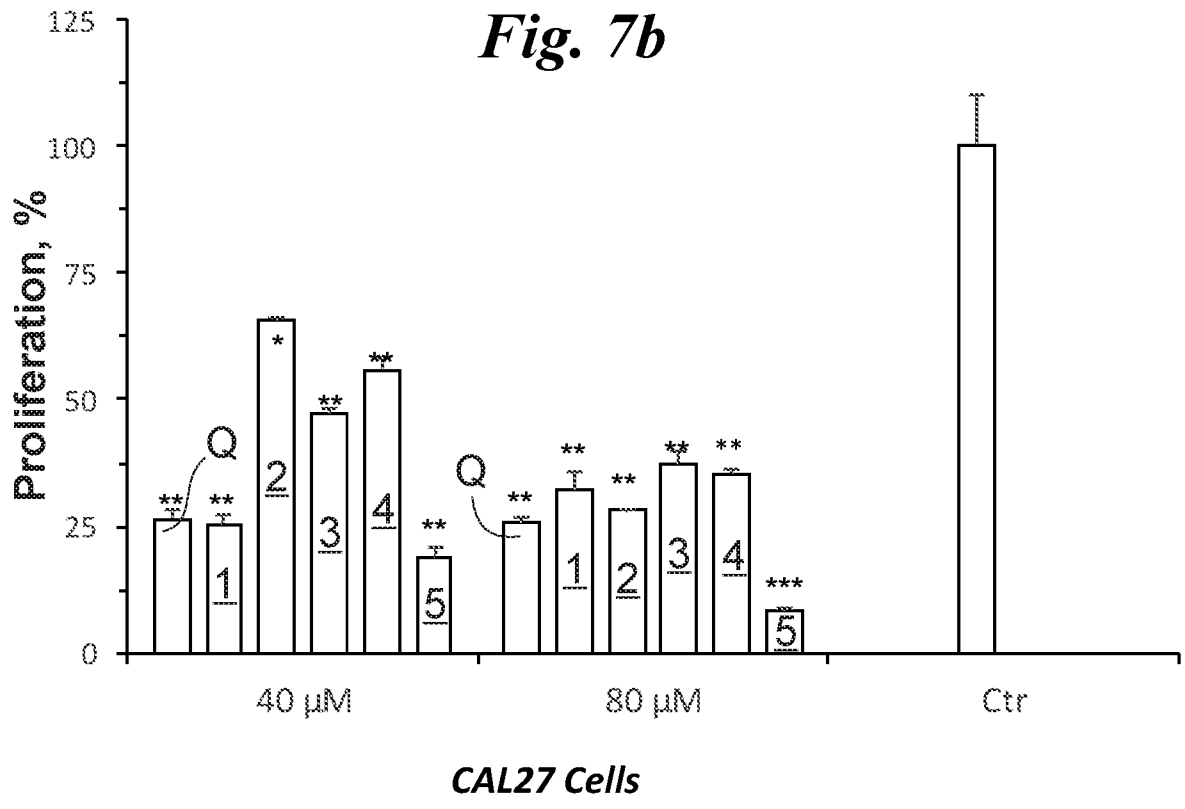


Fig. 7b

CAL27 Cells

Fig. 8a

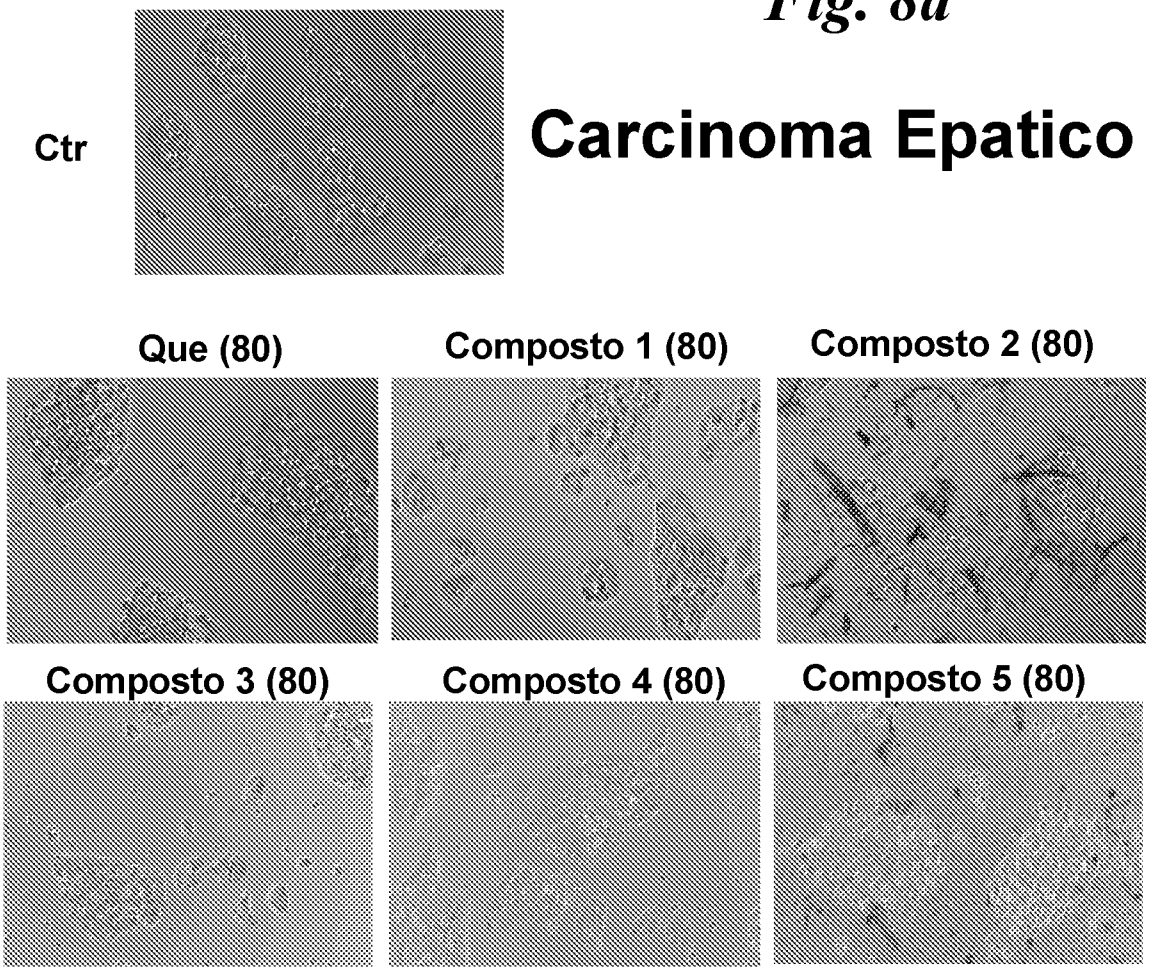
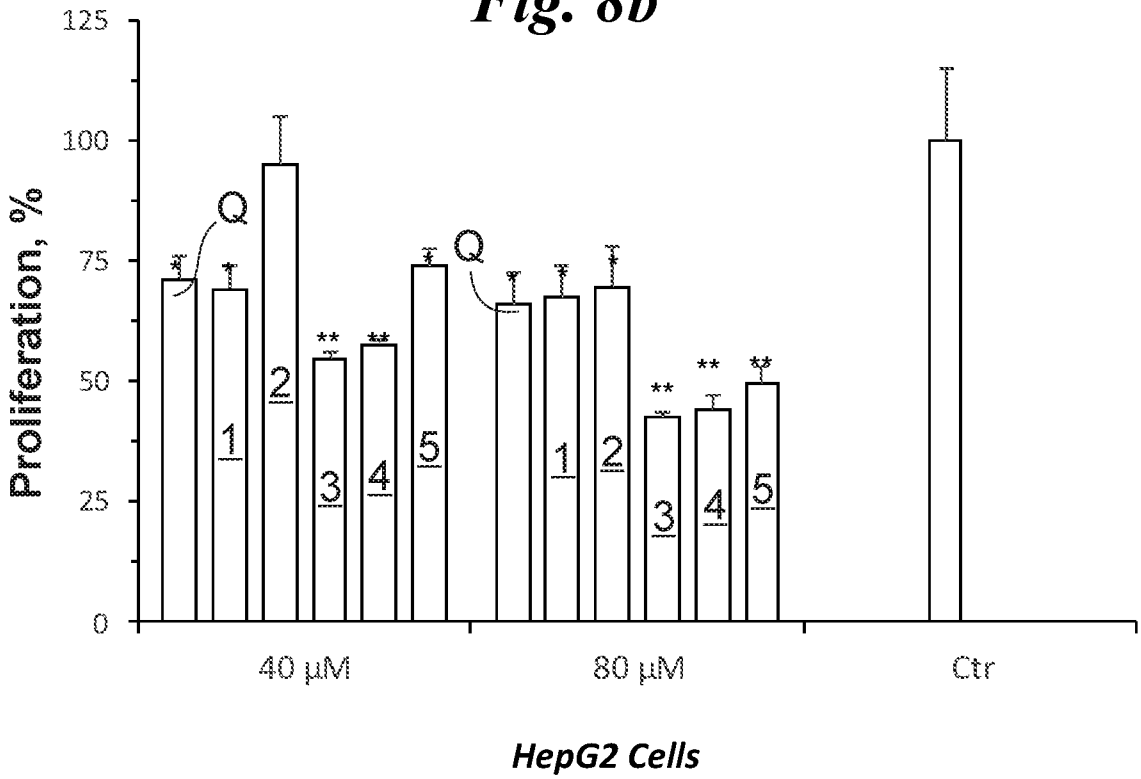


Fig. 8b



HepG2 Cells

Fig. 9a

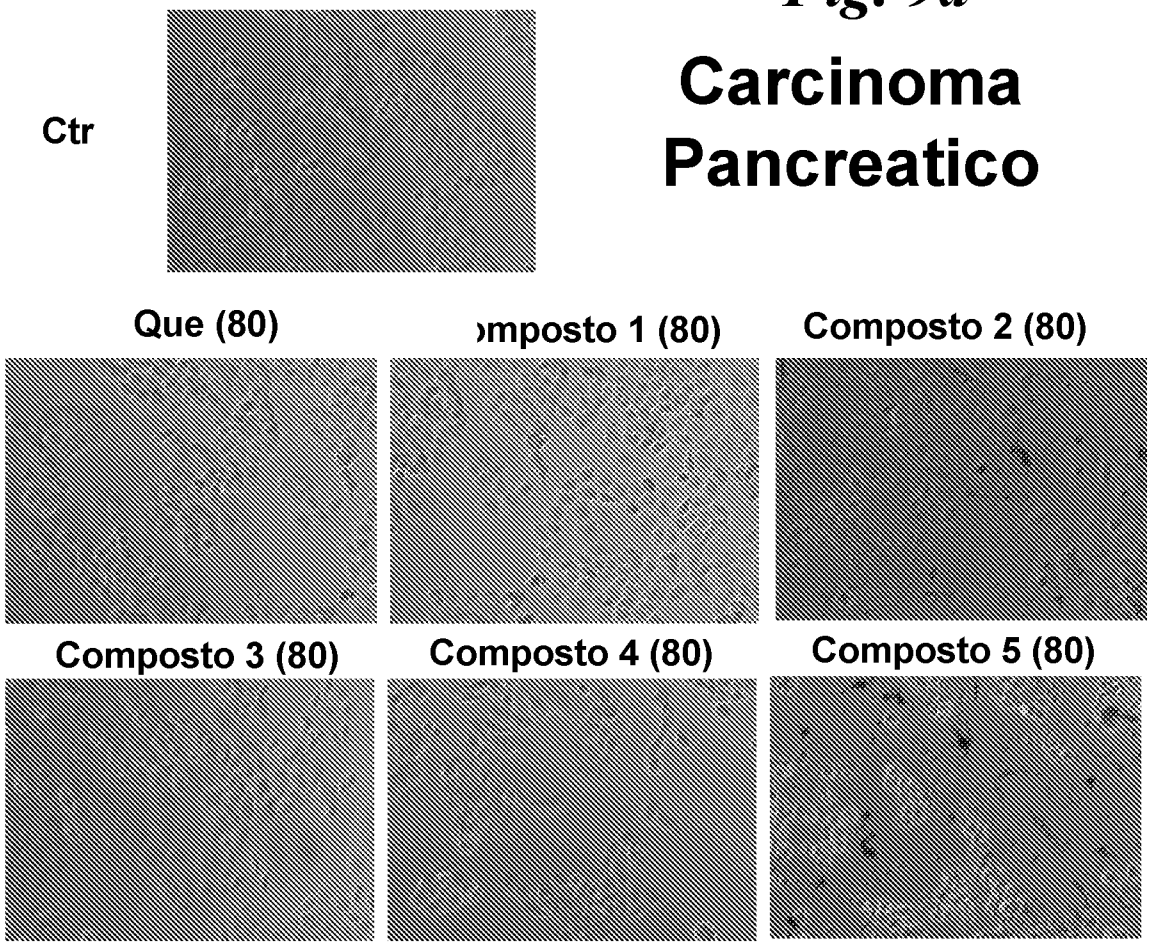

Ctr
Carcinoma Pancreatico
Que (80)
mposto 1 (80)
Composto 2 (80)
Composto 3 (80)
Composto 4 (80)
Composto 5 (80)

Fig. 9b

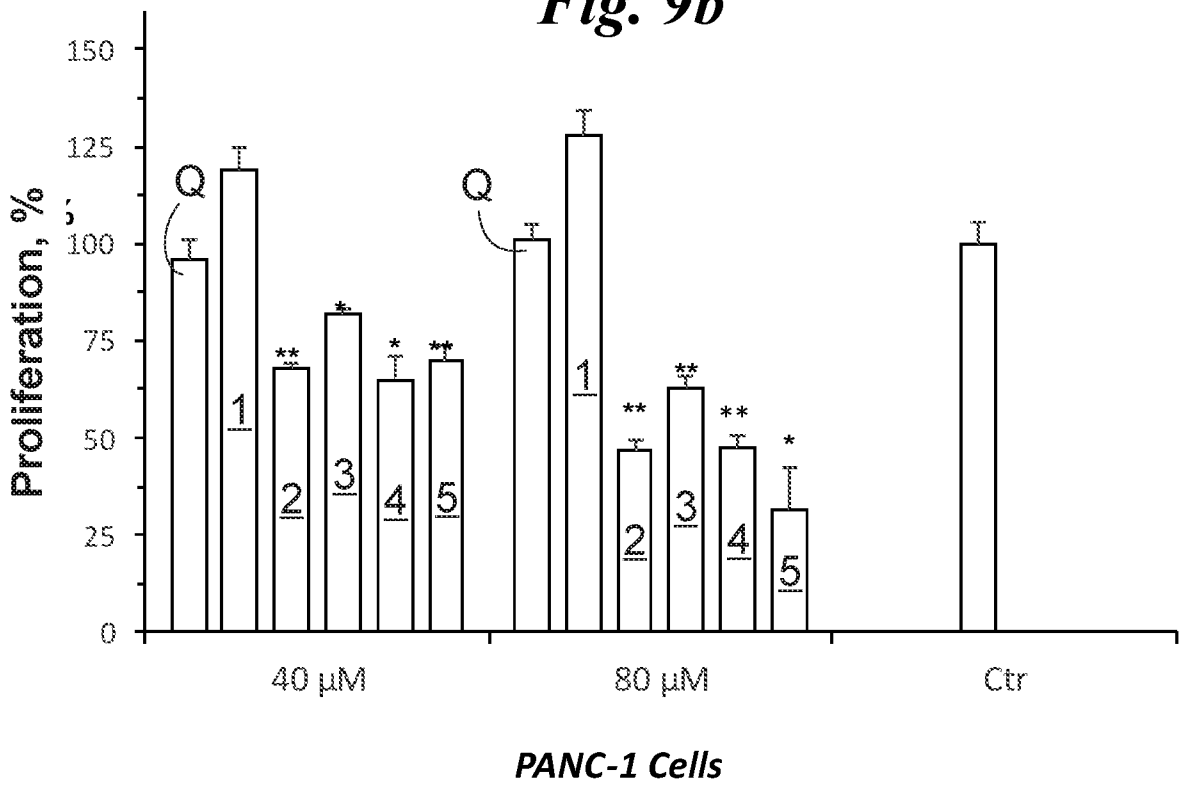

Proliferation, %
150
125
100
75
50
25
0
Q
Q
1
2
3
4
5
40 µM
80 µM
Ctr
PANC-1 Cells

Fig. 10a

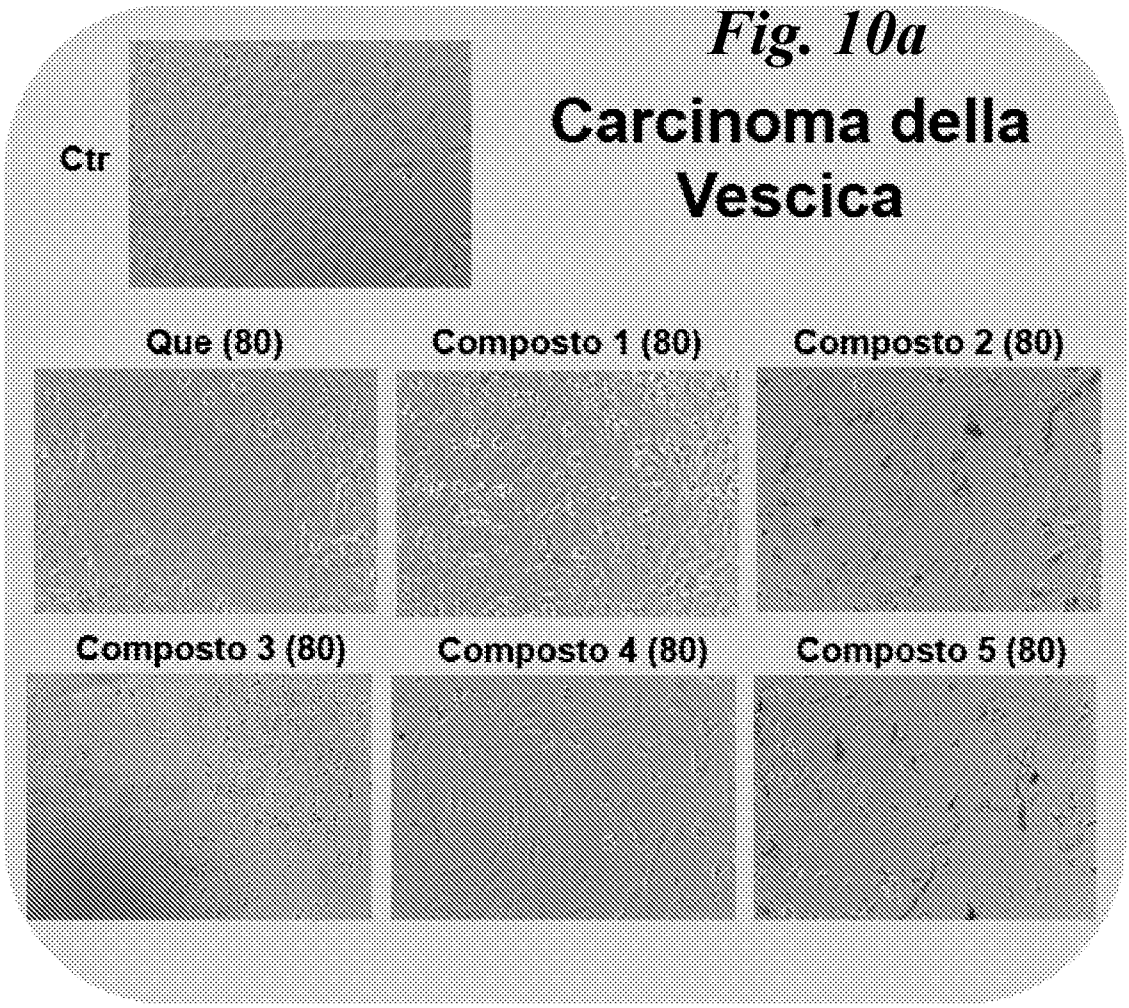
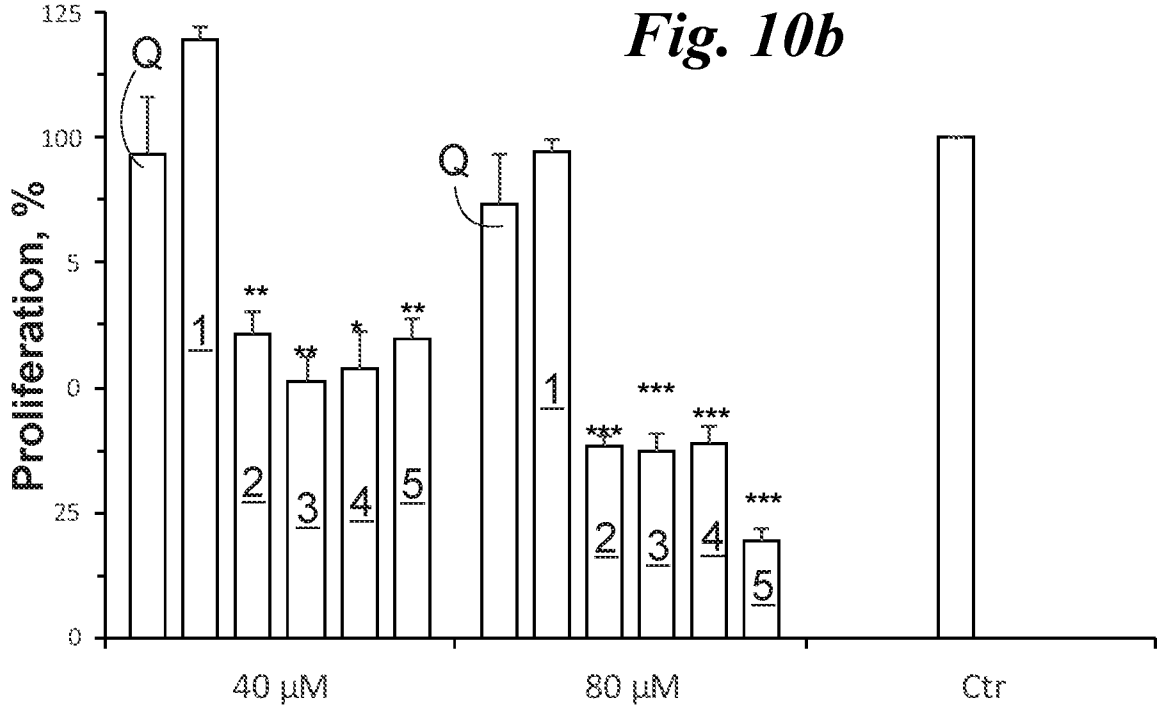


Fig. 10b



T24 Cells

Fig. 11a

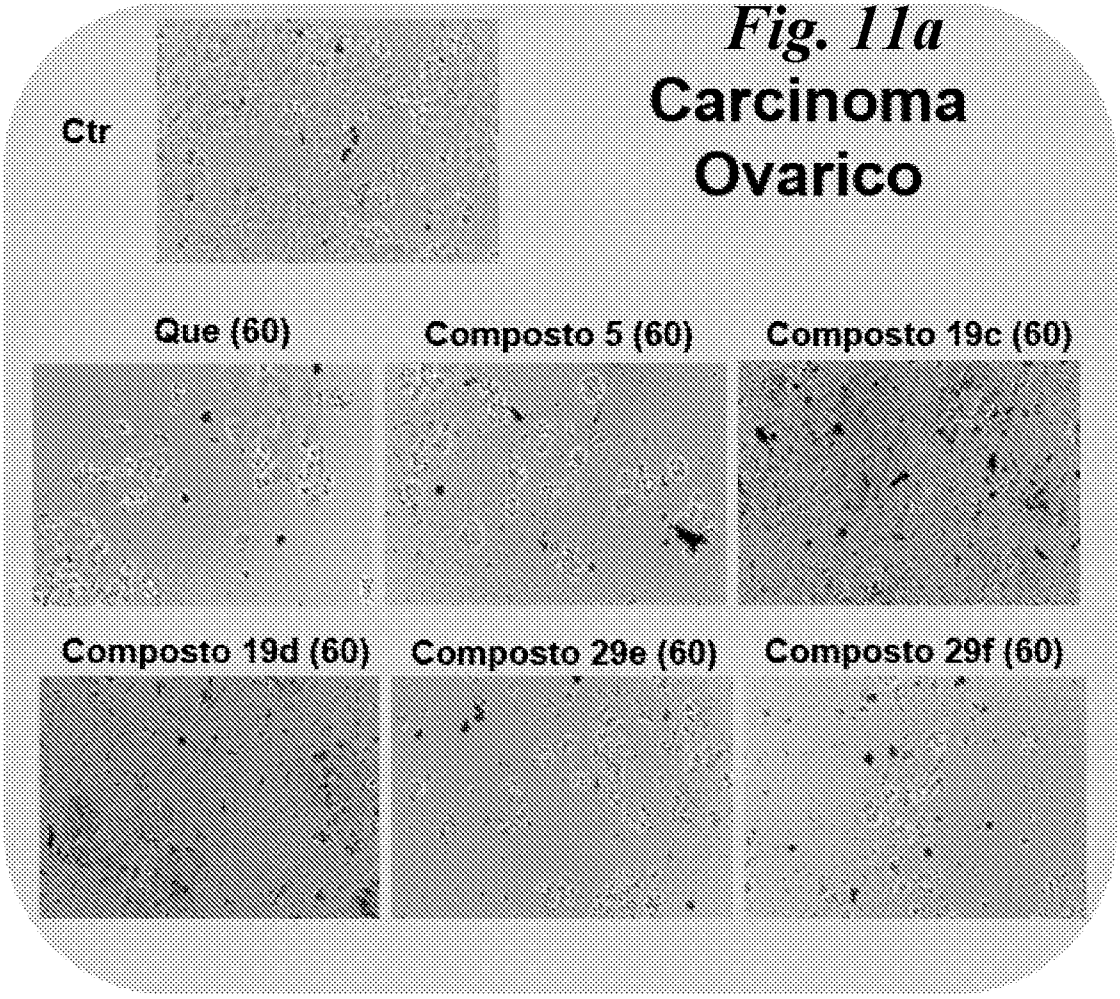
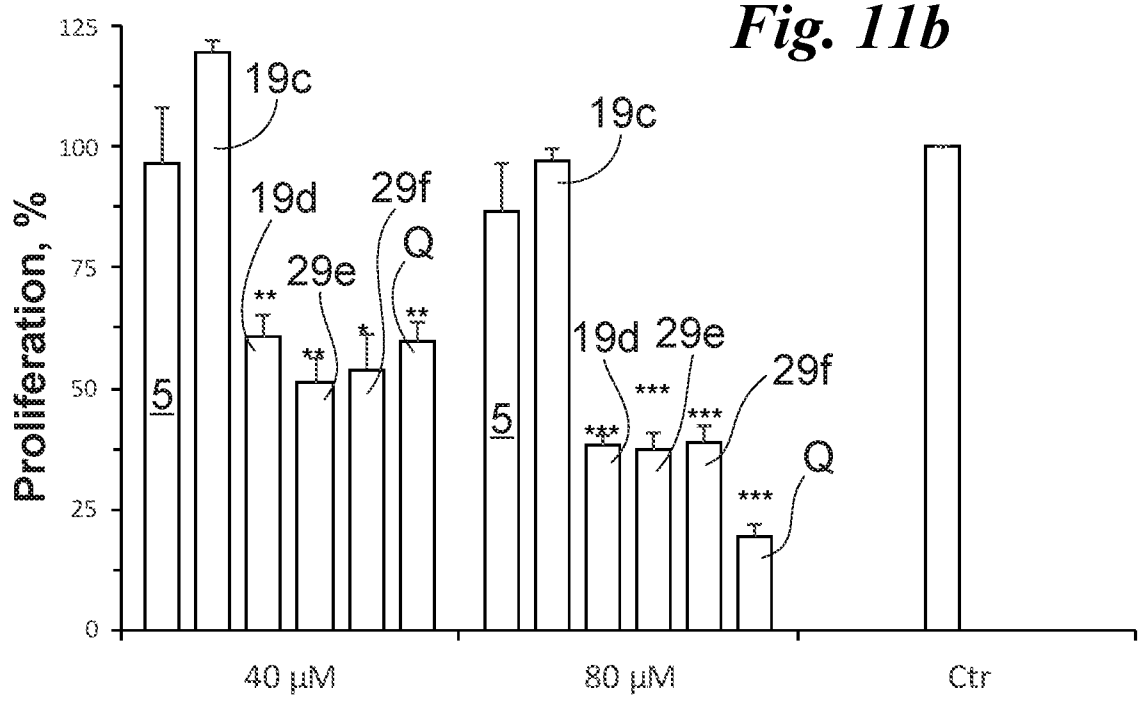
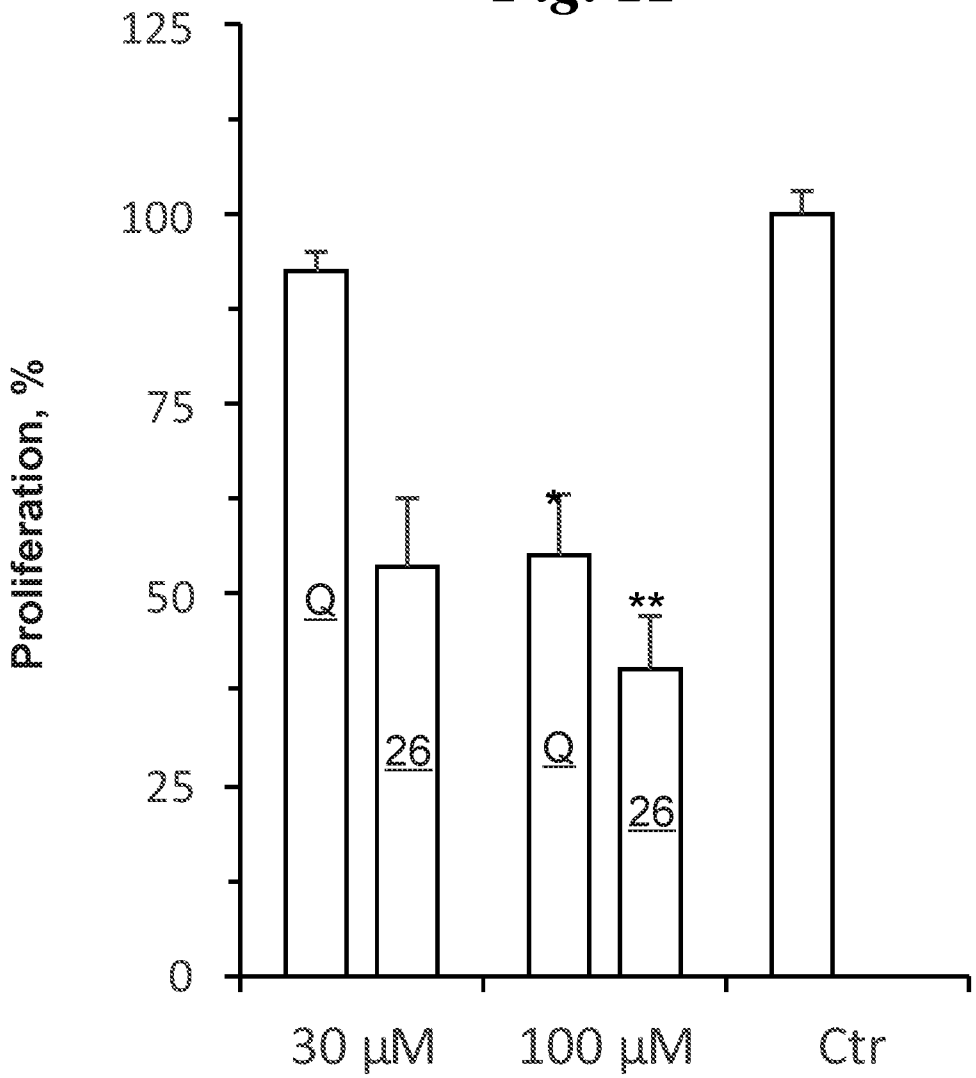


Fig. 11b



T24 Cells

Fig. 12



A375 Cells

Fig. 13a

Cancro del Colon-Retto

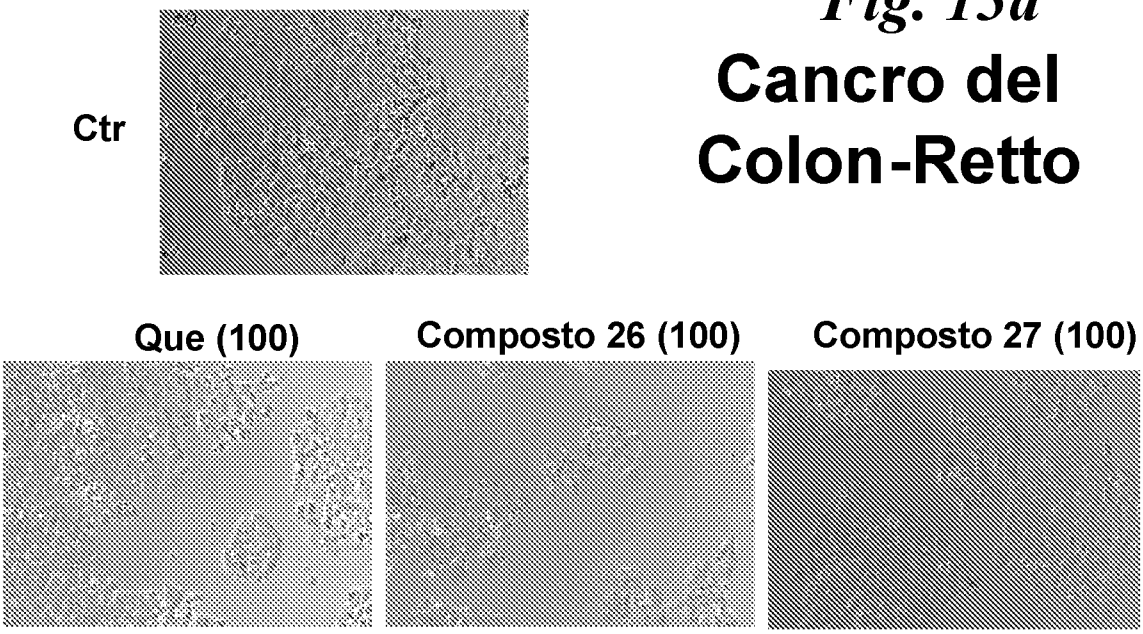
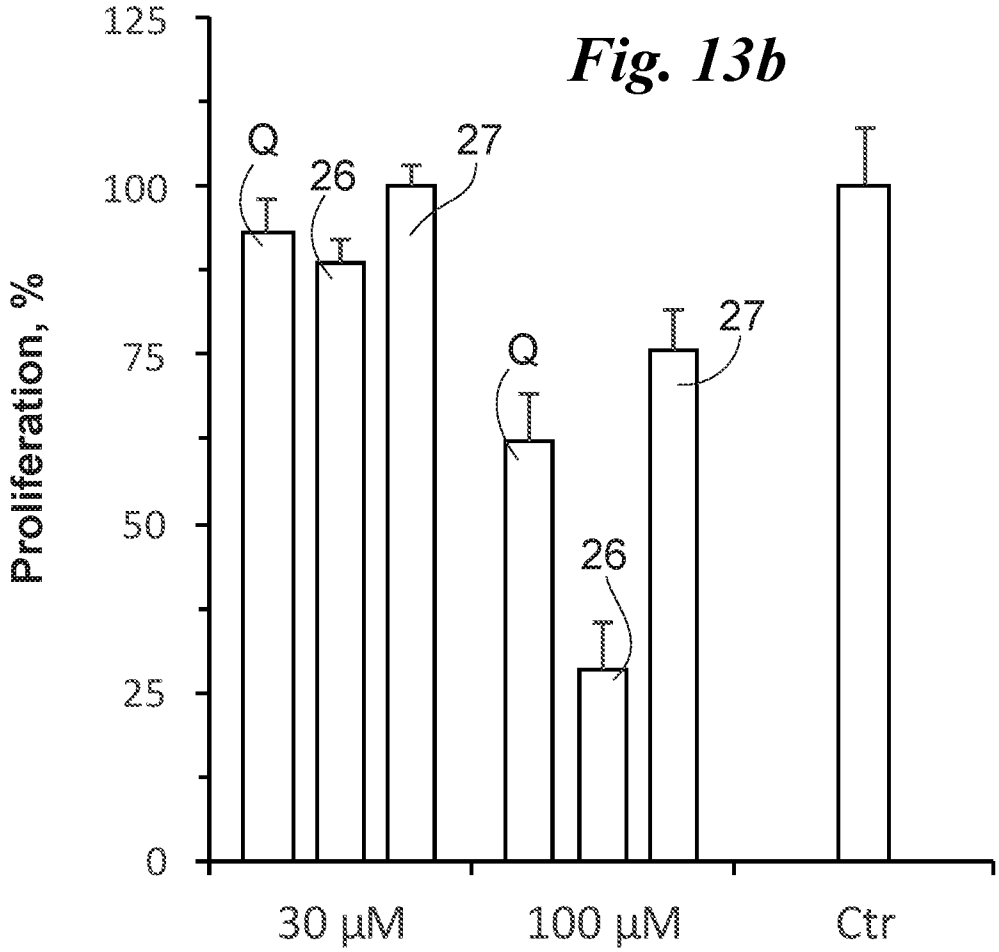


Fig. 13b



HCT116 Cells

Fig. 14

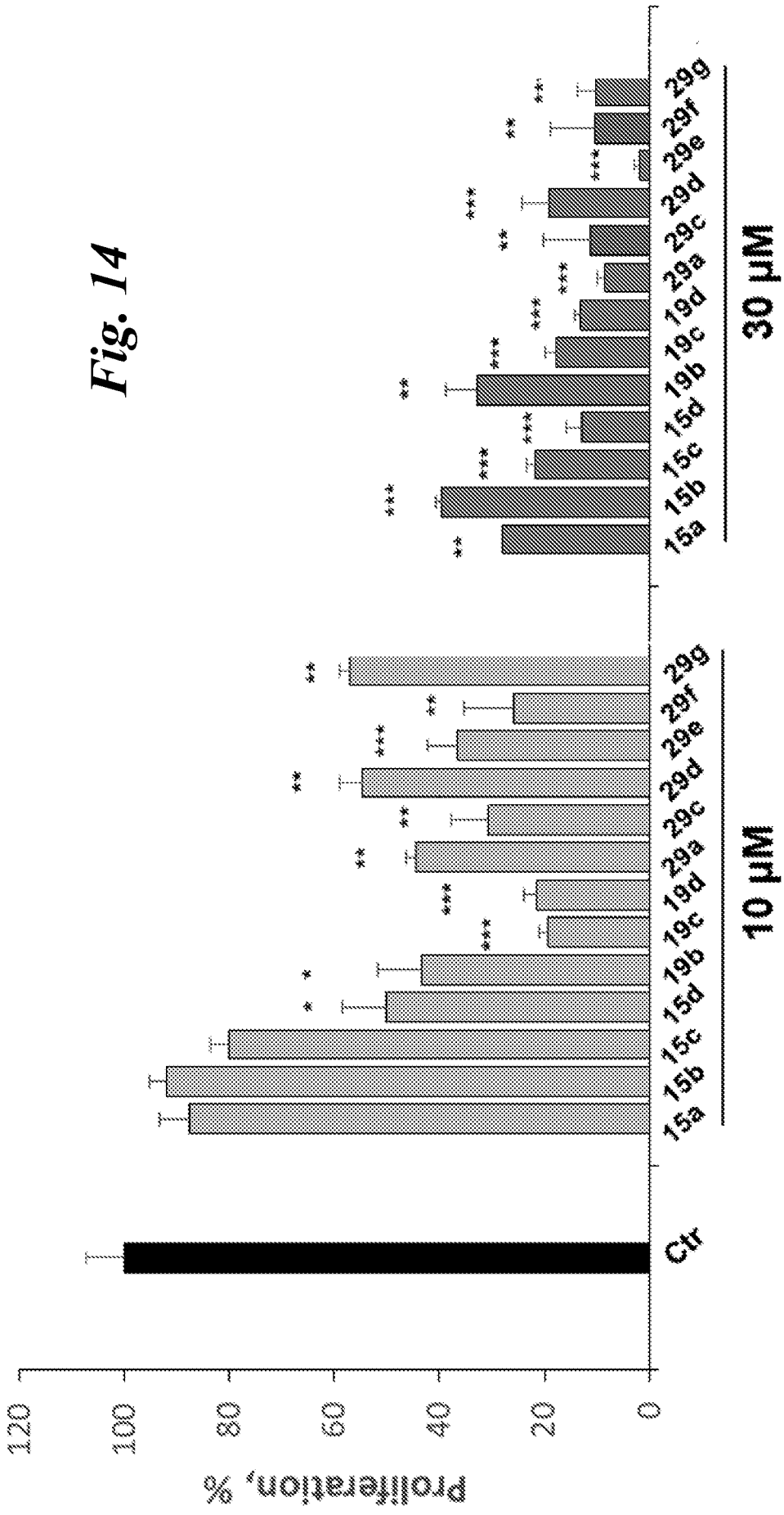
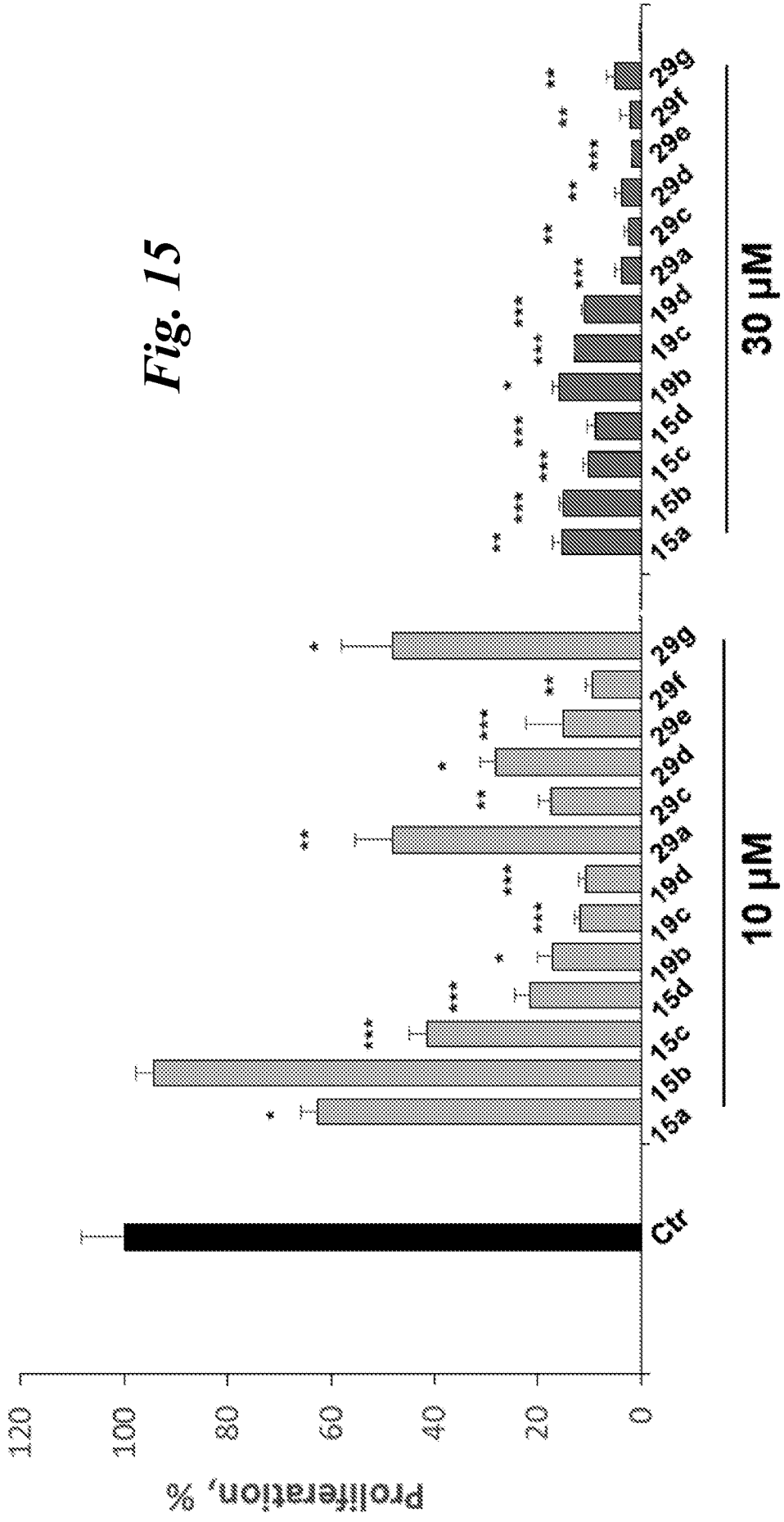

Proliferation, %
120
100
80
60
40
20
0
Ctr
15a
15b
15c
15d
19b
19c
19d
29a
29c
29d
29e
29f
29g
10 µM
30 µM

Fig. 15


Proliferation, %
120
100
80
60
40
20
0
Ctr
15a
15b
15c
15d
19b
19c
19d
29a
29c
29d
29e
29f
29g
10 µM
30 µM

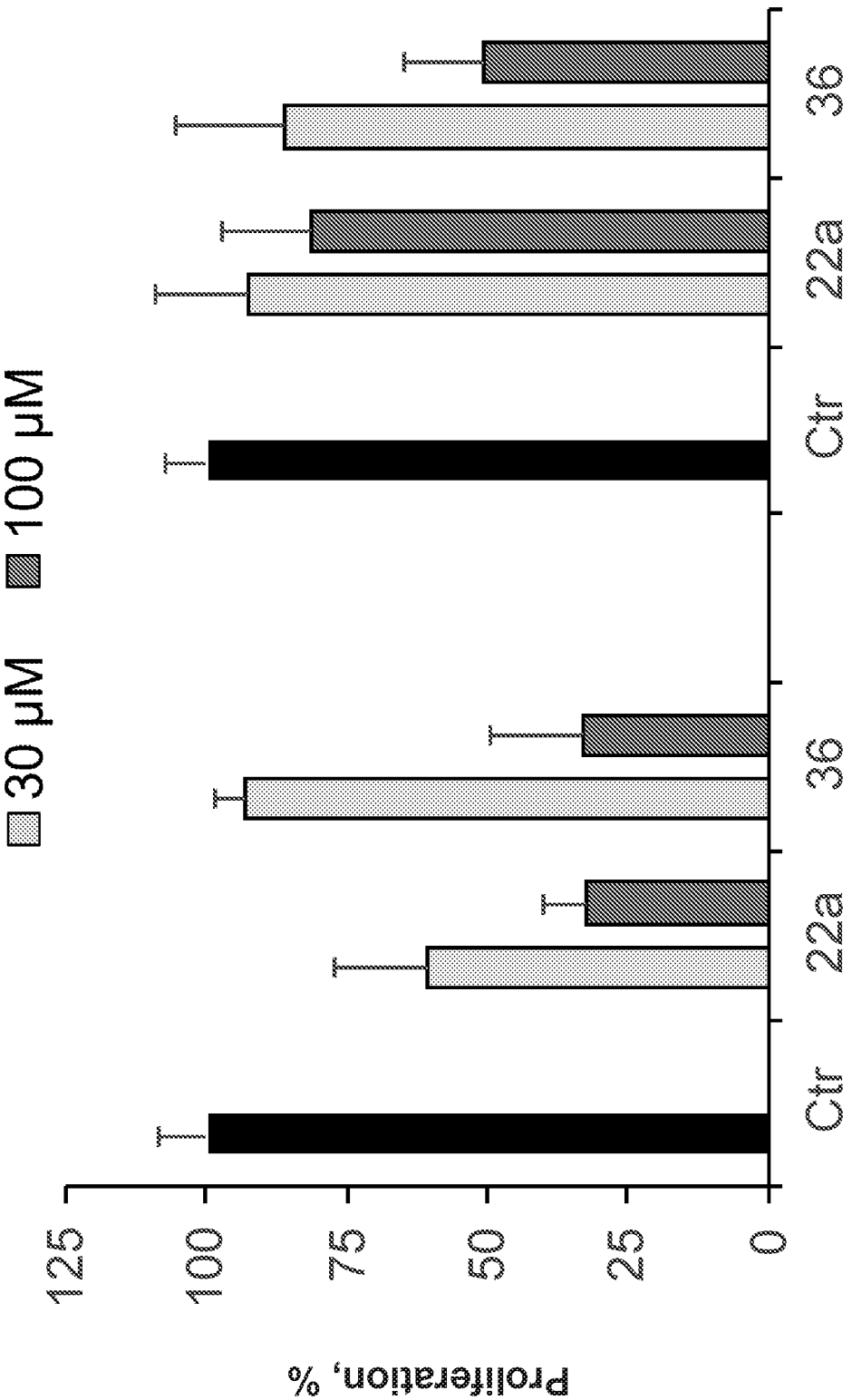

30 µM
100 µM
Proliferation, %
125
100
75
50
25
0
Ctr
22a
36
Ctr
22a
36

Fig. 16

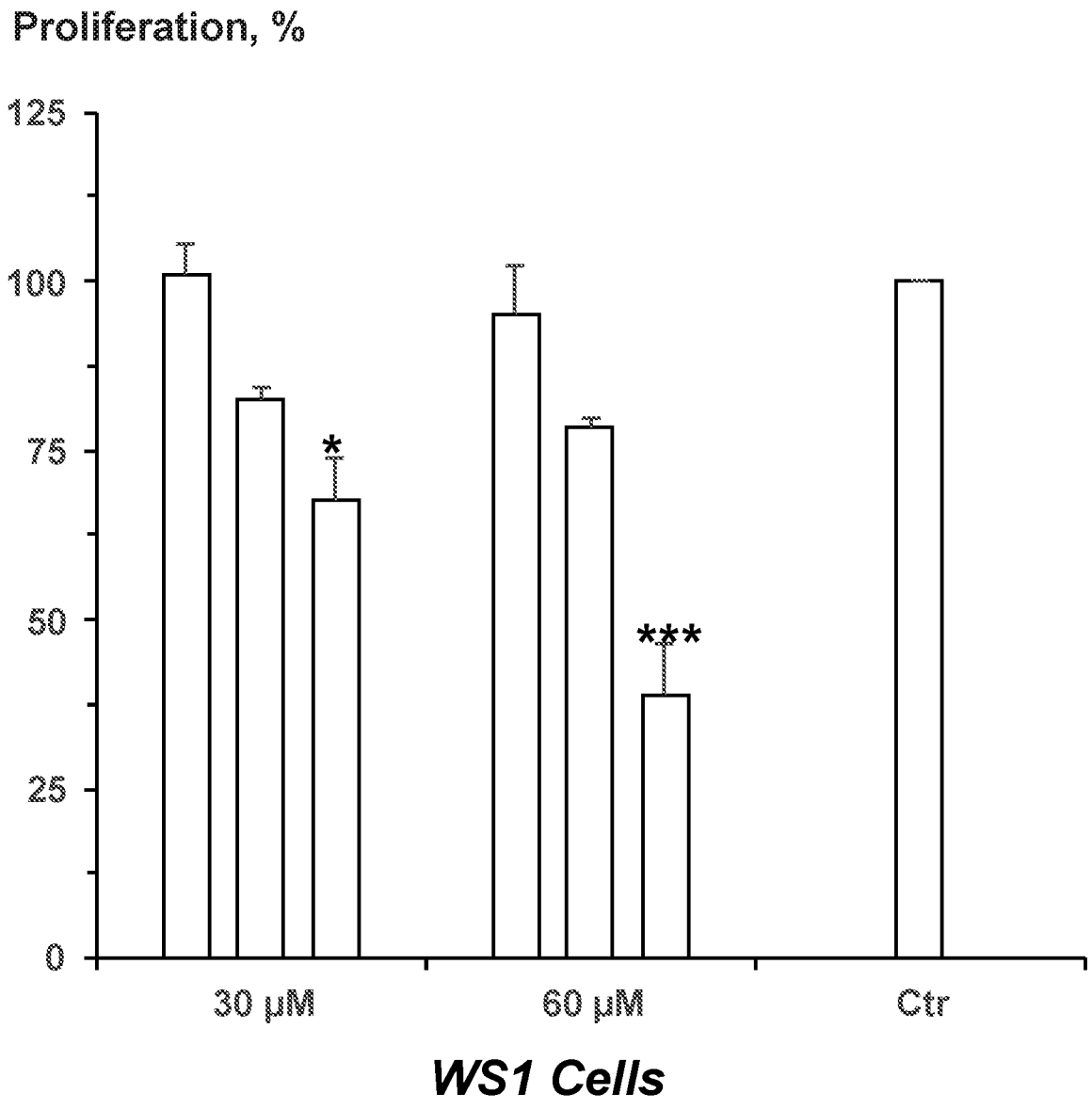


Fig. 17

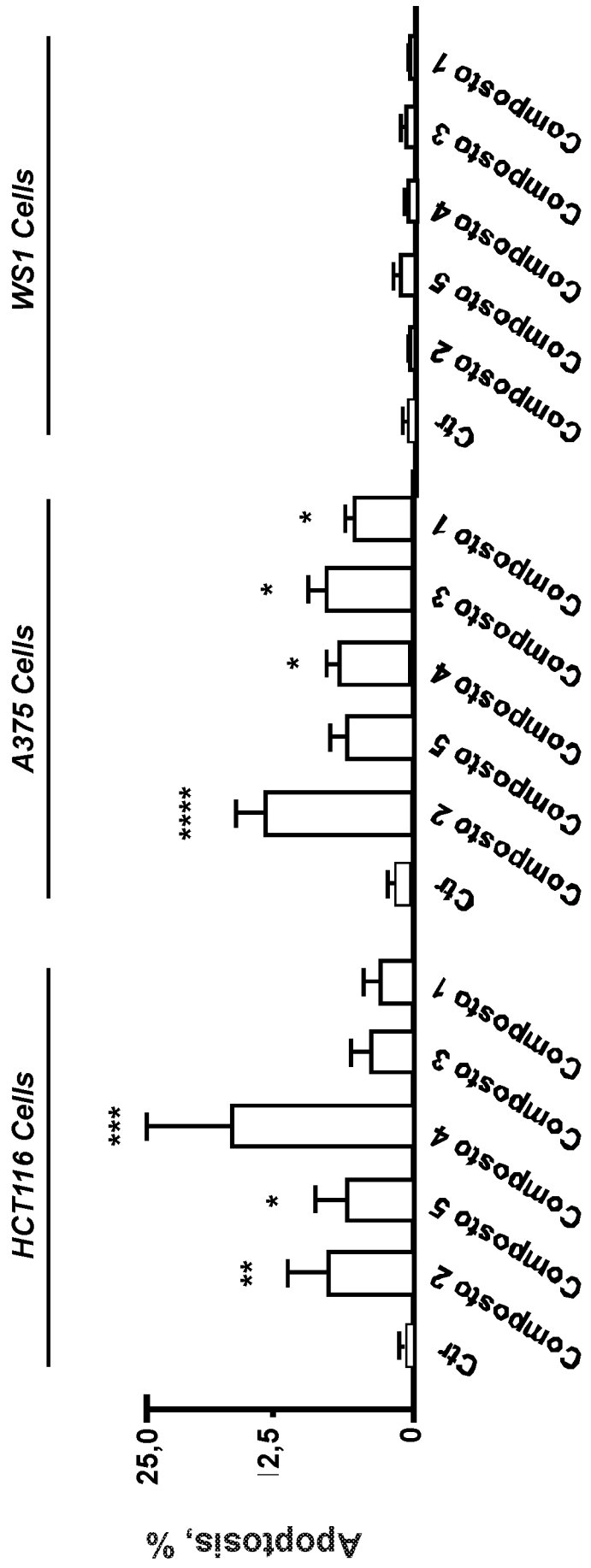

Apoptosis, %
25,0
12,5
0
HCT116 Cells
A375 Cells
WS1 Cells
Ctr
Composto 2
Composto 5
Composto 4
Composto 3
Composto 1
***
**
*
****
*
*
*

Fig. 18

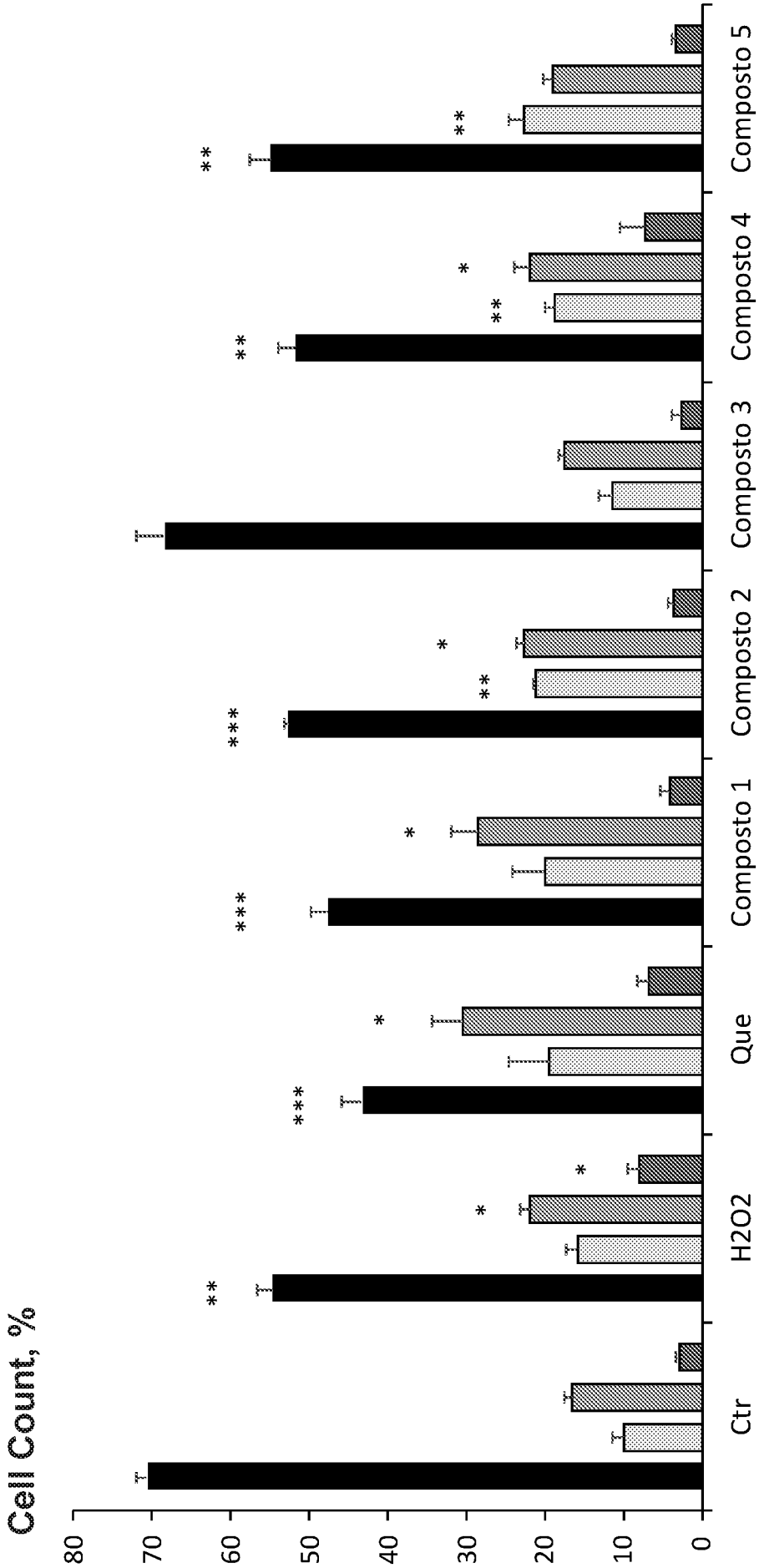

Cell Count, %
80
70
60
50
40
30
20
10
0
Ctr
H2O2
Que
Composto 1
Composto 2
Composto 3
Composto 4
Composto 5

Fig. 19

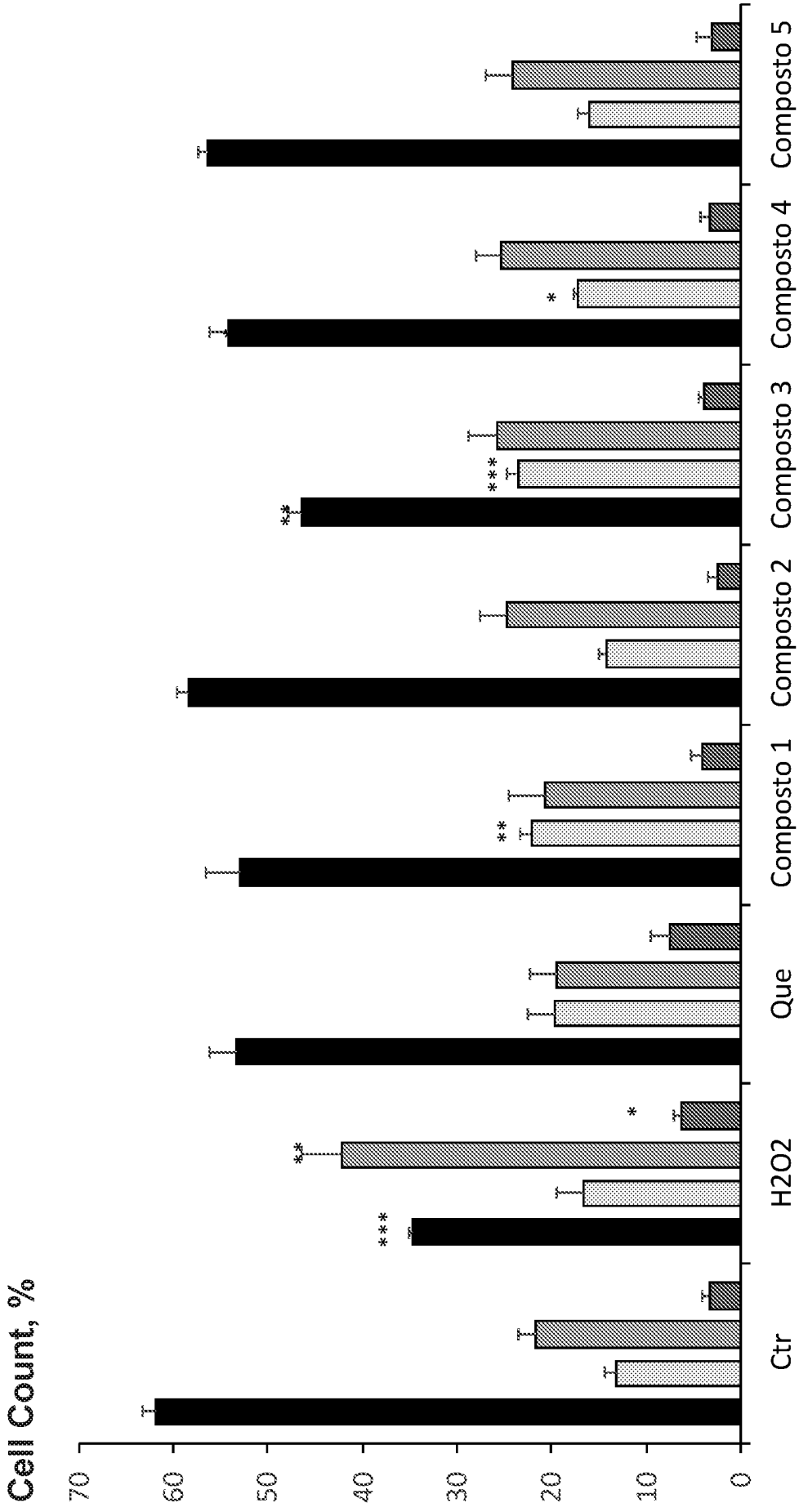

Cell Count, %
70
60
50
40
30
20
10
0
Ctr
H2O2
Que
Composto 1
Composto 2
Composto 3
Composto 4
Composto 5
*
**
***
**
***
*
**
***

Fig. 20

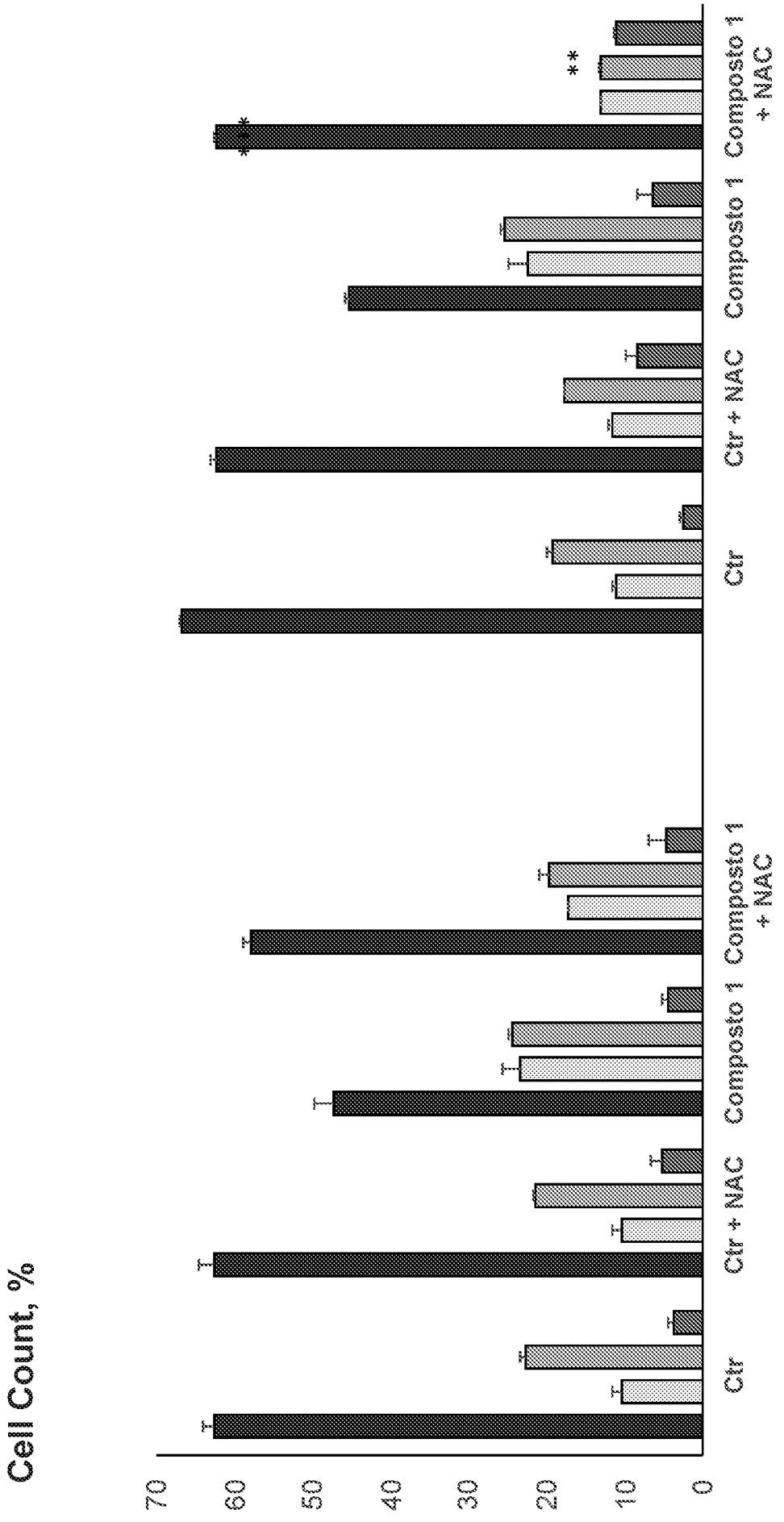

Cell Count, %
70
60
50
40
30
20
10
0
Ctr
Ctr + NAC
Composto 1
Composto 1 + NAC
Ctr
Ctr + NAC
Composto 1
Composto 1 + NAC
**
***

Fig. 21

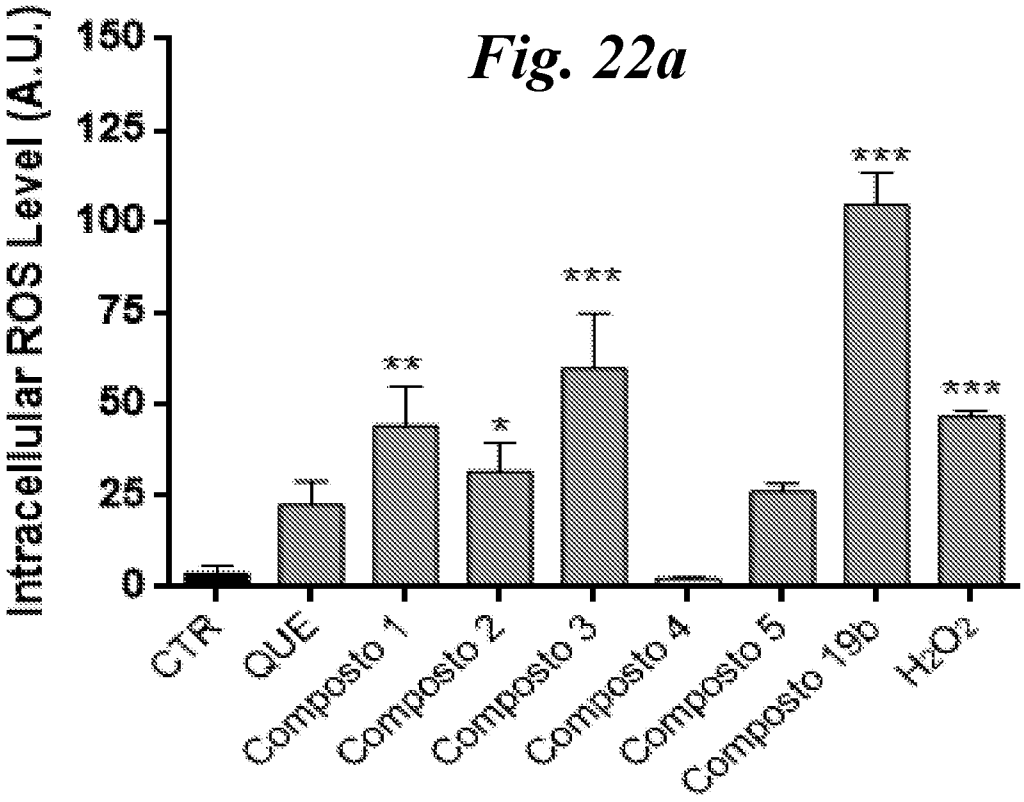


Fig. 22a

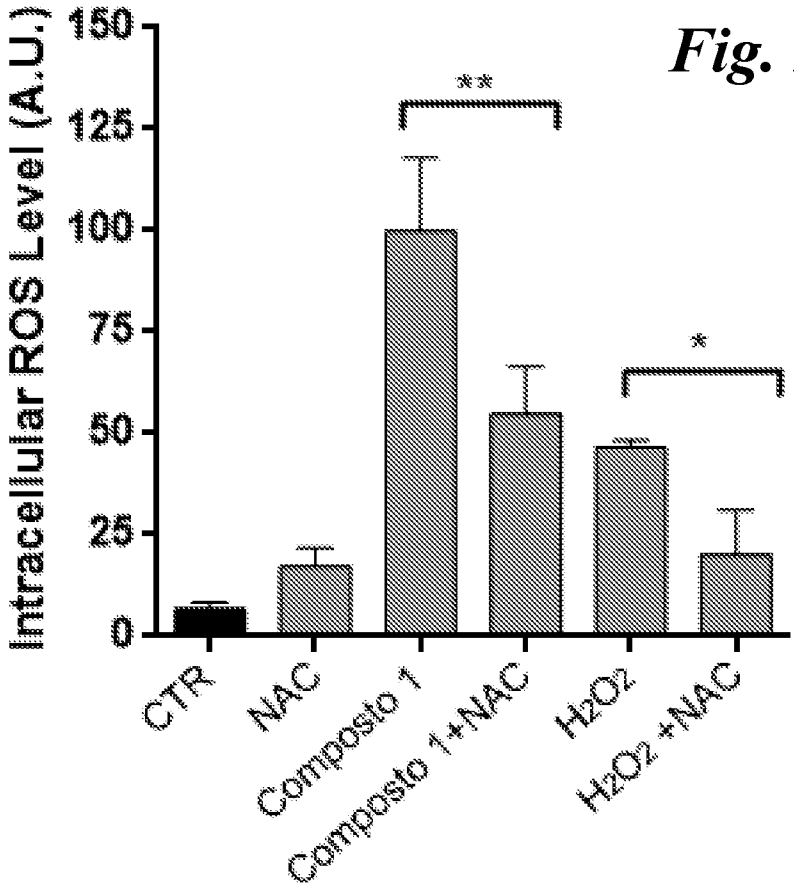


Fig. 22b

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/054981

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/352 A61K47/54 A61K47/55 A61P35/00 C07D311/00
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)
A61K A61P C07D

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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHI ZHI-HAO ET AL: "Synthesis, biological evaluation and SAR analysis of O-alkylated analogs of quercetin for anticancer", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 24, no. 18, 10 August 2014 (2014-08-10), pages 4424-4427, XP029053337, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2014.08.006 page 4424, column 1, paragraph 1 compounds 2a-2d compounds 3a-3d table 1 ----- -/--	1-17,21, 22

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 October 2018	30/10/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Monami, Amélie

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/054981

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	JIXIA LI ET AL: "Quercetin-3-methyl ether inhibits lapatinib-sensitive and -resistant breast cancer cell growth by inducing G 2 /M arrest and apoptosis", MOLECULAR CARCINOGENESIS, vol. 52, no. 2, 1 February 2013 (2013-02-01), pages 134-143, XP055468191, US ISSN: 0899-1987, DOI: 10.1002/mc.21839 abstract page 141, column 1, paragraph 2 - page 142, column 1, paragraph 2	1-4, 6-17,22
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X	Joon Yeol Lee ET AL: "Design and synthesis of novel antidiabetic agents", Archives of pharmacal research, 1 February 2005 (2005-02-01), pages 142-150, XP055516522, Korea (South) DOI: 10.1007/BF02977705 Retrieved from the Internet: URL:https://link.springer.com/content/pdf/10.1007/BF02977705.pdf [retrieved on 2018-10-17] abstract compounds 11, 14 table 1 -----	1,3-5, 15-21
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