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(54) **Titre : VAISSEAU SANGUIN ARTIFICIEL**
(54) **Title: ARTIFICIAL BLOOD VESSEL**

(57) **Abrégé/Abstract:**

Provided is an artificial blood vessel comprising a cylindrical 3D woven textile structure with minimal blood leakage and which combines antithrombotic properties and cellular affinity. This artificial blood cell is a cylindrical textile structure having positioned therein a cylindrical textile, the inner surface of which comes into contact with blood, the cylindrical textile being a textile obtained by interweaving a plurality of warp yarns and a plurality of weft yarns, the warp yarns and weft yarns that constitute the cylindrical textile containing a multi-filament yarn having a single filament fineness not exceeding 0.50dtex, bonded with an antithrombotic material, the antithrombotic material forming an antithrombotic material layer having a thickness of 1-600nm on the inside of the cylindrical textile, and the water permeability when the inner surface is subjected to a pressure of 16kPa being less than 300mL/cm²/min.

ABSTRACT

The present invention aims to provide an artificial blood vessel composed of a cylindrical multiple-woven fabric structure, which allows only a small amount of blood leakage and can achieve both antithrombogenicity and cellular affinity. The present invention provides an artificial blood vessel comprising a cylindrical fabric structure in which a cylindrical fabric whose inside contacts blood is arranged, wherein the cylindrical fabric is a fabric prepared by interlacing a plurality of warp yarns and a plurality of weft yarns with each other into a cylindrical shape; the warp yarns and the weft yarns constituting the cylindrical fabric comprise a multifilament yarn having a single yarn fineness of not more than 0.50 dtex, and are bound to an antithrombogenic material; the antithrombogenic material forms an antithrombogenic material layer having a thickness of 1 to 600 nm inside the cylindrical fabric; and the water permeability under conditions where a pressure of 16 kPa is applied to the inner surface is less than 300 mL/cm²/min.

DESCRIPTION

ARTIFICIAL BLOOD VESSEL

TECHNICAL FIELD

5 [0001]

The present invention relates to a fabric artificial blood vessel which allows only a small amount of blood leakage and can achieve both antithrombogenicity and cellular affinity.

BACKGROUND ART

10 [0002]

An artificial blood vessel is a medical device which is used as an alternative to a living blood vessel suffering from a disease such as arteriosclerosis, or for formation of a bypass or a shunt. Conventional artificial blood vessels can be roughly divided into 1) artificial blood vessels made of a fabric; 2) artificial blood vessels made of polytetrafluoroethylene; 3) artificial blood vessels made of a biomaterial; and 4) artificial blood vessels made of a synthetic macromolecular material. Among these artificial blood vessels, fabric artificial blood vessels made of a woven fabric, knit, or non-woven fabric of fibers have high flexibility, but have a drawback in that blood leakage from gaps between fibers is likely to occur due to blood pressure under actual use conditions. Among fabric artificial blood vessels, artificial blood vessels made of a knit can be produced by a simple production process, and have flexibility. However, they have lower capacities to maintain their shapes, and are likely to have porous structures, so that blood leakage is likely to occur through gaps between fibers. Artificial blood vessels made of a non-woven fabric have uneven structures, and have lower capacities to maintain their shapes, which is not preferred.

25 [0003]

On the other hand, in fabric artificial blood vessels composed of a woven fabric, the gaps between the fibers can be reduced, and the amount of blood leakage can therefore be reduced unlike artificial blood vessels made of a knit. Therefore, fabric artificial blood vessels composed of a woven fabric are highly demanded in surgery of blood vessels such as aortas. As a method for reducing the amount of blood leakage, a method by reducing the size of each gap between fibers is commonly used. However, in this method, the resulting artificial blood vessel is hard because of an increase in the fiber density. Use of such a hard artificial blood vessel often makes the surgery difficult since both ends of the diseased living blood vessel to be replaced, that is, the living blood vessels to be anastomosed with the artificial blood vessel, are also affected by arteriosclerosis or the like.

[0004]

In view of this, for cases where a fabric artificial blood vessel is used in blood vessel surgery, a method in which blood leakage is prevented not only by reducing the size of each gap between fibers, but also by giving a bioabsorbable gel such as collagen or gelatin to the gaps between the fibers to fill the gaps, has been reported (Patent Document 1).

[0005]

Methods in which the so-called preclotting is carried out have also been reported (Patent Documents 2 and 3). In the operation of preclotting, a fabric artificial blood vessel is brought into contact with autologous blood immediately before the transplantation, to allow formation of thrombi, and the gaps between the fibers are filled with the resulting thrombi to prevent blood leakage.

[0006]

When an artificial blood vessel is transplanted, the living body recognizes it as a foreign substance, and blood coagulation reaction proceeds on the surface of the artificial blood vessel contacting blood, that is, on inner surface, leading to formation

of thrombi. Therefore, artificial blood vessels require antithrombogenicity.

[0007]

Conventionally, as a method for increasing the antithrombogenicity of a medical material, a method in which heparin or a heparin derivative is given to a surface of the material has been employed. However, heparin and heparin derivatives cannot be directly given to fabric medical materials made of polyester fibers and the like, and medical materials made of stretched porous polytetrafluoroethylene (hereinafter referred to as “ePTFE”), which constitute artificial blood vessels. In view of this, methods in which a surface of a medical material is modified, and heparin or a heparin derivative is given to the surface of the material by covalent bonding (Patent Documents 4 to 6), or heparin or a heparin derivative is given to the surface of the material by ionic bonding (Patent Documents 7 to 10), have been reported.

[0008]

As methods for giving antithrombogenicity to a fabric artificial blood vessel, methods in which a bioabsorbable gel used for preventing blood leakage, for example, collagen or gelatin, is impregnated with heparin or a heparin derivative, and the resulting gel is given to a surface of a material (Patent Documents 1 and 11), and a method in which a segmented polyurethane dissolved in an organic solvent is impregnated with heparin or a heparin derivative, and the resulting product is given to a surface of a material (Patent Document 12), have been reported.

[0009]

As methods for increasing the antithrombogenicity of a medical material using a compound having antithrombogenicity other than heparin or heparin derivatives, methods in which a compound(s) that inhibit(s) a plurality of blood coagulation factors involved in the blood coagulation reaction (for example, platelets, which are involved in the stage of primary hemostasis), thrombin, which is involved

in the stage of thrombus formation, and/or the like is/are given to a surface of the medical material (Patent Documents 13 to 15) have been reported.

[0010]

Living blood vessels have an intima on their inner surfaces, and can inhibit thrombus formation by having vascular endothelial cells. On the other hand, in conventional artificial blood vessels, the cellular affinity is low, and settlement of vascular endothelial cells is less likely to occur. Moreover, settlement of vascular endothelial cells and formation of the intima take long time. Therefore, not only antithrombogenicity immediately after the transplantation, but also a function to generate cellular affinity with time, have been required.

[0011]

Examples of reported methods for giving cellular affinity to a fabric artificial blood vessel include methods in which an artificial blood vessel is made such that it has a fiber structure which promotes growth and infiltration of cells, such as a method in which the fiber diameter is optimized, and a method in which fluffy, fuzzy, and/or looped fibers are given (Patent Documents 16 to 19).

PRIOR ART DOCUMENTS

[Patent Documents]

[0012]

[Patent Document 1] JP 3799626 B

[Patent Document 2] JP 5-48132 B

[Patent Document 3] JP 5-88611 B

[Patent Document 4] Japanese Translated PCT Patent Application Laid-open

No. 2009-545333

[Patent Document 5] JP 4152075 B

[Patent Document 6] JP 3497612 B

[Patent Document 7] JP 60-41947 B

[Patent Document 8] JP 60-47287 B

[Patent Document 9] JP 4273965 B

[Patent Document 10] JP 10-151192 A

[Patent Document 11] JP 8-24686 B

5 [Patent Document 12] JP 7-265338 A

[Patent Document 13] JP 4461217 B

[Patent Document 14] WO 08/032758

[Patent Document 15] WO 12/176861

[Patent Document 16] JP 61-4546 B

10 [Patent Document 17] JP 61-58190 B

[Patent Document 18] JP 63-52898 B

[Patent Document 19] JP 5-28143 B

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

15 [0013]

However, in cases where the method disclosed in Patent Document 1 is used for a fabric artificial blood vessel, the fiber diameter and microstructures such as gaps between fibers for promotion of the cell growth disappear due to the gel such as collagen or gelatin containing heparin or a heparin derivative given to the fiber surface, leading to a decrease in the cellular affinity. Moreover, adhesion of platelets to the bioabsorbable gel such as gelatin rather promotes thrombus formation, which is problematic.

[0014]

On the other hand, Patent Document 2 and Patent Document 3 disclose methods for preparing an artificial blood vessel having a high-porosity structure, that is, a high-water permeability woven structure, in order to allow quick settlement of vascular endothelial cells on the inner surface of the artificial blood vessel, thereby

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promoting formation of the intima, or in order to reduce foreign substances, thereby increasing the biocompatibility, respectively. However, preclotting is indispensable in these methods, and the fiber diameter and microstructures such as gaps between fibers disappear due to thrombi formed by this operation, leading to a decrease in the cellular affinity. In blood vessel surgery, an anticoagulant (for example, heparin or argatroban) is commonly used for prevention of blood coagulation during the surgery, and the blood vessel is therefore in a state where a thrombus is less likely to be formed. Thus, in some cases, the gaps between the fibers cannot be sufficiently filled by the preclotting. Furthermore, in some cases, thrombi formed by the preclotting are melt due to the action of the fibrinolytic system in blood after the surgery, leading to blood leakage.

[0015]

Patent Documents 4 to 10 describe methods in which heparin or a heparin derivative is given to a surface of a medical material by covalent or ionic bonding of the heparin or the heparin derivative to a surface modifier. However, in terms of use of a fabric artificial blood vessel having a fiber diameter and/or a microstructure such as gaps between fibers for promotion of the cell growth, these documents do not describe an appropriate thickness of the antithrombogenic material layer composed of the surface modifier and the heparin or the heparin derivative.

[0016]

Patent Documents 11 and 12 describe methods in which a bioabsorbable gel containing heparin or a heparin derivative, or an antithrombogenic material dissolved in an organic solvent, is physically given to a surface of a medical material. Since, in these methods, the antithrombogenic material layer is thick, the fiber diameter and microstructures such as gaps between fibers for promotion of the cell growth disappear.

[0017]

Similarly, Patent Documents 13 to 15 describe methods in which two compounds having both anti-platelet adhesion capacity and antithrombin activation capacity, or a compound prepared by giving both anti-platelet adhesion capacity and antithrombin activation capacity to a single molecule, is/are immobilized on a surface of a medical material. However, in terms of use for a fabric artificial blood vessel having a fiber diameter and/or a microstructure such as gaps between fibers for promotion of the cell growth, these documents do not describe any appropriate thickness of the antithrombogenic material layer composed of such a compound(s).
[0018]

Patent Documents 16 to 19 disclose artificial blood vessels having cellular affinity prepared using a fiber of not more than 0.5 denier, that is, not more than 0.56 dtex, for at least a part of the inner surface. However, since antithrombogenicity, which is required immediately after the transplantation, is not given to those artificial blood vessels, they cannot suppress thrombus formation. Although a method for increasing the cellular affinity by giving fluffy, fuzzy, and/or looped fibers has been disclosed, such a method has a problem in that an additional step for forming the fluffy, fuzzy, and/or looped fibers is required, and that this additional step produces waste fibers whose elution into blood may occur. Moreover, this method has a problem in that, since disturbance of the fiber directions of the warp yarns and the weft yarns increases, settlement of vascular endothelial cells is less likely to occur, and the cellular affinity therefore decreases.

[0019]

That is, at present, there is no artificial blood vessel composed of a cylindrical fabric structure which allows only a small amount of blood leakage and can achieve both the antithrombogenicity and the cellular affinity. In particular, in cases of a small-diameter artificial blood vessel having an inner diameter of less than 6 mm, thrombi are likely to be formed because of low blood flow, and even a small

thrombus may have a size comparable to the inner diameter of the blood vessel. Thus, inhibition of the blood flow is likely to occur. Therefore, small-diameter artificial blood vessels show poor long-term performances, and none of them is clinically useful at present.

5 [0020]

In view of this, an object of the present invention is to provide a fabric artificial blood vessel which allows only a small amount of blood leakage and can achieve both the antithrombogenicity and the cellular affinity.

MEANS FOR SOLVING THE PROBLEMS

10 [0021]

As a result of intensive study to solve the problems described above, the present inventors discovered the inventions of (1) to (12).

(1) An artificial blood vessel comprising a cylindrical fabric structure in which a cylindrical fabric whose inside contacts blood is arranged,

15 wherein

the cylindrical fabric whose inside contacts blood is a fabric prepared by interlacing a plurality of warp yarns and a plurality of weft yarns with each other into a cylindrical shape;

20 the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood comprise a multifilament yarn having a single yarn fineness of not more than 0.50 dtex, and are bound to an antithrombogenic material;

the antithrombogenic material forms an antithrombogenic material layer having a thickness of 1 to 600 nm inside the cylindrical fabric whose inside contacts blood; and

25 the water permeability under conditions where a pressure of 16 kPa is applied to the inner surface is less than 300 mL/cm²/min.

(2) The artificial blood vessel according to (1), wherein the cylindrical fabric

structure is a multi-cylindrical fabric structure in which an outer-layer cylindrical fabric is arranged outside the cylindrical fabric whose inside contacts blood, and the outer-layer cylindrical fabric is a fabric prepared by interlacing a plurality of warp yarns and weft yarns with each other into a cylindrical shape.

5 (3) The artificial blood vessel according to (2), wherein the outer-layer cylindrical fabric comprises, as a warp yarn, a multifilament yarn having a single yarn fineness of not less than 1.0 dtex.

(4) The artificial blood vessel according to (3), wherein the percentage of exposure of the multifilament yarn having a single yarn fineness of not less than 1.0
10 dtex on the inner surface is not more than 20%.

(5) The artificial blood vessel according to any one of (1) to (4), wherein the cover factor for the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood is 1800 to 4000.

(6) The artificial blood vessel according to any one of (2) to (5), wherein the
15 outer-layer cylindrical fabric comprises, as a weft yarn, a monofilament yarn having a single yarn fineness of not less than 15.0 dtex.

(7) The artificial blood vessel according to any one of (1) to (6), wherein the antithrombogenic material comprises an anionic compound containing a sulfur atom and having anticoagulant activity.

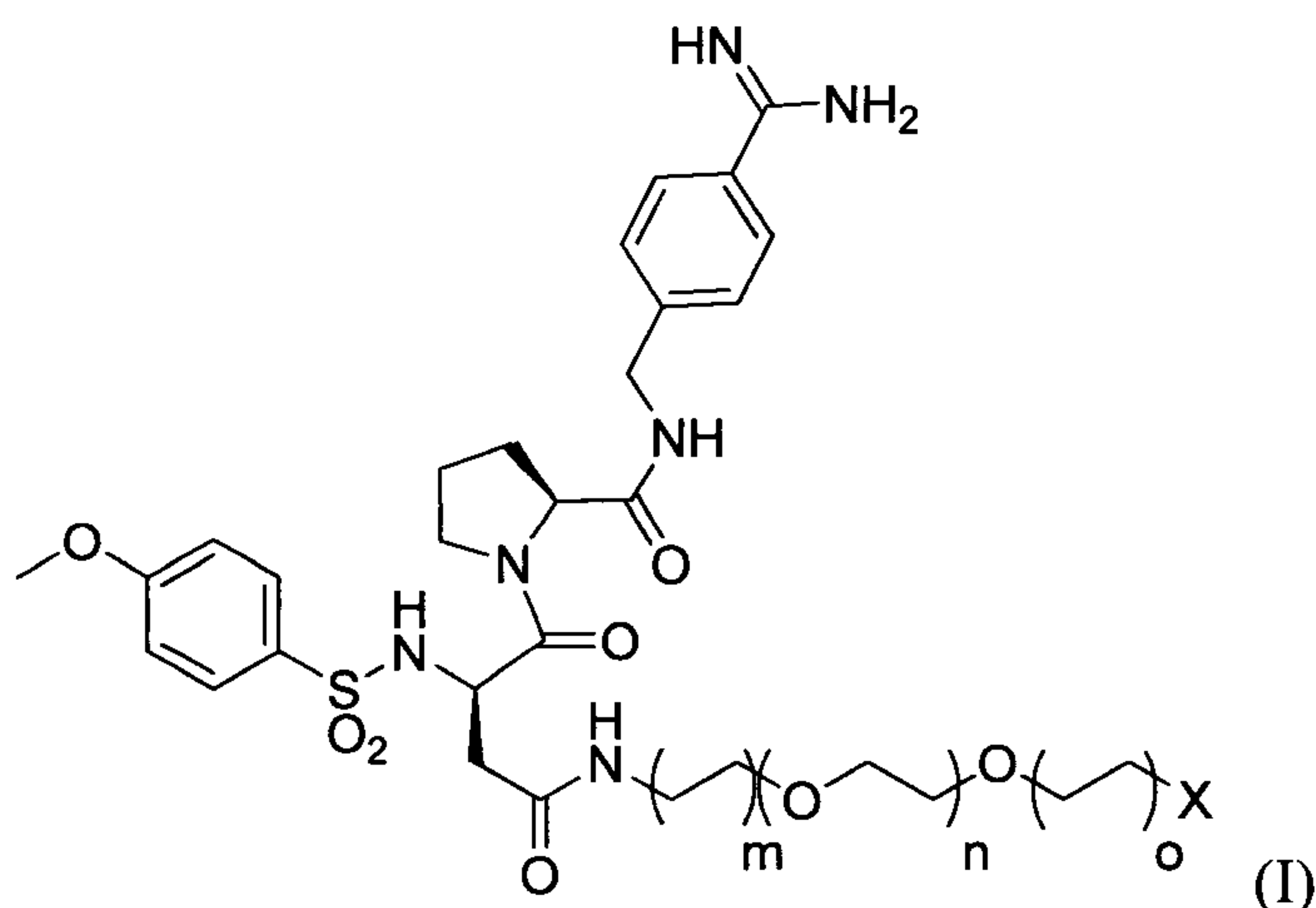
20 (8) The artificial blood vessel according to (7), wherein the ratio of the abundance of sulfur atoms to the abundance of total atoms on the inner surface as measured by X-ray photoelectron spectroscopy (XPS) is 3.0 to 6.0 atomic percent.

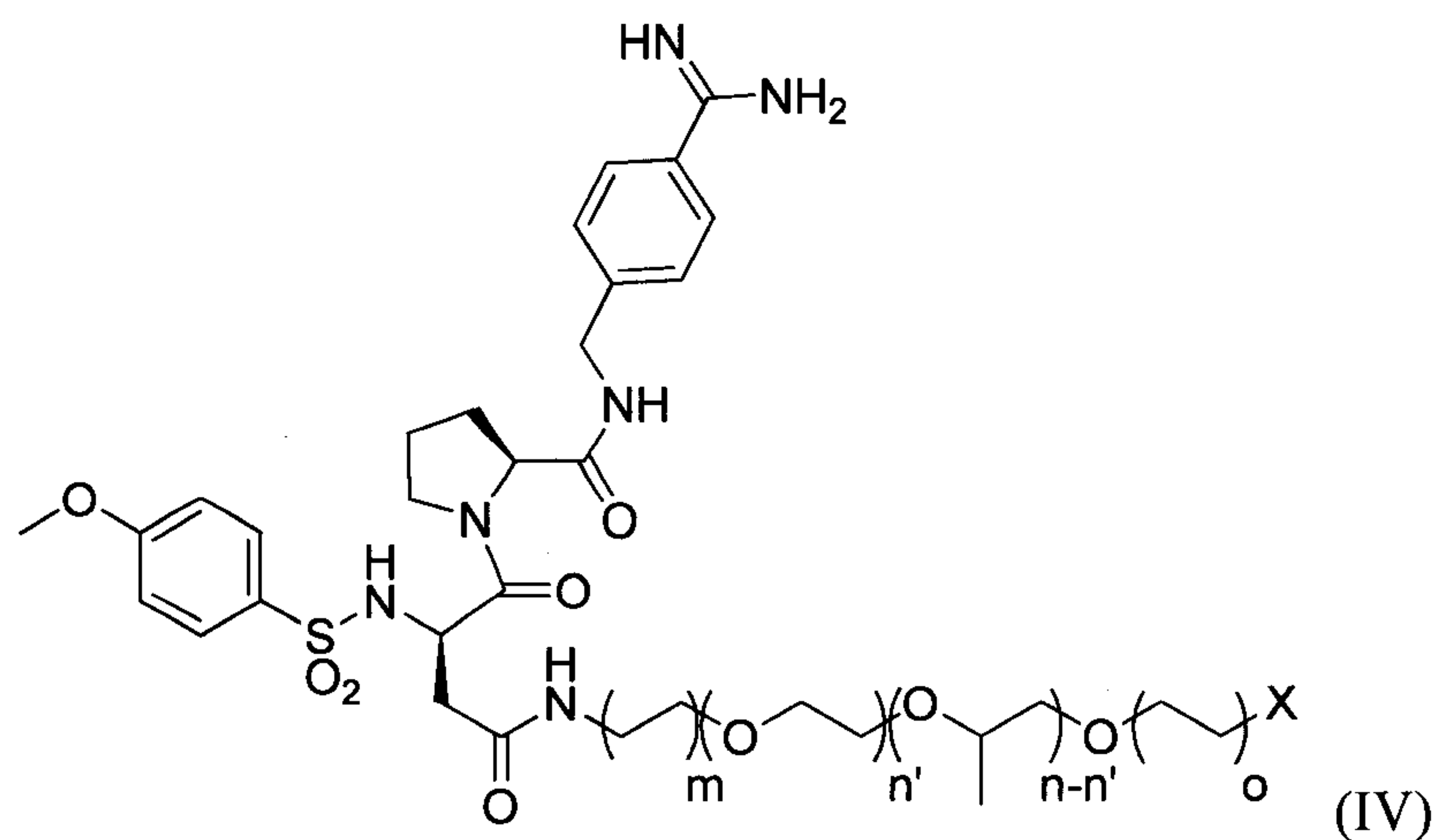
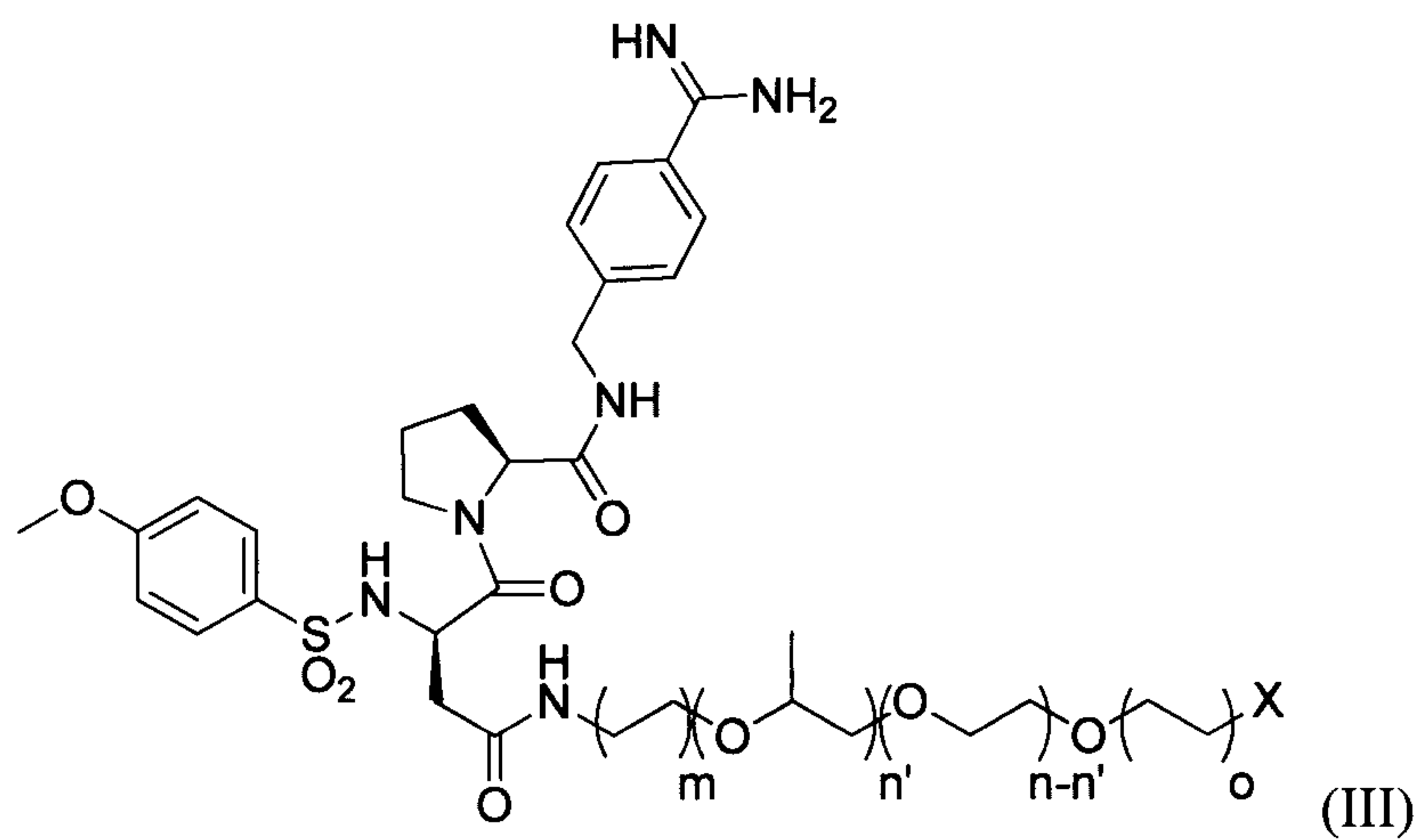
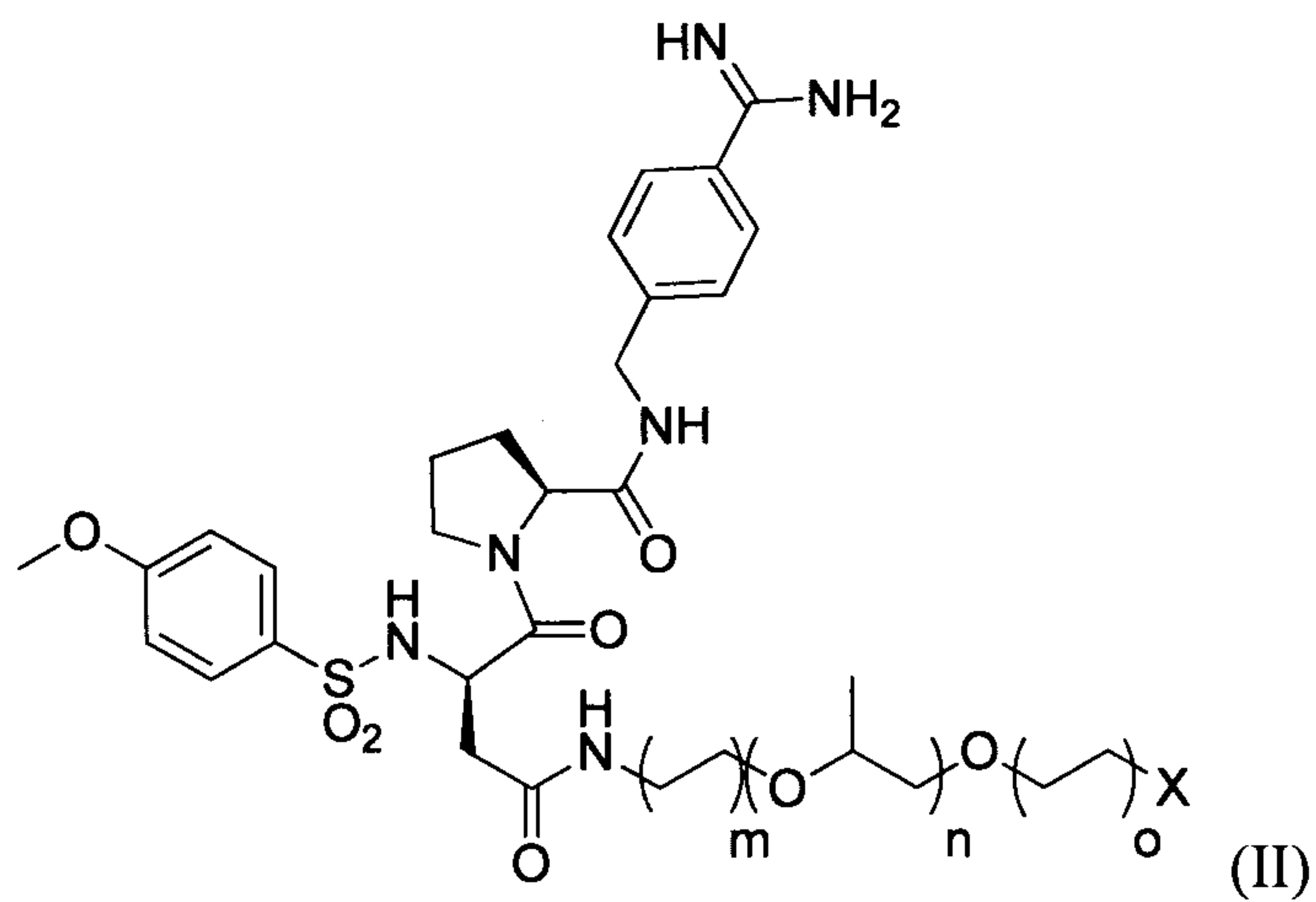
(9) The artificial blood vessel according to any one of (1) to (8), wherein the antithrombogenic material comprises a cationic polymer containing, as a constituent
25 monomer, a compound selected from the group consisting of alkyleneimines, vinylamines, allylamines, lysine, protamine, and diallyldimethylammonium chloride, and the cationic polymer is covalently bound to the warp yarns and the weft yarns

constituting the cylindrical fabric whose inside contacts blood.

(10) The artificial blood vessel according to any one of (1) to (6), wherein the antithrombogenic material is a compound containing the following three kinds of skeletal structures: a skeletal structure composed of a hydrophilic polymer containing, as a constituent monomer, a compound selected from the group consisting of ethylene glycol, propylene glycol, vinylpyrrolidone, vinyl alcohol, vinylcaprolactam, vinyl acetate, styrene, methyl methacrylate, hydroxyethyl methacrylate, and siloxane; a skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine; and a skeletal structure composed of methoxybenzenesulfonic acid amide; wherein the compound containing the three kinds of skeletal structures is covalently bound to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood.

(11) The artificial blood vessel according to (10), wherein the compound containing the three kinds of skeletal structures is a compound represented by any one of the following General Formulae (I) to (IV):





5

[wherein m and o each represent an integer of 0 to 4; n represents an integer of 3 to 1000, and n' represents an integer of 3 to 1000, with the proviso that $n \geq n'$; and X represents a functional group selected from the group consisting of hydroxyl, thiol, amino, carboxyl, aldehyde, isocyanate, and thioisocyanate].

(12) The artificial blood vessel according to any one of (1) to (11), wherein the antithrombogenic material comprises: an anionic polymer comprising, as a constituent monomer, a compound selected from the group consisting of acrylic acid, methacrylic acid, α -glutamic acid, γ -glutamic acid, and aspartic acid; or an anionic compound selected from the group consisting of oxalic acid, malonic acid, succinic acid, fumaric acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, malic acid, tartaric acid, and citric acid.

(13) The artificial blood vessel according to any one of (1) to (12), wherein the multifilament yarn is composed of a polyester.

[0022]

The present invention also provides the artificial blood vessels according to the following (13) to (24).

(13) An artificial blood vessel comprising a multi-cylindrical fabric structure in which an inner-layer cylindrical fabric is arranged inside an outer-layer cylindrical fabric,
wherein

each of the outer-layer cylindrical fabric and the inner-layer cylindrical fabric is a fabric prepared by interlacing a plurality of warp yarns and a plurality of weft yarns with each other into a cylindrical shape;

the warp yarns and the weft yarns constituting the inner-layer cylindrical fabric comprise a multifilament yarn having a single yarn fineness of not more than 0.30 dtex, and are bound to an antithrombogenic material;

the antithrombogenic material forms an antithrombogenic material layer having a thickness of 1 to 600 nm inside the inner-layer cylindrical fabric; and

the water permeability under conditions where a pressure of 16 kPa is applied to the inner surface is less than 300 mL/cm²/min.

(14) The artificial blood vessel according to (13), wherein the outer-layer

cylindrical fabric comprises, as a warp yarn, a multifilament yarn having a single yarn fineness of not less than 1.0 dtex.

(15) The artificial blood vessel according to (14), wherein the percentage of exposure of the multifilament yarn having a single yarn fineness of not less than 1.0 dtex on the inner surface is not more than 20%.

(16) The artificial blood vessel according to any one of (13) to (15), wherein the outer-layer cylindrical fabric comprises, as a weft yarn, a monofilament yarn having a single yarn fineness of not less than 15.0 dtex.

(17) The artificial blood vessel according to any one of (13) to (16), wherein the antithrombogenic material comprises an anionic compound having anticoagulant activity and containing a sulfur atom.

(18) The artificial blood vessel according to (17), wherein the ratio of the abundance of sulfur atoms to the abundance of total atoms on the inner surface as measured by X-ray photoelectron spectroscopy (XPS) is 3.0 to 6.0 atomic percent.

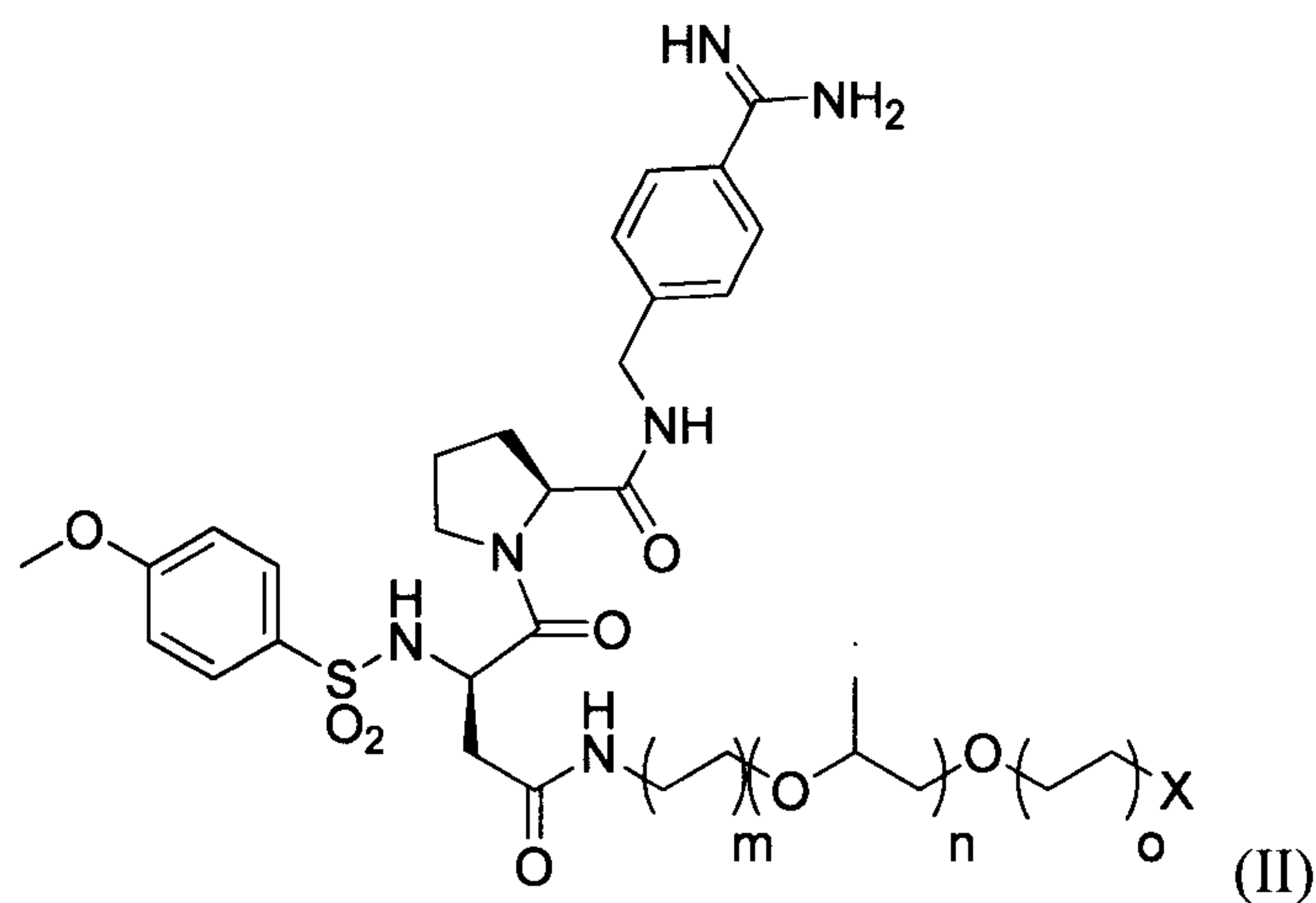
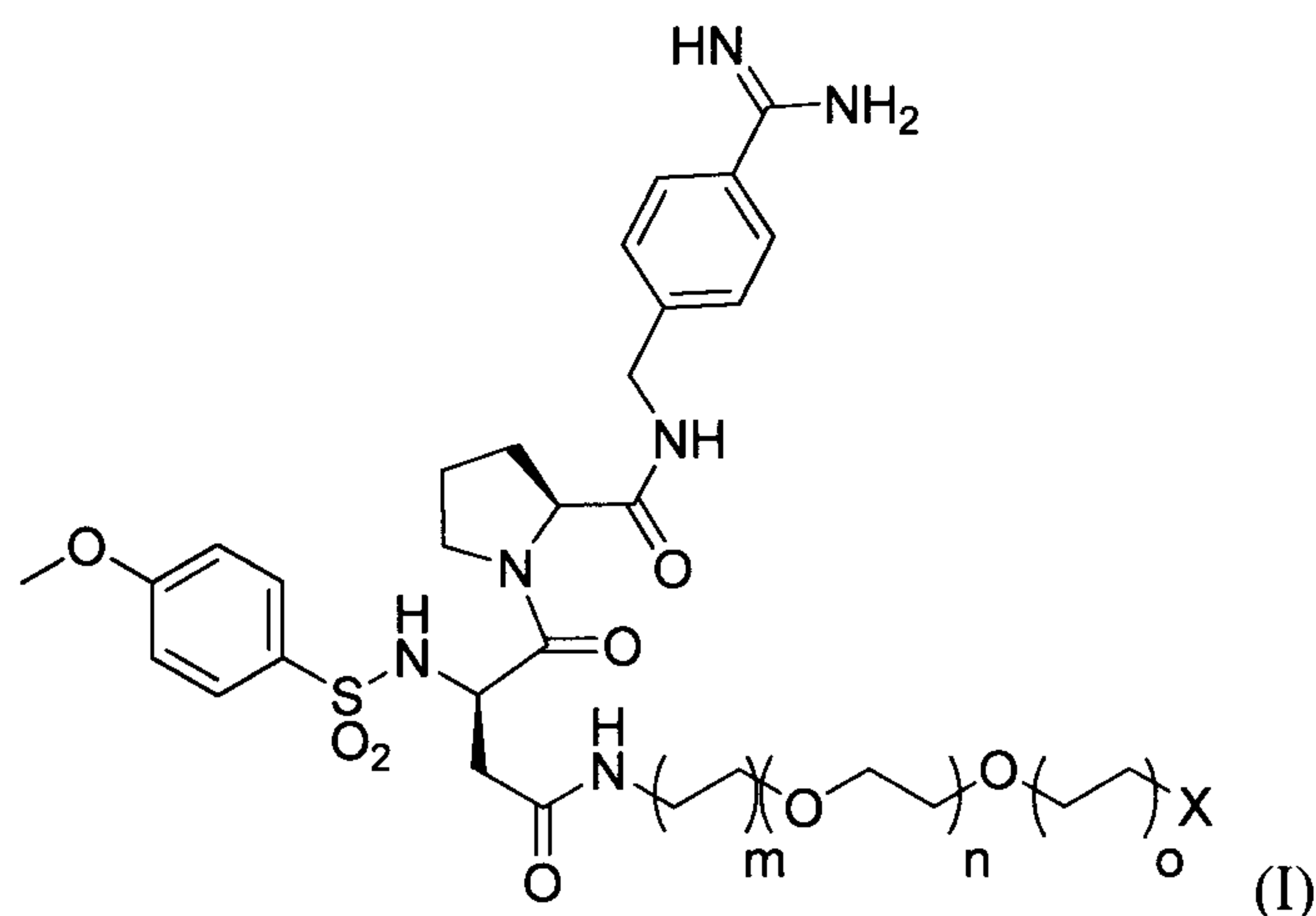
(19) The artificial blood vessel according to any one of (1) to (18), wherein the antithrombogenic material comprises a cationic polymer containing, as a constituent monomer, a compound selected from the group consisting of alkyleneimines, vinylamines, allylamines, lysine, protamine, and diallyldimethylammonium chloride, and the cationic polymer is covalently bound to the warp yarns and the weft yarns constituting the inner-layer cylindrical fabric.

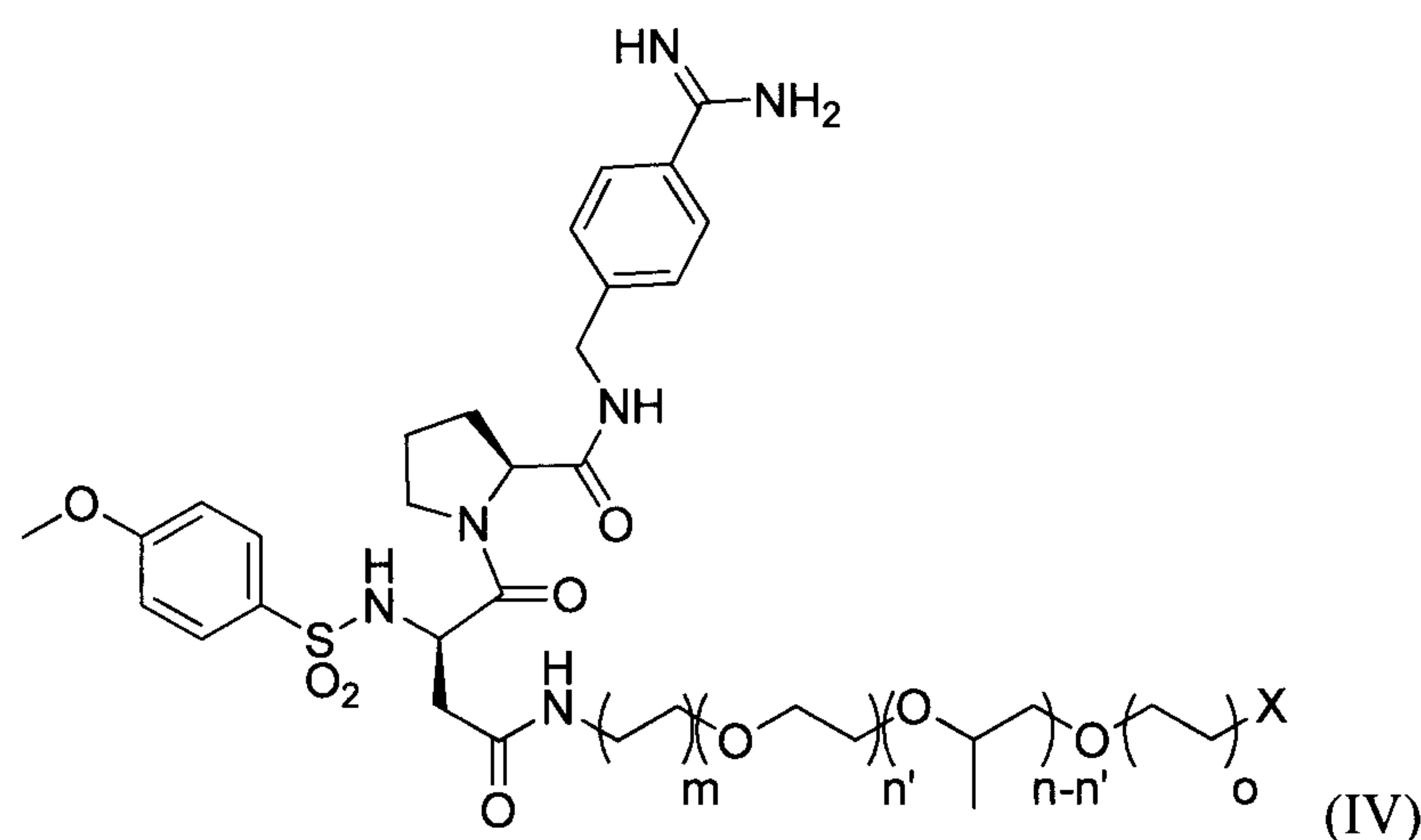
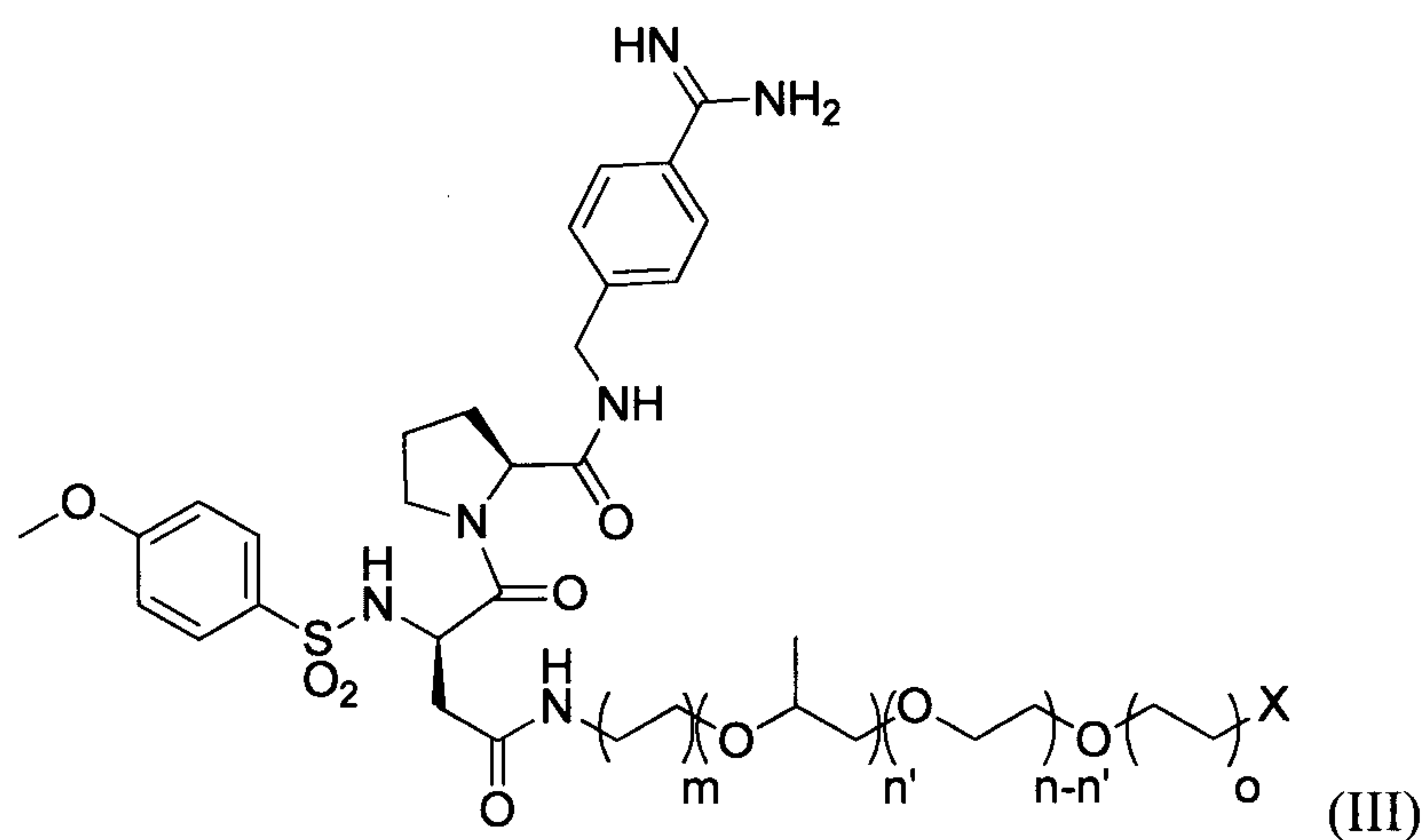
(20) The artificial blood vessel according to (19), wherein the ratio of the abundance of nitrogen atoms to the abundance of total atoms on the inner surface as measured by X-ray photoelectron spectroscopy (XPS) is 7.0 to 12.0 atomic percent.

(21) The artificial blood vessel according to any one of (13) to (16), wherein the antithrombogenic material is a compound containing the following three kinds of skeletal structures: a skeletal structure composed of a hydrophilic polymer containing, as a constituent monomer, a compound selected from the group consisting of

ethylene glycol, propylene glycol, vinylpyrrolidone, vinyl alcohol, vinylcaprolactam, vinyl acetate, styrene, methyl methacrylate, hydroxyethyl methacrylate, and siloxane; a skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine; and a skeletal structure composed of methoxybenzenesulfonic acid amide; wherein the compound containing the three kinds of skeletal structures is covalently bound to the warp yarns and the weft yarns constituting the inner-layer cylindrical fabric.

(22) The artificial blood vessel according to (21), wherein the compound containing the three kinds of skeletal structures is a compound represented by any one of the following General Formulae (I) to (IV):





[wherein m and o each represent an integer of 0 to 4; n represents an integer of 3 to 1000, and n' represents an integer of 3 to 1000, with the proviso that $n \geq n'$; and X represents a functional group selected from the group consisting of hydroxyl, thiol, amino, carboxyl, aldehyde, isocyanate, and thioisocyanate].

(23) The artificial blood vessel according to any one of (13) to (22), wherein the antithrombogenic material comprises: an anionic polymer comprising, as a constituent monomer, a compound selected from the group consisting of acrylic acid, methacrylic acid, α -glutamic acid, γ -glutamic acid, and aspartic acid; or an anionic compound selected from the group consisting of oxalic acid, malonic acid, succinic acid, fumaric acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, malic acid, tartaric acid, and citric acid.

(24) The artificial blood vessel according to any one of (13) to (23), wherein the

multifilament yarn is composed of a polyester.

EFFECT OF THE INVENTION

[0023]

5 The fabric artificial blood vessel of the present invention allows only a small amount of blood leakage, and can achieve both the antithrombogenicity and the cellular affinity.

MODE FOR CARRYING OUT THE INVENTION

[0024]

10 The artificial blood vessel of the present invention is characterized in that, in a cylindrical fabric structure in which a cylindrical fabric whose inside contacts blood is arranged,

the cylindrical fabric whose inside contacts blood is a fabric prepared by interlacing a plurality of warp yarns and a plurality of weft yarns with each other into a cylindrical shape;

15 the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood comprise a multifilament yarn having a single yarn fineness of not more than 0.50 dtex, and are bound to an antithrombogenic material;

the antithrombogenic material forms an antithrombogenic material layer having a thickness of 1 to 600 nm inside the cylindrical fabric whose inside contacts
20 blood; and

the water permeability under conditions where a pressure of 16 kPa is applied to the inner surface is less than 300 mL/cm²/min.

[0025]

25 The following terms used in the present description are defined as described below unless otherwise specified.

[0026]

The cylindrical fabric herein means a fabric prepared by interlacing a

plurality of warp yarns and a plurality of weft yarns with each other into a cylindrical shape. In the artificial blood vessel of the present invention, a structure in which a cylindrical fabric whose inside contacts blood is arranged is defined as a cylindrical fabric structure. In the artificial blood vessel of the present invention, the

5 cylindrical fabric whose inside contacts blood is defined as an inner-layer cylindrical fabric; the cylindrical fabric forming the outer layer of the artificial blood vessel is defined as an outer-layer cylindrical fabric; and the structure in which the outer-layer cylindrical fabric and the inner-layer cylindrical fabric are laminated with each other is defined as a multi-cylindrical fabric structure. The multi-cylindrical fabric

10 structure constituting the artificial blood vessel of the present invention may contain a cylindrical fabric layer other than the inner-layer cylindrical fabric and the outer-layer cylindrical fabric. However, in cases where the number of cylindrical fabric layers is too large, the artificial blood vessel is thick, and therefore the difference between the thickness of the artificial blood vessel and the thickness of the living

15 blood vessel is large. This causes difficulty in anastomosis in the transplantation surgery. In view of this, the number of cylindrical fabric layers is preferably 2 to 4, more preferably 2 to 3. Double-woven artificial blood vessels, whose number of cylindrical fabric layers is 2, can be integrally woven by a well-known method such as inner-layer warp yarn fastening, inner-layer weft yarn fastening, or multi-weft

20 yarn fastening. In cases where double weaving is carried out, the process of laminating the two fabrics with each other by a method such as lamination or sewing is not necessary, and, since the two layers are integrated with each other through warp yarns or weft yarns, the artificial blood vessel obtained can have high flexibility and high mechanical strength.

25 [0027]

The single yarn fineness herein means a value calculated according to the JIS L 1013 (2010) 8.3.1 A method, in which the fineness based on corrected weight is

measured at a predetermined load of 0.045 cN/dtex to determine the total fineness, and the total fineness is then divided by the number of monofilaments.

[0028]

In the present invention, in cases where the single yarn fineness of the warp
5 yarns and the weft yarns constituting the cylindrical fabric whose inside contacts
blood is too large, when the yarns are tightly woven in order to reduce the amount of
blood leakage, the resulting artificial blood vessel is hard, and moreover, settlement
of vascular endothelial cells is less likely to occur, so that the cellular affinity is low.
On the other hand, in cases where the single yarn fineness is too small, the
10 mechanical strength of the artificial blood vessel is less likely to be maintained, and
settlement of vascular endothelial cells is less likely to occur. That is, as a result of
intensive study, the present inventors discovered that, on the inner surface of the
artificial blood vessel which contacts blood, the warp yarns and the weft yarns
constituting the cylindrical fabric whose inside contacts blood preferably comprise a
15 multifilament yarn having a single yarn fineness of 0.05 to 0.50 dtex, more
preferably comprise a multifilament yarn having a single yarn fineness of 0.05 to
0.30 dtex, still more preferably comprise a multifilament yarn having a single yarn
fineness of 0.06 to 0.28 dtex, still more preferably comprise a multifilament yarn
having a single yarn fineness of 0.08 to 0.25 dtex. The inner surface herein means
20 the surface inside the artificial blood vessel including the inside of the cylindrical
fabric whose inside contacts blood, and the antithrombogenic material layer formed
by binding of the antithrombogenic material to the inside of the cylindrical fabric
whose inside contacts blood.

[0029]

25 As the multifilament yarn having a single yarn fineness of not more than 0.50
dtex, the so-called direct-spun type may be used as it is. Alternatively, for example,
a split-yarn type such as a sea-island composite fiber may be used as it is. In cases

of a split-yarn type, when fibers that can be made into ultrafine fibers by chemical or physical means are used, ultrafine fibers can be formed after formation of the artificial blood vessel. Examples of the method for forming the fibers into the ultrafine fibers by chemical or physical means include the methods described in US 3531368 B and US 3350488 B, wherein means such as removal or detachment of a component from multicomponent fibers is used to allow fibrillation of the fibers, or to make the fibers into ultrafine fibers. By this, even in cases where a multifilament yarn having a single yarn fineness of more than 0.50 dtex is used, the fibers can be made into ultrafine fibers having a single yarn fineness of not more than 0.50 dtex after the formation of the artificial blood vessel. Therefore, troubles in the processing, for example, yarn breakage and fluffing associated with various yarn processing means during the weaving or before the weaving, can be minimized.

[0030]

The bond herein means a chemical bond such as a covalent bond, hydrogen bond, ionic bond, or coordinate bond. The covalent bond herein means a chemical bond formed by sharing of an electron(s) between atoms. Examples of the type of the covalent bond include, but are not limited to, an amine bond, azide bond, amide bond, and imine bond. Among these, from the viewpoint of ease of formation of the covalent bond, stability after bonding, and the like, an amide bond is more preferred. The presence of covalent bonds can be confirmed by observing the fact that elution does not occur by washing of the artificial blood vessel with a solvent which dissolves the antithrombogenic material.

[0031]

In the present invention, in cases where the water permeability is too high, the sizes and the amount of the gaps between the fibers are large, so that application of a gel such as collagen or gelatin, preclotting immediately before the transplantation, and/or the like may be necessary, which is not preferred. That is, as a result of

intensive study, the present inventors discovered that the water permeability under conditions where a pressure of 16 kPa is applied to the inner surface is preferably less than 300 mL/cm²/min., more preferably less than 200 mL/cm²/min., still more preferably less than 150 mL/cm²/min.

5 [0032]

On the other hand, in a cylindrical fabric such as the one in the present invention, low water permeability cannot be achieved only by controlling the gaps between the fibers, and its achievement requires an operation of application of a bioabsorbable gel such as collagen or gelatin, as in the known cases. In such a case, the fiber diameter and microstructures such as gaps between fibers for promotion of the cell growth disappear, leading to a decrease in the cellular affinity. Moreover, adhesion of platelets to the bioabsorbable gel such as gelatin rather promotes thrombus formation, which is problematic. That is, as a result of intensive study, the present inventors discovered that the water permeability under conditions where a pressure of 16 kPa is applied to the inner surface is preferably more than 0.1 mL/cm²/min., more preferably more than 0.5 mL/cm²/min., still more preferably more than 1 mL/cm²/min.

[0033]

The water permeability under conditions where a pressure of 16 kPa is applied to the inner surface herein means a value determined according to the guidance in ISO 7198 by applying a pressure (hydrostatic pressure) of 16 kPa to the inner surface of the artificial blood vessel, including the inside of the cylindrical fabric whose inside contacts blood, and the antithrombogenic material layer, and dividing the amount of water (mL) flown out into the outer layer of the artificial blood vessel by the unit area (cm²) and the unit time (min.). The thus determined water permeability can be used as an index representing the sizes and the amount of the gaps between the fibers of the artificial blood vessel. The water permeability

can be adjusted by changing, for example, the component ratios of the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood; the single yarn diameter; the packing density; and/or the thickness and the hydrophilicity of the antithrombogenic material layer.

5 [0034]

In the present invention, in cases where the ratio of the multifilament yarns having a single yarn fineness of not more than 0.50 dtex in the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood is too low on the inner surface of the artificial blood vessel which contacts blood, the sizes and
10 the amount of the gaps between the fibers are large, so that the amount of blood leakage is large. Moreover, settlement of vascular endothelial cells is less likely to occur, and the cellular affinity is likely to be low. In view of this, the present inventors intensively studied to discover that the ratio of the multifilament yarns having a single yarn fineness of not more than 0.50 dtex in the warp yarns and the
15 weft yarns constituting the cylindrical fabric whose inside contacts blood is preferably not less than 50%, more preferably not less than 60%, still more preferably not less than 80%.

[0035]

In the present invention, from the viewpoint of promoting settlement of
20 vascular endothelial cells and increasing the cellular affinity, the single yarn diameter of the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood is preferably 300 nm to 10 μm , more preferably 1 to 5 μm , still more preferably 3 μm . The single yarn diameter of the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood was measured on a
25 micrograph at a magnification of x 400.

[0036]

The cover factor on the inner surface of the artificial blood vessel herein

represents the extent of the gaps between the fibers of the cylindrical fabric whose inside contacts blood, that is, the packing density. The smaller the cover factor, the larger the gaps between the fibers. In cases where the cover factor on the inner surface of the artificial blood vessel is too large, the packing density is high, and the flexibility is therefore lower than that of living blood vessels, resulting in not only hardening of the artificial blood vessel, but also unstable weaving performance. On the other hand, in cases where the cover factor on the inner surface of the artificial blood vessel is too small, the sizes and the amount of the gaps between the fibers are large, and therefore the water permeability is high, and the amount of blood leakage is large. Accordingly, the cover factor on the inner surface of the artificial blood vessel is preferably 1800 to 4000, more preferably 2000 to 3000. The cover factor on the inner surface of the artificial blood vessel is a value calculated from the total fineness and the base fabric density of the multifilament yarns used as the warp yarns and the weft yarns, and is calculated according to the following Equation 1.

[0037]

$$CF = (Dw \times 0.9)^{1/2} \times Nw + (Df \times 0.9)^{1/2} \times Nf \dots \text{Equation 1}$$

CF: cover factor on the inner surface of the artificial blood vessel

Dw: total fineness of the warp yarns (dtex)

Nw: base fabric density of the warp yarns (yarns/2.54 cm)

Df: total fineness of the weft yarns (dtex)

Nf: base fabric density of the weft yarns (yarns/2.54 cm)

The base fabric density was measured by cutting the prepared cylindrical fabric in the longitudinal direction, and then observing the inner surface on a photograph at a magnification of x 50 taken using a microscope manufactured by Keyence Corporation, VHX-2000.

[0038]

In the present invention, a multifilament yarn of not less than 1.0 dtex is

preferably contained as a warp yarn constituting at least one layer other than the cylindrical fabric whose inside contacts blood. Here, in cases where the single yarn fineness of the warp yarn constituting the at least one layer other than the cylindrical fabric whose inside contacts blood is too small, the mechanical strength of the artificial blood vessel is insufficient, and, during long-term transplantation, deterioration of the strength may occur due to hydrolysis of the fibers constituting the artificial blood vessel, which is not preferred. On the other hand, in cases where the single yarn fineness of the warp yarn constituting the at least one layer other than the cylindrical fabric whose inside contacts blood is too large, a kink is generated due to hardness of the artificial blood vessel against bending. That is, as the warp yarn constituting the at least one layer other than the cylindrical fabric whose inside contacts blood, a multifilament yarn having a single yarn fineness of 1.0 to 10.0 dtex is preferably contained. The single yarn fineness is more preferably 2.0 to 5.0 dtex. The at least one layer other than the cylindrical fabric whose inside contacts blood is preferably the outer-layer cylindrical fabric.

[0039]

In cases where the multifilament yarn of not less than 1.0 dtex to be used as a warp yarn constituting the at least one layer other than the cylindrical fabric whose inside contacts blood is exposed on the inner surface portion of the artificial blood vessel which contacts blood, the ratio of the multifilament yarn having a single yarn fineness of not more than 0.50 dtex as a warp yarn constituting the cylindrical fabric whose inside contacts blood, which promotes settlement of vascular endothelial cells, decreases, and moreover, gaps between fibers are likely to be generated, so that the amount of blood leakage increases. In view of this, the percentage of exposure of the multifilament yarn of not less than 1.0 dtex on the inner surface is preferably not more than 20%, more preferably not more than 5%, still more preferably not more than 1%. The percentage of exposure (%) of the multifilament yarn of not less than

1.0 dtex on the inner surface means the ratio corresponding to the number of ridge portions where a multifilament yarn of not less than 1.0 dtex can be found among 100 ridge portions of warp yarns that are randomly selected by visual observation of the inner surface of the artificial blood vessel.

5 [0040]

Further, in the present invention, a monofilament yarn is preferably contained as a weft yarn constituting at least one layer other than the cylindrical fabric whose inside contacts blood. Here, in cases where the single yarn fineness of the weft yarn constituting the at least one layer other than the cylindrical fabric whose inside
10 contacts blood is too small, the shape and the elasticity of the artificial blood vessel cannot be maintained, and the kink resistance cannot be improved. On the other hand, in cases where the single yarn fineness of the weft yarn constituting the at least one layer other than the cylindrical fabric whose inside contacts blood is too large, the artificial blood vessel is hard, and moreover, the weaving performance is unstable.
15 Thus, depending on the type and the performance of the loom, the single yarn fineness is preferably 15.0 to 1000.0 dtex, more preferably 20.0 to 100.0 dtex. The at least one layer other than the cylindrical fabric whose inside contacts blood is preferably the outer-layer cylindrical fabric.

[0041]

20 The antithrombogenicity herein means a property with which blood coagulation does not occur on a surface in contact with blood. For example, the antithrombogenicity means a property that inhibits blood coagulation which proceeds due to platelet aggregation, activation of blood coagulation factors represented by thrombin, and/or the like. The cellular affinity herein means a property with which
25 vascular endothelial cells, which are present on the inner surface of living blood vessels and capable of inhibiting thrombus formation, are likely to be settled, leading to formation of the intima.

[0042]

The antithrombogenic material herein means a material having antithrombogenicity. More specifically, in the present invention,

an antithrombogenic material A, which comprises an anionic compound
5 containing a sulfur atom and having anticoagulant activity, and a cationic polymer;
and

an antithrombogenic material B, which comprises the following three kinds
of skeletal structures: a skeletal structure composed of a hydrophilic polymer, a
skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or
10 benzene amidine, and a skeletal structure composed of methoxybenzenesulfonic acid
amide;
are used as the antithrombogenic material.

[0043]

In the artificial blood vessel of the present invention, the antithrombogenic
15 material is bound to the inside of the cylindrical fabric whose inside contacts blood,
to form the antithrombogenic material layer. In terms of the range of the thickness
of this antithrombogenic material layer, in cases where the layer is too thick, the
microstructure composed of the warp yarns and the weft yarns constituting the
cylindrical fabric whose inside contacts blood on the inner surface of the artificial
20 blood vessel which contacts blood is destroyed, and therefore settlement of vascular
endothelial cells is less likely to occur. On the other hand, in terms of the range of
the thickness, in cases where the layer is too thin, the binding amount of the
antithrombogenic material is small, so that the antithrombogenicity of interest
required immediately after the transplantation cannot be obtained. That is, the
25 range of the thickness of the antithrombogenic material layer bound to the cylindrical
fabric whose inside contacts blood is preferably 1 to 600 nm, more preferably 5 to
500 nm, still more preferably 10 to 400 nm.

[0044]

The thickness of the antithrombogenic material layer herein can be determined by, for example, using the later-described scanning transmission electron microscope (hereinafter referred to as “STEM”). The atomic distribution is observed in the vertical direction from the inner-layer side toward the outer-layer side using, as the start point, the inner surface as measured by STEM. Here, the thickness of the antithrombogenic material layer means the distance from the start point to the end point of the range in which atoms derived from the antithrombogenic material layer are found. The thickness of the antithrombogenic material layer is measured as the mean of the values of the thickness at at least three points.

[0045]

The inner surface as measured by STEM herein means the boundary between the acrylic resin or the like used for embedding in the sample preparation before the measurement by STEM, and

the inner surface including the inside of the cylindrical fabric whose inside contacts blood, and the antithrombogenic material layer.

[0046]

Since the amount of blood leakage needs to be reduced, the artificial blood vessel of the present invention is preferably composed of nonporous fibers. In addition, the antithrombogenic material is preferably present also in the outer-layer side, that is, in the depth direction, of the cylindrical fabric whose inside contacts blood. More specifically, when the position where atoms derived from the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood are present, rather than the inner surface as measured by STEM, is used as the start point, and the atomic distribution in the cylindrical fabric whose inside contacts blood is observed toward the outer-layer side in the vertical direction, the distance from the start point to the end point of the range in which atoms derived from the

antithrombogenic material layer are found is more preferably not less than 15 nm, that is, atoms derived from the antithrombogenic material are more preferably present for a distance of not less than 15 nm in the depth direction from the surface of the cylindrical fabric whose inside contacts blood. In cases where the distance from the start point to the end point of the range in which atoms derived from the antithrombogenic material layer are found is less than 15 nm, the binding amount of the antithrombogenic material is small, so that the antithrombogenicity of interest required immediately after the transplantation cannot be satisfied. On the other hand, the distance from the start point to the end point of the range in which atoms derived from the antithrombogenic material layer are found may exceed 200 nm. However, in order to allow the antithrombogenic material to be present in the outer-layer side, that is, in the depth direction, of the cylindrical fabric whose inside contacts blood, the fibers constituting the artificial blood vessel are moderately subjected to hydrolysis or oxidation treatment using an acid or an alkali, and an oxidizing agent. This may cause deterioration, leading to a decrease in mechanical properties such as the tensile strength of the artificial blood vessel. In view of this, in the present invention, the antithrombogenic material is preferably bound to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood, such that the end point of the atoms derived from the antithrombogenic material is present at a position within the range of 15 to 200 nm in the depth direction.

[0047]

As described above, the present inventors intensively studied to discover that settlement of vascular endothelial cells and formation of the intima can be promoted by maintaining the microstructure composed of the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood on the inner surface of the artificial blood vessel which contacts blood, while binding the antithrombogenic

material to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood, such that an antithrombogenic material layer having an appropriate thickness is formed. The present inventors also discovered that, since, in the present invention, the microstructure can be maintained while a sufficient binding amount of the antithrombogenic material can be achieved, the antithrombogenicity of interest required immediately after the transplantation can be obtained, so that both the antithrombogenicity and the cellular affinity can be achieved.

[0048]

More specifically, the thickness of the antithrombogenic material layer, and the distance from the start point to the end point of the range in which atoms derived from the antithrombogenic material layer are found when the position where the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood are present is used as the start point, and the atomic distribution in the cylindrical fabric whose inside contacts blood is observed toward the outer-layer side in the vertical direction, can be confirmed by combination of, for example, STEM and X-ray photoelectron spectroscopy (hereinafter referred to as “XPS”). A STEM has detectors such as an energy dispersive X-ray spectrometer (hereinafter referred to as “EDX”) and an electron energy-loss spectrometer (hereinafter referred to as “EELS”). Measurement conditions for the STEM are as follows.

[Measurement Conditions]

Apparatus: field emission transmission electron microscope JEM-2100F
(manufactured by JEOL Ltd.)

EELS detector: GIF Tridiem (manufactured by GATAN, Inc.)

EDX detector: JED-2300T (manufactured by JEOL Ltd.)

Image acquisition: Digital Micrograph (manufactured by GATAN, Inc.)

Sample preparation: ultrathin sectioning (suspension using a copper

microgrid; use of an acrylic resin as an embedding resin)

Acceleration voltage: 200 kV

Beam diameter: 0.7-nm diameter

Energy resolution: about 1.0 eV FWHM

5 [0049]

Here, the presence of each kind of atoms is judged based on whether a peak intensity derived from the atoms can be found in a spectrum obtained by STEM measurement after subtraction of the background.

[0050]

10 The antithrombogenic material A in the present invention is preferably an anionic compound containing a sulfur atom and having anticoagulant activity. The antithrombogenic material A preferably further contains a cationic polymer. More specifically, the antithrombogenic material A more preferably contains a cationic polymer containing, as a constituent monomer A, a compound selected from the
15 group consisting of alkyleneimines, vinylamines, allylamines, lysine, protamine, and diallyldimethylammonium chloride.

[0051]

Since these constituent monomers A have a cationic nitrogen atom, the polymer is cationic. On the other hand, the compound having anticoagulant activity
20 and containing a sulfur atom is anionic. Therefore, the polymer and the compound can be ionically bound to each other. Examples of the anionic compound containing a sulfur atom and having anticoagulant activity include heparin and heparin derivatives, dextran sulfate, polyvinyl sulfonate, and polystyrene sulfonate. Heparin and heparin derivatives are more preferred. The heparin and heparin
25 derivatives may be either purified or unpurified, and are not limited as long as they can inhibit blood coagulation reaction. Examples of the heparin and heparin derivatives include heparins which are clinically generally and widely used,

unfractionated heparins, and low-molecular-weight heparins, as well as heparins having high affinity to antithrombin III. Specific examples of the heparin include “heparin sodium” (manufactured by Organon API Inc.).

[0052]

5 Since the cationic polymer has a cationic property, it may exhibit hemolytic toxicity and/or the like. Therefore, elution of the cationic polymer into blood is not preferred. In view of this, the cationic polymer is preferably bound, more preferably covalently bound, to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood.

10 [0053]

The cationic polymer may be either a homopolymer or a copolymer. In cases where the cationic polymer is a copolymer, the copolymer may be any of a random copolymer, block copolymer, graft copolymer, and alternating copolymer. The cationic polymer is more preferably a block copolymer since, in cases where the

15 block copolymer has a block containing consecutive repeat units containing nitrogen atoms, the block portion interacts with the anionic compound containing a sulfur atom and having anticoagulant activity, to form strong ionic bonds.

[0054]

The homopolymer herein means a macromolecular compound obtained by

20 polymerization of a single kind of constituent monomers. The copolymer herein means a macromolecular compound obtained by copolymerization of two or more kinds of monomers. The block copolymer means a copolymer having a molecular structure in which at least two kinds of polymers having different repeat units are covalently bound to each other to form a longer chain. The block means each of the

25 at least two kinds of polymers having different repeat units constituting the block copolymer.

[0055]

In the present invention, the structure of the cationic polymer may be either linear or branched. In the present invention, the polymer is preferably branched since a branched polymer can form more stable ionic bonds at multiple positions with the anionic compound containing a sulfur atom and having anticoagulant activity.

[0056]

In the present invention, the cationic polymer has at least one functional group selected from primary to tertiary amino groups and a quaternary ammonium group. In particular, the cationic polymer more preferably has a quaternary ammonium group rather than primary to tertiary amine groups since a quaternary ammonium group has stronger ionic interaction with the anionic compound containing a sulfur atom and having anticoagulant activity, and hence allows easier control of the elution rate of the anionic compound containing a sulfur atom and having anticoagulant activity.

[0057]

In the present invention, the carbon numbers of the three alkyl groups constituting the quaternary ammonium group are not limited. However, in cases where the carbon numbers are too large, hydrophobicity is high, and steric hindrance is enhanced, so that the anionic compound containing a sulfur atom and having anticoagulant activity cannot effectively bind to the quaternary ammonium group by ionic bonding. Moreover, in cases where the carbon number is too large, the polymer is more likely to show hemolytic toxicity, so that the carbon number per alkyl group bound to the nitrogen atom constituting the quaternary ammonium group is preferably 1 to 12, more preferably 2 to 6. The carbon numbers of the three alkyl groups bound to the nitrogen atom constituting the quaternary ammonium group may be the same as or different from each other.

[0058]

In the present invention, a polyalkyleneimine is preferably used as the cationic polymer since the amount of the anionic compound containing a sulfur atom and having anticoagulant activity adsorbed thereto by ionic interaction is large. Examples of the polyalkyleneimine include polyethyleneimines (hereinafter referred to as "PEI"), polypropyleneimines, and polybutyleneimines, as well as alkoxyated polyalkyleneimines. Among these, PEI is more preferred.

[0059]

Specific examples of the PEI include "LUPASOL" (registered trademark) (manufactured by BASF), and "EPOMIN" (registered trademark) (manufactured by Nippon Shokubai Co., Ltd.). The PEI may be a copolymer with other monomers, or may be a modified body, as long as the effect of the present invention is not deteriorated. The modified body herein means a cationic polymer which has the same monomer A repeat units constituting it, but has partially undergone, for example, radical decomposition or recombination due to the later-mentioned radiation irradiation.

[0060]

In the cationic polymer in the present invention, constituent monomers used for forming the copolymer other than alkyleneimines, vinylamines, allylamines, lysine, protamine, and diallyldimethylammonium chloride are not limited, and examples of the constituent monomers include constituent monomers B such as ethylene glycol, propylene glycol, vinylpyrrolidone, vinyl alcohol, vinylcaprolactam, vinyl acetate, styrene, methyl methacrylate, hydroxyethyl methacrylate, and siloxane. In cases where the weight of the constituent monomers B is too high, the ionic bonding between the cationic polymer and the anionic compound containing a sulfur atom and having anticoagulant activity is weak. Therefore, the weight of the constituent monomers B with respect to the total weight of the cationic polymer is preferably not more than 10 wt%.

[0061]

In the present invention, in cases where the weight average molecular weight of the cationic polymer is too low, and lower than the molecular weight of the anionic compound containing a sulfur atom and having anticoagulant activity, stable ionic bonds cannot be formed, so that the antithrombogenicity of interest is less likely to be obtained. On the other hand, in cases where the weight average molecular weight of the cationic polymer is too high, the anionic compound containing a sulfur atom and having anticoagulant activity is included inside the cationic polymer, resulting in embedding of the antithrombogenic material. Thus, the weight average molecular weight of the cationic polymer is preferably 600 to 2,000,000, more preferably 1000 to 1,500,000, still more preferably 10,000 to 1,000,000. The weight average molecular weight of the cationic polymer can be measured by, for example, gel permeation chromatography or the light scattering method.

[0062]

In the present invention, in order to achieve both the antithrombogenicity and the cellular affinity by the presence of the anionic compound containing a sulfur atom and having anticoagulant activity, while maintaining the microstructure composed of the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood and containing a multifilament yarn having a single yarn fineness of not more than 0.50 dtex, the present inventors intensively studied to discover that there is a preferred value of the abundance ratio of sulfur atoms to the abundance of total atoms on the inner surface as measured by XPS. The abundance ratio of atoms is expressed as “atomic percent”, and the atomic percent means the abundance ratio of a particular kind of atoms to the abundance of total atoms, which is taken as 100, in terms of the number of atoms.

[0063]

That is, in the present invention, the abundance ratio of sulfur atoms to the abundance of total atoms on the inner surface as measured by XPS is preferably 3.0 to 6.0 atomic percent, more preferably 3.2 to 5.5 atomic percent, still more preferably 3.5 to 5.0 atomic percent. In cases where the abundance ratio of sulfur atoms to the abundance of total atoms is less than 3.0 atomic percent, the binding amount of the anionic compound containing a sulfur atom and having anticoagulant activity is small, and therefore the antithrombogenicity of interest required immediately after the transplantation of the artificial blood vessel is less likely to be obtained. On the other hand, in cases where the abundance ratio of sulfur atoms to the abundance of total atoms is higher than 6.0 atomic percent, the binding amount of the anionic compound containing a sulfur atom and having anticoagulant activity is sufficient, and the antithrombogenicity of interest can therefore be obtained, but the amount of the cationic polymer covalently bound to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood, which cationic polymer is used for allowing the ionic bonding, needs to be large. Moreover, as elution of the anionic compound containing a sulfur atom and having anticoagulant activity proceeds, the exposed cationic polymer may exhibit hemolytic toxicity and/or the like, which is not preferred.

[0064]

In cases where the abundance ratio of sulfur atoms to the abundance of total atoms is not more than 6.0 atomic percent, the binding amount of the anionic compound containing a sulfur atom and having anticoagulant activity is appropriate, so that settlement of vascular endothelial cells can be promoted.

[0065]

More specifically, the abundance ratio of sulfur atoms to the abundance of total atoms on the inner surface as measured by XPS can be determined by XPS.

[Measurement Conditions]

Apparatus: ESCALAB 220iXL (manufactured by VG Scientific)

Excitation X-ray: monochromatic AlK α 1, 2 ray (1486.6 eV)

X-ray diameter: 1 mm

5 X-electron escape angle: 90° (the angle of the detector with respect to the surface of the antithrombogenic material)

[0066]

The inner surface as measured by X-ray photoelectron spectroscopy (XPS) herein means the portion from the measurement surface to a depth of 10 nm as detected under the measurement conditions in XPS wherein the X-electron escape angle, that is, the angle of the detector with respect to the inner surface of the artificial blood vessel to which the antithrombogenic material and the cylindrical fabric are bound, is 90°. In the present invention, the cylindrical fabric may or may not contain sulfur atoms.

[0067]

15 By radiating X-ray to the inner surface of the artificial blood vessel, and measuring the energy of photoelectrons generated therefrom, the binding energy values of bound electrons in the substance can be obtained. From the binding energy values, information on the atoms on the inner surface as measured by XPS can be obtained, and, from the energy shift of the peak at each binding energy value, information on the valence and the binding state can be obtained. In addition, by using the area ratio of each peak, quantification, that is, calculation of the abundance ratios of various atoms, valences, and binding states, is possible.

[0068]

25 More specifically, the S2p peak, which indicates the presence of sulfur atoms, appears near a binding energy value of 161 eV to 170 eV. In the present invention, it was discovered that the area ratio of the S2p peak in the whole peak area is preferably 3.0 to 6.0 atomic percent. In the calculation of the abundance ratio of

sulfur atoms to the abundance of total atoms, the obtained value is rounded to one decimal place.

[0069]

Similarly, it was discovered that there is a preferred value of the abundance ratio of nitrogen atoms to the abundance of total atoms on the inner surface as measured by XPS. That is, the abundance ratio of nitrogen atoms to the abundance of total atoms on the inner surface as measured by XPS is preferably 6.0 to 12.0 atomic percent, more preferably 7.0 to 12.0 atomic percent, still more preferably 7.5 to 11.0 atomic percent, still more preferably 8.0 to 10.0 atomic percent. In cases where the abundance ratio of nitrogen atoms to the abundance of total atoms is less than 6.0 atomic percent, the amount of the cationic polymer bound to the cylindrical fabric whose inside contacts blood is small, so that the microstructure composed of the warp yarns and the weft yarns containing a multifilament yarn having a single yarn fineness of not more than 0.50 dtex can be maintained. However, since the amount of the anionic compound containing a sulfur atom and having anticoagulant activity which is ionically bound to the cationic polymer is small in such cases, the antithrombogenicity of interest required immediately after the transplantation is less likely to be obtained. On the other hand, in cases where the abundance ratio of nitrogen atoms to the abundance of total atoms is higher than 12.0 atomic percent, the amount of the cationic polymer bound to the cylindrical fabric whose inside contacts blood is large, so that the anionic compound containing a sulfur atom and having anticoagulant activity bound to the cationic polymer by ionic bonding is present in a sufficient amount. However, it was found that, as elution of the anionic compound containing a sulfur atom and having anticoagulant activity proceeds, a large amount of the cationic polymer is exposed to show hemolytic toxicity.

[0070]

In cases where the abundance ratio of nitrogen atoms to the abundance of

total atoms is not more than 12.0 atomic percent, the binding amount of the anionic compound containing a sulfur atom and having anticoagulant activity is appropriate, so that settlement of vascular endothelial cells is promoted. For achievement of both the antithrombogenicity and the cellular affinity, the abundance ratio of nitrogen atoms to the abundance of total atoms is preferably 6.0 to 12.0 atomic percent, more preferably 6.0 to 9.5 atomic percent, still more preferably 8.0 to 9.5 atomic percent.

[0071]

More specifically, the N1s peak, which indicates the presence of nitrogen atoms, appears near a binding energy value of 396 eV to 403 eV. In the present invention, it was discovered that the area ratio of the N1s peak in the whole peak area is preferably 7.0 to 12.0 atomic percent. The N1s peak can be mainly split into the n1 component (near 399 eV), which is attributed to carbon-nitrogen (hereinafter referred to as "C-N") bonds; and the n2 component (near 401 to 402 eV), which is attributed to ammonium salt, C-N (structure different from n1), and/or nitrogen oxide (hereinafter referred to as "NO"). The abundance ratio of each split peak component can be calculated according to the following Equation 2. In this calculation, the abundance ratio of nitrogen atoms to the abundance of total atoms, and the abundance ratio of each split peak component, are rounded to one decimal place.

[0072]

$$\text{Split}_{\text{ratio}} = \text{N1s}_{\text{ratio}} \times (\text{Split}_{\text{percent}} / 100) \dots \text{Equation 2}$$

$\text{Split}_{\text{ratio}}$: abundance ratio of each split peak component (%)

$\text{N1s}_{\text{ratio}}$: abundance ratio of nitrogen atoms to the abundance of total atoms (%)

$\text{Split}_{\text{percent}}$: abundance ratio of each split peak component in the N1s peak (%)

[0073]

The n2 component, which is attributed to NO, obtained by splitting the N1s peak indicates the presence of quaternary ammonium groups in the present invention. It was discovered that the abundance ratio of the n2 component in the total component of the N1s peak, that is, $\text{Split}_{\text{percent}}(\text{n2})$, is preferably 20 to 70 atomic percent, more preferably 25 to 65 atomic percent, still more preferably 30 to 60 atomic percent. In cases where $\text{Split}_{\text{percent}}(\text{n2})$ is less than 20 atomic percent, the abundance of quaternary ammonium groups is low. Therefore, the ionic interaction with the anionic compound containing a sulfur atom and having anticoagulant activity is weak, and the antithrombogenicity of interest required immediately after the transplantation of the artificial blood vessel is less likely to be obtained because of high elution rate. On the other hand, in cases where $\text{Split}_{\text{percent}}(\text{n2})$ is higher than 70 atomic percent, the ionic interaction with the anionic compound containing a sulfur atom and having anticoagulant activity is too strong. In such cases, because of a decrease in the degree of freedom due to formation of ionic complexes, it is impossible to maintain a high anticoagulant activity for a long period, and the elution rate tends to be low. Because of the above reasons, the abundance ratio of the n2 component, that is, $\text{Split}_{\text{ratio}}(\text{n2})$, which is calculated according to Equation 2, is preferably 1.4 to 8.4 atomic percent, more preferably 1.8 to 7.2 atomic percent, still more preferably 2.4 to 6.0 atomic percent.

[0074]

The C1s peak, which indicates the presence of carbon atoms, appears near a binding energy value of 282 to 292 eV. The C1s peak can be mainly split into the c1 component (near 285 eV), which is attributed to carbon-hydrogen (hereinafter referred to as “CHx”) bonds suggesting the presence of a saturated hydrocarbon(s) and/or the like, to carbon-carbon (hereinafter referred to as “C-C”) bonds, and/or to carbon=carbon (hereinafter referred to as “C=C”) bonds; the c2 component (near 286 eV), which is attributed to carbon-oxygen (hereinafter referred to as “C-O”) bonds

suggesting the presence of an ether(s) and/or hydroxyl groups, and/or to carbon-nitrogen (hereinafter referred to as “C-N”) bonds; the c3 component (near 287 to 288 eV), which is attributed to carbon=oxyen (hereinafter referred to as “C=O”) bonds suggesting the presence of carbonyl groups; the c4 component (near 288 to 289 eV), which is attributed to oxygen=carbon-oxygen (hereinafter referred to as “O=C-O”) bonds suggesting the presence of ester groups and/or carboxyl groups; and the c5 component (near 290 to 292 eV), which is attributed to π - π^* satellite peak (hereinafter referred to as “ π - π ”) bonds suggesting the presence of a conjugated system(s) such as benzene rings. The abundance ratio of each split peak component can be calculated according to the following Equation 3. In this calculation, the abundance ratio of carbon atoms to the abundance of total atoms, and the abundance ratio of each split peak component, are rounded to one decimal place.

[0075]

$$\text{Split}_{\text{ratio}} = \text{C1s}_{\text{ratio}} \times (\text{Split}_{\text{percent}} / 100) \dots \text{Equation 3}$$

$\text{Split}_{\text{ratio}}$: abundance ratio of each split peak component (%)
 $\text{C1s}_{\text{ratio}}$: abundance ratio of carbon atoms to the abundance of total atoms (%)
 $\text{Split}_{\text{percent}}$: abundance ratio of each split peak component in the C1s peak (%)

[0076]

The c3 component, which is attributed to C=O bonds, obtained by splitting the C1s peak indicates the presence of amide groups in the present invention. It was discovered that the abundance ratio of the c3 component in the total component of the C1s peak in the present invention, that is, the abundance ratio of amide groups in the present invention, is preferably not less than 2.0 atomic percent, more preferably not less than 3.0 atomic percent. In cases where the abundance ratio of the amide groups is less than 2.0 atomic percent, the number of covalent bonds due

to amide bonds between the cationic polymer and the cylindrical fabric whose inside contacts blood is small, and therefore the binding amount of the cationic polymer is small. Moreover, since the state of ionic bonding between the cationic polymer and the anionic compound containing a sulfur atom and having anticoagulant activity is poor, the antithrombogenicity of interest is less likely to be obtained.

[0077]

The antithrombogenic material B in the present invention preferably contains the following three kinds of skeletal structures: a skeletal structure composed of a hydrophilic polymer, a skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine, and a skeletal structure composed of methoxybenzenesulfonic acid amide. More specifically, the hydrophilic polymer more preferably contains, as a constituent monomer B, a compound selected from the group consisting of ethylene glycol, propylene glycol, vinylpyrrolidone, vinyl alcohol, vinylcaprolactam, vinyl acetate, styrene, methyl methacrylate, hydroxyethyl methacrylate, and siloxane.

[0078]

Each of the three kinds of skeletal structures described above may be contained in a separate compound, or at least two kinds of the skeletal structures may be bound to a compound by covalent bonding or ionic bonding. In the artificial blood vessel of the present invention, from the viewpoint of achieving both the antithrombogenicity and the cellular affinity, it is more preferred to use, as the antithrombogenic material B, a compound containing all of the skeletal structure composed of a hydrophilic polymer, the skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine, and the skeletal structure composed of methoxybenzenesulfonic acid amide.

[0079]

At least one of the three kinds of skeletal structures described above

preferably contains a functional group selected from the group consisting of, for example, hydroxyl, thiol, amino, carboxyl, aldehyde, isocyanate, and thioisocyanate, more preferably contains amino or carboxyl, still more preferably contains amino.

The functional group is preferably contained in the skeletal structure composed of a hydrophilic polymer, more preferably present at the terminus of the skeletal structure composed of a hydrophilic polymer. The warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood can be covalently bound to the three kinds of skeletal structures through disulfide bonds, amide bonds, ester bonds, urethane bonds, bonds formed by condensation reaction, and/or the like, using a functional group(s) selected from the group consisting of hydroxyl, thiol, amino, carboxyl, aldehyde, isocyanate, and thioisocyanate.

[0080]

In the present invention, the reactive functional group(s) is/are given to the antithrombogenic material in order to allow covalent bonding of the antithrombogenic material to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood. Therefore, the covalent bonding can be carried out without use of a method such as radiation irradiation. In cases where the covalent bonding is carried out by radiation irradiation or the like as described in Patent Documents 14 and 15, the skeletal structure composed of 4-(aminomethyl)benzenecarboxyimide or benzene amidine, and the skeletal structure composed of methoxybenzenesulfonic acid amide, generate highly reactive radicals due to absorption of high energy of the radiation. Reaction of the radicals with arbitrary sites in the compound causes changes in the skeletal structures, mainly leading to a decrease in antithrombin activation capacity.

[0081]

In the achievement of both the antithrombogenicity and the cellular affinity in the antithrombogenic material B using a compound having antithrombogenicity other

than heparin or heparin derivatives in the present invention, especially in order to further increase the anti-platelet adhesion capacity associated with the antithrombogenicity, the present inventors intensively studied to discover that the skeletal structure composed of a hydrophilic polymer is important.

5 [0082]

The skeletal structure composed of a hydrophilic polymer means a skeletal structure composed of a polymer having a hydrophilic functional group and having solubility in water. The hydrophilic polymer may be a copolymer with other monomers, or may be a modified body as long as the effect of the present invention is not deteriorated.

10 [0083]

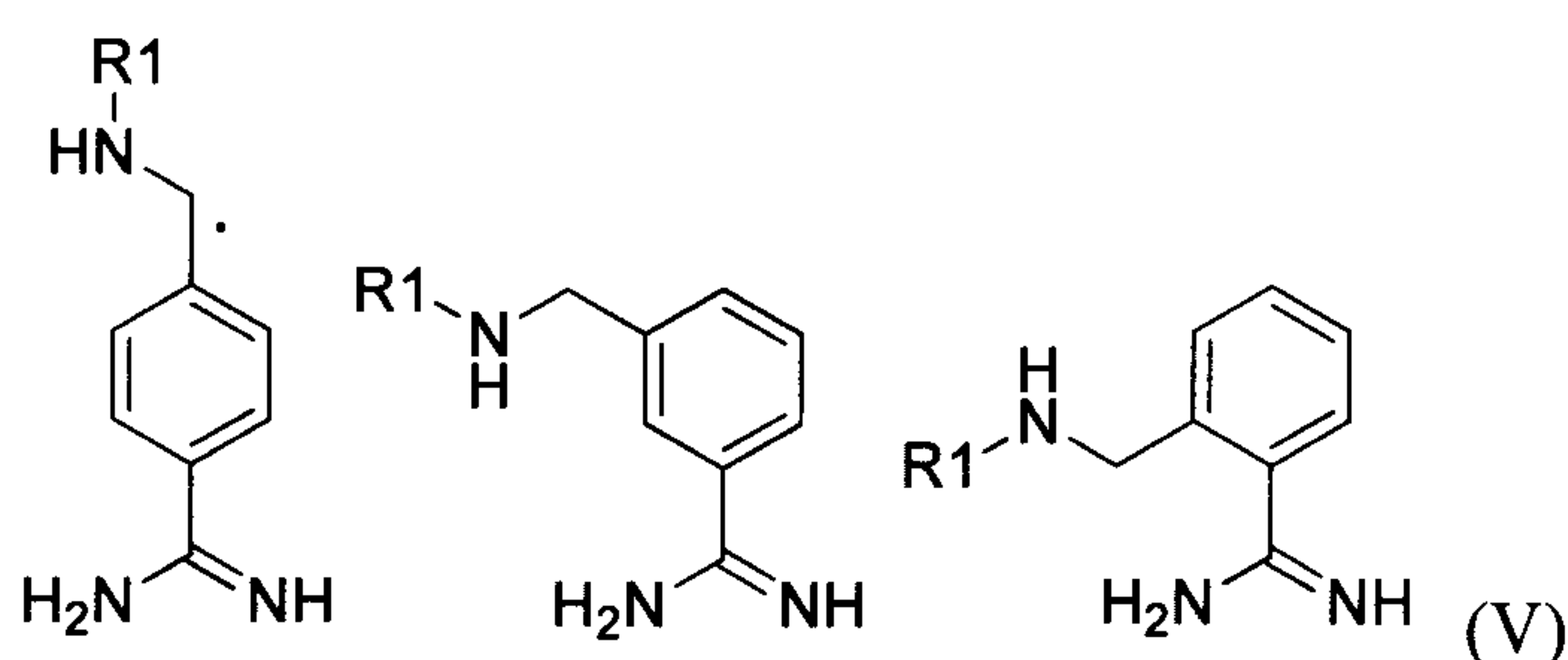
The skeletal structure composed of a hydrophilic polymer may be either a homopolymer or a copolymer as long as the constituent monomer B described above is used. In cases where the hydrophilic polymer is a copolymer, the copolymer may be any of a random copolymer, block copolymer, graft copolymer, and alternating copolymer. The skeletal structure composed of a hydrophilic polymer may be either linear or branched.

15 [0084]

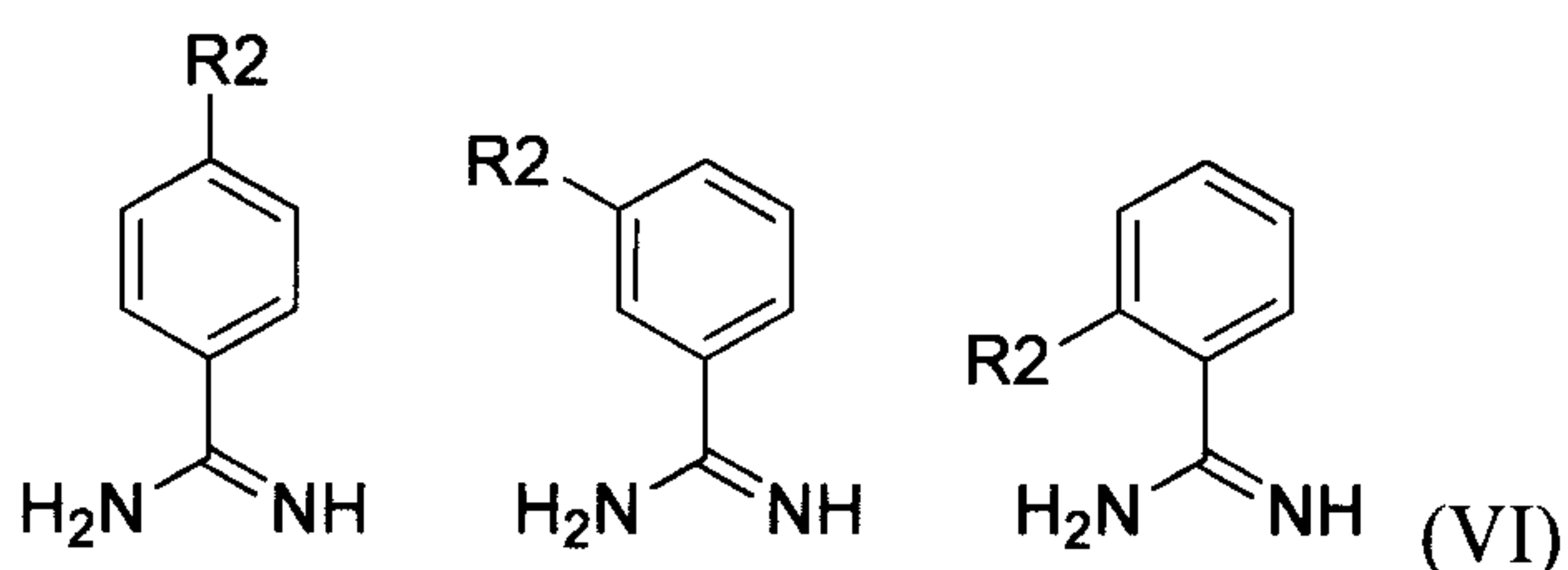
In the achievement of both the antithrombogenicity and the cellular affinity in the antithrombogenic material B using a compound having antithrombogenicity other than heparin or heparin derivatives in the present invention, especially in order to further increase the antithrombin activation capacity associated with the antithrombogenicity, the present inventors intensively studied to discover that the skeletal structure composed of 4-(aminomethyl)benzenecarboxyimide or benzene amidine, and the skeletal structure composed of methoxybenzenesulfonic acid amide, are important.

25 [0085]

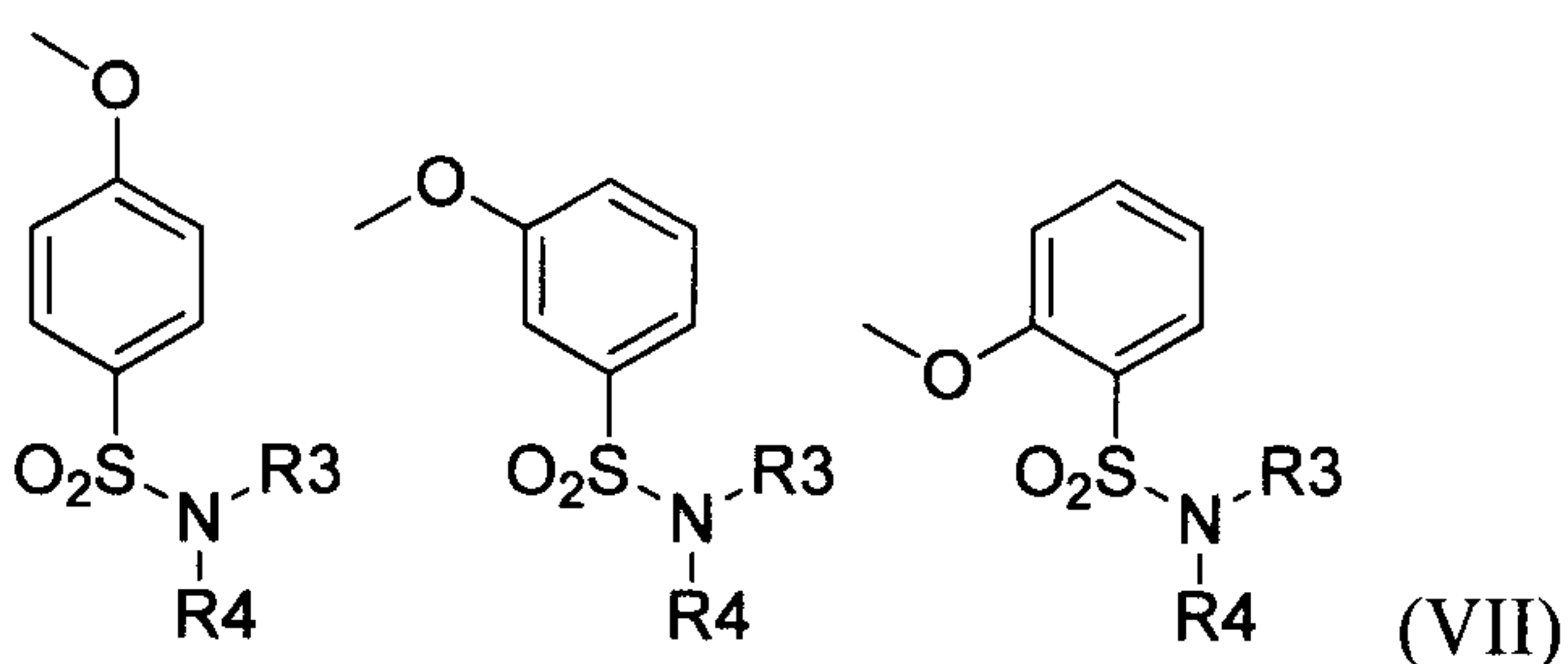
The skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide is a skeletal structure shown in the following General Formula (V); the skeletal structure composed of benzene amidine is a skeletal structure shown in the following General Formula (VI); and the skeletal structure composed of methoxybenzenesulfonic acid amide is a skeletal structure shown in the following General Formula (VII).



[wherein R1 represents a moiety linked to another skeletal structure].



[wherein R2 represents a moiety linked to another skeletal structure].

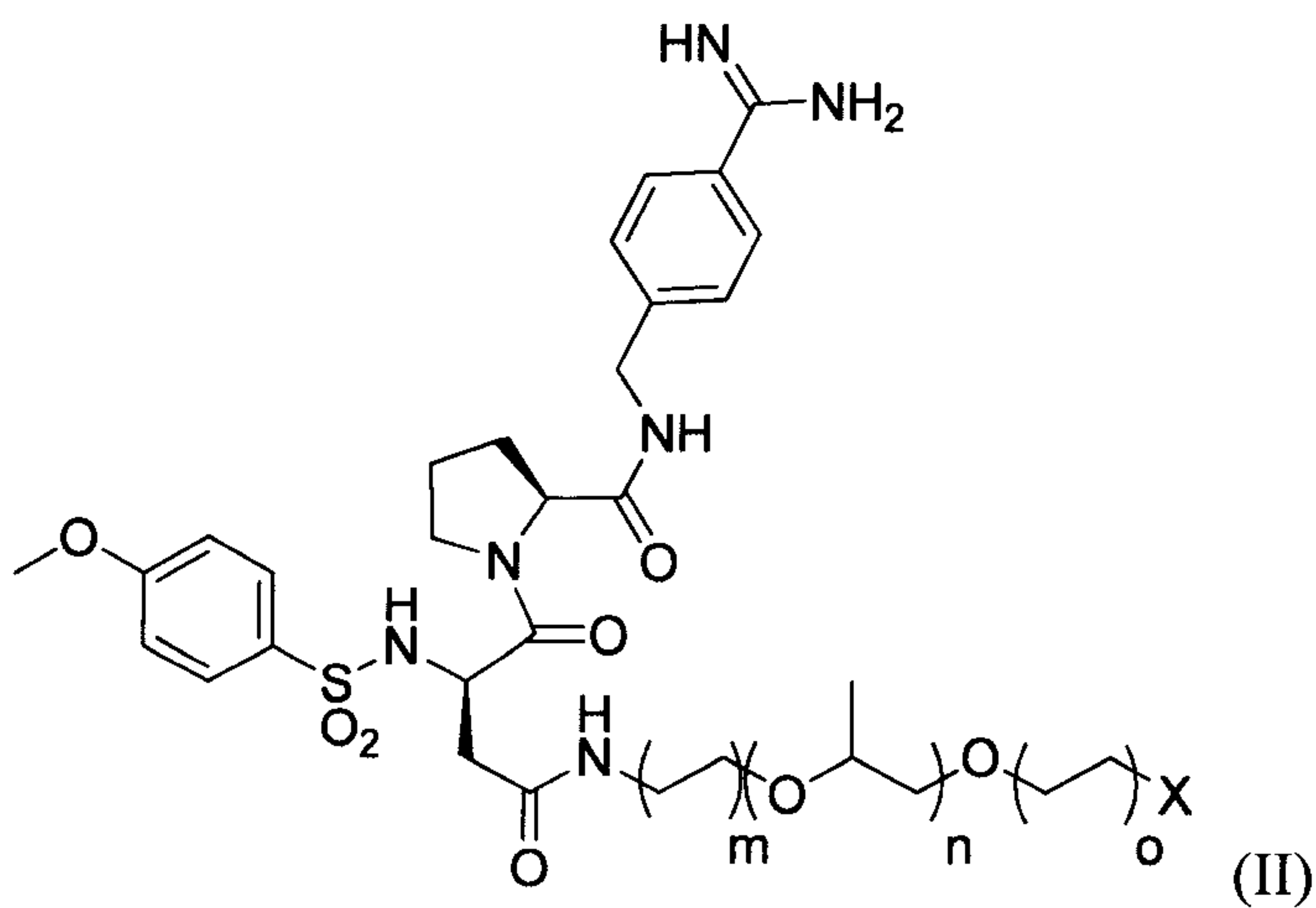
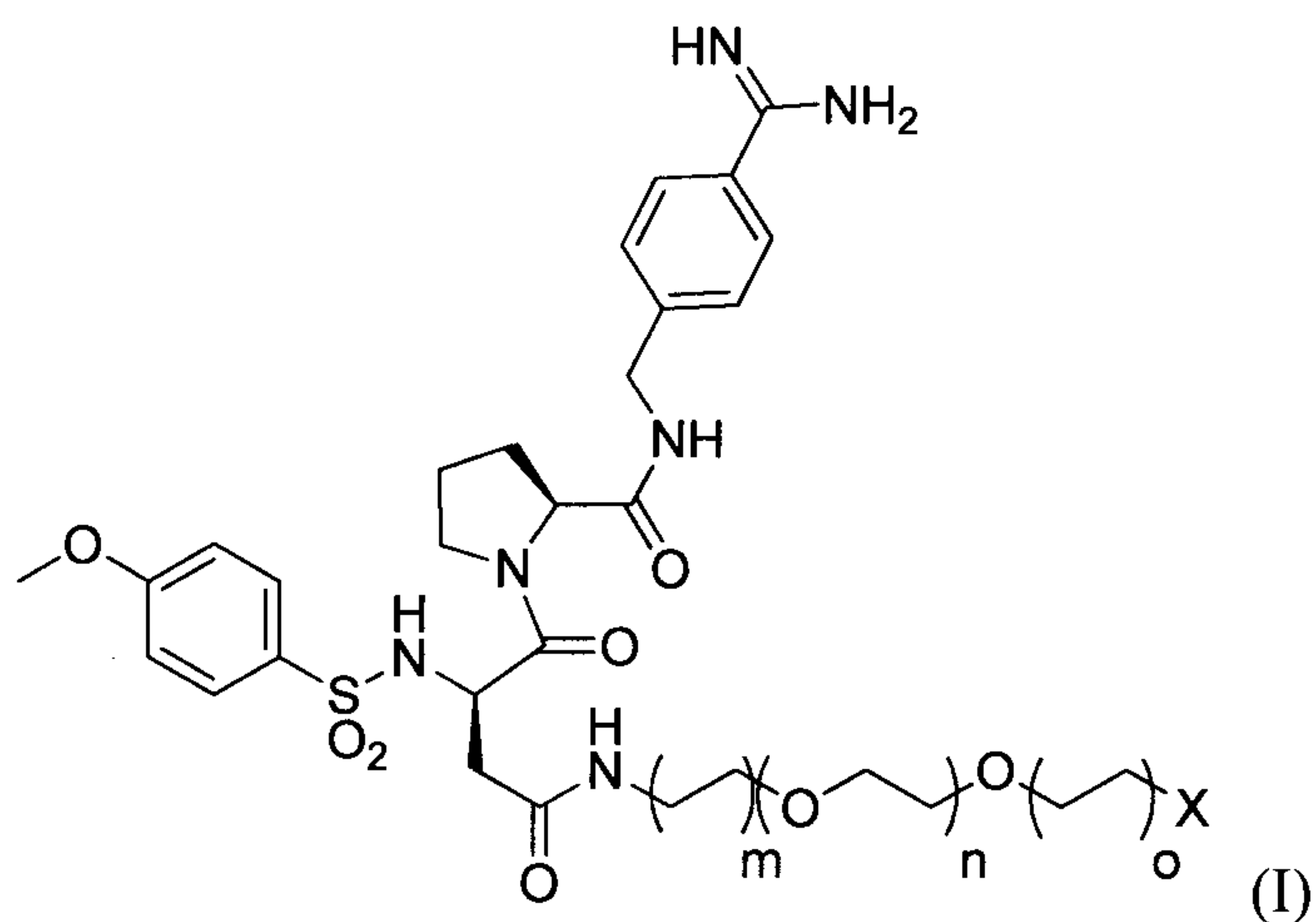


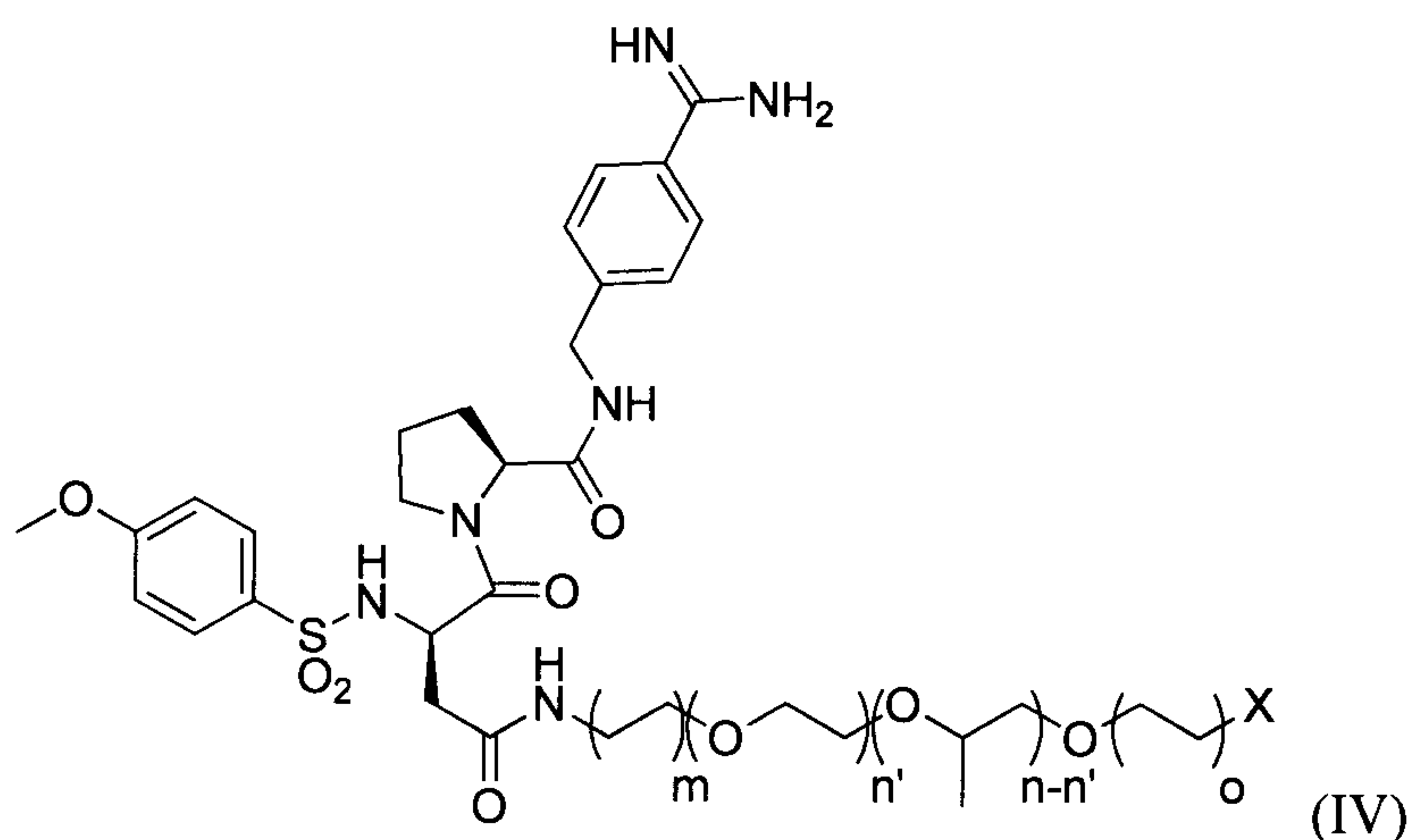
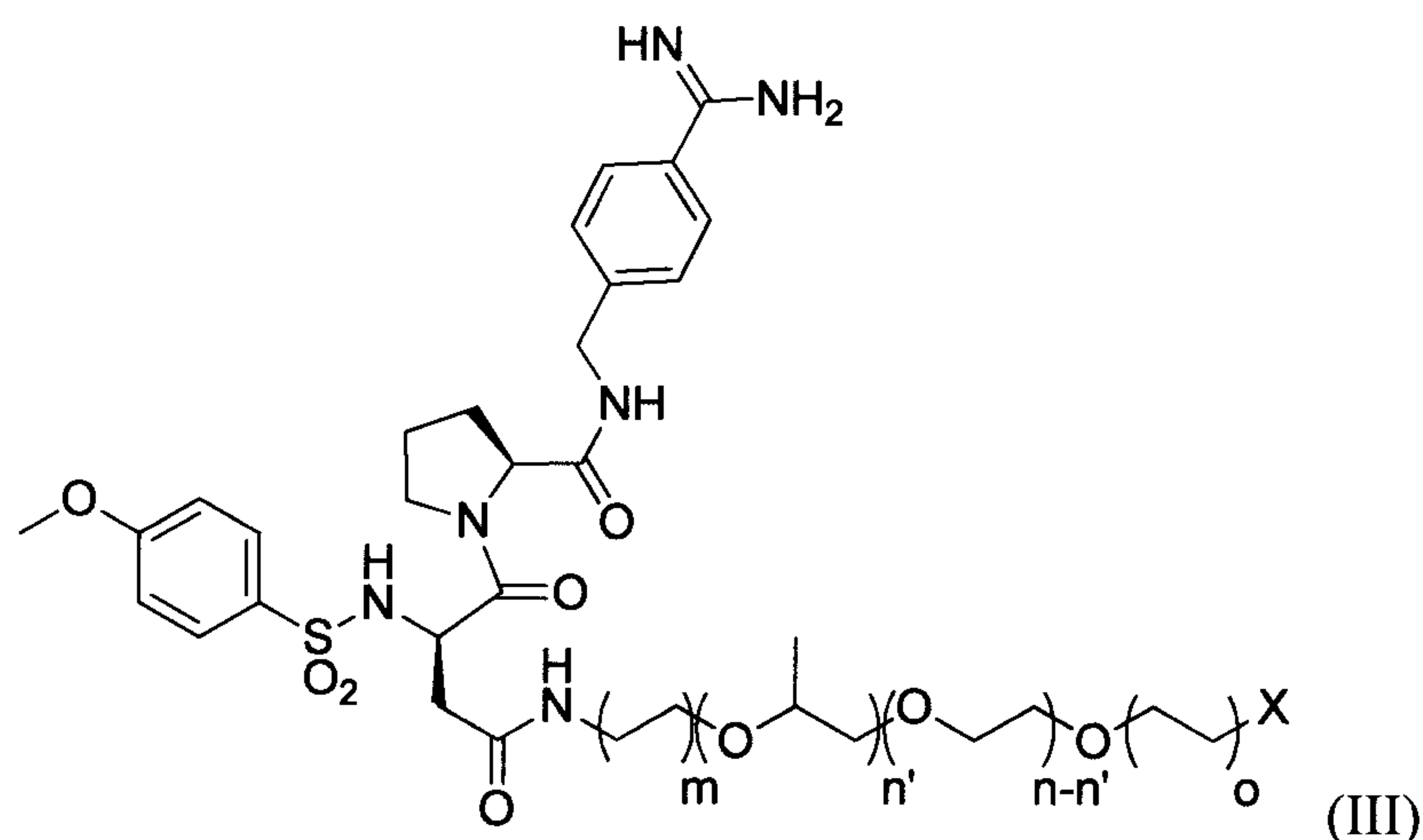
[wherein each of R3 and R4 represents a moiety linked to another skeletal structure].

[0086]

The compound containing all of the three kinds of structures, that is, the

skeletal structure composed of a hydrophilic polymer, the skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine, and the skeletal structure composed of methoxybenzenesulfonic acid amide, is especially preferably any of the compounds represented by the following General Formulae (I) to (IV). In these General Formulae, X is preferably amino or carboxyl. X is more preferably amino.





[wherein m and o each represent an integer of 0 to 4; n represents an integer of 3 to 1000, and n' represents an integer of 3 to 1000, with the proviso that $n \geq n'$; and X represents a functional group selected from the group consisting of hydroxyl, thiol, amino, carboxyl, aldehyde, isocyanate, and thioisocyanate].

[0087]

In the present invention, it was discovered that, although X in the formulae described above may be contained in any of the three kinds of skeletal structures, a high and long-lasting antithrombogenicity can be obtained in cases where the skeletal structure composed of a hydrophilic polymer, which has anti-platelet adhesion capacity, is present in the side in contact with the cylindrical fabric whose inside contacts blood, to which the above compound is bound, and the skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine and the

skeletal structure composed of methoxybenzenesulfonic acid amide, which have antithrombin activation capacity, are present in the side in contact with blood, since the latter skeletal structures have higher thrombin capture capacity in such cases. That is, the reactive functional group (X in the formulae described above) to be covalently bound to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood is preferably contained in the skeletal structure composed of a hydrophilic polymer, more preferably present at the terminus of the skeletal structure composed of a hydrophilic polymer. The warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood can be covalently bound to the compound in the antithrombogenic material through disulfide bonds, amide bonds, ester bonds, urethane bonds, bonds formed by condensation reaction, and/or the like, using the reactive functional group X in the Formulae.

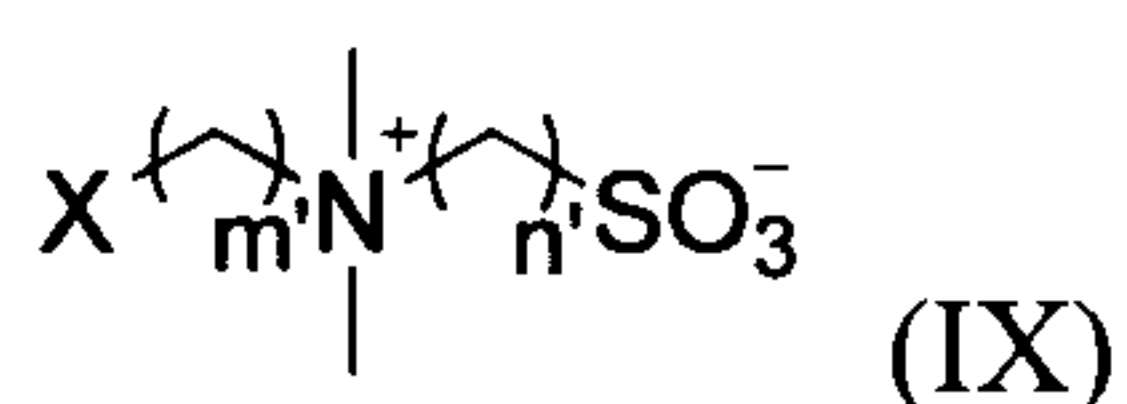
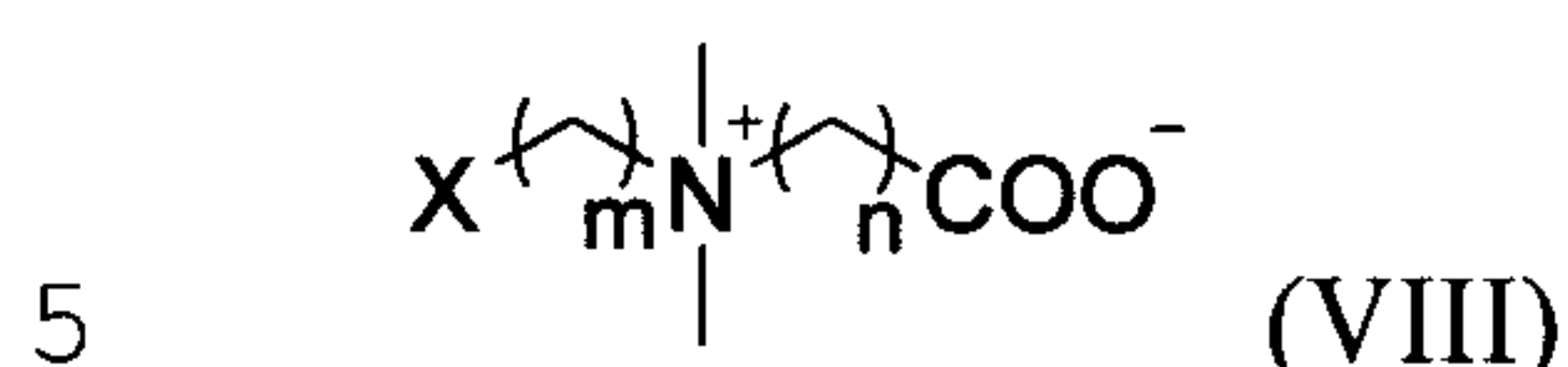
[0088]

In the present invention, it was discovered that, more preferably, for maintenance of a high antithrombogenicity for a longer period, the antithrombogenic material B contains a betaine compound, and the betaine compound is covalently bound to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood, or to the antithrombogenic material B.

[0089]

The betaine compound means a compound which has a positive charge and a negative charge at positions that are not adjacent to each other in a single molecule, wherein no dissociable hydrogen atom is bound to the atom having the positive charge, and the molecule as a whole does not have a charge; or a salt thereof. In the present invention, the compound is not limited as long as it contains a betaine compound in a part thereof. The betaine compound is preferably carboxybetaine, sulfobetaine, or phosphobetaine, more preferably carboxybetaine or sulfobetaine

represented by the following General Formula (VIII) or (IX). X in General Formulae (VIII) and (IX) is preferably amino or carboxyl. X is more preferably amino.



[wherein n represents any of 1 to 4; m represents an integer of 2 to 4; n' represents an integer of 2 to 4; m' represents an integer of 2 to 4; and X represents a functional group selected from the group consisting of hydroxyl, thiol, amino, carboxyl, aldehyde, isocyanate, and thioisocyanate].

[0090]

In cases of an artificial blood vessel of the present invention to which an antithrombogenic material B using a compound having antithrombogenicity other than heparin or heparin derivatives is bound, the presence of the skeletal structure composed of a hydrophilic polymer, the skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine, and the skeletal structure composed of methoxybenzenesulfonic acid amide, on the innermost surface as measured by time-of-flight secondary ion mass spectrometry (hereinafter referred to as "TOF-SIMS") can be determined by TOF-SIMS.

[Measurement Conditions]

Apparatus: TOF.SIMS 5 (manufactured by ION-TOF GmbH)

Primary ion species: Bi_3^{++}

Secondary ion polarity: positive and negative

25 Mass range (m/z): 0 to 1500

Raster size: 300 μm $\times$ 300 μm

Pixel number (each side): 256 pixels

Post-acceleration: 10 kV

Measured degree of vacuum (before sample injection): 4×10^{-7} Mpa

5 Primary ion acceleration voltage: 25 kV

Pulse width: 10.5 ns

Bunching: Yes (high mass resolution measurement)

Charge neutralization: Yes

[0091]

10 The “innermost surface as measured by TOF-SIMS” herein means the portion from the measurement surface to a depth of 1 to 3 nm under the measurement conditions in TOF-SIMS.

[0092]

15 Pulsed primary ions are radiated to the innermost surface placed in an ultrahigh vacuum, and then secondary ions released from the innermost surface as measured by TOF-SIMS, having a certain amount of kinetic energy, are introduced to the time-of-flight mass spectrometer. Since a mass spectrum is obtained according to the mass of the secondary ions, organic substances and inorganic substances present on the innermost surface as measured by TOF-SIMS can be
20 identified, and information on the abundance of each substance can be obtained based on its peak intensity.

[0093]

25 More specifically, the skeletal structure composed of ethylene glycol or propylene glycol on the innermost surface as measured by TOF-SIMS can be confirmed based on at least one kind of peak selected from the group consisting of the $^{45}\text{C}_2\text{H}_5\text{O}^+$ peak, $^{59}\text{C}_3\text{H}_7\text{O}^+$ peak, $^{73}\text{C}_3\text{H}_5\text{O}_2^+$ peak, and $^{87}\text{C}_4\text{H}_7\text{O}_2^+$ peak of positive secondary ions found in TOF-SIMS.

[0094]

The skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide on the innermost surface as measured by TOF-SIMS can be confirmed based on at least one kind of peak selected from the group consisting of the $^{106}\text{C}_7\text{H}_8\text{N}^+$ peak, $^{117}\text{C}_7\text{H}_5\text{N}_2^+$ peak, $^{134}\text{C}_8\text{H}_{10}\text{N}_2^+$ peak, and $^{148}\text{C}_8\text{H}_{10}\text{N}_3^+$ peak of positive secondary ions, and the $^{119}\text{C}_7\text{H}_7\text{N}_2^-$ peak of negative secondary ions, found in TOF-SIMS. The skeletal structure composed of benzene amidine can be confirmed based on the $^{119}\text{C}_7\text{H}_7\text{N}_2^-$ peak of negative secondary ions found in TOF-SIMS. The skeletal structure composed of methoxybenzenesulfonic acid amide can be confirmed based on at least one kind of peak selected from the group consisting of the $^{117}\text{C}_7\text{H}_7\text{SO}_3^+$ peak of positive secondary ions, and the $^{64}\text{SO}_2^-$ peak, $^{171}\text{C}_7\text{H}_7\text{SO}_3^-$ peak, $^{186}\text{C}_7\text{H}_8\text{SNO}_3^-$ peak, and $^{212}\text{C}_9\text{H}_{10}\text{SNO}_3^-$ peak of negative secondary ions.

[0095]

The presence of the betaine compound on the innermost surface as measured by TOF-SIMS can be confirmed based on at least one kind of peak selected from the group consisting of the $^{94}\text{CH}_2\text{SO}_3^-$ peak, $^{150}\text{C}_4\text{H}_8\text{NSO}_3^-$ peak, and $^{166}\text{C}_5\text{H}_{12}\text{NSO}_3^-$ peak of negative secondary ions found in TOF-SIMS.

[0096]

For example, in cases where the later-described cationic polymer is PEI, the presence of the PEI on the innermost surface can be confirmed based on at least one kind of peak selected from the group consisting of the $^{18}\text{NH}_4^+$ peak, $^{28}\text{CH}_2\text{N}^+$ peak, $^{43}\text{CH}_3\text{N}_2^+$ peak, and $^{70}\text{C}_4\text{H}_8\text{N}^+$ peak of positive secondary ions, and the $^{26}\text{CN}^-$ peak and $^{42}\text{CNO}^-$ peak of negative secondary ions, found in TOF-SIMS.

[0097]

For example, in cases where the later-described anionic polymer is polyacrylic acid (hereinafter referred to as "PAA"), the presence of the PAA on the

innermost surface can be confirmed based on the $^{71}\text{C}_3\text{H}_3\text{O}_2^-$ peak of negative secondary ions found in TOF-SIMS.

[0098]

For example, in cases where the multifilament yarn of the artificial blood vessel is polyethylene terephthalate, the presence of the polyethylene terephthalate can be confirmed based on at least one kind of peak selected from the group consisting of the $^{76}\text{C}_6\text{H}_4^+$ peak, $^{104}\text{C}_7\text{H}_4\text{NO}^+$ peak, $^{105}\text{C}_7\text{H}_5\text{O}^+$ peak, and $^{149}\text{C}_8\text{H}_5\text{O}_3^+$ peak of positive secondary ions, and the $^{76}\text{C}_6\text{N}_4^-$ peak, $^{120}\text{C}_7\text{H}_4\text{O}_2^-$ peak, $^{121}\text{C}_7\text{H}_5\text{O}_2^-$ peak, $^{147}\text{C}_9\text{H}_7\text{O}_2^-$ peak, and $^{165}\text{C}_8\text{H}_5\text{O}_4^-$ peak of negative secondary ions, found in TOF-SIMS.

[0099]

In the present invention, in cases where the anionic polymer is PAA, there are preferred ranges of the abundance ratios of the skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine, and the skeletal structure composed of methoxybenzenesulfonic acid amide, to PAA on the innermost surface. In cases where the presence of PAA is confirmed based on the $^{71}\text{C}_3\text{H}_3\text{O}_2^-$ peak of negative secondary ions found in TOF-SIMS, and the presence of the skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine is confirmed based on the $^{119}\text{C}_7\text{H}_7\text{N}_2^-$ peak of negative secondary ions found in TOF-SIMS, the peak ratio of $^{119}\text{C}_7\text{H}_7\text{N}_2^-$ peak / $^{71}\text{C}_3\text{H}_3\text{O}_2^-$ peak is preferably not less than 0.05. In cases where the presence of PAA is confirmed based on the $^{71}\text{C}_3\text{H}_3\text{O}_2^-$ peak of negative secondary ions found in TOF-SIMS, and the presence of the skeletal structure composed of methoxybenzenesulfonic acid amide is confirmed based on the $^{64}\text{SO}_2^-$ peak, $^{171}\text{C}_7\text{H}_7\text{SO}_3^-$ peak, and $^{186}\text{C}_7\text{H}_8\text{SNO}_3^-$ peak of negative secondary ions found in TOF-SIMS, the peak ratio of $^{64}\text{SO}_2^-$ peak / $^{71}\text{C}_3\text{H}_3\text{O}_2^-$ peak is preferably not less than 0.6; the peak ratio of $^{171}\text{C}_7\text{H}_7\text{SO}_3^-$ peak / $^{71}\text{C}_3\text{H}_3\text{O}_2^-$ peak is preferably not less than 1.1; and the peak ratio of $^{186}\text{C}_7\text{H}_8\text{SNO}_3^-$

peak/ $^{71}\text{C}_3\text{H}_3\text{O}_2^-$ peak is preferably not less than 0.5.

[0100]

The present inventors intensively studied to achieve both the antithrombogenicity and the cellular affinity while suppressing elution of the compound in cases where the antithrombogenic material B is used for the artificial blood vessel. As a result, the present inventors discovered that there is a preferred value of the abundance ratio of the c3 split peak component, which is attributed to C=O bonds and suggests the presence of carbonyl groups, to the C1s peak, which indicates the presence of carbon atoms, on the inner surface as measured by XPS.

[0101]

That is, it was discovered that the abundance ratio of the c3 split peak component to the total C1s peak component on the inner surface as measured by XPS is preferably not less than 1.0 atomic percent, more preferably not less than 2.0 atomic percent, still more preferably not less than 3.0 atomic percent. In cases where the abundance ratio of the c3 split peak component to the total C1s peak component on the inner surface as measured by XPS is not less than 1.0 atomic percent, the antithrombogenic material B bound to the cylindrical fabric whose inside contacts blood is present in a sufficient amount, so that a higher and longer-lasting antithrombogenicity can be obtained compared to cases where the antithrombogenic material is covalently bound by radiation irradiation as in Patent Documents 14 and 15. In cases where the abundance ratio of the c3 split peak component to the total C1s peak component on the inner surface as measured by XPS is less than 1.0 atomic percent, the number of covalent bonds due to carbonyl-derived amide bonds between the antithrombogenic material B, and the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood, is small, and therefore the binding amount of the antithrombogenic material B is small, so that the antithrombogenicity of interest is less likely to be obtained.

[0102]

It was discovered that, in cases where the antithrombogenic material B is used for the artificial blood vessel, the abundance ratio of nitrogen atoms to the abundance of total atoms according to the N1s peak, which indicates the presence of nitrogen atoms on the inner surface as measured by XPS, is preferably 1.0 to 12.0 atomic percent, more preferably 2.0 to 11.0 atomic percent, still more preferably 3.0 to 10.0 atomic percent.

[0103]

In the present invention, in cases where the number average molecular weight of the skeletal structure composed of a hydrophilic polymer in the antithrombogenic material B is too low, the anti-platelet adhesion capacity is low, so that the antithrombogenicity of interest required immediately after the transplantation of the artificial blood vessel is less likely to be obtained. On the other hand, in cases where the number average molecular weight of the skeletal structure composed of a hydrophilic polymer is too high, the anti-platelet adhesion capacity is high, but the antithrombogenicity of interest is less likely to be obtained since the portion which exhibits the antithrombin activation capacity is included in the inside. Accordingly, the number average molecular weight of the skeletal structure composed of a hydrophilic polymer is preferably 1500 to 20,000, more preferably 2000 to 10,000.

[0104]

In the present invention, the antithrombogenic material B containing the following three kinds of skeletal structures: a skeletal structure composed of a hydrophilic polymer containing, as a constituent monomer, a compound selected from the group consisting of ethylene glycol, propylene glycol, vinylpyrrolidone, vinyl alcohol, vinylcaprolactam, vinyl acetate, styrene, methyl methacrylate, hydroxyethyl methacrylate, and siloxane; a skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine; and a skeletal

structure composed of methoxybenzenesulfonic acid amide; may further contain the cationic polymer described above.

[0105]

The antithrombogenic materials in the present invention, that is, the antithrombogenic material A and the antithrombogenic material B, preferably further comprise: an anionic polymer containing, as a constituent monomer, a compound selected from the group consisting of acrylic acid, methacrylic acid, α -glutamic acid, γ -glutamic acid, and aspartic acid; or an anionic compound selected from the group consisting of dicarboxylic acids such as oxalic acid, malonic acid, succinic acid, fumaric acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, malic acid, tartaric acid, and dodecanedioic acid; and citric acid.

[0106]

The anionic polymer is preferably, but does not necessarily need to be, PAA, polymethacrylic acid, poly(α -glutamic acid), poly(γ -glutamic acid), or polyaspartic acid since, in cases where the weight ratio of anionic functional groups is high, a larger amount of the polymer can be bound to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood, or to another antithrombogenic material. The anionic polymer is more preferably PAA.

[0107]

Specific examples of the PAA include "polyacrylic acid" (manufactured by Wako Pure Chemical Industries, Ltd.). The PAA may be a copolymer with other monomers, or may be a modified body as long as the effect of the present invention is not deteriorated.

[0108]

The anionic polymer may, but does not necessarily need to, form a copolymer with monomers other than anionic monomers. Examples of such monomers include constituent monomers B such as ethylene glycol, propylene glycol, vinylpyrrolidone,

vinyl alcohol, vinylcaprolactam, vinyl acetate, styrene, methyl methacrylate, hydroxyethyl methacrylate, and siloxane. The amount of the constituent monomers B forming the copolymer with the anionic polymer, other than anionic monomers, is preferably not more than 10 wt% since, in cases where the amount of the constituent monomers B is too large, the amount of the copolymer bound to the cylindrical fabric whose inside contacts blood, or to another antithrombogenic material, is small.

[0109]

From the viewpoint of safety and the like, elution of the anionic polymer into blood is not preferred. Therefore, the anionic polymer is preferably bound, more preferably covalently bound, to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood.

[0110]

The cationic polymer may be either a homopolymer or a copolymer. In cases where the anionic polymer is a copolymer, the copolymer may be any of a random copolymer, block copolymer, graft copolymer, and alternating copolymer.

[0111]

In the anionic polymer in the present invention, constituent monomers used for forming the copolymer other than acrylic acid, methacrylic acid, α -glutamic acid, γ -glutamic acid, and aspartic acid are not limited, and examples of the constituent monomers include constituent monomers B such as ethylene glycol, propylene glycol, vinylpyrrolidone, vinyl alcohol, vinylcaprolactam, vinyl acetate, styrene, methyl methacrylate, hydroxyethyl methacrylate, and siloxane. In cases where the weight of the constituent monomers B is too high, the number of reaction sites for binding to the warp yarns and the weft yarns constituting the cylindrical fabric whose inside contacts blood, or to another antithrombogenic material, is small. Accordingly, the weight of the constituent monomers B with respect to the total weight of the anionic polymer is preferably not more than 10 wt%.

[0112]

The anionic compound is preferably, but does not necessarily need to be, oxalic acid, malonic acid, succinic acid, fumaric acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, malic acid, tartaric acid, or citric acid since, in cases where the weight ratio of anionic functional groups is high, a larger amount of the compound can be bound to the cylindrical fabric whose inside contacts blood, or to another antithrombogenic material. The anionic compound is more preferably succinic acid.

[0113]

In cases where the weight average molecular weight of the anionic polymer is too small, the amount of the polymer bound to the cylindrical fabric whose inside contacts blood, or to another antithrombogenic material is small. It is therefore difficult to obtain a high and long-lasting antithrombogenicity. On the other hand, in cases where the weight average molecular weight of the anionic polymer is too high, the antithrombogenic material is included in the inside. Therefore, the number average molecular weight of the anionic polymer is preferably 600 to 2,000,000, more preferably 10,000 to 1,000,000.

[0114]

In the present invention, various organic fibers may be used as the fiber to be used for the cylindrical fabric, especially as the multifilament yarn. From the viewpoint of water absorbability and resistance to deterioration, the fiber is preferably a polyester fiber. Examples of the polyester fiber include fibers composed of polyethylene terephthalate, polybutylene terephthalate, or the like. The fiber may be composed of a copolymerized polyester prepared by copolymerization of polyethylene terephthalate, polybutylene terephthalate, or the like with an aliphatic dicarboxylic acid such as isophthalic acid, 5-sodium sulfoisophthalate, or adipic acid as an acid component. The fiber constituting the

multifilament yarns and the fiber constituting the warp yarns and the weft yarns may be the same as or different from each other, and an appropriate combination of the fibers may be used.

[0115]

5 Examples of looms which may be used herein include water-jet looms, air-jet looms, rapier looms, and shuttle looms. In particular, a shuttle loom is preferably used since it has an excellent weaving performance for cylindrical shapes, and is capable of producing a uniform cylindrical structure. As the weave of a double-woven artificial blood vessel, whose number of fiber layers is 2, a fabric such as a
10 plain weave fabric, twill weave fabric, or a satin weave fabric, a variation thereof, or a multilayer fabric thereof may be used. As basic weaving methods, known means may be employed.

[0116]

 The artificial blood vessel of the present invention is characterized in that it
15 allows only a small amount of blood leakage and can achieve both the antithrombogenicity and the cellular affinity. Therefore, although the present invention is generally applicable to artificial blood vessels, it is especially suitable for artificial blood vessels having small inner diameters, which show poor long-term performances, and none of which is clinically useful at present. That is, the inner
20 diameter is preferably 1 to 10 mm, more preferably 1 to 6 mm.

EXAMPLES

[0117]

 The present invention is described below in detail by way of Examples and Comparative Examples. However, the present invention is not limited thereto.

25 [0118]

(Example 1)

 As the warp yarns and the weft yarns constituting the inner-layer cylindrical

fabric, polyethylene terephthalate multifilament yarns of 144 filaments having a single yarn fineness of 0.23 dtex and a total fineness of 33 dtex were used. As the warp yarns constituting the outer-layer cylindrical fabric, polyethylene terephthalate multifilament yarns of 24 filaments having a single yarn fineness of 2.33 dtex and a total fineness of 56 dtex were used. As the weft yarns constituting the outer-layer cylindrical fabric, polyethylene terephthalate monofilament yarns having a single yarn fineness of 33 dtex were used. The warp yarns were set in a narrow dobby double-shuttle loom, and the weft yarns were beaten up to perform weaving such that an inner diameter of 3 mm is achieved. Scouring was carried out at 98°C, and heat setting was carried out at 170°C, to obtain a multi-cylindrical fabric structure 1.

[0119]

Thereafter, the cylindrical fabric 1 was immersed in an aqueous solution of 5.0 wt% potassium permanganate (manufactured by Wako Pure Chemical Industries, Ltd.) and 0.6 mol/L sulfuric acid (manufactured by Wako Pure Chemical Industries, Ltd.), and the reaction was allowed to proceed at 60°C for 3 hours, thereby hydrolyzing and oxidizing the multi-cylindrical fabric structure 1.

[0120]

Subsequently, the resulting product was immersed in an aqueous solution of 0.5 wt% DMT-MM (manufactured by Wako Pure Chemical Industries, Ltd.) and 5.0 wt% PEI (LUPASOL (registered trade mark) P, manufactured by BASF), and the reaction was allowed to proceed at 30°C for 2 hours, thereby covalently binding PEI to the multi-cylindrical fabric structure 1 by condensation reaction.

[0121]

Subsequently, the resulting product was immersed in 1 wt% aqueous methanol solution of ethyl bromide (manufactured by Wako Pure Chemical Industries, Ltd.), and the reaction was allowed to proceed at 35°C for 1 hour, and then at 50°C for 4 hours, thereby allowing modification of the PEI covalently bound

to the surface of the multi-cylindrical fabric structure 1, with quaternary ammonium.
[0122]

Finally, resulting product was immersed in an aqueous solution (pH 4) of
0.75 wt% heparin sodium (manufactured by Organon API Inc.) and 0.1 mol/L
sodium chloride, and the reaction was allowed to proceed at 70°C for 6 hours,
thereby obtaining an artificial blood vessel (Sample 1) in which an antithrombogenic
material layer is formed by ionic bonding with the PEI modified with quaternary
ammonium.
[0123]

The resulting artificial blood vessel (Sample 1) was subjected to evaluation of
the blood leakage property, and evaluation of the antithrombogenicity and evaluation
of the cellular affinity by artificial blood vessel transplantation tests for the dog
carotid artery. The results are shown in Table 1. As shown in Table 1, in the
evaluation of the blood leakage property, the amount of blood leakage was small, so
that the blood leakage property was evaluated as “Good”. In the evaluation of the
antithrombogenicity, no complete obstruction was found on Day 28 after the
transplantation, so that the antithrombogenicity was evaluated as “Good”. In the
evaluation of the cellular affinity, the distance of migration of vascular endothelial
cells was long, so that the cellular affinity was evaluated as “Good”.

[0124]

(Example 2)

The same operations as in Example 1 were carried out except that
multifilament yarns having a single yarn fineness of 7.3 dtex and a total fineness 66
dtex, which are untwisted sea-island composite fibers (mixing ratio, sea/island
(weight ratio) = 20/80; island component number, 70), were used as the weft yarns
constituting the inner-layer cylindrical fabric, and that, after the scouring, complete
leaching of the sea component was carried out using 4 wt% aqueous sodium

hydroxide (manufactured by Wako Pure Chemical Industries, Ltd.) solution at 98°C, followed by carrying out heat setting, to obtain polyethylene terephthalate multifilament yarns of 630 filaments having a single yarn fineness of 0.084 dtex and a total fineness 53 dtex. A multi-cylindrical fabric structure 2 was obtained by weaving.

[0125]

Here, in the sea-island composite fiber, the island component polymer is constituted by polyethylene terephthalate multifilament yarns, and the sea component polymer is constituted by polyethylene terephthalate copolymerized with 5-sodium sulfoisophthalate.

[0126]

The resulting multi-cylindrical fabric structure 2 was subjected to the same operations as in Example 1, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 2).

[0127]

The resulting artificial blood vessel (Sample 2) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0128]

(Example 3)

The same operations as in Example 1 were carried out except that the multifilament yarns which are sea-island composite fibers used in Example 2 were used as the warp yarns and the weft yarns constituting the inner-layer cylindrical fabric, and that, after the scouring, complete leaching of the sea component was carried out using 4 wt% aqueous sodium hydroxide (manufactured by Wako Pure Chemical Industries, Ltd.) solution at 98°C, followed by carrying out heat setting, to obtain polyethylene terephthalate multifilament yarns of 630 filaments having a single yarn fineness of 0.084 dtex and a total fineness 53 dtex. A multi-cylindrical fabric structure 3 was obtained by weaving.

[0129]

The resulting multi-cylindrical fabric structure 3 was subjected to the same operations as in Example 1, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 3).

[0130]

The resulting artificial blood vessel (Sample 3) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0131]

(Example 4)

By the same operations as in Example 1, the multi-cylindrical fabric structure

1 was hydrolyzed and oxidized, and PEI was covalently bound thereto by condensation reaction. The resulting product was then immersed in a solution of 0.5 wt% DMT-MM and 40 wt% succinic anhydride (manufactured by Wako Pure Chemical Industries, Ltd.) in dimethylacetamide, followed by allowing the reaction to proceed at 50°C for 17 hours.

[0132]

The resulting product was then immersed in an aqueous solution of 0.5 wt% DMT-MM and 5.0 wt% PEI, and the reaction was allowed to proceed at 30°C for 2 hours. By the same operations as in Example 1, PEI was modified with quaternary ammonium using ethyl bromide, and heparin sodium was used to form an antithrombogenic material layer, thereby obtaining an artificial blood vessel (Sample 4).

[0133]

The resulting artificial blood vessel (Sample 4) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0134]

(Example 5)

By the same operations as in Example 1, the multi-cylindrical fabric structure 1 was hydrolyzed and oxidized, and PEI was covalently bound thereto by

condensation reaction. The resulting product was then immersed in an aqueous solution of 0.5 wt% DMT-MM and 0.5 wt% PAA (weight average molecular weight, 1,000,000; manufactured by Wako Pure Chemical Industries, Ltd.), and the reaction was allowed to proceed at 30°C for 2 hours.

5 [0135]

The resulting product was then immersed in an aqueous solution of 0.5 wt% DMT-MM and 5.0 wt% PEI, and the reaction was allowed to proceed at 30°C for 2 hours. By the same operations as in Example 1, PEI was modified with quaternary ammonium using ethyl bromide, and heparin sodium was used to form an antithrombogenic material layer, thereby obtaining an artificial blood vessel (Sample 5).

[0136]

The resulting artificial blood vessel (Sample 5) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0137]

(Example 6)

25 Artificial blood vessels were obtained by the same operations as in Example 5 except that polyallylamine hydrochloride (hereinafter referred to as “PAH”) (weight average molecular weight, 900,000; manufactured by Sigma-Aldrich) or poly-L-

lysine hydrobromide (hereinafter referred to as PLys) (weight average molecular weight, 30,000 to 70,000; manufactured by Sigma-Aldrich) was used instead of PEI.
[0138]

Here, the artificial blood vessel in which an antithrombogenic material layer was formed using PAH was provided as Sample 6, and the artificial blood vessel in which an antithrombogenic material layer was formed using PLys was provided as Sample 7.
[0139]

The resulting artificial blood vessels (Samples 6 and 7) were subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.
[0140]

(Example 7)

An artificial blood vessel in which an antithrombogenic material layer is formed (Sample 8) was obtained by the same operations as in Example 1 except that dextran sulfate sodium (manufactured by Wako Pure Chemical Industries, Ltd.) was used instead of heparin sodium.

[0141]

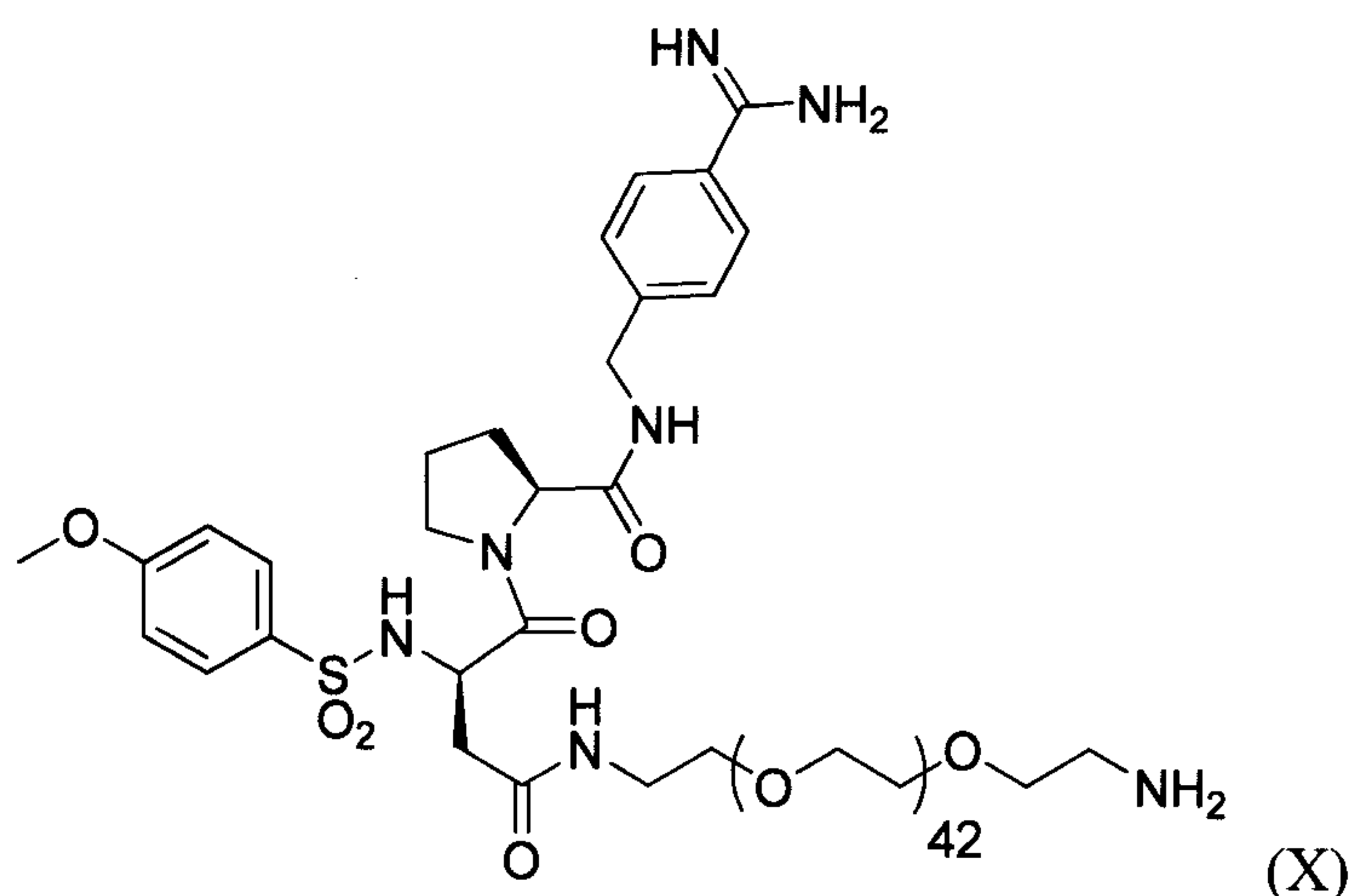
The resulting artificial blood vessel (Sample 8) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation

of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0142]

(Example 8)

By the same operations as in Example 1, the multi-cylindrical fabric structure 1 was hydrolyzed and oxidized. Thereafter, the resulting product was immersed in an aqueous solution in which 1.0 wt% Compound A (the following General Formula (X)), sodium hydroxide in an amount of 2 molar equivalents with respect to Compound A, and DMT-MM in an amount of 3 molar equivalents with respect to Compound A, are dissolved. The reaction was allowed to proceed at 30°C for 2 hours to covalently bind Compound A to the cylindrical fabric 1 by condensation reaction, thereby obtaining an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 9).



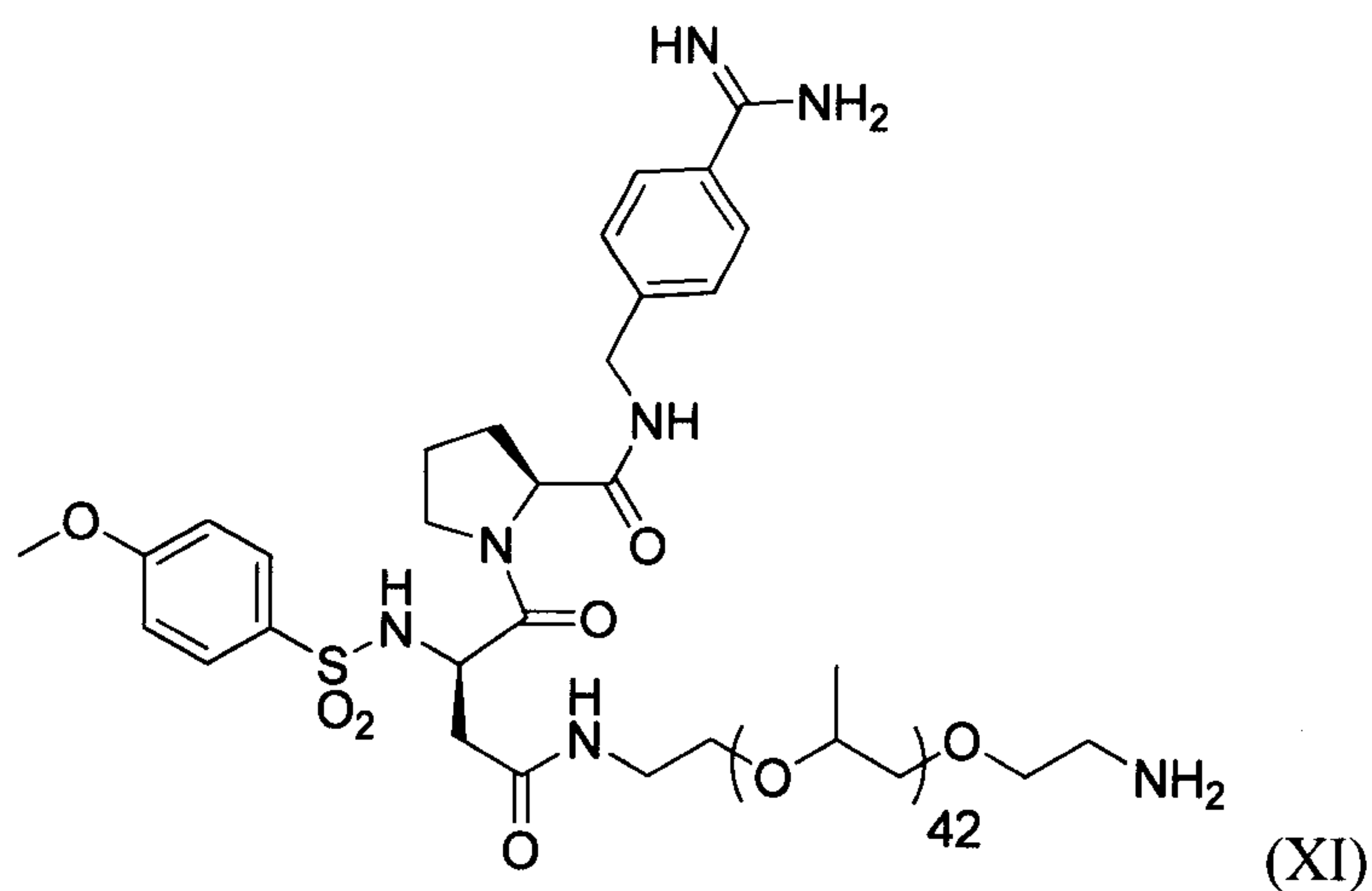
[0143]

The resulting artificial blood vessel (Sample 9) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0144]

(Example 9)

Artificial blood vessels were obtained by the same operations as in Example 8 except that Compound B (the following General Formula (XI)), Compound C (the following General Formula (XII)), or Compound D (the following General Formula (XIII)) was used instead of Compound A.





10

15

The resulting artificial blood vessels (Samples 10 to 12) were subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests

for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0147]

(Example 10)

By the same operations as in Example 1, the multi-cylindrical fabric structure 1 was hydrolyzed and oxidized, and PEI was covalently bound thereto by condensation reaction. The resulting product was then immersed in an aqueous solution of 0.5 wt% DMT-MM and 0.5 wt% PAA (weight average molecular weight, 1,000,000; manufactured by Wako Pure Chemical Industries, Ltd.), and the reaction was allowed to proceed at 30°C for 2 hours.

[0148]

Thereafter, the resulting product was immersed in an aqueous solution in which 1.0 wt% Compound A, sodium hydroxide in an amount of 2 molar equivalents with respect to Compound A, and DMT-MM in an amount of 3 molar equivalents with respect to Compound A, are dissolved. The reaction was allowed to proceed at 30°C for 2 hours to allow covalent bonding of Compound A by condensation reaction, thereby obtaining an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 13).

[0149]

The resulting artificial blood vessel (Sample 13) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for

the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0150]

(Example 11)

Multi-cylindrical fabric structures were obtained by the same operations as in Example 1 except that polyethylene terephthalate monofilament yarns having a single yarn fineness of 13 dtex, polyethylene terephthalate monofilament yarns having a single yarn fineness of 108 dtex, or polyethylene terephthalate monofilament yarns having a single yarn fineness of 333 dtex were used as the weft yarns constituting the outer-layer cylindrical fabric.

[0151]

Here, the fabric woven using the polyethylene terephthalate monofilament yarns having a single yarn fineness of 13 dtex was provided as a multi-cylindrical fabric structure 4; the fabric woven using the polyethylene terephthalate monofilament yarns having a single yarn fineness of 108 dtex was provided as a multi-cylindrical fabric structure 5; and the fabric woven using the polyethylene terephthalate monofilament yarns having a single yarn fineness of 333 dtex was provided as a multi-cylindrical fabric structure 6.

[0152]

The resulting multi-cylindrical fabric structures 4 to 6 were subjected to the same operations as in Example 1, to obtain artificial blood vessels in which an antithrombogenic material layer is formed (Samples 14 to 16).

[0153]

The resulting artificial blood vessels (Samples 14 to 16) were subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0154]

(Comparative Example 1)

The same operations as in Example 1 were carried out except that polyethylene terephthalate multifilament yarns of 24 filaments having a single yarn fineness of 1.38 dtex and a total fineness of 33 dtex were used as the warp yarns constituting the inner-layer cylindrical fabric. A multi-cylindrical fabric structure 7 was obtained by weaving.

[0155]

The resulting multi-cylindrical fabric structure 7 was subjected to the same operations as in Example 1, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 17), or subjected to the same operations as in Example 10, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 18).

[0156]

The resulting artificial blood vessels (Samples 17 and 18) were subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity

and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was large, so that the blood leakage property was evaluated as “Bad”. Thus, the artificial blood vessels were not applicable to the artificial blood vessel transplantation tests for the dog carotid artery. That is, the antithrombogenicity and the cellular affinity were evaluated as “—”.

[0157]

(Comparative Example 2)

The same operations as in Example 1 were carried out except that polyethylene terephthalate multifilament yarns of 24 filaments having a single yarn fineness of 1.38 dtex and a total fineness of 33 dtex were used as the weft yarns constituting the inner-layer cylindrical fabric. A multi-cylindrical fabric structure 8 was obtained by weaving.

[0158]

The resulting multi-cylindrical fabric structure 8 was subjected to the same operations as in Example 1, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 19), or subjected to the same operations as in Example 10, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 20).

[0159]

The resulting artificial blood vessels (Samples 19 and 20) were subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was large, so that the blood leakage property was evaluated as “Bad”. Thus, the

artificial blood vessels were not applicable to the artificial blood vessel transplantation tests for the dog carotid artery. That is, the antithrombogenicity and the cellular affinity were evaluated as “—”.

[0160]

5 (Comparative Example 3)

The same operations as in Example 1 were carried out except that weaving was carried out while the base fabric density was adjusted such that the cover factor was 1600, to obtain a multi-cylindrical fabric structure 9.

[0161]

10 The resulting multi-cylindrical fabric structure 9 was subjected to the same operations as in Example 1, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 21), or subjected to the same operations as in Example 10, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 22).

15 [0162]

The resulting artificial blood vessels (Samples 21 and 22) were subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, 20 in the evaluation of the blood leakage property, the amount of blood leakage was large, so that the blood leakage property was evaluated as “Bad”. Thus, the artificial blood vessels were not applicable to the artificial blood vessel transplantation tests for the dog carotid artery. That is, the antithrombogenicity and the cellular affinity were evaluated as “—”.

25 [0163]

(Comparative Example 4)

An artificial blood vessel (Sample 23) in which no antithrombogenic material

layer is formed in the multi-cylindrical fabric structure 1 was obtained.

[0164]

The resulting artificial blood vessel (Sample 23) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. However, in the evaluation of the antithrombogenicity, complete obstruction was found by Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Bad”. In the evaluation of the cellular affinity, no migration of vascular endothelial cells was found, so that the cellular affinity was evaluated as “Bad”.

[0165]

(Comparative Example 5)

The multi-cylindrical fabric structure 1 was immersed in organic solvents such as methanol and tetrahydrofuran in which PEI, ethyl bromide, and heparin sodium are dissolved, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 24).

[0166]

The resulting artificial blood vessel (Sample 24) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. However,

in the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was short, so that the cellular affinity was evaluated as “Bad”.

[0167]

(Example 12)

5 The same operations as in Example 1 were carried out except that polyethylene terephthalate multifilament yarns of 144 filaments having a single yarn fineness of 0.30 dtex and a total fineness of 44 dtex were used as the warp yarns and the weft yarns constituting the inner-layer cylindrical fabric. A multi-cylindrical fabric structure 10 was obtained by weaving.

10 [0168]

The resulting multi-cylindrical fabric structure 10 was subjected to the same operations as in Example 1, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 25).

[0169]

15 The resulting artificial blood vessel (Sample 25) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small,
20 so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

25 [0170]

(Example 13)

The same operations as in Example 1 were carried out except that weaving

was carried out while the base fabric density was adjusted such that the cover factor was 1700, to obtain a multi-cylindrical fabric structure 11.

[0171]

The resulting multi-cylindrical fabric structure 11 was subjected to the same operations as in Example 1, to obtain an artificial blood vessel in which an antithrombogenic material layer is formed (Sample 26).

[0172]

The resulting artificial blood vessel (Sample 26) was subjected to evaluation of the blood leakage property, and evaluation of the antithrombogenicity and evaluation of the cellular affinity by artificial blood vessel transplantation tests for the dog carotid artery. The results are shown in Table 1. As shown in Table 1, in the evaluation of the blood leakage property, the amount of blood leakage was small, so that the blood leakage property was evaluated as “Good”. In the evaluation of the antithrombogenicity, no complete obstruction was found on Day 28 after the transplantation, so that the antithrombogenicity was evaluated as “Good”. In the evaluation of the cellular affinity, the distance of migration of vascular endothelial cells was long, so that the cellular affinity was evaluated as “Good”.

[0173]

The evaluation methods for the blood leakage property, antithrombogenicity, and cellular affinity of the artificial blood vessels of the present invention are described below.

[0174]

(Evaluation 1: Blood Leakage Property)

Similarly to the measurement of the water permeability described in the guidance in ISO 7198, a pressure (hydrostatic pressure) of 16 kPa was applied to the inner surface of an artificial blood vessel. Thirty seconds later, the amount of bovine blood (mL) flown out into the outer layer of the artificial blood vessel in 5

minutes was measured, and the amount was divided by the unit time (min.) and the unit area (cm^2), to determine the blood leakage property at 16 kPa. The bovine blood was prepared such that the hematocrit was 25 to 30%; the erythrocyte count was 5.0 to $6.2 \times 10^6/\mu\text{L}$; the leukocyte count was 30 to $110 \times 10^2/\mu\text{L}$; the platelet count was 6.0 to $20.0 \times 10^4/\mu\text{L}$; and the total protein was 6.5 g/dL. In cases where the blood leakage property was less than $2.0 \text{ mL}/\text{cm}^2/\text{min.}$, the amount of blood leakage was judged to be small, and the operation such as preclotting was thought to be unnecessary, so that the blood leakage property was evaluated as “Good”. In cases where the blood leakage property was not less than $2.0 \text{ mL}/\text{cm}^2/\text{min.}$, the amount of blood leakage was judged to be large, and the operation such as preclotting was thought to be necessary, so that the blood leakage property was evaluated as “Bad”.

[0175]

(Evaluation 2: Evaluation of Antithrombogenicity by Artificial Blood Vessel Transplantation Test for Dog Carotid Artery)

By referring to a document by P. C. Begovac et al. (Eur Vasc Endovasc Surg 25, 432-437 2003) and the like, an artificial blood vessel was transplanted to the dog carotid artery. The transplanted artificial blood vessel and the living blood vessels in both sides thereof were periodically subjected to ultrasound echo and angiography to judge the presence or absence of a thrombus/thrombi and the presence or absence of obstruction. On Day 28 after the transplantation, in cases where no complete obstruction was found, the antithrombogenicity was judged to be high, and evaluated as “Good”. In cases where complete obstruction was found, the antithrombogenicity was judged to be insufficient, and evaluated as “Bad”.

[0176]

(Evaluation 3: Evaluation of Cellular Affinity by Artificial Blood Vessel Transplantation Test for Dog Carotid Artery)

In the same manner as in Evaluation 2, an artificial blood vessel was transplanted to the dog carotid artery. The artificial blood vessel was removed on Day 28 after the transplantation, and stained with H. E. to prepare a sample. The sample obtained was observed under the microscope to measure the length from a suture site between the artificial blood vessel and a living blood vessel to the portion where vascular endothelial cells settled after migration. In cases where the distance of migration of vascular endothelial cells was not less than 4.0 mm, the cellular affinity was judged to be high, so that the cellular affinity was evaluated as “Good”. In cases where the distance of migration of vascular endothelial cells was less than 4.0 mm, the cellular affinity was judged to be insufficient, so that the cellular affinity was evaluated as “Bad”.

[0177]

[Table 1]

	Sample	Inner layer			Outer layer		Water permeability (mL/cm ² /min.)	Cover factor	Antithrombogenic material	Thickness (nm)	Abundance ratio of nitrogen atoms (atomic percent)	Abundance ratio of sulfur atoms (atomic percent)	Blood leakage property (mL/cm ² /min.)	Antithrombogenicity	Distance of migration (mm)
Example 1	1	0.23	0.23	2.33	33	33	34	2550	Heparin	58	8.2	3.8	0.04	Good	6.5
Example 2	2	0.23	0.084	2.33	33	33	130	2400	Heparin	85	8.3	3.9	0.08	Good	9.8
Example 3	3	0.084	0.084	2.33	33	33	208	2100	Heparin	85	8.3	3.8	1.8	Good	11
Example 4	4	0.23	0.23	2.33	33	33	21	2550	Heparin	510	8.0	3.3	0.10	Good	6.9
Example 5	5	0.23	0.23	2.33	33	33	12	2550	Heparin	585	9.8	3.9	0.42	Good	5.3
Example 6	6	0.23	0.23	2.33	33	33	14	2550	Heparin	483	9.1	3.2	0.51	Good	5.1
Example 7	7	0.23	0.23	2.33	33	33	14	2550	Heparin	495	9.2	3.0	0.48	Good	5.1
Example 8	8	0.23	0.23	2.33	33	33	34	2550	Dextran sulfate	60	8.2	3.6	0.08	Good	4.9
Example 9	9	0.23	0.23	2.33	33	33	27	2550	Compound of General Formula (X)	45	—	—	0.32	Good	4.9
Example 10	10	0.23	0.23	2.33	33	33	23	2550	Compound of General Formula (XI)	42	—	—	0.40	Good	4.9
Example 11	11	0.23	0.23	2.33	33	33	32	2550	Compound of General Formula (XII)	43	—	—	0.40	Good	4.3
Example 12	12	0.23	0.23	2.33	33	33	30	2550	Compound of General Formula (XIII)	42	—	—	0.41	Good	4.5
Example 13	13	0.23	0.23	2.33	33	33	17	2550	Compound of General Formula (X)	470	—	—	0.42	Good	5.2
Example 14	14	0.23	0.23	2.33	13	26	26	2550	Heparin	58	8.2	4.0	0.04	Good	6.4
Example 15	15	0.23	0.23	2.33	108	62	62	2550	Heparin	60	8.1	3.6	0.10	Good	6.3
Example 16	16	0.23	0.23	2.33	333	83	83	2550	Heparin	57	8.4	3.8	0.11	Good	6.5
Comparative Example 1	17	1.38	0.23	2.33	33	280	280	2100	Heparin	35	8.2	4.1	4.5	—	—
Comparative Example 2	18	1.38	0.23	2.33	33	275	275	2100	Compound of General Formula (X)	470	—	—	4.2	—	—
Comparative Example 3	19	0.23	1.38	2.33	33	281	281	2150	Heparin	38	8.2	3.8	4.2	—	—
Comparative Example 4	20	0.23	1.38	2.33	33	273	273	2150	Compound of General Formula (X)	470	—	—	4.3	—	—
Comparative Example 5	21	0.23	0.23	2.33	33	350	350	1600	Heparin	60	8.0	3.5	16	—	—
Comparative Example 6	22	0.23	0.23	2.33	33	320	320	1600	Compound of General Formula (X)	470	—	—	18	—	—
Comparative Example 7	23	0.23	0.23	2.33	33	39	39	2550	—	0	—	—	0.01	Bad	0
Comparative Example 8	24	0.23	0.23	2.33	33	10	10	2550	Heparin	650	12.8	6.3	0.01	Good	1.2
Comparative Example 9	25	0.30	0.30	2.33	33	57	57	2200	Heparin	58	8.2	3.8	0.44	Good	4.1
Comparative Example 10	26	0.23	0.23	2.33	33	251	251	1700	Heparin	58	8.2	3.8	1.9	Good	4.5

INDUSTRIAL APPLICABILITY

[0178]

5 The artificial blood vessel of the present invention can be favorably used in the field of medicine as a fabric artificial blood vessel which allows only a small amount of blood leakage and can achieve both the antithrombogenicity and the cellular affinity.

CLAIMS

1. An artificial blood vessel comprising a cylindrical fabric structure in which a cylindrical fabric whose inside contacts blood is arranged, wherein

5 said cylindrical fabric whose inside contacts blood is a fabric prepared by interlacing a plurality of warp yarns and a plurality of weft yarns with each other into a cylindrical shape;

said warp yarns and said weft yarns constituting said cylindrical fabric whose inside contacts blood comprise a multifilament yarn having a single yarn fineness of not more than 0.50 dtex, and are bound to an antithrombogenic material;

10 said antithrombogenic material forms an antithrombogenic material layer having a thickness of 1 to 600 nm inside said cylindrical fabric whose inside contacts blood; and

the water permeability under conditions where a pressure of 16 kPa is applied to the inner surface is less than 300 mL/cm²/min.

2. The artificial blood vessel according to claim 1, wherein said cylindrical fabric structure is a multi-cylindrical fabric structure in which an outer-layer cylindrical fabric is arranged outside said cylindrical fabric whose inside contacts blood, and said outer-layer cylindrical fabric is a fabric prepared by interlacing a plurality of warp yarns and a plurality of weft yarns with each other into a cylindrical shape.

3. The artificial blood vessel according to claim 2, wherein said outer-layer cylindrical fabric comprises, as a warp yarn, a multifilament yarn having a single yarn fineness of not less than 1.0 dtex.

4. The artificial blood vessel according to claim 3, wherein the percentage of exposure of said multifilament yarn having a single yarn fineness of not less than 1.0 dtex on said inner surface is not more than 20%.

5. The artificial blood vessel according to any one of claims 1 to 4, wherein the cover factor for said warp yarns and said weft yarns constituting said cylindrical fabric whose inside contacts blood is 1800 to 4000.

6. The artificial blood vessel according to any one of claims 2 to 5, wherein said outer-layer cylindrical fabric comprises, as a weft yarn, a monofilament yarn having a single yarn fineness of not less than 15.0 dtex.

7. The artificial blood vessel according to any one of claims 1 to 6, wherein said antithrombogenic material comprises an anionic compound containing a sulfur atom and having anticoagulant activity.

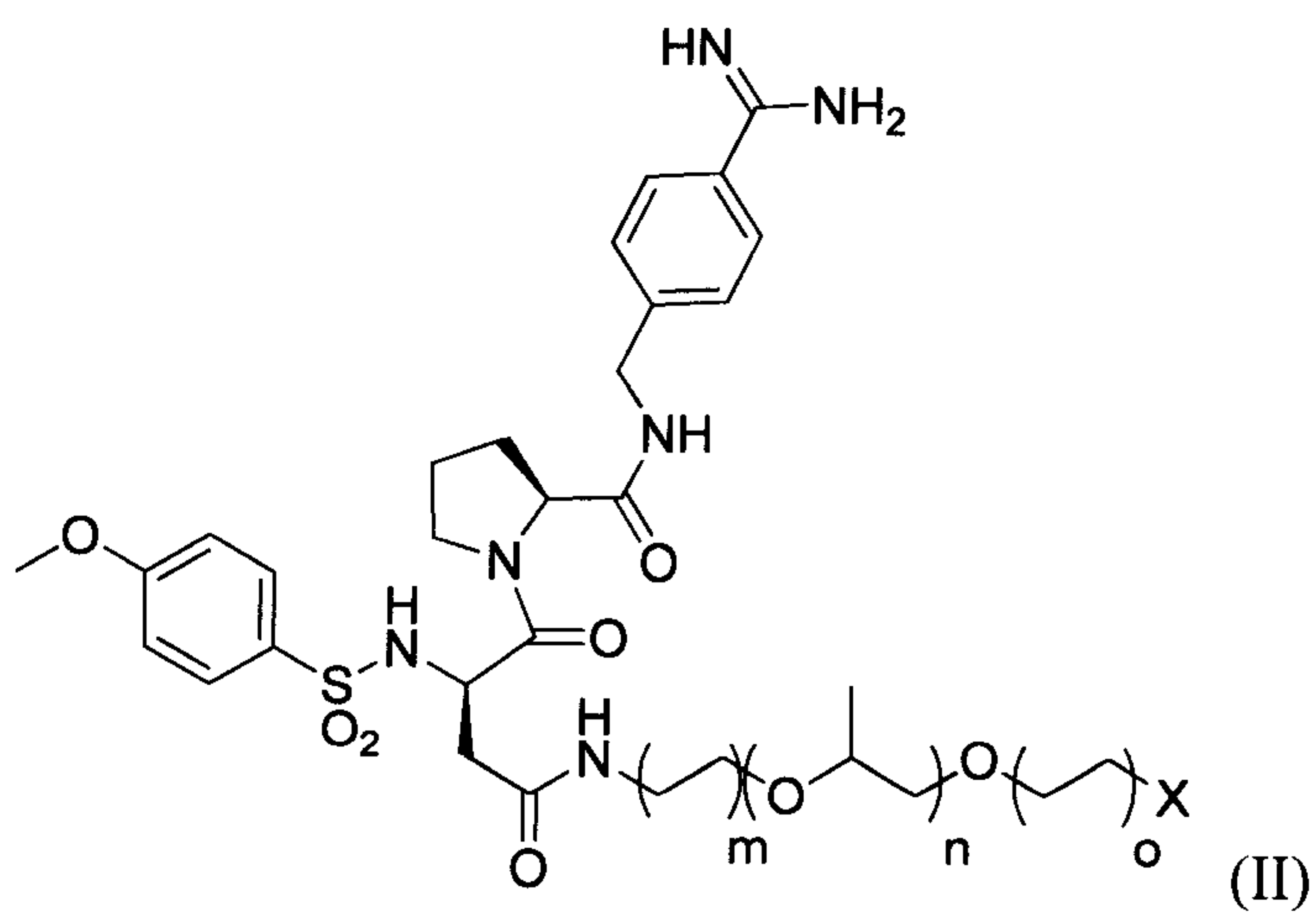
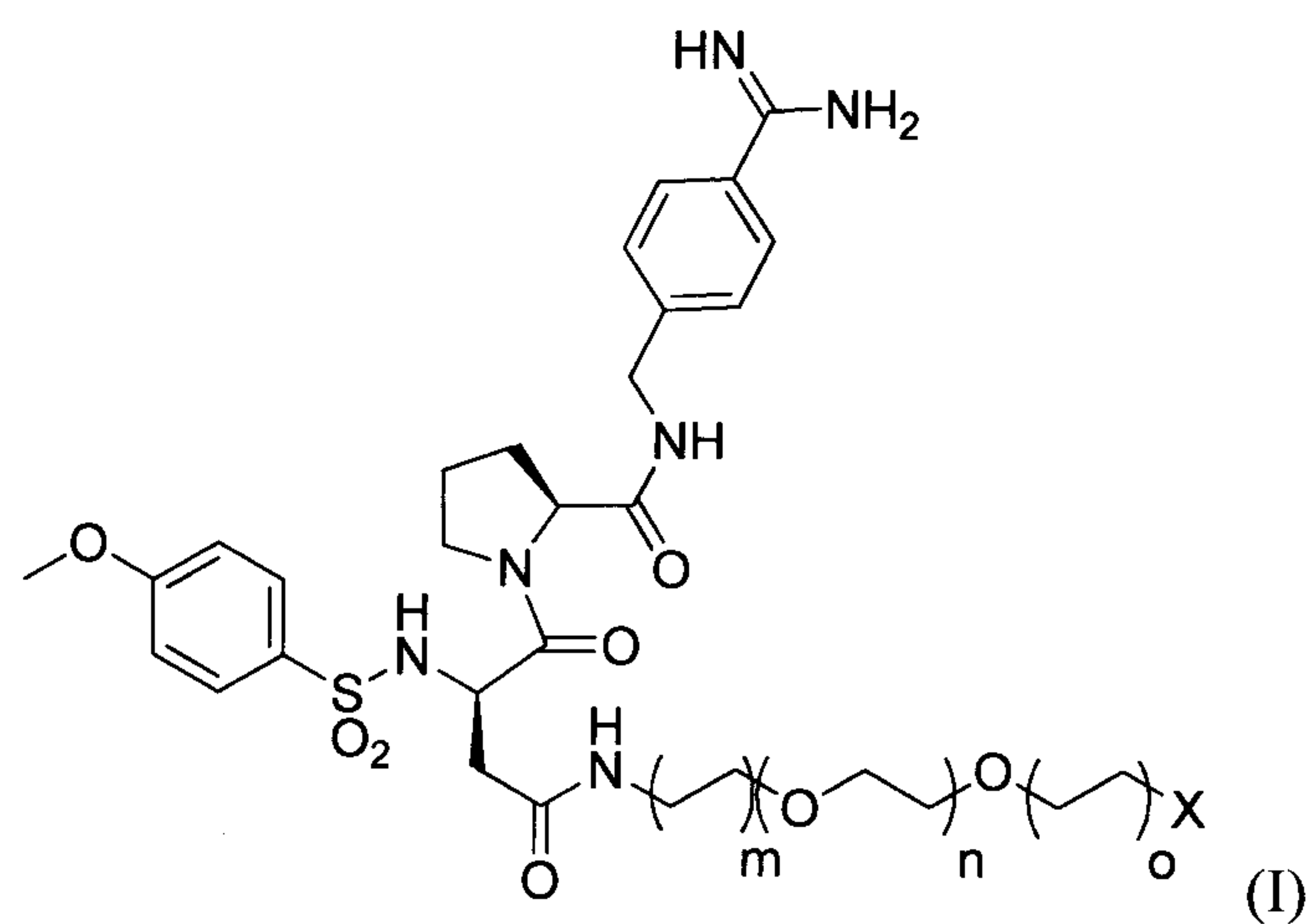
8. The artificial blood vessel according to claim 7, wherein the ratio of the abundance of sulfur atoms to the abundance of total atoms on the inner surface as measured by X-ray photoelectron spectroscopy (XPS) is 3.0 to 6.0 atomic percent.

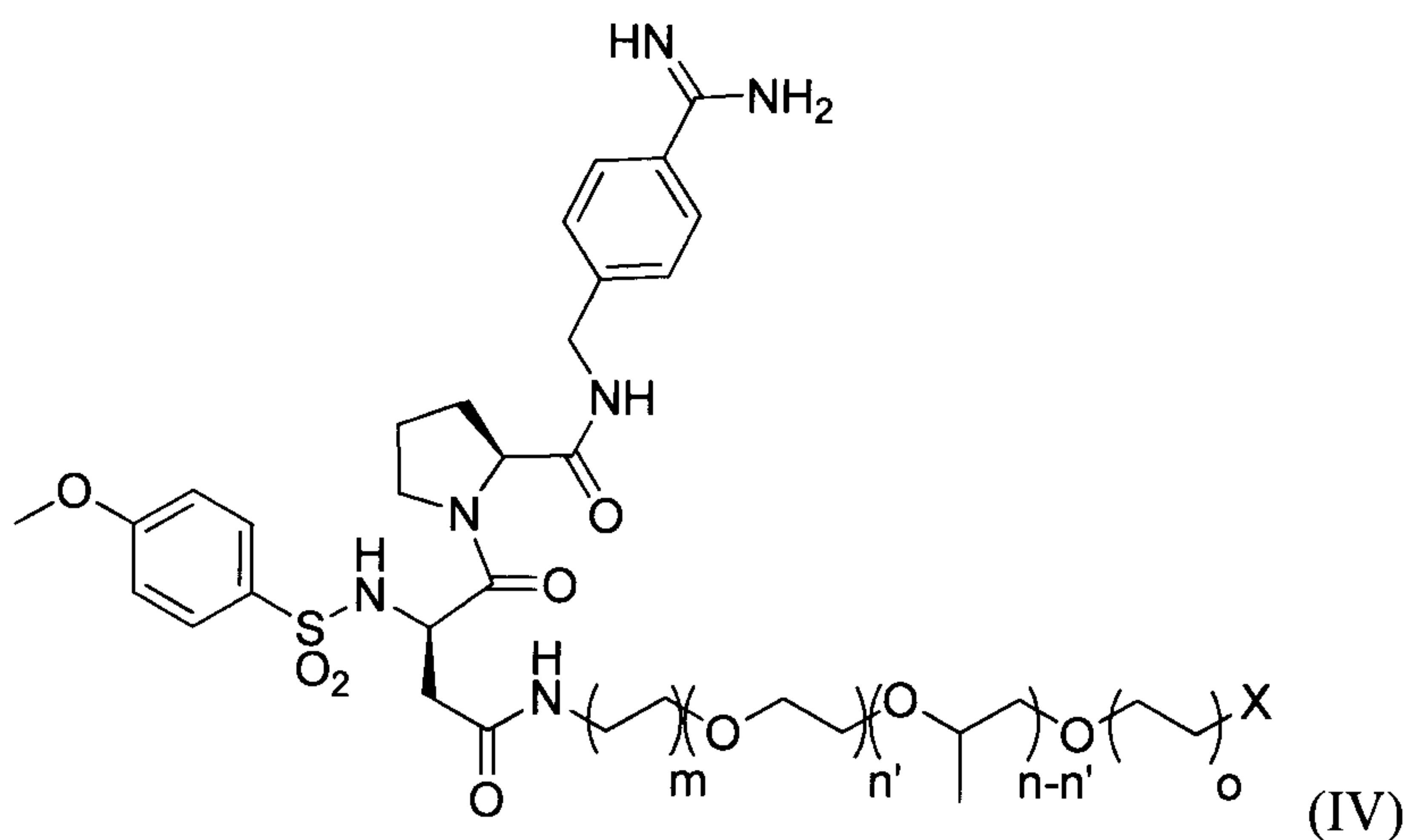
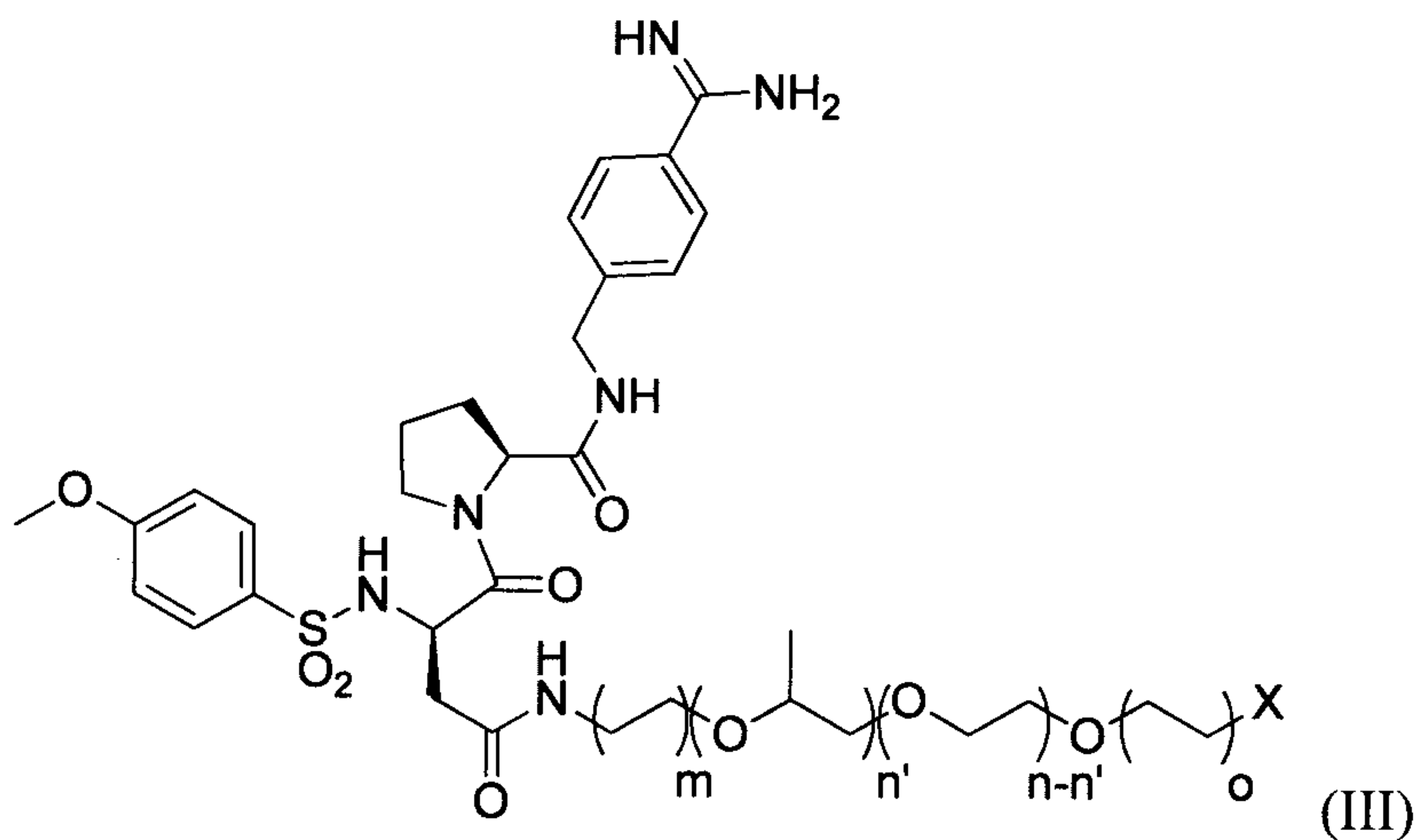
9. The artificial blood vessel according to any one of claims 1 to 8, wherein said antithrombogenic material comprises a cationic polymer containing, as a constituent monomer, a compound selected from the group consisting of alkyleneimines, vinylamines, allylamines, lysine, protamine, and diallyldimethylammonium chloride, and said cationic polymer is covalently bound to said warp yarns and said weft yarns constituting said cylindrical fabric whose inside contacts blood.

10. The artificial blood vessel according to any one of claims 1 to 6, wherein said antithrombogenic material is a compound containing the following three kinds of skeletal structures: a skeletal structure composed of a hydrophilic polymer containing, as a constituent monomer, a compound selected from the group consisting of ethylene glycol, propylene glycol, vinylpyrrolidone, vinyl alcohol, vinylcaprolactam, vinyl acetate, styrene, methyl methacrylate, hydroxyethyl methacrylate, and siloxane; a skeletal structure composed of 4-(aminomethyl)benzenecarboxyimidamide or benzene amidine; and a skeletal structure composed of methoxybenzenesulfonic acid amide; wherein said compound containing said three kinds of skeletal structures is

covalently bound to said warp yarns and said weft yarns constituting said cylindrical fabric whose inside contacts blood.

11. The artificial blood vessel according to claim 10, wherein said compound containing said three kinds of skeletal structures is a compound represented by any one of the following General Formulae (I) to (IV):





[wherein m and o each represent an integer of 0 to 4; n represents an integer of 3 to 1000, and n' represents an integer of 3 to 1000, with the proviso that $n \geq n'$; and X represents a functional group selected from the group consisting of hydroxyl, thiol, amino, carboxyl, aldehyde, isocyanate, and thioisocyanate].

12. The artificial blood vessel according to any one of claims 1 to 11, wherein said antithrombogenic material comprises: an anionic polymer comprising, as a constituent monomer, a compound selected from the group consisting of acrylic acid, methacrylic acid, α -glutamic acid, γ -glutamic acid, and aspartic acid; or an anionic compound selected from the group consisting of oxalic acid, malonic acid, succinic acid, fumaric acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, malic acid, tartaric acid, and citric acid.

13. The artificial blood vessel according to any one of claims 1 to 12, wherein

said multifilament yarn is composed of a polyester.