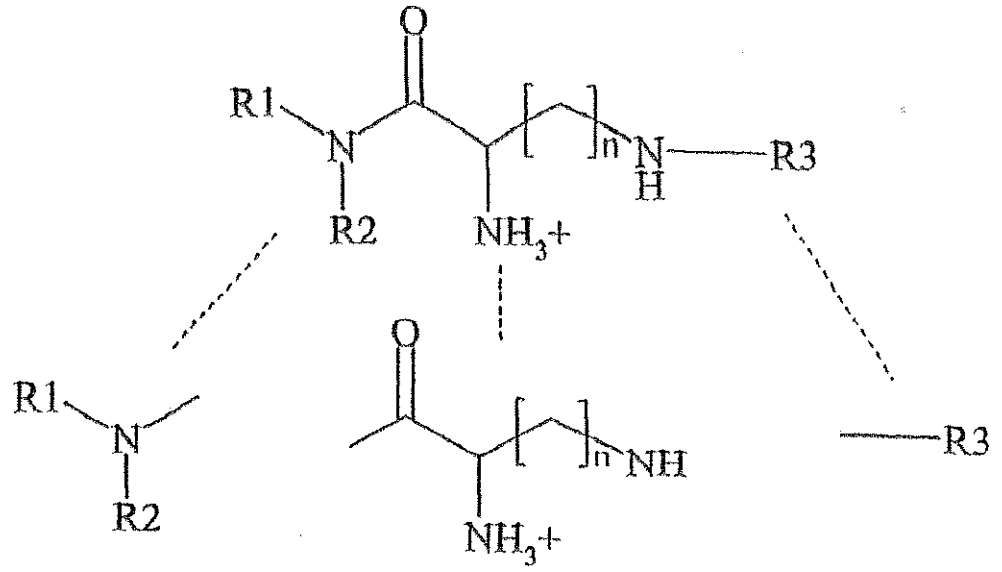
Figure 1

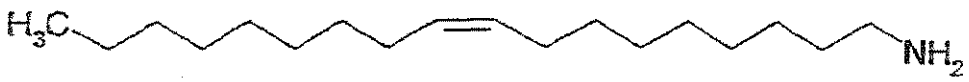
general structure of compounds according to the present invention:



lipophilic group linker group hydrophilic head group

Figure 2

starting material: oleyl amine
Fluka technical grade ≥ 70% (GC)
~30% amines with different alkyl chains



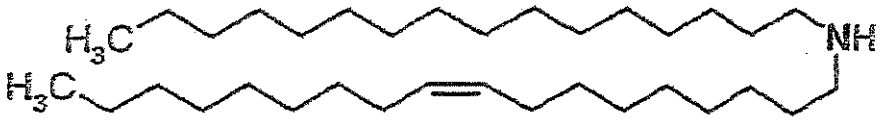
+



1-bromohexadecane (palmityl bromide)

30 min,
100-120°C
neat

(83%)



N-oleyl-palmityl amine

Figure 3

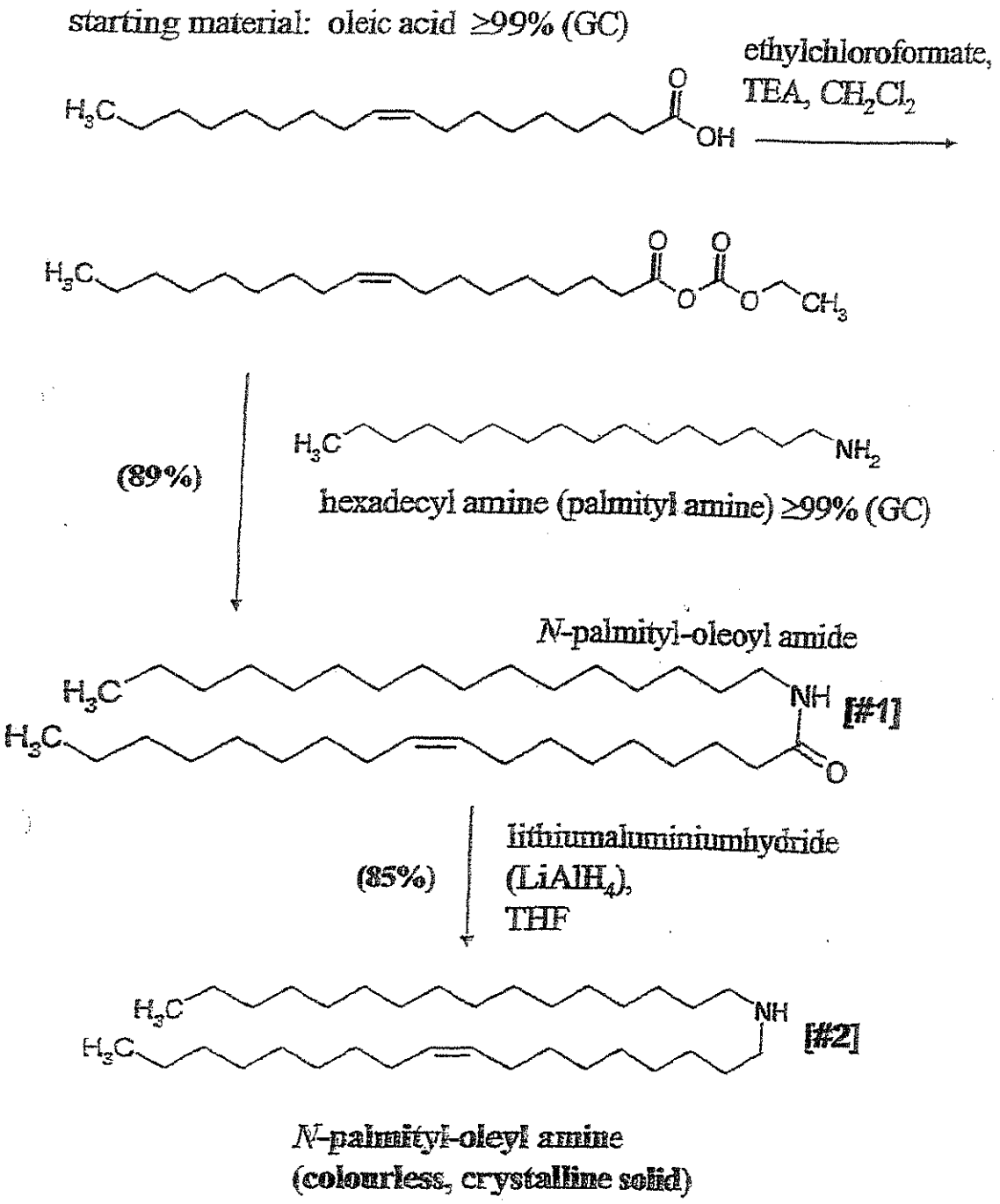

starting material: oleic acid ≥99% (GC)
ethylchloroformate,
TEA, CH_2Cl_2
(89%)
hexadecyl amine (palmityl amine) ≥99% (GC)
N-palmityl-oleoyl amide
[#1]
(85%)
lithiumaluminiumhydride
($LiAlH_4$),
THF
[#2]
N-palmityl-oleyl amine
(colourless, crystalline solid)

Figure 4

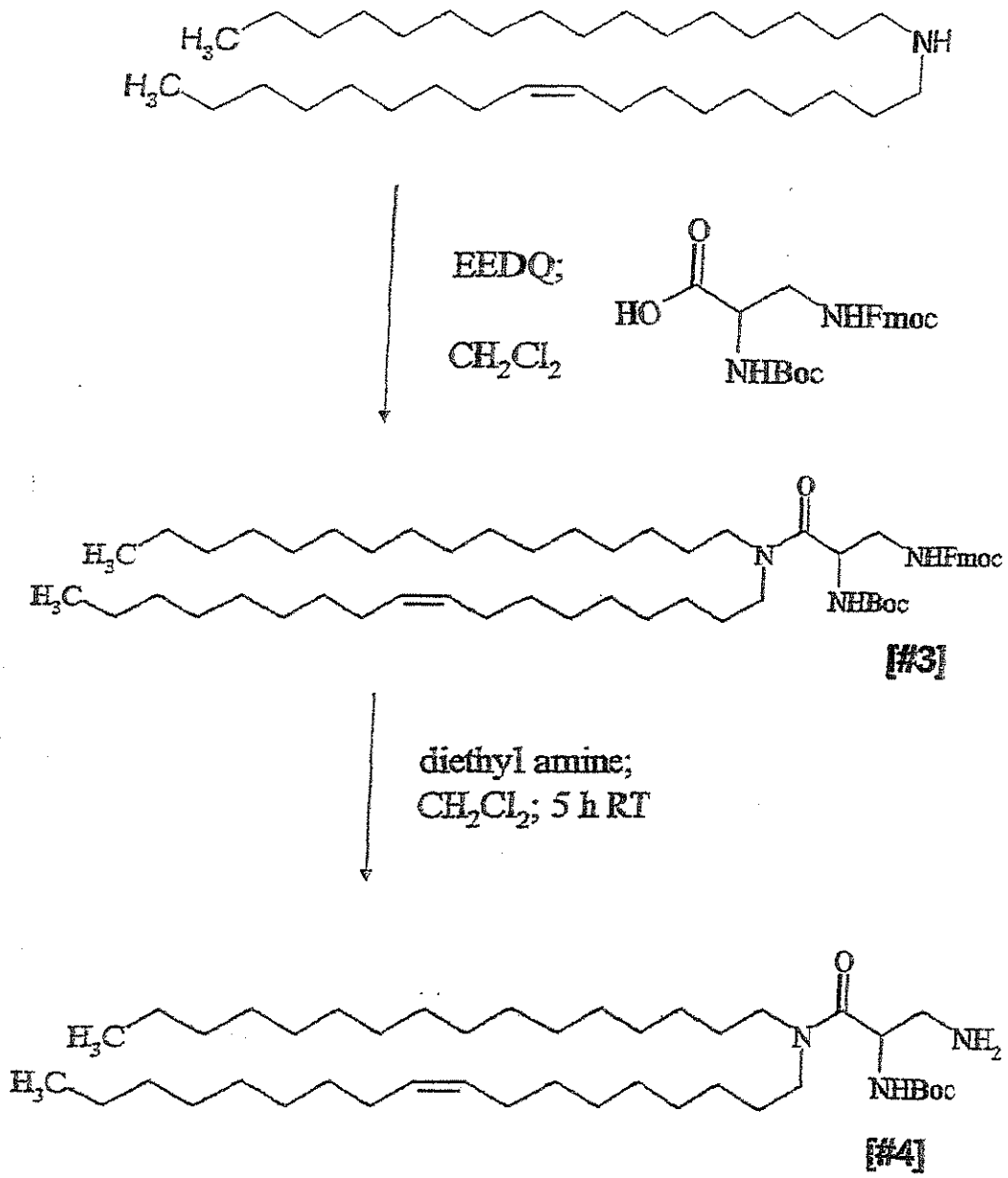
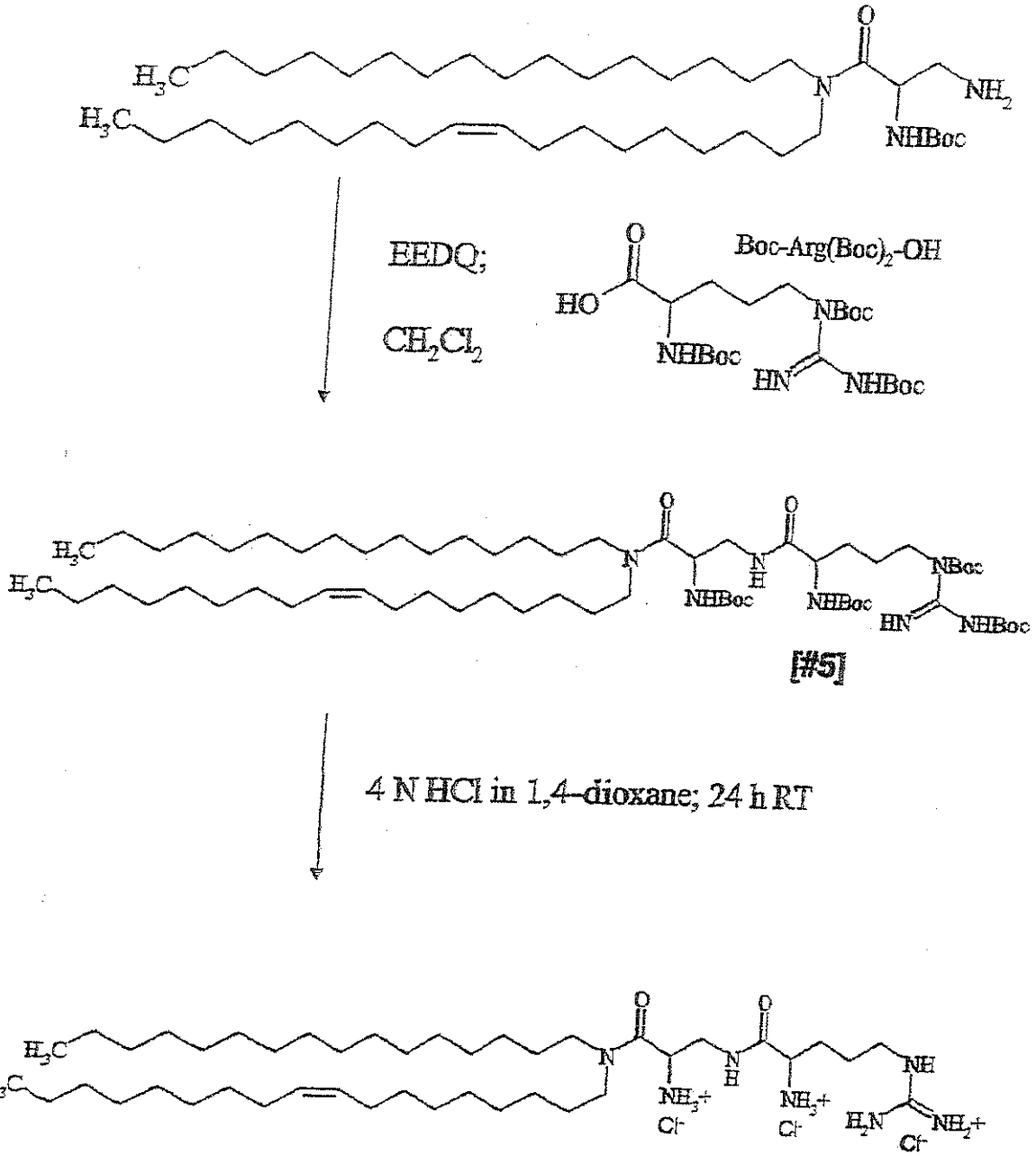

H3C
NH
H3C
EEDQ;
CH2Cl2
O
HO
NHFmoc
NHBoc
O
H3C
N
NHFmoc
H3C
NHBoc
[#3]
diethyl amine;
CH2Cl2; 5 h RT
O
H3C
N
NH2
H3C
NHBoc
[#4]

Figure 5



[#5]

ß-arginyl-2,3-diaminopropionic acid-*N*-palmityl-*N*-oleyl-amide tri-hydrochloride

[#6]

Figure 6

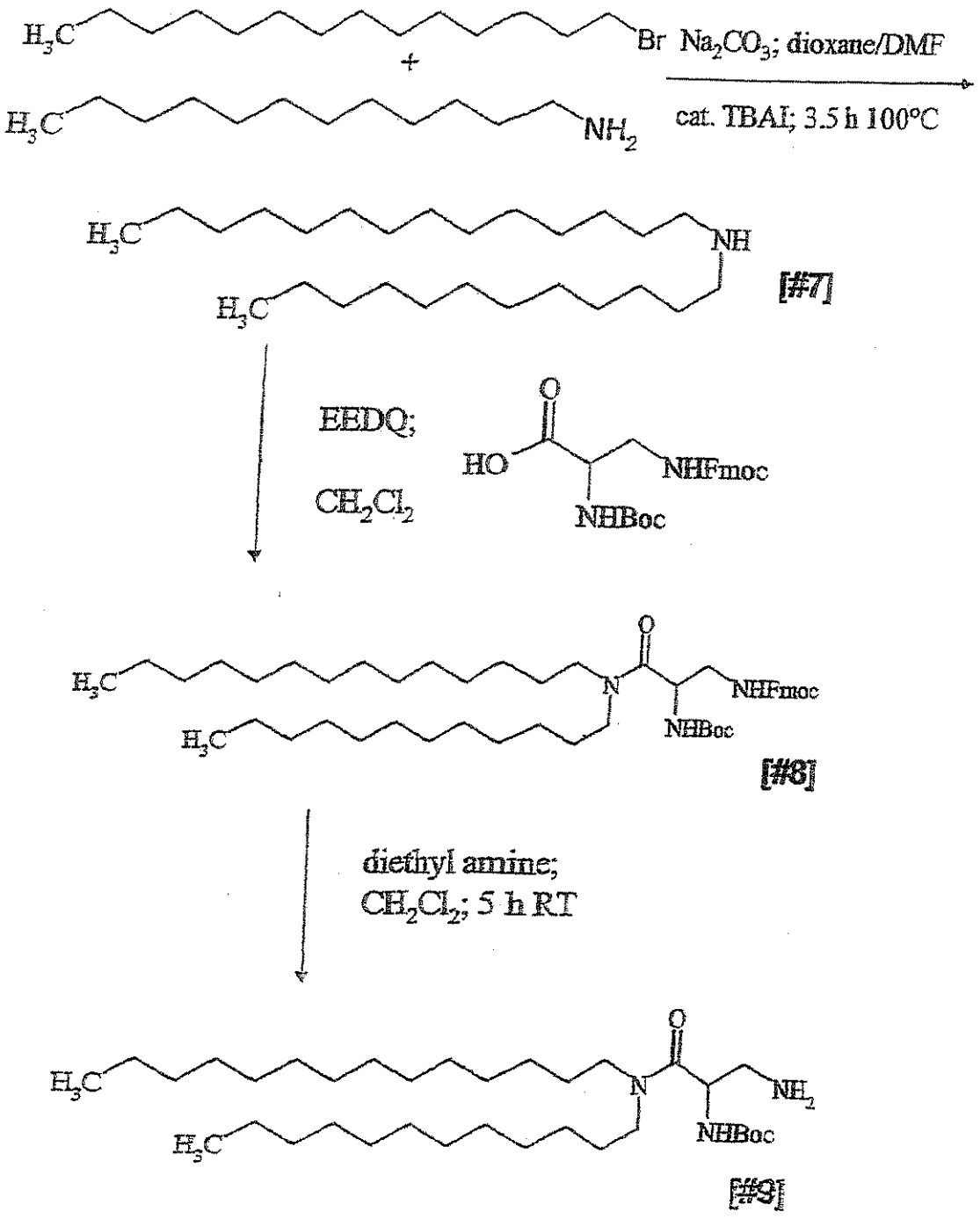
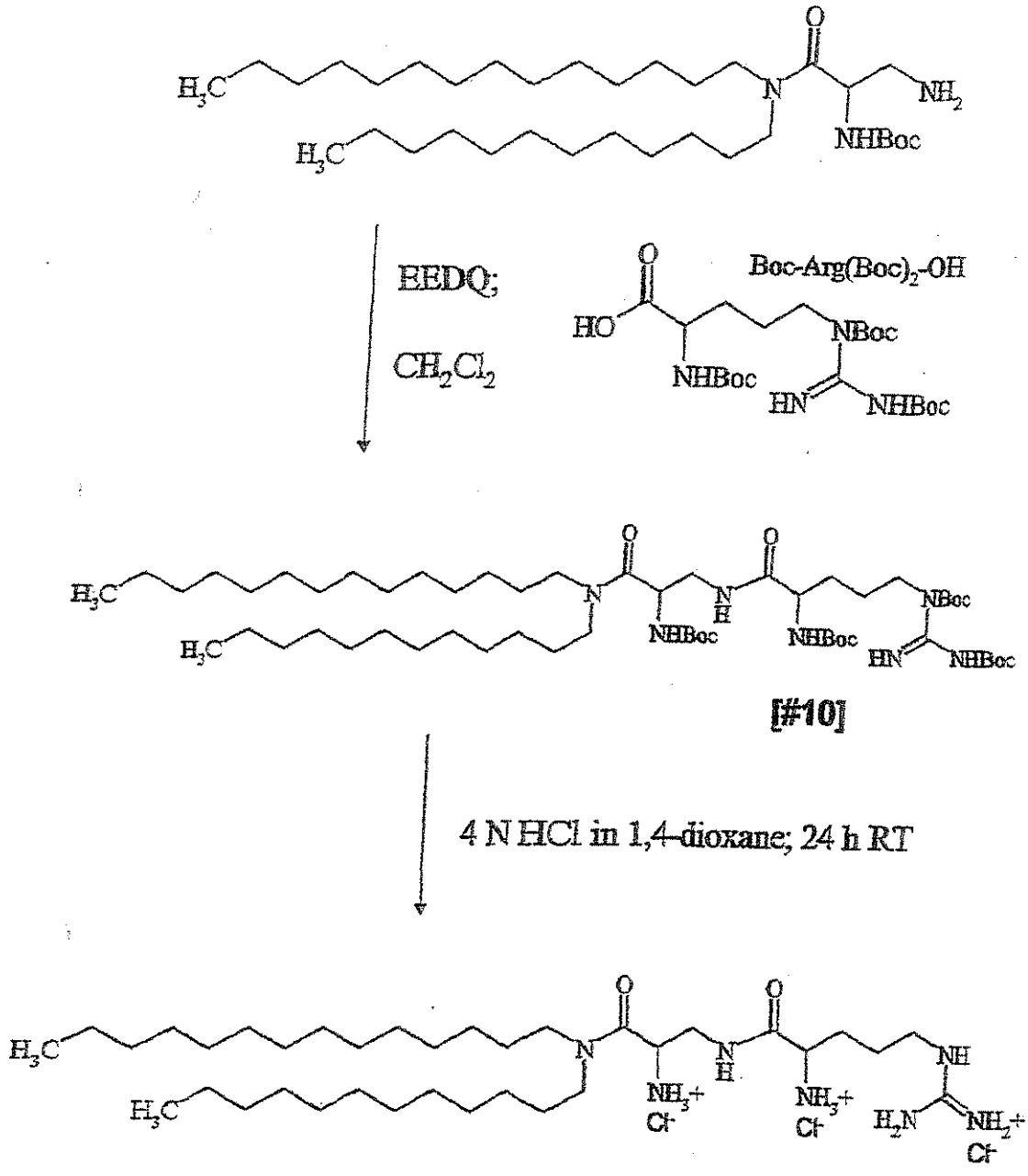

H3C
Br
+
H3C
NH2
Na2CO3; dioxane/DMF
cat. TBAI; 3.5 h 100°C
H3C
NH
H3C
[#7]
EEDQ;
CH2Cl2
HO
O
NHFmoc
NHBoc
H3C
N
O
NHFmoc
H3C
NHBoc
[#8]
diethyl amine;
CH2Cl2; 5 h RT
H3C
N
O
NH2
H3C
NHBoc
[#9]

Figure 7



[#10]

β-arginyl-2,3-diaminopropionic acid-*N*-lauryl-*N*-myristyl-amide tri-hydrochloride

[#11]

Figure 8

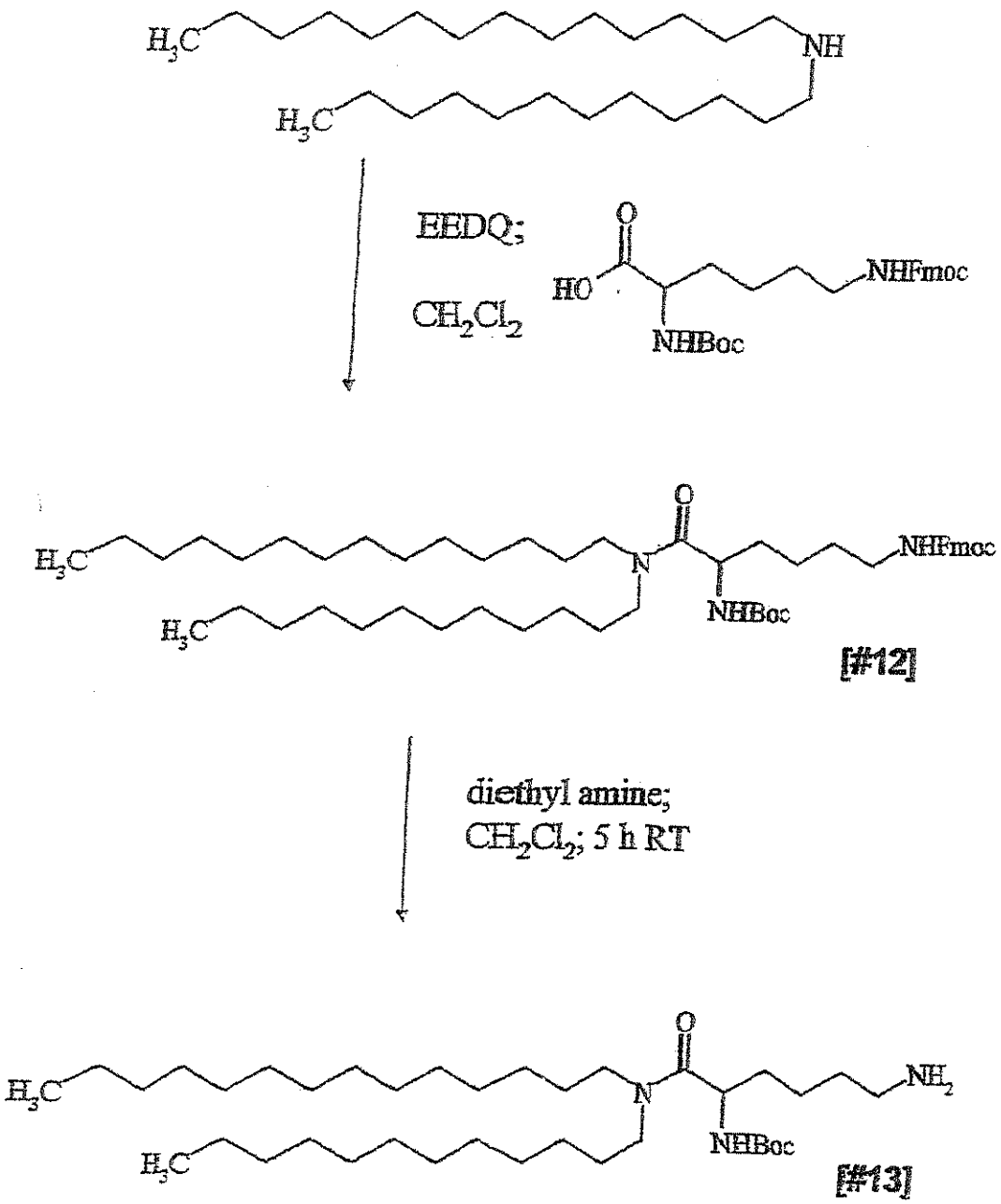
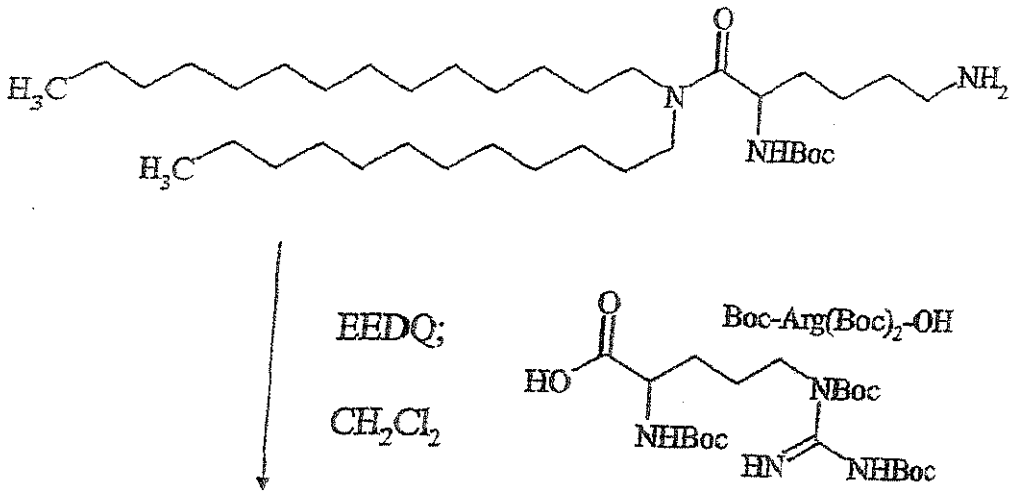
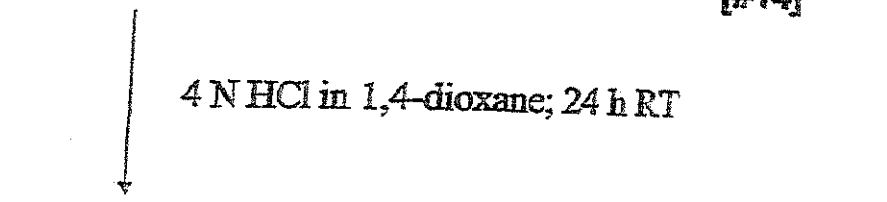

H3C
NH
H3C
EEDQ;
CH2Cl2
HO
O
NHFmoc
NHBoc
H3C
N
O
NHFmoc
NHBoc
H3C
[#12]
diethyl amine;
CH2Cl2; 5 h RT
H3C
N
O
NH2
NHBoc
H3C
[#13]

Figure 9

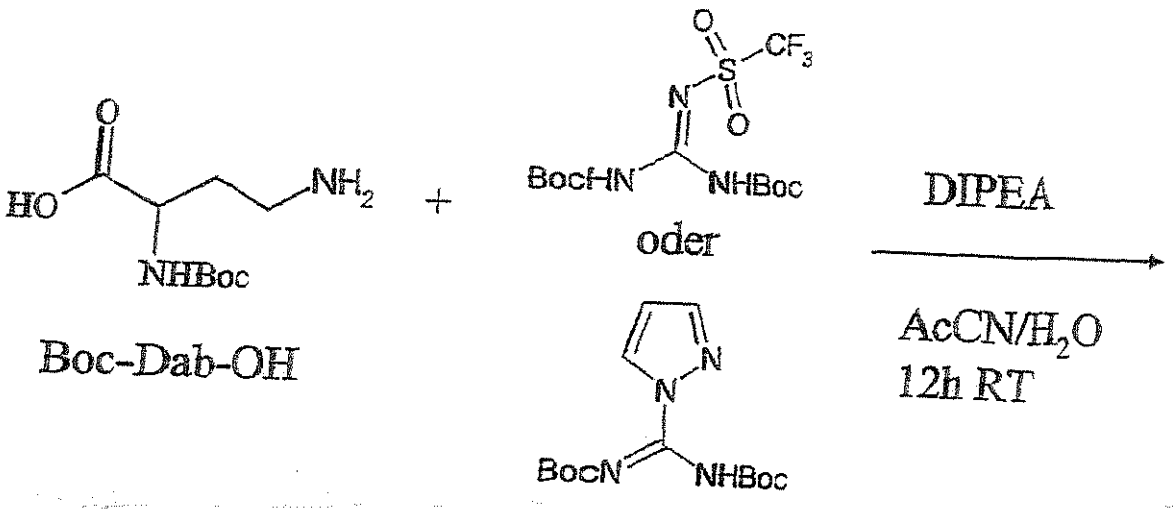


[#14]

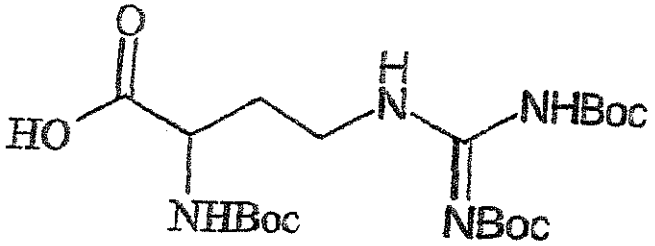


ε-arginyl-lysine-*N*-lauryl-*N*-myristyl-amide tri-hydrochloride [#15]

Figure 10



Boc-Dab-OH



[#16]

tri-Boc-γ-carbamidino-α,γ-diaminobutyric acid

Fig. 11- part 1

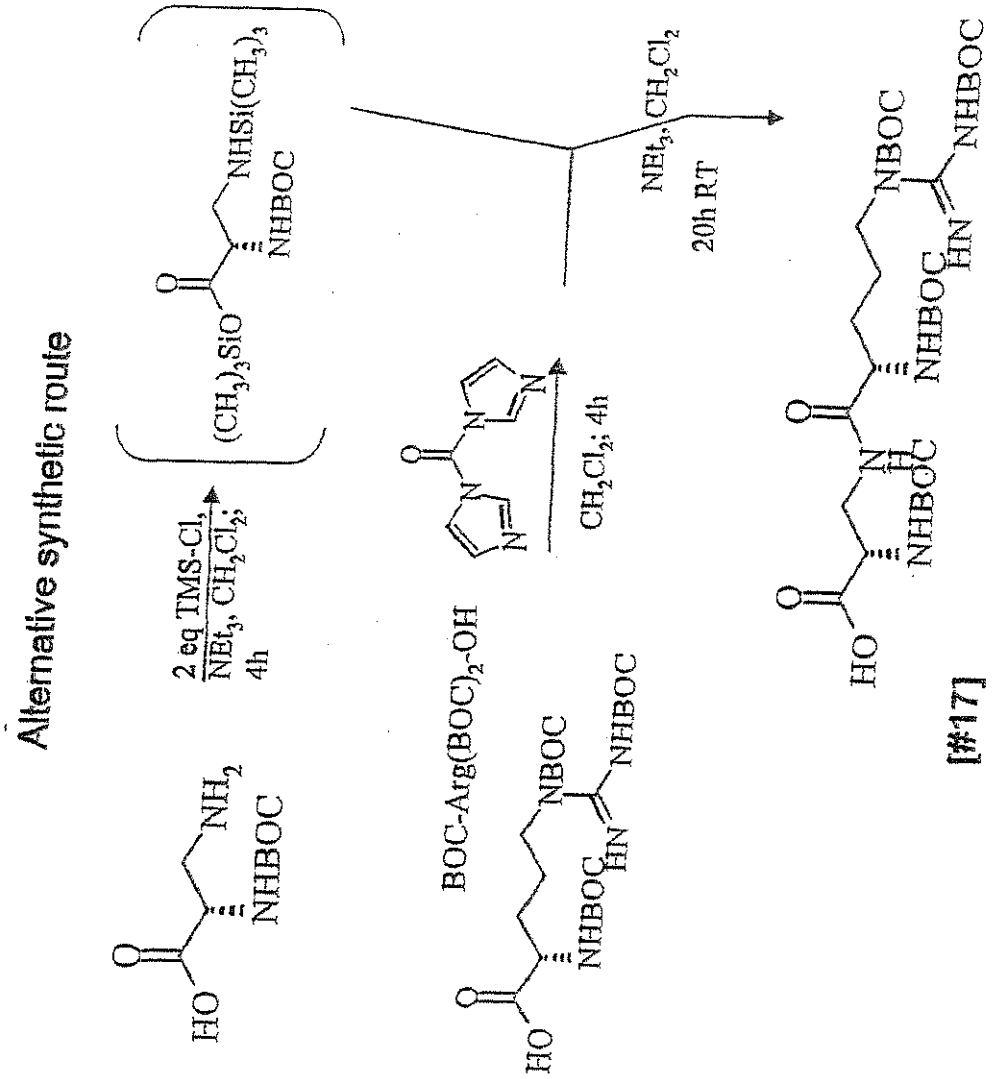

Alternative synthetic route
2 eq TMS-Cl, NEt3, CH2Cl2; 4h
CH2Cl2; 4h
NEt3, CH2Cl2
20h RT
BOC-Arg(BOC)2-OH
[#17]

Fig. 11 – part 2

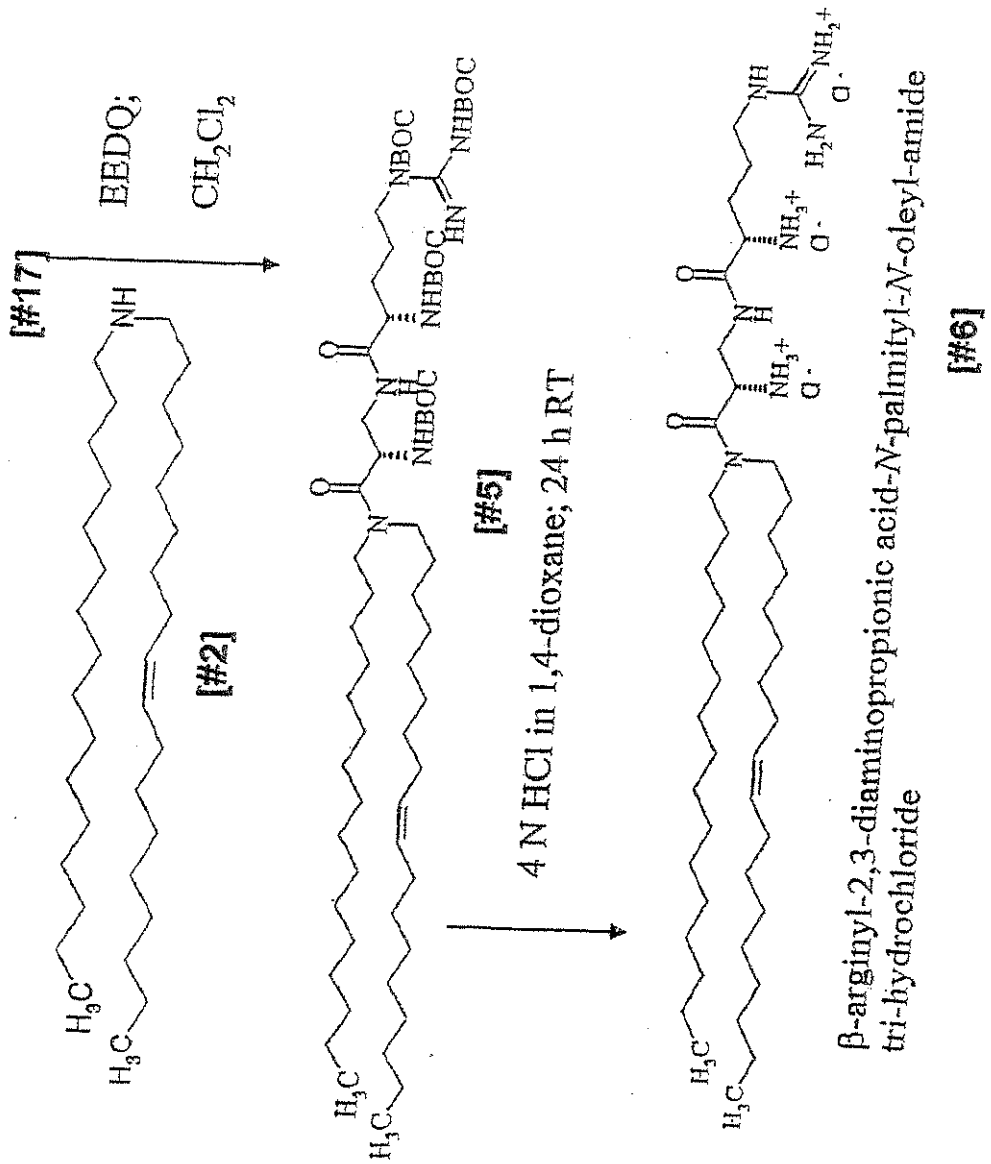

[#17]
EEDQ;
CH_2Cl_2
[#2]
[#5]
4 N HCl in 1,4-dioxane; 24 h RT
β-arginyl-2,3-diaminopropionic acid-*N*-palmityl-*N*-oleyl-amide tri-hydrochloride
[#6]

Fig. 12A

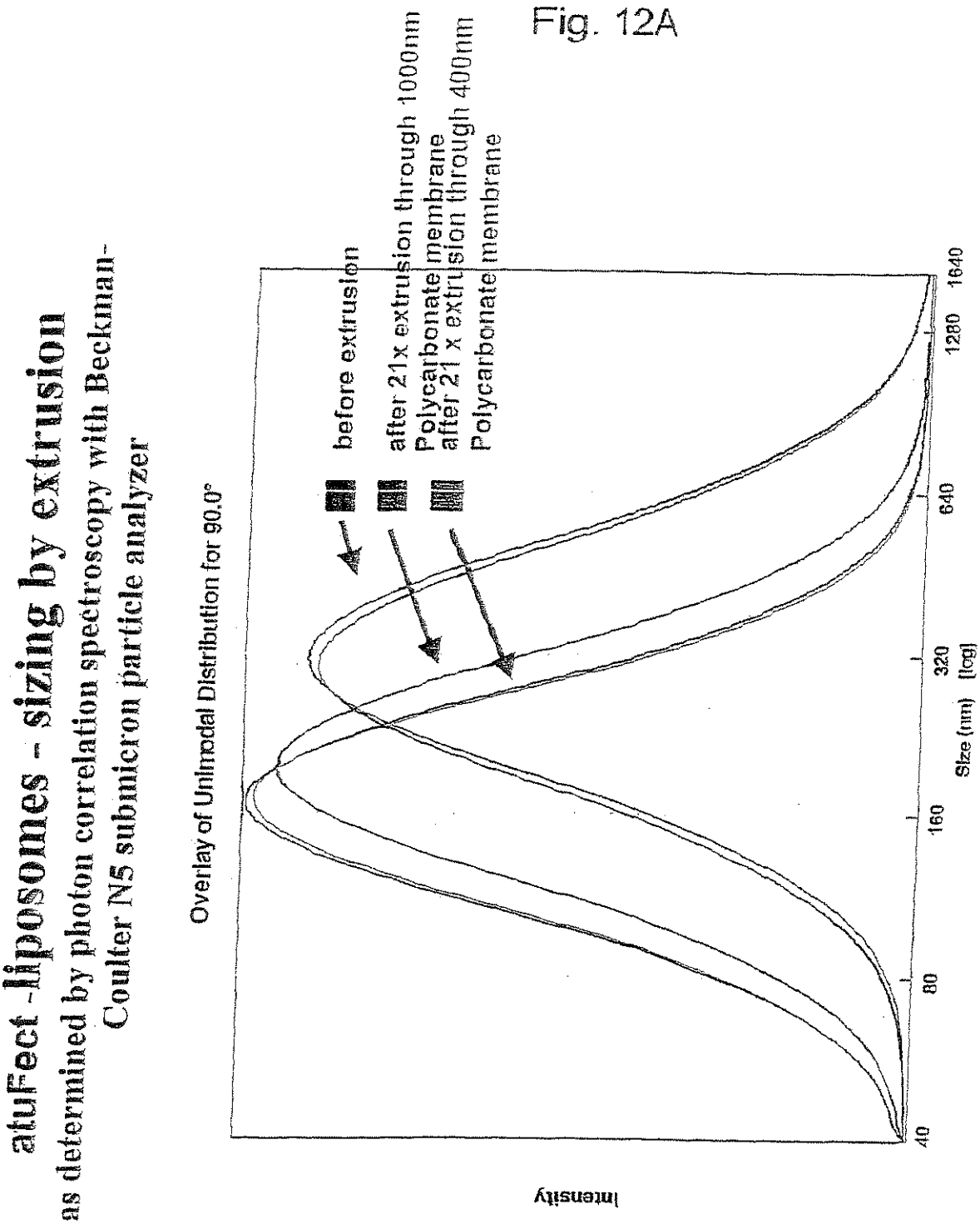
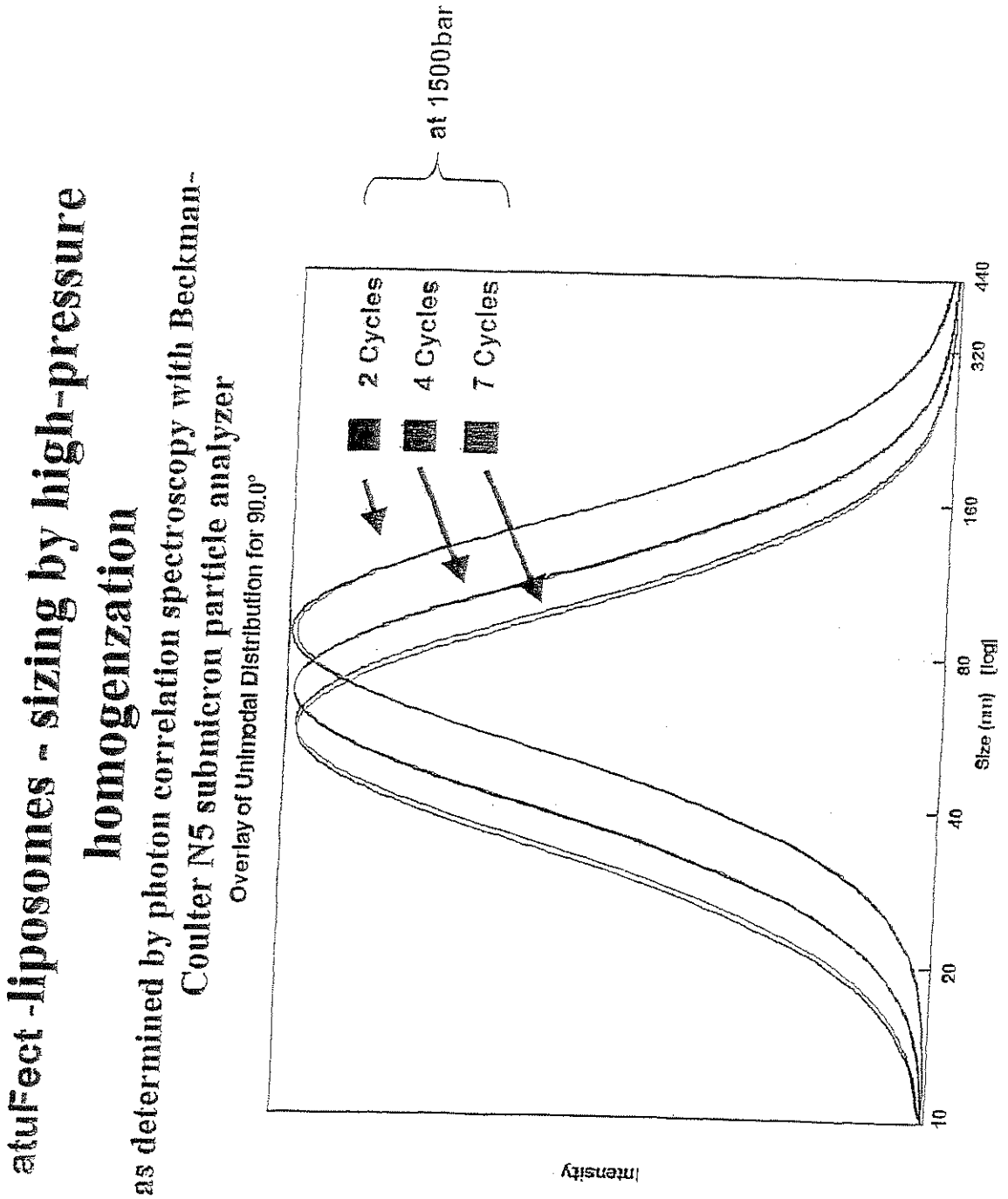

atuFect -liposomes - sizing by extrusion
as determined by photon correlation spectroscopy with Beckman-Coulter N5 submicron particle analyzer
Overlay of Unimodal Distribution for 90.0°
before extrusion
after 21x extrusion through 1000nm Polycarbonate membrane
after 21 x extrusion through 400nm Polycarbonate membrane
Intensity
40
80
160
320
640
1280
1640
Size (nm) [log]

Fig. 12B


atufect -liposomes - sizing by high-pressure homogenization
as determined by photon correlation spectroscopy with Beckman-Coulter N5 submicron particle analyzer
Overlay of Unimodal Distribution for 90.0°
at 1500bar
2 Cycles
4 Cycles
7 Cycles
Intensity
Size (nm) [log]
10
20
40
80
160
320
440

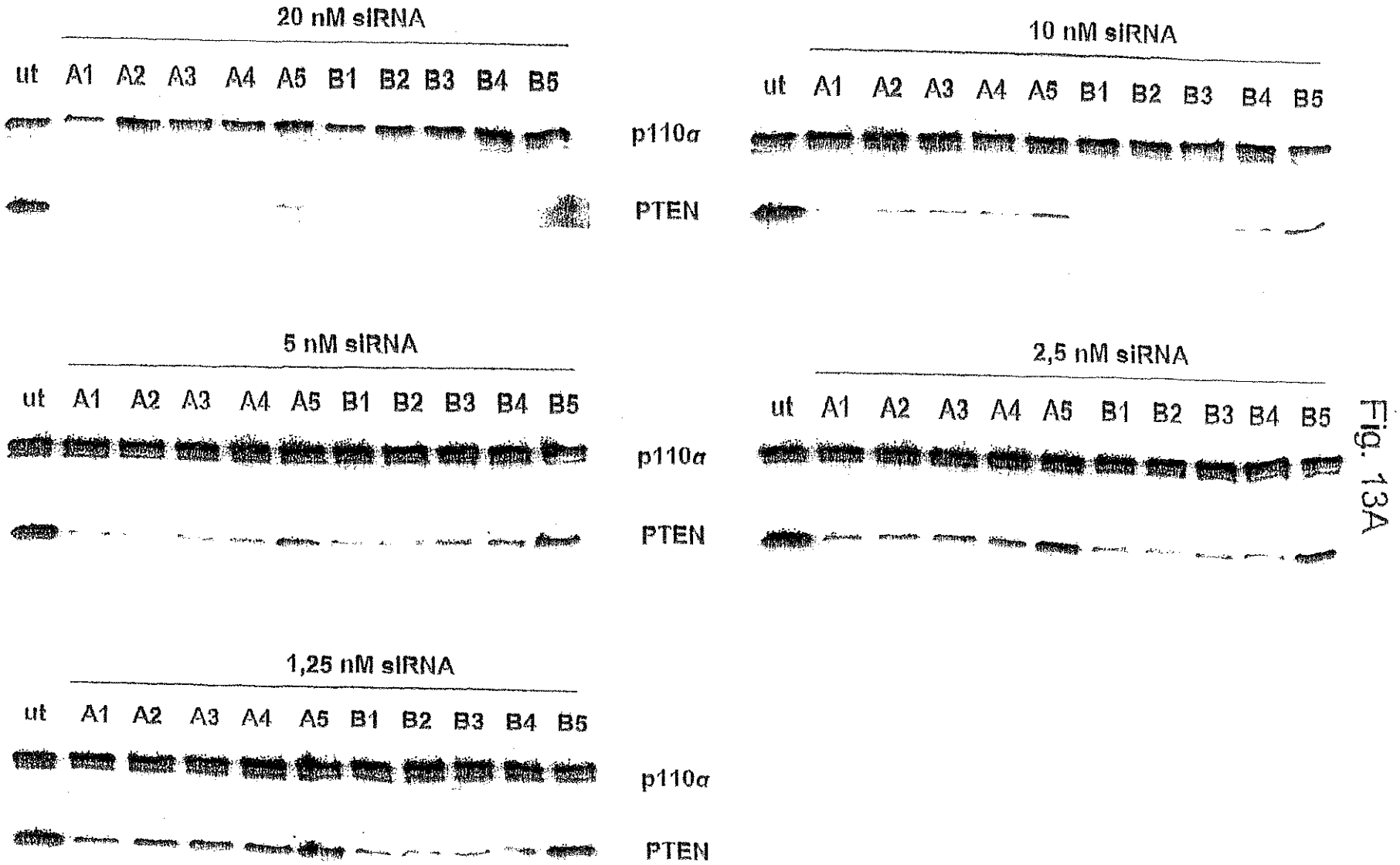

20 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
p110α
PTEN
10 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
5 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
p110α
PTEN
2,5 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
1,25 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
p110α
PTEN

Fig. 13A

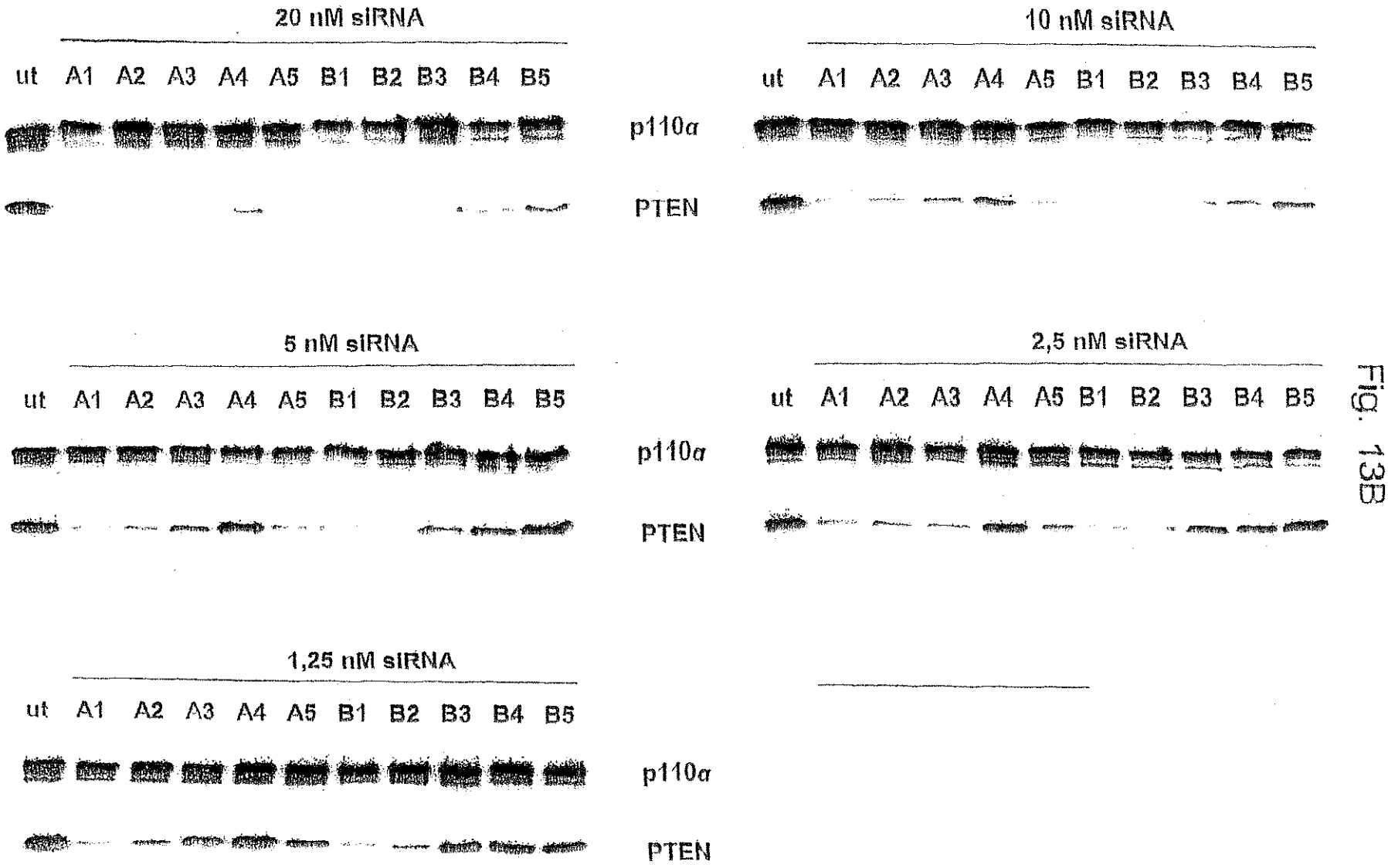

20 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
p110α
PTEN
10 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
5 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
p110α
PTEN
2,5 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
1,25 nM siRNA
ut A1 A2 A3 A4 A5 B1 B2 B3 B4 B5
p110α
PTEN

Fig. 13B

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