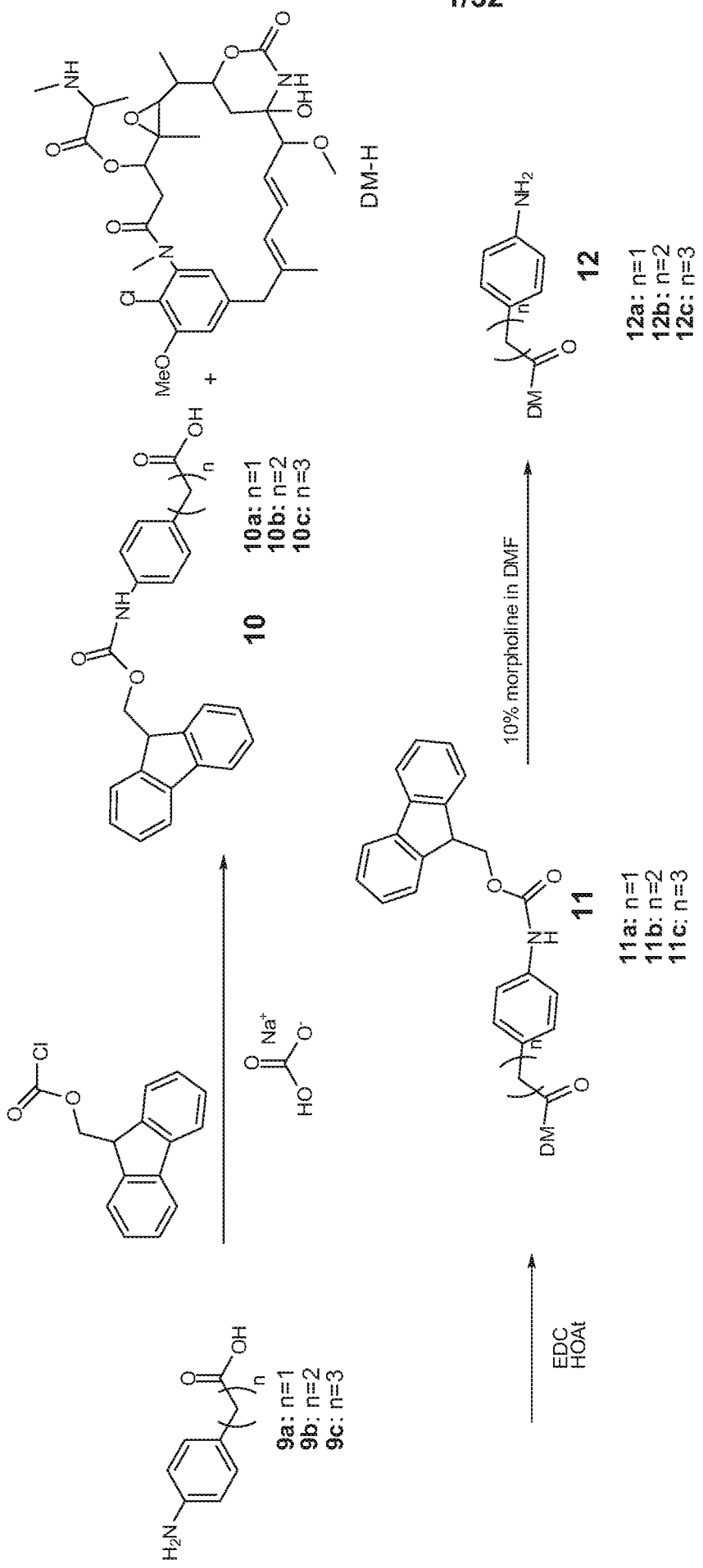

9a: n=1
9b: n=2
9c: n=3
EDC
HOAt
11
11a: n=1
11b: n=2
11c: n=3
10% morpholine in DMF
10
10a: n=1
10b: n=2
10c: n=3
DM-H
12
12a: n=1
12b: n=2
12c: n=3

FIGURE 1

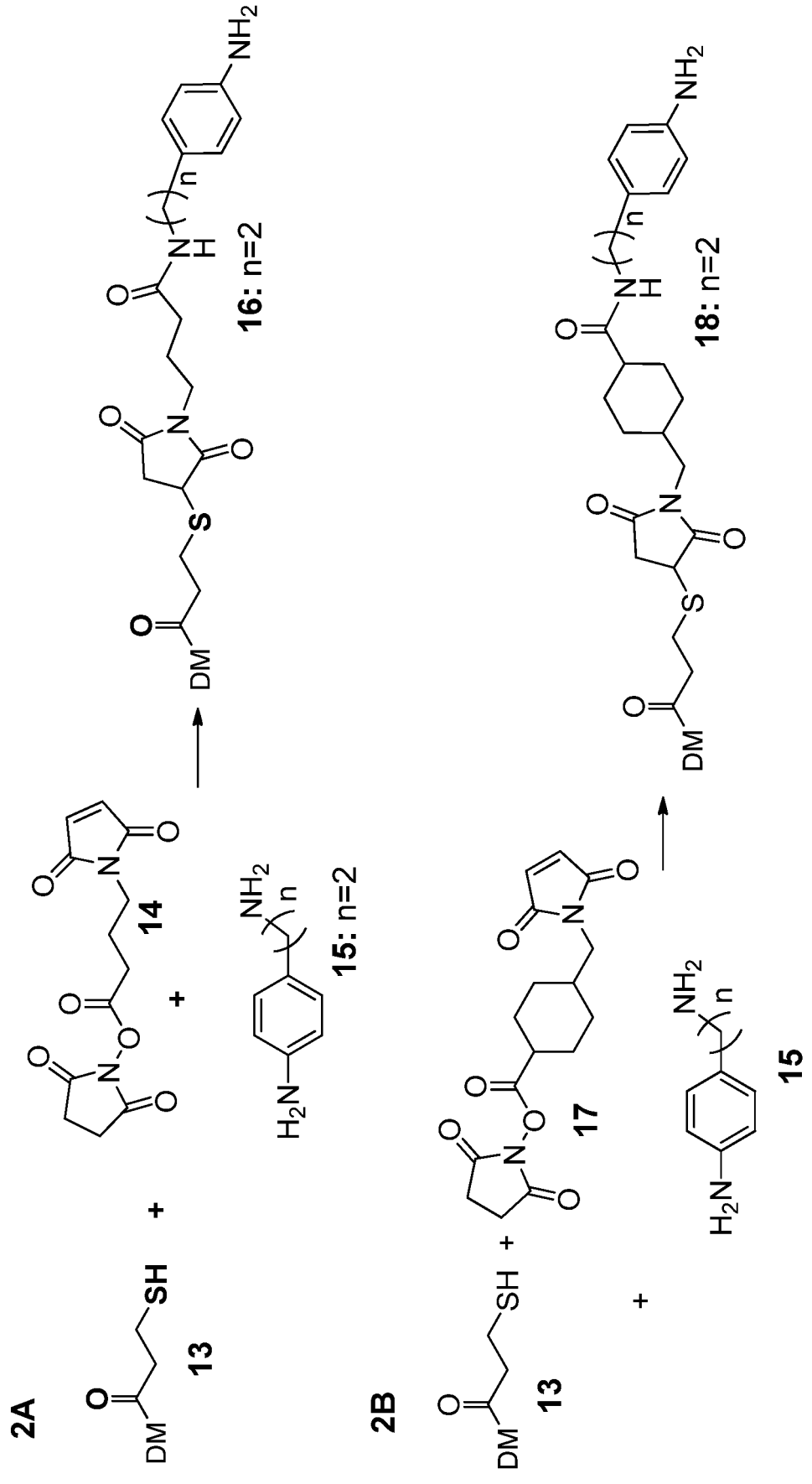


FIGURE 2

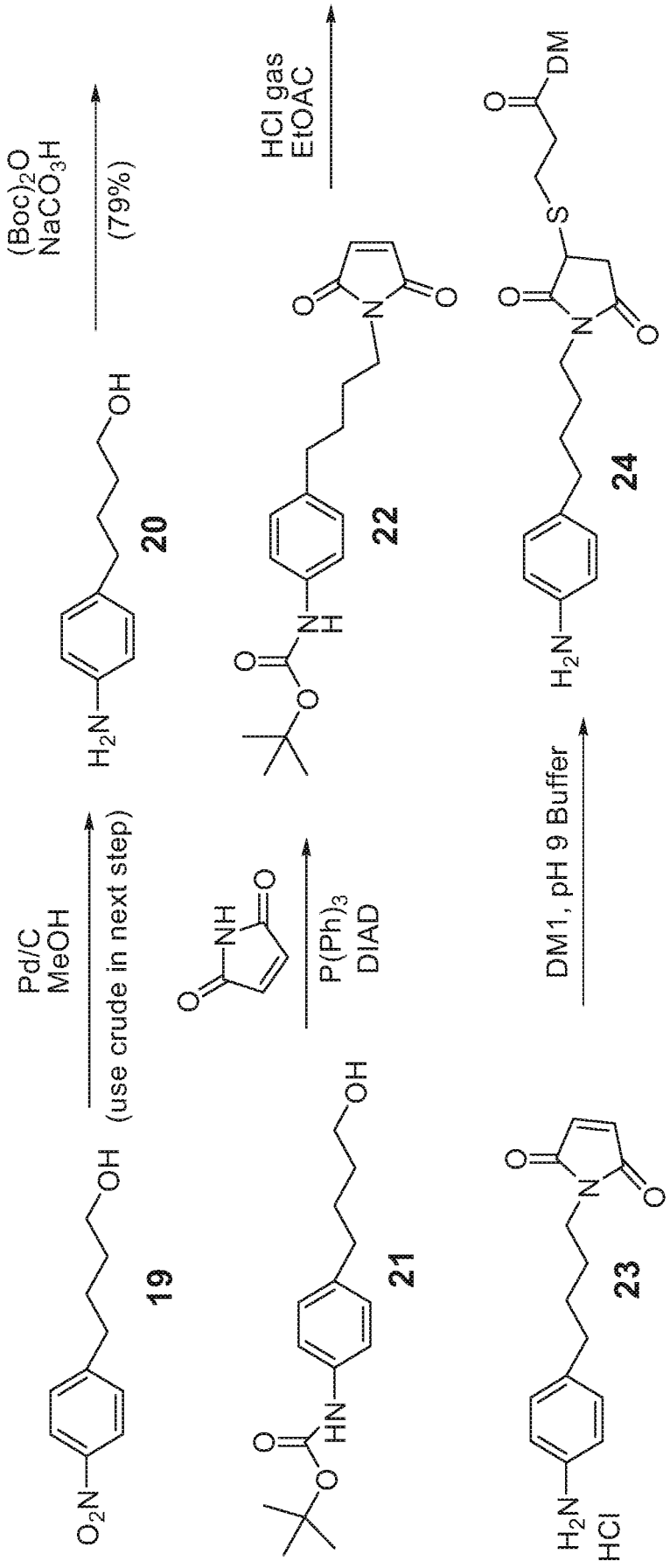

Pd/C
MeOH
(use crude in next step)
(Boc)2O
NaCO3H
(79%)
HCl gas
EtOAC
P(Ph)3
DIAD
DM1, pH 9 Buffer
19
20
21
22
23
24

FIGURE 3

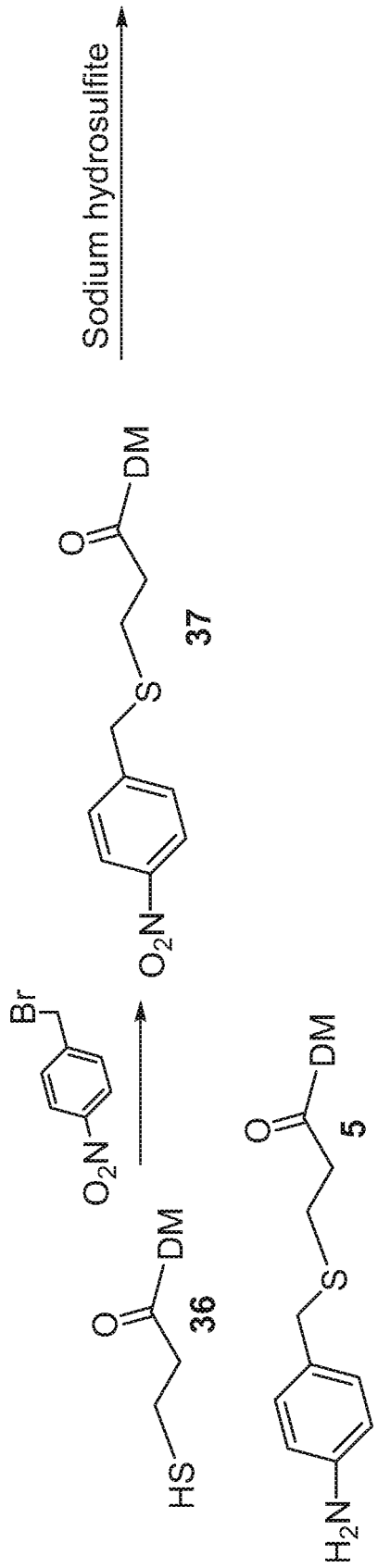


FIGURE 4

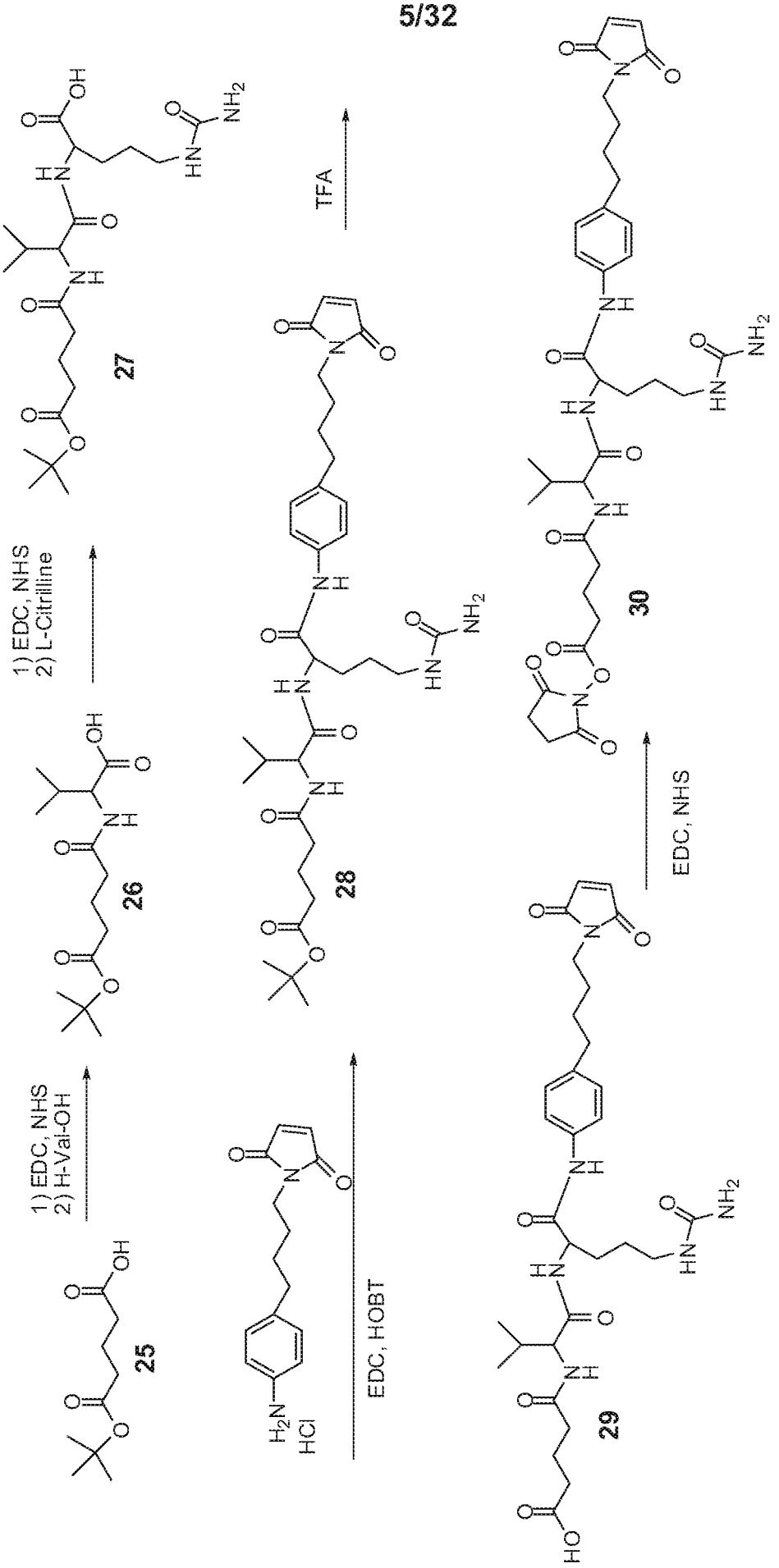

1) EDC, NHS
2) H-Val-OH
1) EDC, NHS
2) L-Citrilline
EDC, HOBT
TFA
EDC, NHS
25
26
27
28
29
30
H_2N
HCl
NH_2
HO

FIGURE 5

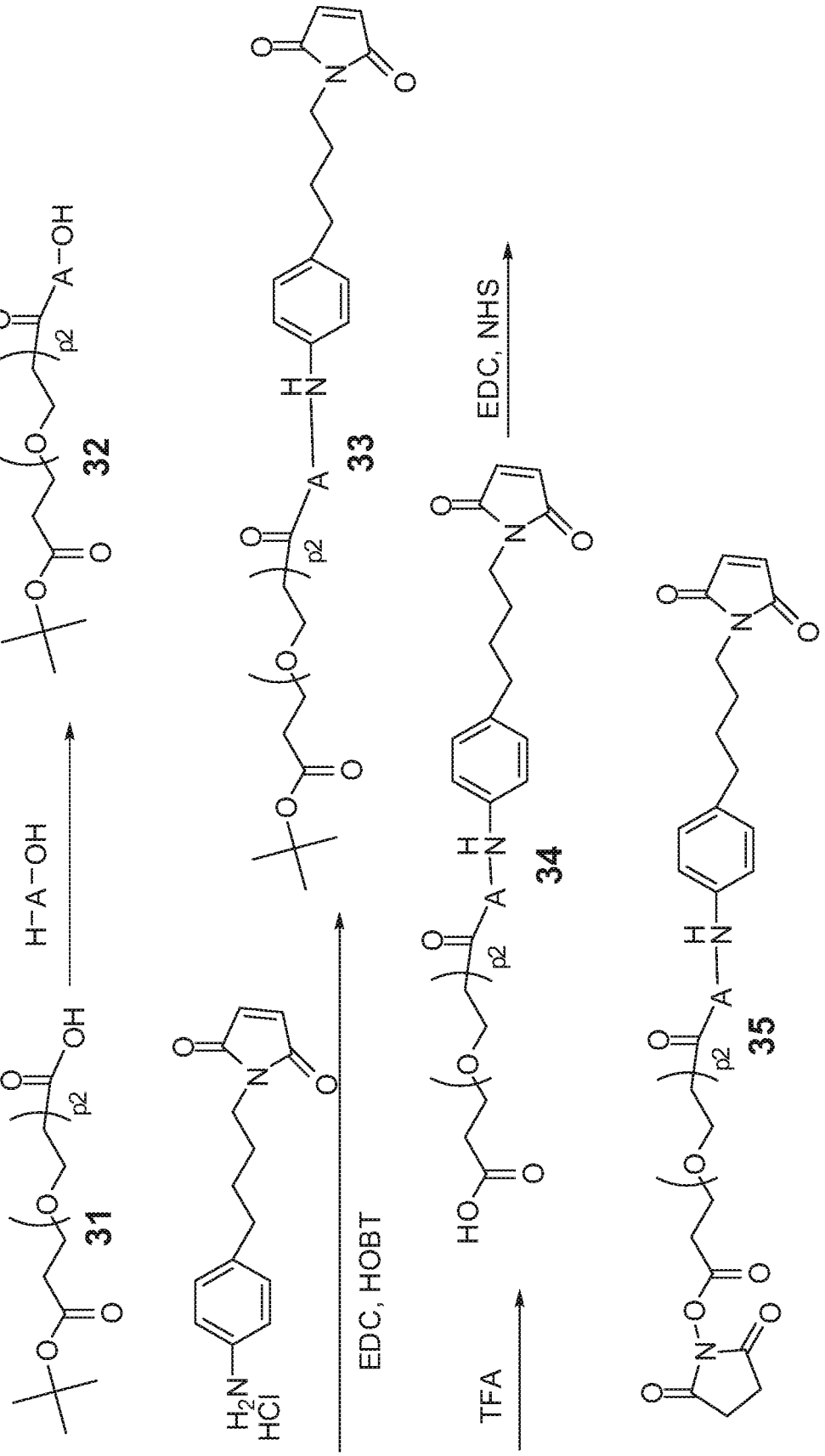


FIGURE 6

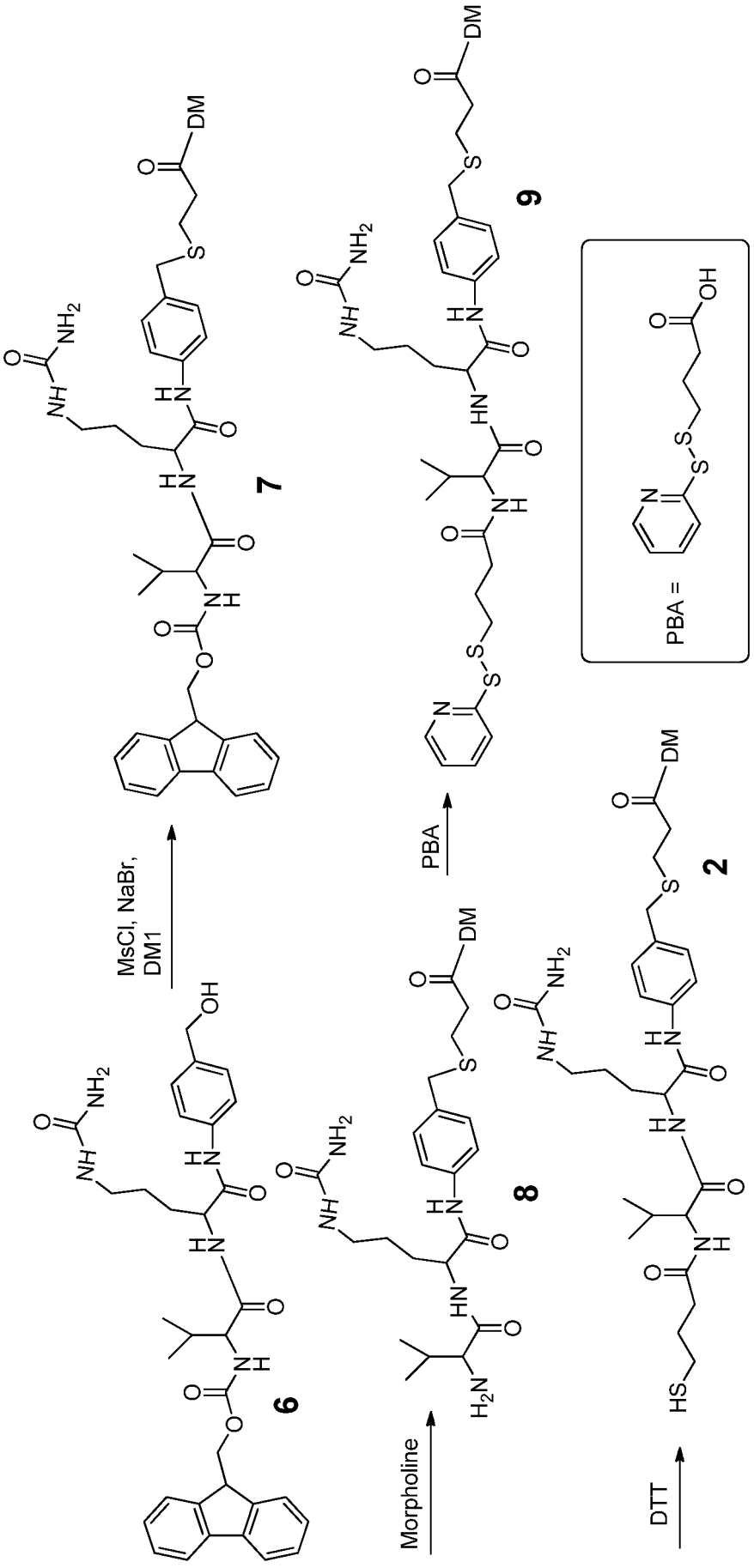


FIGURE 7

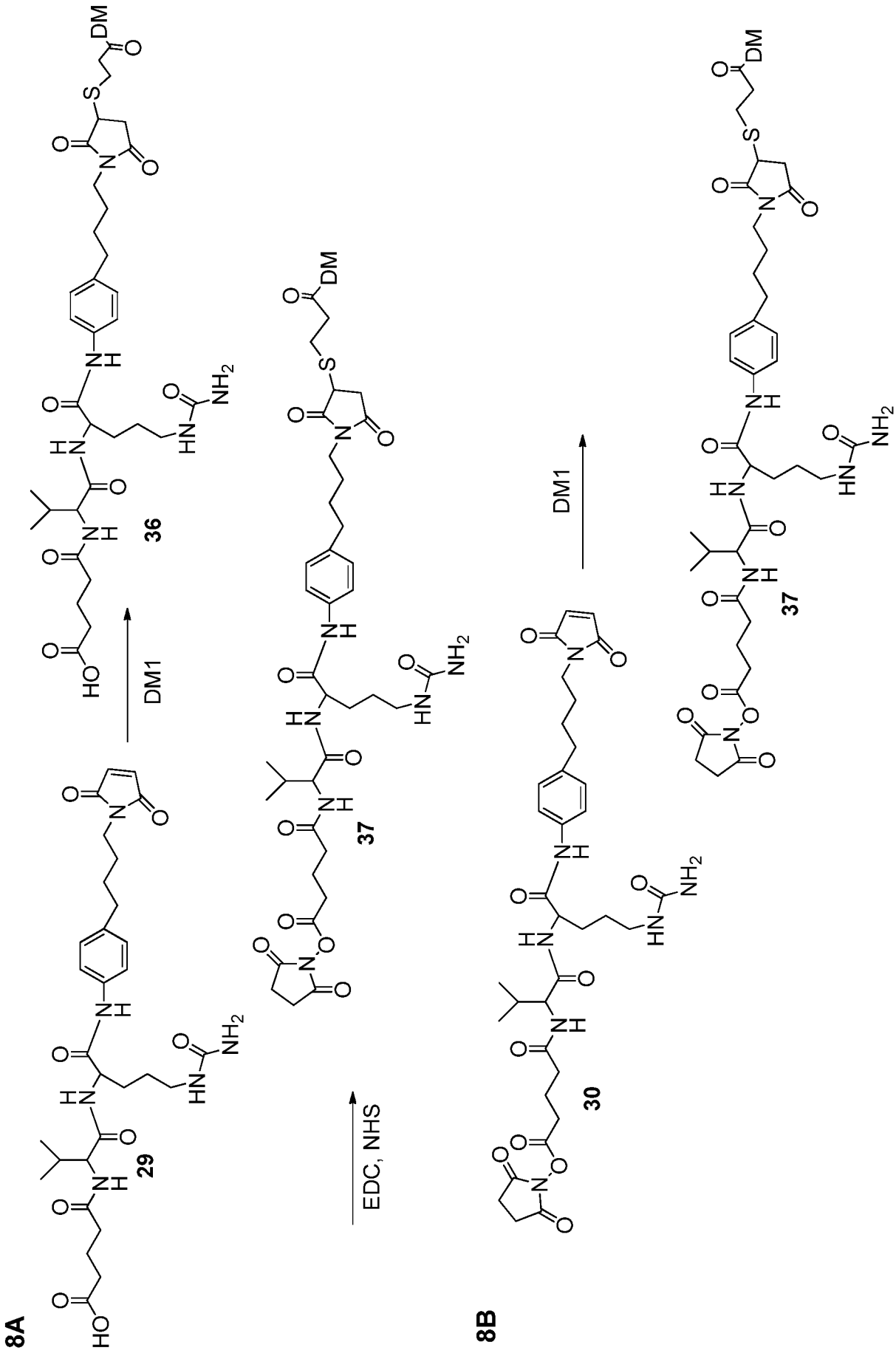


FIGURE 8

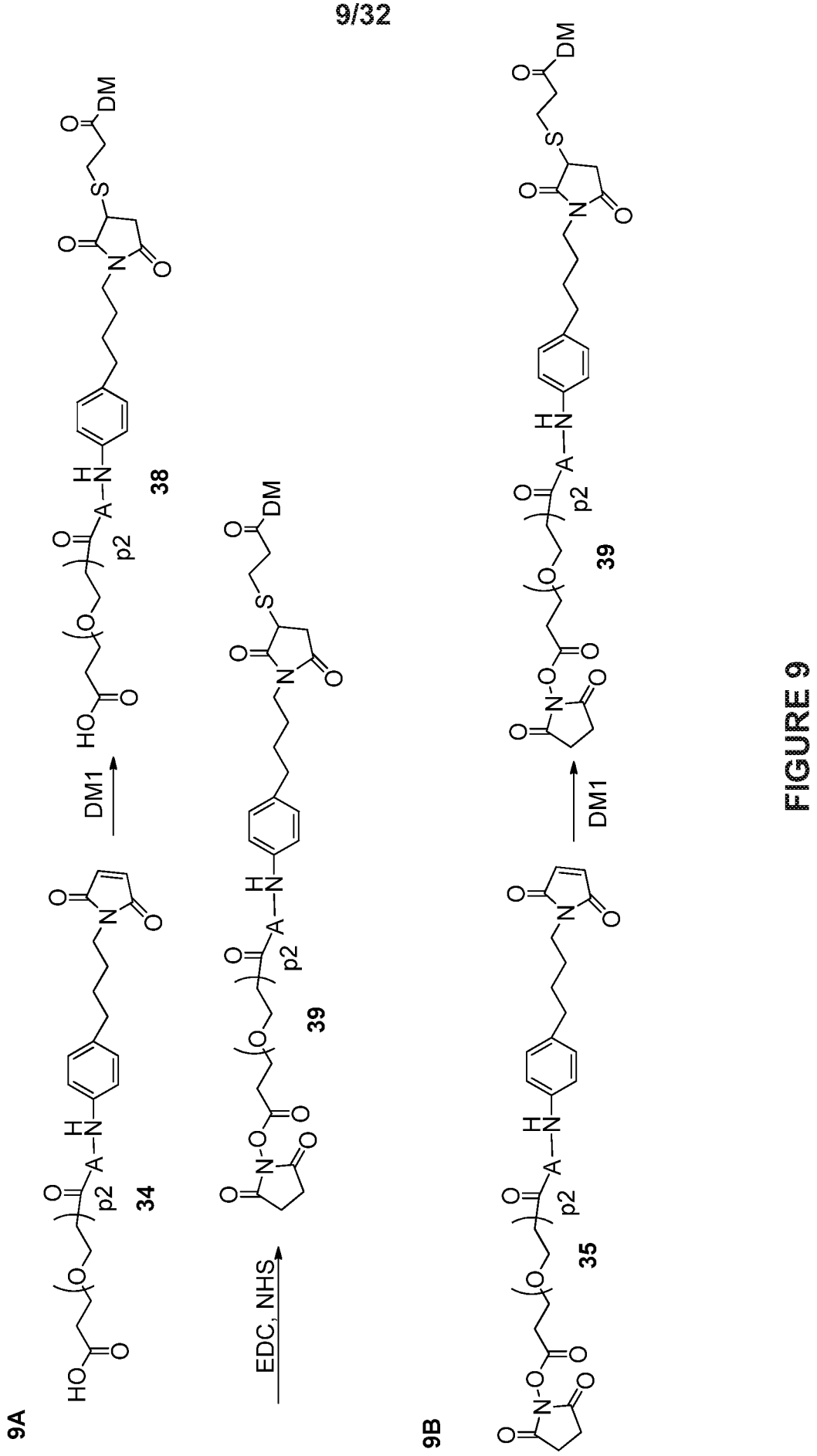


FIGURE 9

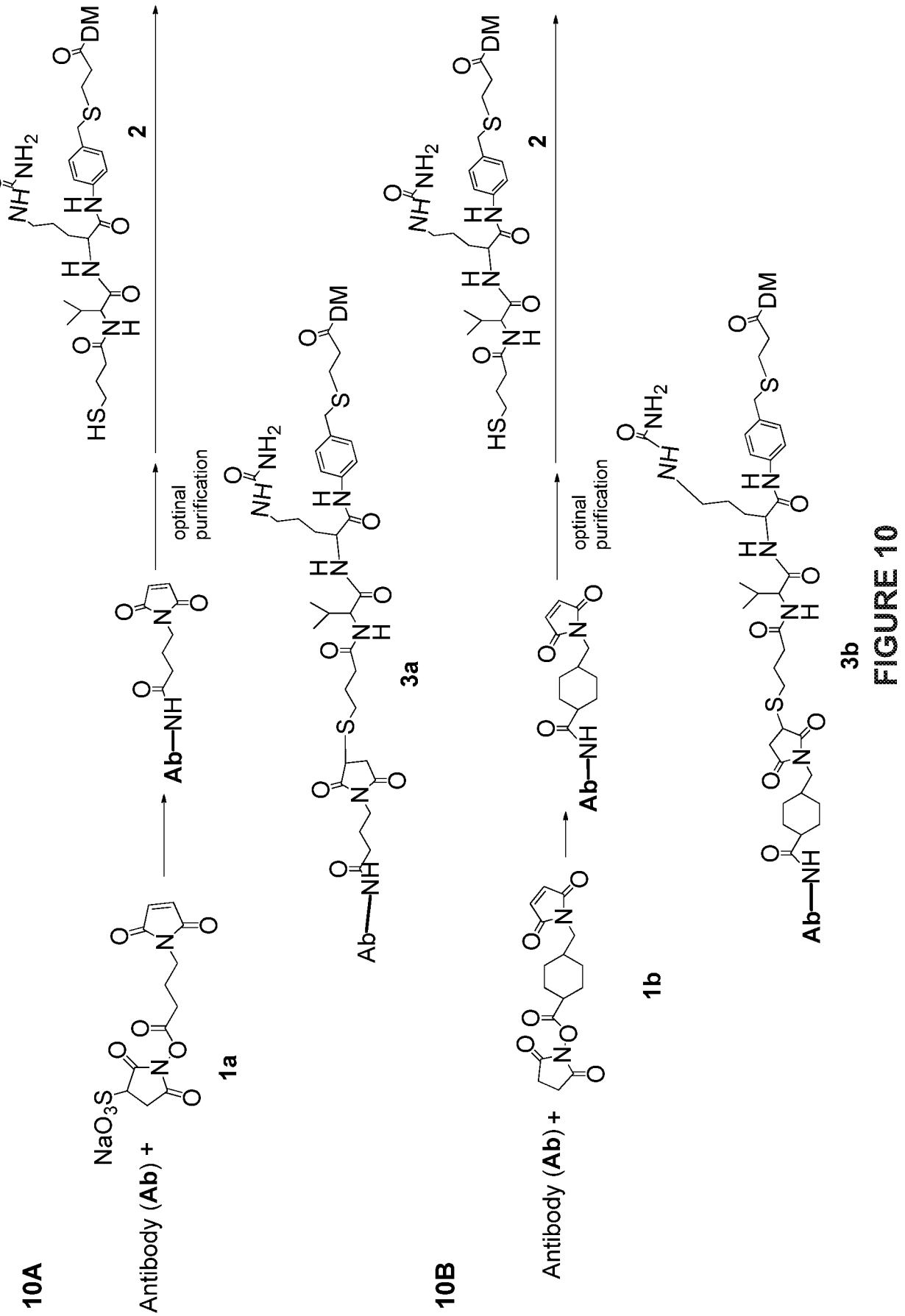

10A
Antibody (Ab) +
1a
Ab—NH
optinal purification
2
3a
10B
Antibody (Ab) +
1b
Ab—NH
optinal purification
2
3b

FIGURE 10

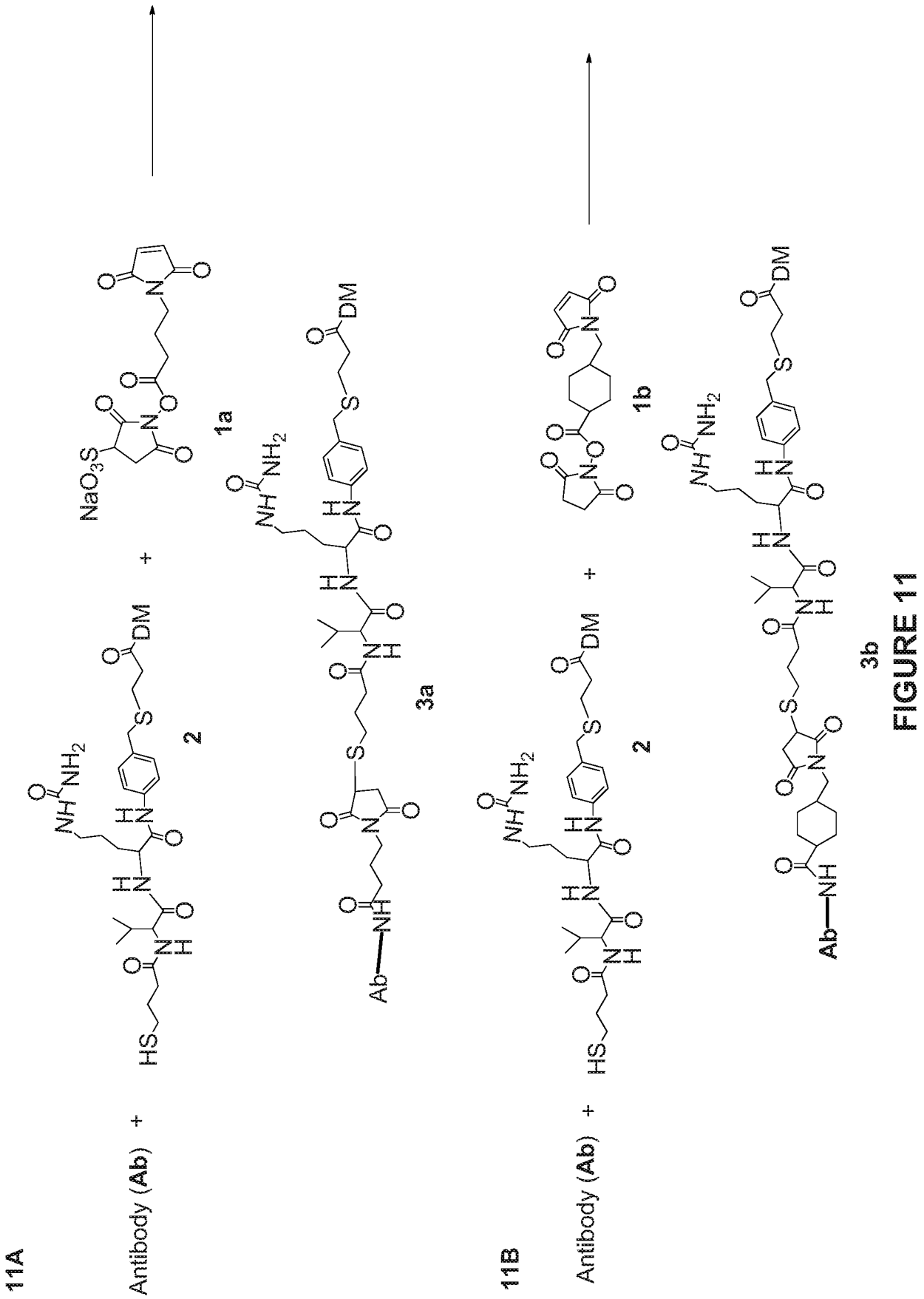


FIGURE 11

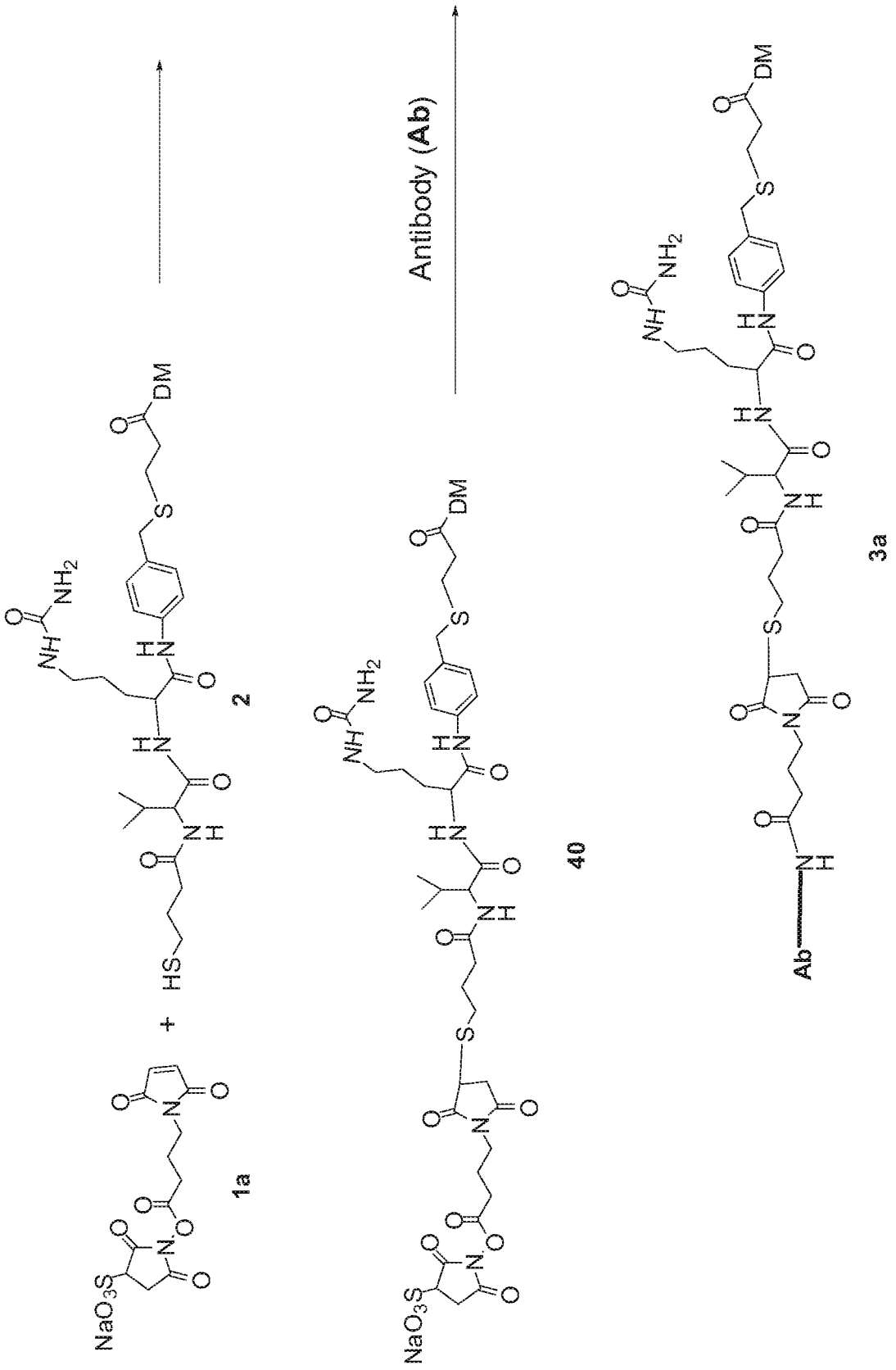


FIGURE 12A

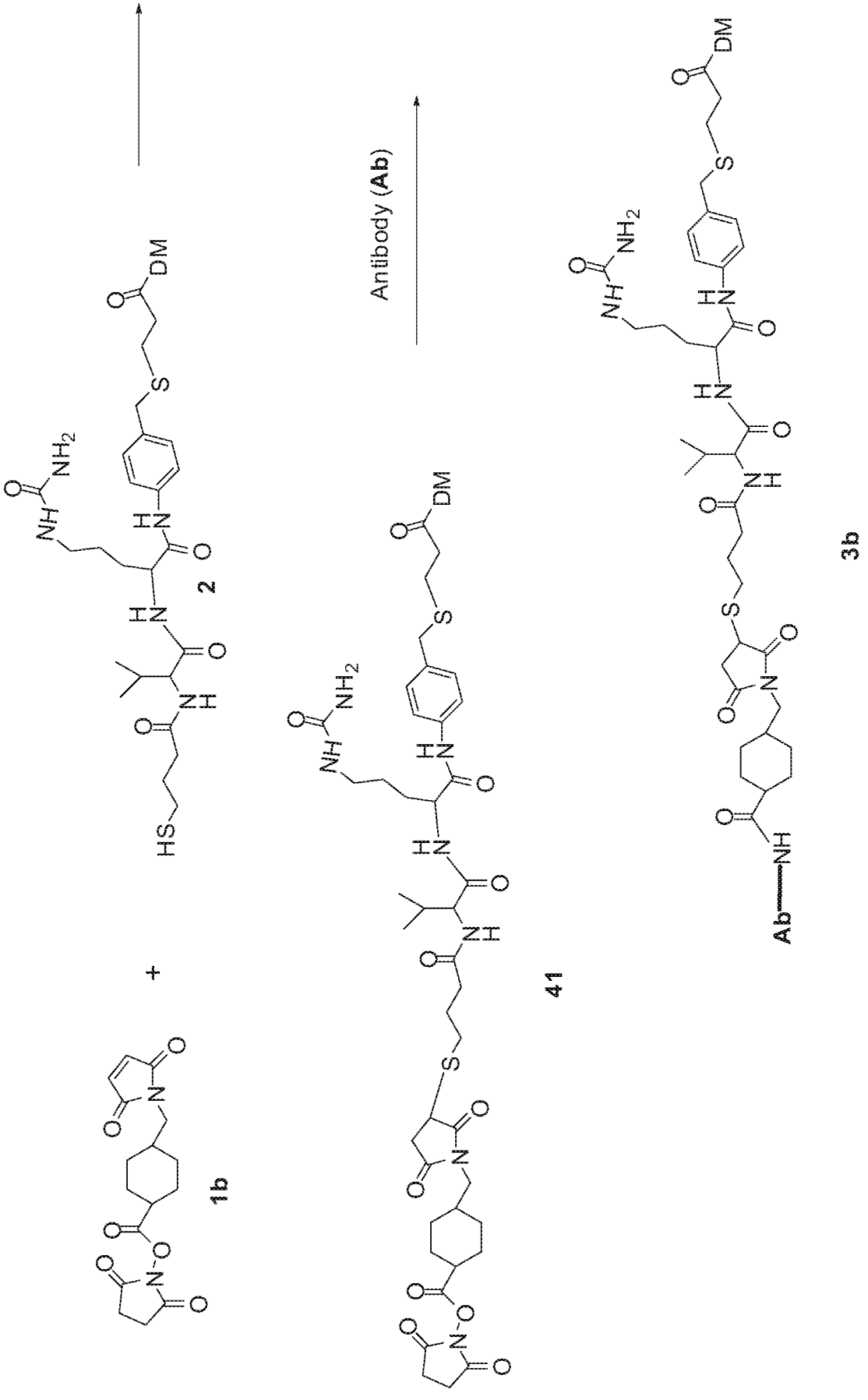


FIGURE 12B

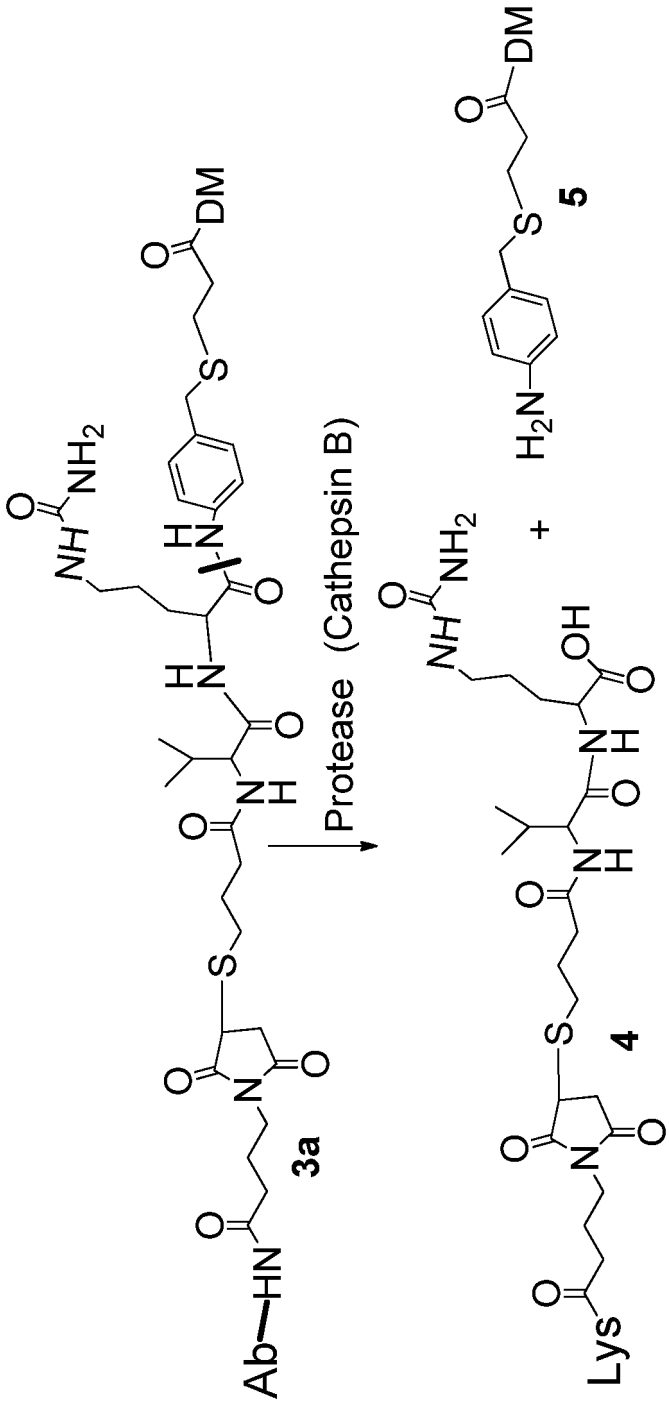
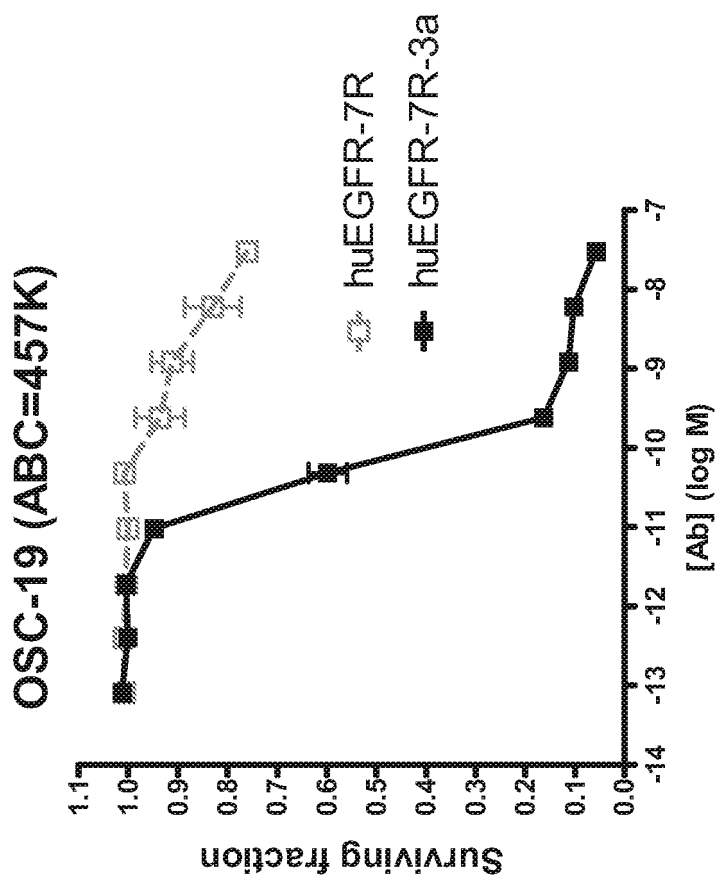


FIGURE 13

14A



14B

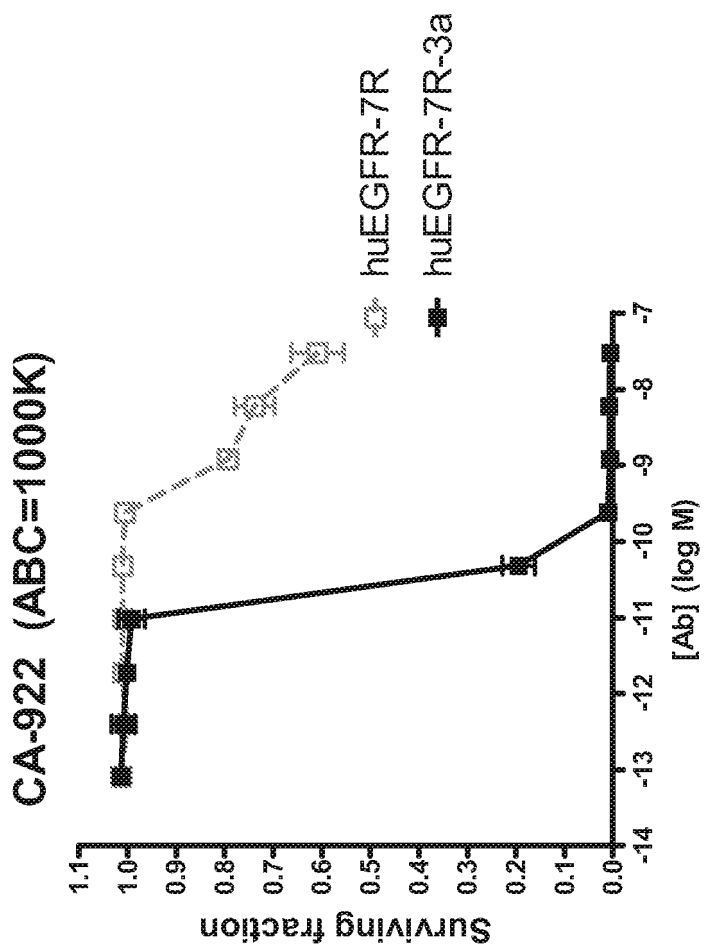
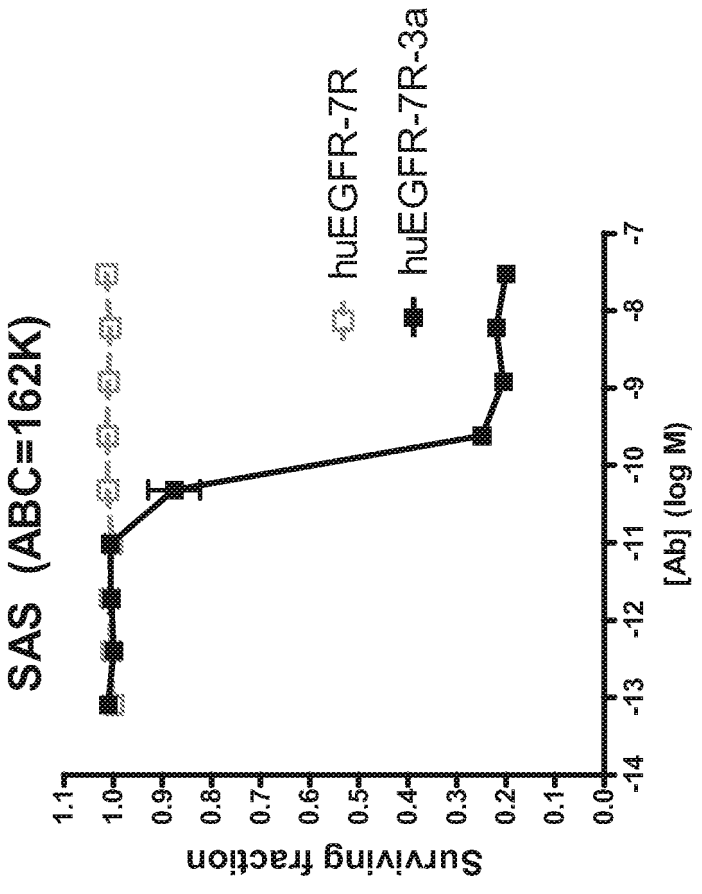


FIGURE 14

14C



14D

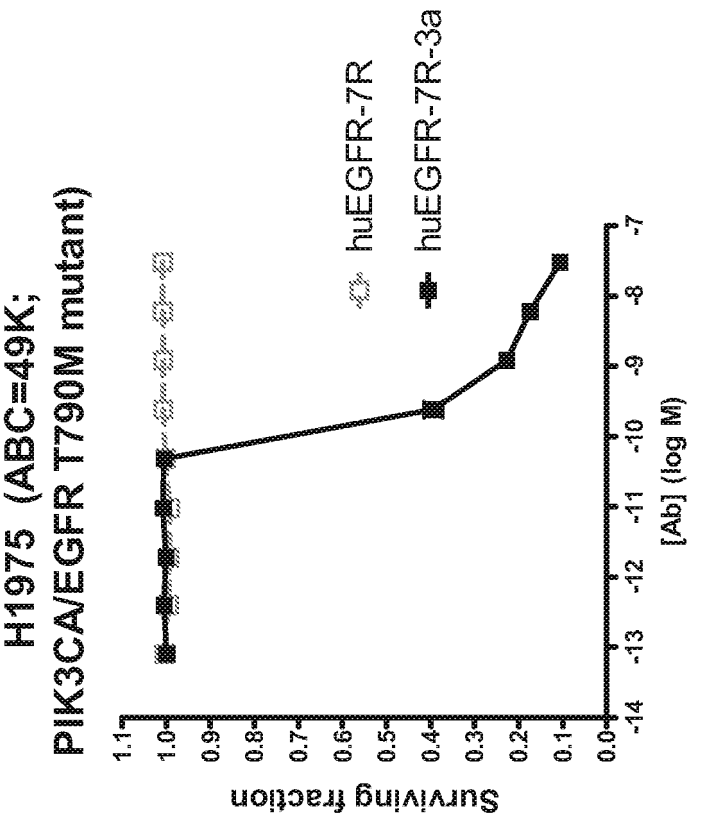


FIGURE 14 – CONT'D.

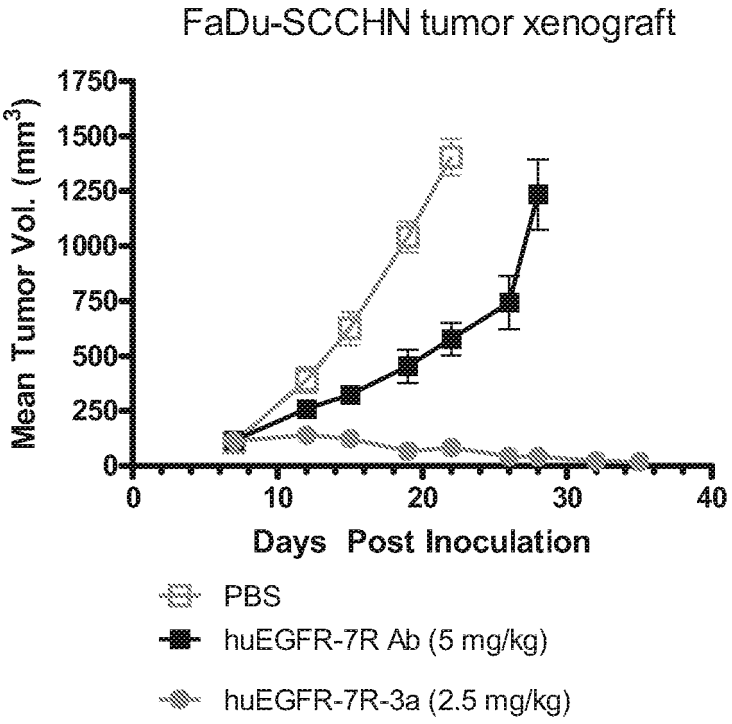


FIGURE 15

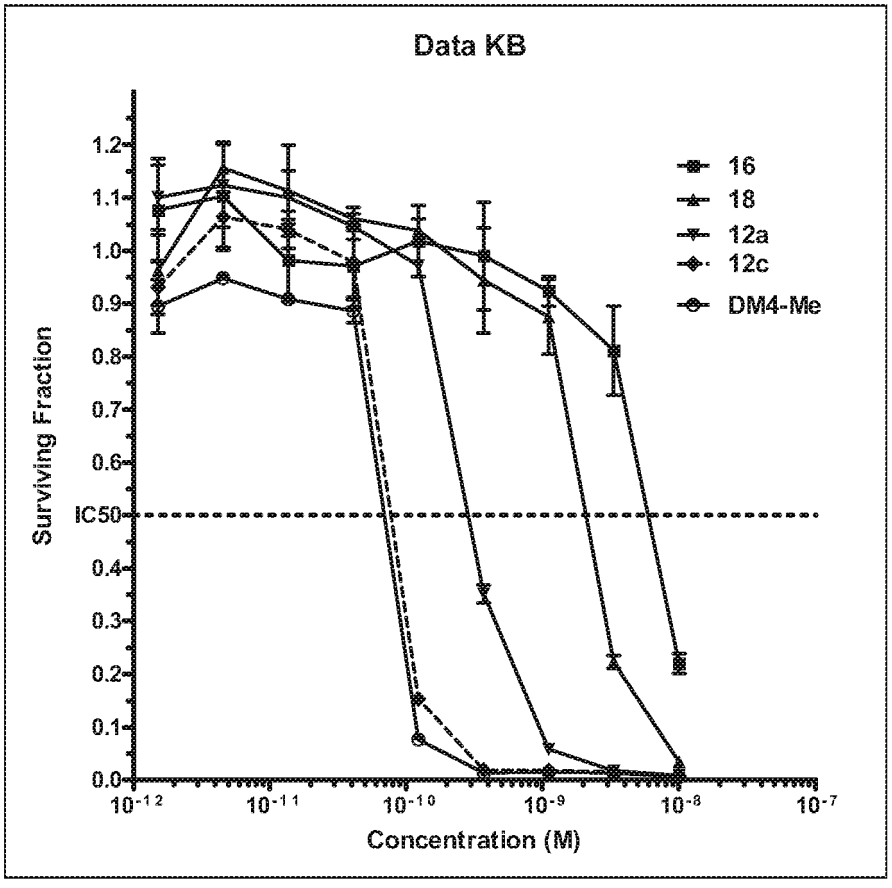


FIGURE 16

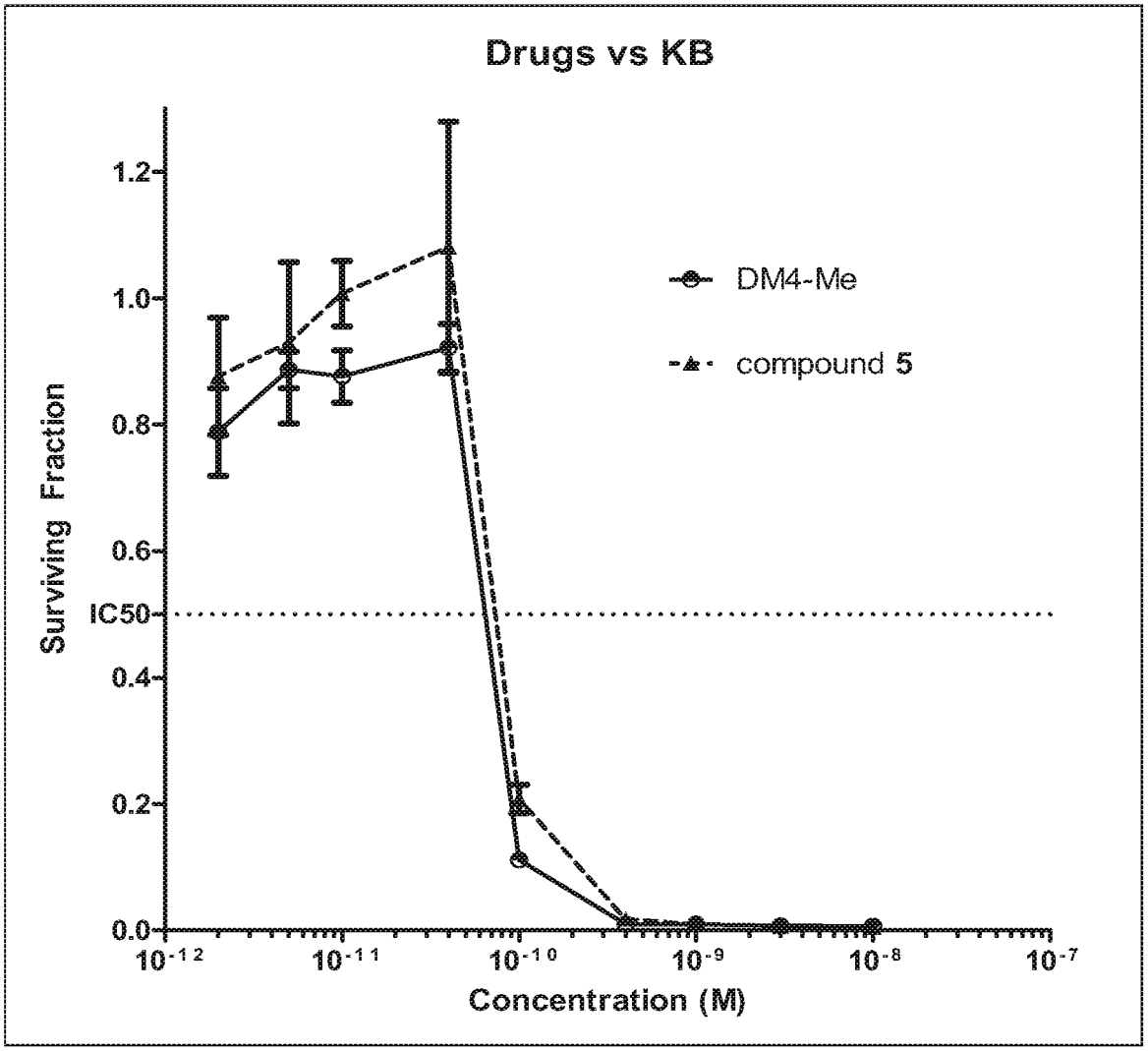

Drugs vs KB
Surviving Fraction
1.2
1.0
0.8
0.6
IC50
0.4
0.2
0.0
DM4-Me
compound 5
10-12
10-11
10-10
10-9
10-8
10-7
Concentration (M)

FIGURE 17

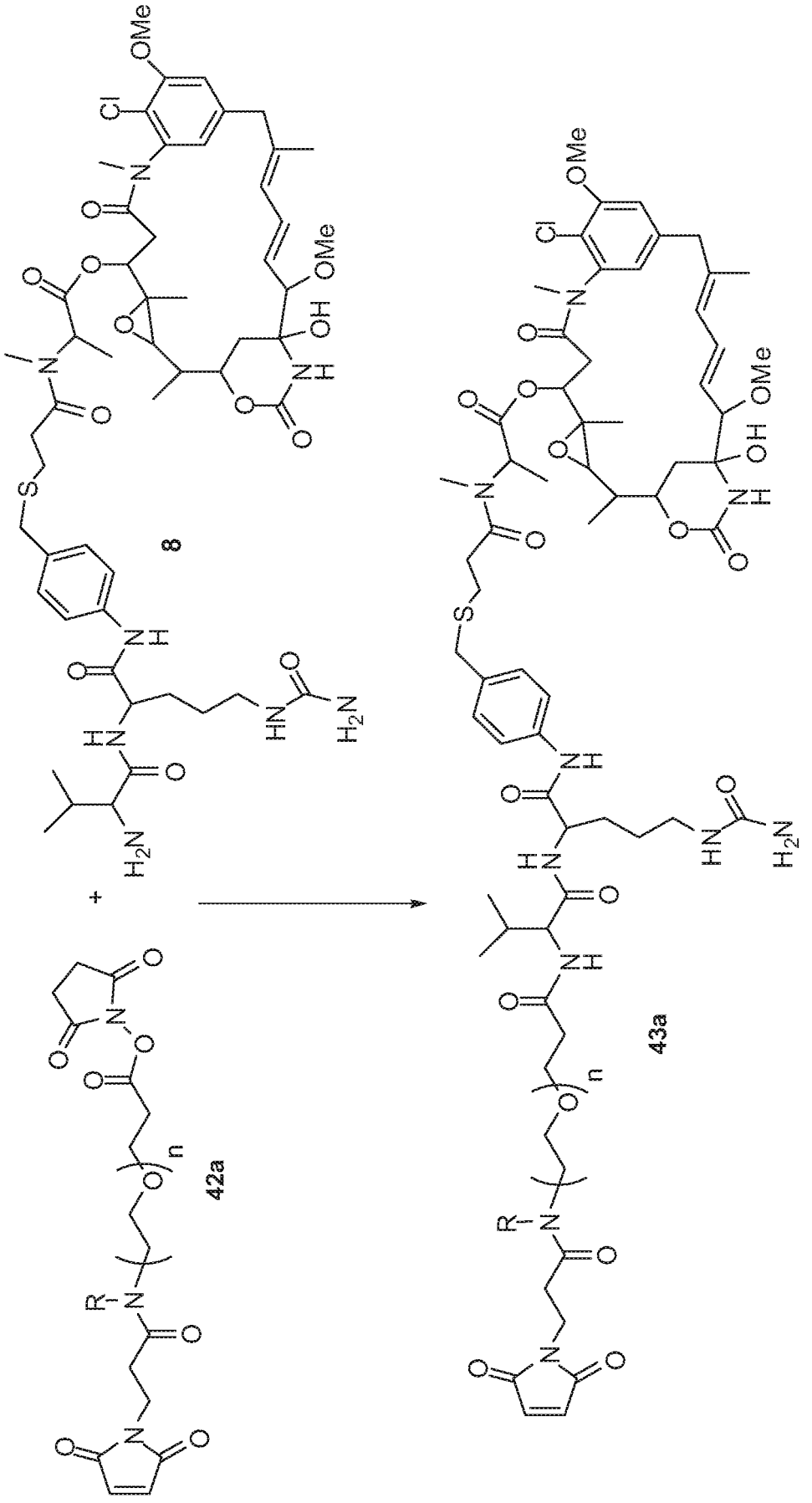

8
42a
43a
R = H or Me
n is an integer from 2 to 100, preferably n is 4, 8, or 24.

FIGURE 18A

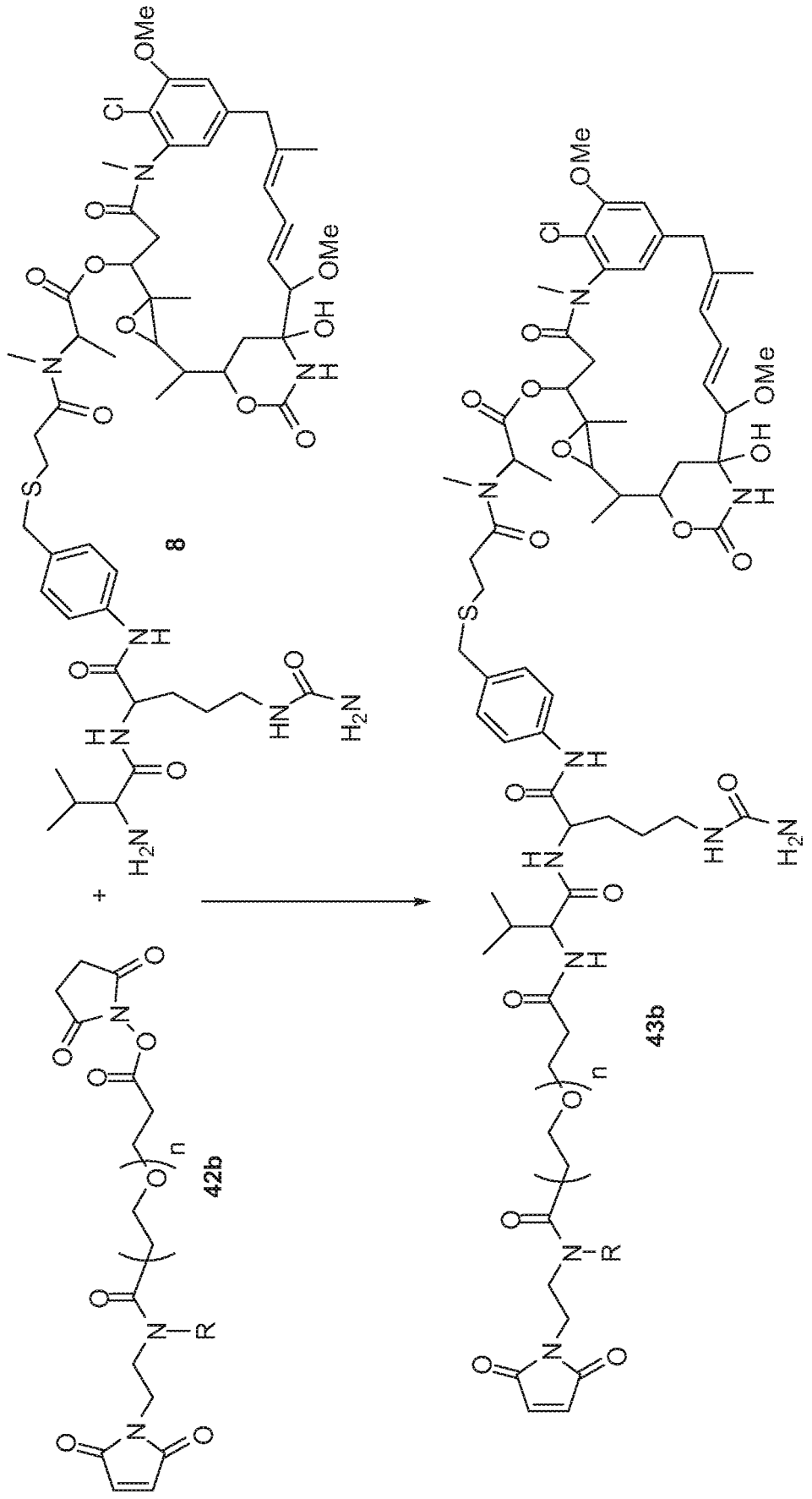
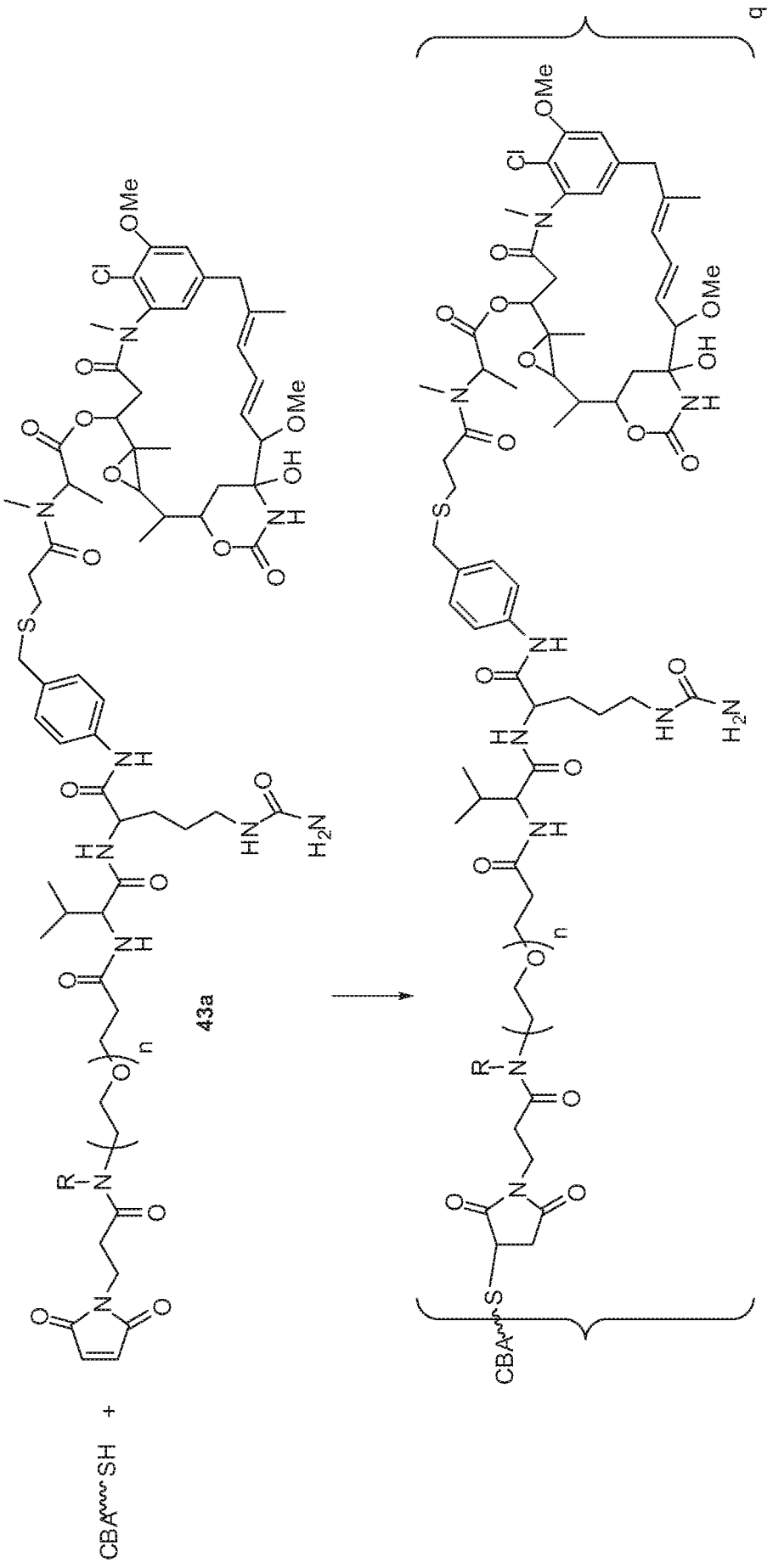

8
42b
43b
R = H or Me
n is an integer from 2 to 100, preferably n is 4, 8, or 24.

FIGURE 18B



R = H or Me
n is an integer from 2 to 100, preferably n is 4, 8, or 24.

FIGURE 18C

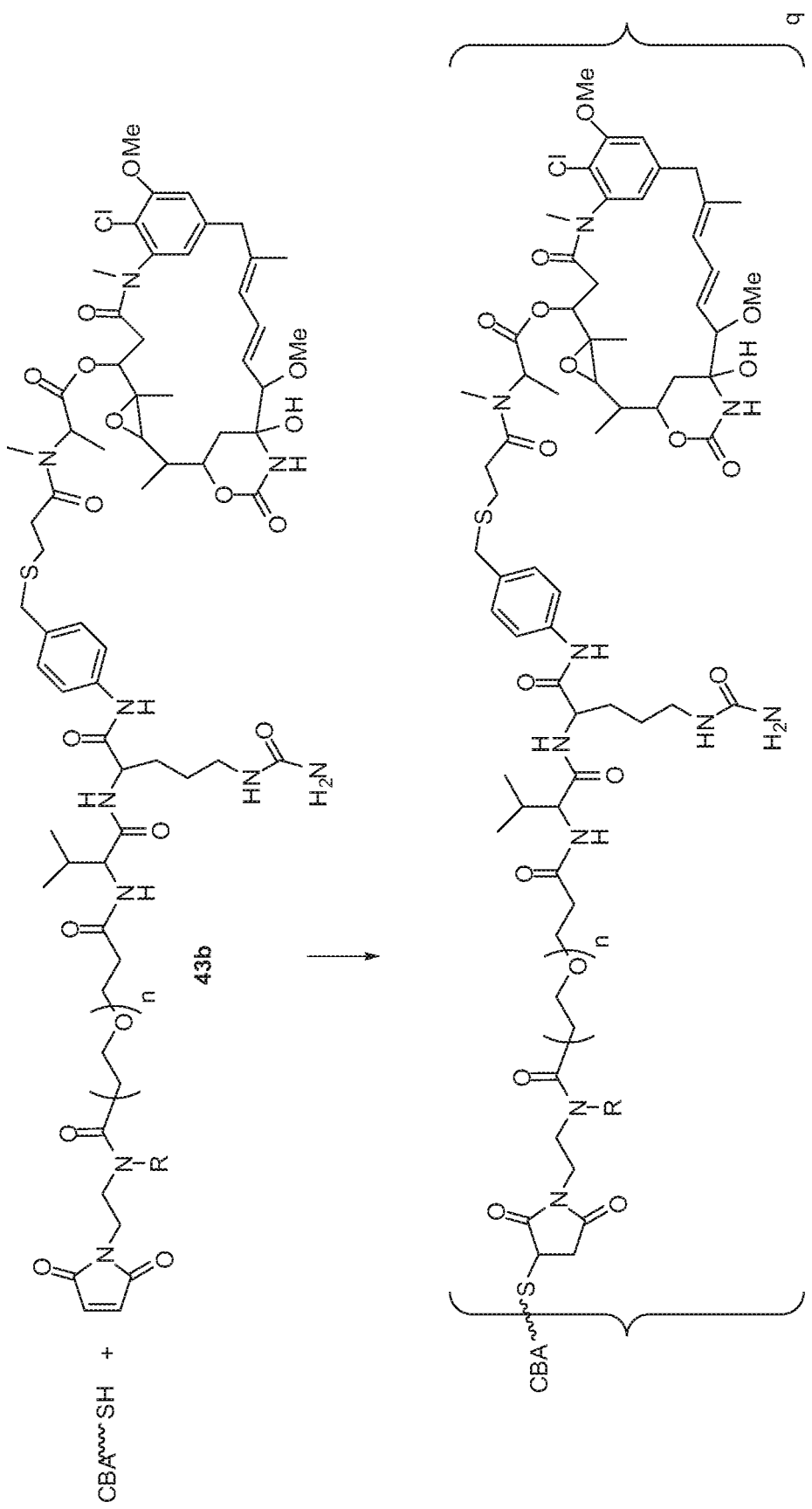

CBA
SH
+
43b
q
R = H or Me
n is an integer from 2 to 100, preferably n is 4, 8, or 24.

FIGURE 18D

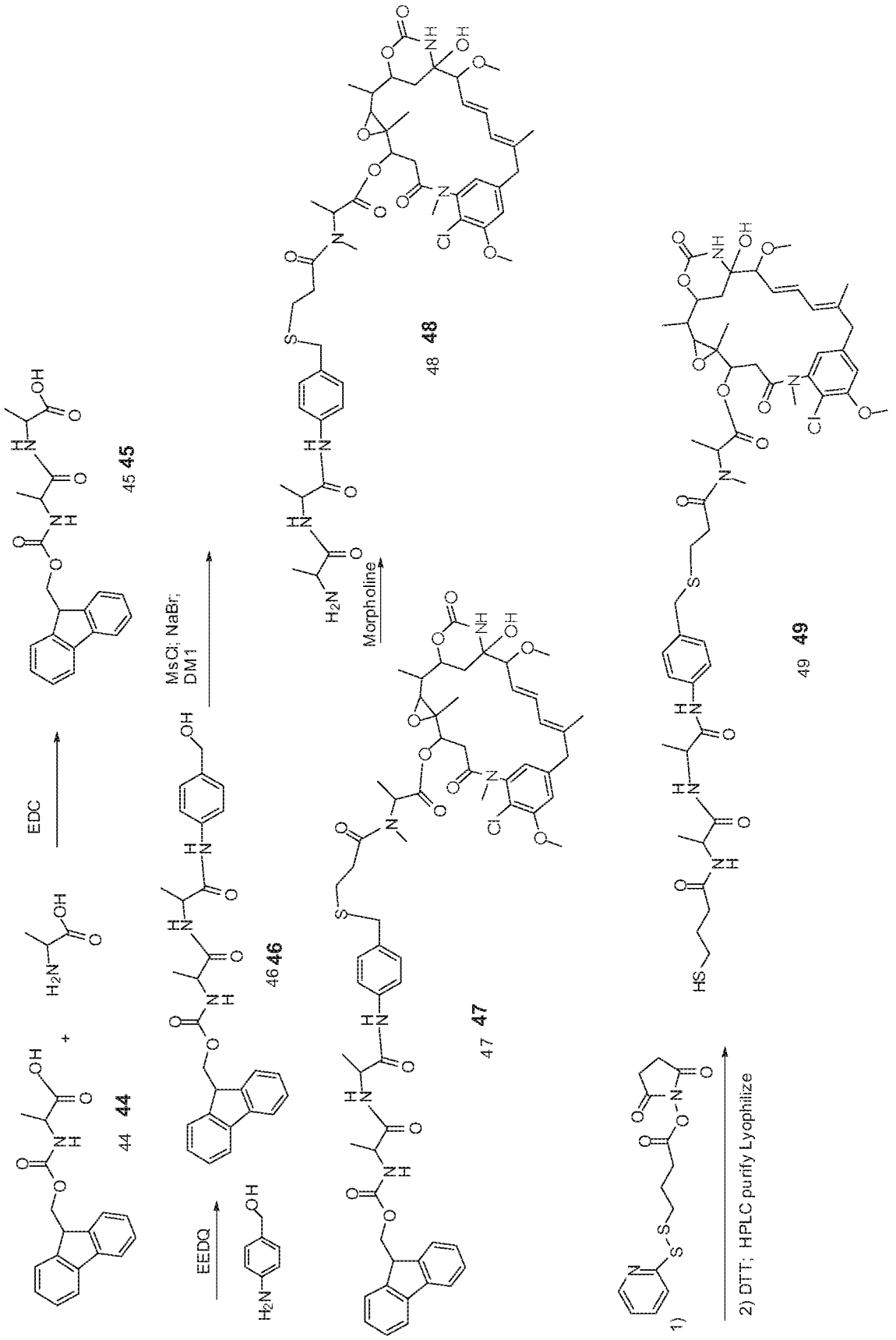

EDC
EEDQ
MsCl; NaBr; DM1
Morpholine
2) DTT; HPLC purify Lyophilize
1)
44
45
46
47
48
49

FIGURE 19

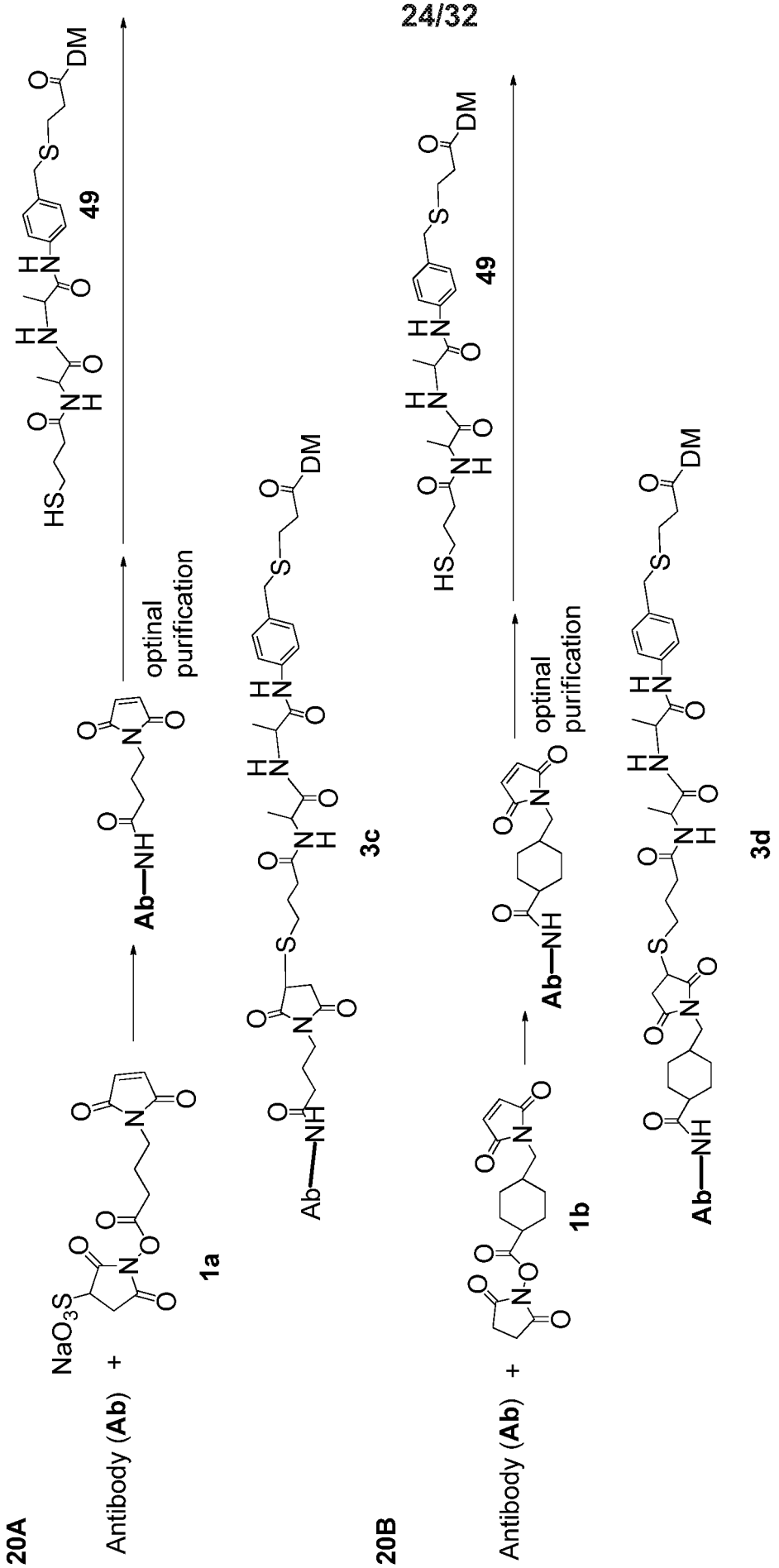

20A
Antibody (Ab)
+
1a
Ab—NH
optinal purification
49
DM
3c
20B
Antibody (Ab)
+
1b
Ab—NH
optinal purification
49
DM
3d

FIGURE 20

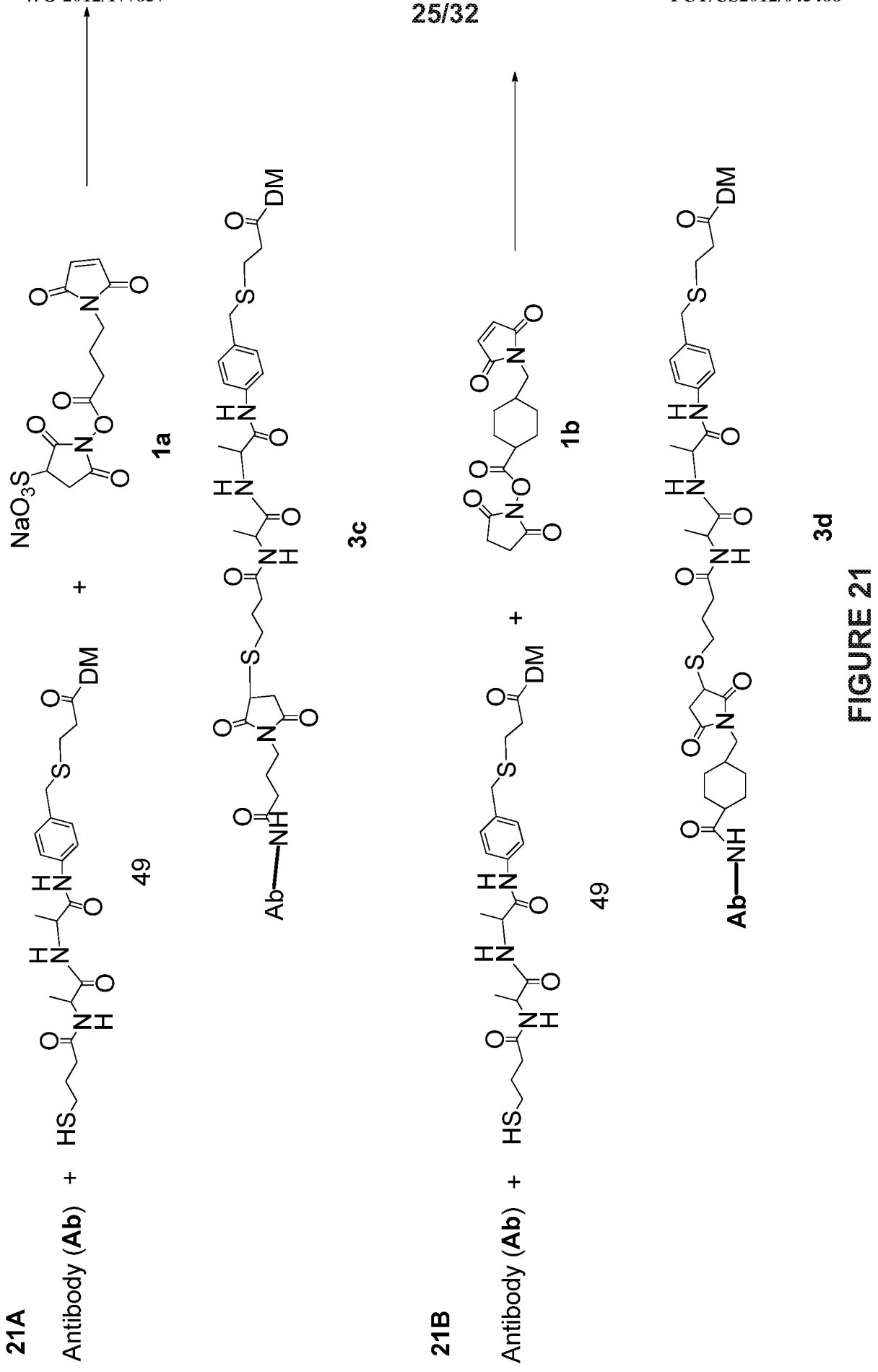

21A
Antibody (Ab)
+
HS
49
+
NaO3S
1a
Ab—NH
3c
21B
Antibody (Ab)
+
HS
49
+
1b
Ab—NH
3d

FIGURE 21

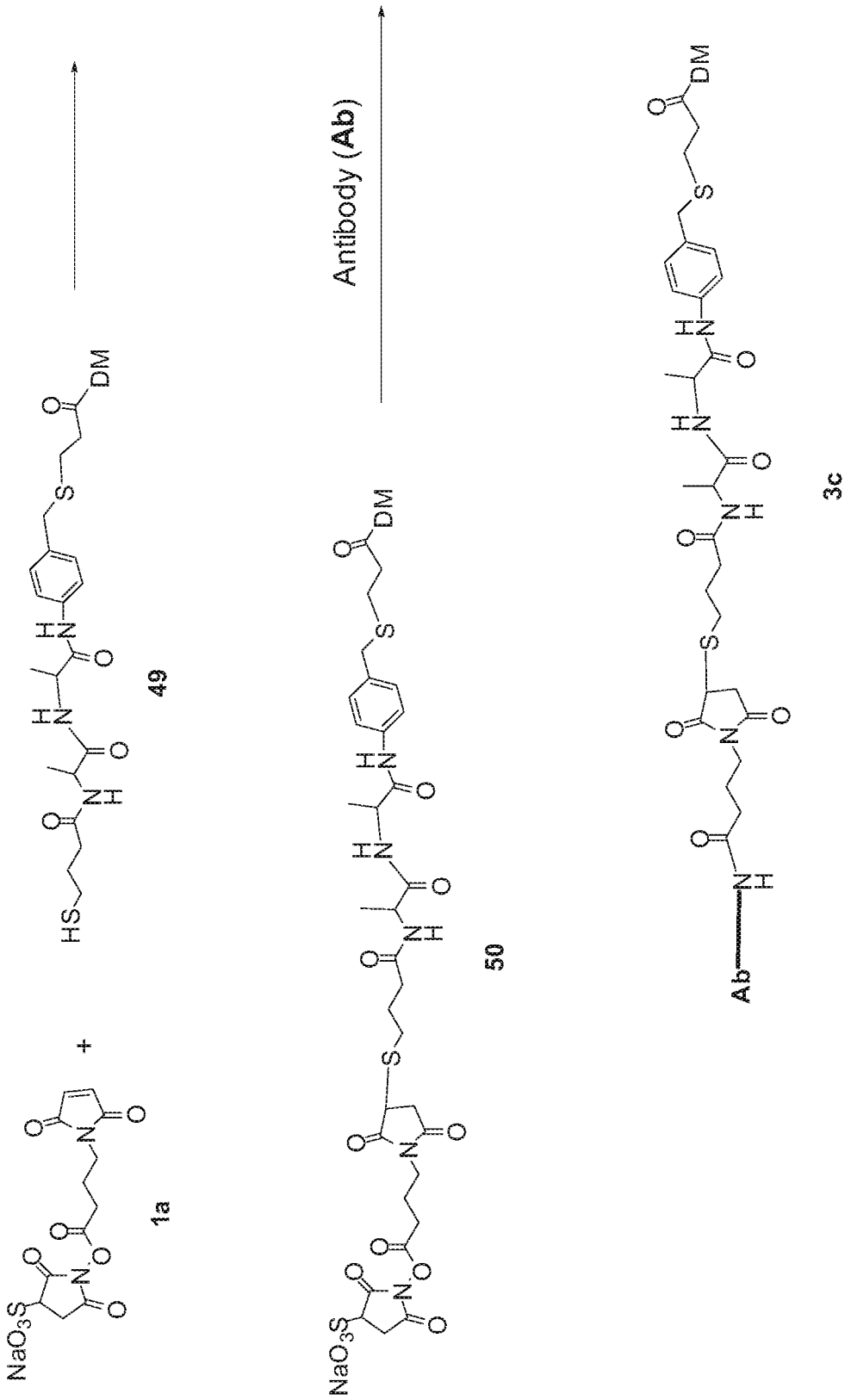


FIGURE 22A

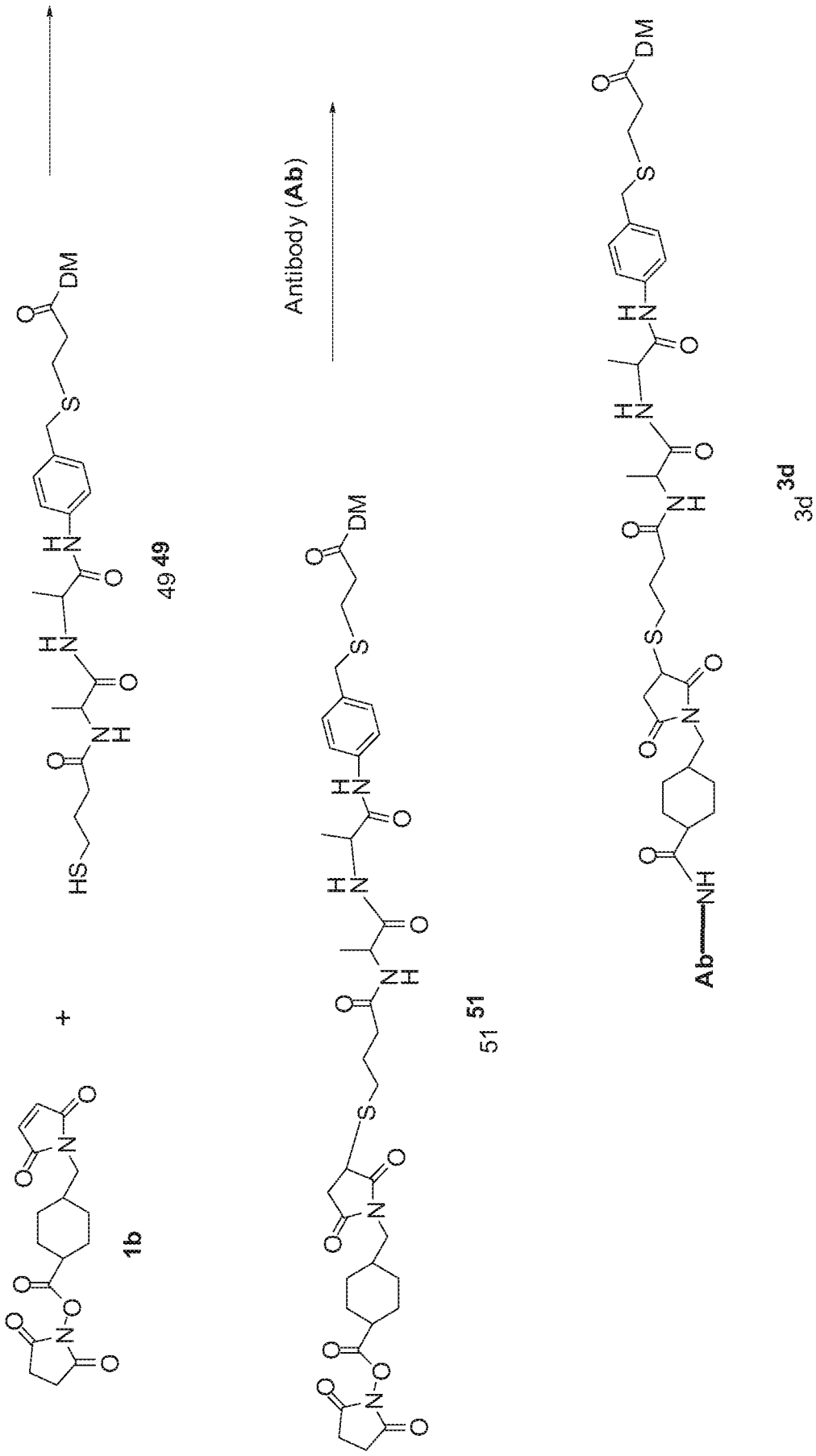


FIGURE 22B

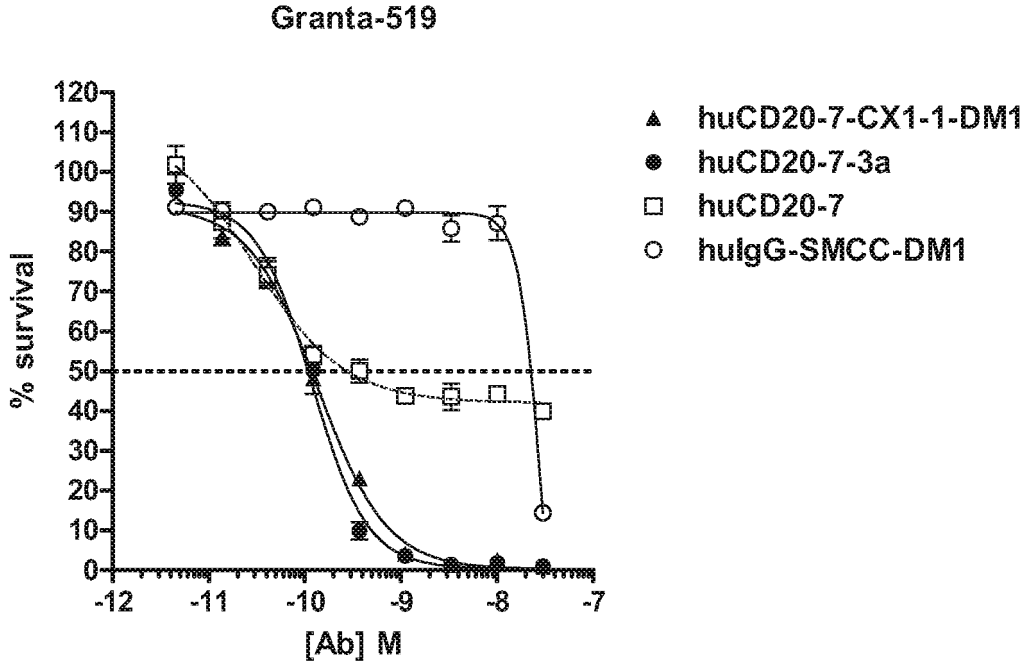


FIGURE 23A

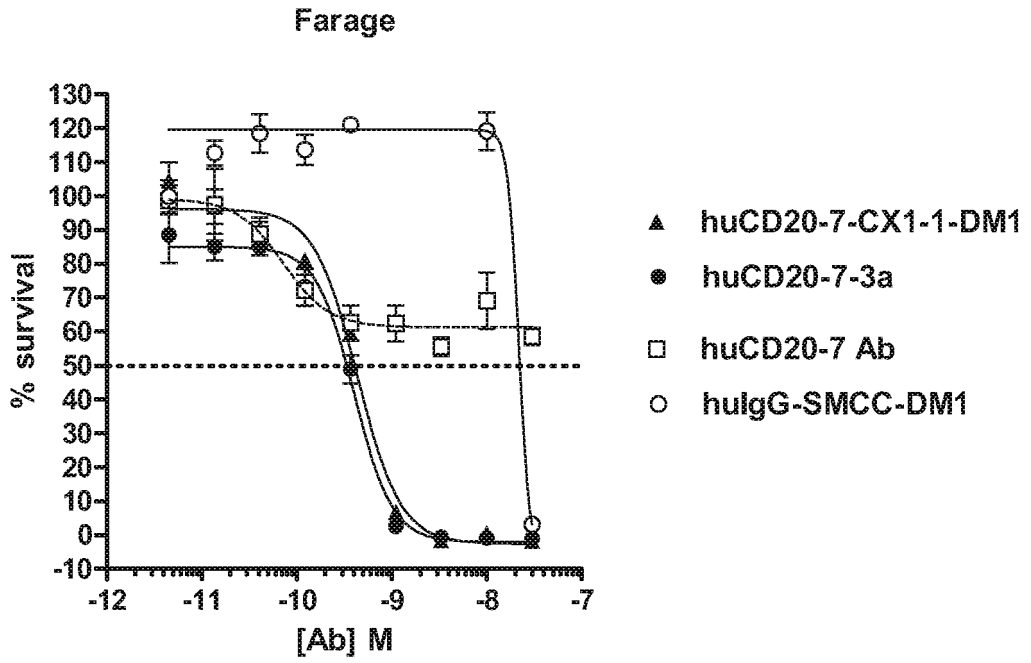


FIGURE 23B

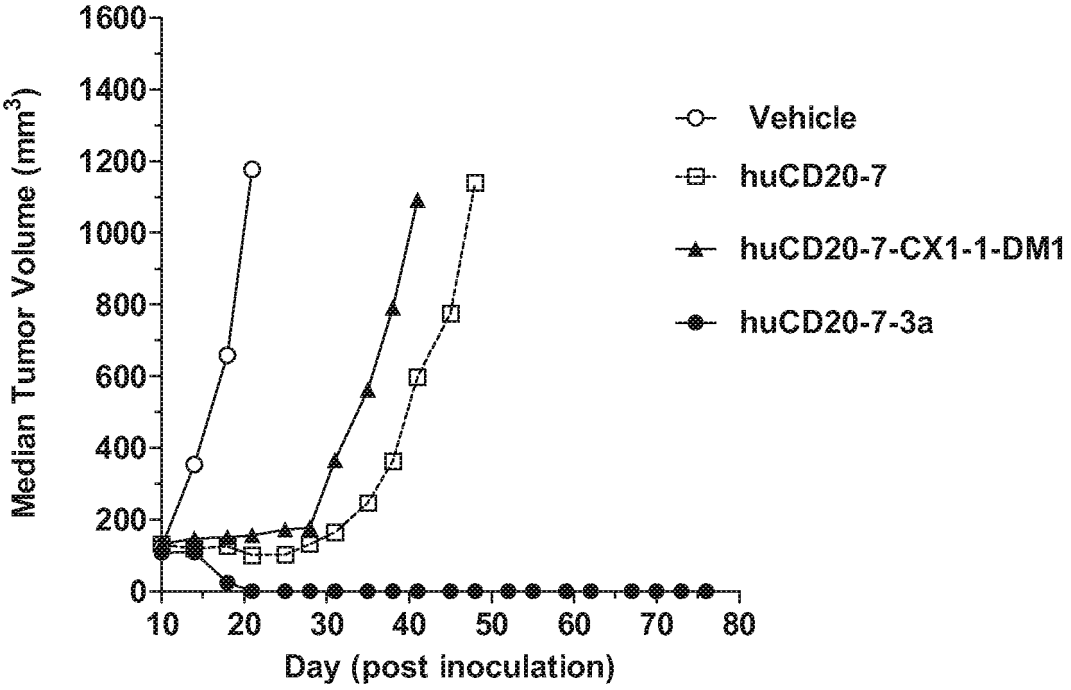
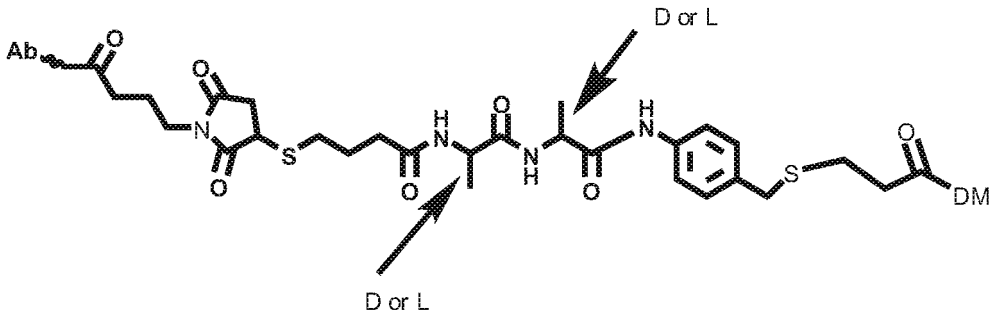


FIGURE 24



huEGFR-7R-(D/L)A(D/L)A-PAB-DM1

FIGURE 25

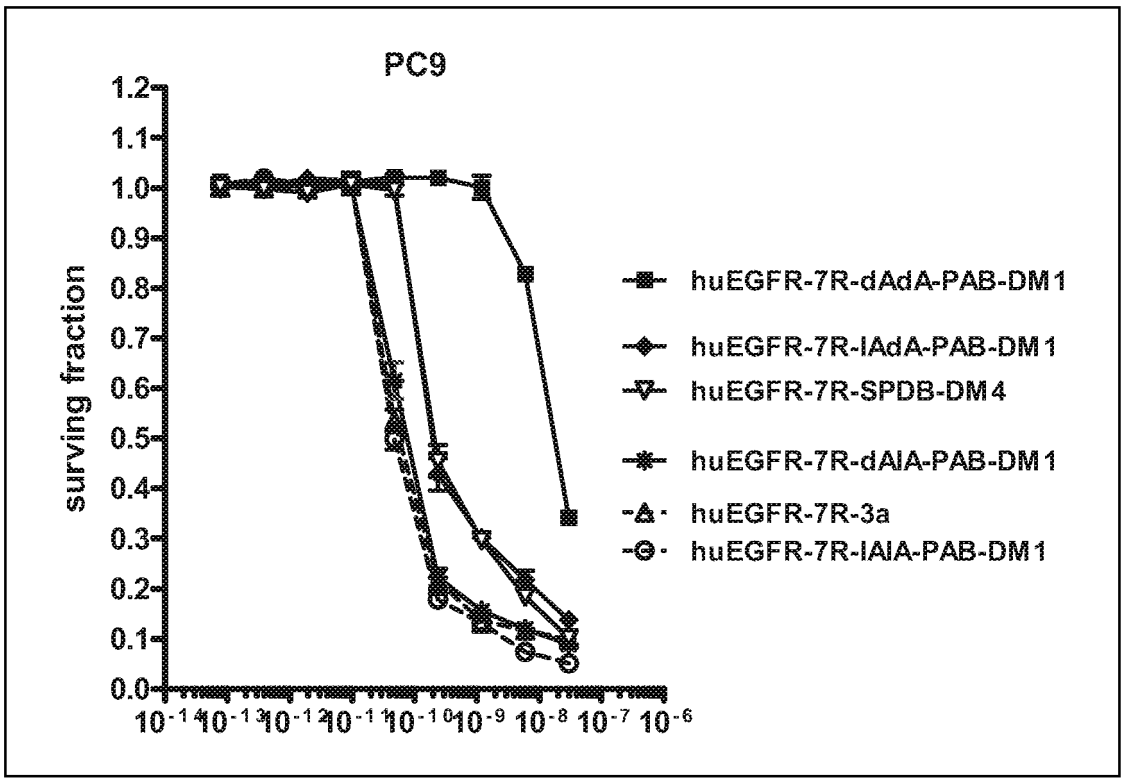


FIGURE 26A

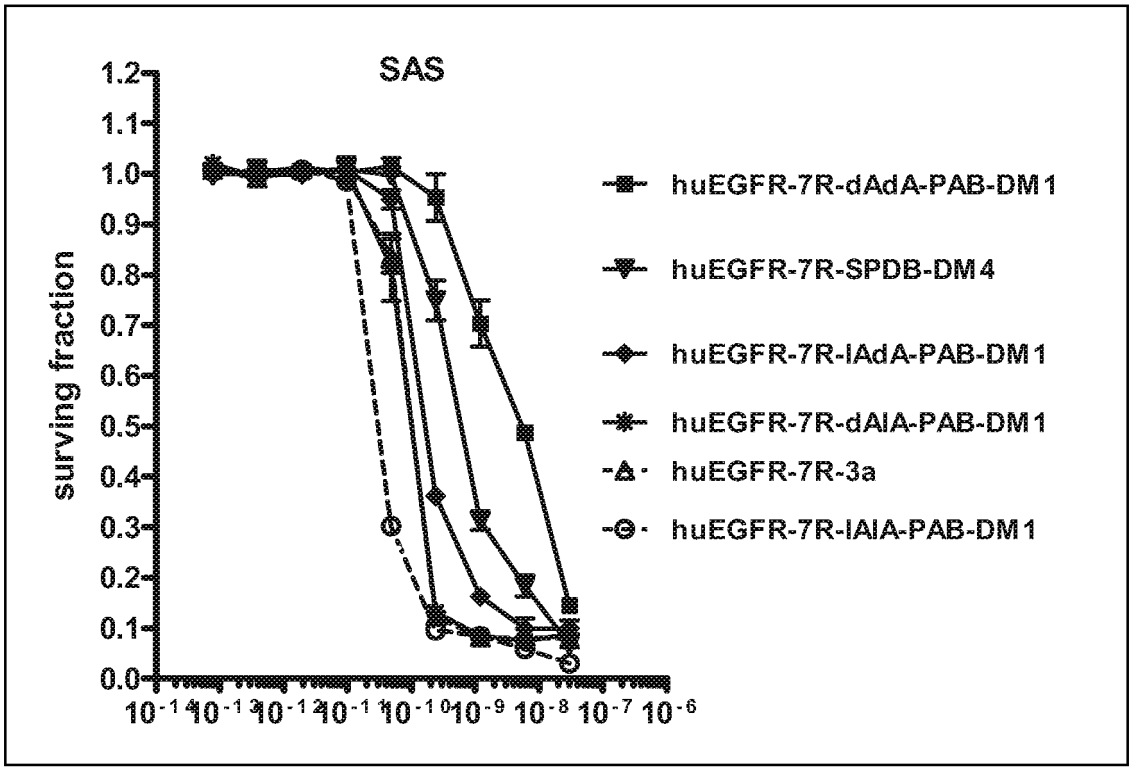


FIGURE 26B

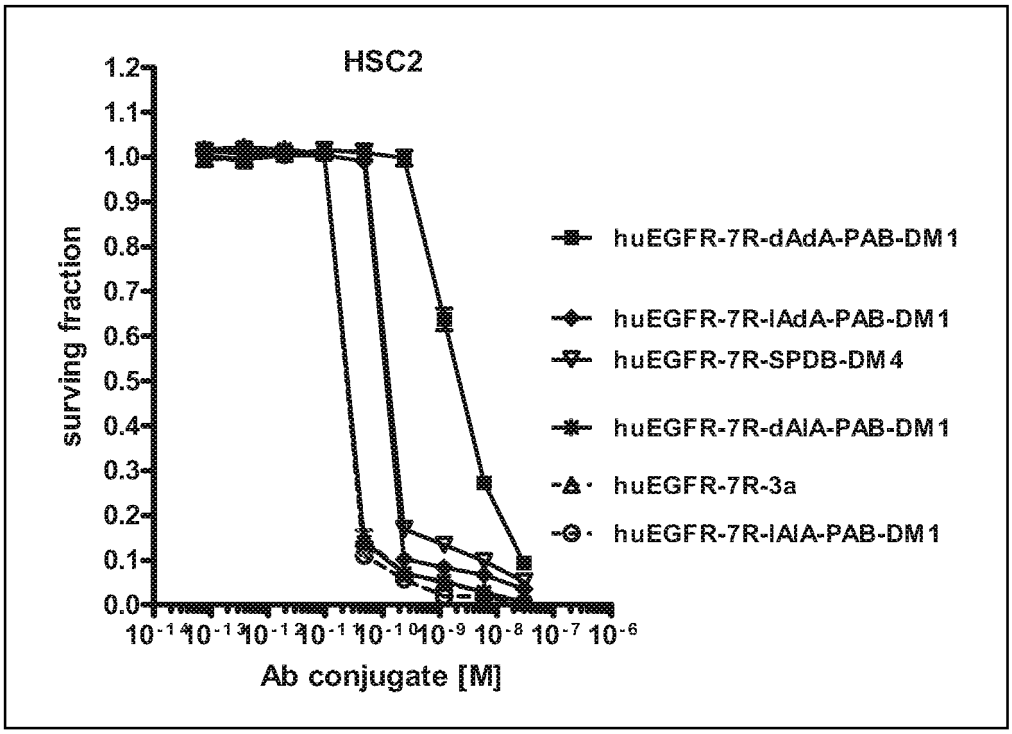


FIGURE 26C

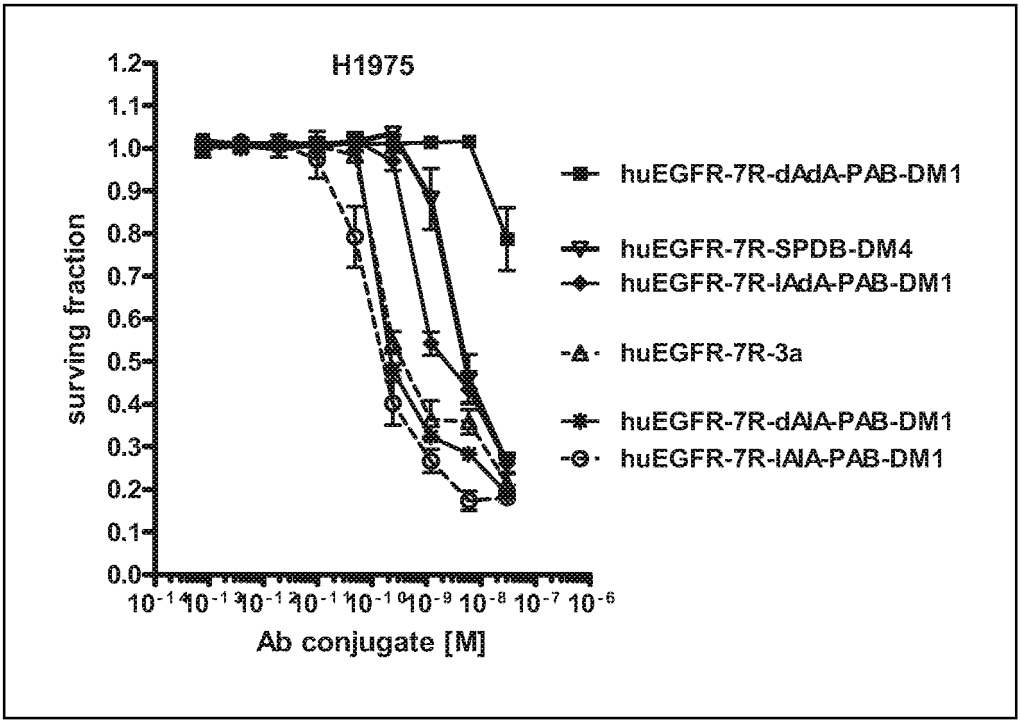


FIGURE 26D

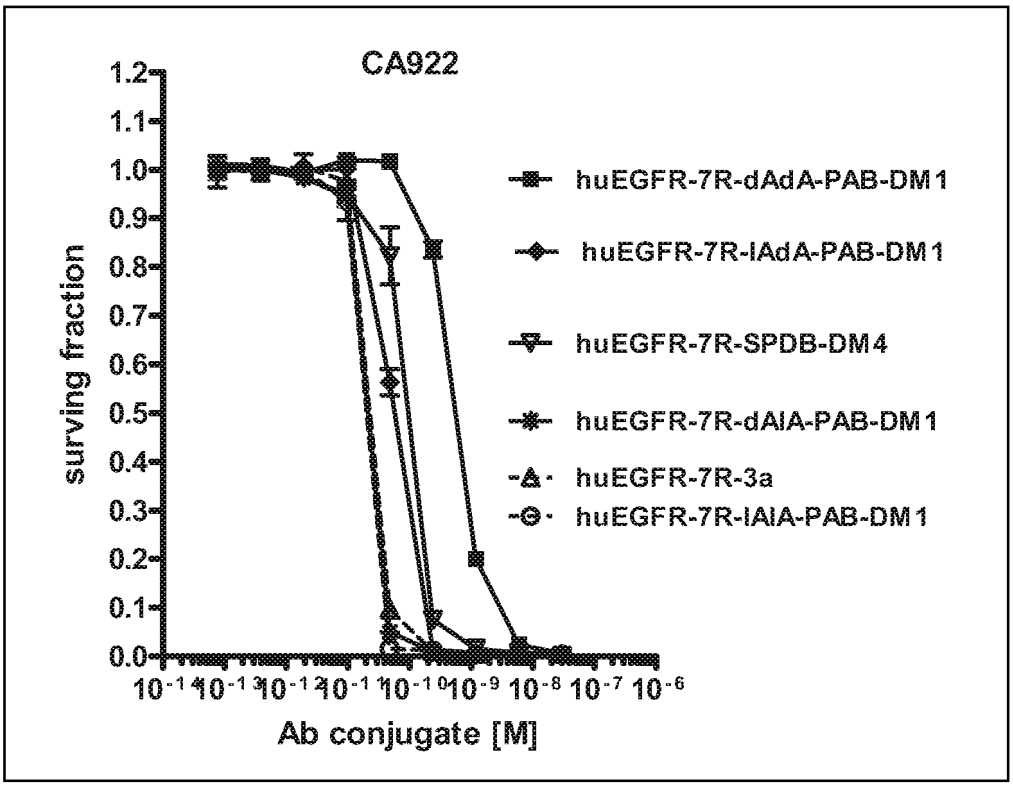


FIGURE 26E

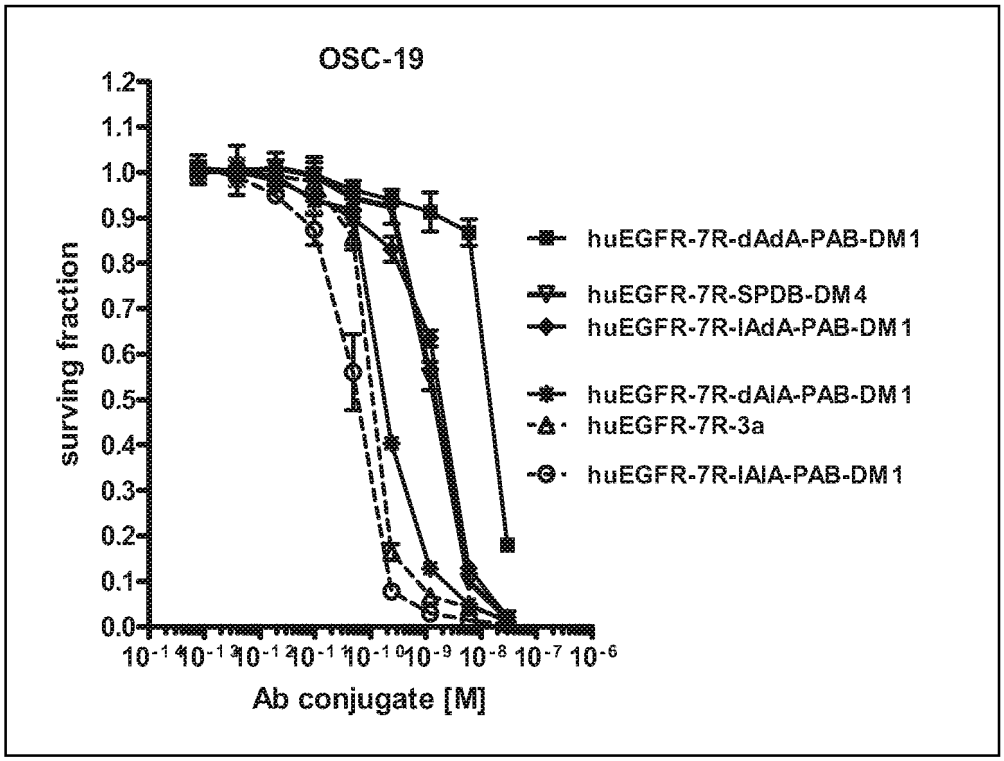


FIGURE 26F