N-terminus proline thereof, but is not limited thereto.

The immunoglobulin Fc region may be one element constituting a moiety of the conjugate of Formula 1 of the present invention, and specifically, may correspond to F in Formula 1.

This immunoglobulin Fc region may include a hinge region in a heavy chain constant region, but is not limited thereto.

In the present invention, the immunoglobulin Fc region may include a specific hinge sequence at the N-terminus.

As used herein, the term “hinge sequence” refers to a site which is located on a heavy chain and forms a dimer of the immunoglobulin Fc region through an inter-disulfide bond.

In the present invention, the hinge sequence may be mutated to have only one cysteine residue by deletion of a part in the hinge sequence having the following amino acid sequence, but is not limited thereto:

Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Ser-Cys-Pro (SEQ ID NO: 103).

The hinge sequence may include only one cysteine residue by deletion of the 8^{th} or 11^{th} cysteine residues in the hinge sequence of SEQ ID NO: 103.
The hinge sequence of the present invention may consist of 3 to 12 amino acids including only one cysteine residue, but is not limited thereto. More specifically, the hinge sequence of the present invention may have the following sequences: Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Pro-Ser-Cys-Pro (SEQ ID NO: 104), Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Ser-Pro (SEQ ID NO: 105), Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Ser (SEQ ID NO: 106), Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro (SEQ ID NO: 107), Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Ser (SEQ ID NO: 108), Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys (SEQ ID NO: 109), Glu-Lys-Tyr-Gly-Pro-Pro-Cys (SEQ ID NO: 110), Glu-Ser-Pro-Ser-Cys-Pro (SEQ ID NO: 111), Glu-Pro-Ser-Cys-Pro (SEQ ID NO: 112), Pro-Ser-Cys-Pro (SEQ ID NO: 113), Glu-Ser-Lys-Tyr-Gly-Pro-

Pro-Ser-Cys-Pro (SEQ ID NO: 114), Lys-Tyr-Gly-Pro-Pro-Pro-Ser-Cys-Pro (SEQ ID NO: 115), Glu-Ser-Lys-Tyr-Gly-Pro-Ser-Cys-Pro (SEQ ID NO: 116), Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys (SEQ ID NO: 117), Lys-Tyr-Gly-Pro-Pro-Cys-Pro (SEQ ID NO: 118), Glu-Ser-Lys-Pro-Ser-Cys-Pro (SEQ ID NO: 119), Glu-Ser-Pro-Ser-Cys-Pro (SEQ ID NO: 120), Glu-Pro-Ser-Cys (SEQ ID NO: 121), Ser-Cys-Pro (SEQ ID NO: 122).

More specifically, the hinge sequence may include an amino acid sequence of SEQ ID NO: 113 (Pro-Ser-Cys-Pro) or SEQ ID NO: 122 (Ser-Cys-Pro), but is not limited thereto.

The immunoglobulin Fc region of the present invention may be in the form in which two molecules of the immunoglobulin Fc chain form a dimer due to the presence of a hinge sequence, and the conjugate of Formula 1 of the present invention may be in the form in which one end of the linker is linked to one chain of the dimeric immunoglobulin Fc region, but is not limited thereto.

As used herein, the term “N-terminus” refers to an amino terminus of a protein or polypeptide, and may include the outermost end of the amino terminus, or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more amino acids from the outermost end. In the immunoglobulin Fc region of the present invention, a hinge sequence may be included in the N-terminus thereof, but is not limited thereto.

The immunoglobulin Fc region of the present invention may be an extended Fc region including a part or the entirety of heavy chain constant region 1 (CH1) and/or light chain constant region 1 (CL1), excluding only heavy chain and light chain variable regions of an immunoglobulin, as long as the immunoglobulin Fc region has a substantially equivalent or improved effect, as compared with the native form. Alternatively, the immunoglobulin Fc region of the present invention may be a region having a deletion of a considerably long partial amino acid sequence corresponding to CH2 and/or CH3.

decision.

As used herein, the term “pharmaceutically acceptable salt” refers to a salt derived from pharmaceutically acceptable inorganic acids, organic acids, or bases. Examples of appropriate acids may include hydrochloric acid, bromic acid, sulfuric acid, nitric acid, perchloric acid, fumaric acid, maleic acid, phosphoric acid, glycolic acid, lactic acid, salicylic acid, succinic acid, toluene-p-sulfonic acid, tartaric acid, acetic acid, citric acid, methanesulfonic acid, formic acid, benzoic acid, malonic acid, naphthalene-2-sulfonic acid, benzenesulfonic acid, etc. Salts derived from appropriate bases may include alkali metals such as sodium, potassium, etc., alkali earth metals such as magnesium, etc., ammonium, etc.

Further, as used herein, the term “solvate” refers to a complex formed between the peptide according to the present invention or a salt thereof and a solvent molecule.

In the present invention, the SGLT-2 inhibitor which is administered in combination with the peptide or the conjugate thereof is also called sodium-glucose cotransporter 2 inhibitor, and may be any one or more selected from the group consisting of empagliflozin, dapagliflozin, canagliflozin, remogliflozin, remogliflozin etabonate, sergliflozin, ipragliflozin, tofogliflozin, luseogliflozin, sotagliflozin, bexagliflozin, atigliflozin, and ertugliflozin, but is not limited thereto.

It is known that the SGLT-2 is involved in the reabsorption of glucose in the proximal tubules, and excessive glucose reabsorption occurs due to SGLT-2 in diabetic patients. The blood glucose lowering effect may be obtained by administering the peptide according to the present invention or the conjugate thereof in combination with the SGLT-2 inhibitor.

As used herein, the “diabetes” is a kind of metabolic disease in which insulin secretion is insufficient or normal functions are not made. Diabetes is