Non Patent Literature 9: Watanabe, T.X. et al., Vasopressor activities of N-terminal fragments of adrenomedullin in anesthetized rat. Biochem Biophys Res Commun, 1996, Volume 219, Issue 1, p. 59-63.

Non Patent Literature 10: Kubo, K et al., Biological properties of adrenomedullin conjugated with polyethylene glycol. Peptides, 2014, Volume 57, p. 118-21.

Non Patent Literature 11: Kato, J., Kitamura, K.. Bench-to-bedside pharmacology of adrenomedullin. European Journal of Pharmacology, 2015, Volume 764, p. 140-148.

SUMMARY OF INVENTION

[0013a] In one aspect, disclosed herein is a compound represented by formula (X):

A'-CO-B (X)

wherein

A' is a modifying group comprising one or more polyethylene glycol groups, and

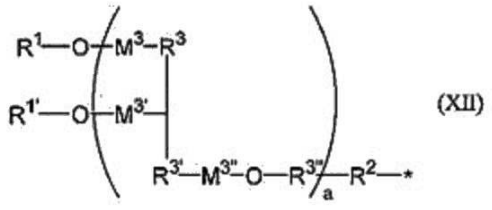
B is a peptide moiety derived from adrenomedullin or a modified form thereof with adrenomedullin activity,

wherein the peptide moiety B is linked to the other moieties through a covalent bond of the nitrogen atom of the N-terminal α-amino group of the peptide moiety B to the carbon atom of the carbonyl group,

the modifying group A' is linked to the other moieties through a covalent bond of the oxygen atom of the modifying group to the carbon atom of the carbonyl group,

A' is a modifying group represented by the following formula (XI) or (XII):

R^1-O-M^1-* (XI)



(XII)

wherein

a is an integer of 1 or larger,

M^1 is a polyethylene glycol group represented by formula (III):

$^{\#}$-$(CH_2CH_2O)_n$-** (III)

wherein

n is an integer of 1 or larger,

** is a binding position to *, and

is a binding position to O,

M^3, $M^{3'}$ and $M^{3''}$ are each independently a bond or a polyethylene glycol group represented by formula (III):

$^{\#}$-$(CH_2CH_2O)_n$-** (III)

wherein

n is an integer of 1 or larger,

** is a binding position to R^3, $R^{3'}$ or CH, and

is a binding position to O,

wherein when a plurality of M^3, $M^{3'}$ or $M^{3''}$ are present, the plurality of M^3, $M^{3'}$ or $M^{3''}$ are the same as or different from each other, and at least one of M^3, $M^{3'}$ and $M^{3''}$ is a polyethylene glycol group represented by formula (III),

R^1 and $R^{1'}$ are each independently hydrogen, unsubstituted C_1-C_{20} alkyl, unsubstituted C_2-C_{20} alkenyl, unsubstituted C_2-C_{20} alkynyl, unsubstituted C_3-C_{20} cycloalkyl, unsubstituted C_4-C_{20} cycloalkenyl, unsubstituted C_4-C_{20} cycloalkynyl, unsubstituted 3- to 6-membered heterocycloalkyl, unsubstituted C_7-C_{20} cycloalkylalkyl, unsubstituted 3- to 6-membered heterocycloalkyl-C_1-C_{20} alkyl, unsubstituted C_4-C_{20} aryl, unsubstituted C_5-C_{20} arylalkyl, unsubstituted 5- to 15-membered heteroaryl, unsubstituted 5- to 15-membered heteroaryl-C_1-C_{20} alkyl, or unsubstituted acyl,

R^2 is a bond ,

R^3 and $R^{3'}$ are each independently a bond, unsubstituted C_1-C_{20} alkylene, unsubstituted C_2-C_{20} alkenylene, unsubstituted C_2-C_{20} alkynylene, unsubstituted C_3-C_{20} cycloalkylene, unsubstituted C_4-C_{20} cycloalkenylene, unsubstituted C_4-C_{20} cycloalkynylene, unsubstituted 3- to 6-membered heterocycloalkylene, unsubstituted C_7-C_{20} cycloalkylalkylene, unsubstituted 3- to 6-membered heterocycloalkyl-C_1-C_{20} alkylene, unsubstituted C_4-C_{20}

arylene, unsubstituted C_5-C_{20} arylalkylene, unsubstituted 5- to 15-membered heteroarylene, or unsubstituted 5- to 15-membered heteroaryl-C_1-C_{20} alkylene (the groups optionally comprise one or more heteroatoms, an amide group (-CO-NH-), an ester group (-CO-O-), or a urethane group (-O-CO-NH-)), an amide group (-CO-NH-), an ester group (-CO-O-), or a urethane group (-O-CO-NH-),

$R^{3''}$ is a bond,

wherein when a plurality of R^3, or $R^{3'}$ are present, the plurality of R^3, or $R^{3'}$ are the same as or different from each other, and

* is a binding position to the other moieties, and

wherein the adrenomedullin or the modified form thereof with adrenomedullin activity is a peptide selected from the group consisting of:

(i) a peptide consisting of an amino acid sequence of adrenomedullin,

(ii) a peptide that consists of an amino acid sequence of adrenomedullin and has a disulfide bond formed by two cysteine residues in the amino acid sequence,

(iii) the peptide of (ii) wherein the disulfide bond of the peptide is substituted with an ethylene group and the peptide has adrenomedullin activity,

(v) any peptide of (i) to (iii) wherein the peptide is amidated at the C-terminus thereof, and

(vi) any peptide of (i) to (iii) and (v) wherein the peptide has a glycine residue added to the C-terminus thereof,

or a salt thereof, or a hydrate thereof.

[0013b] In another aspect, disclosed herein is a pharmaceutical composition comprising the compound according to the disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof and one or more pharmaceutically acceptable carriers.

[0013c] In another aspect, disclosed herein is a use of the pharmaceutical composition according to the disclosure in the manufacture of a medicament for preventing or treating a cardiovascular disease, an inflammatory disease, or a peripheral vascular disease modulated by adrenomedullin.

[0013d] In another aspect, disclosed herein is a use of the compound according to the disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof in the manufacture of a medicament for preventing or treating a condition, disease, and/or disorder modulated by adrenomedullin.

[0013e] In another aspect, disclosed herein is a use of an effective amount of a compound according to the disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof in the manufacture of a medicament for preventing or treating a condition, disease, and/or disorder.

TECHNICAL PROBLEM

[0014] As described above, AM derivatives in which other groups such as a PEG group are linked to AM are known in order to improve the pharmacokinetics of AM from the viewpoint of improvement in sustainability in a living body. However, known AM derivatives are susceptible to improvement. For example, in the case of linking a relatively large group such as a PEG group to a relatively small peptide such as AM, various properties of the resulting AM derivative may vary largely depending on the molecular weight of the PEG group. As described in Patent Literatures 4 and 5 and Non Patent Literature 10, when a peptide moiety and other groups are linked through a bond which may be cleaved by a biological reaction, such as an amide bond or an ester bond, the bond may be cleaved in a relatively short time after administration. As in the AM derivative described in Patent Literature 5, in the case of linking other groups to the side chain of an amino acid residue of AM, the conformation of the AM moiety may be changed to reduce the affinity for an AM receptor recognizing AM. In such a case, pharmacological effects as AM of the resulting AM derivative may be reduced.

[0015] AM has a strong vasodilatory effect, in addition to pharmacological effects such as a cardiovascular protective effect, an anti-inflammatory effect, an angiogenic effect, and a tissue repair promoting effect. This strong vasodilatory effect may cause unwanted side effects such as excessive decreased blood pressure when AM or an AM derivative is administered to subjects. The occurrence of such side effects may become a problem when AM or an AM

CLAIMS

1. A compound represented by formula (X):

A'-CO-B (X)

wherein

A' is a modifying group comprising one or more polyethylene glycol groups, and

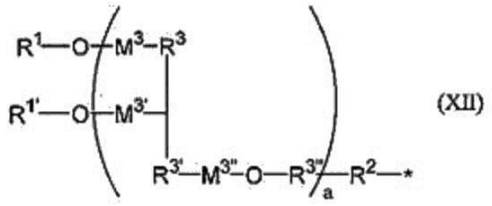
B is a peptide moiety derived from adrenomedullin or a modified form thereof with adrenomedullin activity,

wherein the peptide moiety B is linked to the other moieties through a covalent bond of the nitrogen atom of the N-terminal α-amino group of the peptide moiety B to the carbon atom of the carbonyl group,

the modifying group A' is linked to the other moieties through a covalent bond of the oxygen atom of the modifying group to the carbon atom of the carbonyl group,

A' is a modifying group represented by the following formula (XI) or (XII):

R^1-O-M^1-* (XI)



(XII)

wherein

a is an integer of 1 or larger,

M^1 is a polyethylene glycol group represented by formula (III):

$^{\#}$-$(CH_2CH_2O)_n$-** (III)

wherein

n is an integer of 1 or larger,

** is a binding position to *, and

is a binding position to O,

M^3, $M^{3'}$ and $M^{3''}$ are each independently a bond or a polyethylene glycol group represented by formula (III):

$^{\#}$-$(CH_2CH_2O)_n$-** (III)

wherein

n is an integer of 1 or larger,

** is a binding position to R^3, $R^{3'}$ or CH, and

is a binding position to O,

wherein when a plurality of M^3, $M^{3'}$ or $M^{3''}$ are present, the plurality of M^3, $M^{3'}$ or $M^{3''}$ are the same as or different from each other, and at least one of M^3, $M^{3'}$ and $M^{3''}$ is a polyethylene glycol group represented by formula (III),

R^1 and $R^{1'}$ are each independently hydrogen, unsubstituted C_1-C_{20} alkyl, unsubstituted C_2-C_{20} alkenyl, unsubstituted C_2-C_{20} alkynyl, unsubstituted C_3-C_{20} cycloalkyl, unsubstituted C_4-C_{20} cycloalkenyl, unsubstituted C_4-C_{20} cycloalkynyl, unsubstituted 3- to 6-membered heterocycloalkyl, unsubstituted C_7-C_{20} cycloalkylalkyl, unsubstituted 3- to 6-membered heterocycloalkyl-C_1-C_{20} alkyl, unsubstituted C_4-C_{20} aryl, unsubstituted C_5-C_{20} arylalkyl, unsubstituted 5- to 15-membered heteroaryl, unsubstituted 5- to 15-membered heteroaryl-C_1-C_{20} alkyl, or unsubstituted acyl,

R^2 is a bond ,

R^3 and $R^{3'}$ are each independently a bond, unsubstituted C_1-C_{20} alkylene, unsubstituted C_2-C_{20} alkenylene, unsubstituted C_2-C_{20} alkynylene, unsubstituted C_3-C_{20} cycloalkylene, unsubstituted C_4-C_{20} cycloalkenylene, unsubstituted C_4-C_{20} cycloalkynylene, unsubstituted 3- to 6-membered heterocycloalkylene, unsubstituted C_7-C_{20} cycloalkylalkylene, unsubstituted 3- to 6-membered heterocycloalkyl-C_1-C_{20} alkylene, unsubstituted C_4-C_{20} arylene, unsubstituted C_5-C_{20} arylalkylene, unsubstituted 5- to 15-membered heteroarylene, or unsubstituted 5- to 15-membered heteroaryl-C_1-C_{20} alkylene (the groups optionally comprise one or more heteroatoms, an amide group (-CO-NH-), an ester group (-CO-O-), or a urethane group (-O-CO-NH-)), an amide group (-CO-NH-), an ester group (-CO-O-), or a urethane group (-O-CO-NH-),

$R^{3''}$ is a bond,

wherein when a plurality of R^3, or $R^{3'}$ are present, the plurality of R^3, or $R^{3'}$ are the same as or different from each other, and

* is a binding position to the other moieties, and

wherein the adrenomedullin or the modified form thereof with adrenomedullin activity is a peptide selected from the group consisting of:

(i) a peptide consisting of an amino acid sequence of adrenomedullin,

(ii) a peptide that consists of an amino acid sequence of adrenomedullin and has a disulfide bond formed by two cysteine residues in the amino acid sequence,

(iii) the peptide of (ii) wherein the disulfide bond of the peptide is substituted with an ethylene group and the peptide has adrenomedullin activity,

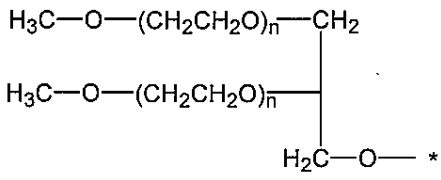
(v) any peptide of (i) to (iii) wherein the peptide is amidated at the C-terminus thereof, and

(vi) any peptide of (i) to (iii) and (v) wherein the peptide has a glycine residue added to the C-terminus thereof,

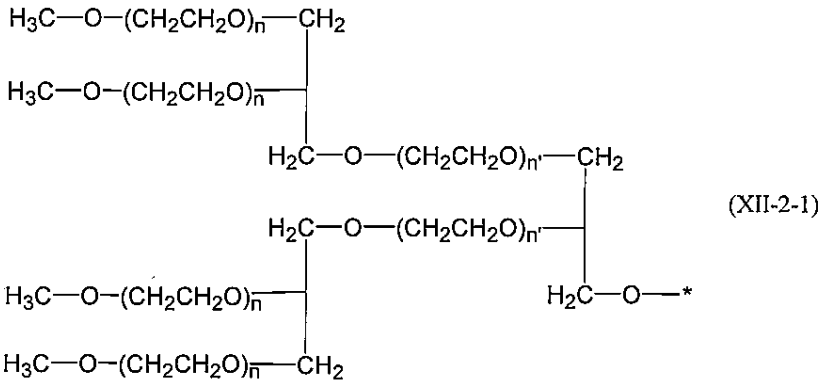
or a salt thereof, or a hydrate thereof.

2. The compound according to claim 1, wherein A' is a modifying group represented by the following formula (XI-1-1), (XII-1-1) or (XII-2-1):

$CH_3O\text{-}(CH_2CH_2O)_n\text{-}*$ (XI-1-1)



(XII-1-1)



(XII-2-1)

wherein

n is as defined in claim 1,

n' is as defined above about n, and

* is a binding position to the other moieties.

3. The compound according to claim 1 or 2, wherein the polyethylene glycol group represented by formula (III) or by group $-(CH_2CH_2O)_n-$ or $-(CH_2CH_2O)_{n'}-$ has a weight-average molecular weight ranging from 1 to 100 kDa in total.

4. The compound according to any one of claims 1 to 3, wherein the adrenomedullin or the modified form thereof is a peptide selected from the group consisting of:

(i) a peptide consisting of an amino acid sequence of adrenomedullin,

(ii) a peptide that consists of an amino acid sequence of adrenomedullin and has a disulfide bond formed by two cysteine residues in the amino acid sequence,

(v) the peptide of (i) or (ii) wherein the peptide is amidated at the C-terminus thereof, and

(vi) the peptide of (i) or (ii) wherein the peptide has a glycine residue added to the C-terminus thereof.

5. The compound according to any one of claims 1 to 3, wherein the adrenomedullin or the modified form thereof is a peptide selected from the group consisting of:

(a) a peptide consisting of the amino acid sequence of SEQ ID NO: 1, or a peptide consisting of the amino acid sequence of SEQ ID NO: 1 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(b) a peptide consisting of the amino acid sequence of the SEQ ID NO: 3, or a peptide consisting of the amino acid sequence of the SEQ ID NO: 3 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(c) a peptide consisting of the amino acid sequence of SEQ ID NO: 5, or a peptide consisting of the amino acid sequence of SEQ ID NO: 5 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(d) a peptide consisting of the amino acid sequence of SEQ ID NO: 7, or a peptide consisting of the amino acid sequence of SEQ ID NO: 7 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(e) a peptide consisting of the amino acid sequence of SEQ ID NO: 9, or a peptide consisting of the amino acid sequence of SEQ ID NO: 9 and having a disulfide bond formed by the cysteine residues at positions 14 and 19;

(f) a peptide consisting of the amino acid sequence of SEQ ID NO: 11, or a peptide consisting of the amino acid sequence of SEQ ID NO: 11 and having a disulfide bond formed by the cysteine residues at positions 14 and 19;

(g) any peptide of (a) to (f) wherein the disulfide bond of the peptide is substituted with an ethylene group and the peptide has adrenomedullin activity;

(i) any peptide of (a) to (g) wherein the peptide is amidated at the C-terminus thereof; and

(j) any peptide of (a) to (g) wherein the peptide has a glycine residue added to the C-terminus thereof.

6. The compound according to claim 5, wherein the adrenomedullin or the modified form thereof is a peptide selected from the group consisting of:

(a) a peptide consisting of the amino acid sequence of SEQ ID NO: 1, or a peptide consisting of the amino acid sequence of SEQ ID NO: 1 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(b) a peptide consisting of the amino acid sequence of SEQ ID NO: 3, or a peptide consisting of the amino acid sequence of SEQ ID NO: 3 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(c) a peptide consisting of the amino acid sequence of SEQ ID NO: 5, or a peptide consisting of the amino acid sequence of SEQ ID NO: 5 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(d) a peptide consisting of the amino acid sequence of SEQ ID NO: 7, or a peptide consisting of the amino acid sequence of SEQ ID NO: 7 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(e) a peptide consisting of the amino acid sequence of SEQ ID NO: 9, or a peptide consisting of the amino acid sequence of SEQ ID NO: 9 and having a disulfide bond formed by the cysteine residues at positions 14 and 19;

(f) a peptide consisting of the amino acid sequence of SEQ ID NO: 11, or a peptide consisting of the amino acid sequence of SEQ ID NO: 11 and having a disulfide bond formed by the cysteine residues at positions 14 and 19;

(i) any peptide of (a) to (f) wherein the peptide is amidated at the C-terminus thereof; and

(j) any peptide of (a) to (f) wherein the peptide has a glycine residue added to the C-terminus thereof.

7. The compound according to claim 5, wherein the adrenomedullin or the modified form thereof is a peptide selected from the group consisting of:

(i) any peptide of (a) to (d)wherein the peptide is amidated at the C-terminus thereof; and

(j) any peptide of (a) to (d)wherein the peptide has a glycine residue added to the C-terminus thereof.

8. A pharmaceutical composition comprising the compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof and one or more pharmaceutically acceptable carriers.

9. Use of the pharmaceutical composition according to claim 8 in the manufacture of a medicament for preventing or treating a cardiovascular disease, an inflammatory disease, or a peripheral vascular disease modulated by adrenomedullin.

10. Use of the compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof in the manufacture of a medicament for preventing or treating a condition, disease, and/or disorder modulated by adrenomedullin.

11. The use according to claim 10 wherein the condition, disease, and/or disorder is a cardiovascular disease, an inflammatory disease, or a peripheral vascular disease.

12. Use of an effective amount of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof in the manufacture of a medicament for preventing or treating a condition, disease, and/or disorder.

13. The use according to claim 12 wherein the condition, disease, and/or disorder is a cardiovascular disease, an inflammatory disease, or a peripheral vascular disease.