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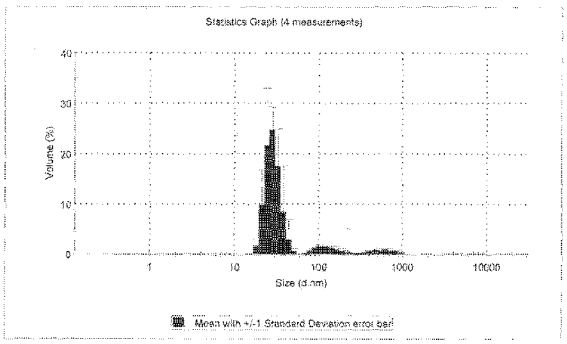


fig. 1

(57) **Abstract**: The present invention relates to branched polyethyleneglycol (PEG) derivatives consisting of a molecule with a quaternary carbon connected to three PEG chains, wherein all three PEG chains are of equal length and each comprises 1 -30 $-OCH_2CH_2-$ units, and one group with at least one carbon atom, wherein said at least one carbon atom is attached to the quaternary carbon. Also compositions containing such derivatives and use of such derivatives are disclosed.

WO 2011/123031 A1

BRANCHED, COMPACT POLYETHYLENEGLYCOL DERIVATIVES

Filed of the invention

The present invention relates to branched polyethyleneglycol (PEG) derivatives with advantages over currently available PEG derivatives. They are especially applicable for conjugation with nanoparticles, proteins, peptides, pharmaceutically active small molecules, liposomes, homogenous catalysts and bio-inert surfaces.

Background

Bio-inert polar polymers, and in particular polyethyleneglycol ($HO(CH_2CH_2O)H$, PEG, also called polyethyleneoxide; PEO), have found extensive technical use, notably in the area of pharmaceuticals and medical devices. Lately covalent grafting with PEG have been used to modify proteins, peptides, oligonucleotides, antibody fragments, small molecule drugs, catalysts, surfaces and particles. These modified conjugates often obtain superior properties such as decreased immunogenicity or antigenicity, improved pharmacokinetic and pharmadynamic properties, enhanced solubility in aqueous media, increased stability and reduced clearance rate from the body.

Several PEG-derivatives of macromolecules have now been approved for pharmaceutical use. The first one was PEG-adenosine deaminase for treatment of adenosine deaminase deficiency (ADA deficiency).

Organic catalysts have also been covalently modified with PEG-derivatives to allow reactions in water (Hong and Grubbs, J. Am. Chem. Soc. 2006, 128, 3508).

Traditionally, polydisperse linear PEG-derivatives have been used for PEG grafting but recently monodisperse PEG derivatives or PEG derivatives of defined mass have been applied to obtain homogeneous products, simplifying characterization of the PEG-derivatives, thus facilitating the regulatory process.

Branched PEG, characterized by two or more PEG chains linked to a common center, has been developed as an alternative to the more common

linear PEG derivatives. Monfardini *et al*. (Bioconj. Chem. 1995, 6, 62-69) reported that surface modification of proteins using branched PEG derivatives resulted in increased biocompatibility and better stability. These PEGs allows for a better masking and protection of the connected surface/molecule. In addition, the modification of protein using branched PEG provides a more efficient usage of amino acids/amino acid side chains available for chemical linking, thus more PEG polymer per modification. Fewer chemical modifications of the protein increase the probability of retaining the native structure of the biomolecule and hence the biological activity.

The strategies for attaching PEG to macromolecules and small organic molecules, respectively, differ in terms of size and number of PEG molecules that can be attached. Large macromolecules are commonly modified using PEG polymer of molecular weights ranging from 5 kDa to 90 kDa to obtain reduced clearance from the blood, better specificity while preserving biological activity. However, large PEG molecules are not suitable for modifications of small organic molecules. Conjugates of pharmaceutically active small molecules and large PEG polymers prevents, in most cases, the conjugate to interact with receptors or binding pockets due to sterical hindrance or even alter the ability of the molecule to diffuse through membranes to reach their target. Conjugates with large PEG moieties have low diffusion rates, just like any large molecules. Therefore, PEG derivatives with molecular weights of less than 2 kDa are generally used for modification of small organic molecules. (Ouchi, T. in Poly(ethylene glycol): Chemistry and biological applications, Harris and Zalipsky Eds, Chapter 19). In general, macromolecules tolerate attachment of PEG to several positions using smaller PEG although it is normally beneficial to have as few as possible. On the other hand, small organic compounds have few points for the attachment of PEG and it is much more difficult to obtain conjugates that retain the unmodified molecule's bioactive properties.

In WO 95/025763 is disclosed branched PEG-like structures (as part of a larger structure) which have a superficial likeness to the structures present

invention but lack the essential feature of being discrete and useful for the applications disclosed here.

In WO 2007/025763 is disclosed branched PEG derivatives of defined character. However, their structure differs from the present invention in the following non-beneficial ways; They utilize 2,2,2-tris(hydroxymethyl)methyl-amine as the core structure so the detailed structures are more complex and thus more expensive to produce. The core is based on amides and hence more sensitive to hydrolysis, and the individual branched PEG derivatives contain thioethers, a functionality known for being notoriously sensitive to oxidization, which can be a further source of heterogeneity of the product. The core structure is not compact and thus not useful for some of the applications disclosed here.

Definitions of terms

The term “nanoparticle” is used to describe a particle of any shape with a longest measure from 1-100 nm.

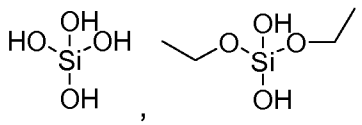
“Bio-inert” refers to a material that is bio-compatible, i.e. harmless to a living organism and at the same time stable to degradation *in-vivo*.

“Monolayer” refers to a one molecule thick layer.

“Oriented” in the context of coatings refers to a layer of coating molecules where all the heads and tails (as arbitrarily defined from case to case but as intended in the present invention we consistently refer to the silane, where present, as the head) of the coating molecules are oriented in the same way in relation to the particle core surface.

“Activated silane” refers to a silane of the following type $R_nSi(X)_{4-n}$, where X is an alkoxy group, aryloxy group, a halogen, a dialkylamino group, a nitrogen containing heterocycle or an acyloxy group and R is an organic group.

“Oxysilane” refers to any organic compounds with one or more oxygen atoms attached to the silicon atom. Non-limiting examples thereof are:



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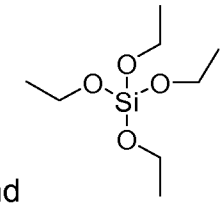
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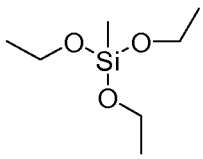
"Organosilane" refers to organic compounds containing one or more carbon silicon bonds.

"Organic residue" refers to organic compounds covalently bond to a molecular entity.

"Organo-oxysilane" refers to organic compounds containing one or more carbon atoms and one or more oxygen atoms attached to the silicon atom. Non-limiting examples thereof are: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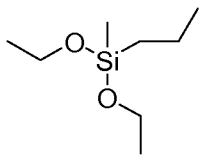
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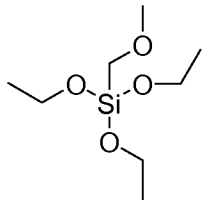
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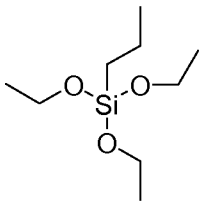
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"Hydrocarbon" or "hydrocarbon chain" is an organic residue consisting of hydrogen and carbon. As used in the present invention a hydrocarbon may, when indicated, comprise heteroatoms selected from O, S and N. This means that one or more of the carbon atoms have been replaced by a heteroatom selected from O, S or N. The hydrocarbon may be fully saturated or it may comprise one or more unsaturations. Unless otherwise specified, the hydrocarbon may contain any number of carbon atoms between 1 and 50. The hydrocarbon group of the compounds may then be designated as "C_{1-8} hydrocarbon" or similar designations. Typical hydrocarbon groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, phenyl, benzyl.

"Alkyl" refers to a straight or branched hydrocarbon chain fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may

have 1 to 8 carbon atoms. The alkyl group of the compounds may be designated as "C_{1-8} alkyl" or similar designations. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, and the like.

Whenever it appears herein, a numerical range such as "from 1 to 8" or "1-8" refer to each integer in the given range; *e.g.*, "from 1 to 8 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 8 carbon atoms.

As used herein, "alkoxy" refers to the formula –OR wherein R is a C_{1-8} alkyl, e.g. methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, amyloxy, iso-amyloxy and the like. An alkoxy may be optionally substituted.

As used herein, "aryloxy" refers to RO- in which R is an aryl wherein, "aryl" refers to a carbocyclic (all carbon) ring or two or more fused rings (rings that share two adjacent carbon atoms) that have a fully delocalized pi-electron system. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be optionally substituted, e.g., phenoxy, naphthalenyloxy, azulenyloxy, anthracenyloxy, naphthalenylthio, phenylthio and the like. An aryloxy may be optionally substituted

As used herein, "acyl" refers to a carbonyl group, i.e. -C(=O)-.

As used herein, "acyloxy" refers to an oxygen atom connected via a carbonyl group, i.e. -C(=O)-O-.

As used herein, "heterocycle" refers to a stable 3- to 18 membered ring which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. The heterocycle may be monocyclic, bicyclic or tricyclic.

"Strong base" refers in the current context to bases that are stronger than hydroxide and not compatible with aqueous environments.

"Conjugate" refers to a molecular entity that is a fluorescence marker, dye, spin-label, radioactive marker, ligand to a biological receptor, chelate, enzyme inhibitor, enzyme substrate, antibody or anti-body related structure.

See e.g. “Bioconjugate Techniques”, Greg T. Hermanson second edition, Elsevier 2008, ISBN 978-0-12-370501-3 for background on the subject.

“Handle for conjugation” or “attachment point” refers to a bifunctional molecule that can bind to, or be incorporated in, the silane coating but leaving one reactive group that can be linked to a conjugate, as defined above. A typical, but not exclusive, example would be $(EtO)_3SiCH_2CH_2CH_2NH_2$.

“m-PEG” refers to structures CH_3-$(OCH_2CH_2)_n$-OH where n depends on the circumstances.

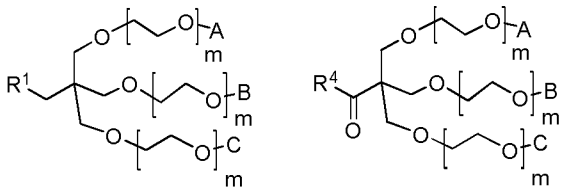
“Aprotic solvent” refers to solvents which have no protons that can be removed or rapidly exchanged in an aqueous environment. Typical, but not limiting, examples of such solvents are tetrahydrofuran (THF), diethyl ether, glyme, diglyme, dimethyl formamide (DMF), dimethylsulfoxide, or N-methyl pyrrolidinone (NMP).

DCM is an acronym for dichloromethane.

Detailed description of the invention

A first aspect of the present invention is a branched polyethyleneglycol (PEG) derivative comprising three PEG chains attached to a common quaternary carbon atom. It may be preferred that all three PEG chains are of equal length and each comprises 1-30 $-OCH_2CH_2-$ units The fourth group attached to said quaternary carbon atom can be any of a large number of different organic groups. This forth group shall contain a carbon atom, which is attached to the quaternary carbon atom. A non-limiting list of examples of the fourth group attached to the quaternary carbon atom is given in the list describing group R^1 below.

The branched polyethyleneglycol (PEG) derivative according to the invention may have formula **I** or formula **II:**



I **II**

wherein:

m is selected from 1-30;

R^1 is selected from the list given in Table 1 below;

A, B and C are independently selected from -C_1-C_8 hydrocarbon, -$(CH_2)_2N_3$, -$(CH_2)_2NR^5_2$, CH_2COOR^4;

R^2 is selected from C_1-C_8 hydrocarbon;

R^3 is selected from C_{1-8} alkoxy group, aryloxy group, a halogen, a di-C_{1-8}-alkylamino group, a nitrogen containing heterocycle or an acyloxy group;

R^4 is selected from H, OH, OR^2, NHR^2, $N(R^2)_2$, halogen, N-hydroxysuccinimidyl (NHS ester) and perfluorophenolate, wherein R^2 is as above;

R^5 is independently selected from -H, -C_1-C_8 hydrocarbon, -$(C=O)NH_2$, -$(C=O)$-OCH_3, -$(C=O)OCH_2CH_3$.

Table 1: Different options for R^1

Variant of formula I	R^1
Ia	-OH
Ib	-OSO_2CH3
Ic	-OSO_2PhCH3
Id	-$OCH_2CH=CH_2$
Ie	-Obenzyl
If	-halogen
Ig	-NH_2
Ih	-NHR^2
Ii	-$N(R^2)_2$
Ij	-$NHCO_2R^2$
Ik	-$NHCONHR^2$
Il	-$NHCON(R^2)_2$
Im	-NCO
In	-NCS

Io	-NHCO$(CH_2)_4$ CH(SH)CH_2CH_2SH
Ip	-NHCOCH_2SH
Iq	-SH
Ir	-SR^2
Is	-SO_3H
It	-SO_2Cl
Iu	-S=OR^2
Iv	-SO_2R^2
Ix	-SONHR^2
Iy	- O$(CH_2)_3SH$
Iz	-OCH_2CH(SH)CH_2SH
Iaa	-OCO$(CH_2)_4$ CH(SH)CH_2CH_2SH
Iab	-PO_3H_2
Iac	-PO3$(R^2)_2$
Iad	-OCH_2COOH
Iae	-OCH_2COR^4
Iaf	-O$(CH_2)_2NH_2$
Iag	- O$(CH_2)_2$NHR^2
Iah	- O$(CH_2)_2$N$(R^2)_2$
Iai	- O$(CH_2)_2$NHCO_2R^2
Iaj	- O$(CH_2)_2$NHCONHR^2
Iak	- O$(CH_2)_2$NHCON$(R^2)_2$
Ial	- O$(CH_2)_2$NCO
Iam	- O$(CH_2)_3$Si$(R^3)_3$
Ian	- O$(CH_2)_2$NHCO$(CH_2)_4$ CH(SH)CH_2CH_2SH

In some embodiments R^1 in formula **I** is O$(CH_2)_3$Si$(R^3)_3$, and R^3 may then be selected from the group consisting of C_{1-8} alkoxy, acyloxy, dialkylamino and aryloxy.

In some embodiments R^1 in formula **I** is CH_2NH_2 or OCH_2COOH.

In some embodiments m is 3-20.

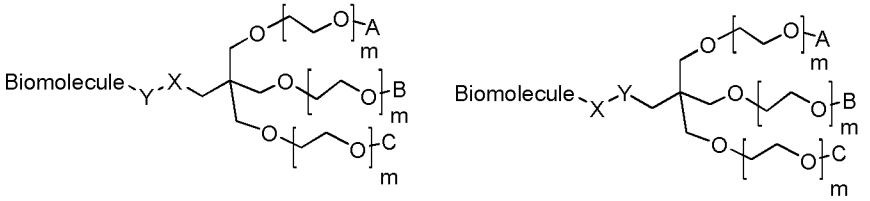
In some embodiments m is 3-10.

In some embodiments m is 3-5.

In some embodiments A, B and C are all equal.

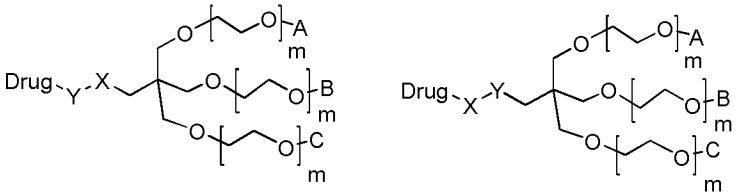
In some embodiments A, B and C are all $-CH_3$.

Alternatively, the branched polyethyleneglycol (PEG) derivative according to the invention may have formula:



where "Biomolecule" denotes a peptide or an antibody fragment or a ribonucleic acid or a carbohydrate and X is a residue of the functionality used for coupling and Y is a spacer group with structure $–(OCH2CH2)_nO-$ where n is selected from 1-50 and m is selected from 2-30 and A, B and C are independently selected from $-C_1-C_8$ hydrocarbon, $-(CH_2)_2N_3$, $-(CH_2)_2NR^5_2$ and $-CH_2COOR^4$; and; R^2 is selected from C_1-C_8 hydrocarbon; and R^3 is selected from C_{1-8} alkoxy group, aryloxy group, a halogen, a di-C_{1-8}-alkylamino group, a nitrogen containing heterocycle or an acyloxy group and; R^4 is selected from H, OH, OR^2, NHR^2, $N(R^2)_2$, halogen, N-hydroxysuccinimidyl (NHS ester) and perfluorophenolate; and R^5 is independently selected from -H, $-C_1-C_8$ hydrocarbon, $-(C=O)NH_2$, $-(C=O)-OCH_3$, or $-OCH_2CH_3$.

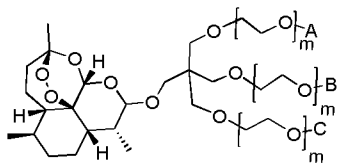
Alternatively, the compound according to the invention may have one of the two formulas:



wherein "Drug" denotes a pharmaceutically active drug of molecular weight less than 1000 g/mol and X is a residue of the functionality used for coupling and Y is a spacer group with structure $–(OCH2CH2)_nO-$ where n is selected from 1-50 and m is selected from 2-30 and A, B and C are independently selected from $-C_1-C_8$ hydrocarbon, $-(CH_2)_2N_3$, $-(CH_2)_2NR^5_2$ and $-CH_2COOR^4$;

and; R^2 is selected from C_1-C_8 hydrocarbon; and R^3 is selected from C_{1-8} alkoxy group, aryloxy group, a halogen, a di-C_{1-8}-alkylamino group, a nitrogen containing heterocycle or an acyloxy group and; R^4 is selected from H, OH, OR^2, NHR^2, $N(R^2)_2$, halogen, N-hydroxysuccinimidyl (NHS ester) and perfluorophenolate; and R^5 is independently selected from -H, -C_1-C_8 hydrocarbon, -$(C=O)NH_2$, or -$(C=O)$-OCH_3.

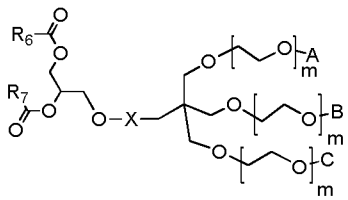
Alternatively, the compound according to the invention may have formula **Va**



Va

wherein m=1-30 and A, B, and C independently are selected from the group consisting of H and methyl.

Alternatively, the compound according to the invention may have formula **IXa**



IXa

wherein:

R^6 and R^7 are independently selected from the group consisting of C_8-C_{25} hydrocarbons;

m is selected from 2-30;

A, B and C are independently selected from the group consisting of -C_1-C_8 hydrocarbon, $-(CH_2)_2N_3$, $-(CH_2)_2NR^5{}_2$ and $-CH_2COOR^4$;

R^2 is selected from C_1-C_8 hydrocarbon;

R^3 is selected from C_{1-8} alkoxy group, aryloxy group, a halogen, a di-C_{1-8}-alkylamino group, a nitrogen containing heterocycle or an acyloxy group;

R^4 is selected from H, OH, OR^2, NHR^2, $N(R^2)_2$, halogen, N-hydroxysuccinimidyl (NHS ester) and perfluorophenolate;

R^5 is independently selected from -H, -C_1-C_8 hydrocarbon, -(C=O)NH_2, -(C=O)-OCH_3, or -OCH_2CH_3;

X is a bond, a chain or a ring structure with 0-10 linear atoms chosen independently from C, O, N, P and S to form chemical compounds according to normal valency rules; and

Crucial to some embodiments of the invention is that the composition is essentially free from molecules where any of the chain lengths m have a different value than the desired one, i.e. the product is of defined molecular weight or, synonymously, monodisperse; so that the purity of the product is more than 50%. Suitable purities are for example more than 80% , more than 90%, more than 95%, more than 99%. In one embodiment of the present invention the purity is above 95%.

This type of PEG derivatives are readily produced from inexpensive starting materials using a concise synthetic strategy outlined in scheme 3. Compounds according to formula **I** also has the advantage of being economically viable. In particular are the starting materials for **I** with m= 3 or 4 favourable. The following calculation shows the economical advantage of the present invention: If R_1 in structure **I** is -OH and m= 4, the molecular weight of the product is 707 g/mol. The cost of the starting materials are 20 $/g product when bought on a small scale. Commercially available linear m-PEGs with a similar molecular weight are isolated from PEG mixtures using expensive and time consuming chromatography. A typical example is m-PEG with 11 repeating ethylene glycol units, which is available at a cost of $ 240/g (Polypure, Norway). A branched amide based monodisperse PEG analog is available from Quanta Biodesign at $1300/g.

The present invention thus enables formation of PEG derivatives based on low cost starting materials.

PEG alcohols of defined molecular weight are commercially available up to lengths of about 30 monomer units so the present invention relates to

generic structures **I** wherein m is 1-30, or for example 2-20, 3-12; 3-6 and 3-4. In one embodiment m is 3-4.

Depending on the origin of the PEG alcohol used in the synthesis of the branched PEG derivatives of the present invention, the final product will have a spectrum of minor impurities. Some of those impurities may not have m in general structure **I** or **II** equal and are thus not a desired material but considered as impurities. In general, it is advisable to use pure starting materials. Suitable purities of the starting materials are higher than 70% or higher than 90% or higher than 95% or higher than 99%. There may also be residues from incomplete reaction of the intermediates which can be minimized on a case by case basis by optimizing reaction time, reaction temperature, amount of solvent, identity of the solvent, or identity of the base.

A second aspect of the present invention relates to the process of producing molecules according to the first aspect. Products **I** or **II** are possible to produce by several routes obvious to the one skilled in the art but the process that is described here as a second aspect of this invention has the advantage of using a cheap, commercially available trihaloalcohol as a key intermediate and source of the quaternary carbon as outlined in scheme 3.

The process comprises the steps of:

a. Contacting the key starting material 3-halo-2,2-bis(halomethyl)propanol, preferably in the form of 3-bromo-2,2-bis(bromomethyl)propanol, with an allylation reagent such as, allyl chloride, allyl mesylate, or allyl tosylate or, preferably, allyl bromide, optionally in a solvent inert to the reaction conditions, in the presence of a strong base, for example sodium hydride. The intermediate may then be isolated by any standard technique described in organic chemistry textbooks (Advanced practical organic chemistry, Leonard, Lygo and Procter 1998, 2nd ed, Stanley Thornes Publishers, Cheltenham). It is also conceivable to proceed with the next step without isolating the intermediate 3-(3-bromo-2,2-bis(bromomethyl)propoxy)prop-1-ene.

b. Contacting the intermediate product with a PEG-oligomer of structure A-$(OCH_2CH_2)_mO$- ; or base and A-$(OCH_2CH_2)_mOH$; where A is selected from -C_1-C_8 hydrocarbon, -$(CH_2)_2N_3$, -$(CH_2)_2NR^5{}_2$ and -CH_2COOR^4; and; R^2 is selected from C_1-C_8 hydrocarbon; and R^3 is selected from C_{1-8} alkoxy group, aryloxy group, a halogen, a di-C_{1-8}-alkylamino group, a nitrogen containing heterocycle or an acyloxy group and; R^4 is selected from H, OH, OR^2, NHR^2, $N(R^2)_2$, halogen, N-hydroxysuccinimidyl (NHS ester) and perfluorophenolate; and R^5 is independently selected from -H, -C_1-C_8 hydrocarbon, -$(C=O)NH_2$, -$(C=O)$-OCH_3, -OCH_2CH_3 and m is selected from 1-30, with a defined molecular weight, optionally in a solvent inert to the reaction conditions, in the presence of a strong base, such as sodium hydride. The temperature in this step may advantageously be above room temperature such as between 30 and 150 °C or between 70 and 120 °C or preferably between 90 and 110 °C. Optionally the resulting branched PEG intermediate may be isolated by any standard technique described in organic chemistry textbooks (Advanced practical organic chemistry, Leonard, Lygo and Procter 1998, 2nd ed, Stanley Thornes Publishers, Cheltenham).

c. The intermediate of step b is then transformed into the actual derivatizing agent by any of the many methods obvious to one skilled in the art and some but not limiting examples are discussed below and further elaborated in examples 3-6.

In one embodiment an extractive procedure or vacuum distillation was found to be favourable to use in a).

In one embodiment an extractive procedure followed by a simple chromatography was found to be favourable to use in b).

If the allyl group of **Id** is removed by a standard protective group manipulation, e.g. DMSO/ KOt-Bu (Potassium tert-butoxide), followed by HCl (hydrochloric acid) (example 4) the ensuing alcohol **Ia** can be elaborated into

several other functional groups. Some, non limiting, examples are given here: mild oxidation of the hydroxyl group of **Ia** with e.g. pyridinium chloro chromate or Dess-Martin periodinane gives the aldehyde **II** (R^4 = H) whereas stronger oxidizing conditions like fuming nitric acid or potassium permanganate give the corresponding carboxylic acid **II** (R^4 = OH). The carboxylic acid can in turn be activated and derivatized in a multitude of ways. If the aldehyde is subjected to reductive amination conditions i.e. $NaCNBH_3/NH_3$ the amine **Ig** is obtained. If the alcohol instead it treated with a halogenation reagent such as $SOCl_2$ or PBr_3, the halogencompound **Iu** is obtained. This can in turn be used to produce the thiol **Iq**, for example, by reaction with thiourea followed by hydrolysis in NaOH/EtOH. The thiol can in turn be alkylated to **Ir** or oxidized to the sulfonic acid **Is**. **It** can then be oxidized to the sulfoxide **Iu** or the sulfone **Iv**. Alternatively can **Iu** be converted to the phosphonate **Iac** by reaction with dimethyl or diethyl phosphite. This can be hydrolyzed to the corresponding phosphonic acid **Iab** by treatment with trimethyl silylbromide.

To obtain **Iam** with Z= $(R^3)_3Si(CH_2)_3O$-, where R^3 is as defined in table 1,from the intermediate **Id**, the method of hydrosilylation is preferred. This involves adding a trialkoxy silane across the double bond in the presence of a catalyst. Preferred are catalysts based on platinum and, in particular, Karstedt's catalyst has been found to be effective.

Directly accessible from **Id** is the aldehyde **Iae** (R^4 = H) by means of two alternative procedures. On a small scale ozonization followed by a reductive work up can be contemplated. On a larger scale, reaction with osmium tetroxide to give the vicinal dialcohol followed by cleavage with periodic acid, is preferred.

Further advantages of the above process are that it is short and that the branched PEG-derivative is free from labile bonds. The commercially available branched PEG derivatives are based on amides and hence more sensitive to hydrolysis, which can be a further source of heterogeneity of the product and hence lead to regulatory complications during development for clinical use.

In a third aspect of the present invention, a composition comprising the general structures **I** or **II** covalently linked to a nanosized material, such as a nanoparticle, to enhance its properties with regard to solubility, viscosity, stability, biological compatibility, or pharmacokinetics or pharmacodynamics, is contemplated. For the purpose of derivatizing nanoparticles designed for renal clearance, it is imperative to use coatings that give the best compromise between, on one hand, the best protection and stabilization of the core and, on the other hand, the smallest size, or the material will not be filtered through the kidneys, and the branched PEG described in the present invention is eminently suited for this purpose. In particular would this be important in the context of nanoparticles containing materials foreign to the body, like transition metals, heavy metals, or lanthanides. These materials are of interest as diagnostics or therapeutics or both of the previous in combination. In particular, it is of interest to use heavy elements like gold, tantalum or tungsten incorporated in nanoparticles as contrast agents for CT (computed tomography) and they would benefit from being coated with a monolayer of the materials the general structures **I** or **II**. The efficacy of those materials is tightly correlated with the volume fraction of the heavy element in the nanoparticle and a coating with a monolayer of **I** or **II** will give materials with very good properties since the protective layer will be very thin while still achieving stabilization.

Linear PEG-derivatives with terminal alkylsilanoxy groups are suitable for surface modification of nanoparticles with a core of metal oxide. These siloxanes connect with hydroxyl groups present on the surface with the PEG tails oriented into the surrounding solution. Although, improved solubility and stability properties, there are still gaps in the PEG-coating exposing the core metal oxide due to the curvature of the particle surface and the folding of PEG-tails. Therefore an ideal coating molecule should contain one surface reactive group e.g. siloxane and two or more tails e.g. PEG producing a cone shaped structure. This type of branched PEG-siloxanes would lead to a denser PEG layer exposing less of the metal oxide core. In line with this reasoning, although not directly dealing with nanoparticles, Monfardini *et al.* (Bioconj. Chem. 1995, 6, 62-9) have shown that surface modification of proteins

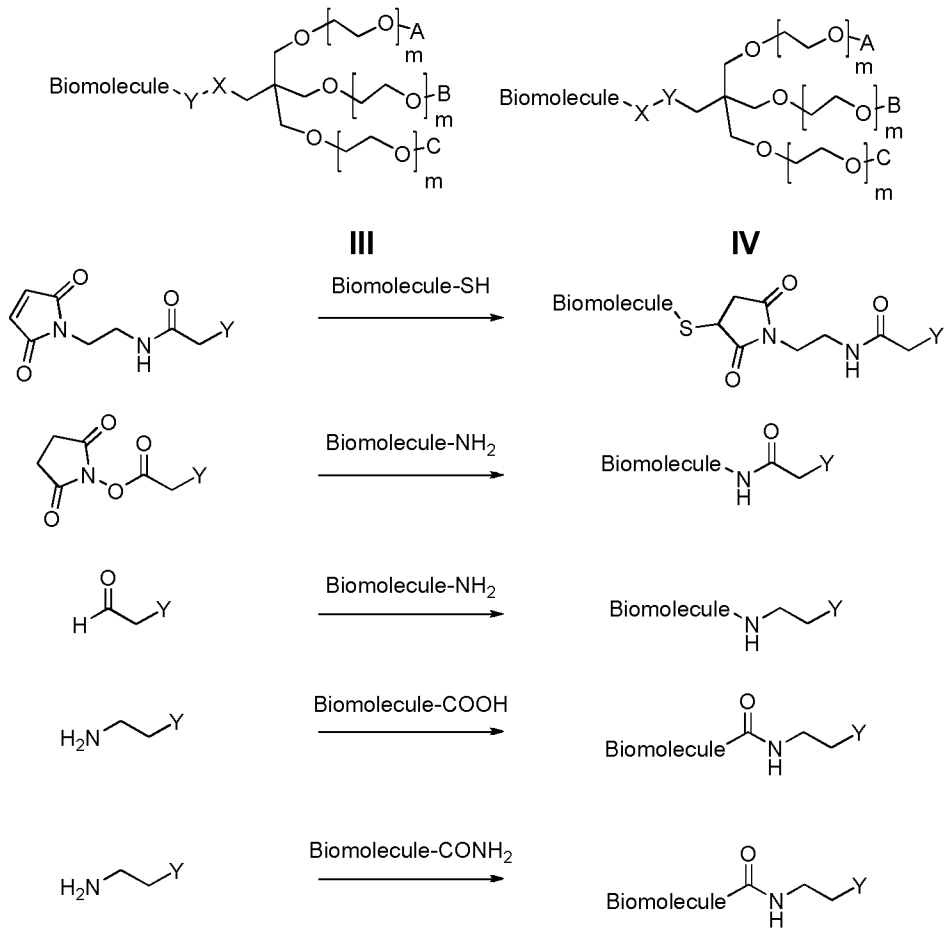
using branched PEG derivatives results in increase biocompability and better stability.

In particular would **Iam** with R^1= $(R^3)_3Si(CH_2)_3O$- where R^3 is as defined in table 1, **Iae** (R^4 = OH) with R^1= HO_2CCH_2O-, **Is** with R^1= $HO_3S(CH_2)_3O$-, **Iab** with R^1= $(HO)_2PO(CH_2)_3O$-, **Iq** with R^1= $HS(CH_2)_3O$-, **Iz** with R^1= $HSCH_2(HS)CHCH_2O$- or **Ian** R^1= - $O(CH_2)_2NHCO(CH_2)_4$ $CH(SH)CH_2CH_2SH$ be favourable for the stabilization of such particles. To our knowledge, no branched PEG-siloxanes are commercially available and have not been described in literature.

Luminescent nanoparticles, often called nanodots, based on various semiconductor materials like CdS, ZnS or InS, also need to be eliminated from the body through the kidneys and will benefit from being coated with a monolayer of **I** or **II**. In particular would **I** or **II** with Z selected from $HS(CH_2)_3O$-, $HSCH(HS)(CH_2)_2O$- or R^1 = $-O(CH_2)_2NHCO(CH_2)_4$ $CH(SH)CH_2CH_2SH$ be favourable for the stabilization of such particles.

In a fourth aspect of the present invention the molecules of general structures **I** or **II** are linked to a biomolecule like a protein, a peptide, a ribonucleic acid or a carbohydrate, forming structure **III**, or **IV**, where X is a residue of the group used for coupling and Y is a bond or a linker such as – $NH(C=O)CH_2(OCH_2CH_2)_n$- where n is selected from1-50 and m is selected from 1-30 and A, B, and C are independently selected from -C_1-C_8 hydrocarbon, $-(CH_2)_2N_3$, $-(CH_2)_2NH_2$ and derivatives thereof such as, but not limited to amides, carbamates and ureas, CH_2COOH and derivatives thereof such as, but not limited to, esters, anhydrides, acid chlorides, amides, carbamates.

The purpose of this derivatization of the biomolecule is to enhance its properties with regard to solubility, reconstitutability after lyophilization, viscosity, stability to processing, stability in formulation, stability in-vivo, biological compatibility, immunogenicity, antigenicity, or pharmacokinetics or pharmacodynamics. The viscosity aspect is of considerable importance for products for injection and these more compact PEG derivatives give lower viscosities than the corresponding linear derivatives. In scheme 1 below is shown some methods to derivatize biomolecules in one or more positions.

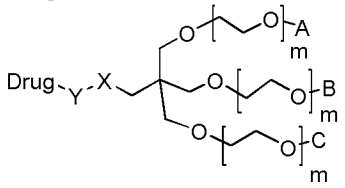


Scheme 1

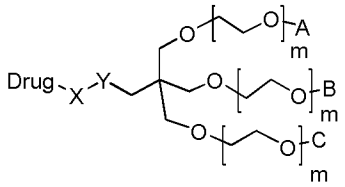
In a fifth aspect of the present invention the generic structures **I** or **II** is linked to a pharmaceutically active small molecule to enhance its properties with regard to solubility, viscosity, stability in formulation, stability in-vivo, biological compatibility, pharmacokinetics, or pharmacodynamics. Of particular importance is the effect to keep a drug out of the CNS since PEG derivatives lowers the ability of a drug to pass the blood brain barrier. The larger molecular size can also give slower clearance from the bloodstream and thus a more even drug concentration over time.

A non-limiting example where this concept has been used with polydisperse materials and where it would be beneficial to use the branched PEG derivative of the present invention can be found in WO2008112288 where opioids are directed to peripheral organs but not to the central nervous system.

For small molecules there is usually only one site of modification available so the branched structures of the present invention confer advantages since three PEG chains are introduced instead of one. The shorter chain length also lessens the likelihood of unwanted interference with the biological effect of the drug.

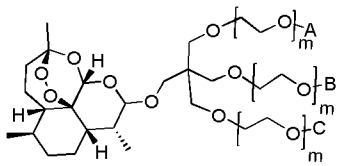


V



VI

where X is a residue of the group used for coupling as outlined for the derivatization in scheme 1 and Y is a bond or a linker such as – $NH(C=O)CH2(OCH_2CH_2)_n$- where n is selected from 1-50. A non-limiting example is structure **Va** where m=1-30 and A, B, and C are H or methyl. In one aspect m=1-10 and A,B, and C are methyl. In one aspect m=1-5 and A,B, and C are methyl.

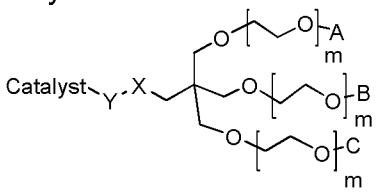


Va

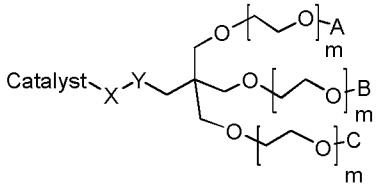
A number of trivial variations of the link betweeen the artemisinin moiety and the PEG can be envisioned. For example, a spacer group may be inserted and/or the link may contain an ester, amide or sulfonamide. It is also possible to substitute the hemiacetal oxygen with a sulfur, carbon or nitrogen atom.

In a sixth aspect of the present invention the molecules of general formula **I** or **II** is linked to a catalytically active molecule to form compounds **VII** or **VIII**, where X is a residue of the group used for coupling as outlined for the derivatization in scheme 1 and Y is a bond or a linker such as – $NH(C=O)CH2(OCH_2CH_2)_n$- where n is selected from 1-50. The catalyst would

normally be a homogenous catalyst, to enhance its solubility in various solvents, particularly in water, improve stability in solid form or in solution, to modify solubility properties to facilitate removal from the product, or to enhance the activity of the catalyst. In particular this is of interest in the context of olefin metathesis catalysts, catalytic hydrogenation catalysts and cross-coupling catalysts.



VII



VIII

In Hong and Grubbs, J. Am. Chem. Soc. 2006, 128, 3508 is described a catalyst made water soluble by the derivatization with a polydisperse linear m-PEG through several synthetic steps and this material would be more tractable and hence cheaper to produce with a monodisperse PEG such as a PEG of general formula **I** or **II** instead.

Most homogenous catalysts have a phosphine as an integral part of the structure and it is often convenient to incorporate the solubilizing group I via the phosphine. There are many possibilities for this but if an aromatic phosphine is desired **I** or **II** can be linked via an ether oxygen. If an aliphatic phosphine is desired it is often possible to use **I** or **II** as a group linked directly to the phosphorous atom, introduced via alkylation.

It is also of importance that the more compact structure of the branched PEG derivatives of the present invention lowers the risk of interference with the catalytic process.

In a seventh aspect of the present invention, the general structures **I** or **II** is linked to a surface of a device. Of interest is a device for medical use and in particular when such a device is in contact with body fluids like a prostetic device or screw, a device through which body fluids are circulated and returned to the body, or an implant or an electrode implant. The surfaces of such devices may benefit from being coated with **I** or **II** to reduce the interaction with proteins of the body with the device. In particular this may reduce the

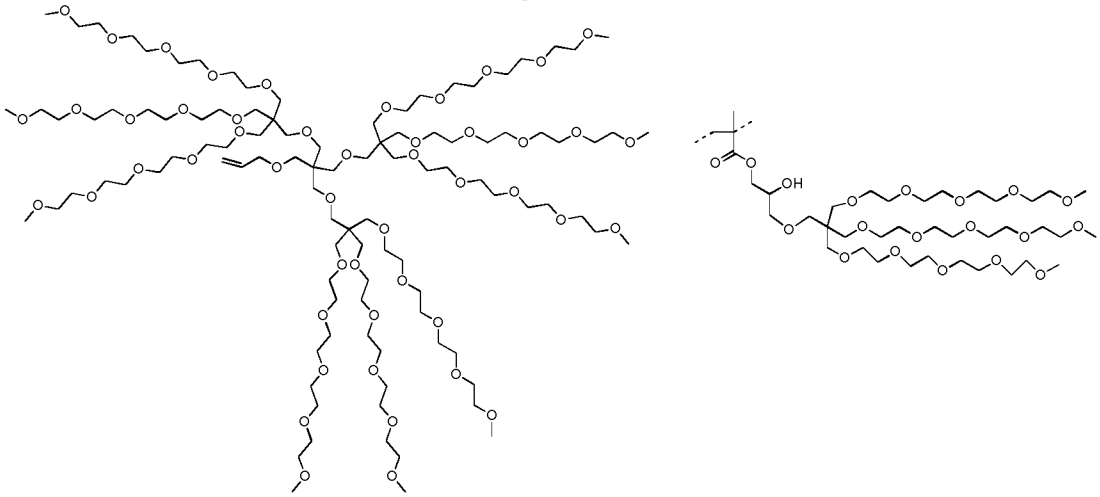
formation of scar tissue around the device, reduce the formation of biofilms on the device, reduce the risk of infections around the device, reduce the risk of inflammation around the device, reduce the risk of corrosion of the device or reduce the risk of an immune response to the device.

The linking of the branched PEG derivative depends on the material of the device and there are a number of standard methods in the field. One is to use an oxy-silane like **Iam** in the presence of aqueous ammonia to attach the PEG derivative to the surface. Another is to use a phopsphonate like **Iab**, where the phosphonate has a high affinity for the surface.

In an eighth aspect of the present invention, the generic structures **I** or **II** is grafted to a polymeric structure (macromolecular framework) , preferably of defined molecular weight or of low polydispersity. This has the advantage of creating materials of high but well defined molecular weight which may be of particular benefit when derivatizing proteins as mentioned above where relatively few attachment points are available. In scheme 2 is shown some representative structures according to this aspect.

In one aspect the fourth and the eighth aspect are combined.

In one aspect the seventh and the eighth aspect are combined.

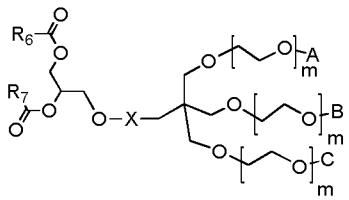


Scheme 2. Examples of branched PEG grafted to macromolecular frame-works.

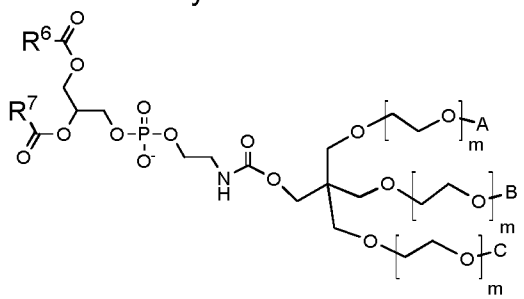
In a ninth aspect of the present invention general structures **I** and **II** are combined with a nonpolar moiety to yield amphiphilic molecules. There is an interest in using liposomes as vehicles for drug delivery and to suppress the immune response towards such products they are often derivatized with PEG on their surface. One aspect of the present invention is to use the molecules of general formula **I** or **II** linked to a lipid as part of the liposome. This has the advantage of giving a more uniform product and thus simplifying the regulatory process for approval. Structure IX with m selected from 1-30, for example 2-20, or, 3-12 or, 3-6 or 3-4.. R^6 and R^7 are independently selected from C_{8-25} hydrocarbon. A. B, and C are as previously defined. Other lamellar structures than liposomes may also ce considered. Non-limiting examples are micells, inverted micells, vesicles and liquid crystals.

In one aspect of the invention m is 3-4.

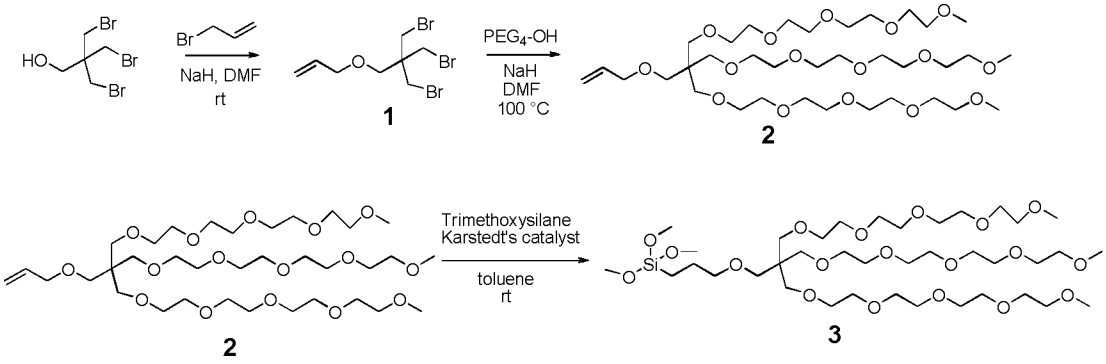
Structure **IXa** is a generic structure of compounds suitable for the formation of liposomes according to the current invention. Structures **IXb** and **10** are non-limiting example suitable for the incorporation into liposomes or other lamellar structures.



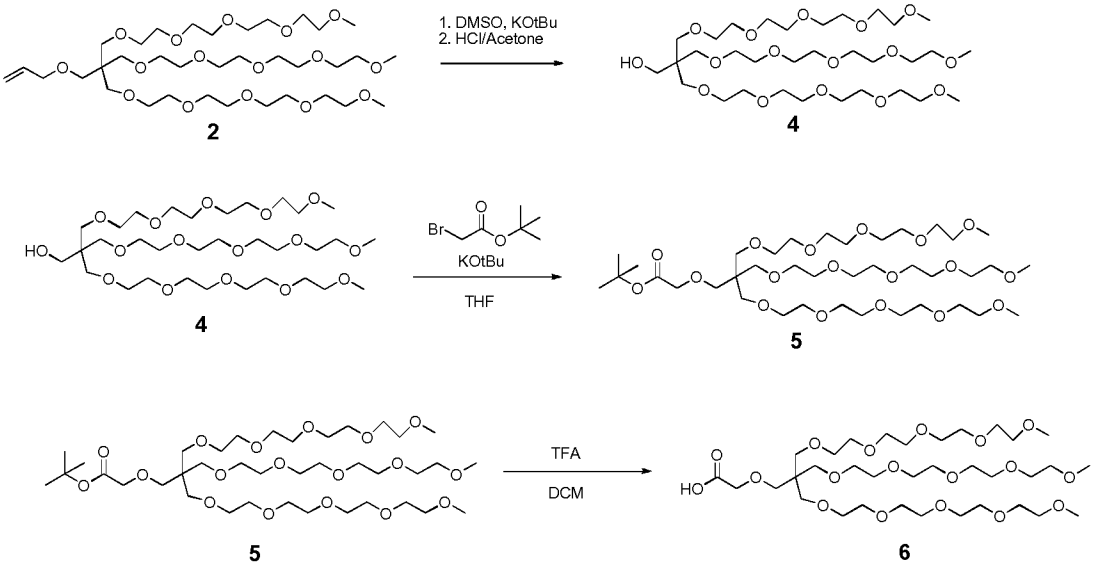
Structure **IXa** , X is a bond, a chain or a ring structure with 0-10 linear atoms chosen independently from C, O, N, P and S to form chemical compounds according to normal valency rules.



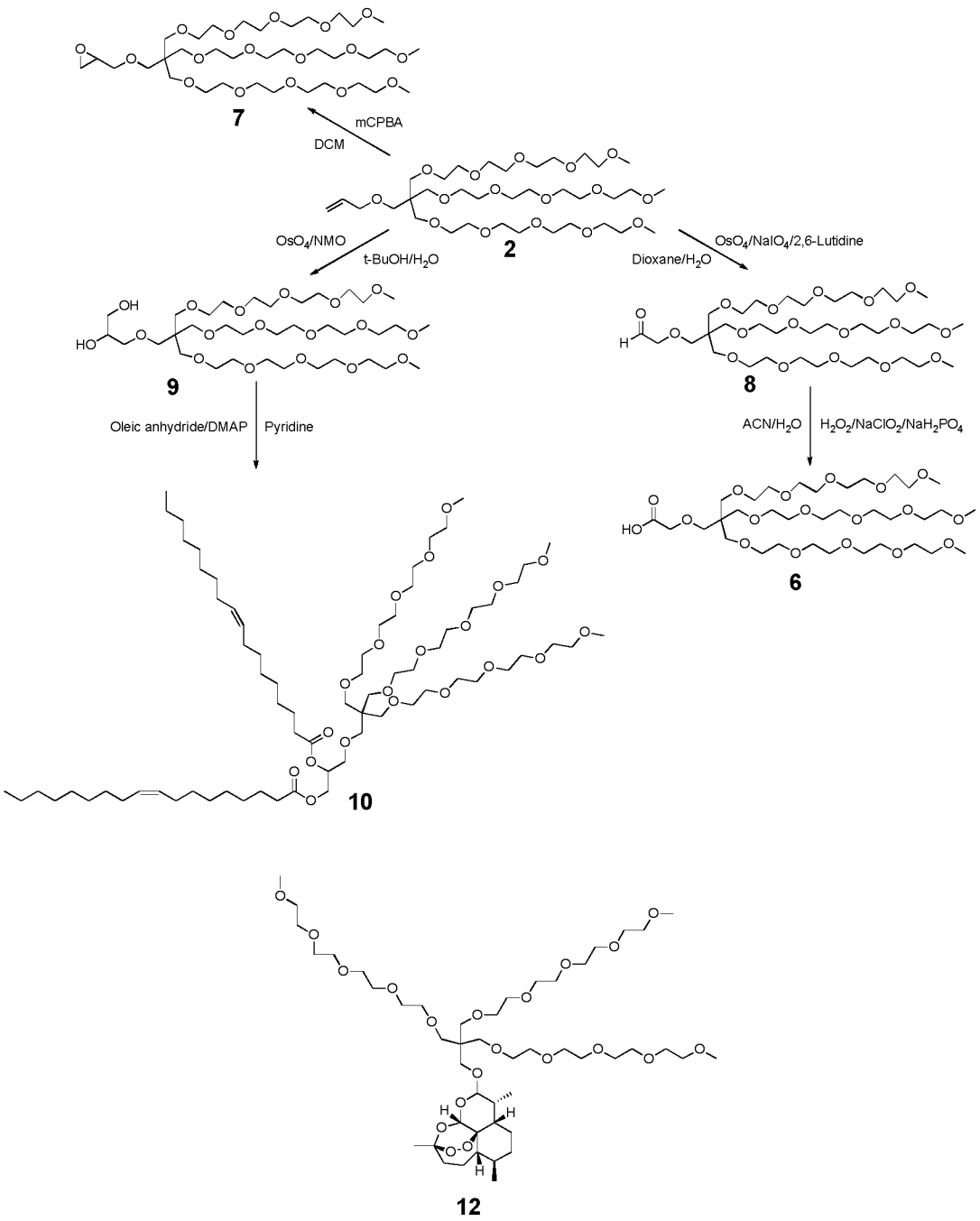
Structure **IXb,** m, A, B, and C are defined as for compounds I and II.



Scheme 3



Scheme 4



Scheme 5

Brief description of the drawing

In the examples below reference is made to the drawing on which Fig. 1 illustrates DLS analysis of material from Example 11.

Examples

Example 1: 3-(3-bromo-2,2-bis(bromomethyl)propoxy)prop-1-ene (1). Sodium hydride (1.68 g, 42 mmol) was portion-wise added to 3-Bromo-2,2-bis(bromomethyl)propanol (9.75g, 30 mmol) and allyl bromide (12.9 ml, 150 mmol) in dry and degassed (by vacuum) DMF (40 ml, 4Å MS for 24h) under nitrogen at 0 °C. The temperature was then increased to room temperature (22 °C) and the reaction mixture was stirred for another 3h. The reaction mixture was then carefully added to aqueous saturated NH_4Cl (50 ml). The H_2O-phase was then extracted with diethyl ether (2 x 50 ml) and the combined organic phases were washed with H_2O (5 x 50 ml) and the brine (50 ml). The organic phase was dried with Na_2SO_4 followed by filtration. The volatile materials were removed at reduced pressure to give a pale yellow oil (9.7 g). Column chromatography (heptane:EtOAc 9:1) gave 6.6 g (62%) of **1** as a clear oil. The product could also be isolated using distillation at reduced pressure, boiling point 85-87 °C at 0.05 mbar. ^{1}H-NMR ($CDCl_3$); 5.93 (m, 1H), 5.28 (m, 2H), 4.05 (d, 2H), 3.58 (s, 6H), 3.52 (s, 2H).

Example 2: 16-(allyloxymethyl)-16-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18,21,24,27,30-decaoxahentriacontane (2). Tetraethyleneglycol monomethyl ether (1.91 ml, 9 mmol) dissolved in dry and degassed DMF (3.5 ml, dried 24h, 4Å MS) was added carefully to sodium hydride (365 mg, 9 mmol) in dry and degassed DMF (15 ml, dried 24h, 4Å MS) under nitrogen at 0 °C using a syringe. The temperature was then raised to room temperature and the reaction mixture was stirred for another 30 min. Tribromide **1** (730 mg, 2.0 mmol) was then added and the temperature was raised to 100 °C. After 14h the reaction was completed (HPLC-ELSD-C18, 95:5 to 5:95 H_2O/ACN in 25 min, R_t product = 19.5 min) the temperature was decreased to room temperature and the reaction mixture was carefully added to H_2O (150 ml) and the H_2O-phase was washed with diethyl ether (2x 50 ml). Sodium chloride was then added to the H_2O-phase until saturation. The H_2O-

phase was extracted with EtOAc (4x50 ml) and the combined organic phases were washed with brine (2x30 ml). Sodium sulfate and charcoal was added to the organic phase. The clear organic phase was filtered and the volatile material was removed at reduced pressure (8 mmHg, 40 °C then 0.1 mmHg (oil pump) and 40 °C to remove residual DMF). Column chromatography (EtOAc:MeOH 9:1) gave 1.05 g (70%) of **2**. ^{1}H-NMR ($CDCl_3$); 5.90 (m, 1H), 5.20 (m, 2H), 3.94 (dt, 2H), 3.70-3.55 (m, 48H), 3.45 (s, 6H), 3.43 (s, 2H), 3.40 (s, 9H).

Example 3: 3,3-dimethoxy-9,9-di-2,5,8,11,14-pentaoxapentadecyl-2,7,11,14,17,20,23-heptaoxa-3-silatetracosane (3). Platinum(0)-1,3-divinyl-1,1,3,3-tetramethylsiloxane (20 μl, 2% in xylene) was added to **2** (0.75g, 1.0 mmol) and trimethoxysilane (255 μl, 2.0 mmol) in dry toluene (6 ml) under nitrogen at room temperature. The reaction mixture was shaken at room temperature for 24 h. Charcoal was then added and the reaction mixture was filtered after 2 minutes. The volatile material was removed at reduced pressure, which gave 830 mg (96%) of the title product containing 35% of 16-2,5,8,11,14-pentaoxapentadecyl-16-((prop-1-enyloxy)methyl)-2,5,8,11,14,18,21,24,27,-30-decaoxahentriacontane (HPLC-ELSD-C18, 95:5 to 5:95 H_2O/ACN in 25 min).

Example 4: 16,16-di-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14-pentaoxaheptadecan-17-ol (4). Potassium tert-butoxide (74 mg, 0.66 mmol) was added to **2** (500 mg, 0.66 mmol) in DMSO (3 ml). The reaction mixture was shaken at 100 °C for 15 min. HPLC analysis (HPLC-ELSD-C18, 95:5 to 5:95 H_2O/ACN in 25 min) indicated complete conversion to the product. Brine (20 ml) was added at room temperature and the aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic phases were washed with brine (3 x 20 ml) and the dried with sodium sulfate. Filtration and removal of volatile material at reduced pressure gave 16-2,5,8,11,14-pentaoxapentadecyl-16-((prop-1-enyloxy)methyl)-2,5,8,11,14,18,21,24,27,30-decaoxahentriacontane as a clear oil. HCl (0.1 M) was then added to the oil

dissolved in acetone (4 ml) and the mixture was shaken at 55 °C for 30 min. The volatile material was then removed at reduced pressure, which gave 420 mg (89%) of **4** as a clear oil. ^{1}H-NMR ($CDCl_3$); 3.66-3.52 (m, 48H), 3.47 (s, 6H), 3.37 (s, 9H).

Example 5: *tert*-butyl 16,16-di-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18-hexaoxaicosan-20-oate (5). Potassium *tert*-Butoxide (32 mg, 0.28 mmol) was added to **4** (100 mg, 0.14 mmol) and *tert*-butyl-2-bromo acetate (105 mg, 0.54 mmol) in dry THF (3 ml). The reaction mixture was shaken for 30 min. Diethyl ether (10 ml and brine (5 ml) were added and the aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic phases were washed with brine and then dried with sodium sulfate. The volatile material was removed at reduced pressure and the crude product was purified by column chromatography (ethyl acetate/methanol 9:1), which gave 60 mg (52%) of **5**. ^{1}H-NMR ($CDCl_3$); 3.91 (s, 2H), 3.66-3.52 (m, 48H), 3.51 (s, 2H), 3.45 (s, 6H), 3.37 (s, 9H), 1.46 (s, 9H).

Example 6a: 16,16-di-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18-hexaoxaicosan-20-oic acid (6). Trifluoroacetic acid (TFA, 0.5 ml) and dichloromethane (DCM, 0.5 ml) was added to 20 mg of **5**. The mixture was shaken at room temperature for 1h and the volatile materials was then removed at reduced pressure to give 18 mg of **6** as a yellow oil.

Example 6b: Alternative synthesis of 6,16-di-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18-hexaoxaicosan-20-oic acid (6). Hydrogen peroxide (145 mg, 4.26 mmol) dissolved in H_2O (9.5 ml) was added to mono sodium phosphate (588 mg, 3.87 mmol). This mixture was then transferred to PEG aldehyde **8** (example 8, 2.20 g, 2.94 mmol) dissolved in acetonitrile (7 ml). The reaction mixture was cooled to 0 °C and sodium chlorite (898 mg, 7.94 mmol) in H_2O (9 ml) was added. The reaction mixture was stirred at room temperature for 4.5 h. Aqueous, ice cooled sodium metabisulfite (12 ml of 1M) was added and the mixture was stirred for another 25 min.

The reaction mixture was then saturated with sodium chloride and the pH was raised to 7 by the addition of sodium hydroxide (1M). The mixture was extracted twice by EtOAc and then the pH of the aqueous phase was adjusted to 2 with HCl (6 M). The mixture was extracted with DCM (4 x 25 ml) and the combined organic phases were washed with brine and dried with sodium sulphate. Filtration followed by removal of the solvent at reduced pressure afforded 1.30 g of the product as an oil. HPLC analysis (HPLC-ELSD-C18, 90:10 to 10:90 H_2O/ACN in 20 min) displayed a single peak at 10.2 min.

Example 7: 16-(2-peroxypropoxymethyl)-16-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18,21,24,27,30-decaoxahentriacontane (7). To 3-chloroperoxy bensoic acid (247 mg, 1.0 mmol) was added to 6-(allyloxymethyl)-16-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18,21,24,27,30-decaoxahentriacontane (example 2) (374 mg, 0.50 mmol) dissolved in DCM (10 ml) at room temperature. The reaction mixture was stirred for 72 h at room temperature and then washed with aqueous sodium bisulphite saturated with sodium chloride, aqueous saturated sodium bicarbonate, and finally, brine and then filtered. The solvent was removed at reduced pressure and toluene was added to the residue. The mixture was filtered and the solvent was removed from the filtrate at reduced pressure to give 320 mg of the product. HPLC analysis (HPLC-ELSD-C18, 90:10 to 10:90 H_2O/ACN in 20 min) displayed a single peak at 15 min.

Example 8: 16,16-di-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18-hexaoxaicosan-20-al (8): 2,6 Lutidine (1.15 g, 10.7 mmol), osmiumtetraoxide (1.36 ml of 2% aqueous solution, 0.11 mmol) and sodiumperiodinate (4.58 g, 21.4 mmol) were consecutively added to 16-(allyloxymethyl)-16-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18,21,24,27,30-decaoxahentriacontane (**2**) (4.0 g, 5.35 mmol) dissolved in dioxane/H_2O (3:1, 65 ml) at room temperature. The reaction mixture was stirred for 4.5 h and the volatile material was removed at reduced pressure. Brine (20 ml) was added to the residue and the aqueous phase was

extracted with DCM (5 x 25 ml). The combined organic phases were washed twice with brine (20 ml) and then dried with sodium sulfate. Filtration and removal of the solvent at reduced pressure followed by column chromatography (DCM/methanol 95:5) of the crude product gave 2.65 g of the final product. HPLC analysis (HPLC-ELSD-C18, 90:10 to 10:90 H_2O/ACN in 20 min) displayed a single peak at 13.5 min. ^{1}H-NMR ($CDCl_3$); 9.70 (s, 1H), 4.01 (s, 2H), 3.7-3.4 (m, 56H), 3.37 (9H).

Example 9: 16-(2,3-dihydroxypropoxymethyl)-16-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18,21,24,27,30-decaoxahentriacontane (9): Osmium tetroxide (127 μl of a 2% aqueous solution, 0.01 mmol) followed by 4-methylmorpholine N-oxide (176 mg, 1,5 mmol) were added to 6-(allyloxymethyl)-16-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18,21,24,27,30-decaoxahentriacontane (**2**) (747 mg, 1.0 mmol) in t-BuOH/H_2O 4:1 (5 ml). The reaction was stirred for 20 h at room temperature. Sodium bisulphate (100 mg) was added and the reaction mixture was stirred for another 10 min. The volatile materials were removed at reduced pressure and the residue was purified by column chromatography (DCM 100% to DCM/MeOH 9:1) which gave 600 mg of the product as a clear oil. HPLC analysis (HPLC-ELSD-C18, 90:10 to 10:90 H_2O/ACN in 20 min) displayed a single peak at 12 min. ^{1}H-NMR ($CDCl_3$); 3.66-3.52 (m, 48H), 3.47 (s, 6H), 3.37 (s, 9H).

Example 10: 16-(2,3-dioleyloxypropoxymethyl)-16-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18,21,24,27,30-decaoxahentriacontane (10): Oleic anhydride (492 mg, 0.9 mmol) dissolved in dry pyridine (0.5 ml, dried with 4Å MS) was added to PEG diol **9** (234 mg, 0.3 mmol) dissolved in dry pyridine (1 ml) at room temperature. N,N-dimethylaminopyridine (0.5 mg) was then added to the reaction mixture and the stirring was continued for 4h at room temperature. More oleic anhydride (246 mg, 0.45 mmol) was then added and the reaction mixture was stirred for another 20 h. The volatiles were removed at reduced pressure and the residue was purified by column

chromatography (DCM 100% to DCM/MeOH 95:5) which afforded 360 mg of the product as a clear oil. ^{1}H-NMR ($CDCl_3$); 5.36 (m, 4H), 5.20 (m, 1H), 4.33 (dd, 1H, *J* = 12.0 and 3.2 Hz), 4.14 (dd, 1H, *J* = 12 and 6.4 Hz), 3.70-3.50 (m, 50H), 3.44 (s, 2H), 3.42 (6H), 3.40 (9H), 2.31 (m, 4H), 2.03 (m, 8H), 1.62 (m, 4H), 1.30 (m, 44H), 0.90 (t, 6H, *J* = 7.2 Hz).

Example 11: Liposomes of 10: PEG-glyceryldioleate **10** (20 mg) was dissolved in H_2O (1 ml). The mixture was shaken for 30 min at 37 °C and 30 min at room temperature. The clear solution was filtered (0.2 um syringe filter) and the size of the generated nanostructure was determined by DLS (Malvern Zetasizer) to have a typical hydrodynamic diameter of30 nm (volume average).

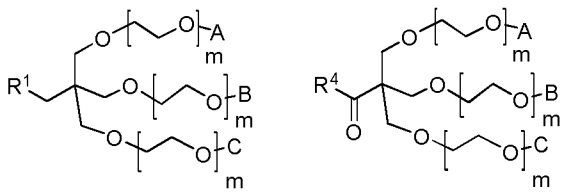
The results of DLS analysis of material from example 11 are shown in Figure 1.

Example 12: Dihydroartemisinin-PEG conjugate 12: Bortrifluoride etherate (104 μl, 1.0 mmol) was added to 16-(hydroxymethyl)-16-2,5,8,11,14-pentaoxapentadecyl-2,5,8,11,14,18,21,24,27,30-decaoxahentriacontane (**Ia** with m = 4; A, B, C = Me)(707 mg, 1.0 mmol) and dihydroartemisinin (426 mg, 1.5 mmol) in dry diethyl ether (20 ml) at room temperature. After 4 h, more bortrifluoride etherate (31 μl, 0.25 mmol) was added and the reaction mixture was stirred for another 20 h. Dilute aqueous sodium bicarbonate (2%) was added and the reaction mixture was stirred for another 30 min. The reaction mixture was extracted with EtOAc (3 x 30 ml) followed by DCM (2 x 25 ml). The combined organic phases were dried with sodium sulphate. Filtration and removal of the solvent at reduced pressure followed by column chromatography (EtOAc/heptane 1:1 then DCM/MeOH 9:1) of the crude product gave 780 mg of the product. HPLC analysis (HPLC-ELSD-C18, 90:10 to 5:95 H_2O/ACN in 20 min, then 5 min 5:95 H_2O/ACN) displayed the product peak at 23.5 min. MS (ESP+) [$M+Na^+$]: 995.6.

CLAIMS

1. A branched polyethyleneglycol (PEG) derivative consisting of a molecule with a quaternary carbon connected to three PEG chains, wherein all three PEG chains are of equal length and each comprises 1-30 -OCH_2CH_2- units, and one group with at least one carbon atom, wherein said at least one carbon atom is attached to the quaternary carbon.

2. A branched PEG derivative according to claim 1, having the general formula **I** or **II**



I II

wherein:

R^1 is selected from the group consisting of -OH, $-OSO_2CH_3$, $-OSO_2PhCH_3$, $-OCH_2CH=CH_2$, -OBenzyl, -halogen, $-NH_2$, $-NHCO_2R^2$, $-NHCONHR^2$, $-NHCON(R^2)_2$, -NCO, $-NHCO(CH_2)_4CH(SH)CH_2CH_2SH$, $-NHCOCH_2SH$, -SH, $-SR^2$, $-SO_3H$, $-O(CH_2)_3SH$, $-OCH_2CH(SH)CH_2SH$, $-OCO(CH_2)_4CH(SH)CH_2CH_2SH$, $-PO_3H_2$, $-PO3(R^2)_2$, $-OCH_2COOH$, $-OCH_2COR^4$, $-O(CH_2)_2NH_2$, $-O(CH_2)_2NHR^2$, $-O(CH_2)_2N(R^2)_2$, $-O(CH_2)_2NHCO_2R^2$, $-O(CH_2)_2NHCONHR^2$, $-O(CH_2)_2NHCON(R^2)_2$, $-O(CH_2)_2NCO$, $-O(CH_2)_3Si(R^3)_3$, $-O(CH_2)_2NHCO(CH_2)_4$ and $CH(SH)CH_2CH_2SH$;

A, B and C are independently selected from the group consisting of -C_1-C_8 hydrocarbon, $-(CH_2)_2N_3$, $-(CH_2)_2NR^5{}_2$ and $-CH_2COOR^4$;

R^2 is selected from the group consisting of C_1-C_8 hydrocarbons;

R^3 is selected from the group consisting of $C_{1\text{-}8}$ alkoxy groups, aryloxy group, a halogen, a di-$C_{1\text{-}8}$-alkylamino group, a nitrogen containing heterocycle or an acyloxy group;

R^4 is selected from the group consisting of H, OH, OR^2, NHR^2, $N(R^2)_2$, halogen, N-hydroxysuccinimidyl (NHS ester) and perfluorophenolate; and

R^5 is independently selected from the group consisting of -H, -C_1-C_8 hydrocarbon, -(C=O)NH_2, -(C=O)-OCH_3, -OCH_2CH_3 and m is selected from 1-30.

3. A branched PEG derivative according to claim 1 or 2, wherein m is 3-20.

4. A branched PEG derivative according to any one of the claims 1-3, wherein m is 3-10.

5. A branched PEG derivative according to any one of the claims 1-4, wherein m is 3-5.

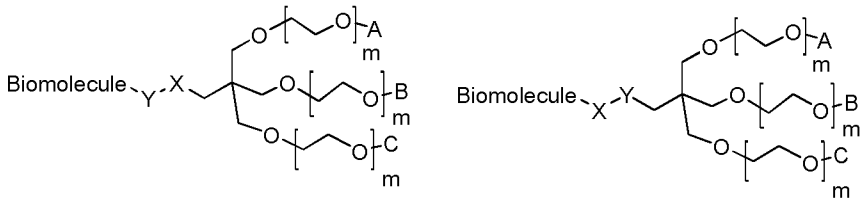
6. A branched PEG derivative according to any one of the claims 2-5, wherein A, B and C all are the same.

7. A branched PEG derivative according to claim 6, wherein A, B and C all are –CH_3.

8. A branched PEG derivative according to any one of the claims 2-7, wherein said compound has formula I and wherein R^1 is $O(CH_2)_3Si(R^3)_3$, wherein R^3 is selected from the group consisting of C_{1-8} alkoxy, acyloxy, dialkylamino and aryloxy.

9. A branched PEG derivative according to any one of the claims 2-7, wherein said compound has formula I and wherein R^1 is CH_2NH_2 or OCH_2COOH.

10. A branched PEG derivative according to claim 1 having one of the following two general formulas:



wherein:

"Biomolecule" denotes a peptide or an antibody fragment or a ribonucleic acid or a carbohydrate;

X is a residue of the functionality used for coupling;

Y is a spacer group with the structure $–(OCH2CH2)_nO-$, wherein n is 1-50;

m is 2-30;

A, B and C are independently selected from the group consisting of -C_1-C_8 hydrocarbon, $-(CH_2)_2N_3$, $-(CH_2)_2NR^5_2$ and $-CH_2COOR^4$;

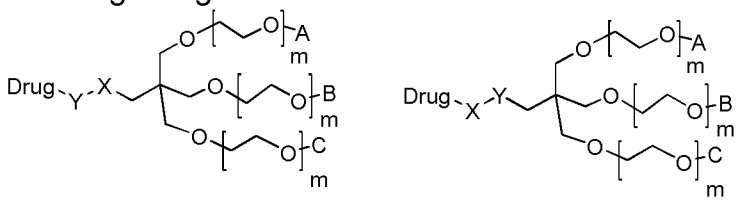
R^2 is selected from the group consisting of C_1-C_8 hydrocarbons;

R^3 is selected from the group consisting of from C_{1-8} alkoxy groups, aryloxy group, halogens, di-C_{1-8}-alkylamino groups, nitrogen containing heterocycles or acyloxy groups;

R^4 is selected from the group consisting of H, OH, OR^2, NHR^2, $N(R^2)_2$, halogen, N-hydroxysuccinimidyl (NHS ester) and perfluorophenolate;

and R^5 is independently selected from the group consisting of -H, -C_1-C_8 hydrocarbon, $-(C=O)NH_2$, $-(C=O)-OCH_3$, and $-OCH_2CH_3$.

11. A branched PEG derivative according to claim 1 having one of the following two general formulas:



wherein:

"Drug" denotes a pharmaceutically active drug of molecular weight less than 1000 g/mol;

X is a residue of the functionality used for coupling;

Y is a spacer group with the structure $–(OCH2CH2)_nO-$, wherein n is 1-50,

m is 2-30;

A, B and C are independently selected from the group consisting of -C_1-C_8 hydrocarbon, $-(CH_2)_2N_3$, $-(CH_2)_2NR^5_2$ and $-CH_2COOR^4$;

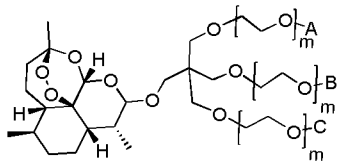
R^2 is selected from the group consisting of C_1-C_8 hydrocarbons;

R^3 is selected from the group consisting of C_{1-8} alkoxy groups, aryloxy groups, halogens, di-C_{1-8}-alkylamino groups, nitrogen containing heterocycles and acyloxy groups;

R^4 is selected from the group consisting of H, OH, OR^2, NHR^2, $N(R^2)_2$, halogen, N-hydroxysuccinimidyl (NHS ester) and perfluorophenolate;

and R^5 is independently selected from the group consisting of -H, -C_1-C_8 hydrocarbon, $-(C=O)NH_2$, and $-(C=O)-OCH_3$.

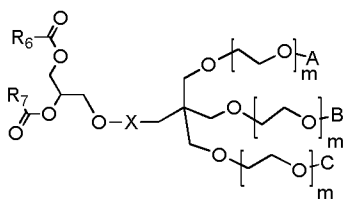
12. A branched PEG derivative according to claim 1, having the general formula **Va**



Va

wherein m=1-30 and A, B, and C independently are selected from the group consisting of H and methyl.

13. A branched PEG derivative according to claim 1, having the general formula **IXa**



IXa

wherein:

R^6 and R^7 are independently selected from the group consisting of C_8-C_{25} hydrocarbons;

m is selected from 2-30;

A, B and C are independently selected from the group consisting of -C_1-C_8 hydrocarbon, -$(CH_2)_2N_3$, -$(CH_2)_2NR^5{}_2$ and -CH_2COOR^4;

R^2 is selected from C_1-C_8 hydrocarbon;

R^3 is selected from C_{1-8} alkoxy group, aryloxy group, a halogen, a di-C_{1-8}-alkylamino group, a nitrogen containing heterocycle or an acyloxy group;

R^4 is selected from H, OH, OR^2, NHR^2, $N(R^2)_2$, halogen, N-hydroxysuccinimidyl (NHS ester) and perfluorophenolate;

R^5 is independently selected from -H, -C_1-C_8 hydrocarbon, -$(C=O)NH_2$, -$(C=O)$-OCH_3, or -OCH_2CH_3;

X is a bond, a chain or a ring structure with 0-10 linear atoms chosen independently from C, O, N, P and S to form chemical compounds according to normal valency rules;

14. A branched PEG derivatives according to any one of the claims 1-13 where the quaternary central carbon originates from 3-halo-2,2-bis(halomethyl)propanol.

15. A branched PEG derivative according to claim 14, wherein the 3-halo-2,2-bis(halomethyl)propanol is 3-bromo-2,2-bis(bromomethyl)propanol.

16. A composition comprising branched PEG derivatives according to any one of the claims 1-15.

17. A composition comprising nanoparticles with a surface coating comprising branched PEG derivatives according to any one of the claims 1-15.

18. A composition comprising branched PEG derivatives according to claim 13, according to claim 14 when dependent on claim 13 or according to

claim 15 when dependent on claim 13, wherein said composition comprises liposomes comprising said branched PEG derivatives.

19. A composition according to any one of the claims 16-18, wherein major part of the composition consists of branched PEG derivatives according to any one of the claims 1-15.

20. A composition according to any one of the claims 16-19, wherein the branched PEG derivatives are of defined molecular weight or monodisperse so that the purity of the product is more than 50%.

21. A composition according to claim 20, wherein the purity is more than 80%.

22. A composition according to claim 20 or 21, wherein the purity is more than 90%.

23. A composition according to any one of the claims 20-22, wherein the purity is more than 95%.

24. A composition according to any one of the claims 20-23, wherein the purity is more than 99%.

25. A method for producing branched PEG derivatives according to any one of the claims 1-15, wherein a solution of (3-halo-2,2-bis(halomethyl)propanol) in an aprotic solvent is contacted with A-$(OCH_2CH_2)_nO^-$; or a base and A-$(OCH_2CH_2)_nOH$ wherein A is selected from C_{1-8} hydrocarbon, benzyl, N_3CH_2, -$(CH_2)_2NH_2$, or CH_2COOR wherein R is a C_{1-8} hydrocarbon, and wherein said solution is heated at temperature of 30-150 ^oC for a duration from 30 minutes to 30 hours.

26. A method according to claim 25, wherein said solution is heated at a temperature of 70-120 °C for a duration from 30 minutes to 30 hours.

27. A method according to claim 25, wherein said solution is heated at a temperature of 90-110 °C for a duration from 30 minutes to 30 hours.

28. Use of a branched PEG derivative according to any one of the claims 1-15 or a composition according to any one of the claims 16-24 for structural modification of a biomolecule selected from the group consisting of proteins, peptides, antibodies, antibody fragments, carbohydrates, and nucleic acids or small molecule drugs.

29. Use of a branched PEG derivative according to any one of the claims 1-15 or a composition according to any one of the claims 16-24 in a nanoparticle.

30. Use of a branched PEG derivative according to any one of the claims 1-15 or a composition according to any one of the claims 16-24 in a homogeneous catalyst.

31. Use of a branched PEG derivative according to any one of the claims 1-15 or a composition according to any one of the claims 16-24 in a medical device.

32. A medical device, or a prostetic device or a screw, or a device through which body fluids are circulated and returned to the body, or an implant or an electrode implant with a surface coating comprising a branched PEG derivative according to any one of the claims 1-15 or a composition according to any one of the claims 16-24.

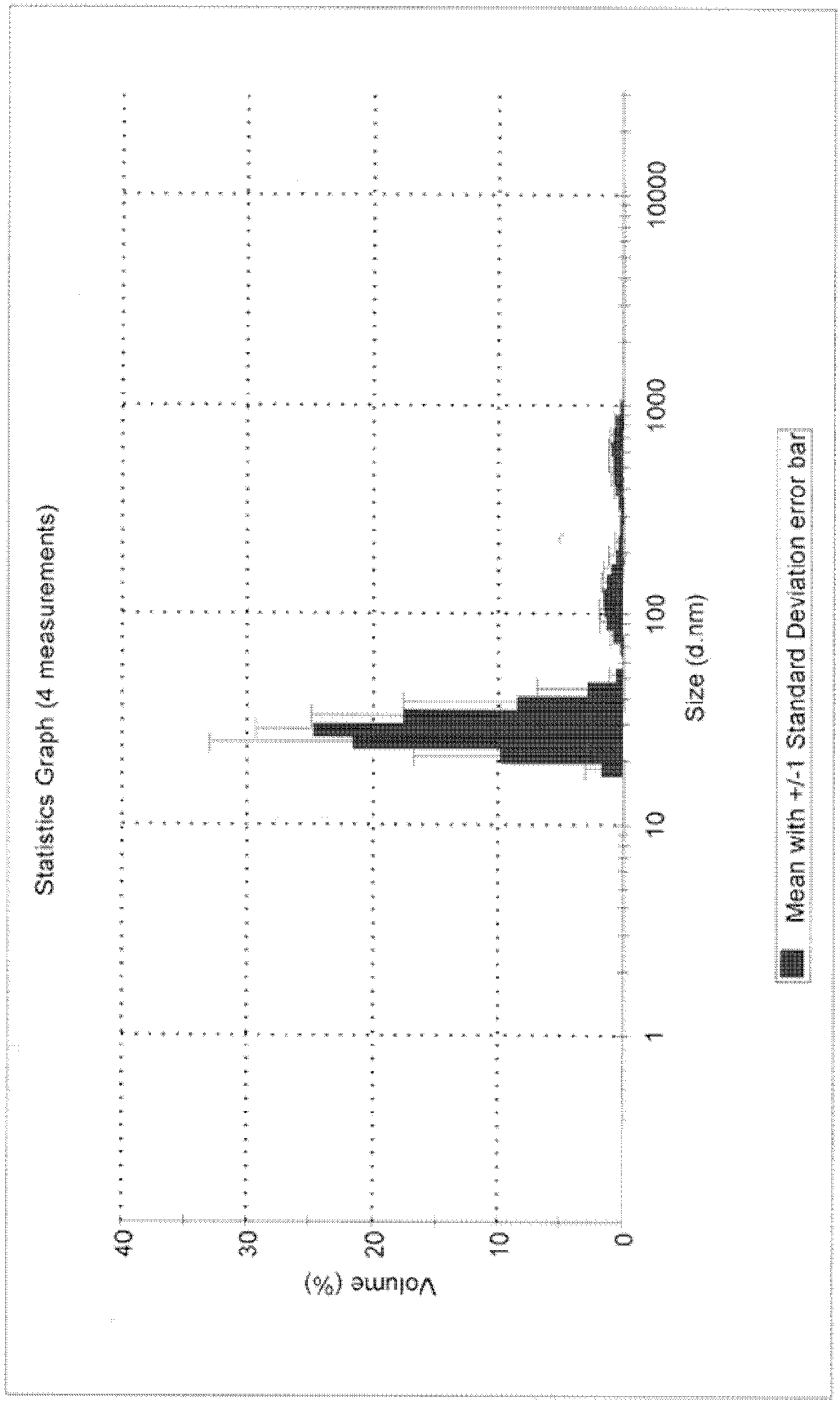

Statistics Graph (4 measurements)
Volume (%)
0
10
20
30
40
1
10
100
1000
10000
Size (d.nm)
Mean with +/-1 Standard Deviation error bar

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2011/050346

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC: C08G

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

SE, DK, FI, NO classes as above

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

EPO-Internal, PAJ, WPI data, CHEM ABS Data, Reaxys

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LI K. et al. "Synthesis and characterization of pentaerythritol-derived oligoglycol and their application to catalytic Wittig-type reactions" In: Journal of Organic Chemistry, 2004, May, Vol. 69, No. 11, p. 3986-3989, ISSN: 0022-3263; Scheme 2 --	1, 14-15, 25-27
P, X	KIM S. H. et al. " Magnetoresponsive Microparticles with Nanoscopic Surface Structures for Remote-Controlled Locomotion" In: Angewandte Chemie-International Edition, 2010, Vol. 49, No. 22, p. 3786-3790, ISSN: 1433-7851; Experimental section --	1, 16, 19-24, 29

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25-07-2011	26-07-2011
Name and mailing address of the ISA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Ingemar Wistrand Telephone No. + 46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2011/050346

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 5331039 A (KOSE CORP), 14 December 1993 (1993-12-14); (abstract) Retrieved from: WPI database; Original document: [0034]; [0034] --	1-7, 16, 19-24, 28
X	US 20090286878 A1 (ELDER STEWART TODD ET AL), 19 November 2009 (2009-11-19); claim 10 -- --------	1, 3-5, 16, 19-24

Continuation of: second sheet
International Patent Classification (IPC)
C08G 81/02 (2006.01)
C08G 65/32 (2006.01)

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Cited literature, if any, will be enclosed in paper form.

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				CA	2723024	A1	19/11/2009
				EP	2315528	A2	04/05/2011
				KR	20110006681	A	20/01/2011
				MX	2010012093	A	07/12/2010
				WO	2009138341	A3	22/04/2010