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(54) Title: BIODEGRADABLE RADIOPAQUE STENTS AND OTHER IMPLANTS

(57) Abstract: The invention is in the field of medical devices, in particular biodegradable polymer stents and other implants with radiopacity (i.e. X-ray contrast), as well as to the uses thereof. This invention also relates to a novel compound suitable for use as a contrast agent, a method of producing said compound as well as the use thereof, in particular in stents and other implants.

Title: Biodegradable radiopaque stents and other implants

The invention is in the field of medical devices, in particular biodegradable polymer stents and other implants with radiopacity (*i.e.* X-ray contrast), as well as to the uses thereof. This invention also relates to a novel compound suitable for use as a contrast agent, a method of producing said compound as well as the use thereof, in particular in stents and other implants.

Stent implantation is a routine procedure to resolve partial or complete occlusions (also called stenoses) in arteries or veins. Not all vascular occlusions can be treated through stenting. Those that can are usually first dilated with a catheter-mounted balloon, in a procedure known as percutaneous transluminal angioplasty (PTA). In the case of a coronary artery, the procedure is called percutaneous transluminal coronary angioplasty (PTCA). PTCA is followed by the implantation of a stent. This is usually a balloon-expandable mesh-type structure, but can also be a self-expanding structure.

Particularly well known are metallic balloon-expandable stents, which are fenestrated tubular structures. Such stents are manufactured out of thin metallic tubes through the use of precisely controlled laser cutting techniques. These medical devices are also known as “slotted tube” stents. Alternatively, metallic stents can also consist of wires or strips which are woven, coiled, or braided. Treatment of coronary arterial stenoses is mostly done with slotted-tube metallic balloon expandable stents.

Metal stents, unlike stents consisting of polymeric materials, undergo a so-called plastic deformation *i.e.* balloon dilatation bends the struts of the metal stent upon going from a narrow into a wide configuration. Each of the stent struts will easily and permanently adopt the new widened geometry. Such a transition from a narrow state into a wide state is much more difficult to achieve with stents consisting out of one

or more polymer materials. Yet, this problem has been solved. Different technologies for the production of polymer stents have been described. For example, US-A-6 623 521 discloses a locking polymer stent. These constructions are formed out of a flat sheet (or sheets) of metal or polymer, and locking radial elements or struts. Another example is found in US-A-2004/0249442. Therein, a stent is disclosed which is a lattice with an open and closed configuration. The lattice consists of hoops or struts that interlock with each other through teeth on the struts, while moving from a closed to an open configuration.

Furthermore, biodegradable polymers can be applied in this manner to produce biodegradable stents. These stents can be engineered in such a manner that they provide the required structural support to dilated vascular lesions, typically for a period of at least 9 months. Thereafter, the stent material slowly degrades, while degradation products are metabolized and transported away from the site of the lesion. This has been achieved successfully, particularly with stents based on poly(lactic acid), as is described in, *e.g.* WO-A-2011/011242, US-A-5 670 161, US-A-5 085 629 and in scientific publications, such as: Circulation **125**(2012)2343-2353.

The present invention is directed towards stents and other implants that are constructed from biodegradable polymer materials. These biodegradable polymer materials typically comprise polyesters, such as poly(lactic acid) (*e.g.* poly(L-lactic acid), poly(D-lactic acid) and/or poly(D,L-lactic acid)), poly(glycolic acid), poly(D-lactic-co-glycolic acid), poly(L-lactic-co-glycolic acid), poly(D,L-lactic-co-glycolic acid), poly(e-caprolactone), poly(valero-lactone), poly(hydroxybutyrate), poly(dioxanone), poly(hydroxyl butyrate), poly(hydrovalerate), and the like; as well as including copolymers such as polyglyconate (*i.e.* copolymers of trimethylene carbonate and glycolic acid), copolymers of poly(glycolic acid) and e-caprolactone, copolymers of poly(lactic acid) and e-caprolactone, poly(lactic acid)-poly(ethylene glycol) block copolymers, poly(ethyleneoxide)-poly(butyleneterephthalate),

poly(lactic acid-co-trimethylene carbonate), and the like. It will be appreciated that biodegradable stents can also be made out of various combinations of the materials listed above. Preferably, the polyester used is poly(lactic acid) and more preferably poly(L-lactic acid) and/or poly(D,L-lactic acid).

Poly(L-lactic acid) is particularly suitable as a stent material because of its relatively high strength and rigidity (*i.e.* stiffness) at human body temperature which is typically about 37 °C. The glass transition temperature of poly(L-lactic acid) is between about 60 and 65 °C (Medical Plastics and Biomaterials Magazine, March 1998), and therefore the material remains rigid and stiff at human body temperature. This property facilitates the ability of a stent to maintain a lumen at or near a deployed diameter without significant recoil.

In another embodiment, the stents (and other implants) according to the present invention may also include a nonbiodegradable polymer which results in a more stable medical device. Such medical devices may last for years. In such embodiments, suitable nonbiodegradable polymers which may be used include, but are not limited to, poly-n-butyl methacrylate (PBMA), polyethylene-co-vinyl acetate (PEVA), poly (styrene-b-isobutylene-b-styrene) (SIBS), and combinations thereof.

The polymer materials used in the stents and other implants of the present invention, are also typically capable of accommodating at least one active pharmaceutical ingredient (API), and preferably more than one API. These APIs may include anti-thrombotic agents, anti-proliferative agents, anti-inflammatory agents, anti-migratory agents, agents affecting extracellular matrix production and organization, anti-mitotic agents, anesthetic agents, anti-coagulant agents, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol-lowering agents, vasodilating agents, and/or agents that interfere with endogenous vasoactive mechanisms. Examples of such APIs include sirolimus, tacrolimus,

everolimus, zotarolimus, temsirolimus, invamycin and neuroimmunophilins, and combinations or analogs thereof. These APIs are antimitotic agents, inhibiting the proliferation of smooth muscle cells. APIs may be embedded in the stent material, and they are released in the vicinity of the stent in a concerted fashion with the biodegradation process. Examples of this technique can be found in, for instance: US-A-2013/0084322, EP-A-1 520 594, and US-A- 6 939 376. In a preferred embodiment, one or more of the APIs selected for use are suitable for inhibiting restenosis.

In a particularly successful embodiment, the biodegradable stent is composed of an interior consisting of poly(L-lactic acid), which is a crystalline biodegradable polymer with relatively slow biodegradation. This stent typically has an exterior layer of poly(D,L-lactic acid), which is loaded with the drug everolimus as the API. Poly(D,L-lactic acid) shows relatively fast degradation. In such a manner, it can be realized that the API is released during the first few weeks post implantation, when inhibition of cell proliferation (*e.g.* of smooth muscle cells) is critical, while the body of the stent will last much longer, providing the required mechanical support to the vessel wall of the lesion for a duration at least 9 months. This has been described in the scientific literature, for instance in EuroIntervention **7**(2012)1060-1061.

Furthermore, it is particularly desirable to include a second type of additive in the polymer material used in the stents of the present invention. These type of additives (also referred to herein as contrast agents) serve to introduce radiopacity into the stent, *i.e.* these additives are not APIs. Radiopacity means that the stent material will absorb X-radiation. Consequently, the stent is "visible" when using X-ray fluoroscopic imaging techniques.

In the prior art, several additives have been used to impart radiopacity into stents. These known additives include barium sulfate, and -particularly- iodine containing organic compounds, which are already in

clinical use, for instance as contrast agents for angiography. Typical iodine-containing contrast agents include iopamidol (non-ionic), iohexol (non-ionic), ioxilan (non-ionic), iopromide (non-ionic), iodixanol (non-ionic), diatrizoate (ionic), metrizoate (ionic) and ioxaglate (ionic). For this particular purpose, it is logical to select contrast agents which are already in clinical use, as this eliminates concerns about possible toxicity. It should be noted that the amount of contrast agent to be used in a stent is much lower than the amount that would be injected in a typical angiography procedure.

While the iodine containing contrast agents as mentioned appear to introduce "X-ray visibility" for the stents, it is clear that they also have significant shortcomings. Two of these are:

(1) The known iodine-containing contrast agents are all highly soluble in aqueous media (blood), and they will, therefore, leach prematurely out of the stent after its implantation. This will not only diminish the stent's visibility, but it will also leave nano- and microvoids in the material. These will be filled with body fluids (*e.g.* blood serum), and this will accelerate the biodegradation of the stent. Most importantly, biodegradation can start within such voids, and these are not necessarily located at the stent's surface. Hence, biodegradation will start to occur throughout the material. This is unwanted so-called bulk degradation, and this is associated with a risk for disintegration of the stent, in such a way that relatively large fragments fall off. These may be carried into the vasculature by the blood stream, acting as emboli. Controlled biodegradation requires surface degradation only, which is well known in the art; and,

(2) The known iodine containing contrast agents as described herein above typically have molecular structures which differ widely from the biodegradable polymers (such as poly(lactides)) in which they are embedded. The contrast agents do not show structural compatibility with the biodegradable polymers, in particular with poly(lactide) type matrices,

i.e. phase separation will occur. Then, the contrast agent forms domains (islands) in the polymer material. Such phase separation is well known to affect the strength and other physical/mechanical properties of polymer materials (particularly fatigue resistance) in a negative sense.

Occurrence of the complications as described in (1) and (2) herein above is certainly unacceptable for biodegradable polymer materials which are to be used for the construction of stents. Strength and other crucial properties like fatigue resistance must be well defined, and the kinetics of their deterioration *in situ*, must be secured. Hence, it must be concluded that the application of known iodine containing contrast agents to introduce radiopacity in biodegradable polymer material based stents, such as poly(lactide) type stents, will not provide a feasible road toward stents that should feature (i) controlled biodegradation over time; (ii) controlled release of one or more APIs over time, and (iii) adequate radiopacity. Premature leaching from, and phase separation within, biodegradable polymer materials, such as poly(lactides), actually disqualify these contrast agents for use in biodegradable stents.

Accordingly, it is an object of the invention to provide an iodine containing contrast agent with improved properties for use in medical device, in particular in stents and other implants.

Herein, a novel iodine containing compound suitable for use as a contrast agent is disclosed herein that meets these objects. Its molecular structure was designed to be structurally compatible with biodegradable polymer materials, such as polyesters, and particularly for poly(lactides).

Surprisingly it has been found that this compound can be combined with biodegradable polymer materials, by mixing with the compound (*e.g.* using a polymer blending equipment, or through extrusion) to yield homogeneously blended materials in which essentially no phase separation occurs for a compound concentration of at least 30 wt.% in the blended materials. Such homogenous materials have, therefore, predictable

and reproducible kinetics of degradation, which is an absolute requirement in the context of stent engineering. Furthermore, the novel contrast agent that is disclosed herein has low solubility in water, as well as an extremely low toxicity profile (comparable with L-lactic acid monomer).

This invention is particularly important, since use of the iodine containing compounds according to the invention as a contrast agent will provide biodegradable and radiopaque polymer materials suitable for the manufacture of stents (and other biodegradable implants). These uniquely feature combined controlled kinetics of biodegradation, controlled local release kinetics of API(s), and a level of radiopacity that allows real-time monitoring of the stent during deployment. Further, the level of radiopacity will gradually diminish as the stent degrades *in situ*. Hence, such formulations allow physicians to monitor stent degradation *in situ*.

The biodegradable and radiopaque polymer materials according to the present invention are suitable for use as a multifunctional platform in medical devices, such as stents and other implants, and in particular for biodegradable drug-eluting endovascular stents. For example, kinetics of biodegradation can be varied, multiple APIs can be embedded, and existing X-ray imaging techniques can be exploited better, in particular when the novel iodine containing contrast agent of the invention is used. The biodegradable and radiopaque polymer materials of the present invention, as disclosed herein, will contribute to enhanced safety and accuracy of the stent technique for revascularization of one or more partially or completely occluded arteries or veins in a human or animal body. Most likely, this will translate into lower treatment cost.

It will be clear to anyone skilled in the art that the same principle can be applied to stenting of other partially or completely occluded or stenosed lumens in a human or animal body, such as, but not limited to, peripheral arteries and veins, urinary channels, bile duct, trachea, esophagus, *etc*. Furthermore, it will be clear to anyone skilled in the art that

the same principle can be used to manufacture radiopaque, biodegradable implants for locally controlled drug delivery. These can be monitored non-invasively in the course of the drug delivery process, using X-ray imaging techniques, such as computed tomography (CT).

A novel type of compound suitable for use as a contrast agent in X-ray fluoroscopic imaging techniques was invented. The molecular structure of this compound was designed with two boundary conditions in mind: (i) the compound is organic and containing one or more covalently linked iodine atoms, (ii) mixing of the compound into biodegradable polymer materials, particularly polyester materials, and more particularly poly(L-lactic acid) and/or poly(D,L-lactic acid), to obtain homogeneous materials. The compound should be miscible with the polymer materials, thus avoiding phase separation.

Such homogeneous materials were engineered with regard to (i), their physical-mechanical properties and (ii) kinetics of biodegradation. These are, evidently, properties that are extremely relevant for the intended application *i.e.* the manufacture of stents. Importantly, such engineering requires that the materials be homogeneous and monophasic. In the case of phase-separated blends, the physical-mechanical properties will be inferior, and engineering of determined kinetics of degradation is impossible. Accordingly, the present invention is directed to a compound suitable for use as contrast agent having the formula (I):

$$I_m - Y_r - X_p - (CH(OH) - (CH_2)_z - COOH)_q \qquad (I)$$

wherein:

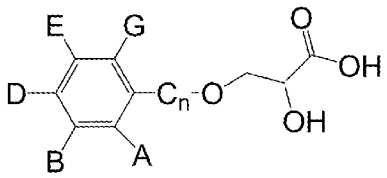
I is an iodine atom;

Y is an aryl group;

X is a linear or branched alkyl, alkenyl or alkoxy group having 1 to 20 carbon atoms, which is optionally substituted with one or more ester, amide and/or carbonate groups; or a cycloalkyl group having 5 to 6 carbon atoms;
m = 1 to 10, or alternatively 1-5;
r = 1 to 2, preferably 1;
p = 0 or 1, preferably 1;
z = 0 to 2, preferably 0 to 1, and more preferably 0; and,
q = 1 to 2;

If X is substituted with one or more ester, amide and/or carbonate groups, it is preferred that substitution is with one or more ester and/or amide groups; carbonate groups are less preferred.

Preferred compounds having the formula (I) are selected from one or more of the following formulae:

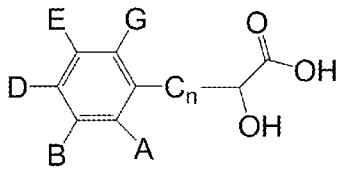


(II)

wherein:
A=iodine atom, B=D=E=G = hydrogen, and n=1;
A=G=iodine atom, B=D=E=hydrogen, and n=1;
A=D=G=iodine atom, B=E=hydrogen; n=1;
A=B=G=D=E= iodine atom, and, n=1;
A=iodine atom, B=D=E=G = hydrogen, and n=1-20;
A=G=iodine atom, B=D=E=hydrogen, and n=1-20;
A=D=G=iodine atom, B=D=hydrogen, n=1-20;
A=B=G=D=E= iodine atom, and n=1-20;

B=iodine atom, A=D=G=E=hydrogen, and n=1-20; and,

D=iodine atom, A=B=G=E=hydrogen, and n=1-20;



(III)

wherein:

A=iodine atom, B=D=E=G = hydrogen, and n=1-20;

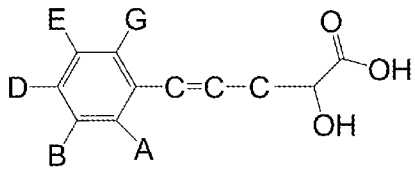
A=G=iodine atom, B=D=E=hydrogen, and n=1-20;

A=D=G=iodine atom, B=D=hydrogen, n=1-20;

A=B=G=D=E= iodine atom, and n=1-20;

B=iodine atom, A=D=G=E=hydrogen, and n=1-20; and,

D=iodine atom, A=B=G=E=hydrogen, and n=1-20;



(IV)

wherein:

A=iodine atom, B=D=E=G = hydrogen;

A=G=iodine atom, B=D=E=hydrogen;

A=D=G=iodine atom, B=D=hydrogen;

A=B=G=D=E= iodine atom;

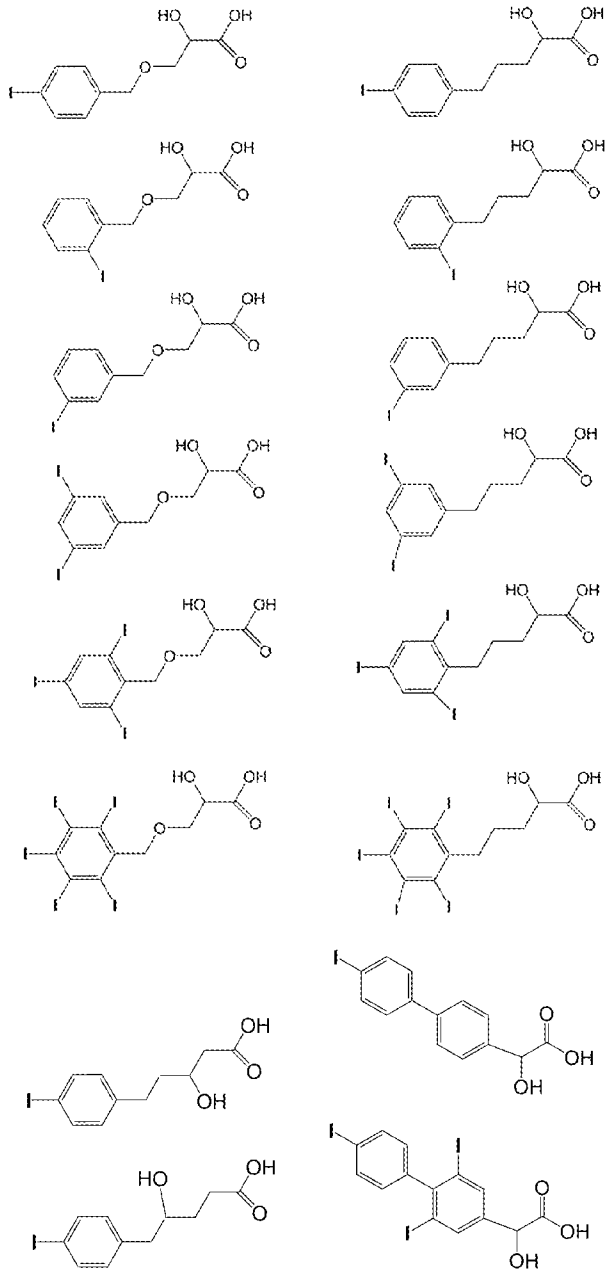
B=iodine atom, A=D=G=E=hydrogen, and n=1-20; and,

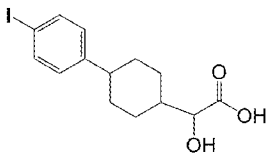
D=iodine atom, A=B=G=E=hydrogen, and n=1-20.

In all cases above, atoms depicted "C" are neutral atoms, with hydrogen atoms attached where required as is common in the art.

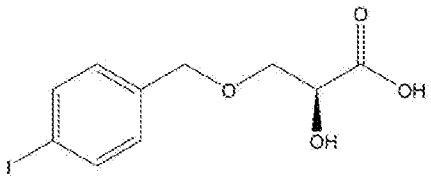
Alternatively, covalently attached fluor (F) atoms may render the atoms depicted "C" neutral.

More preferably the compound having the formula (I) is selected from one or more of the following formulae:





The compound that has been invented which is particularly suitable for use as a contrast agent is (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid. The molecular structure of (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid is depicted in formula (V):



(V)

Surprisingly this compound of the present invention has not been described previously.

The compound of the present invention typically comprises:

1. a terminal carboxylic acid(-COOH) group, as well an α-, ß- or γ-hydroxyl (-OH) group, preferably an α-hydroxyl (-OH) group. This particular combination of these two groups, located on one end of the compound, have a structural resemblance to L-lactic acid and D-lactic acid. Further, the location of the carboxylic acid group as well as that of the hydroxyl group means that they can be engaged in hydrogen bonding; and,

2. an aryl group, to which at least one iodine atom is linked covalently (preferably in the para-position). The iodine atom is required to absorb X-radiation. Iodine is found relatively low in the periodic table and has a relatively heavy nucleus, which explains why iodine effectively absorbs X-radiation. The advantage of using iodine is that the covalent bond between iodine and a carbon atom of an aromatic ring is relatively strong. It

is well known that such a bond is stable; it will not be disrupted in vivo which makes it suitable for use as an X-ray contrast agent.

A compounds depicted in formula I and/or VII is preferably prepared in a method which comprises the steps of:

(i) reacting a compound having the formula (VI)

$$I_m - Y_r - X_p - LG \qquad (VI)$$

wherein:

I is an iodine atom;

Y is an aryl group;

X is a linear or branched alkyl, alkenyl or alkoxy group having 1 to 20 carbon atoms, which is optionally substituted with one or more ester, amide and/or carbonate groups; or a cycloalkyl group having 5 to 6 carbon atoms;

LG = any leaving group known in the art, such as I, Br, Cl, mesylate, tosylate or triflate;

m = 1 to 10, or alternatively 1-5; and,

r = 1 to 2, preferably 1;

p = 0 or 1, preferably 1;

with an amino acid with a protective group or with an α-substituted carboxylate, which is nucleophilic at the α-position and which α-substitution represents a protective group which can be converted into a hydroxyl-group within one or two reaction steps;

ii) converting the protective group within one or two reaction steps into a hydroxyl group.

Step i) can be accomplished by reaction of the compound of general formula VI with an amino acid with a protective group. An amino acid, in this

context, is an α-amino acid. Preferably, the amino acid is as serine, preferably L-serine, with a protective group. The protective group can be any group known to protect the amino group of the amino acid during nucleophilic substitution reactions, such as for example Boc (t-butyloxycarbonyl). In case the amino acid with a protective group is serine, reaction occurs through deprotonation of the serine -OH group to result in an nucleophilic species, which reacts with the compound of general formula VI to result in an intermediate product, which by deprotection and subsequent conversion of the amine to the hydroxylgroup results in the product of formula V.

Step i) can also be accomplished with an α-substituted carboxylate, which is nucleophilic at the α-position and which α-substitution represents a protective group which can be converted into a hydroxyl-group within one or two reaction steps. This is generally a nucleophilic compound, derived from a carboxylic acid, which at the α-carbon comprises a group which can be converted into a hydroxyl group within one or two reaction steps.

In addition, the α-substituted carboxylate is nucleophilic at the α-carbon. This means that the α-carbon has (partial) negative charge, and reacts with carbon atoms having a (partial) positive charge, such as carbon atoms bearing a leaving group.

A group which can be converted into a hydroxyl group within one or two reaction steps may for example be a protected amine group, such as a Boc-protected amine, which can be converted to a hydroxyl group by deprotection, such as by reaction with acid, and conversion through diazotization and hydrolysis.

Preferably, in step i) an amino acid with a protective group is used, preferably serine, more preferably L-serine, and most preferably Boc-protected L-serine.

Preferably, step ii) is accomplished through removing the protective group of the product of the first reaction step, for example through treatment with an acid; and substituting the deprotected group, for example an amine group, in the deprotected product with a hydroxyl (OH) group. In case the deprotected group is an amine group, this substitution can preferably be done using diazotization and hydrolysis, such as by reaction with an aqueous solution of sodium nitrite, $NaNO_2$.

The amino acid preferably used in the method step (i) is L-serine and derivatives thereof. The use of such an amino acid will result in a compound according to the invention with an α-hydroxyl (-OH) group.

Although many protective groups can be used in the method step (i), it is preferred to use Di-tert-butyl dicarbonate (Boc_2O) and its derivatives to form the protective group.

Suitable acids which may be used in the method step (ii) are strong acids, such as hydrochloric acid, nitric acid, sulfuric acid, CF_3COOH and the like.

The advantage of this method is that it is simple, provides good yields and can be readily scaled up for industrial production.

The preferred compound (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid can be synthesized in three steps according to the above-mentioned method. The first reaction step is a nucleophilic addition of 4-iodobenzylbromide and Boc-L-serine; the second reaction step is the removal of the protective Boc group; and, the third reaction step is the substitution of the amine group with an alcohol group. It is a smooth synthetic route, which can be scaled up, and which is commercially feasible.

It was found that (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid is a solid white crystalline compound, which has not been described hitherto. The purity and identity of the synthesized (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid were established by NMR spectroscopy and the X-ray crystallography. The X-ray crystal structure of (S)-2-Hydroxy-3-(4-iodobenzyloxy) propanoic acid is shown in detail in Fig. 1. The molecules of (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid in the crystal are hydrogen- bonded to form a one-dimensional chain along the crystallographic a-axis (see Fig. 1, where the dashed lines indicate hydrogen bonding). Also shown in Fig. 1 is that the crystal consists of hydrogen-bonded linear polymers in a parallel arrangement. The encountered patterns of hydrogen bonding in the crystal structure of (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid demonstrate that the compound can form hydrogen bonds.

It is the structure of the compound according to the present invention which is of critical importance to this invention. This is because it is by virtue of hydrogen bonding that there is structural compatibility between the biodegradable polymer materials, in particular polyester materials, that constitute the stent on the one hand, and the compound used as a contrast agent on the other hand. It should be noted that polyester materials, such as poly(L-lactic acid) have ester groups, which can readily take part in hydrogen bonding. It is this hydrogen bonded interaction, that is responsible for the structural compatibility, and the absence of phase separation. It must be noted that the compound of the present invention can be mixed with the biodegradable polymer materials, in particular polyester materials, irrespective of the mean molecular mass of the polymers used. The loading of such a compound into the polymer material may vary between 2 and 50 wt. %, based on the total weight of the polymer material. Clearly, the X-ray visibility will improve upon higher loads of compounds used as contrast agent in the polymer material.

While at least one compound of the present invention is typically combined with a biodegradable polymer material by mixing, said compound may also be coated directly on the stent, or be included within a further polymer coating. It may also be sandwiched between the stent and a further polymer coating, or any combination of these techniques. Such a further polymer coating may comprise any of the polymers described herein above.

The present invention must be regarded as a technical improvement over the technology described in US-A-2013/0150952. Therein, clinically used and commercially available iodinated contrast agents (in particular: iohexol) are used to introduce radiopacity in biodegradable stents (in particular: in poly(lactic acid) stents). According to US-A-2013/0150952, the contrast agent is mixed with the bulk of the stent material, or it is applied as a surface coating on the stent, or it is sandwiched between different layers of a layers stent design. Such blends of poly(lactic acid)s and said commercial iodinated contrast agents are phase-separated structures. Inherently, these have (i) inferior physical-mechanical properties and (ii) hard-to-predict kinetics of degradation *in situ*. It is the crux of the present invention that the novel iodine containing compounds of the present invention (such as (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid) yield homogeneous biocompatible and biodegradable blended materials which overcome the drawbacks (i) and (ii) of phase-separated blends. Evidently, this is a essential requirement in the context of biodegradable stents. It is well known that premature mechanical failure of a stent is a life-threatening condition.

It is, furthermore, important to realize that the radiopaque biocompatible and biodegradable polymer materials of the present invention can be applied in the manufacture of all known designs, geometries and constructions of polymeric biodegradable stents. For example, the present invention is compatible with the techniques disclosed in (i) US-A-6 623 521, in which a locking stent is disclosed, formed out of one or more flat sheets,

bearing sliding radial locking elements or struts; (ii) US-A-6 540 777; (iii) US-A-6 156062; (iv) US-A-2004/0,249,442; (v) US-A-5 441 515. The radiopaque biocompatible and biodegradable polymer materials of the present invention may also be used in other implants, such as orthopedic bone cements, cements for vertebroplasty, materials and implants to augment or partially replace the spine or elements of the spine, such as intervertebral discs or vertebrae, fillable implants for controlled local drug release, intraocular lenses, dental filling materials, injectable materials and particles for augmentation or correction of soft tissues, injectable materials and particles to be used in cosmetic, reconstructive surgery, or corrective surgery, such as wrinkle corrections, radiopaque markers which are used to mark the exact location of a tumor, in order to precisely steer and control the radiation beam during radiotherapy, and radiopaque materials for use in breast prostheses or for breast filling or augmentation.

Although the invention has been described with respect to (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid, and with respect to particular embodiments and applications as stent building biomaterials, it will be appreciated that various changes and modifications may be made without departing from the invention.

The invention will now be illustrated by the following non-limiting single-sentence descriptions and examples.

SINGLE SENTENCE DESCRIPTIONS

1. A compound suitable for use as a contrast agent having the formula (VII):

$$I_m - Y_r - X_p - (CH(OH)) - (CH_2)_z - COOH)_q \qquad (I)$$

wherein:

I is an iodine atom;

Y is an aryl group;

X is a linear or branched alkyl, alkenyl or alkoxy group having 1 to 20 carbon atoms, which is optionally substituted with one or more ester, amide and/or carbonate groups; or a cycloalkyl group having 5 to 6 carbon atoms;

m = 1 to 10, preferably 1-5;

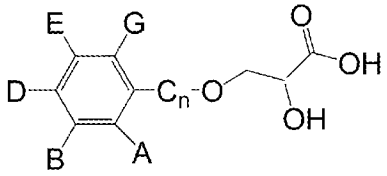
r = 1 to 2, preferably 1;

p = 0 or 1, preferably 1;

z = 0 to 2, preferably 0 to 1, and more preferably 0; and,

q = 1 to 2.

2. Compound according to single sentence description 1, wherein said compound is selected from one or more of the following formulae:



(IIa)

wherein:

A=iodine atom, B=D=E=G = hydrogen, and n=1;

A=G=iodine atom, B=D=E=hydrogen, and n=1;

A=D=G=iodine atom, B=E=hydrogen; n=1;

A=B=G=D=E= iodine atom, and, n=1;

A=iodine atom, B=D=E=G = hydrogen, and n=1-20;

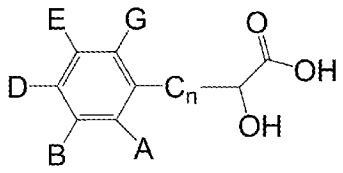
A=G=iodine atom, B=D=E=hydrogen, and n=1-20;

A=D=G=iodine atom, B=D=hydrogen, n=1-20;

A=B=G=D=E= iodine atom, and n=1-20;

B=iodine atom, A=D=G=E=hydrogen, and n=1-20; and,

D=iodine atom, A=B=G=E=hydrogen, and n=1-20;



(IIIa)

wherein:

A=iodine atom, B=D=E=G = hydrogen, and n=1-20;

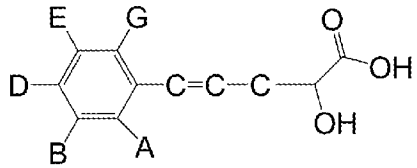
A=G=iodine atom, B=D=E=hydrogen, and n=1-20;

A=D=G=iodine atom, B=D=hydrogen, n=1-20;

A=B=G=D=E= iodine atom, and n=1-20;

B=iodine atom, A=D=G=E=hydrogen, and n=1-20; and,

D=iodine atom, A=B=G=E=hydrogen, and n=1-20;



(IVa)

wherein:

A=iodine atom, B=D=E=G = hydrogen;

A=G=iodine atom, B=D=E=hydrogen;

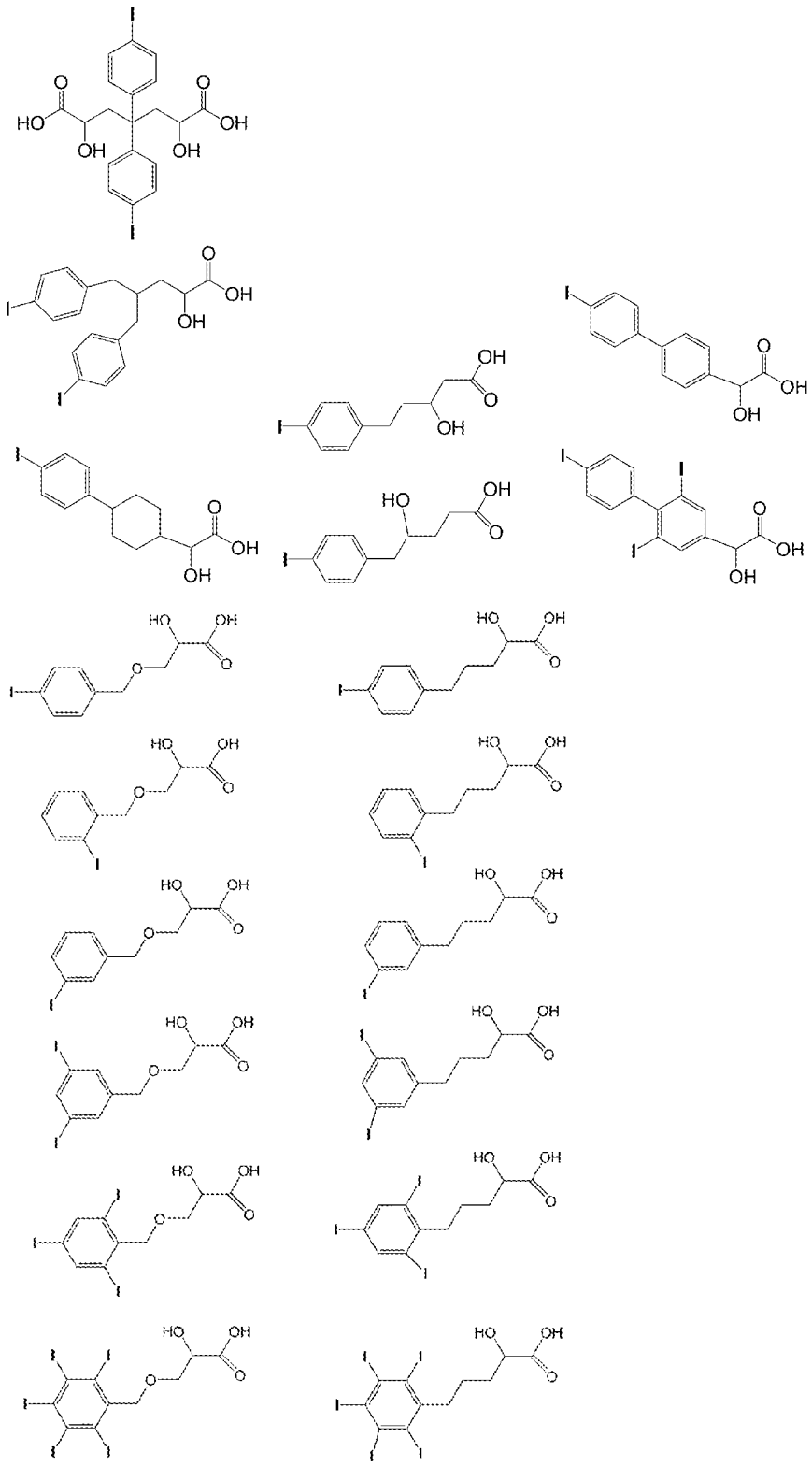
A=D=G=iodine atom, B=D=hydrogen;

A=B=G=D=E= iodine atom;

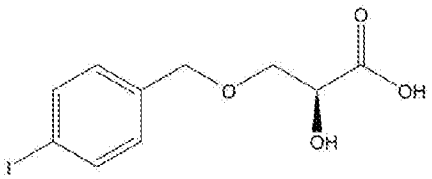
B=iodine atom, A=D=G=E=hydrogen, and n=1-20; and,

D=iodine atom, A=B=G=E=hydrogen, and n=1-20.

3. Compound according to single sentence description 1, wherein said compound from formula VII is selected from one or more of the following formulae:



4. Compound according to single sentence description 1, wherein said compound is (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid which has the formula (V):



(V)

5. Method for preparing a compound according to single sentence description 1 having the formula (I), wherein I, Y, X, m, r, p, and q are as defined in single sentence description 1, and z = 0,

or a compound according to single sentence description 2 or 4, wherein said method comprises the steps of:

(i) reacting a compound having the formula (VI)

$$I_m - Y_r - X - \text{halogen} \qquad \text{(VI)}$$

wherein:

I is an iodine atom;

Y is an aryl group;

halogen = Br, Cl or F atom, or alternatively I, preferably Br, Cl or I; alternatively, "halogen" may be replaced by any leaving group known in the art, such as for example mesylate, tosylate or triflate;

m = 1 to 10, or alternatively 1-5; and,

r = 1 to 2, preferably 1;

with a nucleophilic amino acid having a protective group, preferably protected serine, or an α-substituted carboxylate, which is nucleophilic at the α-position and which α-substitution represents a

protective group which can be converted into a hydroxyl-group within one or two reaction steps;

ii) removing the protective group of the product of the first reaction step through treatment with an acid; and,

iii) substituting a group, such as an amine group, in the deprotected product with a hydroxyl (OH) group.

6. Use of a compound according to any of the single sentence descriptions 1 to 4 as a contrast agent in biodegradable medical devices, wherein said medical devices includes stents and other implants.

7. Radiopaque polymer material suitable for use in medical devices, wherein said material comprises a biodegradable polymer material, preferably a polyester; and, at least one compound according to any of the single sentence descriptions 1 to 4, and wherein preferably said compound is (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid.

8. Method of preparing a radiopaque polymer material according to single sentence description 7, wherein said method comprises the steps of combining a biodegradable polymer material with at least one compound according to any of the single sentence descriptions 1 to 4 by mixing to produce a homogeneously blended material.

9. Stent comprising a biodegradable polymer material, at least one compound according to any of the single sentence description 1-4, wherein preferably said compound is (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid, and optionally one or more active pharmaceutical ingredients.

10. Stent according to single sentence description 9, wherein said biodegradable polymer material comprises a polyester.

11. Stent according to single sentence description 10, wherein the polyester is selected from the group consisting of poly(lactic acid), poly(L-lactic acid), poly(D-lactic acid), poly(D,L-lactic acid), poly(glycolic acid), poly(e-caprolactone), poly(valero-lactone),

poly(hydroxybutyrate), poly(dioxanone), poly(hydroxyl butyrate), poly(hydrovalerate), polyglyconate, copolymers of poly(glycolic acid) and e-caprolactone; copolymers of poly(lactic acid) and e-caprolactone, poly(lactic acid)-poly(ethylene glycol) block copolymers, poly(ethyleneoxide)-poly(butyleneterephthalate), poly(lactic acid-co-trimethylene carbonate); and, combinations thereof, preferably poly(lactic acid), and more preferably poly(L-lactic acid) and/or poly(D,L-lactic acid).

12. Stent according to any of the single sentence descriptions 9-11, wherein the one or more active pharmaceutical ingredients are selected from the group consisting of anti-thrombotic agents, anti-proliferative agents, anti-inflammatory agents, anti-migratory agents, agents affecting extracellular matrix production and organization, anti-mitotic agents, anesthetic agents, anti-coagulant agents, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol-lowering agents, vasodilating agents, agents that interfere with endogenous vasoactive mechanisms and combinations thereof, preferably one or more of the active pharmaceutical ingredients selected are suitable for inhibiting restenosis.

13. Stent according to any of the single sentence descriptions 9-12, wherein said stent further comprises a nonbiodegradable polymer, and wherein preferably said nonbiodegradable polymer is selected from the group consisting of poly-n-butyl methacrylate, polyethylene-co-vinyl acetate, poly (styrene-b-isobutylene-b-styrene) and combinations thereof.

14. Stent according to any of the single sentence descriptions 9-13, wherein said compound is present in a blend with the biodegradable polymer material; a coating directly on the stent; and /or a further polymer coating.

15. Use of a stent according to any of the single sentence descriptions 9-14 for revasculation of one more partially or completely

occluded arteries or veins in a human or animal body; or, in one or more partially or completely occluded lumens in a human or animal body.

16. Compound according to any of the single sentence descriptions 1 - 4 for use in a method for treatment of the human or animal body by surgery or therapy or in a diagnostic method practiced on the human or animal body.

EXAMPLES

Synthesis of (S)-2-Hydroxy-3-(4-iodobenzyloxy)propanoic acid

Synthesis of (S)-2-Hydroxy-3-(4-iodobenzyloxy) propanoic acid comprises three steps. The first step was a nucleophilic addition of 4-iodobenzylbromide and Boc-L-serine, the second step was the removal of the protective Boc group and the third step was the substitution of the amine group with an alcohol group to complete the lactic acid structure.

First step: NaH (11.98 g in a 60% dispersion of mineral oil, 299.6 mmol) and 450 mL of DMF were placed in a 1 L flask and stirred at 0 °C. In another flask, Boc-L-serine (15.00 g, 73.1 mmol) was dissolved in 115 mL DMF. This solution was stirred at 0 °C, and then added carefully to the NaH suspension. The flask was closed with a drying tube, while continually stirring at 0 °C, and the evolution of a gas (hydrogen) was noted. Then, 4-iodobenzylbromide (23.00 g, 77.5 mmol) was added and the mixture was stirred for 4 hours at room temperature (about 25 °C). The reaction progress was tracked through thin layer chromatography (TLC) using dichloromethane/methanol (9:1) as eluent. When TLC confirmed that the reaction had completed, the mixture was poured into 400 mL ice water and extracted with Et_2O three times. The aqueous phase was then acidified to pH 3 with citric acid, saturated with NaCl and extracted with EtOAc five times. The combined organic layers were washed with 0.01 M NH_4OAc solution (twice), H_2O (twice), dried ($MgSO_4$), filtered and evaporated under

reduced pressure. O-Benzyl-4-Iodine-Boc-L-serine was obtained as an orange oil/solid in almost 100 wt.% yield (30.78 g, 73.1 mmol) and was used without further purification. TLC (CH_2Cl_2/MeOH, v/v = 9:1): Rf = 0.32; 1H NMR (300 MHz, $CDCl_3$, δ): 7.58 (d, J = 8.3, 2H; CHAr), 6.96 (d, J = 8.1, 2H; CHAr), 4.40 (s, 2H; –O–CH_2–C_6H_4I), 4.05 (q, J = 7.1, 1H; –CH– CH_2–O), 3.93 – 3.50 (m, 2H; –CH–CH_2–O), 1.38 (s, 9H; –O–C–$(CH_3)_3$).

Second step: O-Benzyl-4-Iodine-Boc-L-serine (30.78 g, 73.1 mmol) was dissolved in 100 mL of dichloromethane. Trifluoroacetic acid (70 mL, 939.3 mmol) was added to the solution and the reaction mixture was stirred for 3.5 hours at room temperature. The reaction was monitored by TLC (butanol/acetic acid/ H_2O, v/v/v = 4:1:1). Volatile components of the reaction mixture were removed under reduced pressure and the residue was precipitated into Et_2O. The precipitate, O-Benzyl-4-Iodine-L-serine, was isolated by filtration. This intermediate was obtained as a white powder in 94 wt.% yield (22.06 g, 68.7 mmol). TLC (BuOH/AcOH/H2O, v/v/v = 4:1:1): Rf = 0.47; 1H NMR (300 MHz, DMSO-d6, δ): 7.73 (d, J = 8.2, 2H; CHAr), 7.17 (d, J = 8.2, 2H; CHAr), 4.57 – 4.44 (m, 2H; –O–CH_2–C_6H_4I), 4.22 (t, 1H; –CH–CH_2–O), 3.80 (ddd, J = 13.5, 10.5, 3.7, 2H; –CH–CH_2–O).

Third step: .O-Benzyl-4-Iodine-L-serine (22.06 g, 68.7 mmol) was dissolved in 210 mL of 1 M H_2SO_4 and 210 mL of acetonitrile in a round-bottomed flask. $NaNO_2$ (19.00 g, 274.9 mmol) dissolved in 150 mL of H_2O was added dropwise. The reaction mixture was stirred for 20 hours at room temperature. The aqueous layer was extracted with CH_2Cl_2 four times. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuum. The raw residue was dissolved in 225 mL acetonitrile/chloroform (8:2) while heating to boiling point, filtered and then left for 3 days to crystalize at room temperature. Then, the flask was put at 4 °C for 1 day, after which the crystals were filtered off. The iodine containing contrast agent (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid was obtained as a white crystalline solid (needle shapes crystals) in 38 wt.% yield (31.72 g,

98.48 mmol). TLC (BuOH:AcOH:H_2O, v/v/v = 4:1:1): Rf = 0.66; 1H NMR (300 MHz, DMSO-d6, δ): 7.61 (d, J = 8.2, 2H; CHAr), 6.99 (d, J = 8.1 Hz, 2H; CHAr), 4.54 – 4.40 (m, 2H; –O–CH_2–C_6H_4I), 4.32 (t, J = 4.0 Hz, 1H; –CH–CH_2–O), 3.80 – 3.67 (m, J = 9.9, 4.1, 2H; –CH–CH_2–O).

Characterization of (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid. 1H NMR spectroscopy (300 MHz) was recorded at room temperature on a Bruker Avance 300 NMR spectrometer, using deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO- d6) as solvent. Tetramethylsilane was used as an internal standard.

Preparation of Blends and Films

Poly(D,L-lactic acid) was blended with sodium diatrizoate and (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid respectively in a DSM XPlore 15cc Twin Screw Micro-Compounder under N_2 atmosphere to minimize the risk of degrading the poly(D,L-lactic acid). The temperature was 180 °C and the blending time was 5 minutes. The melt was cooled in room temperature after blending.

Four different blends were prepared by extrusion: poly(D,L-lactic acid) with 5 wt.% sodium diatrizoate (hereinafter called material 3), poly(D,L-lactic acid) with 10 wt.% sodium diatrizoate (hereinafter called material 4), poly(D,L-lactic acid) with 5 wt.% (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid (hereinafter called material 5), and poly(D,L-lactic acid) with 10 wt.% (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid (hereinafter called material 6). The blends were compressed into films using an Atlas Manual 15T Hydraulic Press. The temperature was set at 150 °C and pressure was 2 ton. The compressing time was 5 mins and the thickness of each film was 250 μm.

In addition, comparative examples corresponding to non-extruded/non-blended poly(D,L-lactic acid) (hereinafter called material 1)

and extruded/blended poly(D,L-lactic acid) were prepared in the same manner as described for materials 3-6.

Characterization of Materials, methods

Differential scanning calorimetry (DSC) analysis was carried out using a Perkin-Elmer instrument under nitrogen flow (20 mL/min). All samples were first heated from 0 °C to 200 °C at 10 °C/min and held for 3 mins to erase the thermal history, then cooled to 0 °C at 10 °C/min, and finally heated to 200 °C at 10 °C/min. Morphology of the films was characterized by scanning electron microscopy (SEM). Small film samples were coated with carbon and examined under a RJ Lee PSEM75 SEM (Goffin Meyvis, Etten Leur, The Netherlands) in the backscattered electron imaging (BEI) mode.

X-ray visibility of the blends was determined by a Philips BV Pulsera (C-bow), which has a fixed (relatively) big distance (approx. 75 cm) between X-ray source and detector. Films of blends were cut into small round films with a diameter of approximately 6 mm. The films of materials 2 – 6 were cut into small round films with a diameter of approximately 6 mm. X-ray visibility of both the single-layer film (with a thickness of 240 μm) and double-layer films (with a thickness of 500 μm) as well as an aluminum film as a comparative example (with a thick ness of 120 μm) were investigated. The test was operated at 75 kV and all images were taken under the same condition.

Cytotoxicity of (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid.

Human coronary arterial endothelial cells were cultured in Lonza EGM-2-MV BulletKit cell medium (Lonza, Verviers, Belgium). Porcine skin fibroblasts (PSFs) and aortic smooth muscle cells (PSMCs) were isolated from porcine tissue by standard collagen digestion and cultured in Lonza

SmGM-2 BulletKit or EGM-2-MV BulletKit, on the films as described herein above. These cell types were used for all experiments.

The MTT assay was used to determine the cytotoxicity of the materials 2 to 6. 0.2 g of each of the materials was cut into small pieces which were then sterilized with ethanol for 20 min. The sterilized materials were subsequently incubated in culture medium (2 mL for each blend) at 37 °C for 48 h. Culture medium used was eagle medium/F-12 nutrient mix containing Glutamax-I and 10 wt.% fetal bovine serum and antibiotic/antimycotic solution (1x) were added to it. Mouse fibroblast cells (L929 Line) were transferred to a 96-well tissue culture plate (TCP) with a seeding density of about 103 cells/well and cultured in an incubator at 37 °C and 5 vol. % CO_2 at high (near 100%) relative humidity. The medium was replaced with that extracted from blends after 24 h and incubated for another 48 h. Then 20 L medium containing thiazolyl blue (MTT, 3 mg/mL) was added to each well. After culturing for 2 h, the medium was removed and 100 µL isopropanol was added to dissolve the formed precipitated formazan. The absorbance of the samples was measured in a microtiter plate reader at 570 nm. TCP wells with medium were used as negative control and those with medium extracted from latex were used as positive control.

Both mouse L929 cells and human microvascular endothelial cell-line (HMEC-1) were used in the live/dead cells test. The culture medium of 3T3 cells was the same as that used in MTT assay mentioned above. For HMEC-1 cells the culture medium was MCDB-131 medium supplemented with 10 wt.% FBS, 2 mm l-glutamine, 1 µg/ml hydrocortisone, 10 ng/ml h-EGF, and antibiotics (100 U/ml penicillin, 100 µg/ml streptomycin, 0.25 µg/ml amphothericin B). Films of materials 2-6 were cut into small triangle films with each side around 8 mm and sterilized with ethanol for 20 min. Then the sterilized films were placed in a 24-well tissue culture plate (TCP) and 50 µL medium containing 104 3T3 cells or HMEC-1 cells were cultured

respectively on the films in an incubator at 37 °C and 5 vol.% (CO_2 at high (near 100%) relative humidity. 2 mL medium were added to each well after 2 h and the plated was incubated for another 24 h. Afterwards, the films were rinsed in PBS and stained with 1.25 µL calcein-AM and 5 µL ethidium homodimer (EthD-1) in PBS for 20 min in the dark. Calcein AM transported into cells then changed to highly fluorescent calcein by intracellular esterase activity and it stained viable cells green. EthD-1 permeated the permeabilized membranes and bound to DNA, staining dead cells red. Images were immediately acquired using a microscope (Nikon Diaphot 200). The images taken of the materials 2-6 showed no indication of cytotoxicity.

Thrombin Generation Test:

Films of materials 2-6 were cut into small round films with a diameter of approximately 6 mm and placed in an Immulon 2 HB 96-well plate. Blood was obtained by venipuncture from healthy donors. The blood (approximately 20 mL) was collected in Na-citrate tube followed by centrifuging the blood at 200 G for 15 min at 22 °C. Then platelets rich plasma (PRP) was removed with plastic pipette and supplemented with fluorescent thrombin-specific substrate and 40 µL/mL 0.5 M calcium chloride solution. 200 µL recalcified PRP was added to each well. Fluorescence spectroscopies of the samples were measured with a microtiter plate reader at 37 °C. The measure time was 1 h and interval time was 30 sec. For each material, six samples were tested.

Properties of radiopaque blends:

The pressed films of materials 2 to 6 were studied further with scanning electron microscopy (SEM) in the backscatter mode (Fig. 2). Materials containing the contrast agent (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid (5 or 10 wt.%), as well as the poly(D,L-lactic acid) starting material, appeared as homogeneous surfaces. Materials containing the

commercial contrast agent sodium diatrizoate (5 or 10 wt.%), on the other hand, were clearly heterogeneous: white dots (contrast agent) are scattered over the surface, thus revealing phase-separation. Fig. 2 (a) shows scanning electron microscopic image of 10 wt.% blend of the commercial contrast agent sodium diatrizoate in the poly(D,L-lactic acid) matrix. Phase separation is clearly visible in this image. The contrast agent forms clumps, due to structural non-compatibility. The formation of "islands" of contrast agent inside the polymer material has a negative impact on the physical-mechanical properties. Fig. 2 (b) shows an example of the material according to the invention comprising a 10 wt.% blend of (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid in poly(D,L-lactic acid). In this case, a homogeneous grey image is obtained, reflecting the monophasic (completely mixed) nature of this blend.

The materials 2 to 6 described above were also analyzed for their capacity to absorb X-radiation. Fig. 3 combines X-ray images of two partially overlapping specimens per material (circles with a diameter of 6 mm, cut out of the pressed films). Fig. 3 shows X-ray images of: (a) 10 layers of aluminum foil (comparative example); (b), two partially overlapping circular specimens (diameter 6 mm, thickness 250 μm) comprising poly(D,L-lactic acid); (c), idem, now comprising a 5 wt.% blend of sodium diatrizoate in poly(D,L-lactic acid); (d), idem, now comprising a 10 wt.% blend of sodium diatrizoate in poly(D,L-lactic acid); (e), idem, now comprising a 5 wt.% blend of (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid in poly(D,L-lactic acid); (f), idem, now comprising a 10 wt.% blend of (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid in poly(D,L-lactic acid).

Fig.3 (d) and (f) illustrate that the blends materials have excellent radiopaque properties which make the materials very suitable for visualization under clinical conditions. The grey values (scored on a 256-unit scale with white = 0 and black = 255) are compiled in Table 1 below.

Table 1. Grey levels measured for the different matrix material and blends.

Material	Grey level single layer	Grey level double layer
1. Poly(D,L-lactic acid) untreated	22.5	44.9
2. Poly(D,L-lactic acid), after extrusion	22	45
3. Blend containing poly(D,L-lactic acid) and sodium diatrizoate (5 wt.%)	33.2	65.4
4. Blend containing poly(D,L-lactic acid) and sodium diatrizoate (10 wt.%)	49.0	99.7
5. Blend containing poly(D,L-lactic acid) and (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid (5 wt.%)	33.5	70.2
6. Blend containing poly(D,L-lactic acid) and (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid (10 wt.%)	47.3	93.1

These data reveal that the materials which include (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid have excellent X-ray visibility, comparable to that of the known contrast agent . This should enable the the stent to be visualized prior to, during, and after deployment at the site of the lesion. It is also possible, at least in principle, to monitor the degradation of the stent *in situ*, in a non-invasive manner, using advanced X-ray imaging techniques, such as CT.

Cytotoxicity of the contrast agent and biocompatibility of the blends:

It is a *conditio sine qua non* that the compound of the present invention will not invoke any toxic effect on neighboring cells or tissues. The cellular toxicity of (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid was also studied through comparison with L-lactic acid. Different concentrations of both compounds (range 0-10 mM end concentration) were added to cultured

human coronary arterial endothelial cells (HCAECs), porcine skin fibroblast cells (PSFs) or porcine aortic smooth muscle cells (PSMCs), and incubated for 24 hours. A low but negligible cytotoxicity was found for most monomer concentrations and cell types tested as compared with negative control (0 mM), whereas the positive condition (2.5 vol.% DMSO) revealed considerable cytotoxicity.

Cytotoxicity of the materials 2 to 6 as described above in vitro was studied by two methods. First, the MTT test of was used (mouse fibroblast (3T3) cells, protocol according to ISO 10993-5:2009, Biological Evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity). The cells that had been in contact with (poly(D,L-lactic acid)) had a viability score of 97.2 ± 13.5%. For the materials 3 and 4 with the commercial contrast agent, viability percentages were: 92.7 ± 12.0 and 88.9 ± 9.4, respectively; for the materials 5 and 6 with the new contrast agent (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid: 92.4 ± 12.0 and 83.3 ± 12.1, respectively. These data reveal that all materials of this evaluation were not cytotoxic in the MTT test.

Secondly, *in vitro* LIVE/DEAD assay was used, for 3T3 mouse fibroblast cells, as well as on human microvascular endothelial cells (HMECs). The microscopic fields for all materials of this evaluation predominantly show living HMEC cells (green), with almost no red dots (red dots represent dead cells). This data revealed that the blends which include (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid are not cytotoxic. Their interaction with cells is comparable with poly(L-lactic acid).

In vitro hemocompatibility of the materials 2 to 6 was assessed. For each material, a thrombin-generation curve was measured with fresh human platelet-rich blood plasma (in 4-fold). Each curve is characterized by: (i), a lag-phase (no thrombin is formed during the first few minutes of the test, which starts on the moment of "recalcification" of the plasma that is in contact with the biomaterial); (ii) a steep rise of the thrombin concentration;

(iii), a maximum; (iv), a decline of the thrombin concentration due to inactivation of the enzyme by antithrombin-III and complexation with α2-macroglobulin. In this assay, thrombin formation is triggered exclusively by the contact between the material and the plasma (*i.e.* no tissue factor is used). The lag time (tlag), *i.e.* the interval between the start of the test, and the onset of the steep rise of the thrombin concentration provides a measure for the material's thrombogenicity (*i.e.* a more thrombogenic material has a shorter tlag than a less thrombogenic material). Two other materials were included for comparison: (i) a commercial diagnostic catheter that is used in direct contact with blood (samples were 4-mm pieces cut from the catheter tube; experiments were done with 1 or 2 catheter pieces per well); (ii) a stainless steel stent (samples were cut from a non-expanded stent, sample length = 4 mm; experiments were done with 1 or 2 stent pieces per well). The data revealed that the blends which include (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid have excellent blood compatibility. The data are comparable to poly(L-lactic acid).

Thermal analysis of different radiopaque biodegradable blends of poly(D,L-lactic acid) and poly(L-lactic acid)

Differential scanning calorimetry experiments were also performed, on a number of representative materials of this invention. These materials include materials 1-6 and also materials 7-12. Materials 7-12 were prepared in the same manner as materials 1-6, except that poly(L-lactic acid) was used. The materials 5, 6, 11 and 12, containing the (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid show decreasing glass transition temperature (T_g) values with increasing concentration, which is in line with monophasic mixing. The data are compiled in Tables 2 and 3 shown below.

Table 2. Experimental data of Poly(D,L-lactic acid) and its blends from differential scanning calorimetry

Material	T_g [°C]
1. Poly(D,L-lactic acid) untreated	47.8
2. Poly(D,L-lactic acid), after extrusion	46.3
3. Blend containing sodium diatrizoate (5 wt.%)	48.0
4. Blend containing sodium diatrizoate (10 wt.%)	45.4
5. Blend containing (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid (5 wt.%)	41.1
6. Blend containing (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid (10 wt.%)	34.4

Table 3. Experimental data of Poly(L-lactic acid) and its blends from differential scanning calorimetry

Material	T_g [°C]
7. Poly(L-lactic acid) untreated	60.1
8. Poly(L-lactic acid), after extrusion	55.4
9. Blend containing poly(L-lactic acid) and sodium diatrizoate (5 wt.%)	53.5
10. Blend containing poly(L-lactic acid) and sodium diatrizoate (10 wt.%)	57.5
11. Blend containing poly (L-lactic acid) and (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid (5 wt.%)	55.1
12. Blend containing poly(L-lactic acid) and (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid (10 wt.%)	47.0

The data in Table 3 refers to poly(L-lactic acid) and shows that the materials 11 and 12 have T_gs which make them particularly suitable for use in stents.

Claims

1. A compound suitable for use as a contrast agent having the formula (VII):

$$I_m - Y - X_p - (CH(OH) - COOH)_q \qquad (VII)$$

wherein:

I is an iodine atom;

Y is an aryl group;

X is a linear or branched alkyl, alkenyl or alkoxy group having 1 to 20 carbon atoms, which is optionally substituted with one or more ester, amide and/or carbonate groups; or a cycloalkyl group having 5 to 6 carbon atoms;

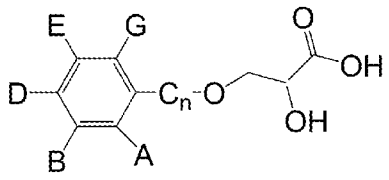
m = 1 to 5;

p = 0 or 1;

and

q = 1 to 2.

2. Compound according to claim 1, wherein said compound is selected from one or more of the following formulae:



(II)

wherein:

A=iodine atom, B=D=E=G = hydrogen, and n=1;

A=G=iodine atom, B=D=E=hydrogen, and n=1;

A=D=G=iodine atom, B=E=hydrogen; n=1;

A=B=G=D=E= iodine atom, and, n=1;

A=iodine atom, B=D=E=G = hydrogen, and n=1-20;

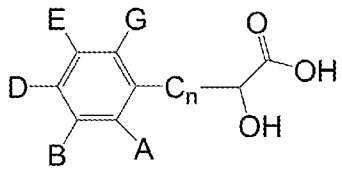
A=G=iodine atom, B=D=E=hydrogen, and n=1-20;

A=D=G=iodine atom, B=D=hydrogen, n=1-20;

A=B=G=D=E= iodine atom, and n=1-20;

B=iodine atom, A=D=G=E=hydrogen, and n=1-20; and,

D=iodine atom, A=B=G=E=hydrogen, and n=1-20;



(III)

wherein:

A=iodine atom, B=D=E=G = hydrogen, and n=1-20;

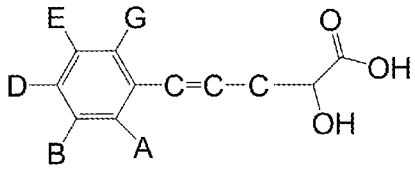
A=G=iodine atom, B=D=E=hydrogen, and n=1-20;

A=D=G=iodine atom, B=D=hydrogen, n=1-20;

A=B=G=D=E= iodine atom, and n=1-20;

B=iodine atom, A=D=G=E=hydrogen, and n=1-20; and,

D=iodine atom, A=B=G=E=hydrogen, and n=1-20;



(IV)

wherein:

A=iodine atom, B=D=E=G = hydrogen;

A=G=iodine atom, B=D=E=hydrogen;

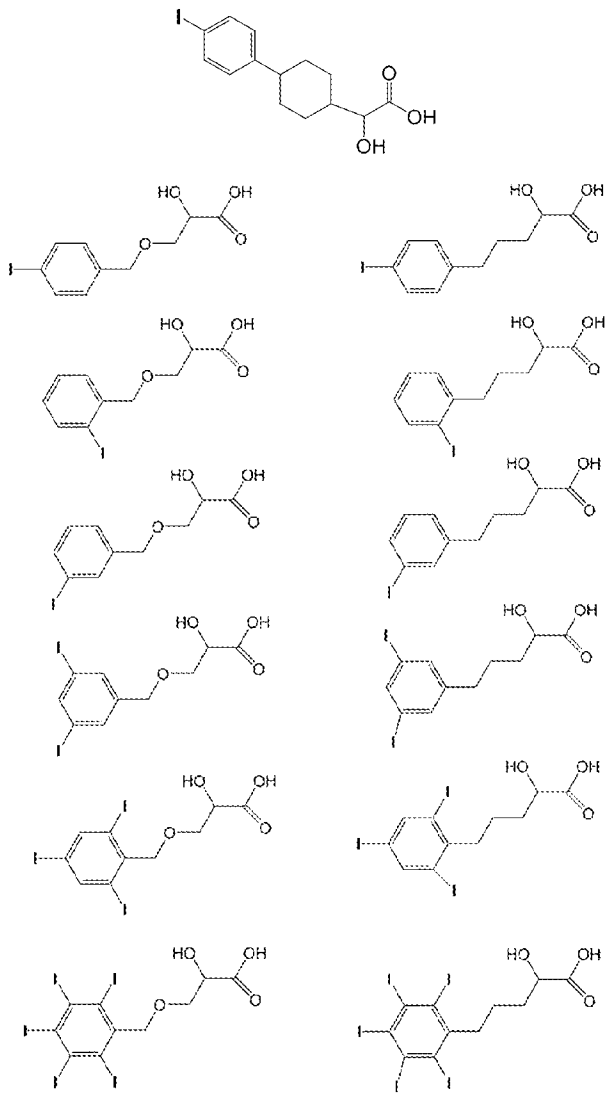
A=D=G=iodine atom, B=D=hydrogen;

A=B=G=D=E= iodine atom;

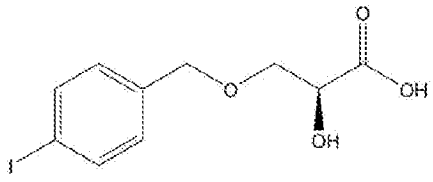
B=iodine atom, A=D=G=E=hydrogen, and n=1-20; and,

D=iodine atom, A=B=G=E=hydrogen, and n=1-20.

3. Compound according to claim 1, wherein said compound is selected from one or more of the following formulae:



4. Compound according to claim 1, wherein said compound is (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid which has the formula (V):



(V)

5. Method for preparing a compound according to claim 1 having the formula (VII), wherein I, Y, X, m, p, and q are as defined in claim 1, or a compound according to claims 2 or 4, wherein said method comprises the steps of:

(i) reacting a compound having the formula (VI)

$$I_m - Y - X_p - LG \qquad (VI)$$

wherein:

I is an iodine atom;

Y is an aryl group;

X is a linear or branched alkyl, alkenyl or alkoxy group having 1 to 20 carbon atoms, which is optionally substituted with one or more ester, amide and/or carbonate groups; or a cycloalkyl group having 5 to 6 carbon atoms;

LG = a leaving group, preferably I, Br, Cl, mesylate, tosylate or triflate;

m = 1 to 5;

p = 0 or 1;

with an amino acid with a protective group or with an α-substituted carboxylate, which is nucleophilic at the α-position and which α-substitution represents a protective group which can be converted into a hydroxyl-group within one or two reaction steps;

ii) converting the protective group within one or two reaction steps into a hydroxyl group.

6. Use of a compound according to formula (I):

$$I_m - Y_r - X_p - (CH(OH) - (CH_2)_z - COOH)_q \qquad (I)$$

wherein:

I is an iodine atom;

Y is an aryl group;

X is a linear or branched alkyl, alkenyl or alkoxy group having 1 to 20 carbon atoms, which is optionally substituted with one or more ester, amide and/or carbonate groups; or a cycloalkyl group having 5 to 6 carbon atoms;

m = 1 to 10, preferably 1-5;

r = 1 to 2, preferably 1;

p = 0 or 1, preferably 1;

z = 0 to 2, preferably 0 to 1, and more preferably 0; and,

q = 1 to 2

as a contrast agent in biodegradable medical devices, wherein said medical devices includes stents and other implants.

7. Radiopaque polymer material suitable for use in medical devices, wherein said material comprises a biodegradable polymer material, preferably a polyester; and, at least one compound according to formula VII as defined in claim 6, and wherein preferably said compound is (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid.

8. Method of preparing a radiopaque polymer material according to claim 7, wherein said method comprises the steps of combining a biodegradable polymer material with at least one compound according to any of the claims 1 to 4 by mixing to produce a homogeneously blended material.

9. Stent comprising a biodegradable polymer material, at least one compound according to formula VII as defined in claim 6, wherein preferably said compound is (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid, and optionally one or more active pharmaceutical ingredients.

10. Stent according to claim 9, wherein said biodegradable polymer material comprises a polyester.

11. Stent according to claim 10, wherein the polyester is selected from the group consisting of poly(lactic acid), poly(L-lactic acid), poly(D-lactic acid), poly(D,L-lactic acid), poly(glycolic acid), poly(e-caprolactone), poly(valero-lactone), poly(hydroxybutyrate), poly(dioxanone), poly(hydroxyl butyrate), poly(hydrovalerate), polyglyconate, copolymers of poly(glycolic acid) and e-caprolactone; copolymers of poly(lactic acid) and e-caprolactone, poly(lactic acid)-poly(ethylene glycol) block copolymers, poly(ethyleneoxide)-poly(butyleneterephthalate), poly(lactic acid-co-trimethylene carbonate); and, combinations thereof, preferably poly(lactic acid), and more preferably poly(L-lactic acid) and/or poly(D,L-lactic acid).

12. Stent according to any of the claims 9-11, wherein the one or more active pharmaceutical ingredients are selected from the group consisting of anti-thrombotic agents, anti-proliferative agents, anti-inflammatory agents, anti-migratory agents, agents affecting extracellular matrix production and organization, anti-mitotic agents, anesthetic agents, anti-coagulant agents, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol-lowering agents, vasodilating agents, agents that interfere with endogenous vasoactive mechanisms and combinations thereof, preferably one or more of the active pharmaceutical ingredients selected are suitable for inhibiting restenosis.

13. Stent according to any of the claims 9-12, wherein said stent further comprises a nonbiodegradable polymer, and wherein preferably said nonbiodegradable polymer is selected from the group consisting of poly-n-butyl methacrylate, polyethylene-co-vinyl acetate, poly (styrene-b-isobutylene-b-styrene) and combinations thereof.

14. Stent according to any of the claims 9-13, wherein said compound is present in a blend with the biodegradable polymer material; a coating directly on the stent; and /or a further polymer coating.

15. Use of a stent according to any of the claims 9-14 for revasculation of one more partially or completely occluded arteries or veins in a human or

animal body; or, in one or more partially or completely occluded lumens in a human or animal body.

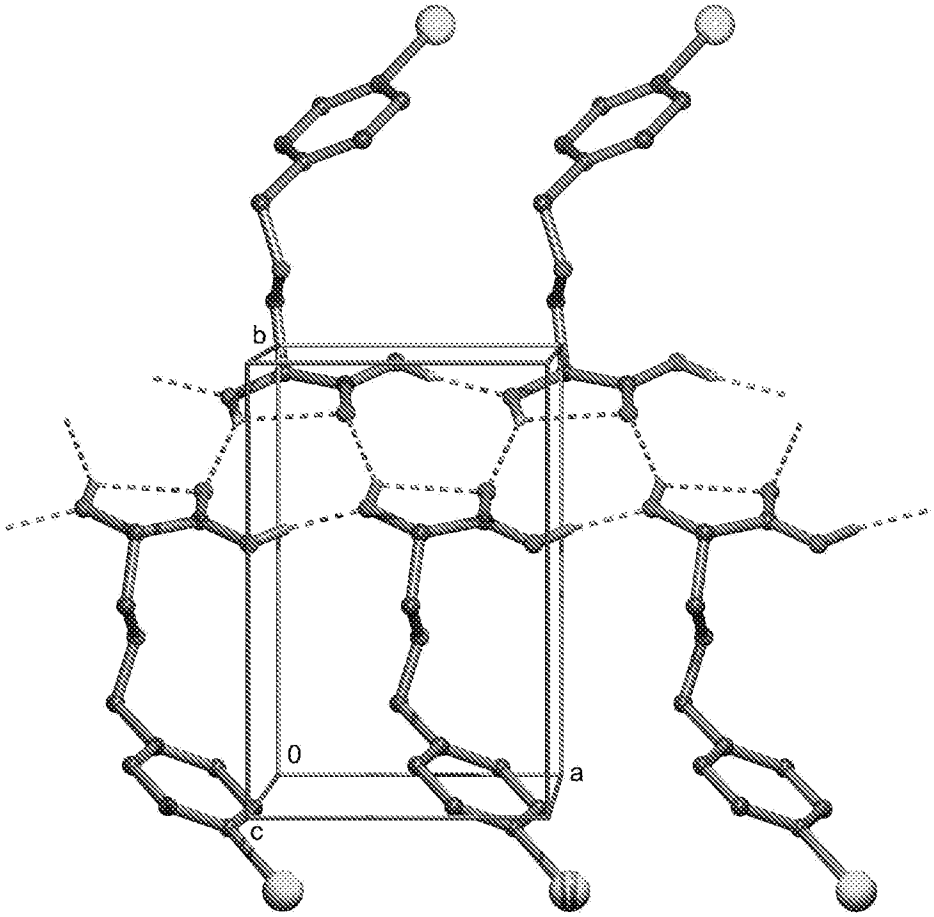


Fig. 1.

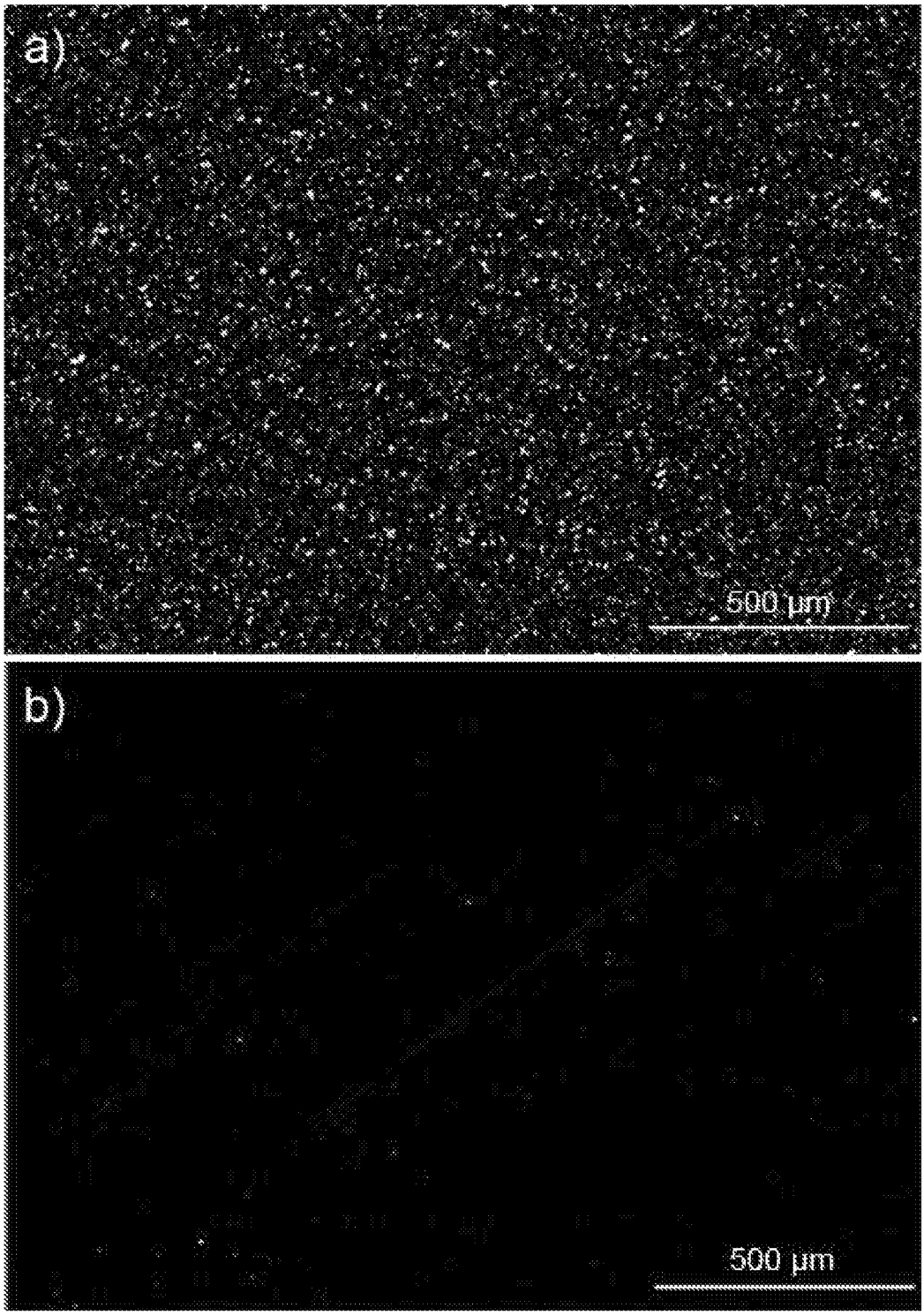


Fig. 2.

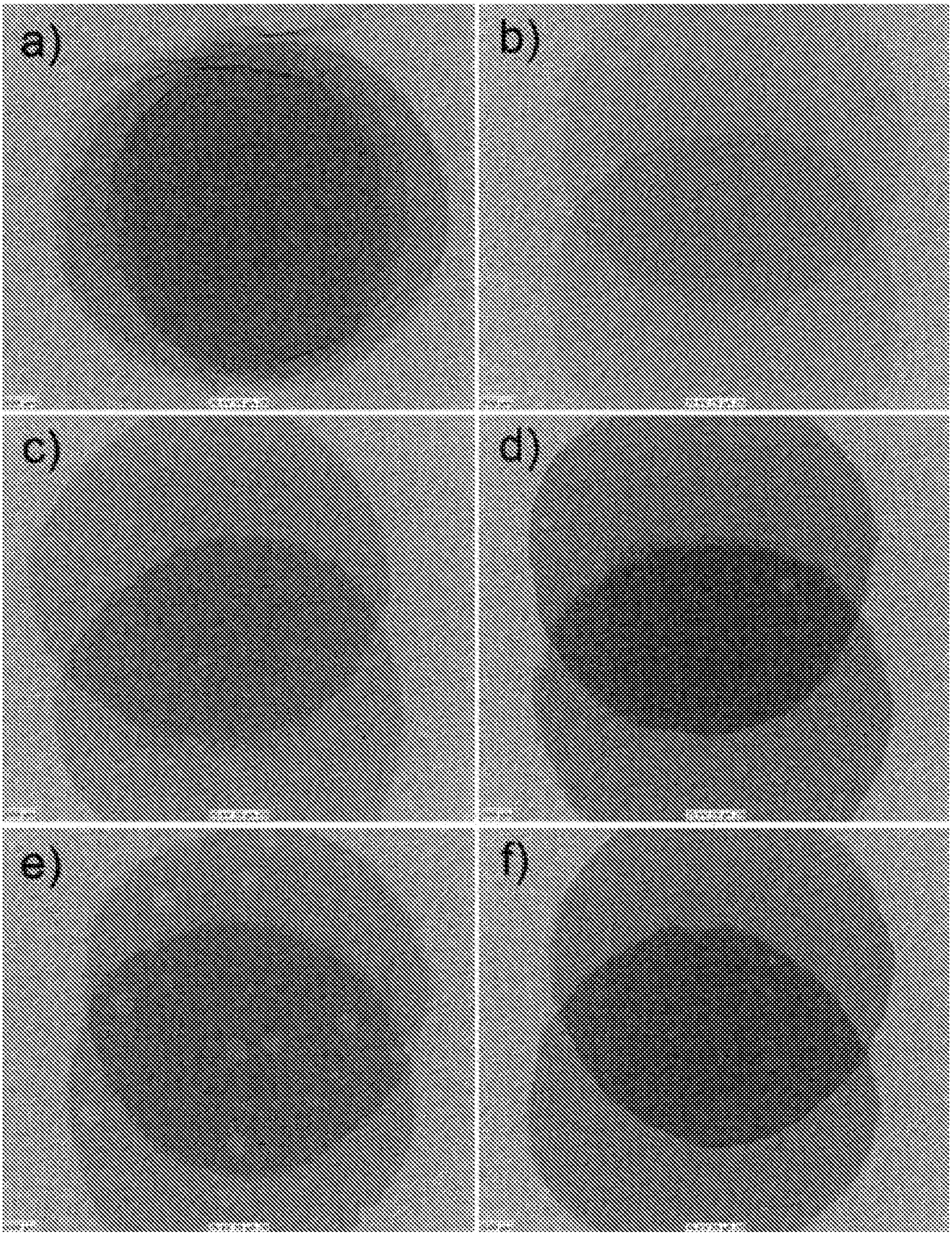


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2014/050555

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C59/56 A61L29/06 A61L31/06 A61L31/12 C08G18/42
A61K31/192 A61K31/194 C07C59/66
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)
C07C A61L C08G

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J Nucl ET AL: "Metabolism of Iodine-123-BMIPP in Perfused Rat Hearts", The Journal of Nuclear Medicine Copyright, 1 January 1995 (1995-01-01), pages 1043-1050, XP055148529, Retrieved from the Internet: URL:http://jnm.snmjournals.org/content/36/6/1043.full.pdf	1,2,5
A	page 1045, left-hand column, paragraph 3 see compound alpha-OH-BMIPP; page 1046; table 1	3,4,6-15

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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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
23 October 2014	31/10/2014

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	Bedel, Christian

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INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2014/050555

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. L. RIEBSOMER ET AL: "The Preparation of Substituted Mandelic Acids and their Bacteriological Effects. II", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 60, no. 12, 1 December 1938 (1938-12-01), pages 2974-2976, XP055148533, ISSN: 0002-7863, DOI: 10.1021/ja01279a045 see p-iodomandelic acid; page 2975; table 1	1
X	JANE MÜLLER ET AL: "In vitro Synthesis of New Cyclodepsipeptides of the PF1022-Type: Probing the [alpha]-D-Hydroxy Acid Tolerance of PF1022 Synthetase", CHEMBIOCHEM, vol. 10, no. 2, 26 January 2009 (2009-01-26), pages 323-328, XP055148523, ISSN: 1439-4227, DOI: 10.1002/cbic.200800539 See reference to p-iodobenzyl hydroxyacetic acid 33 in scheme 4; page 326 - page 327; compound 33	1,2
A	EP 1 702 628 A2 (CORDIS CORP [US]) 20 September 2006 (2006-09-20) paragraph [[0018]] paragraph [[0035]]; figures	1-15
A	WO 2009/081169 A2 (IOPHARMA TECHNOLOGIES AB [SE]; WANG JIAN SHENG [SE]; KIDD SARA [GB]; A) 2 July 2009 (2009-07-02) examples	1-15
A	EP 0 420 541 A2 (GOLDBERG JAY [US] ET AL) 3 April 1991 (1991-04-03) cited in the application the whole document	1-15

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/NL2014/050555

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