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(54) **INSULIN DERIVATIVES**

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

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(57) **ABSTRACT**

The present invention relates to insulin derivatives which are naturally occurring insulins or analogues thereof which have a side chain attached either to the α-amino group of the N-terminal amino acid residue of the B chain or to the ϵ-amino group of a Lys residue present in the B chain of the parent insulin, the side chain being of the general formula:

-W-X—Y-Z

wherein W, X, Y and Z are as defined in the disclosure.

12 Claims, No Drawings

INSULIN DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application No. PCT/DK2004/000511, filed Jul. 22, 2004, which claims priority from Danish Patent Application No. PA 2003 01129 filed Aug. 5, 2003 and to U.S. Patent Application No. 60/495,451 filed Aug. 14, 2003.

FIELD OF THE INVENTION

The present invention relates to novel human insulin derivatives which are soluble at physiological pH values and have a prolonged profile of action. The invention also relates to methods of providing such derivatives, to pharmaceutical compositions containing them, to a method of treating diabetes and hyperglycemia using the insulin derivatives of the invention and to the use of such insulin derivatives in the treatment of diabetes and hyperglycemia.

BACKGROUND OF THE INVENTION

Currently, the treatment of diabetes, both type 1 diabetes and type 2 diabetes, relies to an increasing extent on the so-called intensive insulin treatment. According to this regimen, the patients are treated with multiple daily insulin injections comprising one or two daily injections of a long acting insulin to cover the basal insulin requirement supplemented by bolus injections of a rapid acting insulin to cover the insulin requirement related to meals.

Long acting insulin compositions are well known in the art. Thus, one main type of long acting insulin compositions comprises injectable aqueous suspensions of insulin crystals or amorphous insulin. In these compositions, the insulin compounds utilized typically are protamine insulin, zinc insulin or protamine zinc insulin.

Certain drawbacks are associated with the use of insulin suspensions. Thus, in order to secure an accurate dosing, the insulin particles must be suspended homogeneously by gentle shaking before a defined volume of the suspension is withdrawn from a vial or expelled from a cartridge. Also, for the storage of insulin suspensions, the temperature must be kept within more narrow limits than for insulin solutions in order to avoid lump formation or coagulation.

While it was earlier believed that protamines were non-immunogenic, it has now turned out that protamines can be immunogenic in man and that their use for medical purposes may lead to formation of antibodies. Also, evidence has been found that the protamine-insulin complex is itself immunogenic. Therefore, with some patients the use of long acting insulin compositions containing protamines must be avoided.

Another type of long acting insulin compositions are solutions having a pH value below physiological pH from which the insulin will precipitate because of the rise in the pH value when the solution is injected. A drawback with these solutions is that the particle size distribution of the precipitate formed in the tissue on injection, and thus the release profile of the medication, depends on the blood flow at the injection site and other parameters in a somewhat unpredictable manner. A further drawback is that the solid particles of the insulin may act as a local irritant causing inflammation of the tissue at the site of injection.

The action profile of these complexes is only moderately prolonged and the bioavailability is reduced relative to human insulin.

Human insulin has three primary amino groups: the N-terminal group of the A-chain and of the B-chain and the ε-amino group of Lys^{B29}. Several insulin derivatives which are substituted in one or more of these groups are known in the prior art. Thus, U.S. Pat. No. 3,528,960 (Eli Lilly) relates to N-carboxyaroyl insulins in which one, two or three primary amino groups of the insulin molecule has a carboxyaroyl group.

According to GB Patent No. 1.492.997 (Nat. Res. Dev. Corp.), it has been found that insulin with a carbamyl substitution at $N^{\epsilon B29}$ has an improved profile of hypoglycaemic effect.

JP laid-open patent application No. 1-254699 (Kodama Co., Ltd.) discloses insulin wherein a fatty acid is bound to the amino group of Phe^{B1} or to the ε-amino group of LyS^{B29} or to both of these. The stated purpose of the derivatisation is to obtain a pharmacologically acceptable, stable insulin preparation.

Insulins, which in the B30 position have an amino acid having at least five carbon atoms which cannot necessarily be coded for by a triplet of nucleotides, are described in JP laid-open patent application No. 57-067548 (Shionogi). The insulin analogues are claimed to be useful in the treatment of diabetes mellitus, particularly in patients who are insulin resistant due to generation of bovine or porcine insulin antibodies.

WO 95/07931 (Novo Nordisk A/S) discloses human insulin derivatives wherein the ε-amino group of LyS^{B29} has a lipophilic substituent. These insulin derivatives have a prolonged profile of action and are soluble at physiological pH values.

EP 894095 discloses insulin derivatives wherein the N-terminal group of the B-chain and/or the ε-amino group of Lys in position B28, B29 or B30 has a substituent of the formula —CO—W—COOH where W can be a long chain hydrocarbon group. These insulin derivatives have a prolonged profile of action and are soluble at physiological pH values.

However, there is still a need for insulins having a more prolonged profile of action than the insulin derivatives known up till now and which at the same time are soluble at physiological pH values and have a potency which is comparable to that of human insulin.

SUMMARY OF THE INVENTION

The present invention is based on the recognition that the overall hydrophobicity of an insulin derivative molecule plays an important role for the in vivo potency of the derivative.

In one aspect the present invention relates to an insulin derivative which is a naturally occurring insulin or an analogue thereof which has a side chain attached either to the α-amino group of the N-terminal amino acid residue of the B chain or to the ε-amino group of a Lys residue present in the B chain of the parent insulin, the side chain being of the general formula:

-W-X—Y-Z

wherein W is:

an α-amino acid residue having a carboxylic acid group in the side chain which residue forms, with one of its car-

the B chain or together with the ε-amino group of a Lys residue present in the B chain of the parent insulin;

a chain composed of two, three or four α-amino acid residues linked together via amide bonds, which chain—via an amide bond—is linked to the α-amino group of the N-terminal amino acid residue of the B chain or to the ε-amino group of a Lys residue present in the B chain of the parent insulin, the amino acid residues of W being selected from the group of amino acid residues having a neutral side chain and amino acid residues having a carboxylic acid group in the side chain so that W has at least one amino acid residue which has a carboxylic acid group in the side chain; or

a covalent bond from X to the α-amino group of the N-terminal amino acid residue of the B chain or to the ε-amino group of a Lys residue present in the B chain of the parent insulin;

X is:

—CO—;
—CH(COOH) CO—;
—N(CH_2COOH)CH_2CO—;
—N(CH_2COOH)CH_2CON(CH_2COOH)CH_2CO—;
—N(CH_2CH_2COOH)CH_2CH_2CO—;
—N(CH_2CH_2COOH)CH_2CH_2CON(CH_2CH_2COOH) CH_2CH_2CO—;
—NHCH(COOH)$(CH_2)_4$NHCO—;
—N(CH_2CH_2COOH)CH_2CO—; or
—N(CH_2COOH)CH_2CH_2CO—.

that

a) when W is an amino acid residue or a chain of amino acid residues, via a bond from the underscored carbonyl carbon forms an amide bond with an amino group in W, or

b) when W is a covalent bond, via a bond from the underscored carbonyl carbon forms an amide bond with the N-terminal α-amino group in the B chain or with the ε-amino group of a Lys residue present in the B chain of the parent insulin;

Y is:

—$(CH_2)_m$— where m is an integer in the range of 6 to 32;

a divalent hydrocarbon chain comprising 1, 2 or 3-CH═CH— groups and a number of —CH_2— groups sufficient to give a total number of carbon atoms in the chain in the range of 10 to 32;

a divalent hydrocarbon chain of the formula —$(CH_2)_v$ $C_6H_4(CH_2)_w$— wherein v and w are integers or one of them is zero so that the sum of v and w is in the range of 6 to 30; and

Z is:

—COOH;
—CO-Asp;
—CO-Glu;
—CO-Gly;
—CO-Sar;
—$CH(COOH)_2$;
—$N(CH_2COOH)_2$;
—SO_3H; or
—PO_3H;

and any Zn^{2+} complexes thereof, provided that when W is a covalent bond and X is —CO—, then Z is different from —COOH.

In one embodiment of the invention, the side chain -W-X—Y-Z is attached to the ε-amino group of a Lys residue present in the B chain of the parent insulin. In one more specific aspect of this embodiment, the side chain —W-X—Y-Z is attached to the ε-amino group of a Lys residue present in position 28 of the B chain. In a further more specific aspect of this embodiment, the side chain -W-X—Y-Z is attached to the ε-amino group of a Lys residue present in position 29 of the B chain. In a further more specific aspect of this embodiment, the side chain -W-X—Y-Z is attached to the ε-amino group of a Lys residue present in position 30 of the B chain.

The substructure W of the side chain -W-X—Y-Z can be a covalent bond. Alternatively, W can be a residue of an α-amino acid having a carboxylic acid group in the side chain and comprising a total of from 4 to 10 carbon atoms. Specifically, W can be the residue of an α-amino acid, that can be coded for by the genetic code. Thus, W can, for example, be selected from the group consisting of α-Asp, β-Asp, α-Glu, and γ-Glu. Further options for W are for example α-hGlu and δ-hGlu.

In a further embodiment, W is a chain composed of two α-amino acid residues of which one has from 4 to 10 carbon atoms and a carboxylic acid group in the side chain while the other has from 2 to 11 carbon atoms but no free carboxylic acid group. The α-amino acid residue with no free carboxylic acid group can be a neutral, codable α-amino acid residue. Examples of W according to this embodiment are: α-Asp-Gly; Gly-α-Asp; β-Asp-Gly; Gly-β-Asp; α-Glu-Gly; Gly-α-Glu; γ-Glu-Gly; Gly-γ-Glu; α-hGlu-Gly; Gly-α-hGlu; δ-hGlu-Gly; and Gly-δ-hGlu.

In a further embodiment, W is a chain composed of two α-amino acid residues, independently having from 4 to 10 carbon atoms, and both having a carboxylic acid group in the side chain. One of these α-amino acid residues or both of them can be codable α-amino acid residues. Examples of W according to this embodiment are: α-Asp-α-Asp; α-Asp-α-Glu; α-Asp-α-hGlu; α-Asp-β-Asp; α-Asp-γ-Glu; α-Asp-δ-hGlu; β-Asp-α-Asp; β-Asp-α-Glu; β-Asp-α-hGlu; β-Asp-β-Asp; β-Asp-γ-Glu; β-Asp-δ-hGlu; α-Glu-α-Asp; α-Glu-α-Glu; α-Glu-α-hGlu; α-Glu-β-Asp; α-Glu-γ-Glu; α-Glu-δ-hGlu; γ-Glu-α-Asp; γ-Glu-α-Glu; γ-Glu-α-hGlu; γ-Glu-β-Asp; γ-Glu-γ-Glu; γ-Glu-δ-hGlu; α-hGlu-α-Asp; α-hGlu-α-Glu; α-hGlu-α-hGlu; α-hGlu-β-Asp; α-hGlu-γ-Glu; α-hGlu-δ-hGlu; δ-hGlu-α-Asp; δ-hGlu-α-Glu; δ-hGlu-α-hGlu; δ-hGlu-β-Asp; δ-hGlu-γ-Glu; and δ-hGlu-δ-hGlu.

In a further embodiment, W is a chain composed of three α-amino acid residues, independently having from 4 to 10 carbon atoms, the amino acid residues of the chain being selected from the group of residues having a neutral side chain and residues having a carboxylic acid group in the side chain so that the chain has at least one residue which has a carboxylic acid group in the side chain. In one embodiment, the amino acid residues are codable residues.

In a further embodiment, W is a chain composed of four α-amino acid residues, independently having from 4 to 10 carbon atoms, the amino acid residues of the chain being selected from the group having a neutral side chain and residues having a carboxylic acid group in the side chain so that the chain has at least one residue which has a carboxylic acid group in the side chain. In one embodiment, the amino acid residues are codable residues.

In one embodiment W can be connected to the ε-amino group of the Lys residue in the B-chain via an urea derivative.

The substructure X of the side chain -W-X—Y-Z can be a

amino group in W or, when W is a covalent bond, with the N-terminal α-amino group in the B chain or with the ε-amino group of a Lys residue present in the B chain of the parent insulin.

In a further embodiment, the substructure X of the side chain can be a group of the formula —CH(COOH)CO— that, via a bond from the underscored carbonyl carbon, forms an amide bond with an amino group in W or, when W is a covalent bond, with the N-terminal α-amino group in the B chain or with the ε-amino group of a Lys residue present in the B chain of the parent insulin.

In a further embodiment, the substructure X of the side chain can be a group of the formula —$N(CH_2COOH)CH_2$ CO— that, via a bond from the underscored carbonyl carbon, forms an amide bond with an amino group in W or, when W is a covalent bond, with the N-terminal α-amino group in the B chain or with the ε-amino group of a Lys residue present in the B chain of the parent insulin.

In a further embodiment, the substructure X of the side chain can be a group of the formula —$N(CH_2CH_2COOH)$ CH_2CO— that, via a bond from the underscored carbonyl carbon, forms an amide bond with an amino group in W or, when W is a covalent bond, with the N-terminal α-amino group in the B chain or with the ε-amino group of a Lys residue present in the B chain of the parent insulin.

In a further embodiment, the substructure X of the side chain can be a group of the formula —$N(CH_2COOH)$ CH_2CH_2CO— that, via a bond from the underscored carbonyl carbon, forms an amide bond with an amino group in W or, when W is a covalent bond, with the N-terminal α-amino group in the B chain or with the ε-amino group of a Lys residue present in the B chain of the parent insulin.

In a further embodiment, the substructure X of the side chain can be a group of the formula —$N(CH_2COOH)$ $CH_2CON(CH_2COOH)CH_2CO$— that, via a bond from the underscored carbonyl carbon, forms an amide bond with an amino group in W or, when W is a covalent bond, with the N-terminal α-amino group in the B chain or with the f-amino group of a Lys residue present in the B chain of the parent insulin.

In a further embodiment, the substructure X of the side chain can be a group of the formula —$N(CH_2CH_2COOH)$ CH_2CH_2CO— that, via a bond from the underscored carbonyl carbon, forms an amide bond with an amino group in W or, when W is a covalent bond, with the N-terminal α-amino group in the B chain or with the ε-amino group of a Lys residue present in the B chain of the parent insulin.

In a further embodiment, the substructure X of the side chain can be a group of the formula —$N(CH_2CH_2COOH)$ $CH_2CH_2CON(CH_2CH_2COOH)CH_2CH_2CO$— that, via a bond from the underscored carbonyl carbon, forms an amide bond with an amino group in W or, when W is a covalent bond, with the N-terminal α-amino group in the B chain or with the ε-amino group of a Lys residue present in the B chain of the parent insulin.

The substructure Y of the side chain -W-X—Y-Z can be a group of the formula —$(CH_2)_m$— where m is an integer in the range of from 6 to 32, from 8 to 20, from 12 to 20, or from 12-16.

In another embodiment, Y is a divalent hydrocarbon chain comprising 1, 2 or 3—CH═CH— groups and a number of —CH_2— groups sufficient to give a total number of carbon atoms in the chain in the range of from 6 to 32, from 10 to 32, from 12 to 20, or from 12-16.

integers or one of them is zero so that the sum of v and w is in the range of from 6 to 30, from 10 to 20, or from 12-16.

In one embodiment, the substructure Z of the side chain -W-X—Y-Z is —COOH provided that when W is a covalent bond and X is —CO—, then Z is different from —COOH.

In another embodiment, Z is —CO-Asp.

In another embodiment, Z is —CO-Glu.

In another embodiment, Z is —CO-Gly.

In another embodiment, Z is —CO-Sar.

In another embodiment, Z is —$CH(COOH)_2$.

In another embodiment, Z is —$N(CH_2COOH)_2$.

In another embodiment, Z is —SO_3H.

In another embodiment, Z is —PO_3H.

In a further embodiment W is selected from the group consisting of α-Asp, β-Asp, α-Glu, and γ-Glu; X is —CO— or —CH(COOH)CO; Y is —$(CH_2)_m$— where m is an integer in the range of 12-18 and Z is —COOH or —$CH(COOH)_2$.

The insulin moiety—in the present text also referred to as the parent insulin—of an insulin derivative according to the invention can be a naturally occurring insulin such as human insulin or porcine insulin. Alternatively, the parent insulin can be an insulin analogue.

In one group of parent insulin analogues, the amino acid residue at position A21 is Asn.

In another group of parent insulin analogues, the amino acid residue at position A21 is Gly. Specific examples from this group of analogues are Gly^{A21} human insulin, Gly^{A21} des(B30) human insulin; and $Gly^{A21}Arg^{B31}Arg^{B32}$ human insulin.

In another group of parent insulin analogues, the amino acid residue at position B1 has been deleted. A specific example from this group of parent insulin analogues is des (B1) human insulin.

In another group of parent insulin analogues, the amino acid residue at position B30 has been deleted. A specific example from this group of parent insulin analogues is des (B30) human insulin.

In another group of parent insulin analogues, the amino acid residue at position B28 is Asp. A specific example from this group of parent insulin analogues is Asp^{B28} human insulin.

In another group of parent insulin analogues, the amino acid residue at position B28 is Lys and the amino acid residue at position B29 is Pro. A specific example from this group of parent insulin analogues is $Lys^{B28}Pro^{B29}$ human insulin.

In another group of parent insulin analogues the amino acid residue in position B30 is Lys and the amino acid residue in position B29 is any codable amino acid except Cys, Met, Arg and Lys. An example is an insulin analogue where the amino acid residue at position B29 is Thr and the amino acid residue at position B30 is Lys. A specific example from this group of parent insulin analogues is $Thr^{B29}LyS^{B30}$ human insulin.

In another group of parent insulin analogues, the amino acid residue at position B3 is Lys and the amino acid residue at position B29 is Glu. A specific example from this group of parent insulin analogues is $Lys^{B3}Glu^{B29}$ human insulin.

Examples of insulin derivatives according to the invention are the following compounds:

$N^{\epsilon B29}$—(N^{α}—(HOOC$(CH_2)_{14}$CO)-γ-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(HOOC$(CH_2)_{15}$CO)-γ-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(HOOC$(CH_2)_{16}$CO)-γ-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(HOOC(CH_2)$_{18}$CO)-γ-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(HOOC(CH_2)$_{16}$CO)-γ-Glu-N-(γ-Glu)) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(Asp-OC(CH_2)$_{16}$CO)-γ-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(Glu-OC(CH_2)$_{14}$CO)-γ-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(Glu-OC(CH_2)$_{14}$CO—) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(Asp-OC(CH_2)$_{16}$CO—) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(HOOC(CH_2)$_{16}$CO)-α-Glu-N-(β-Asp)) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(Gly-OC(CH_2)$_{13}$CO)-γ-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(Sar-OC(CH_2)$_{13}$CO)-γ-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(HOOC(CH_2)$_{13}$CO)-γ-Glu) des(B30) human insulin;

($N^{\epsilon B29}$—(N^{α}—(HOOC(CH_2)$_{13}$CO)-β-Asp) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(HOOC(CH_2)$_{13}$CO)-α-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(HOOC(CH_2)$_{16}$CO)-γ-D-Glu) des(B30) human insulin;

$N^{\epsilon B29}$—(N^{α}—(HOOC(CH_2)$_{14}$CO-β-D-Asp) des(B30) human insulin;

$N^{\epsilon B29}$—(N—HOOC(CH_2)$_{16}$CO-β-D-Asp) des(B30) human insulin;

$N^{\epsilon B29}$—(N—HOOC(CH_2)$_{14}$CO-IDA) des(B30) human insulin;

$N^{\epsilon B29}$—[N—(HOOC(CH_2)$_{16}$CO—N-(carboxyethyl)-Gly] des(B30) human insulin;

$N^{\epsilon B29}$—[N—(HOOC(CH_2)$_{14}$CO)—N-(carboxyethyl)-Gly] des(B30) human insulin; and

$N^{\epsilon B29}$—[N—(HOOC(CH_2)$_{14}$CO)—N-(carboxymethyl)-β-Ala] des(B30) human insulin.

Insulin derivatives according to the invention may be provided in the form of essentially zinc free compounds or in the form of zinc complexes. When zinc complexes of an insulin derivative according to the invention are provided, two Zn^{2+} ions, three Zn^{2+} ions or four Zn^{2+} ions can be bound to each insulin hexamer. Solutions of zinc complexes of the insulin derivatives will contain mixtures of such species.

In a further aspect of the invention, a pharmaceutical composition comprising a therapeutically effective amount of an insulin derivative according to the invention together with a pharmaceutically acceptable carrier can be provided for the treatment of type 1 diabetes, type 2 diabetes and other states that cause hyperglycemia in patients in need of such a treatment. An insulin derivative according to the invention can be used for the manufacture of a pharmaceutical composition for use in the treatment of type 1 diabetes, type 2 diabetes and other states that cause hyperglycaemia.

In a further aspect of the invention, there is provided a pharmaceutical composition for treating type 1 diabetes, type 2 diabetes and other states that cause hyperglycaemia in a patient in need of such a treatment, comprising a therapeutically effective amount of an insulin derivative according to the invention in mixture with an insulin or an insulin analogue which has a rapid onset of action, together with pharmaceutically acceptable carriers and additives.

In one embodiment the invention provides a pharmaceutical composition comprising an insulin derivative according to the invention in mixture with an insulin or an insulin analogue which has a rapid onset of action, together with pharmaceutically acceptable carriers and additives, wherein the insulin analogue is selected from the selected group consisting of Asp^{B28} human insulin; $Lys^{B28}Pro^{B29}$ human insulin and $LyS^{B3}Glu^{B29}$ human insulin.

In one embodiment the invention provides a pharmaceutical composition comprising $N^{\epsilon B29}$—N^{α}—(HOOC(CH_2)$_{14}$CO)-γ-Glu) des(B30) human insulin and AspB28 human insulin together with pharmaceutically acceptable carriers and additives.

The insulin derivative according to the invention and the rapid acting insulin analogue can be mixed in a ratio from about 90/10%; about 70/30% or about 50/50%.

In a further aspect of the invention, there is provided a method of treating type 1 diabetes, type 2 diabetes and other states that cause hyperglycaemia in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of an insulin derivative according to the invention together with a pharmaceutically acceptable carrier and pharmaceutical acceptable additives.

In a further aspect of the invention, there is provided a method of treating type 1 diabetes, type 2 diabetes and other states that cause hyperglycaemia in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of an insulin derivative according to the invention in mixture with an insulin or an insulin analogue which has a rapid onset of action, together with a pharmaceutically acceptable carrier and pharmaceutical acceptable additives.

In a further aspect, the present invention relates to insulin derivatives which have an overall hydrophobicity which is essentially similar to that of human insulin.

In further aspect, the present invention relates to insulin derivatives which have a hydrophobic index, k'_{rel}, which is in the range of from about 2 to about 200.

In a further aspect, the insulin derivatives of the present invention have a hydrophobic index, k'_{rel}, which is in the range from about 0.02 to about 10, from about 0.1 to about 5; from about 0.5 to about 5; or from about 0.5 to about 2.

According to one embodiment of the present invention the insulin derivatives will comprise a side chain -W-X—Y-Z as defined above which has at least one hydrophilic and at least one hydrophobic region.

According to another embodiment of the present invention, the insulin derivatives will comprise a side chain -W-X—Y-Z as defined above which has at least one free carboxylic acid group and according to a further embodiment, the side chain will have at least two free carboxylic acid groups.

In another embodiment, the invention relates to a pharmaceutical composition comprising an insulin derivative according to the invention which is soluble at physiological pH values.

In another embodiment, the invention relates to a pharmaceutical composition comprising an insulin derivative according to the invention which is soluble at pH values in the interval from about 6.5 to about 8.5.

In another embodiment, the invention relates to a pharmaceutical composition with a prolonged profile of action which comprises an insulin derivative according to the invention.

In another embodiment, the invention relates to a pharmaceutical composition which is a solution containing from about 120 nmol/ml to about 2400 nmol/ml, from about 400 nmol/ml to about 2400 nmol/ml, from about 400 nmol/ml to about 1200 nmol/ml, from about 600 nmol/ml to about 2400 nmol/ml, or from about 600 nmol/ml to about 1200 nmol/ml of an insulin derivative according to the invention or of a

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