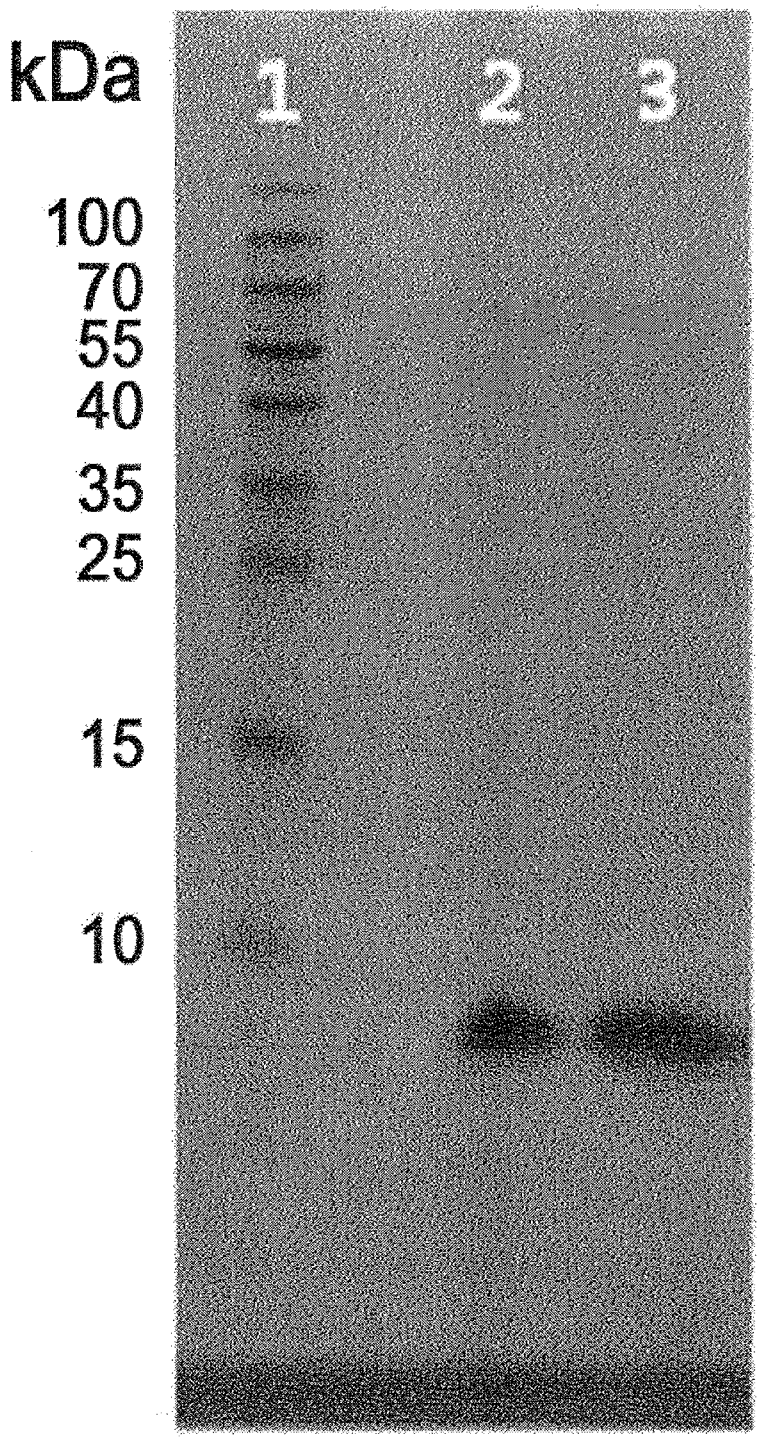
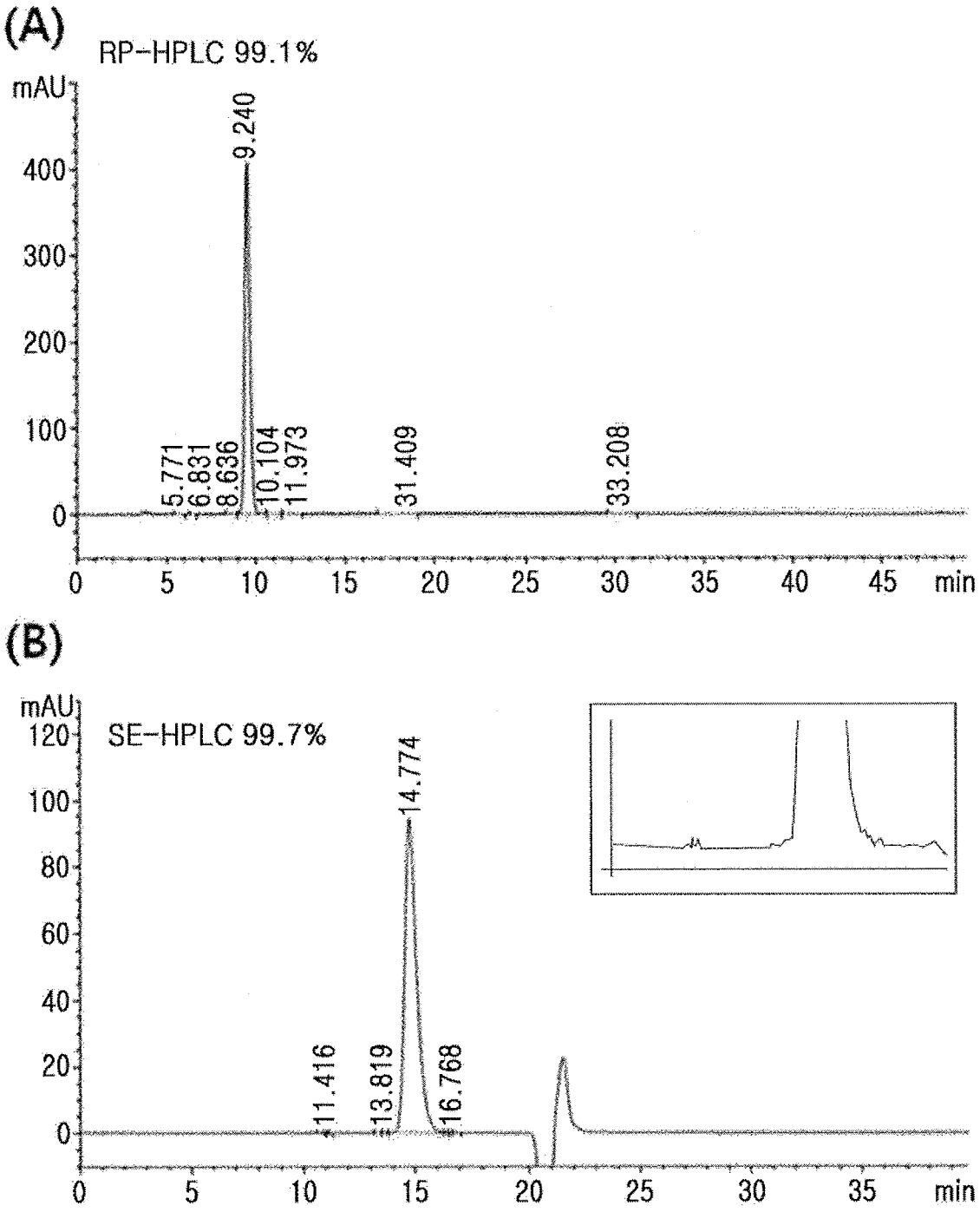
[DRAWINGS]

[FIG. 1]



[FIG. 2]


(A)
RP-HPLC 99.1%
mAU
400
300
200
100
0
9.240
5.771
6.831
8.636
10.104
11.973
31.409
33.208
0
5
10
15
20
25
30
35
40
45
min
(B)
mAU
120
100
80
60
40
20
0
SE-HPLC 99.7%
14.774
11.416
13.819
16.768
0
5
10
15
20
25
30
35
min

[FIG. 3]

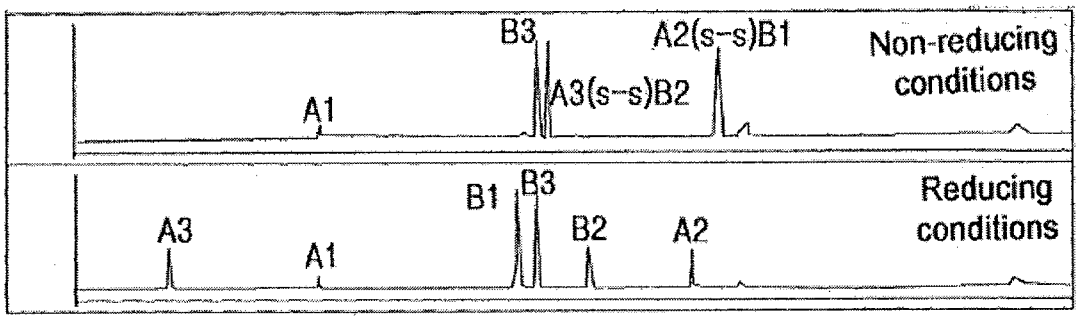
(A) Glu-C cleavage fragment of native insulin sequence

A1 A2 A3

A chain: GIVE QCCTSICSLYQLE NYCN

B chain: FVNQHLCGSHLVE ALYLVCGE RGFFYTPKT

B1 B2 B3



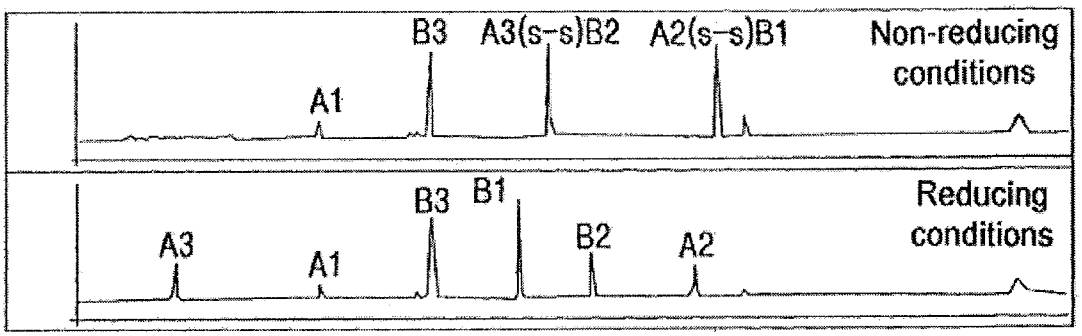
(B) Glu-C cleavage fragment of insulin analog (No. 7) sequence

A1 A2 A3

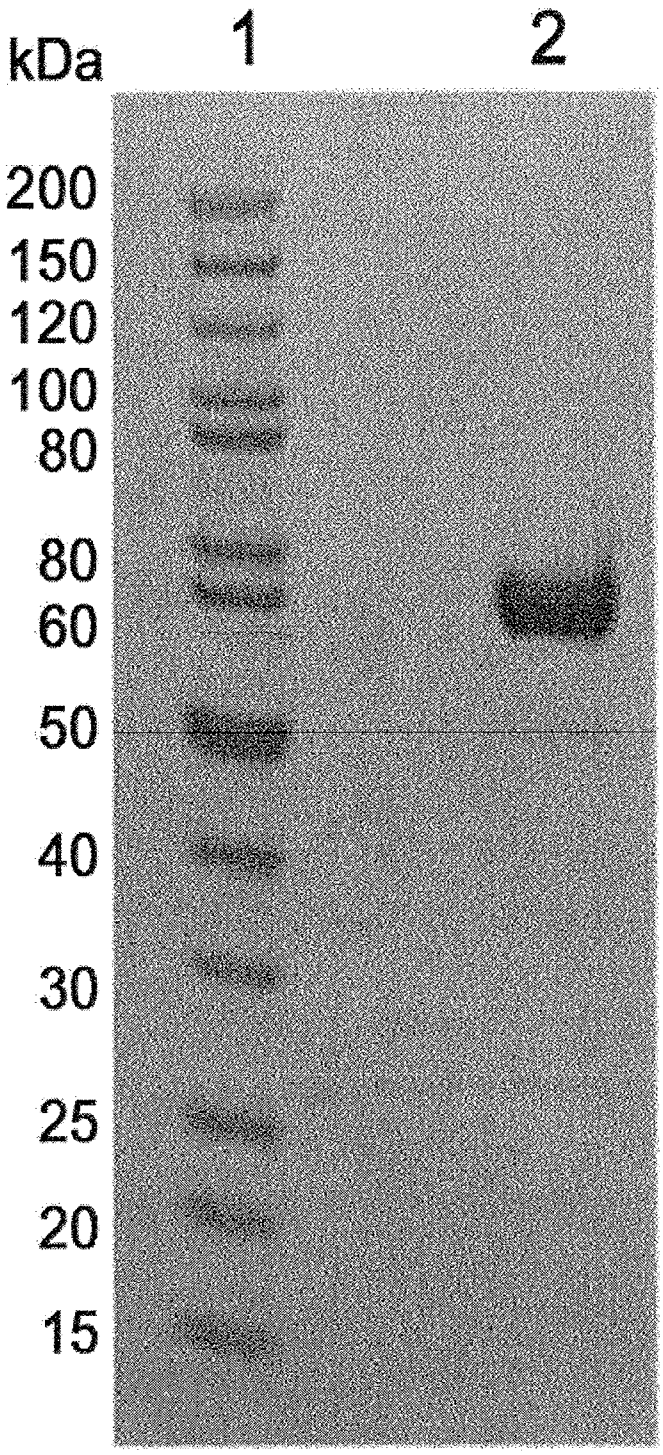
A chain: GIVE QCCTSICSLYQLE NYCN

B chain: FVNQHLCGSHLVE ALYLVCGE RGF*AYTPKT

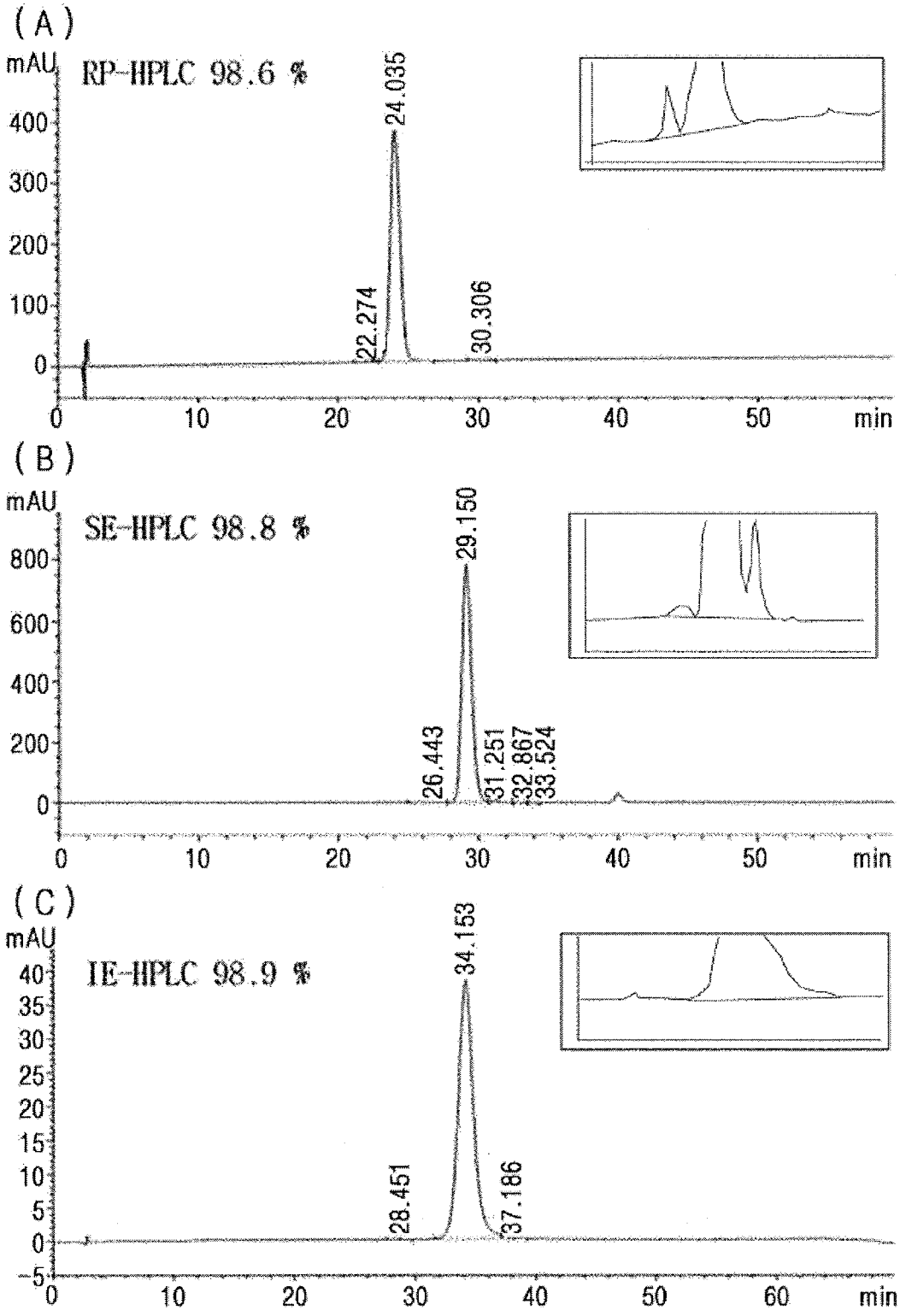
B1 B2 B3



[FIG. 4]

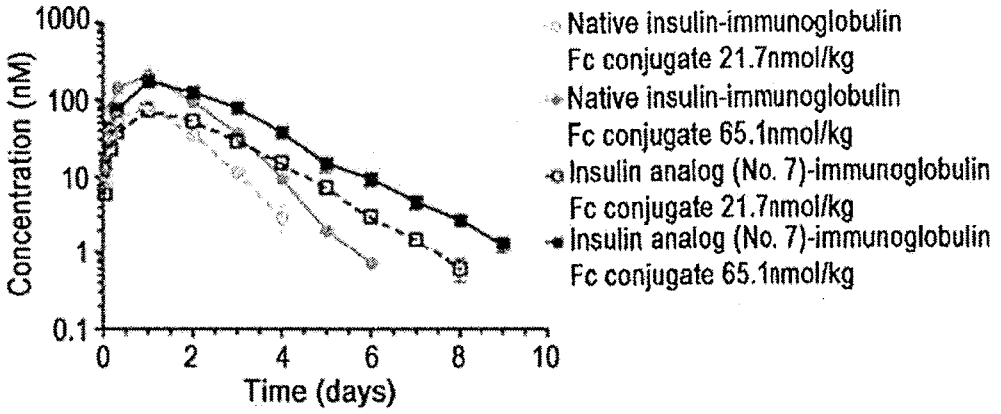


[FIG. 5]

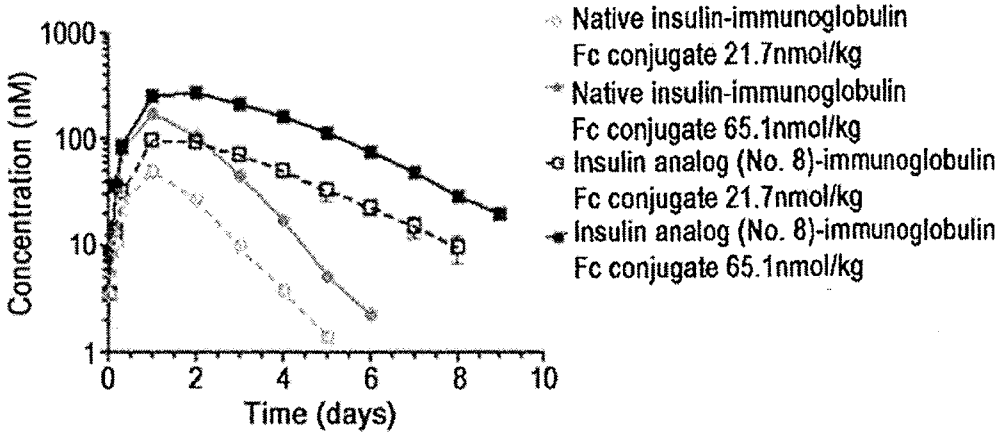

(A)
mAU
RP-HPLC 98.6 %
24.035
22.274
30.306
400
300
200
100
0
0
10
20
30
40
50
min
(B)
mAU
SE-HPLC 98.8 %
29.150
26.443
31.251
32.867
33.524
800
600
400
200
0
0
10
20
30
40
50
min
(C)
mAU
IE-HPLC 98.9 %
34.153
28.451
37.186
40
35
30
25
20
15
10
5
0
-5
0
10
20
30
40
50
60
min

[FIG. 6]

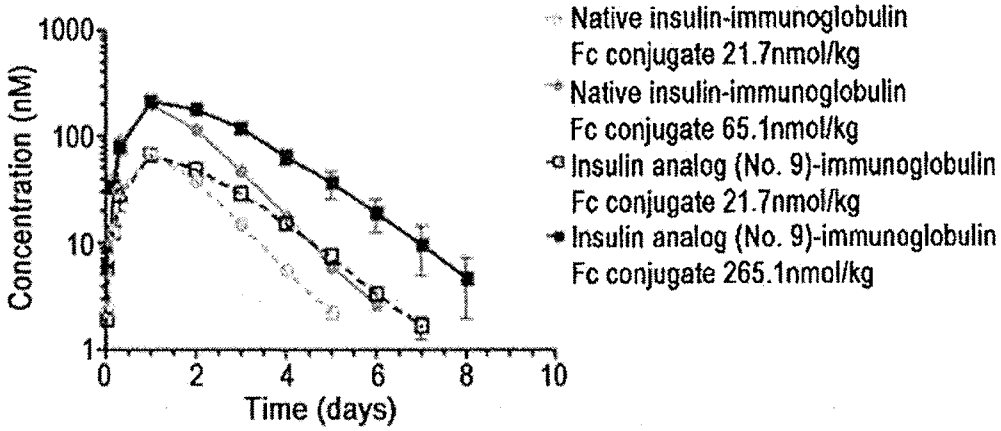
(A)


1000
100
10
1
0.1
Concentration (nM)
0
2
4
6
8
10
Time (days)
Native insulin-immunoglobulin Fc conjugate 21.7nmol/kg
Native insulin-immunoglobulin Fc conjugate 65.1nmol/kg
Insulin analog (No. 7)-immunoglobulin Fc conjugate 21.7nmol/kg
Insulin analog (No. 7)-immunoglobulin Fc conjugate 65.1nmol/kg

(B)


1000
100
10
1
Concentration (nM)
0
2
4
6
8
10
Time (days)
Native insulin-immunoglobulin Fc conjugate 21.7nmol/kg
Native insulin-immunoglobulin Fc conjugate 65.1nmol/kg
Insulin analog (No. 8)-immunoglobulin Fc conjugate 21.7nmol/kg
Insulin analog (No. 8)-immunoglobulin Fc conjugate 65.1nmol/kg

(C)


1000
100
10
1
Concentration (nM)
0
2
4
6
8
10
Time (days)
Native insulin-immunoglobulin Fc conjugate 21.7nmol/kg
Native insulin-immunoglobulin Fc conjugate 65.1nmol/kg
Insulin analog (No. 9)-immunoglobulin Fc conjugate 21.7nmol/kg
Insulin analog (No. 9)-immunoglobulin Fc conjugate 265.1nmol/kg

<110> HANMI PHARM. CO., LTD.

<120> Novel insulin analog and use thereof

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<150> KR 10-2013-0020703
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39

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39

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39

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36

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39

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39

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39

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<210> 12
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39

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39

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39

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<220>
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37

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<211> 37

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37

<210> 17
<211> 34
<212> DNA
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<220>
<223> Primer

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34

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<220>
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34

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<211> 258
<212> DNA
<213> Artificial Sequence

<220>
<223> Analog 1

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60

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120

caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg
180

tccctgcaga agcgtgcgat tgtggaacaa tgctgtacca gcatctgctc cctctaccag
240

ctggagaact actgcaac
258

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<211> 86
<212> PRT
<213> Artificial Sequence

<220>
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<400> 20
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg
20 25 30

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
35 40 45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
50 55 60

Arg Ala Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65 70 75 80

Leu Glu Asn Tyr Cys Asn
85

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<211> 258
<212> DNA
<213> Artificial Sequence

<220>
<223> Analog 2

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60

gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcaggtgggg
120

caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg
180

tccctgcaga agcgtggcgc ggtggaacaa tgctgtacca gcatctgctc cctctaccag
240

ctggagaact actgcaac
258

<210> 22
<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> Analog 2

<400> 22
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg
20 25 30

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
35 40 45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
50 55 60

Arg Gly Ala Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65 70 75 80

Leu Glu Asn Tyr Cys Asn
85

<210> 23
<211> 258
<212> DNA
<213> Artificial Sequence

<220>
<223> Analog 3

<400> 23
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60

gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcaggtgggg
120

caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg
180

tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag
240

ctggagaacg cgtgcaac
258

<210> 24
<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> Analog 3

<400> 24
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg
20 25 30

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
35 40 45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
50 55 60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65 70 75 80

Leu Glu Asn Ala Cys Asn
85

<210> 25
<211> 258
<212> DNA
<213> Artificial Sequence

<220>
<223> Analog 4

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60

gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcaggtgggg
120

caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg
180

tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag
240

ctggagaact actgcaac
258

<210> 26

<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> Analog 4

<400> 26
Phe Val Asn Gln His Leu Cys Ala Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg
20 25 30

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
35 40 45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
50 55 60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65 70 75 80

Leu Glu Asn Tyr Cys Asn
85

<210> 27
<211> 258
<212> DNA
<213> Artificial Sequence

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<223> Analog 5

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gaacgagcgt tcttctacac acccaagacc cgccgggagg cagaggacct gcaggtgggg
120

caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg
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tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag
240

ctggagaact actgcaac
258

<210> 28
<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> Analog 5

<400> 28
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Ala Phe Phe Tyr Thr Pro Lys Thr Arg Arg
20 25 30

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
35 40 45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
50 55 60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65 70 75 80

Leu Glu Asn Tyr Cys Asn
85

<210> 29
<211> 258
<212> DNA
<213> Artificial Sequence

<220>
<223> Analog 6

<400> 29
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60

gaacgaggcg cgttctacac acccaagacc cgccgggagg cagaggacct gcaggtgggg
120

caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg
180

tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag
240

ctggagaact actgcaac
258

<210> 30
<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> Analog 6

<400> 30

```
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
  1               5                  10                  15

Leu Val Cys Gly Glu Arg Gly Ala Phe Tyr Thr Pro Lys Thr Arg Arg
             20                  25                  30

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
         35                  40                  45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
     50                  55                  60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
 65                  70                  75                  80

Leu Glu Asn Tyr Cys Asn
                 85
```

<210> 31
<211> 258
<212> DNA
<213> Artificial Sequence

<220>
<223> Analog 7

<400> 31

```
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60

gaacgaggct tcgcgtacac acccaagacc cgccgggagg cagaggacct gcaggtgggg
120

caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg
180

tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag
240

ctggagaact actgcaac
258
```

<210> 32
<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> Analog 7

<400> 32

Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Ala Tyr Thr Pro Lys Thr Arg Arg
20 25 30

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
35 40 45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
50 55 60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65 70 75 80

Leu Glu Asn Tyr Cys Asn
85

<210> 33
<211> 261
<212> DNA
<213> Artificial Sequence

<220>
<223> Analog 8

<400> 33
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60

gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcaggtgggg
120

caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg
180

tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctcgaacag
240

ctggagaact actgcaactg a
261

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<212> PRT
<213> Artificial Sequence

<220>
<223> Analog 8

<400> 34
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

```
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg
            20                  25                  30

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
        35                  40                  45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
    50                  55                  60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Glu Gln
65                  70                  75                  80

Leu Glu Asn Tyr Cys Asn
                85
```

<210> 35
<211> 261
<212> DNA
<213> Artificial Sequence

<220>
<223> Analog 9

<400> 35
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60

gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcaggtgggg
120

caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg
180

tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctcaaccag
240

ctggagaact actgcaactg a
261

<210> 36
<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> Analog 9

<400> 36
```
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
  1               5                  10                  15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg
            20                  25                  30
```

```
Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
         35                  40                  45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
     50                  55                  60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Asn Gln
 65                  70                  75                  80

Leu Glu Asn Tyr Cys Asn
                 85
```

<210> 37
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> A chain of insulin

<400> 37

```
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu
  1               5                  10                  15

Glu Asn Tyr Cys Asn
             20
```

<210> 38
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> B chain of insulin

<400> 38

```
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
  1               5                  10                  15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
             20                  25                  30
```