CLAIMS

1. An insulin derivative, or a pharmaceutically acceptable salt, amide or ester thereof, wherein an insulin comprises an A-chain (SEQ ID NO: 1) and a B-chain (SEQ ID NO: 2);

wherein said insulin derivative comprises:

i. a B-chain B5Y or B5F substitution;

ii a B-chain B26G, B26A, or B26K substitution, or a wild-type residue (Y) in position 26 of the B-chain;

iii. at least one of the B-chain substitutions B28K, B26K, or B29K; and

iv. a B-chain substituent comprising an acyl group;

wherein said substituent comprising an acyl group is attached to B28K, B26K, or B29K and has the formula (I):

Acy-L1-L2-L3

(I);

wherein:

(a) Acy is an acyl group and is represented by lithocholic acid or comprises at least one functional group of formulae:

Chem. 1: CO-(CH2)x1-COOH; or

Chem. 2: CO-(CH2)x1-tetrazolyl;

wherein x1 represents an integer in the range of from 12 to 20; and the tetrazolyl group is 1H-tetrazol-5-yl;

or is a fatty acid of formula:

Chem. 3: CO-(CH2)x2-CH3

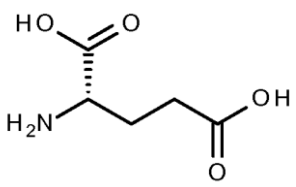
wherein x2 represents an integer in the range from 8 to 16;

(b) L1 is absent and represents a covalent bond, or represents OEG, gGlu, DgGlu or sulfonimide C-4;

(c) L2 is absent and represents a covalent bond, or represents OEG, gGlu, DgGlu or sulfonimide C-4;

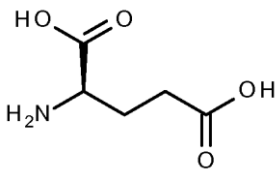
(d) L3 is absent and represents a covalent bond, or represents OEG, gGlu, DgGlu or sulfonimide C-4;

wherein gGlu represents a gamma glutamic acid residue represented by the following structure:



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DgGlu represents a gamma glutamic acid residue represented by the following structure:



, and

OEG represents [2-(2-aminoethoxy)ethoxy]acetyl.

2. The insulin derivative according to claim 1, wherein said insulin derivative further comprises an A-chain A14E substitution and/or a B-chain desB30 deletion and/or a B-chain desB29-30 deletion and/or a B-chain desB27-30 deletion.

3. The insulin derivative according to any of the previous claims, wherein said insulin derivative comprises substitution(s) and deletion(s) selected from the group consisting of:
   i. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5Y, B26A, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 4;
   ii. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5Y, B26G, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 5;
   iii. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5Y, B26A, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 7;
   iv. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5Y, B26G, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 8;
   v. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5Y, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 9;
   vi. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5F, B26G, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 10;

vii. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5F, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 11;

viii. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5Y, B26K substitutions and a B-chain desB27-desB30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 12;

ix. a derivative comprising an A-chain defined in SEQ ID NO: 1, and a B-chain B5Y substitution and a B-chain desB30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 13;

x. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5Y, B26G substitutions and a B-chain desB30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 14;

xi. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5Y, B26A substitutions and a B-chain desB30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 15;

xii. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5F, B26A, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 6;

xiii. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5Y, B26A, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 4;

xiv. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5Y, B26G, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 5;

xv. a derivative comprising an A-chain defined in SEQ ID NO: 1, and B-chain B5F, B26G, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO:10;

xvi. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5F, B26A, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 6;

xvii. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5Y, B26A, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 7;

xviii. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5Y, B26G, B28K substitutions

and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 8;

xix. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5Y, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO: 9;

xx. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5F, B28K substitutions and a B-chain desB29-30 deletion, wherein said derivative B-chain is defined in SEQ ID NO:11;

xxi. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5Y, B26K substitutions and a B-chain desB27-desB30 deletion, wherein said derivative B-chain is defined in SEQ ID NO:12;

xxii. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and a B-chain B5Y substitution and a B-chain desB30 deletion, wherein said derivative B-chain is defined in SEQ ID NO:13;

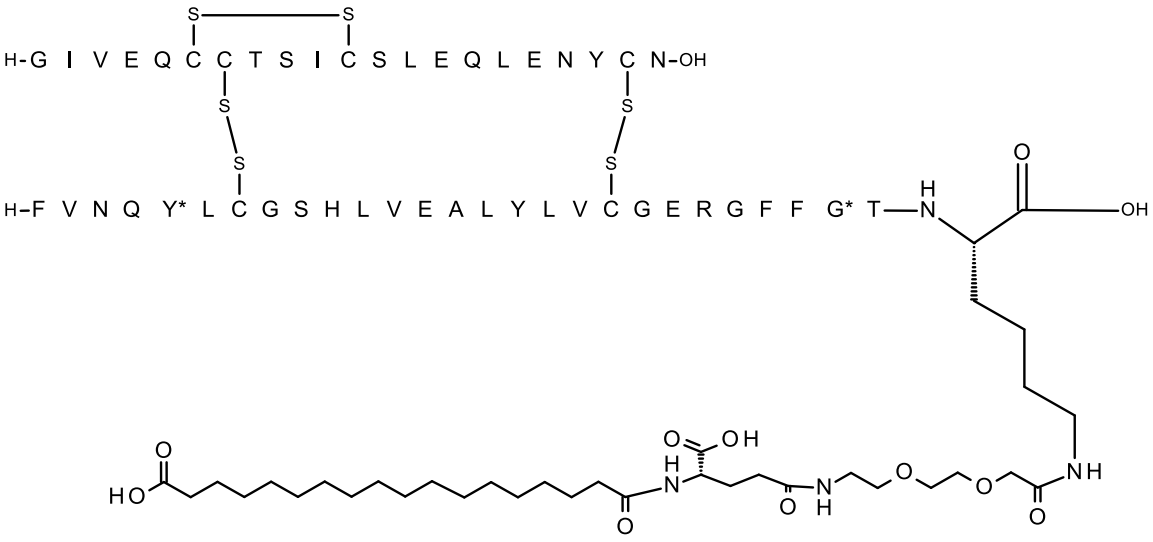
xxiii. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5Y, B26G substitutions and a B-chain desB30 deletion, wherein said derivative B-chain is defined in SEQ ID NO:14; and

xxiv. a derivative comprising an A-chain A14E substitution, wherein said derivative A-chain is defined in SEQ ID NO: 3, and B-chain B5Y, B26A substitutions and a B-chain desB30 deletion, wherein said derivative B-chain is defined in SEQ ID NO:15.

4. The insulin derivative according to claim 1 or claim 3, wherein Acy is selected from the group consisting of: lithocholic acid, 1,16-hexadecanedioic acid, 1,18-octadecanedioic acid, 1,20-eicosanedioic acid, tetrazole-C16, tetrazole-C17, tetrazole C18 and tetradecanoic acid.

5. The insulin derivative according to claim1 or claim 3, wherein -L1-L2-L3 represents a divalent linking group selected from DgGlu, gGlu, gGlu–gGlu, gGlu-OEG, gGlu-OEG-OEG, OEG, sulfonimide-C4, and sulfonimide-C4-sulfonimide-C4.

6. The insulin derivative according to any of the previous claims, wherein said insulin derivative is the compound N{Epsilon-B28}-[2-[2-[2-[[(4S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butanoyl]amino]ethoxy]ethoxy]acetyl]-[GluA14,TyrB5,GlyB26,LysB28],des-(B29-B30)-Insulin, represented by the structure



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7. An insulin derivative according to any one of claims 1-6, for use as a medicament.

8. Use of an insulin derivative according to any one of claims 1-6, in the manufacture of a medicament for the prevention or treatment of diabetes, cardiovascular disease, atherosclerosis, and/or endothelial dysfunction and/or for preventing or reducing liver triglyceride content and/or for preventing or reducing body weight gain.

9. Use of an insulin derivative according to any one of claims 1-6, in the manufacture of a medicament for the treatment or prevention of diabetes, diabetes of Type 1, diabetes of Type 2, impaired glucose tolerance, hyperglycemia, dyslipidemia, obesity, metabolic syndrome (metabolic syndrome X, insulin resistance syndrome), hypertension, cognitive disorders, atherosclerosis, myocardial infarction, stroke, cardiovascular disorders, coronary heart disease, stroke, inflammatory bowel syndrome, dyspepsia, hypotension or gastric ulcers.