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(54) Titre : ANALOGUES D'EGF(A) AVEC SUBSTITUANTS ACIDES GRAS
(54) Title: EGF(A) ANALOGUES WITH FATTY ACID SUBSTITUENTS

(57) **Abrégé/Abstract:**

The invention relates to compounds derived from the EGF(A) domain of LDL-R, in particular compounds comprising a peptide analogue of the wild-type EGF(A) (LDL-R(293- 332)) sequence and at least one substituent comprising at least one fatty acid group. The invention also relates to a pharmaceutical composition thereof and use a medicament. The novel EGF(A) compounds of the invention are useful as treatment e.g. in the field of cholesterol lowering, dyslipidaemia and cardiovascular disease.

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- (54) Title: EGF(A) ANALOGUES WITH FATTY ACID SUBSTITUENTS

(57) Abstract: The invention relates to compounds derived from the EGF(A) domain of LDL-R, in particular compounds comprising a peptide analogue of the wild-type EGF(A) (LDL-R(293- 332)) sequence and at least one substituent comprising at least one fatty acid group. The invention also relates to a pharmaceutical composition thereof and use a medicament. The novel EGF(A) compounds of the invention are useful as treatment e.g. in the field of cholesterol lowering, dyslipidaemia and cardiovascular disease.

Example no	<u>C_{max}/dose (kg/l)</u>	<u>C_{max}/dose for ref. Example 3 (kg/l)</u>
Example 31	0.108 ± 0.086	0.053 ± 0.050
Example 81	0.024 ± 0.005	0.079 ± 0.013
Example 91	0.116 ± 0.032	0.083 ± 0.023
Example 95	0.106 ± 0.029	0.087 ± 0.023
Example 128	0.130 ± 0.013	0.087 ± 0.019
Example 133	0.071 ± 0.017	0.057 ± 0.015
Example 143	0.151 ± 0.038	0.096 ± 0.029
Example 144	0.100 ± 0.025	0.057 ± 0.015

5 Forming part of the disclosure is an electronic copy of a sequence listing. The contents of the sequence listing are summarized and presented as a sequence table in Table 11 below.

1
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Asn Gly Gly Cys Ser His Val Cys
1 5 10 15
Asn Asp Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

2
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Ala Asn Leu Gly Gly Cys Ser His Ile Cys
1 5 10 15

Arg Lys Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

3
 40
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

4
 41
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

5
 40
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Pro Leu Gly Gly Cys Ser His Ile Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

6
 40
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

7
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Lys Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

8
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Lys Cys Glu
35 40

9
41
PRT
Artificial Sequence
Synthetic Sequence

Asn Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Ile Cys
1 5 10 15

Arg Asp Leu Asp Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

10
41
PRT
Artificial Sequence
Synthetic Sequence

Asn Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Asp Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

200

11

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Lys
 35 40

12

40

PRT

Artificial Sequence

Synthetic Sequence

Lys Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
 35 40

13

41

PRT

Artificial Sequence

Synthetic Sequence

Lys Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

14

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Lys His Arg Cys Glu
 35 40

15

41

PRT
Artificial Sequence
Synthetic Sequence

Gly	Thr	Asn	Glu	Cys	Leu	Asp	Asn	Leu	Gly	Gly	Cys	Ser	His	Val	Cys
1				5					10					15	
Arg	Asp	Leu	Glu	Ile	Gly	Tyr	Glu	Cys	Leu	Cys	Pro	Asp	Gly	Phe	Gln
			20					25					30		
Leu	Val	Ala	Gln	Arg	Arg	Cys	Lys	Lys							
		35					40								

16
41
PRT
Artificial Sequence
Synthetic Sequence

Gly	Thr	Asn	Glu	Cys	Leu	Asp	Asn	Leu	Gly	Gly	Cys	Ser	His	Val	Cys
1				5					10					15	
Arg	Asp	Leu	Glu	Ile	Gly	Tyr	Glu	Cys	Leu	Cys	Pro	Asp	Gly	Phe	Gln
			20					25					30		
Leu	Val	Ala	Gln	Arg	Lys	Cys	Glu	Lys							
		35					40								

17
41
PRT
Artificial Sequence
Synthetic Sequence

Gly	Thr	Asn	Glu	Cys	Leu	Asp	Asn	Leu	Gly	Gly	Cys	Ser	His	Val	Cys
1				5					10					15	
Arg	Asp	Leu	Glu	Ile	Gly	Tyr	Glu	Cys	Leu	Cys	Pro	Lys	Gly	Phe	Gln
			20					25					30		
Leu	Val	Ala	Gln	Arg	Arg	Cys	Glu	Lys							
		35					40								

18
41
PRT
Artificial Sequence
Synthetic Sequence

Gly	Thr	Asn	Glu	Cys	Leu	Asp	Asn	Leu	Gly	Gly	Cys	Ser	His	Val	Cys
1				5					10					15	
Arg	Asp	Leu	Lys	Ile	Gly	Tyr	Glu	Cys	Leu	Cys	Pro	Asp	Gly	Phe	Gln
			20					25					30		
Leu	Val	Ala	Gln	Arg	Arg	Cys	Glu	Lys							
		35					40								

19
41
PRT
Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Glu Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

20

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asp Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Lys
35 40

21

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Lys Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

22

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Lys
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

23

40

PRT

Artificial Sequence

Synthetic Sequence

203

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Gln Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

24
 40
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Glu Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Lys
 35 40

25
 40
 PRT
 Artificial Sequence
 Synthetic Sequence

Lys Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Glu Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

26
 40
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Ile Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

27
 40
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Lys Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

204

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

28
40
PRT
Artificial Sequence
Synthetic Sequence

Lys Lys Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

29
40
PRT
Artificial Sequence
Synthetic Sequence

Lys Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

30
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Lys Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

31
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Lys Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

32
41
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

33
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Lys Ala Gln Arg Arg Cys Glu
35 40

34
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Lys Val Ala Gln Arg Arg Cys Glu
35 40

35
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Lys Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

36

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Lys Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

37

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Lys Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

38

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Lys Arg Cys Glu
35 40

39

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

40

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Lys Arg Arg Cys Glu
35 40

41

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Lys Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

42

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Lys Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

43

41

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Arg Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

44
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Lys Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

45
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Lys Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

46
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Lys Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

47
41
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Ser Asp Leu Arg Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

48

41

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Ser Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

49

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser Tyr Val Cys
1 5 10 15

Ser Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

50

40

PRT

Artificial Sequence

Synthetic Sequence

Asn Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Ser Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

51

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser Lys Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
35 40

52

40

PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Lys His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

53
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Lys Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

54
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Lys Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

55
41
PRT
Artificial Sequence
Synthetic Sequence

Asn Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Arg Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

56
40
PRT
Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Lys Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

57

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Lys Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

58

41

PRT

Artificial Sequence

Synthetic Sequence

Asn Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Arg Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

59

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Ile Cys
 1 5 10 15
 Asn Asp Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Lys
 35 40

60

40

PRT

Artificial Sequence

Synthetic Sequence

212

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser Tyr Val Cys
1 5 10 15
Asn Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Lys
35 40

61
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Ile Cys
1 5 10 15
Asn Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Lys
35 40

62
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

63
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Lys Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

64
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Lys Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

65
 41
 PRT
 Artificial Sequence
 Synthetic Sequence

Lys Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val
 1 5 10 15
 Cys Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe
 20 25 30
 Gln Leu Val Ala Gln Arg Arg Cys Glu
 35 40

66
 39
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys Arg
 1 5 10 15
 Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln Leu
 20 25 30
 Val Ala Lys Arg Arg Cys Glu
 35

67
 41
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser Asp Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gly
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

68
 41
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser Asp Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

69

41

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

70

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Lys Arg Arg Cys Glu
 35 40

71

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

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

Leu Val Ala Gln Arg Arg Cys Glu
 35 40

72

41

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Lys
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

73
 40

PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Lys Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
 35 40

74
 40

PRT
 Artificial Sequence
 Synthetic Sequence

Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys Arg
 1 5 10 15

Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln Leu
 20 25 30

Val Ala Gln Arg Arg Cys Glu Lys
 35 40

75
 41

PRT
 Artificial Sequence
 Synthetic Sequence

Ala Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val
 1 5 10 15

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

Gln Leu Val Ala Gln Arg Arg Cys Glu
 35 40

76
 39

PRT
 Artificial Sequence
 Synthetic Sequence

Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys Arg
 1 5 10 15

Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln Leu
 20 25 30

Val Ala Gln Arg Arg Cys Glu
 35

77
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Lys
35 40

78
41
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Lys Arg Arg Cys Glu Lys
35 40

79
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Ala Asn Leu Gly Gly Cys Ser His Ile Cys
1 5 10 15
Arg Asp Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

80
40
PRT
Artificial Sequence
GTNECLDNLG GCSHVCRKLG IGYECLCPDG FQLVAQRRCE

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Lys Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

81
40

PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Asn Asp Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

82
41
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

83
39
PRT
Artificial Sequence
Synthetic Sequence

Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys Arg Asp
1 5 10 15
Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln Leu Val
20 25 30
Ala Gln Arg Arg Cys Glu Lys
35

84
41
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Lys Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

85
41
PRT
Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser Tyr Val Cys
 1 5 10 15
 Asn Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Lys
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

86

41

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Lys Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

87

41

PRT

Artificial Sequence

Synthetic Sequence

Gly Trp Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

88

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Lys Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Lys Arg Arg Cys Glu
 35 40

89

40

PRT

Artificial Sequence

Synthetic Sequence

219

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Lys Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30
 Leu Val Ala Gln Arg Arg Cys Glu
 35 40

90
 40
 PRT
 Artificial Sequence
 Synthetic Sequence

Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys Arg
 1 5 10 15
 Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln Leu
 20 25 30
 Val Ala Gln Arg Arg Cys Glu Lys
 35 40

91
 40
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15
 Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Lys
 20 25 30
 Leu Val Ala Lys Arg Arg Cys Glu
 35 40

92
 42
 PRT
 Artificial Sequence
 Synthetic Sequence

Ala Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val
 1 5 10 15
 Cys Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe
 20 25 30
 Gln Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

93
 41
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser Tyr Val Cys
 1 5 10 15

220

Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

94
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Lys Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Lys
35 40

95
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Lys Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Lys
35 40

96
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Lys
35 40

97
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Glu Gly Phe Gln
20 25 30

221

Leu Val Ala Gln Arg Arg Cys Lys
 35 40

98

41

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Glu Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu Lys
 35 40

99

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Glu Lys Lys Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
 35 40

100

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Lys Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
 35 40

101

40

PRT

Artificial Sequence

Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
 1 5 10 15

Arg Asp Leu Lys Ile Lys Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
 20 25 30

Leu Val Ala Gln Arg Arg Cys Glu
 35 40

102
40
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Lys Glu Lys Gly Tyr Glu Cys Leu Cys Pro Asp Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu
35 40

103
41
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp His Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Lys Gly Tyr Glu Cys Leu Cys Pro Glu Gly Phe Gln
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

104
41
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Glu Gly Phe Gln
20 25 30
Leu Val Ala Lys Arg Arg Cys Glu Lys
35 40

105
41
PRT
Artificial Sequence
Synthetic Sequence

Gly Thr Asn Glu Cys Leu Asp Asn Leu Gly Gly Cys Ser His Val Cys
1 5 10 15
Arg Asp Leu Glu Ile Gly Tyr Glu Cys Leu Cys Pro Glu Gly Phe Lys
20 25 30
Leu Val Ala Gln Arg Arg Cys Glu Lys
35 40

106

40
 PRT
 Artificial Sequence
 Synthetic Sequence

Gly	Thr	Asn	Glu	Cys	Leu	Asp	Asn	Leu	Gly	Gly	Cys	Ser	His	Val	Cys
1				5					10					15	
Lys	Asp	Leu	Glu	Ile	Gly	Tyr	Glu	Cys	Leu	Cys	Pro	Asp	Gly	Phe	Lys
			20					25					30		
Leu	Val	Ala	Gln	Arg	Arg	Cys	Glu								
		35					40								

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

CLAIMS

1. An EGF(A) derivative comprising an EGF(A) peptide analogue of the EGF(A) domain of LDL-R defined by SEQ ID NO 1, comprising 301Leu and a substituent comprising at least one fatty acid group.
2. The EGF(A) derivative according to claim 1, wherein said substituent comprises a carboxylic acid, a sulphonic acid, a tetrazole moiety, a methylsulfonylcarbamoylamino moiety or a 3-hydroxy-isoxazole moiety and 8-20 consecutive $-\text{CH}_2-$ groups.
3. The EGF(A) derivative according to claim 1, wherein said substituent has Formula I:
 $\text{Z}_1\text{-Z}_2\text{-Z}_3\text{-Z}_4\text{-Z}_5\text{-Z}_6\text{-Z}_7\text{-Z}_8\text{-Z}_9\text{-Z}_{10}$ [I] wherein
 Z_1 is selected from:
 Chem. 1: $\text{HOOC-(CH}_2)_n\text{-CO-}^*$,
 Chem. 2: $\text{tetrazolyl-(CH}_2)_n\text{-CO-}^*$,
 Chem. 3: $\text{HOOC-(C}_6\text{H}_4\text{)-O-(CH}_2)_m\text{-CO-}^*$,
 Chem. 4: $\text{HOS(O)}_2\text{-(CH}_2)_n\text{-CO-}^*$,
 Chem. 5: $\text{MeS(O)}_2\text{NH(CO)N-(CH}_2)_n\text{-CO-}^*$ and
 Chem. 6: $\text{3-HO-Isoxazole-(CH}_2)_n\text{-CO-}^*$
 wherein
 n is an integer in the range of 8-20,
 m is an integer in the range of 8-11,
 the $-\text{COOH}$ group in Chem. 3 can be attached to position 2, 3 or 4 on the phenyl ring, the symbol $*$ indicates the attachment point to the nitrogen in Z_2 or, if Z_2 is a bond, to the nitrogen on the neighbouring Z element;
 Z_2 is selected from
 Chem. 7: $^*\text{-NH-SO}_2\text{-(CH}_2)_3\text{-CO-}^*$,
 Chem. 8: $^*\text{-NH-CH}_2\text{-(C}_6\text{H}_{10}\text{)-CO-}^*$ and
 a bond;
 Z_3 is selected from:
 γGlu , Glu and a bond;
 Z_4 , Z_5 , Z_6 , Z_7 , Z_8 , Z_9 are selected, independently of each other, from:
 Glu , γGlu , Gly , Ser , Ala , Thr , Ado , Aep , Aeeep , TtdSuc and a bond;
 Z_{10} is selected from:
 Chem. 14: $^*\text{-NH-CH}_2\text{-(C}_6\text{H}_4\text{)-CH}_2\text{-}^*$ and a bond.

4. The EGF(A) derivative according to any of the previous claims, wherein the EGF(A) derivative comprises one or two substituent(s) selected from the group consisting of:

HOOC-(CH₂)₁₈-CO-gGlu-2xADO-
 HOOC-(CH₂)₁₈-CO-NH-CH₂-(C₆H₁₀)-CO-gGlu-2xADO-
 HOOC-(CH₂)₁₆-CO-gGlu-2xADO-
 HOOC-(CH₂)₁₆-CO-gGlu-2xADO-NH-CH₂-(C₆H₄)-CH₂-
 HOOC-(CH₂)₁₆-CO-gGlu-
 HOOC-(CH₂)₁₆-CO-NH-CH₂-(C₆H₁₀)-CO-gGlu-2xADO-
 HOOC-(CH₂)₁₄-CO-gGlu-2xADO-
 HOOC-(CH₂)₁₄-CO-gGlu-
 HOOC-(CH₂)₁₄-CO-gGlu-2xADO-
 HOOC-(CH₂)₁₂-CO-gGlu-2xADO-
 4-HOOC-(C₆H₄)-O-(CH₂)₁₀-CO-gGlu-2xADO-
 4-HOOC-(C₆H₄)-O-(CH₂)₁₀-CO-gGlu-3xADO-
 4-HOOC-(C₆H₄)-O-(CH₂)₁₀-CO-gGlu-
 4-HOOC-(C₆H₄)-O-(CH₂)₁₀-CO-2xgGlu-
 4-HOOC-(C₆H₄)-O-(CH₂)₁₀-CO-gGlu-3xGly-
 4-HOOC-(C₆H₄)-O-(CH₂)₁₀-CO-2xgGlu-2xADO-
 4-HOOC-(C₆H₄)-O-(CH₂)₁₀-CO-gGlu-TtdSuc-
 4-HOOC-(C₆H₄)-O-(CH₂)₉-CO-
 4-HOOC-(C₆H₄)-O-(CH₂)₁₀-CO-gGlu-4xADO-
 4-HOOC-(C₆H₄)-O-(CH₂)₁₀-CO-NH-CH₂-(C₆H₁₀)-CO-gGlu-2xADO-
 4-HOOC-(C₆H₄)-O-(CH₂)₉-CO-gGlu-2xADO-
 3-HOOC-(C₆H₄)-O-(CH₂)₉-CO-gGlu-2xADO-
 3-HO-Isoxazole-(CH₂)₁₂-CO-gGlu-2xADO-
 HOS(O)₂-(CH₂)₁₅-CO-gGlu-2xADO-NH-CH₂-(C₆H₄)-CH₂-
 HOS(O)₂-(CH₂)₁₃-CO-gGlu-2xADO-
 Tetrazolyl-(CH₂)₁₅-CO-NH-SO₂-(CH₂)₃-CO-ADO-ADO-NH-CH₂-(C₆H₄)-CH₂-
 Tetrazolyl-(CH₂)₁₂-CO-gGlu-2xADO-
 Tetrazolyl-(CH₂)₁₅-CO-gGlu-2xADO- and
 MeS(O)₂NH(CO)NH-(CH₂)₁₂-CO-gGlu-2xADO-.

5. The EGF(A) derivative according to any of the previous claims, wherein the EGF(A) peptide analogue comprises one, two, three, four or all five of the following (wild type) amino acid residue(s): 295Asn, 296Glu, 298Leu, 302Gly and 310Asp.

6. The EGF(A) derivative according to any of the previous claims, wherein the EGF(A) peptide analogue comprises the wild-type residue 310Asp.

7. The EGF(A) derivative according to any of the previous claims, wherein the EGF(A) peptide analogue comprises the wild-type residue 295Asn.
8. The EGF(A) derivative according to any of the previous claims wherein at least one substituent is attached to a Lys residue in the EGF(A) peptide analogue selected from the group consisting of: 292Lys, 293Lys, 294Lys, 296Lys, 299Lys, 300Lys, 303Lys, 305Lys, 306Lys, 309Lys, 311Lys, 312Lys, 313Lys, 314Lys, 315Lys, 316Lys, 318Lys, 320Lys, 321Lys, 322Lys, 323Lys, 324Lys, 325Lys, 326Lys, 327Lys, 328Lys, 329Lys, 330Lys, 332Lys and 333Lys.
9. The EGF(A) derivative according to claim 1, wherein the EGF(A) derivative is selected from the group of EGF(A) derivatives consisting of: Example compounds 1-44, 46-47, 51-55, 57, 60-64, 66-69, 71-102 and 106-159.
10. An EGF(A) peptide analogue of the EGF(A) domain of LDL-R defined by SEQ ID NO 1, wherein the EGF(A) peptide analogue comprises 301Leu, 310Asp and an amino acid substitution of 312Lys.
11. An EGF(A) peptide analogue of the EGF(A) domain defined by SEQ ID NO 1, wherein the EGF(A) peptide analogue comprises 301Leu and 310Asp and wherein the peptide does not have a substitution of 299Asp to Glu, Val or His.
12. The EGF(A) peptide analogue according to claim 10 or 11, wherein the EGF(A) peptide analogue comprises Cys residues 297Cys, 304Cys, 308Cys, 317Cys, 319Cys and 331Cys.
13. The EGF(A) peptide analogue according any of the previous claims 10 - 12, further comprising one, two, three, four or all five of the following (wild type) amino acid residue(s): 295Asn, 296Glu, 298Leu, 302Gly and 310Asp.
14. The EGF(A) peptide analogue according any of the previous claims 10- 12, EGF(A) further comprising at least one Lys substitution selected from the group consisting of: 292Lys, 293Lys, 294Lys, 296Lys, 299Lys, 300Lys, 303Lys, 305Lys, 306Lys, 309Lys, 311Lys, 313Lys, 314Lys, 315Lys, 316Lys, 318Lys, 320Lys, 321Lys, 322Lys, 323Lys, 324Lys, 325Lys, 326Lys, 327Lys, 328Lys, 329Lys, 330Lys, 332Lys and 333Lys.

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15. The EGF(A) peptide analogue according to any of the previous claims 10- 12, wherein said peptide sequence is selected from the group consisting of: SEQ ID NO.: 2-47 and 49-106.

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Fig. 1

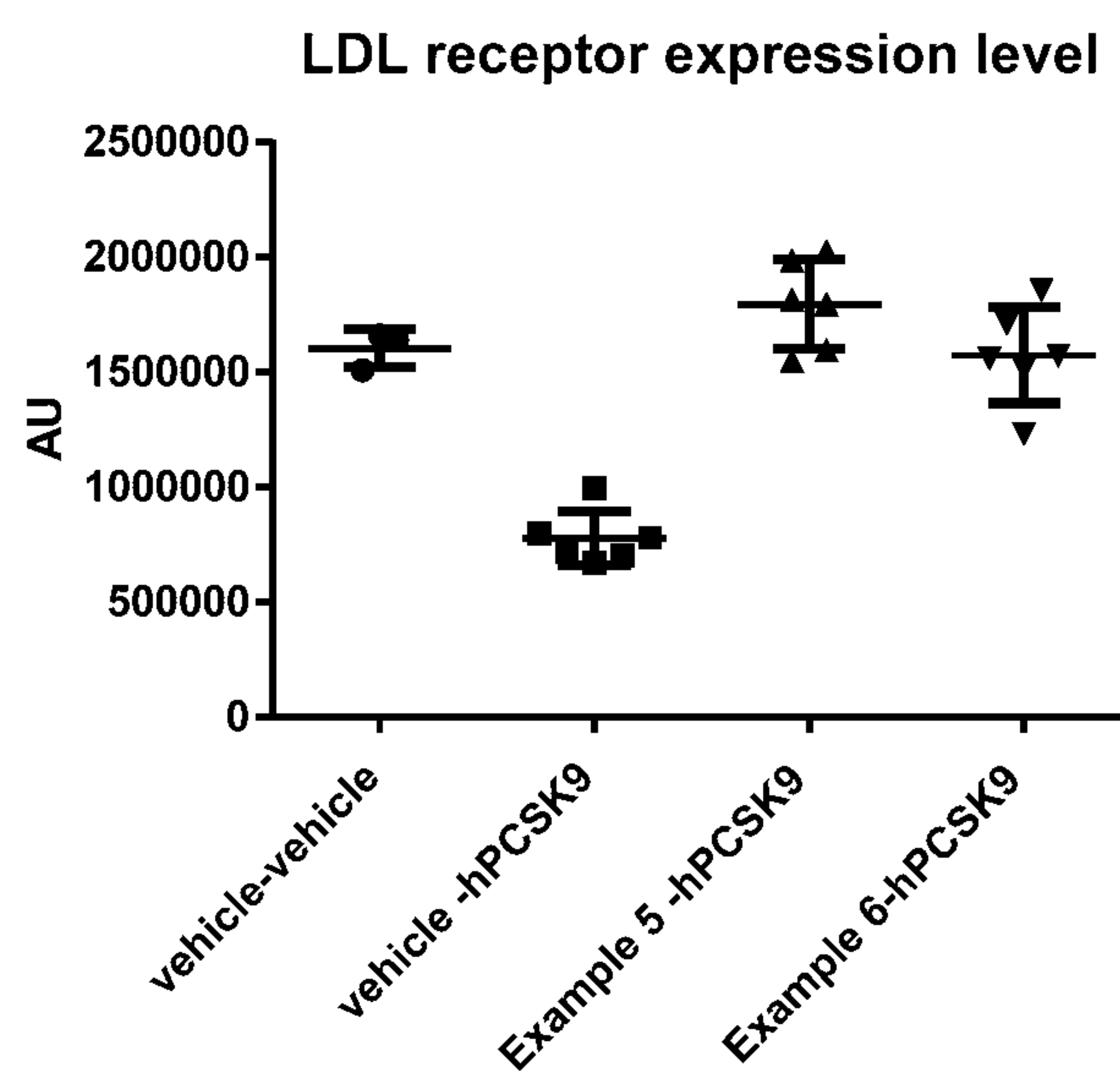
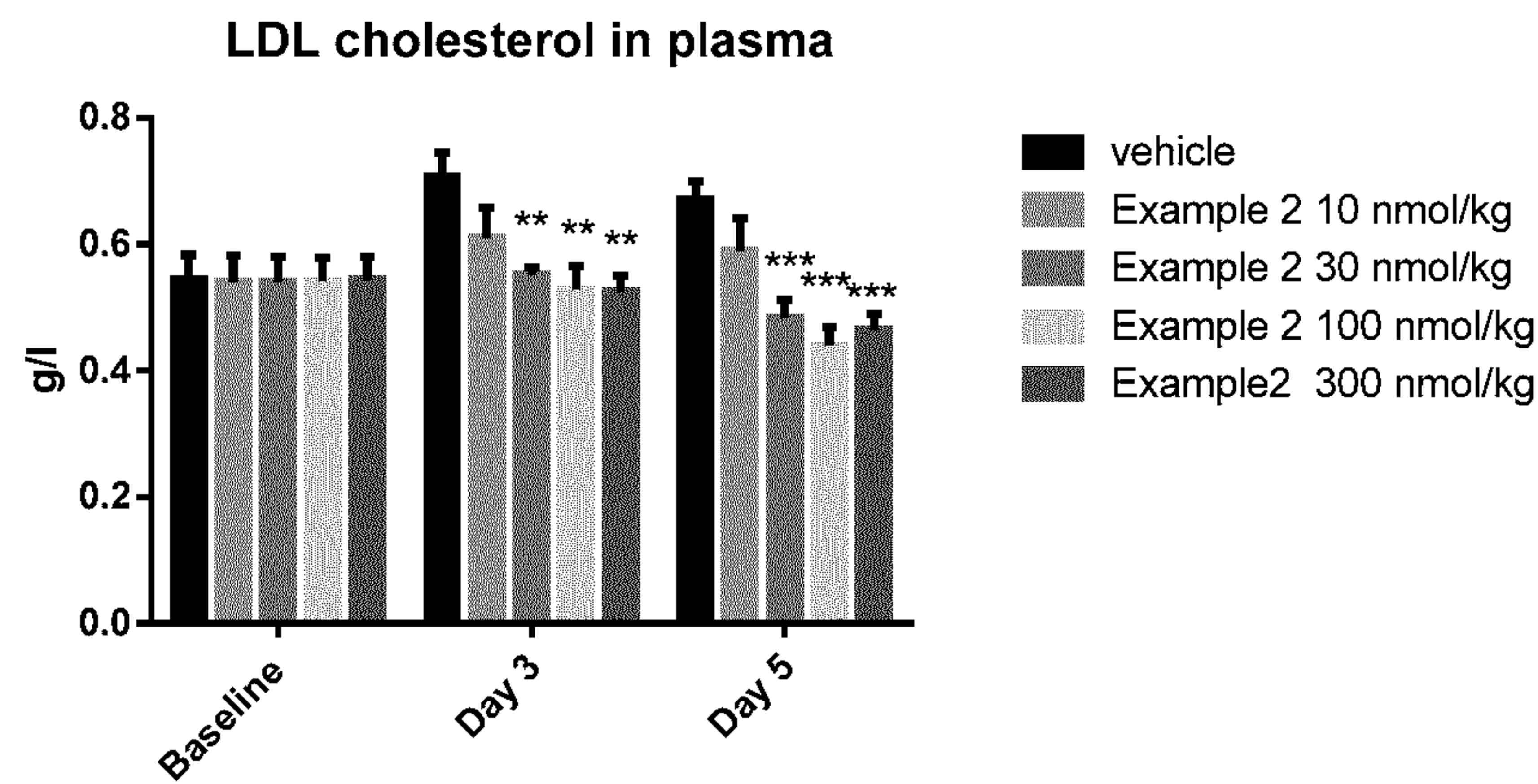


Fig. 2



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Fig. 3