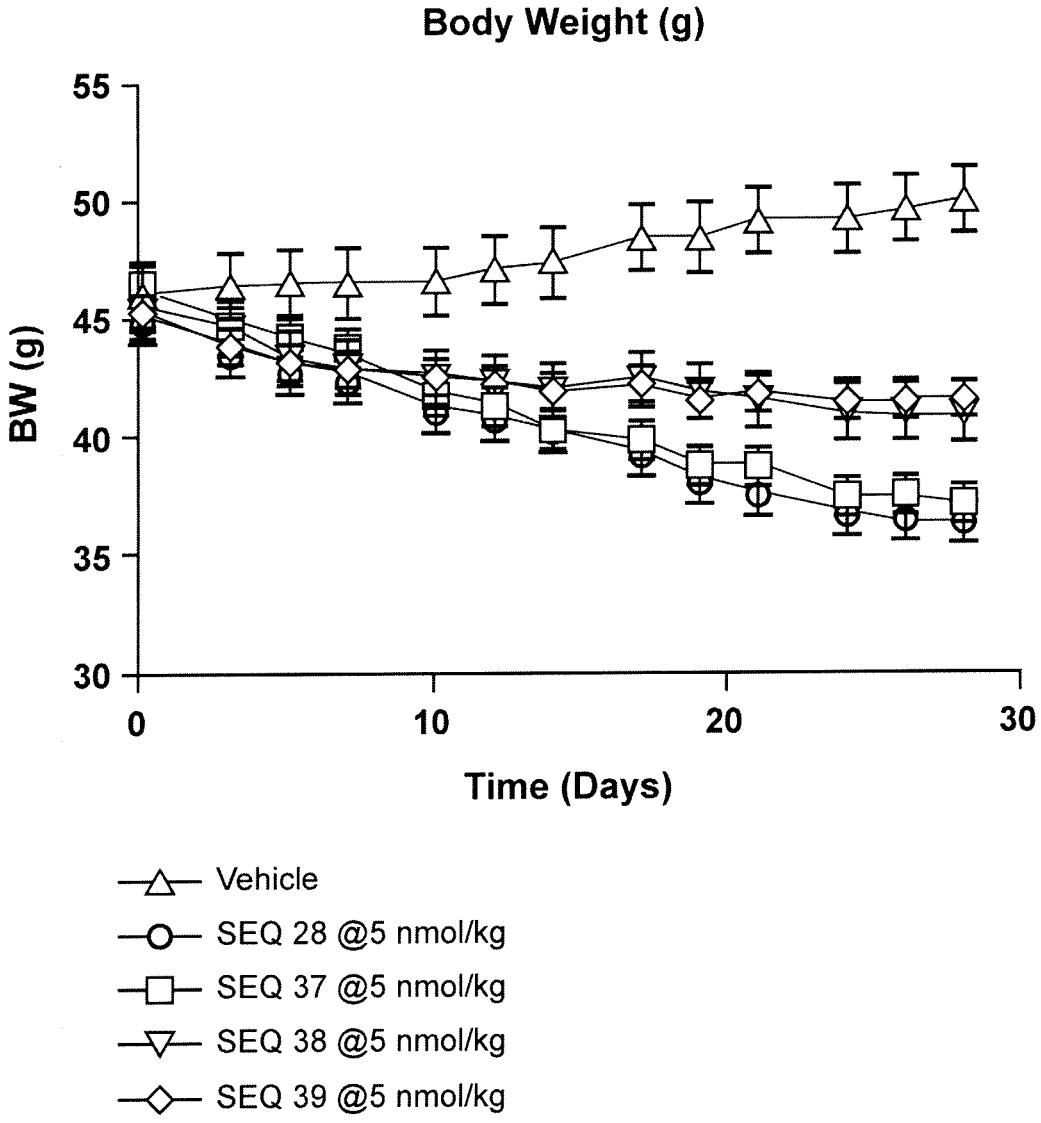

Body Weight (g)
BW (g)
55
50
45
40
35
30
0
10
20
30
Time (Days)
Vehicle
SEQ 28 @5 nmol/kg
SEQ 37 @5 nmol/kg
SEQ 38 @5 nmol/kg
SEQ 39 @5 nmol/kg

FIGURE 1

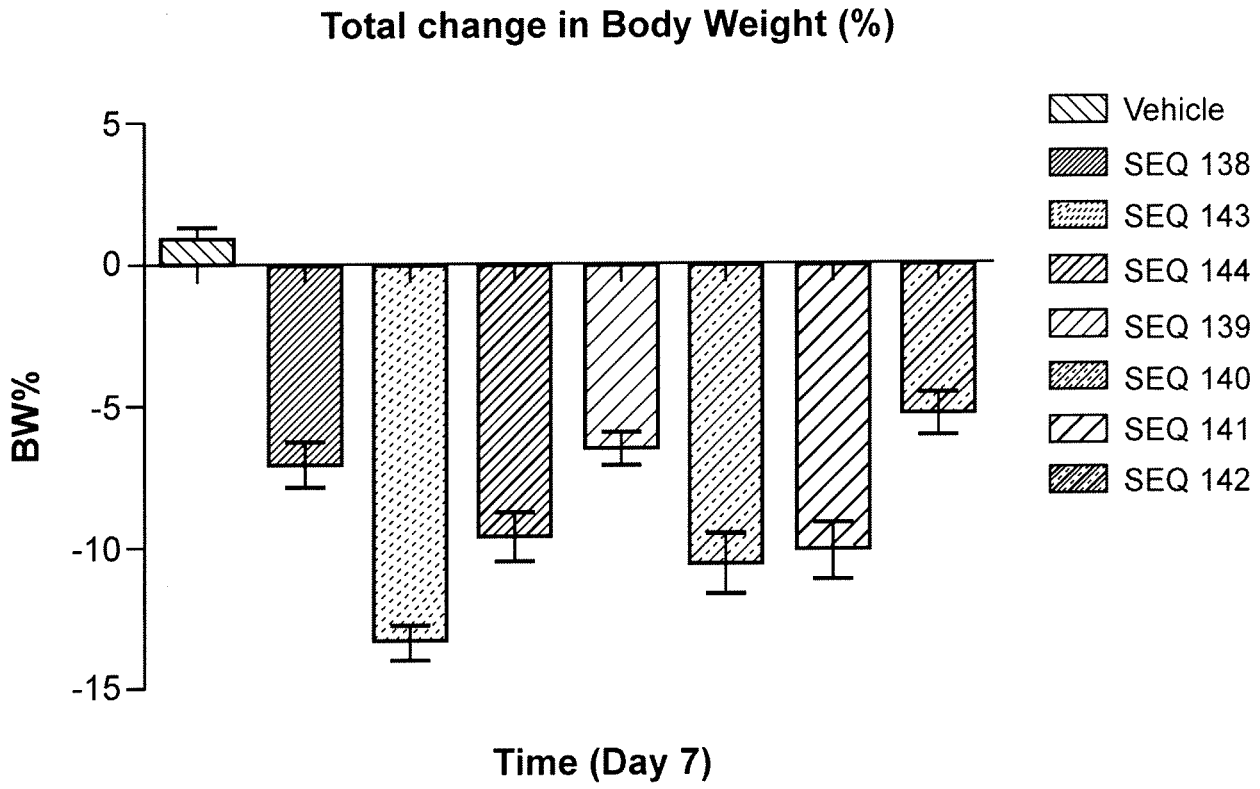

Total change in Body Weight (%)
BW%
5
0
-5
-10
-15
Time (Day 7)
Vehicle
SEQ 138
SEQ 143
SEQ 144
SEQ 139
SEQ 140
SEQ 141
SEQ 142

FIGURE 2

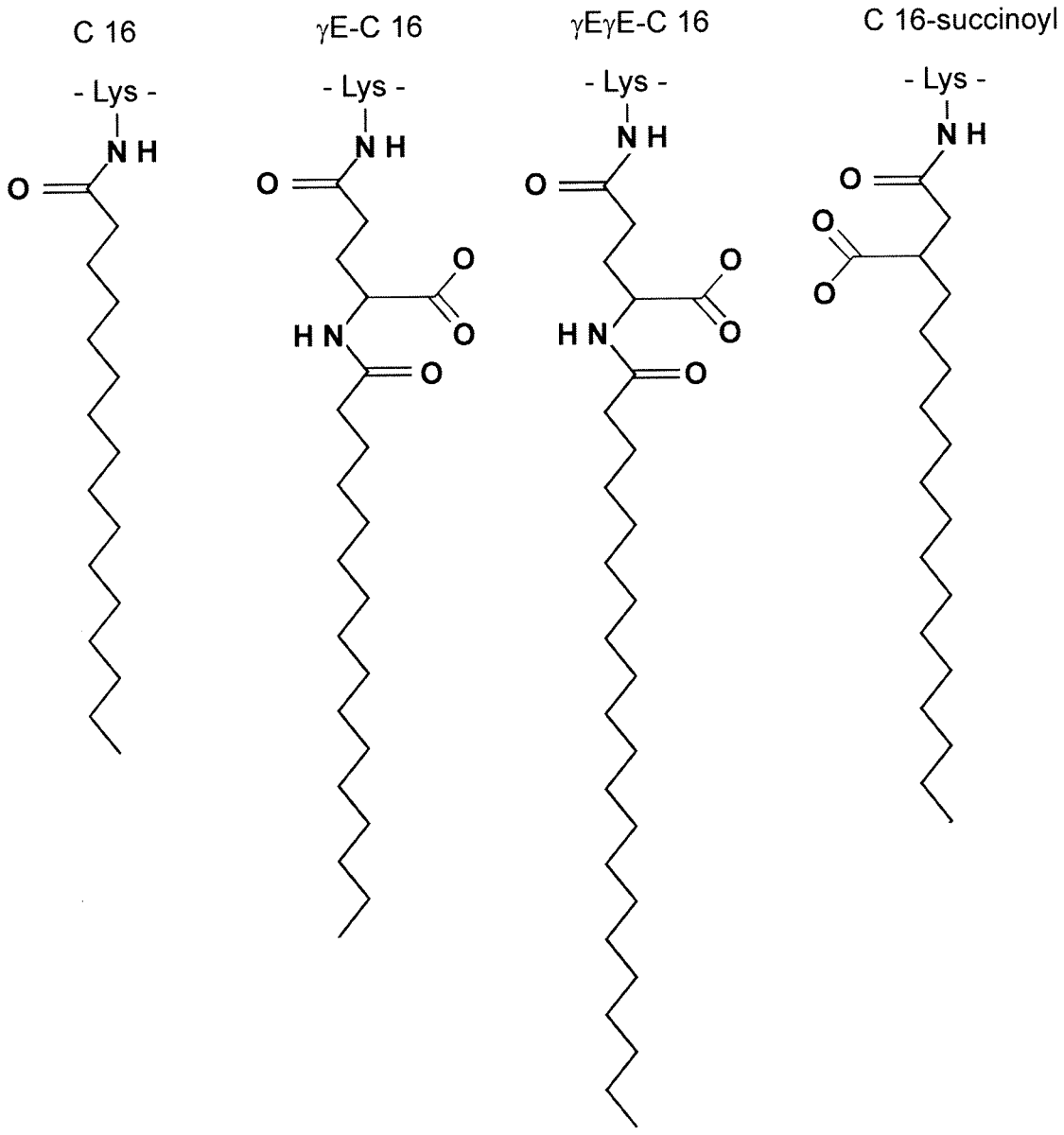
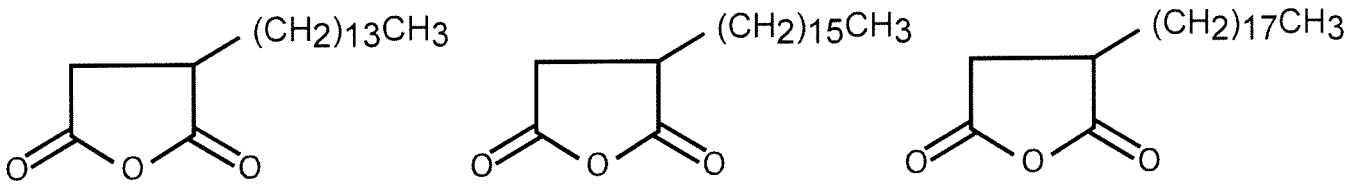

C 16
- Lys -
NH
O
γE-C 16
- Lys -
NH
O
O
O
HN
O
γEγE-C 16
- Lys -
NH
O
O
O
HN
O
C 16-succinoyl
- Lys -
NH
O
O
O

FIGURE 3A



tetradecyl hexadecyl octadecyl

FIGURE 3B

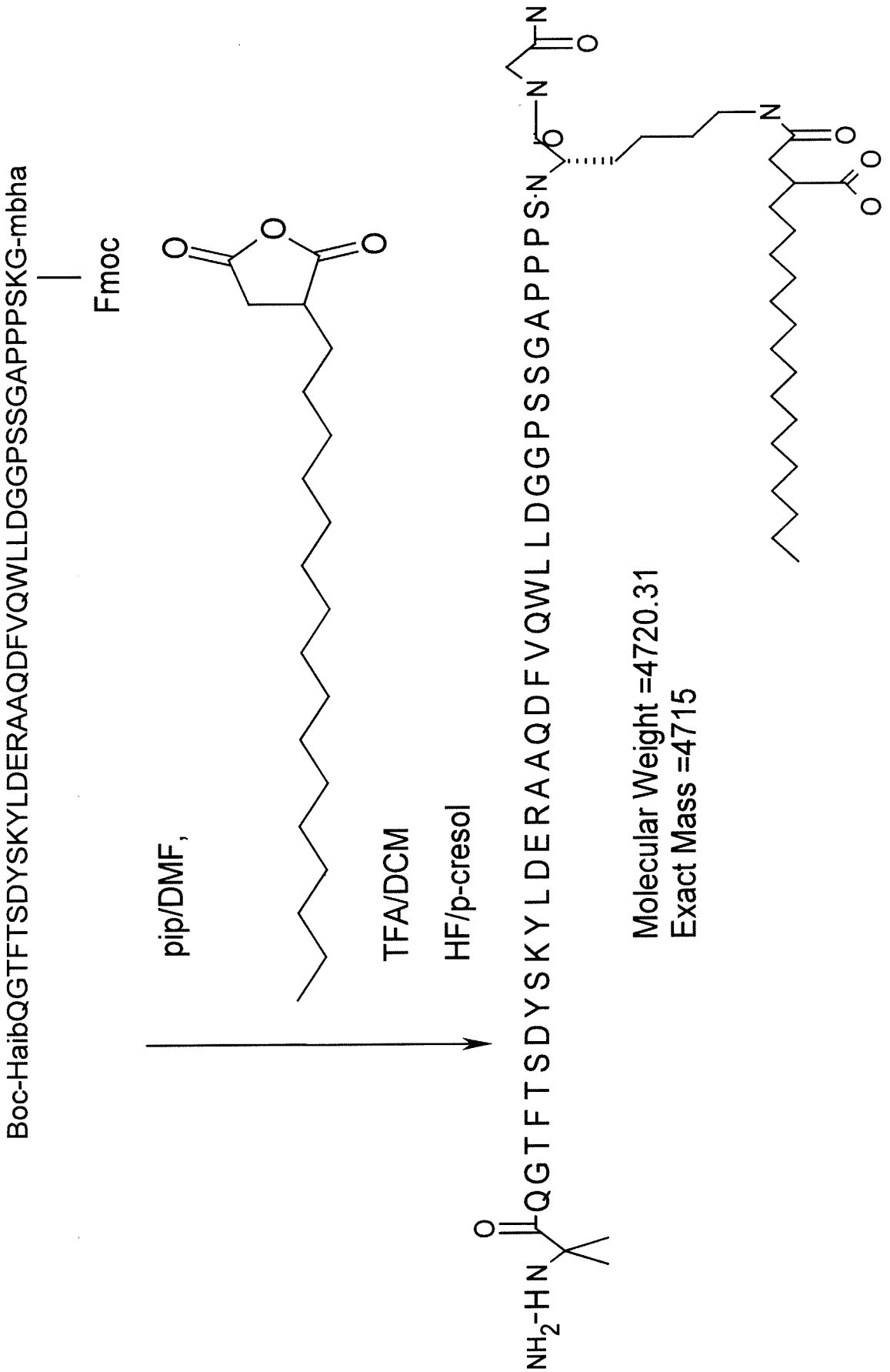

Boc-HaibQGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPSKG-mbha
Fmoc
pip/DMF,
TFA/DCM
HF/p-cresol
NH2-HN
QGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPS
Molecular Weight =4720.31
Exact Mass =4715

FIGURE 3C

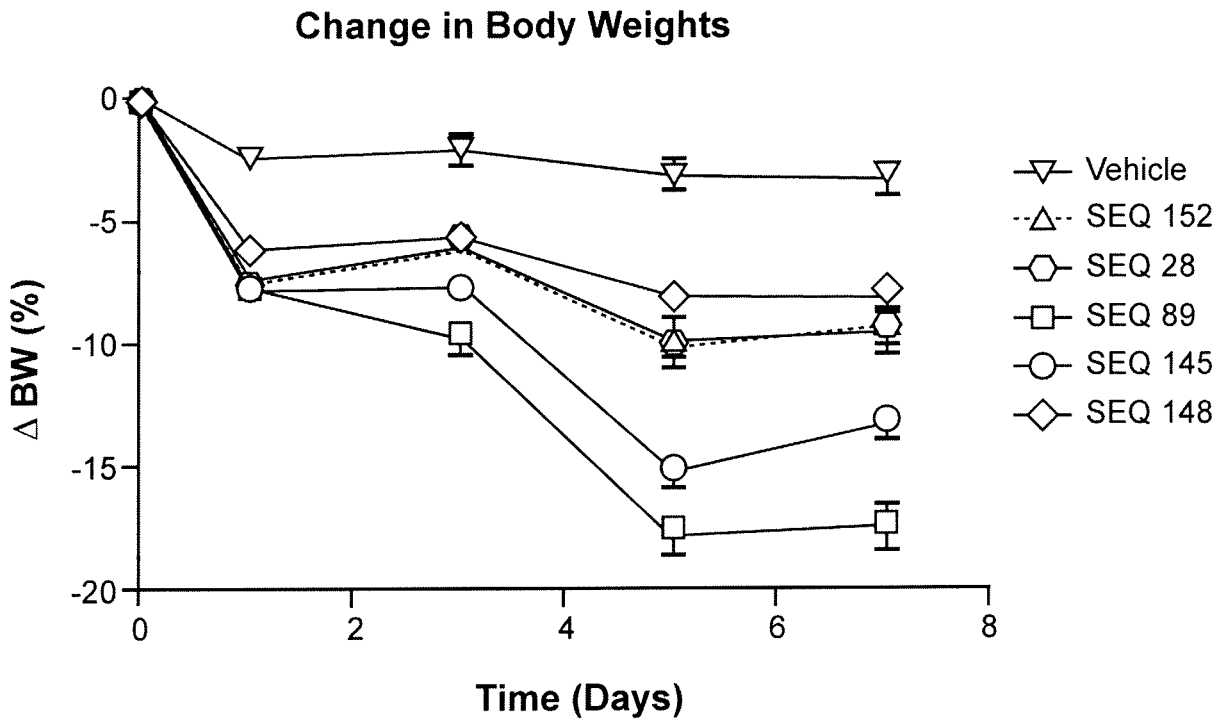

Change in Body Weights
0
-5
-10
-15
-20
Δ BW (%)
0
2
4
6
8
Time (Days)
Vehicle
SEQ 152
SEQ 28
SEQ 89
SEQ 145
SEQ 148

FIGURE 4

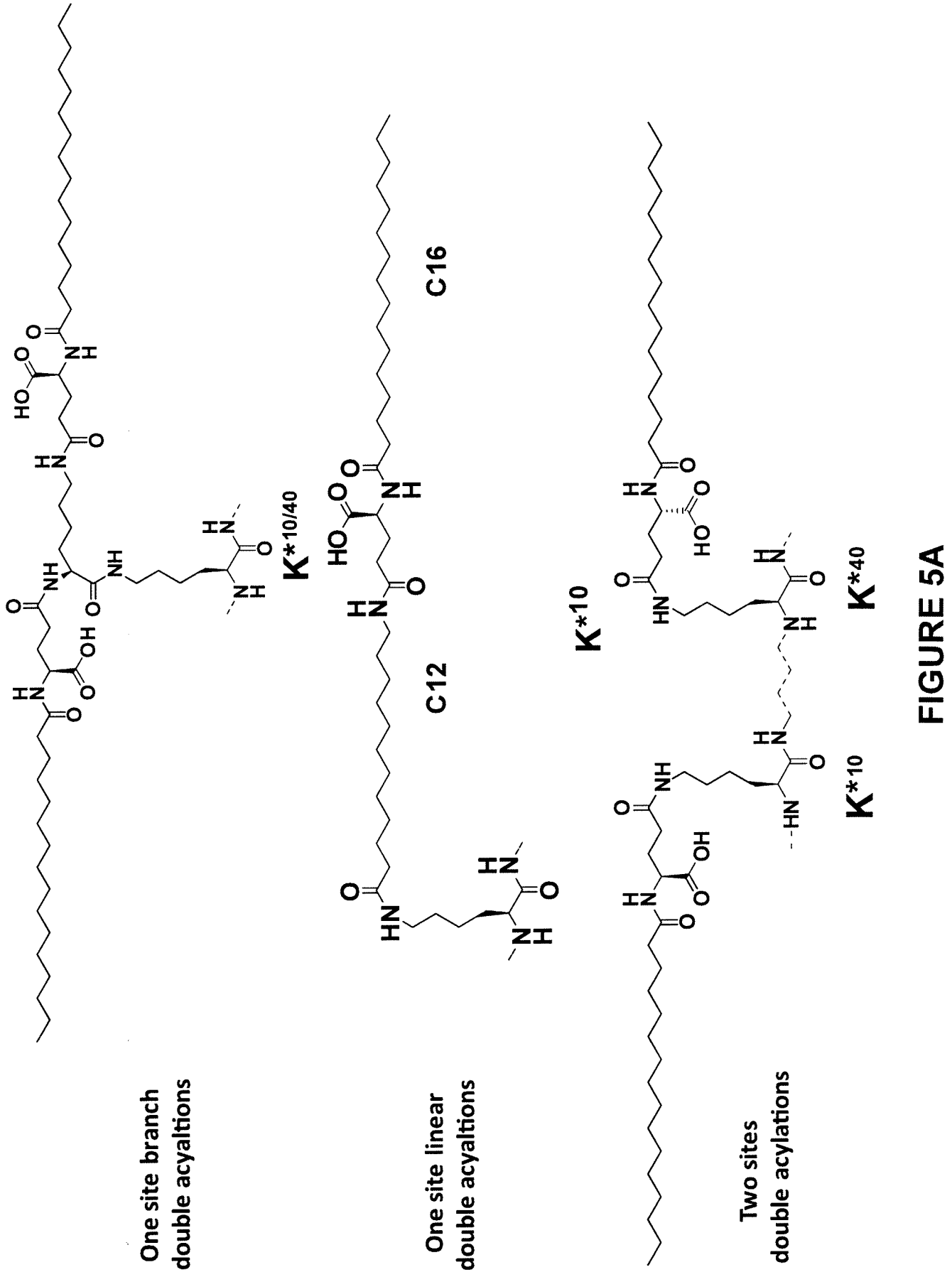

One site branch double acyaltions
K*10/40
One site linear double acyaltions
C16
C12
Two sites double acylations
K*10
K*40
K*10

FIGURE 5A

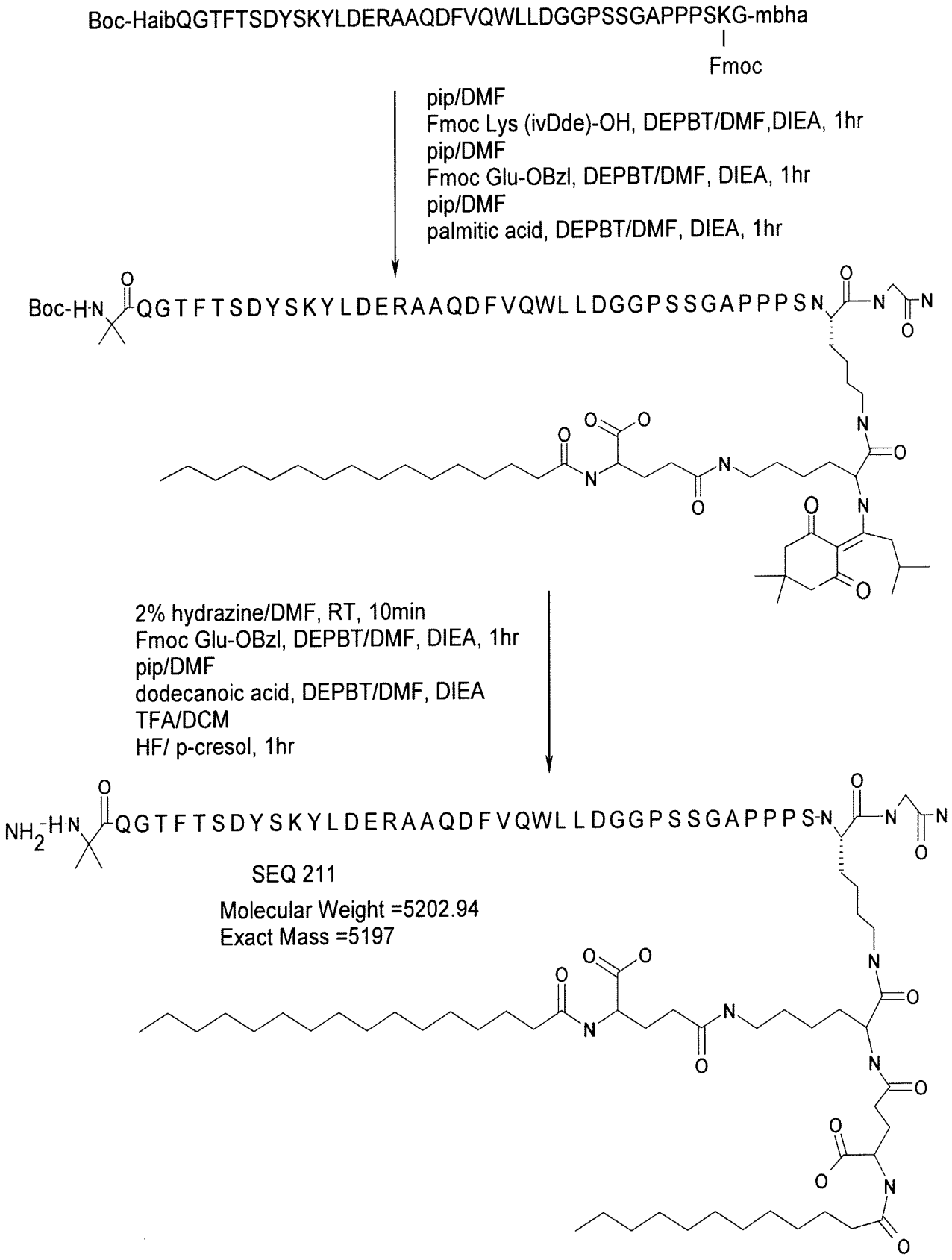

Boc-HaibQGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPSKG-mbha
Fmoc
pip/DMF
Fmoc Lys (ivDde)-OH, DEPBT/DMF,DIEA, 1hr
pip/DMF
Fmoc Glu-OBzl, DEPBT/DMF, DIEA, 1hr
pip/DMF
palmitic acid, DEPBT/DMF, DIEA, 1hr
2% hydrazine/DMF, RT, 10min
Fmoc Glu-OBzl, DEPBT/DMF, DIEA, 1hr
pip/DMF
dodecanoic acid, DEPBT/DMF, DIEA
TFA/DCM
HF/ p-cresol, 1hr
SEQ 211
Molecular Weight =5202.94
Exact Mass =5197

FIGURE 5B

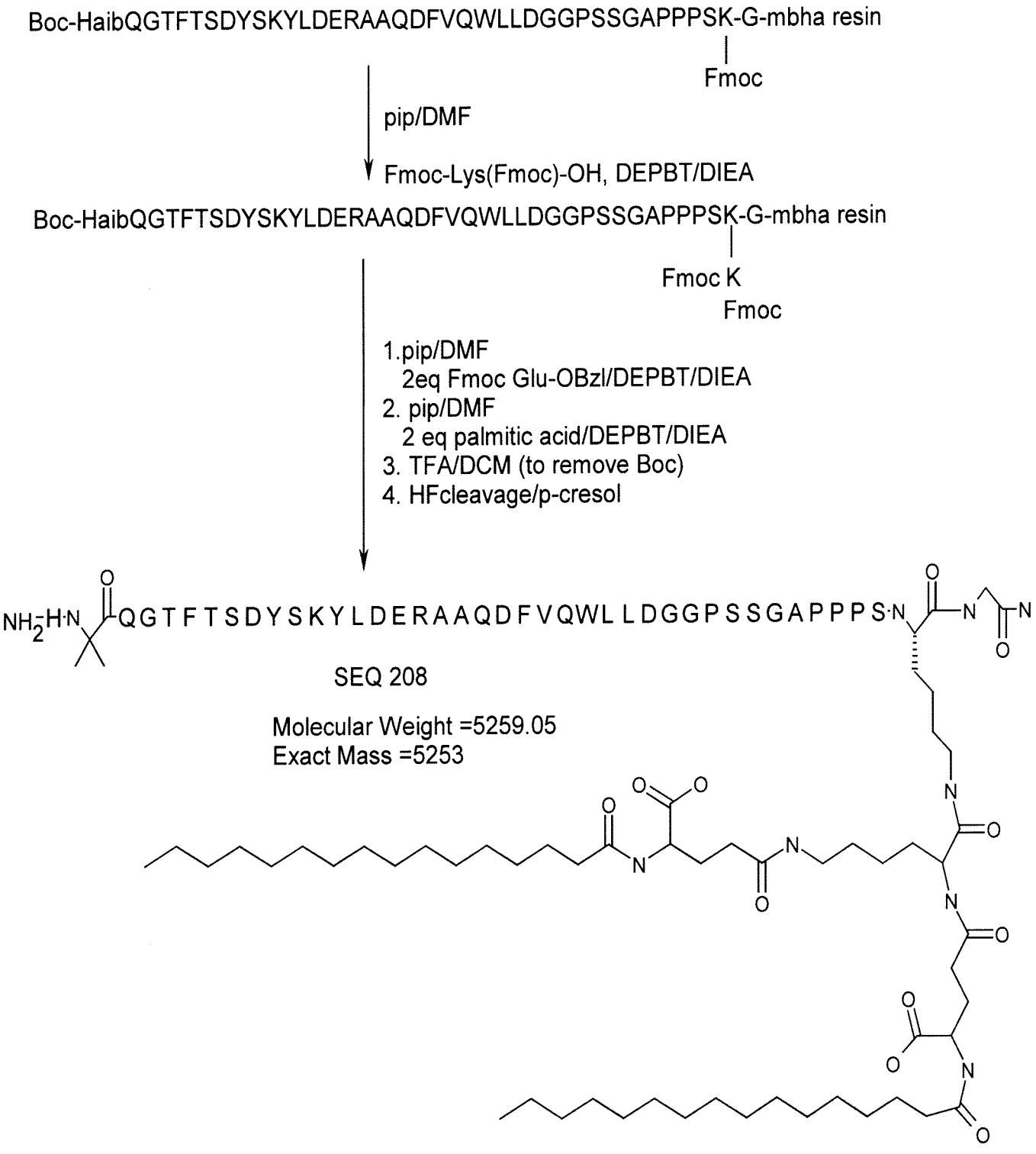

Boc-HaibQGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPSK-G-mbha resin
Fmoc
pip/DMF
Fmoc-Lys(Fmoc)-OH, DEPBT/DIEA
Boc-HaibQGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPSK-G-mbha resin
Fmoc K
Fmoc
1.pip/DMF
2eq Fmoc Glu-OBzl/DEPBT/DIEA
2. pip/DMF
2 eq palmitic acid/DEPBT/DIEA
3. TFA/DCM (to remove Boc)
4. HFcleavage/p-cresol
NH2-H-N
QGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPS-N
SEQ 208
Molecular Weight =5259.05
Exact Mass =5253

FIGURE 5C

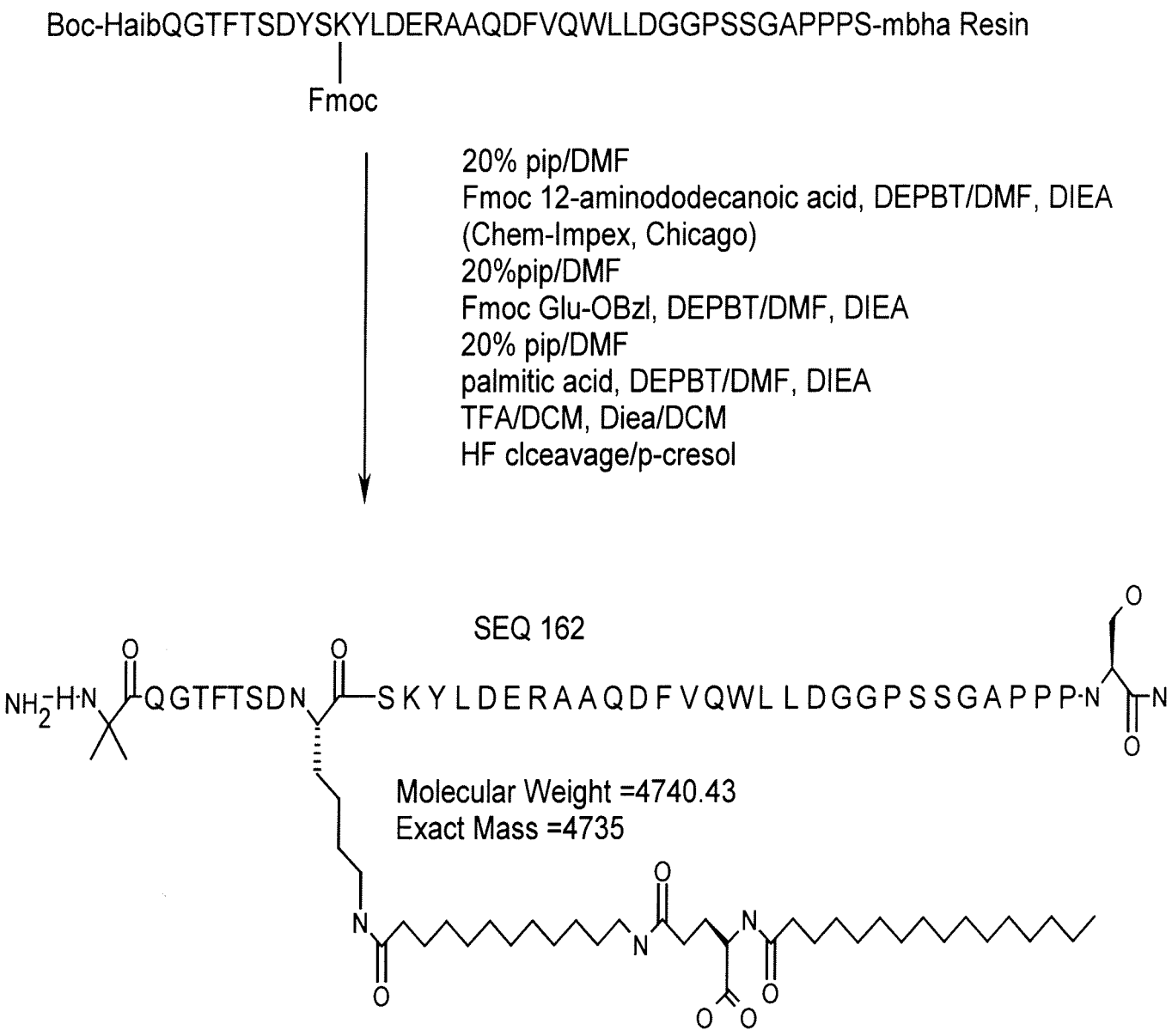

Boc-HaibQGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPS-mbha Resin
Fmoc
20% pip/DMF
Fmoc 12-aminododecanoic acid, DEPBT/DMF, DIEA
(Chem-Impex, Chicago)
20%pip/DMF
Fmoc Glu-OBzl, DEPBT/DMF, DIEA
20% pip/DMF
palmitic acid, DEPBT/DMF, DIEA
TFA/DCM, Diea/DCM
HF clceavage/p-cresol
SEQ 162
NH2-H·N
QGTFTSDN
SKYLDERAAQDFVQWLLDGGPSSGAPPP·N
N
Molecular Weight =4740.43
Exact Mass =4735

FIGURE 5D

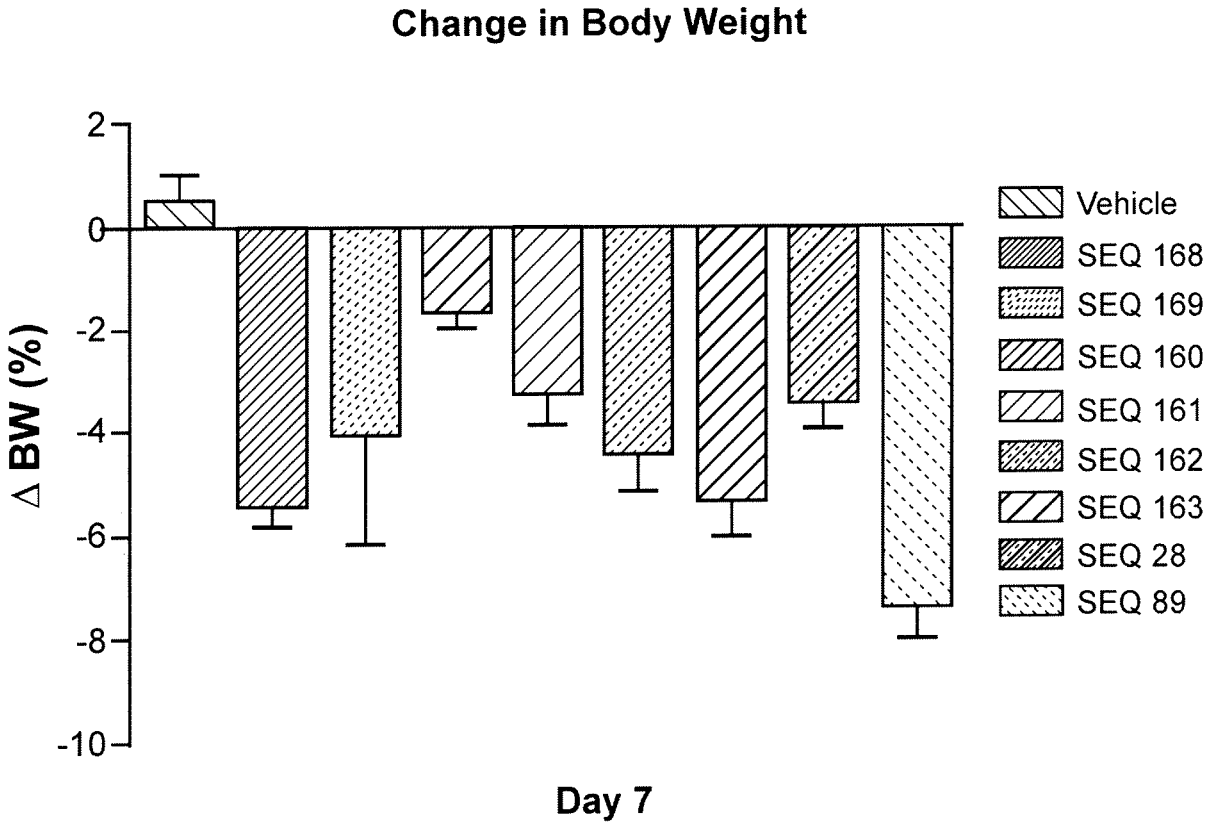

Change in Body Weight
2
0
-2
-4
-6
-8
-10
Δ BW (%)
Vehicle
SEQ 168
SEQ 169
SEQ 160
SEQ 161
SEQ 162
SEQ 163
SEQ 28
SEQ 89
Day 7

FIGURE 5E

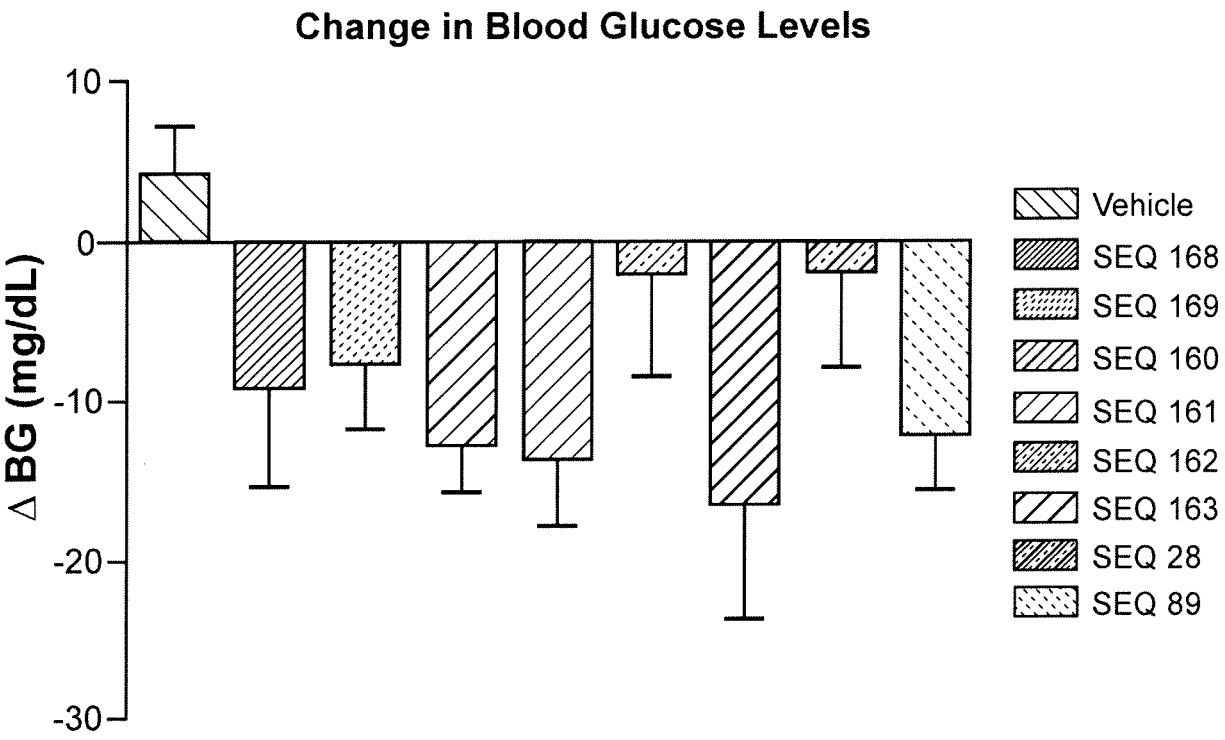

Change in Blood Glucose Levels
10
0
-10
-20
-30
Δ BG (mg/dL)
Vehicle
SEQ 168
SEQ 169
SEQ 160
SEQ 161
SEQ 162
SEQ 163
SEQ 28
SEQ 89
Day 7

FIGURE 5F

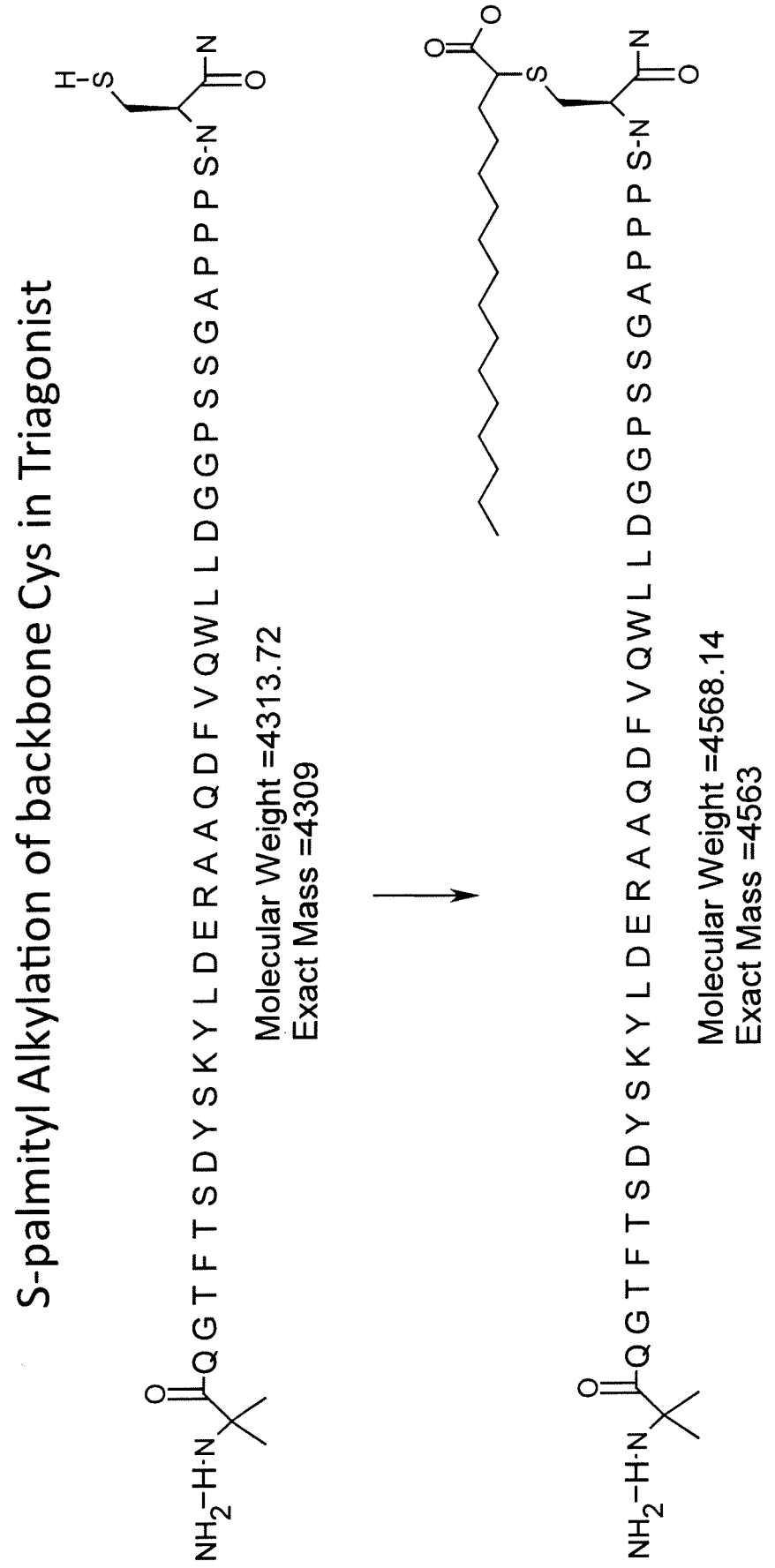

S-palmityl Alkylation of backbone Cys in Triagonist
Molecular Weight =4313.72
Exact Mass =4309
Molecular Weight =4568.14
Exact Mass =4563

FIGURE 6

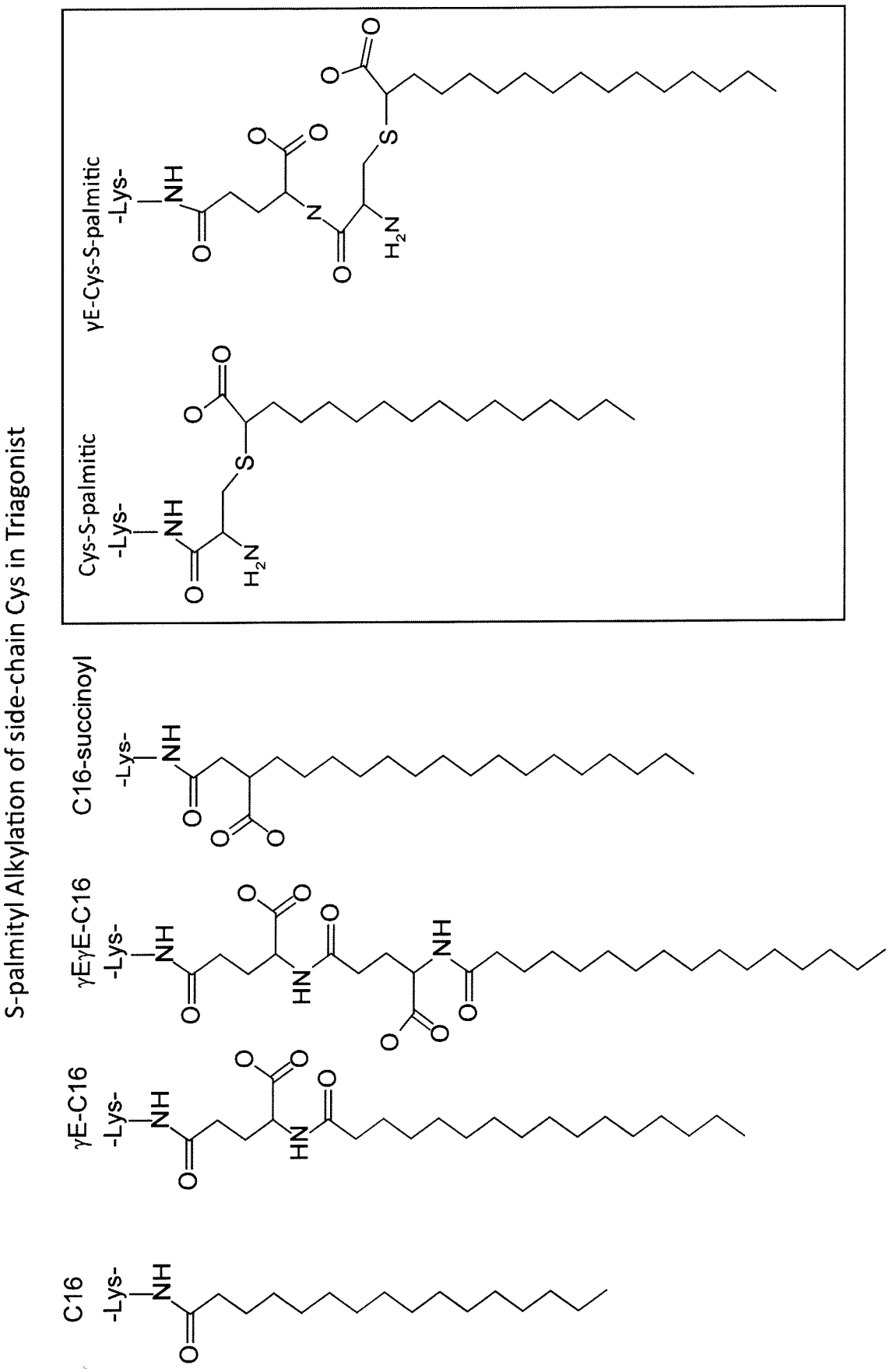

S-palmityl Alkylation of side-chain Cys in Triagonist
C16
-Lys-
γE-C16
-Lys-
γEγE-C16
-Lys-
C16-succinoyl
-Lys-
Cys-S-palmitic
-Lys-
γE-Cys-S-palmitic
-Lys-

FIGURE 7

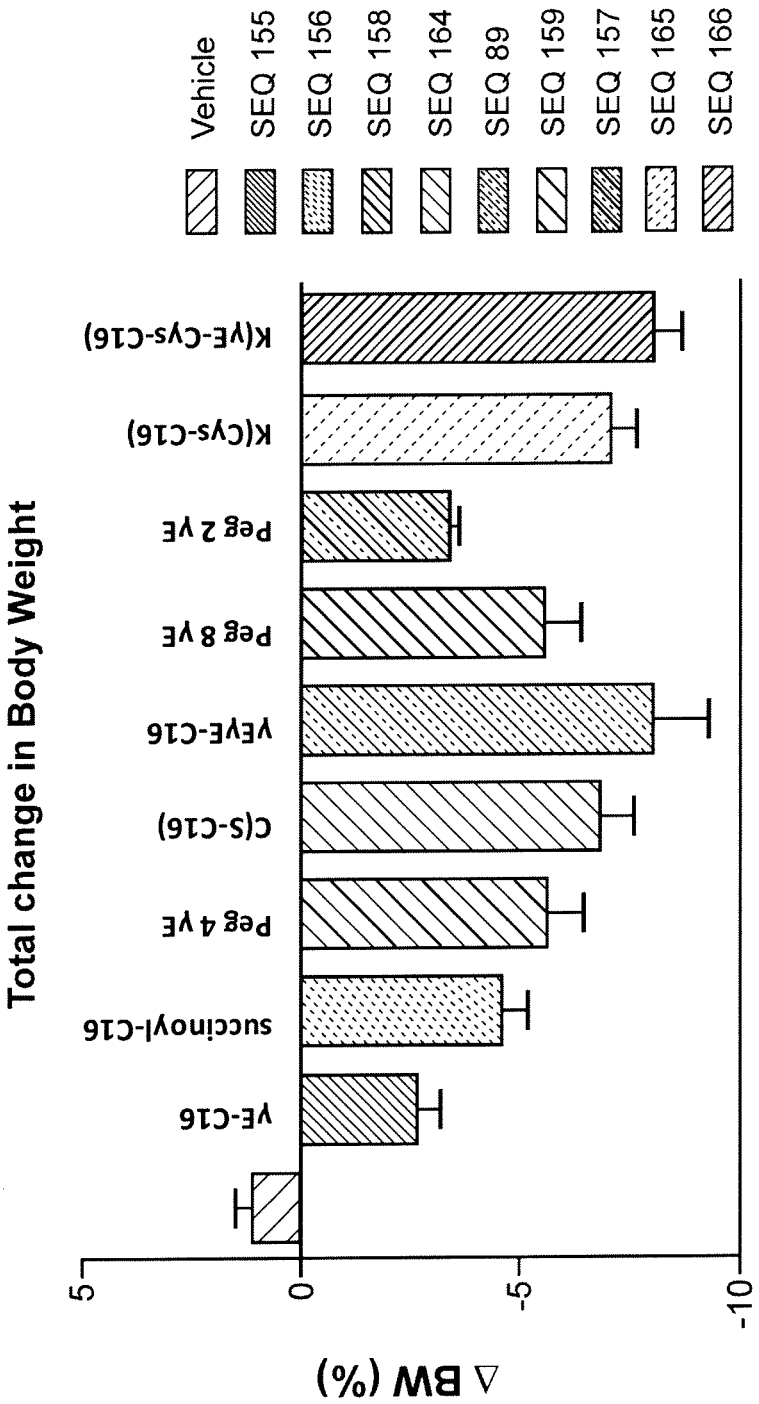

Vehicle
SEQ 155
SEQ 156
SEQ 158
SEQ 164
SEQ 89
SEQ 159
SEQ 157
SEQ 165
SEQ 166
Total change in Body Weight
K(yE-Cys-C16)
K(Cys-C16)
Peg 2 yE
Peg 8 yE
yEyE-C16
C(S-C16)
Peg 4 yE
succinoyl-C16
yE-C16
5
0
-5
-10
Δ BW (%)
Day 7

FIGURE 8

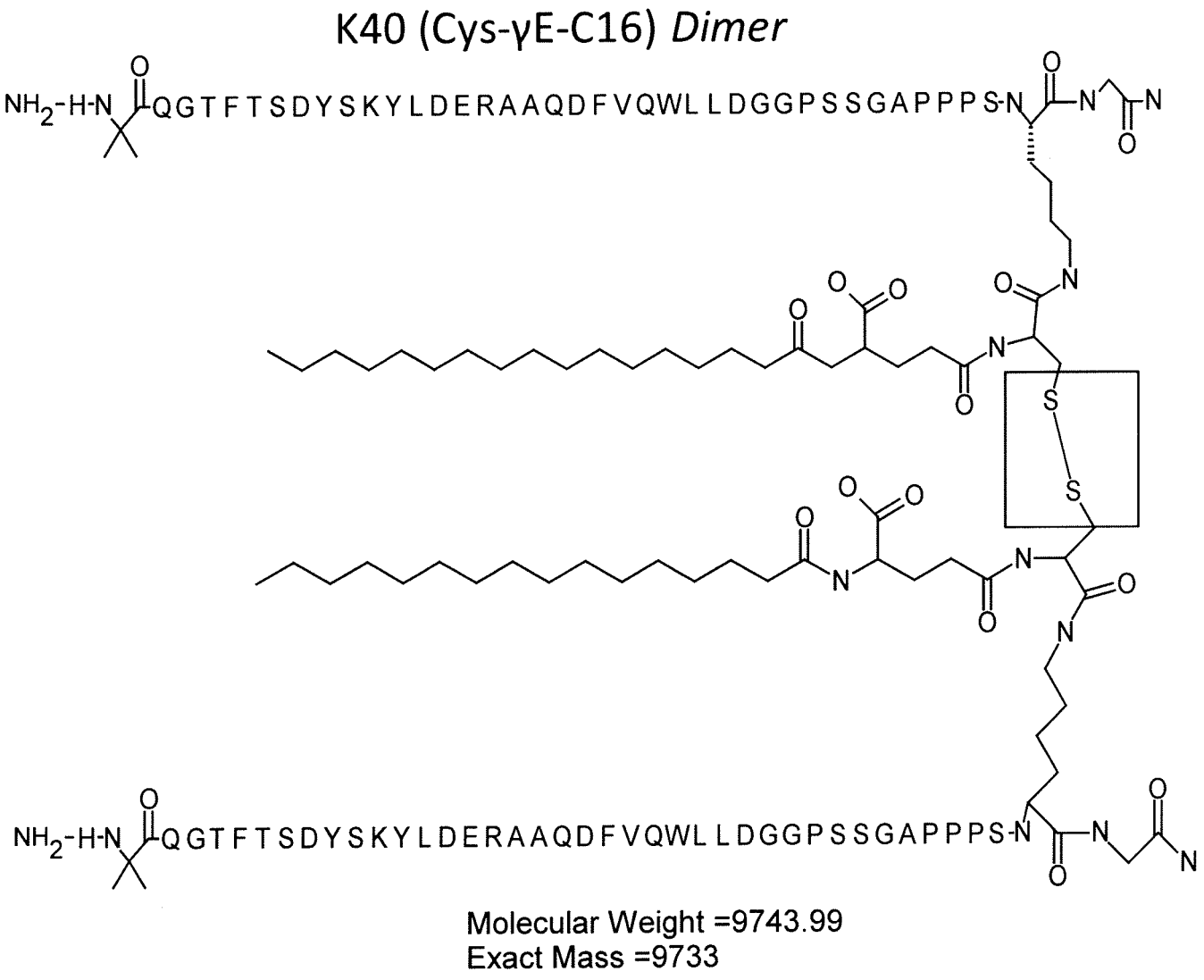

K40 (Cys-γE-C16) Dimer
NH2-H-N
QGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPS-N
Molecular Weight =9743.99
Exact Mass =9733

FIGURE 9A

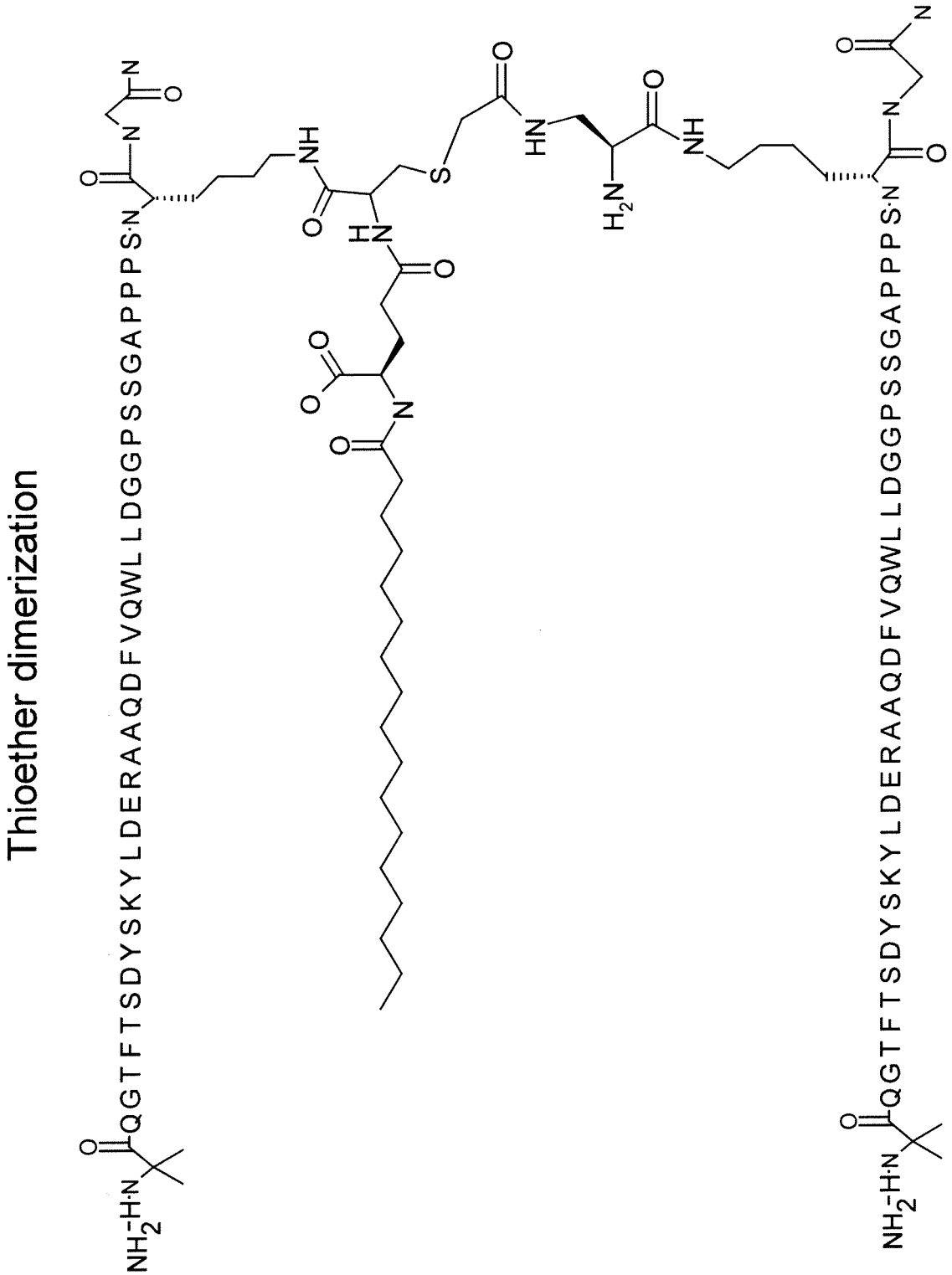

Thioether dimerization
QGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPS
NH2-H·N
QGTFTSDYSKYLDERAAQDFVQWLLDGGPSSGAPPPS
NH2-H·N

FIGURE 9B

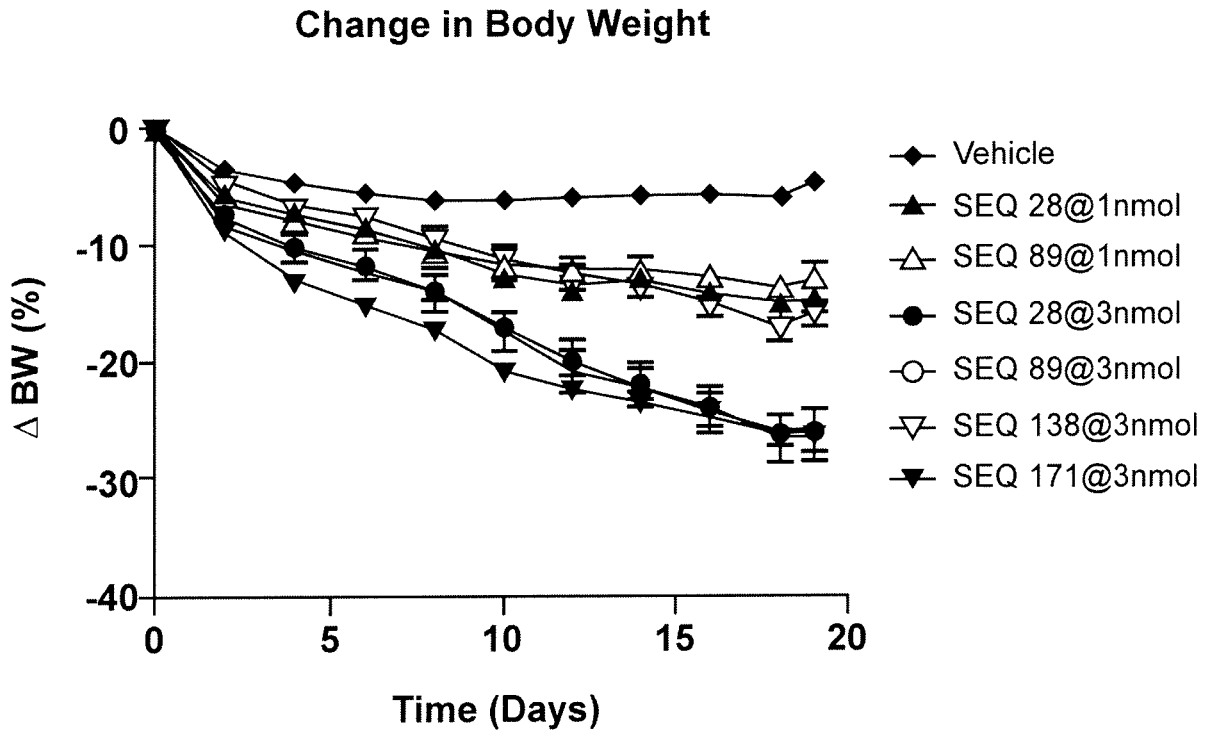

Change in Body Weight
0
-10
-20
-30
-40
Δ BW (%)
0
5
10
15
20
Time (Days)
Vehicle
SEQ 28@1nmol
SEQ 89@1nmol
SEQ 28@3nmol
SEQ 89@3nmol
SEQ 138@3nmol
SEQ 171@3nmol

FIGURE 10

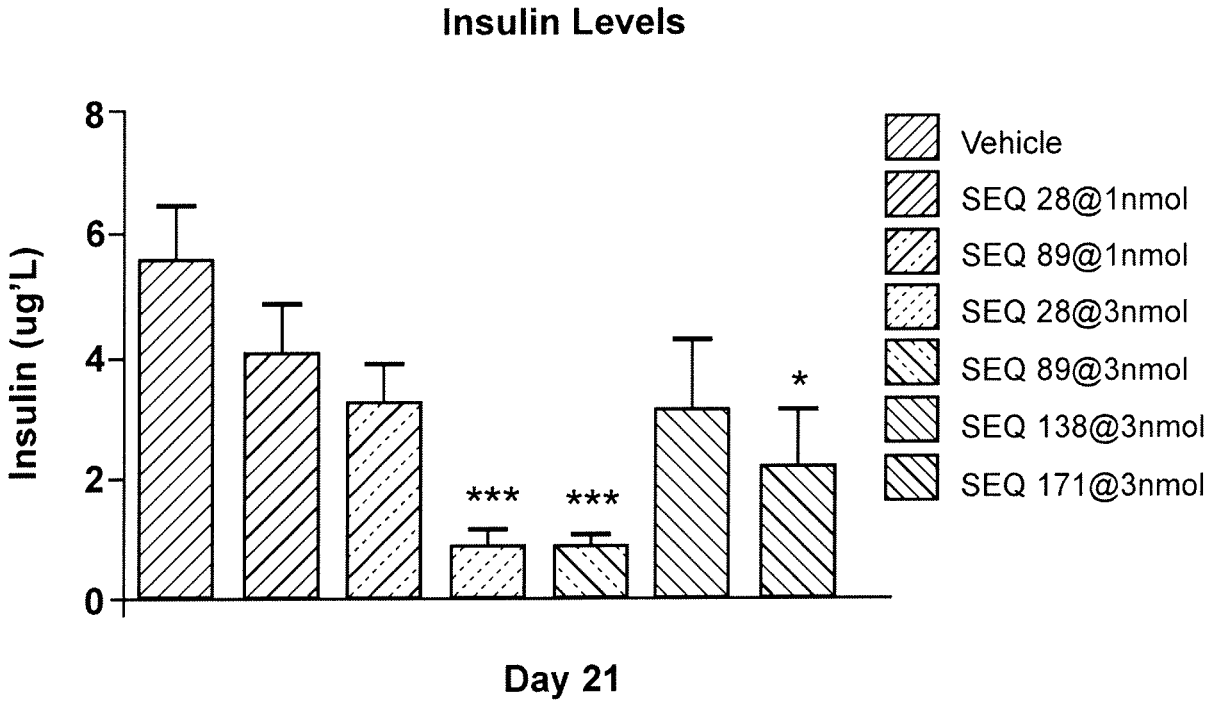

Insulin Levels
Insulin (ug'L)
8
6
4
2
0
***
***
*
Vehicle
SEQ 28@1nmol
SEQ 89@1nmol
SEQ 28@3nmol
SEQ 89@3nmol
SEQ 138@3nmol
SEQ 171@3nmol
Day 21

FIGURE 11

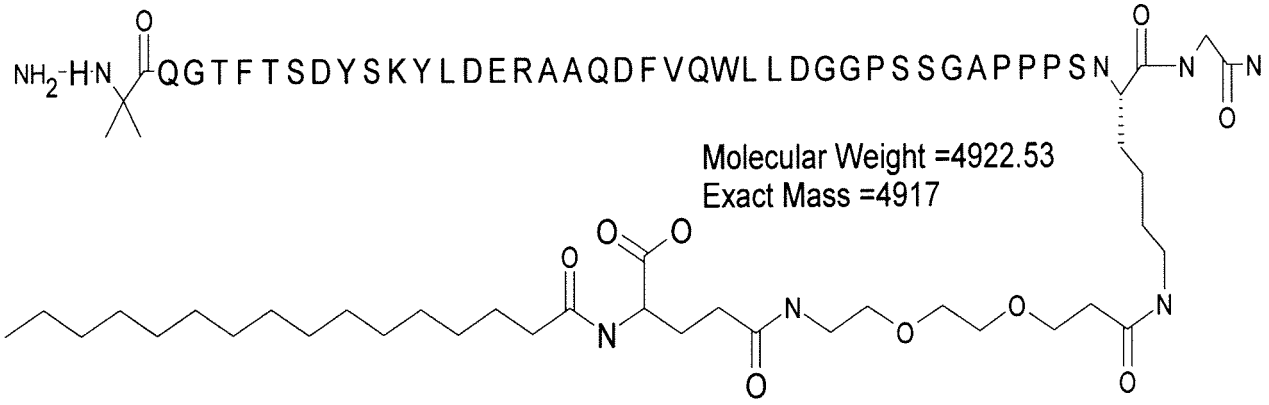


FIGURE 12A

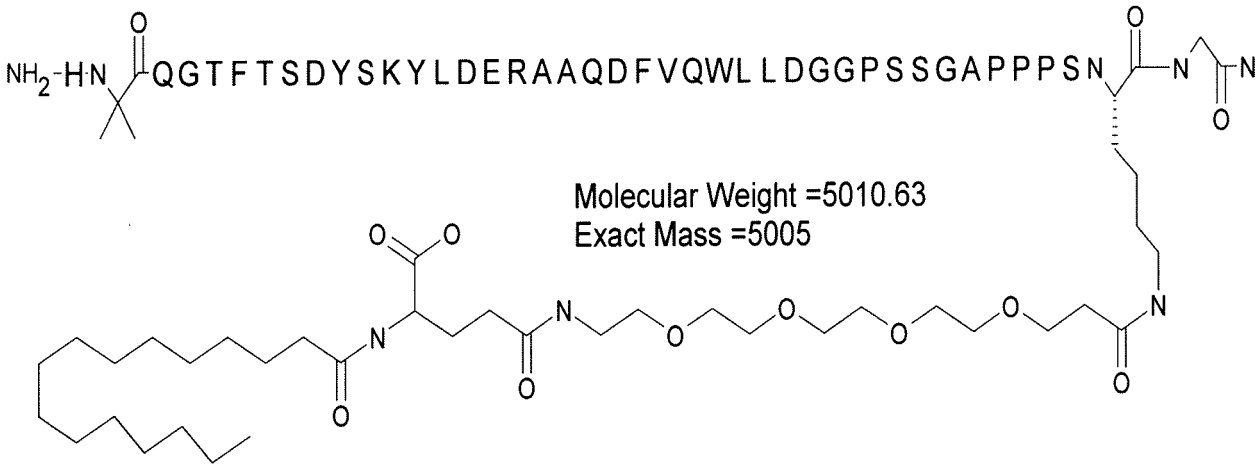


FIGURE 12B

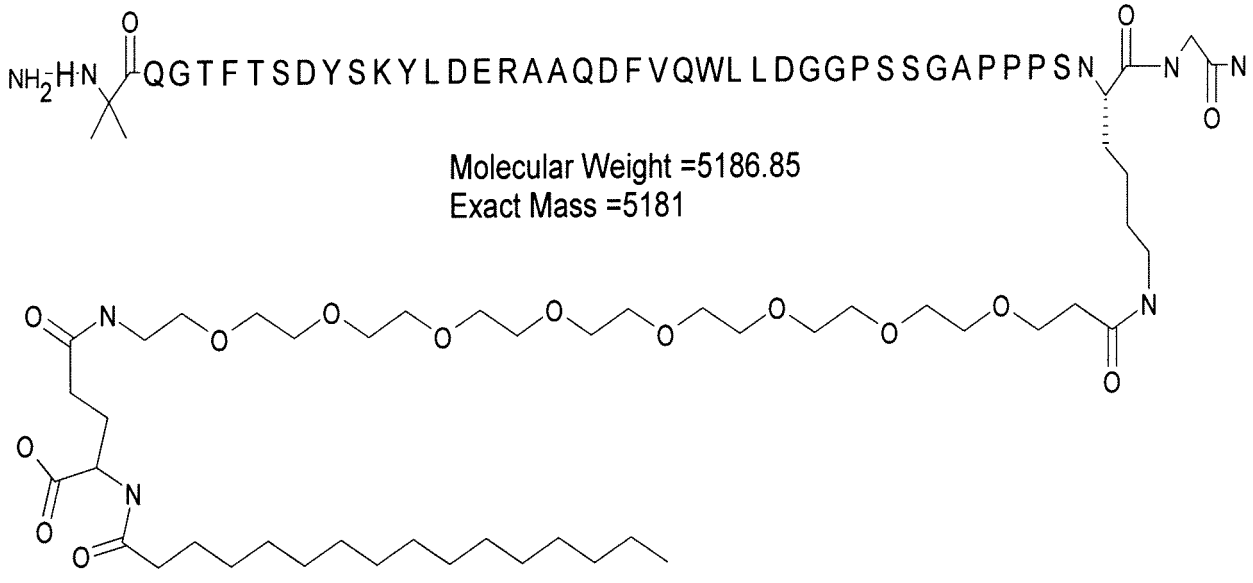


FIGURE 12C