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Fig. 1

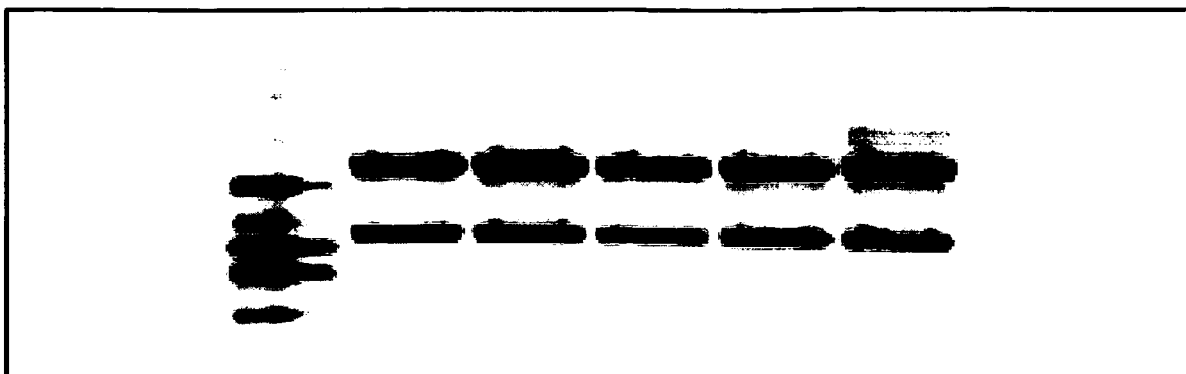


Fig. 2

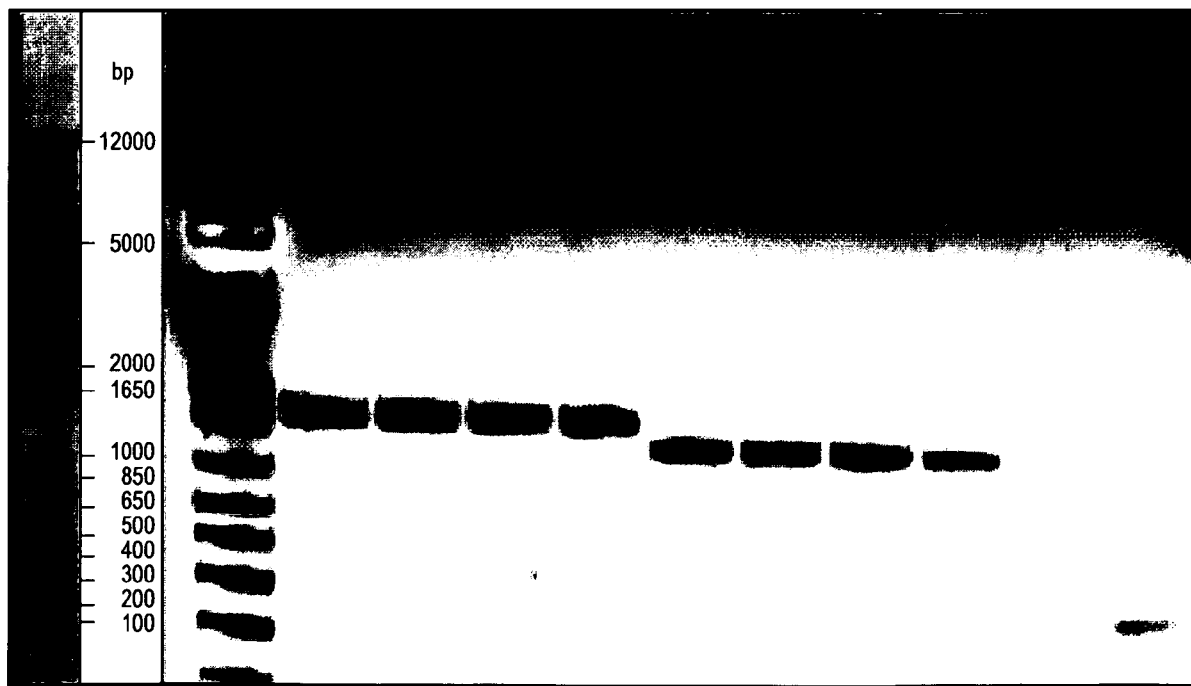


Fig. 3

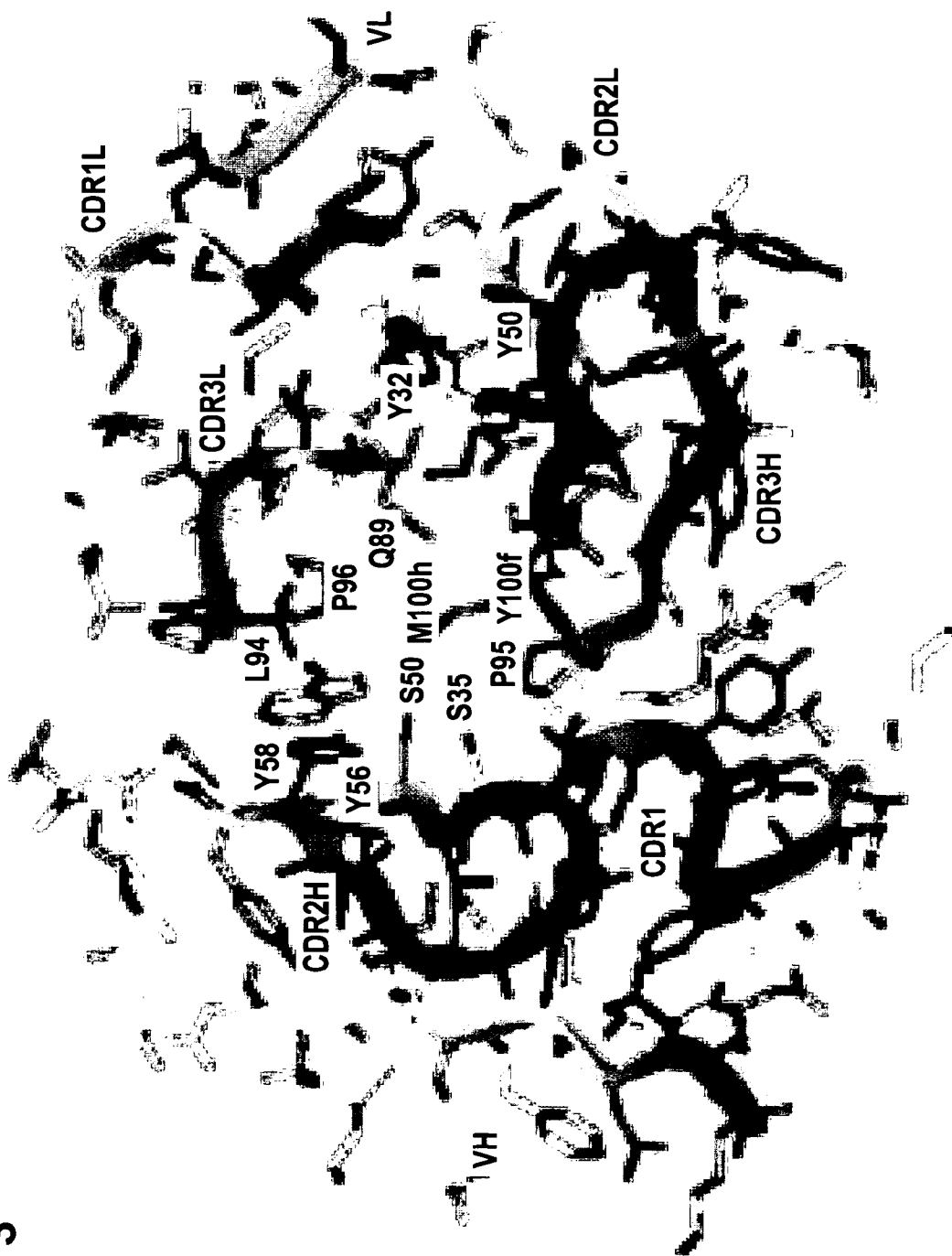
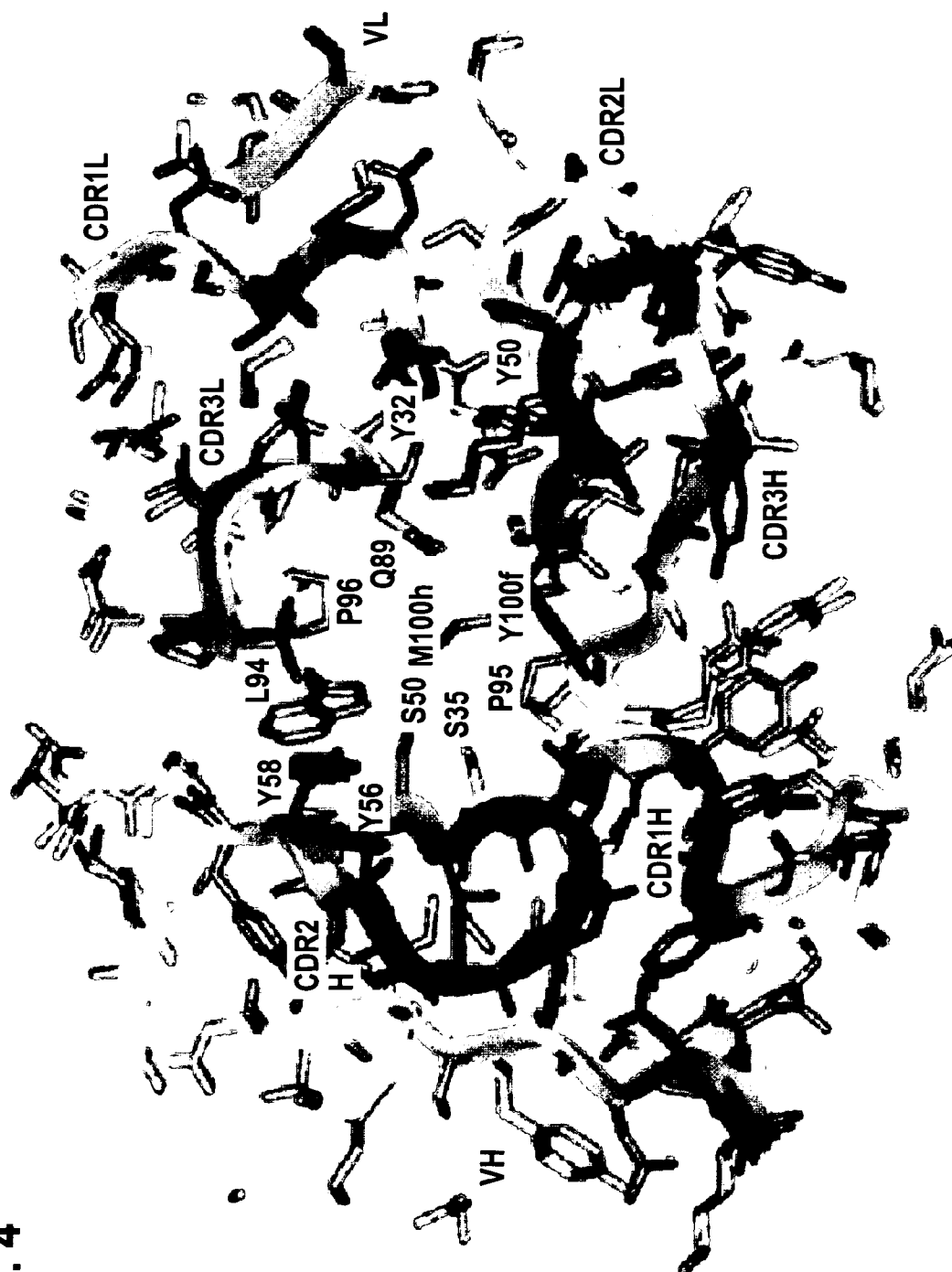
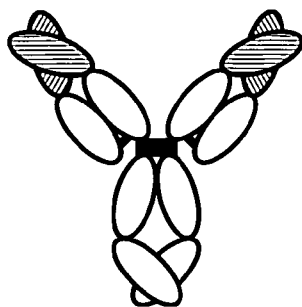
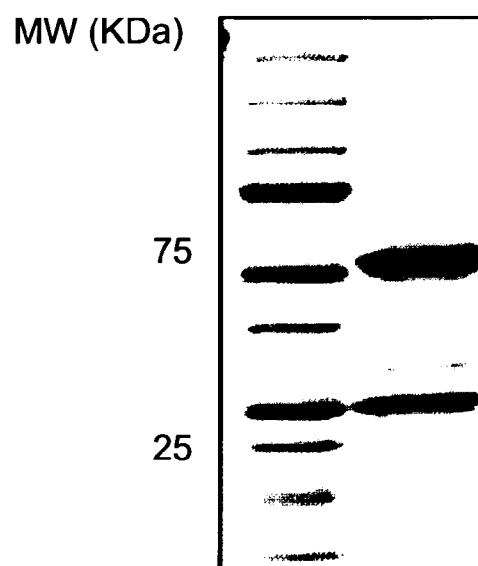
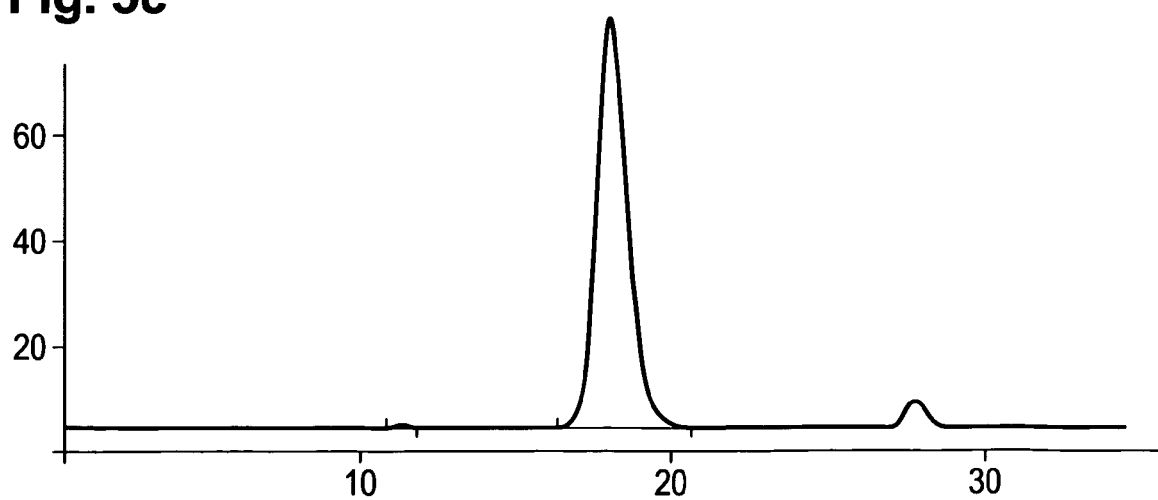


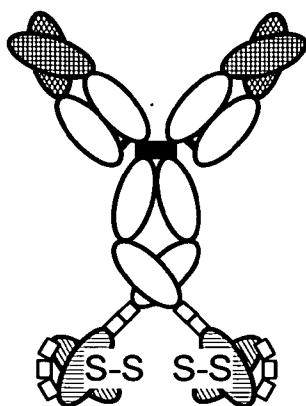
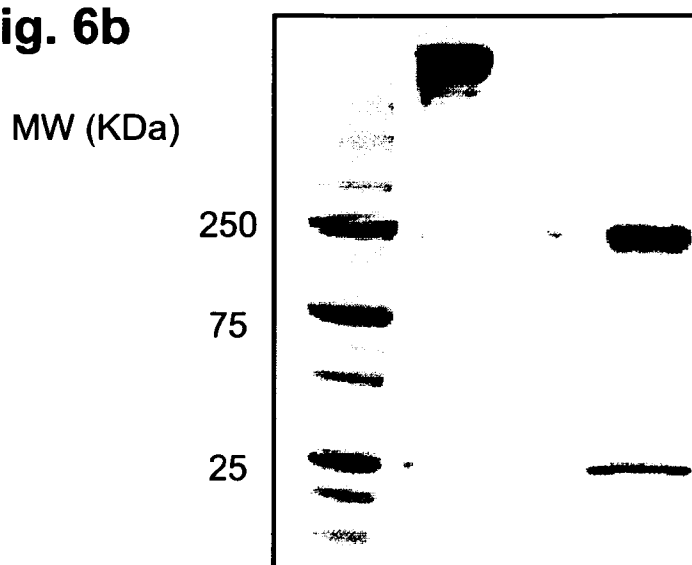
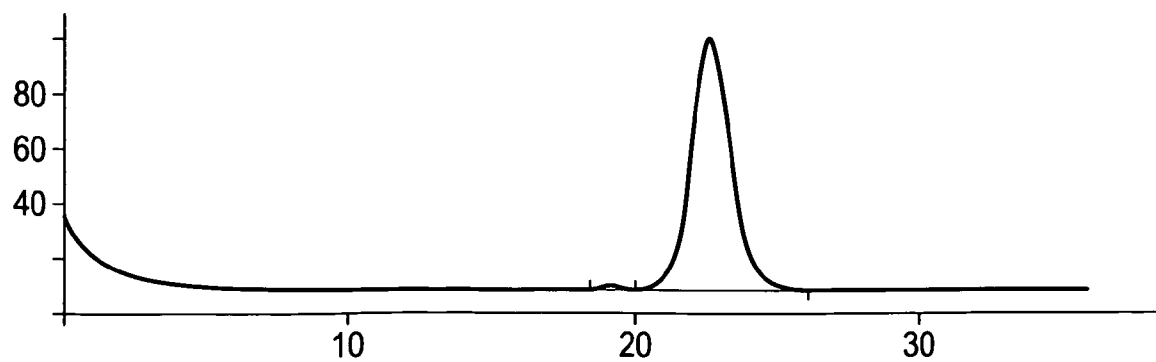
Fig. 4



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Fig. 5a**Fig. 5b****Fig. 5c**

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Fig. 6a**Fig. 6b****Fig. 6c**

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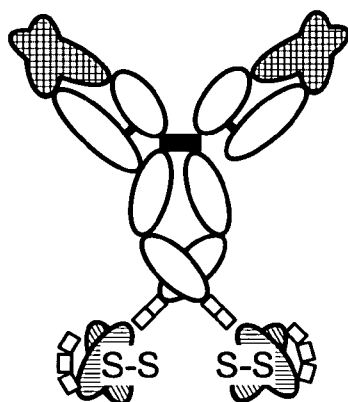
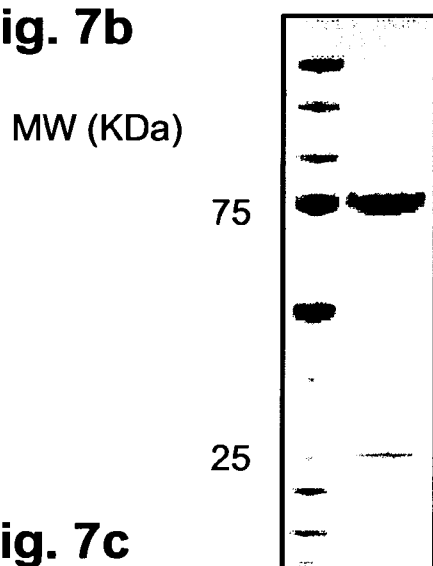
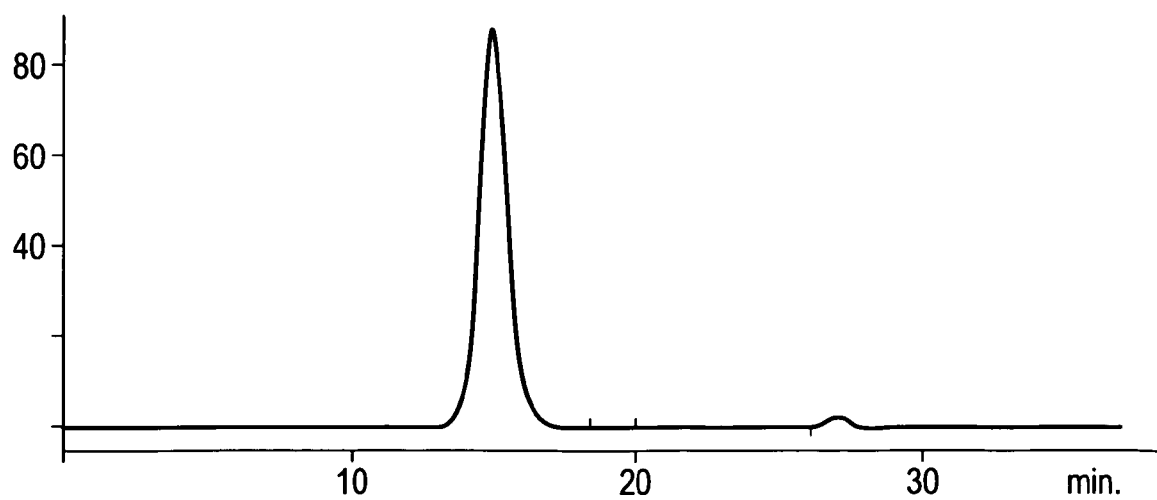
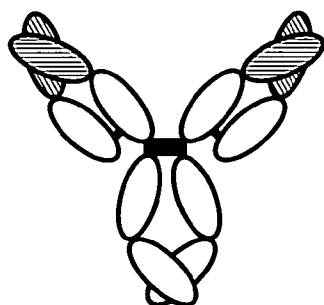
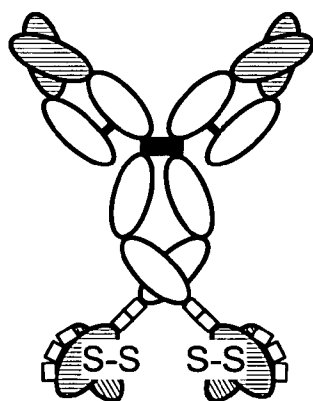
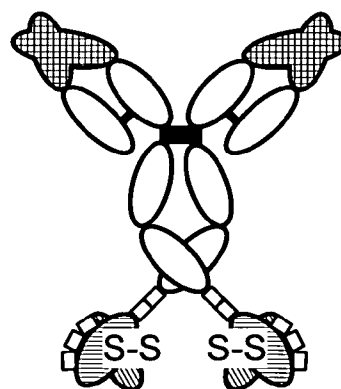
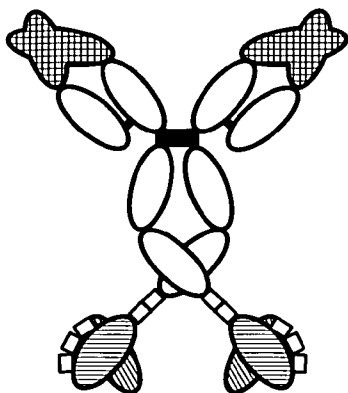
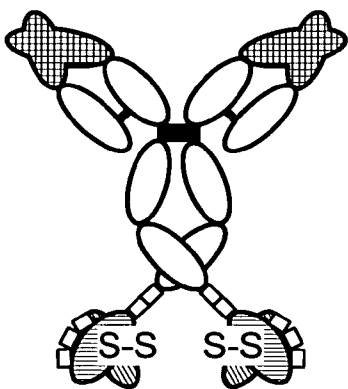
Fig. 7a**Fig. 7b****Fig. 7c**

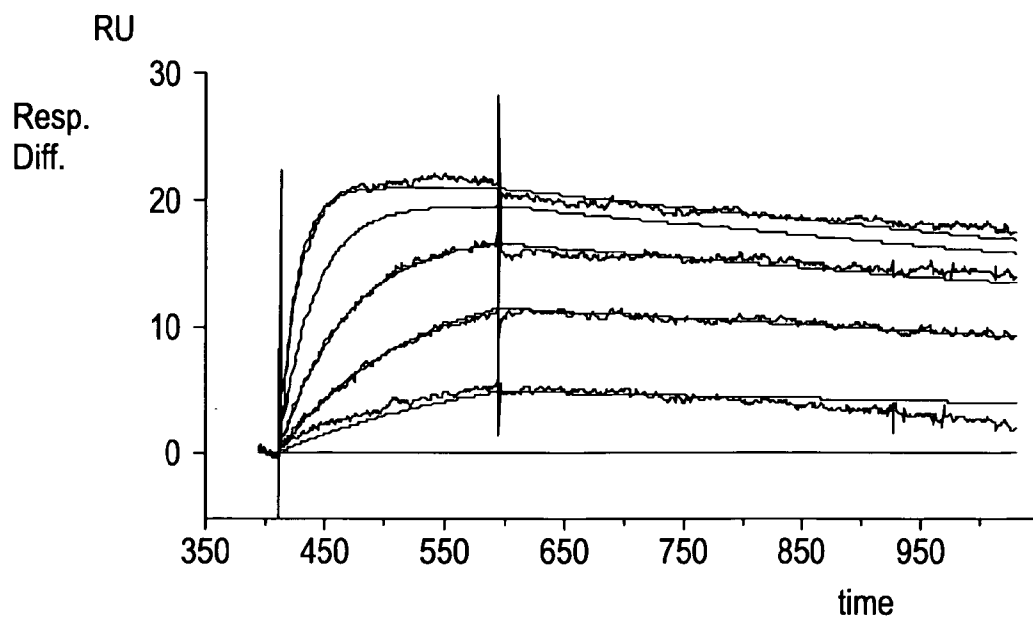
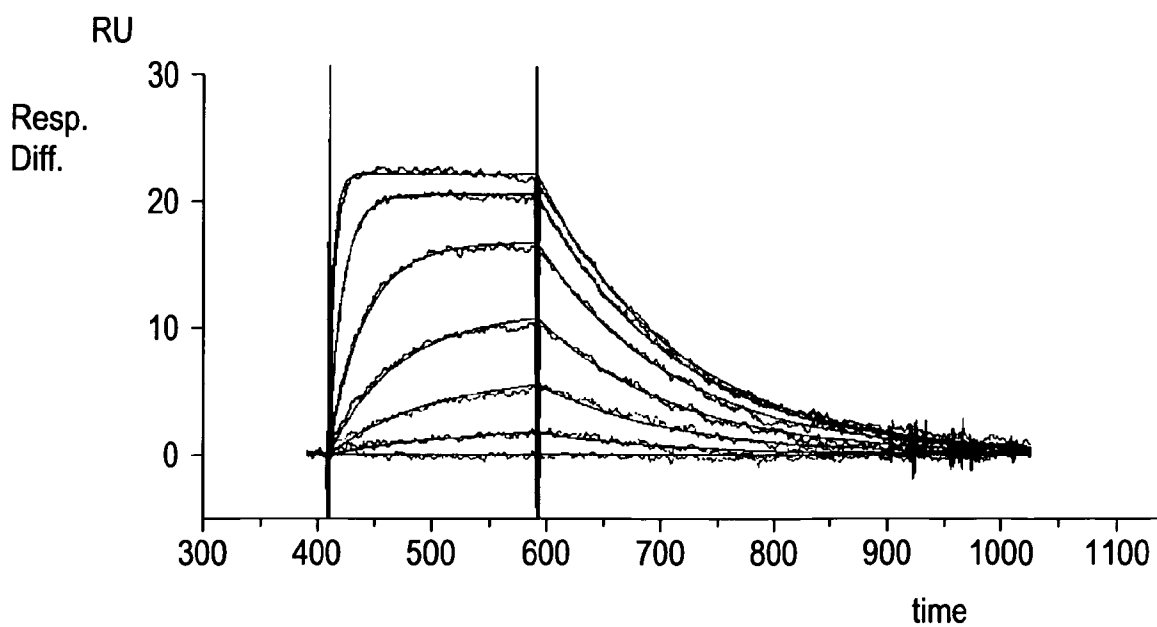
Fig. 8a**Fig. 8b****Fig. 8c****Fig. 8d**

Construct Name	Expression mg/L
A - hu<Dig> IgG	18.8
B - <IGF1R-DIG>2321 (disulfide-stabilized)	6.4
C - <Her2-DIG>2321 (disulfide-stabilized)	34.3

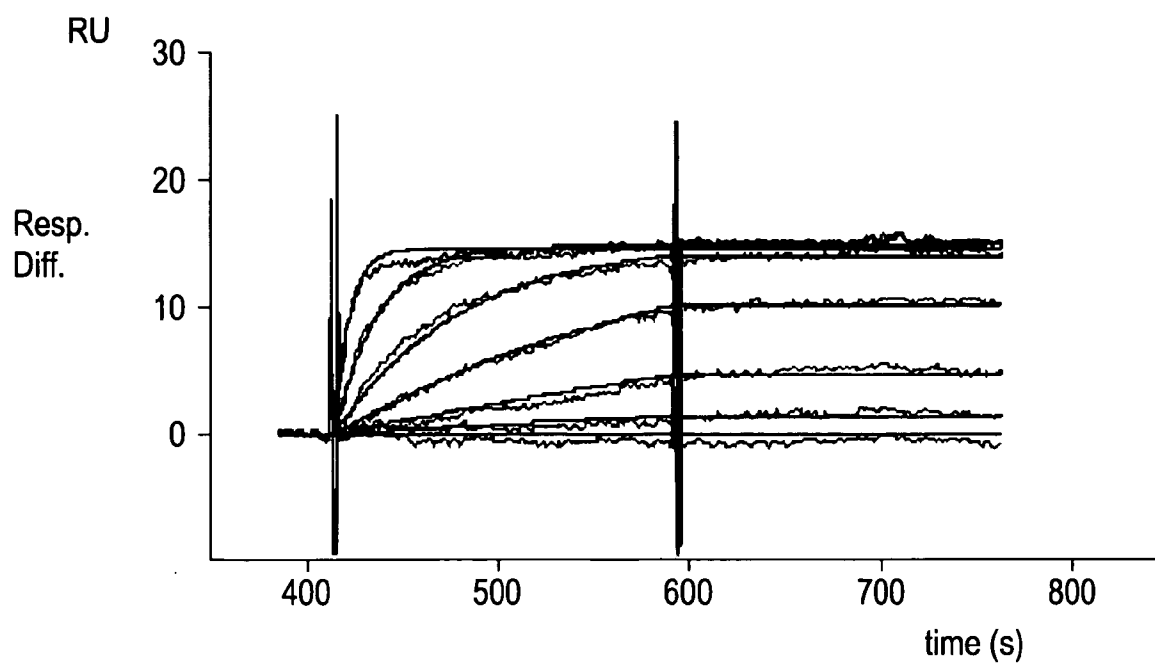
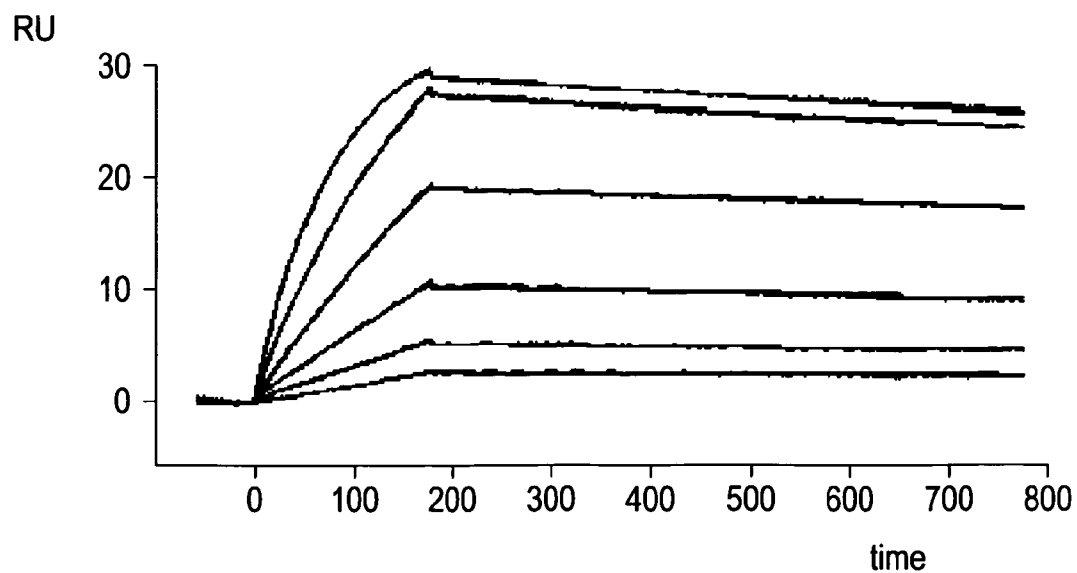
Fig. 9a**Fig. 9b****Fig. 9c**

Sample	Σ (mg)	Aggregates
Her2DIGHu2-2320	1	22 %
Her2DIGHu2-2321	31	0 %

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Fig. 10a**Fig. 10b**

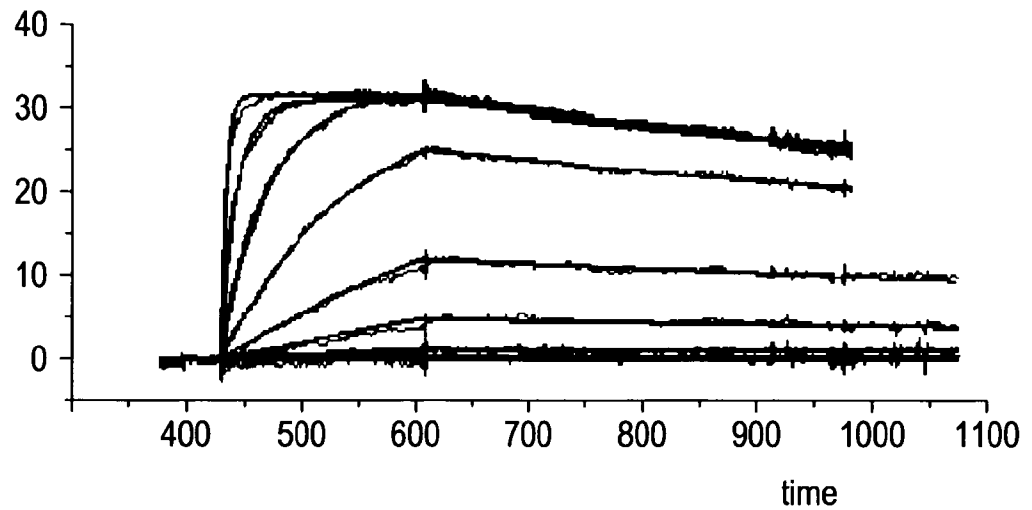
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Fig. 10c**Fig. 10d**

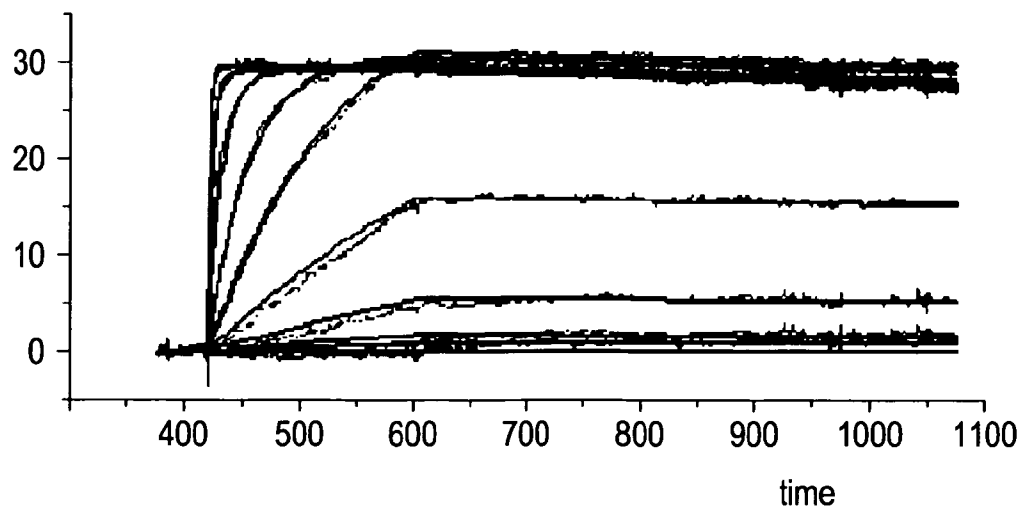
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Fig. 10e

RU

**Fig. 10f**

RU



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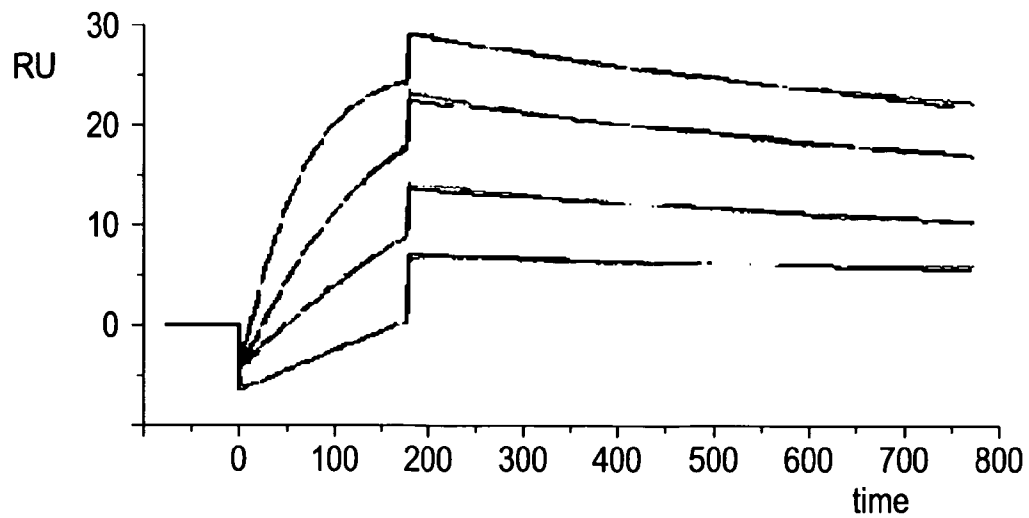
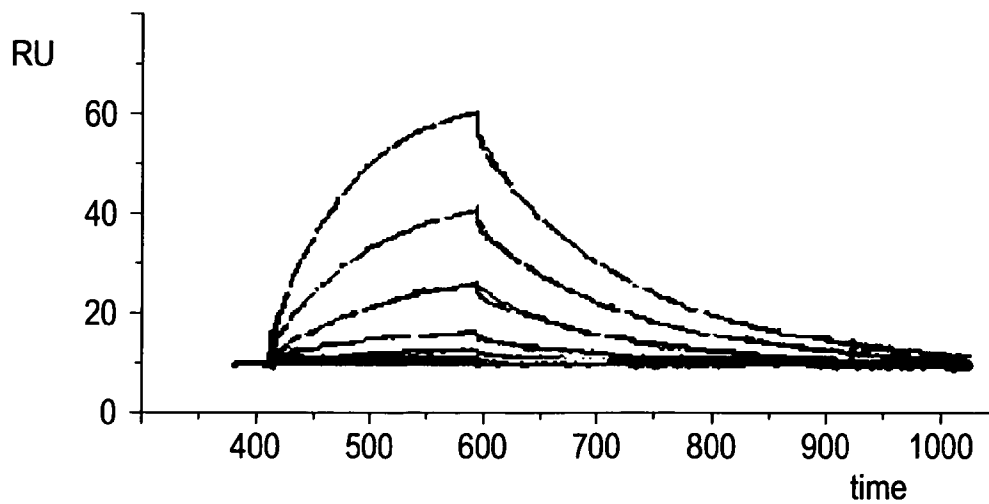
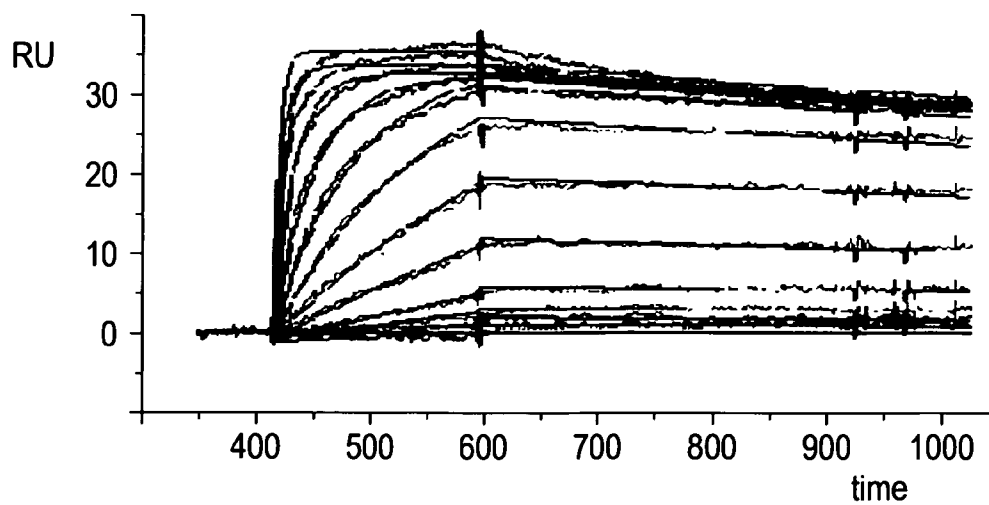
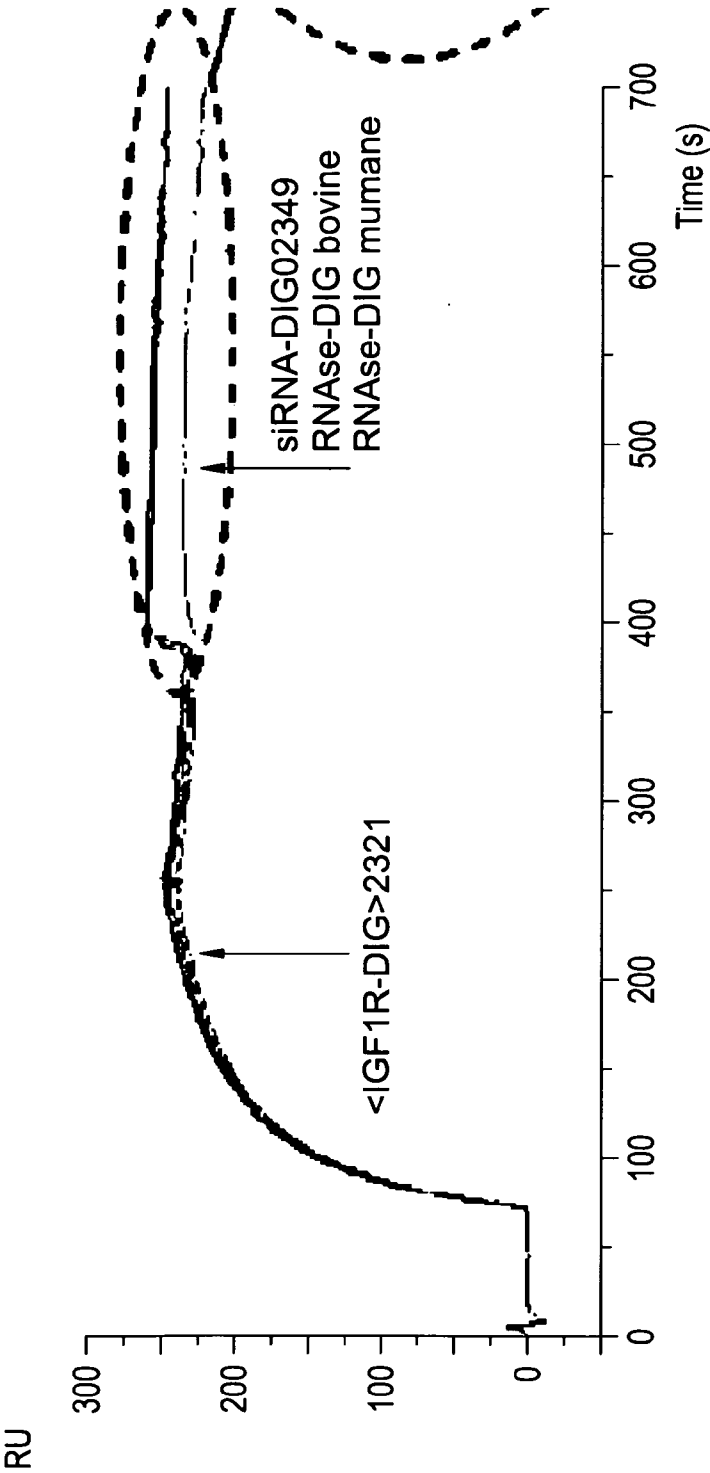
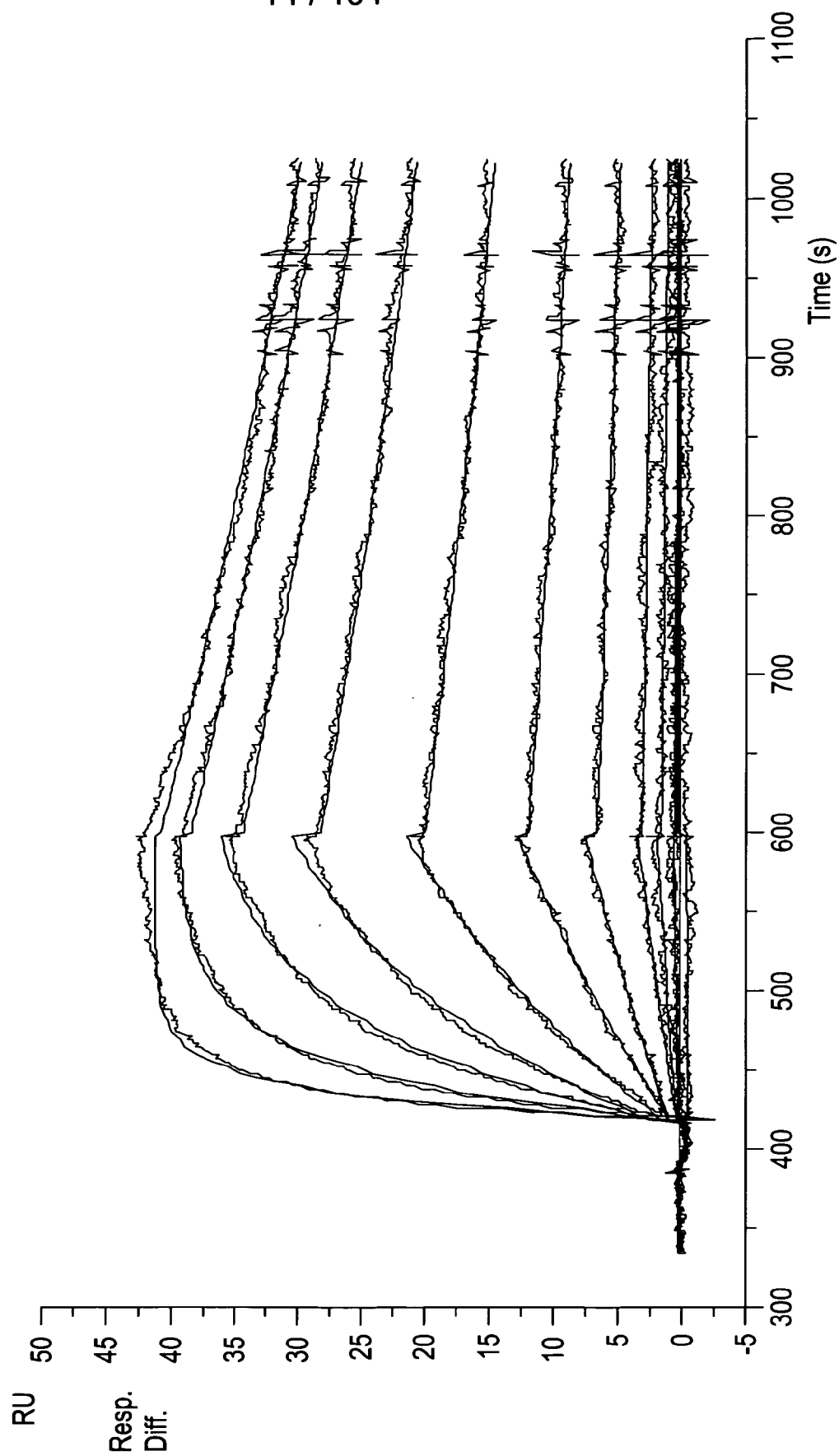
Fig. 11a**Fig. 11b****Fig. 11c**

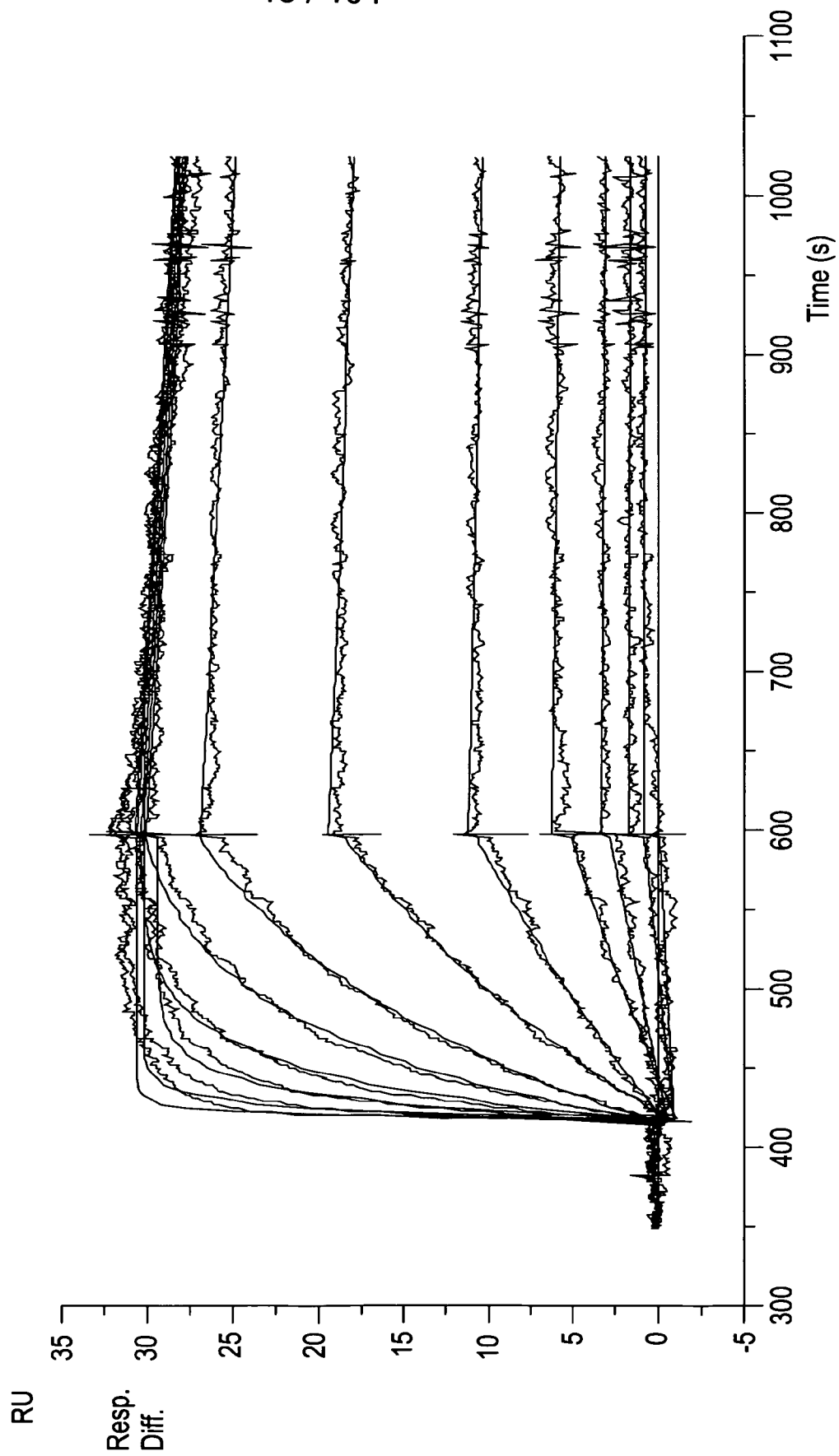
Fig. 12



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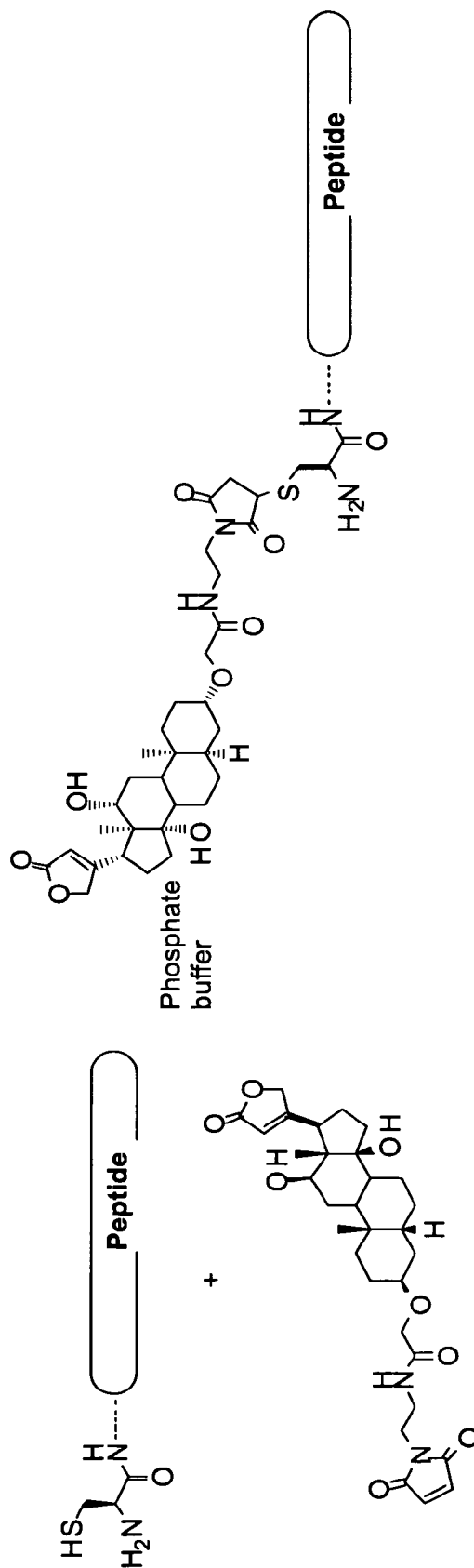
Fig. 13a

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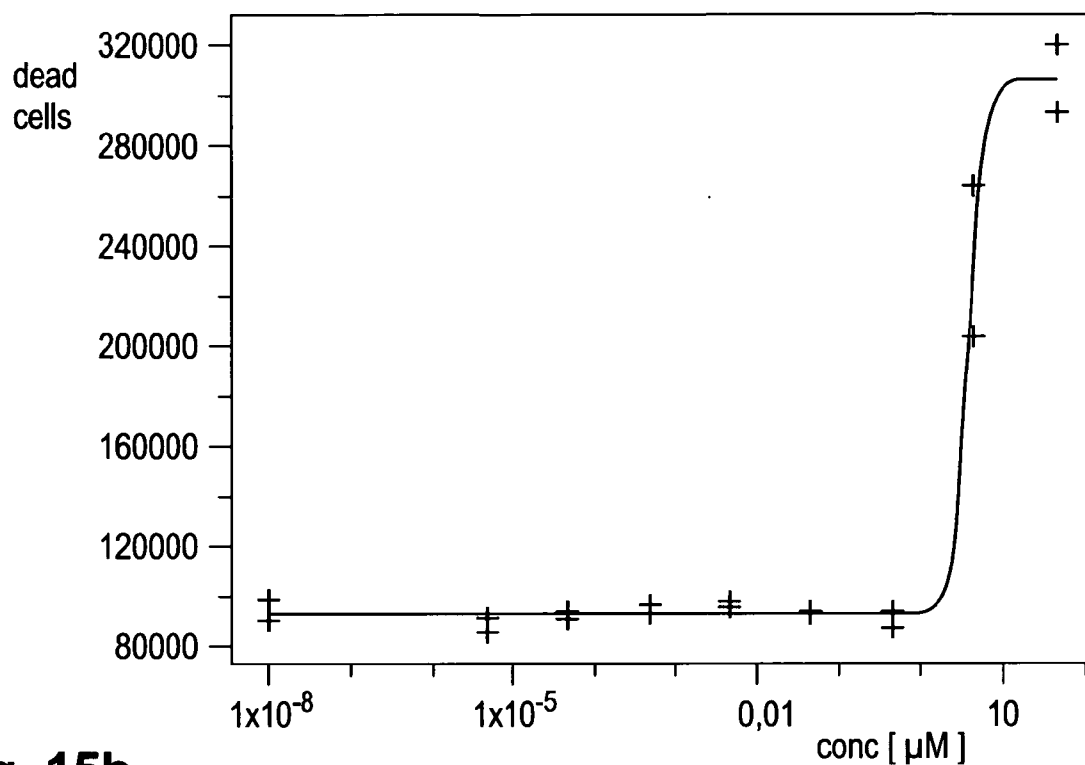
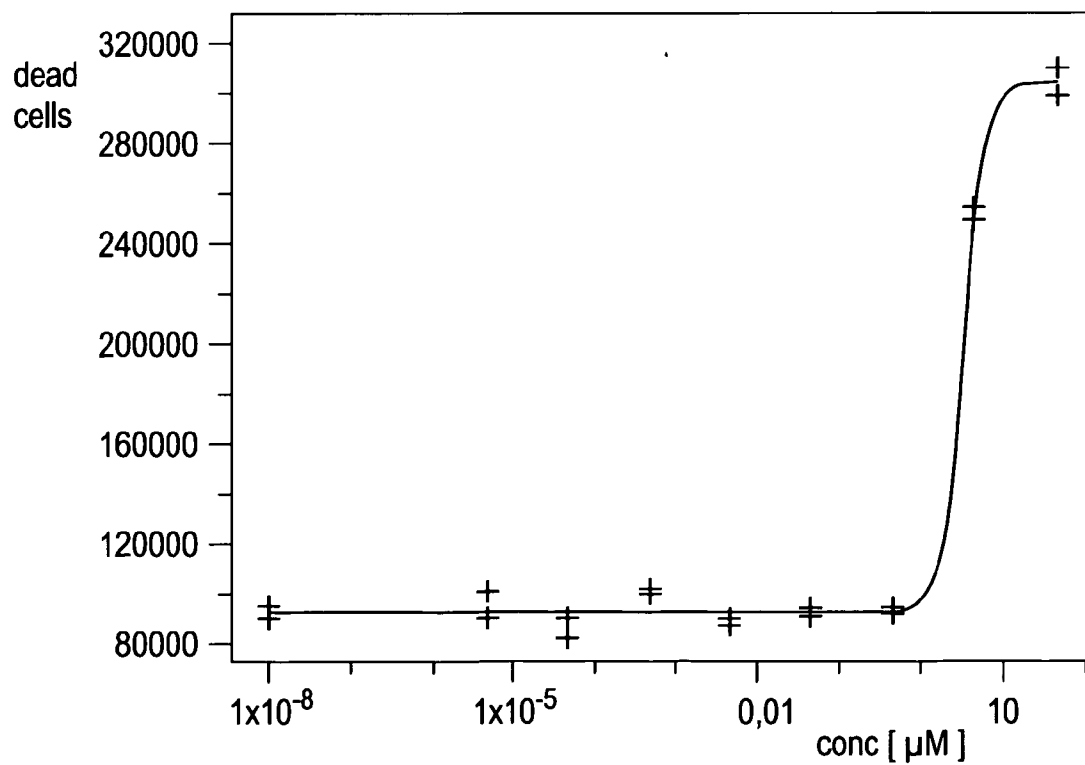
Fig. 13b

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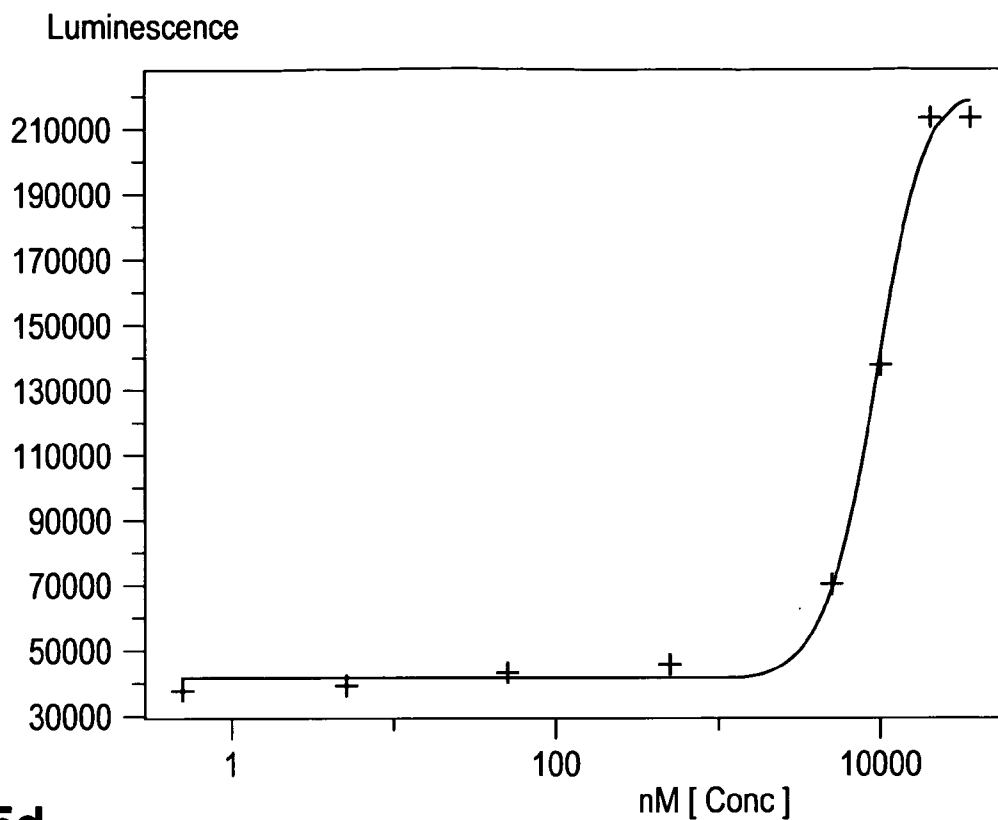
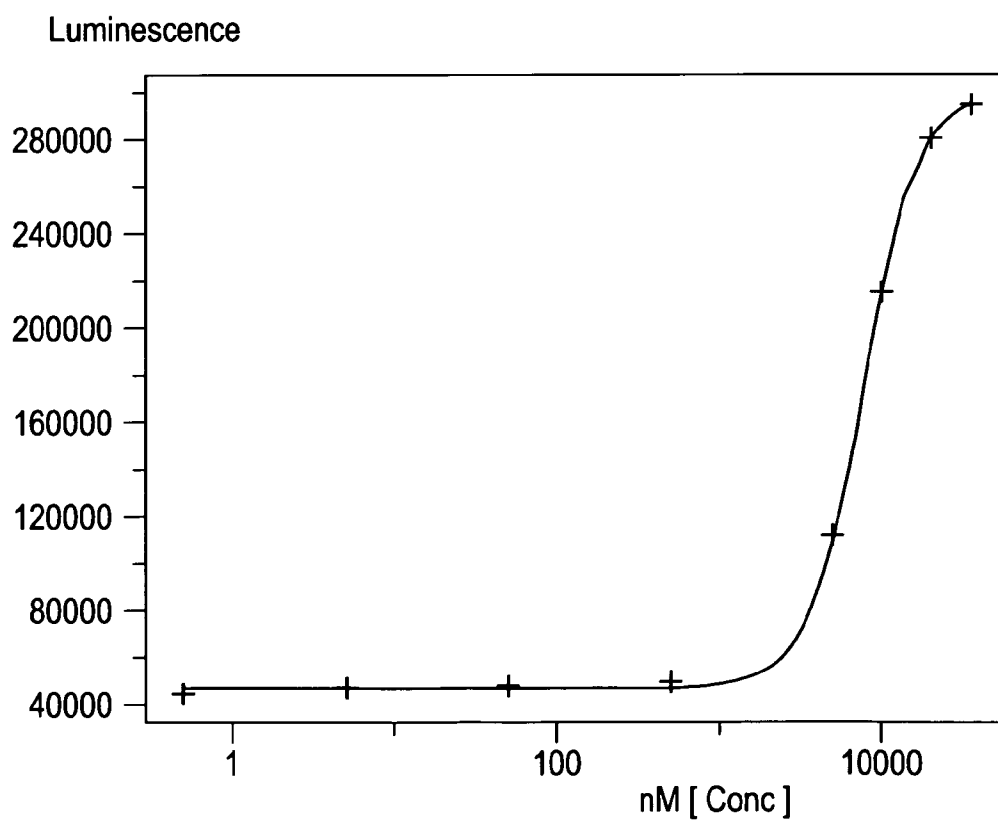
Fig. 14



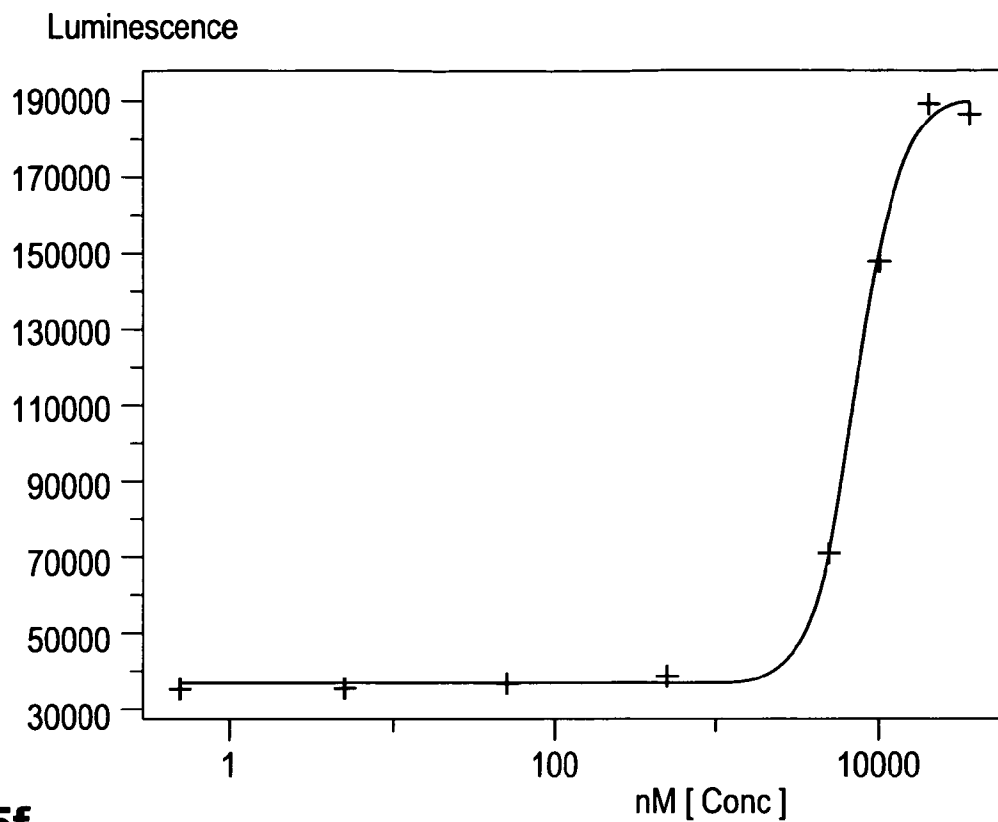
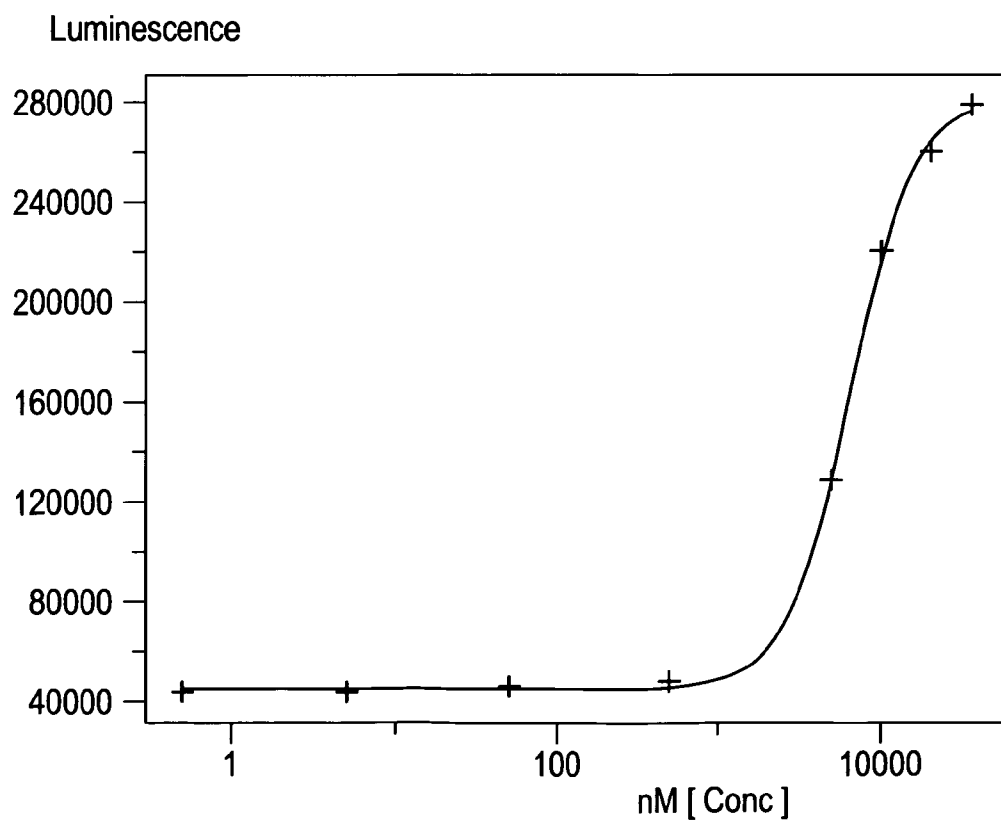
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Fig. 15a**Fig. 15b**

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Fig. 15c**Fig. 15d**

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Fig. 15e**Fig. 15f**

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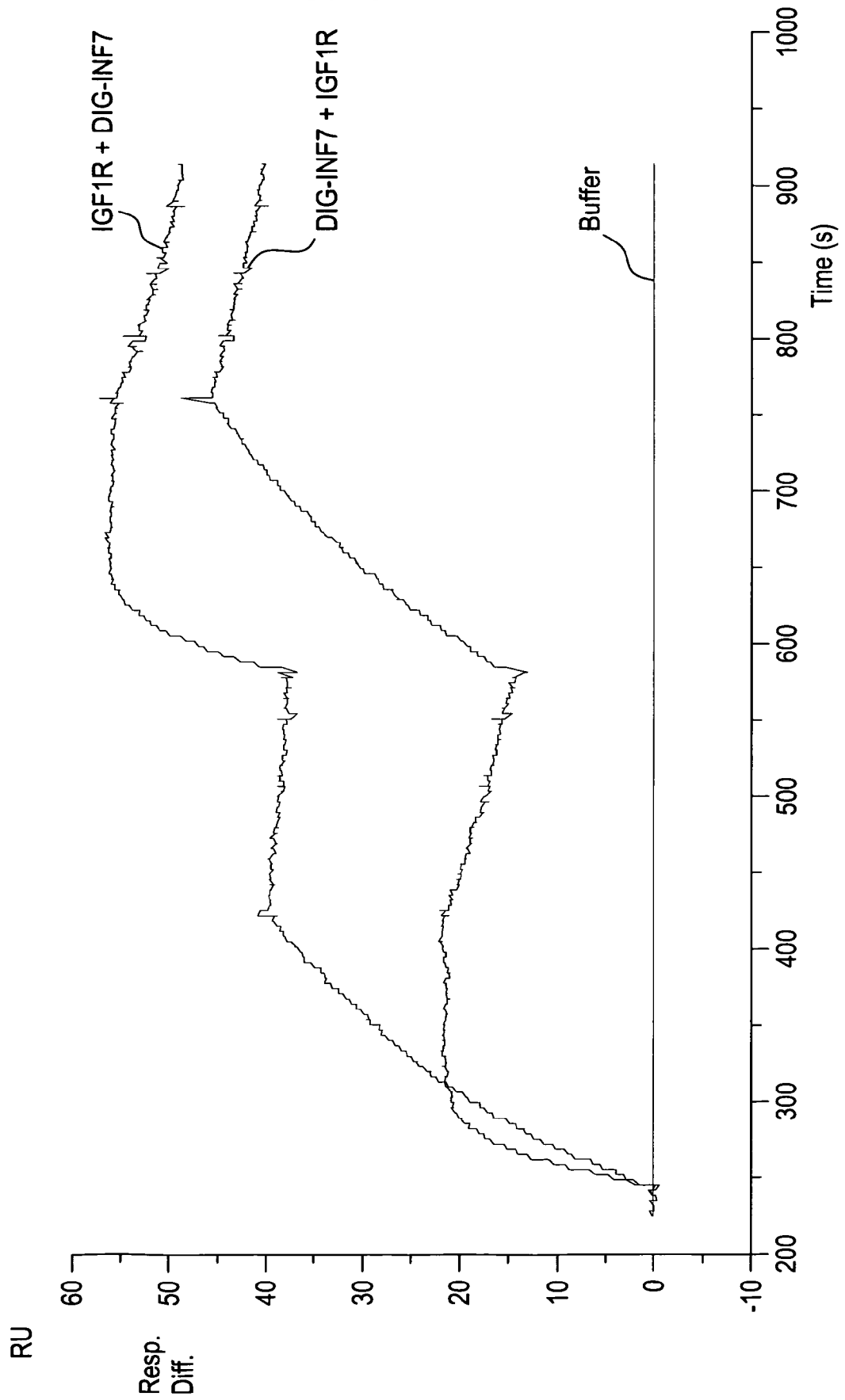
Fig. 16a

Fig. 16b

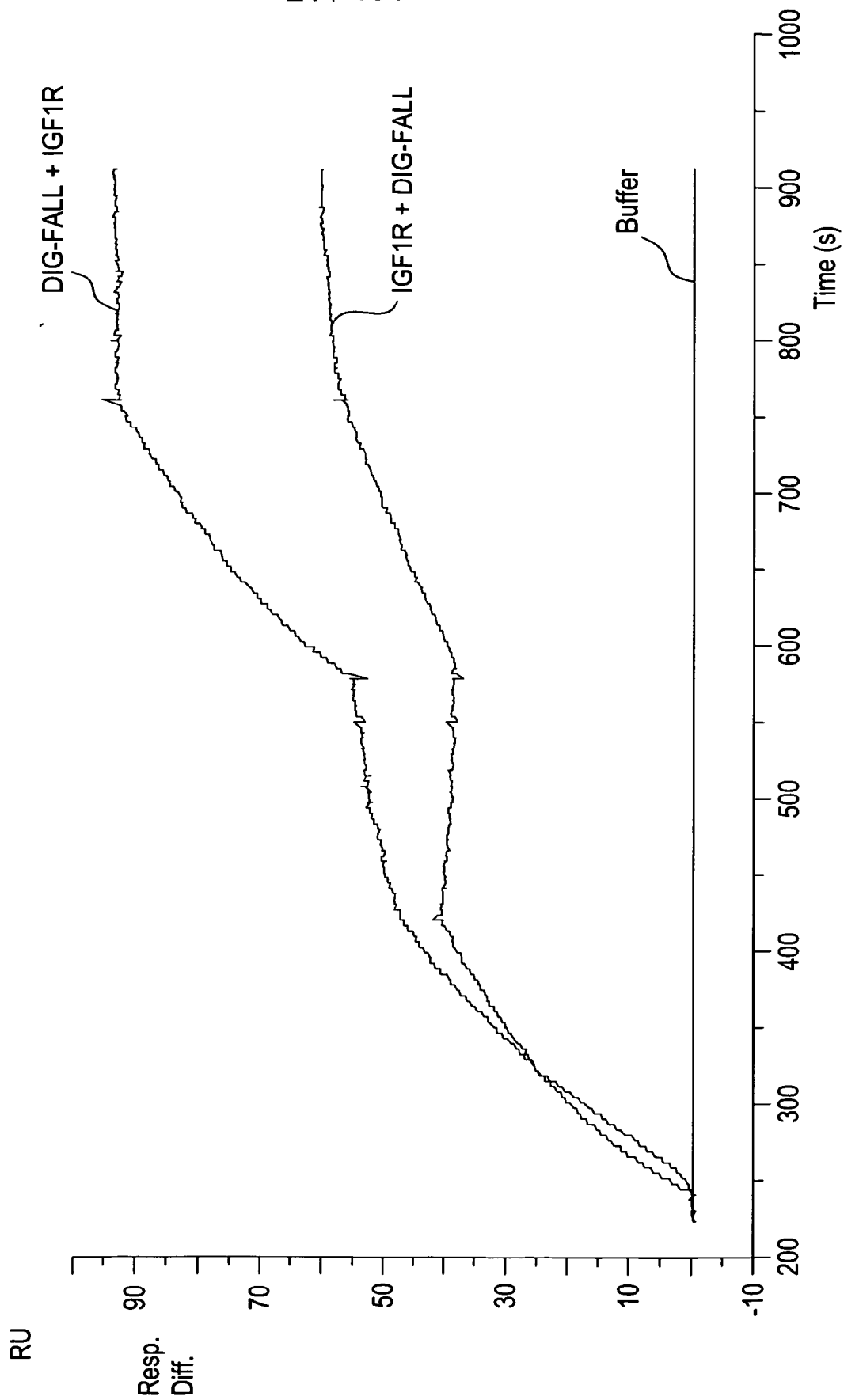
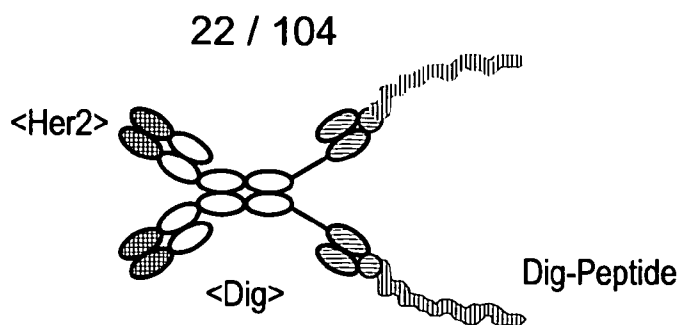
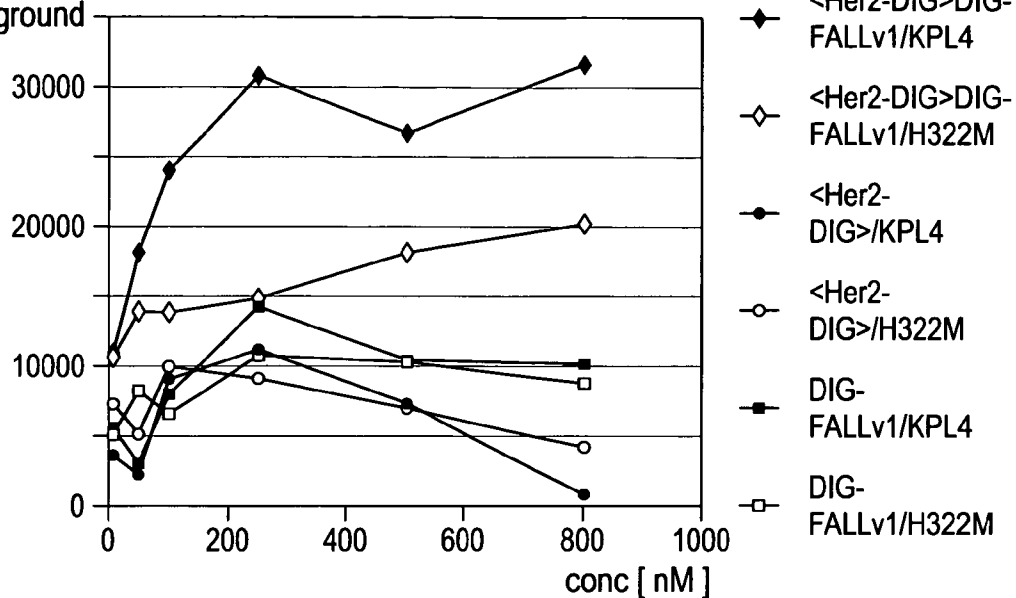


Fig. 17a**Fig. 17b**

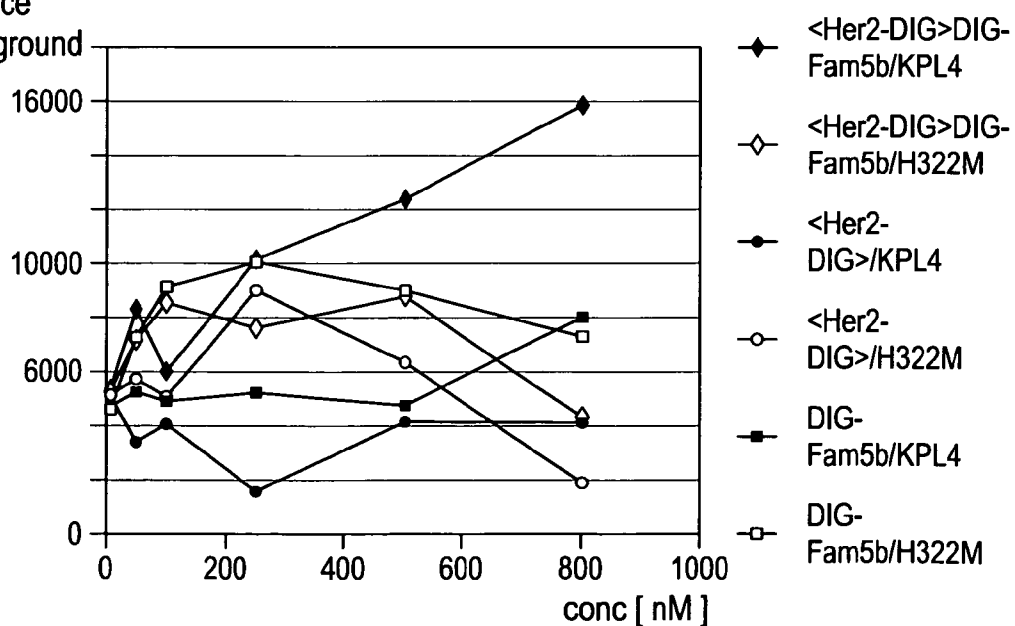
Luminescence

above background

**Fig. 17c**

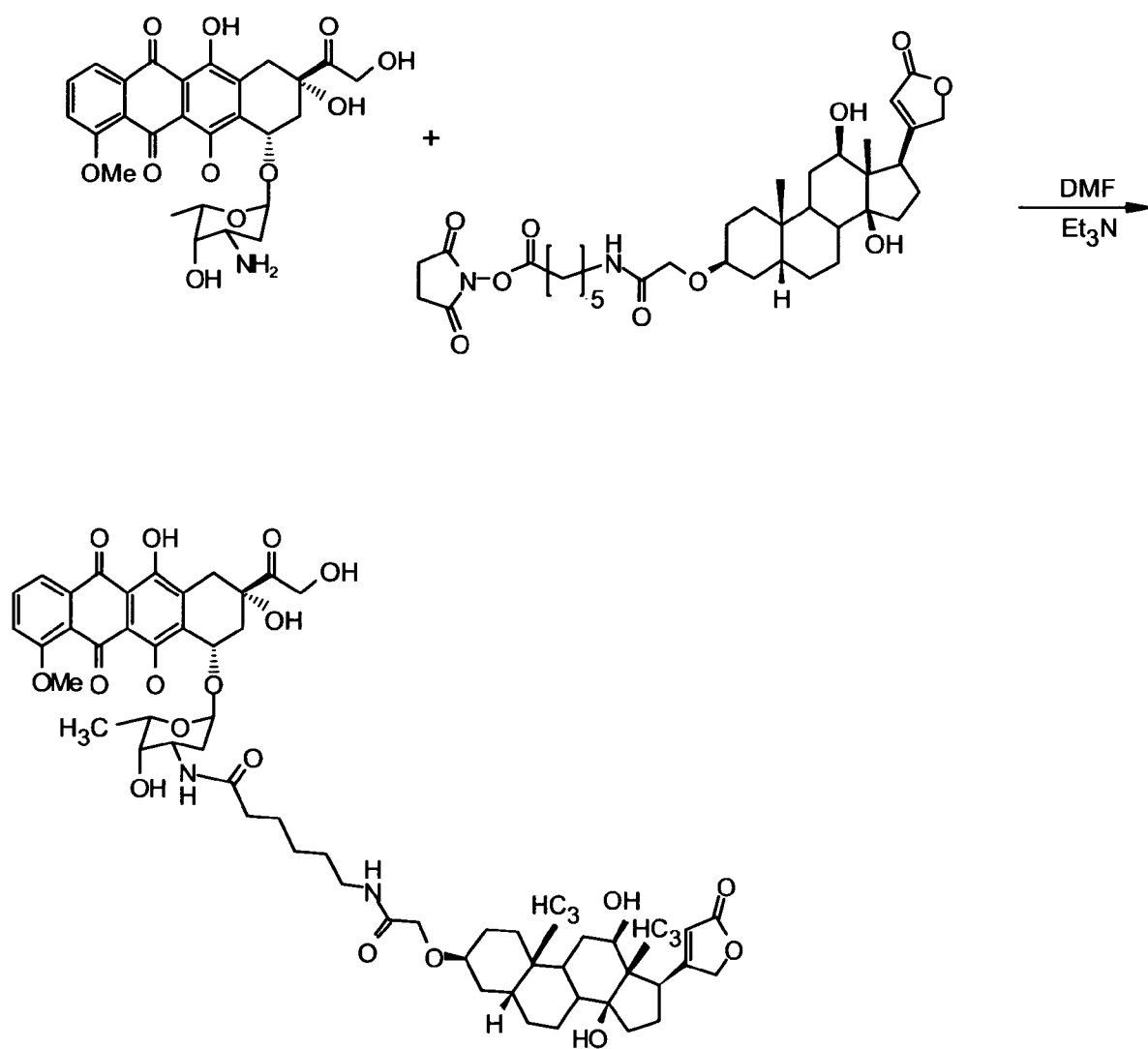
Luminescence

above background

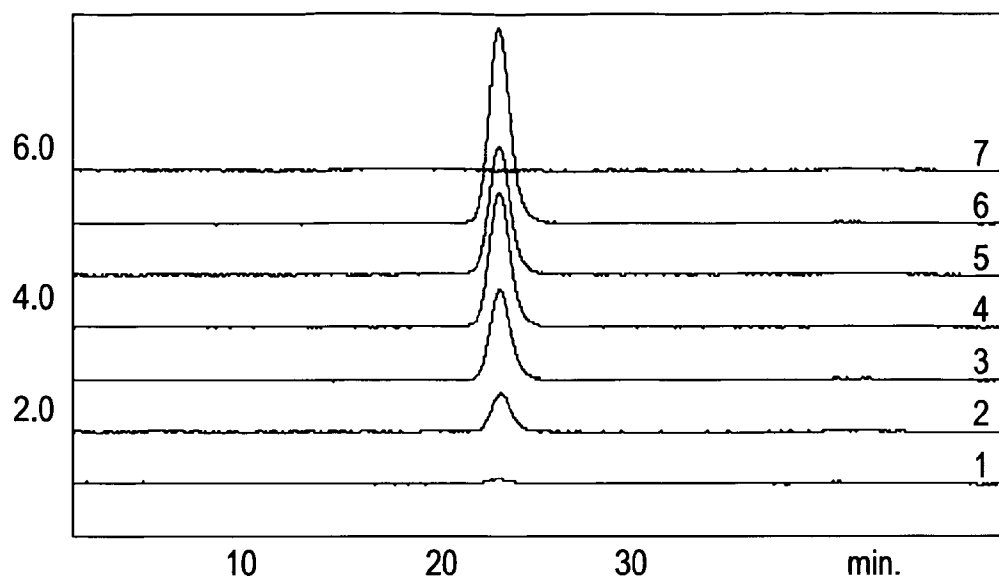


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Fig. 18

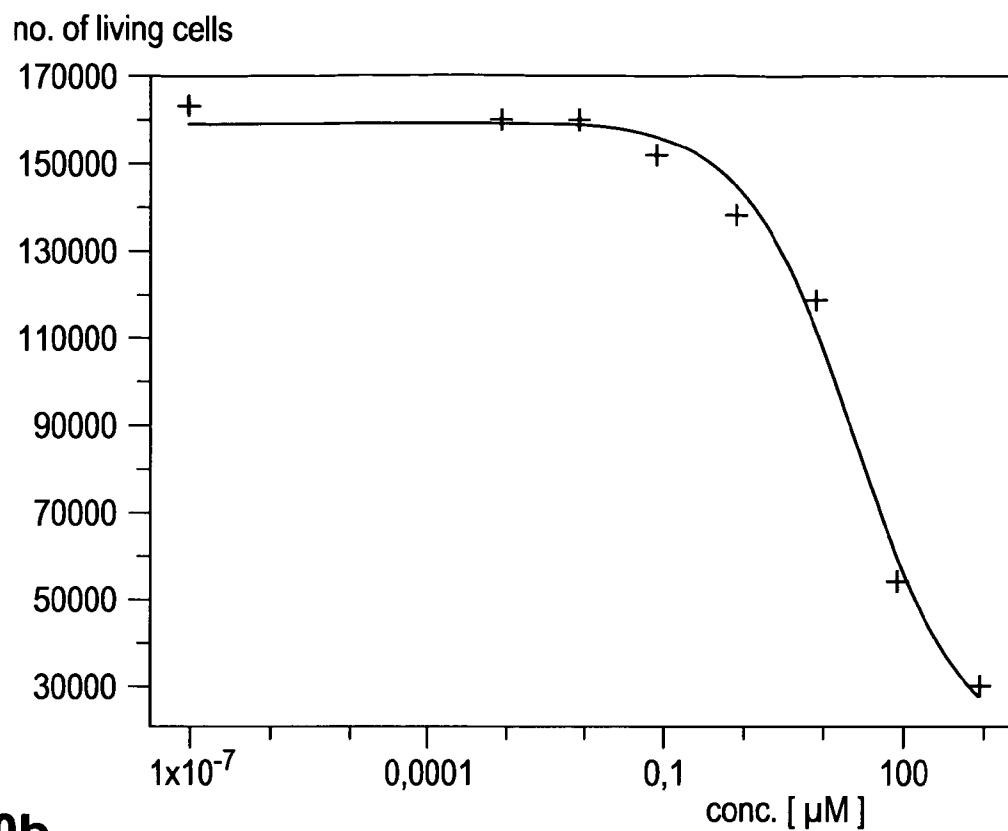
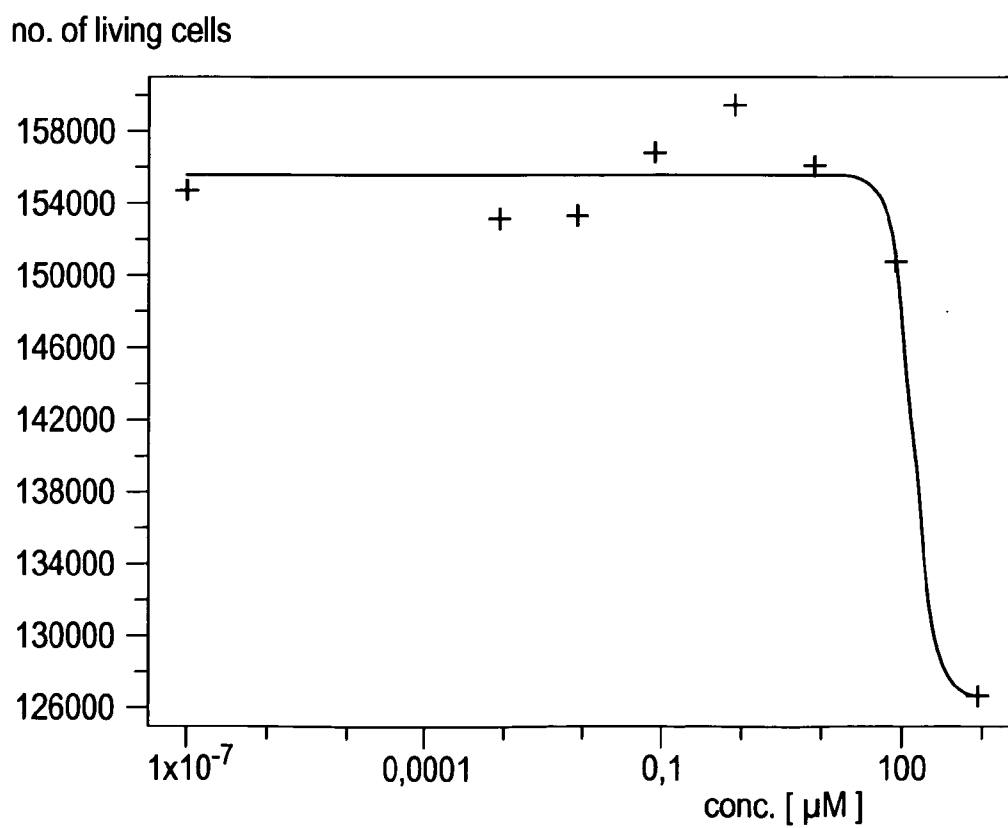


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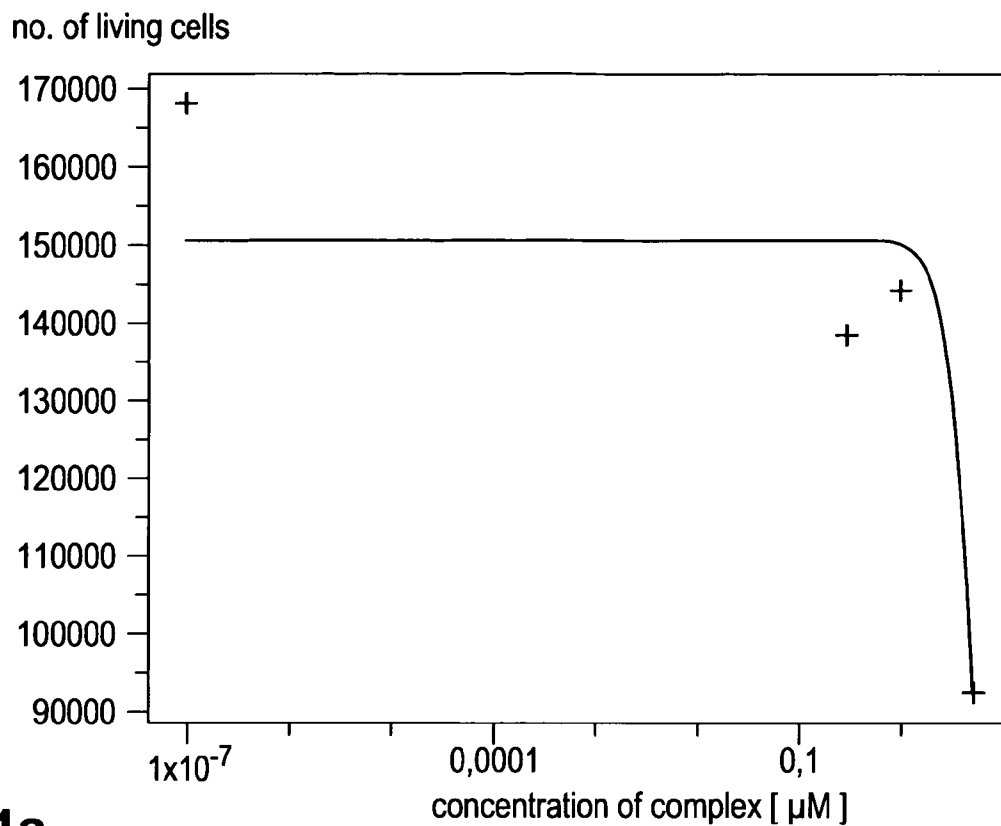
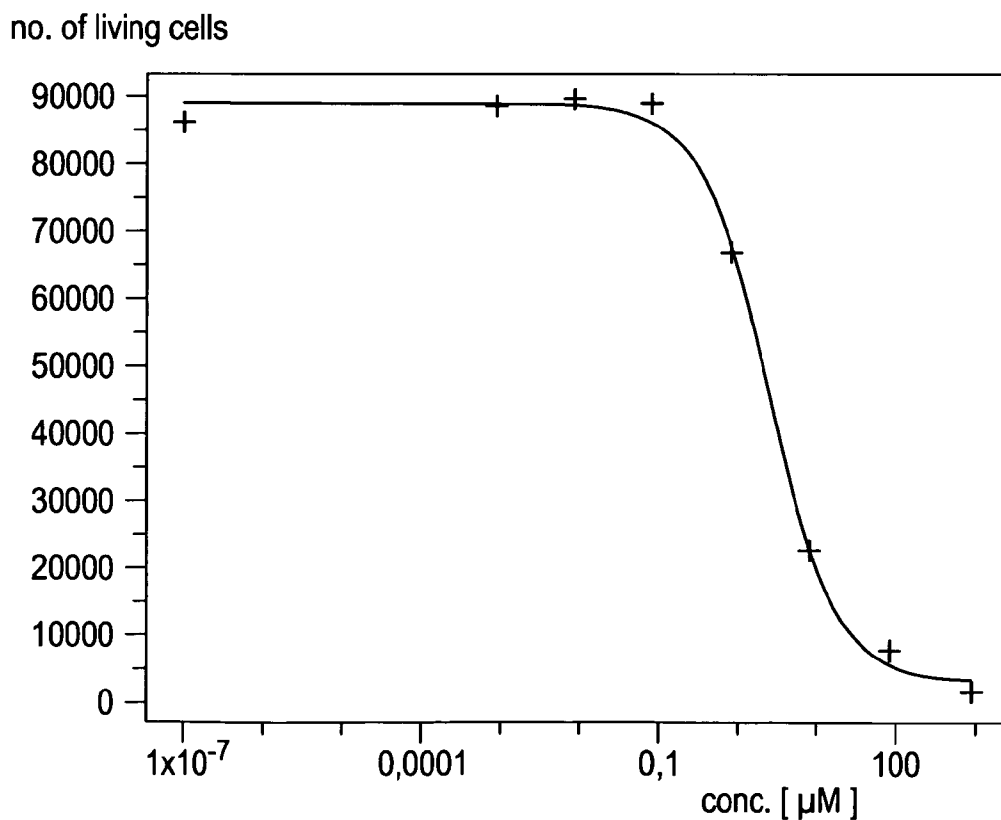
Fig. 19a**Fig. 19b**

ratio <Her2- Dig>:Doxo	Area (Ex: 488 nm / Em: 540 nm) [mAU*min]
1:0	0
1:0,5	1,1
1:1	2,4
1:2	3,4
1:3	3,3
1:5	4,9
0:1	0

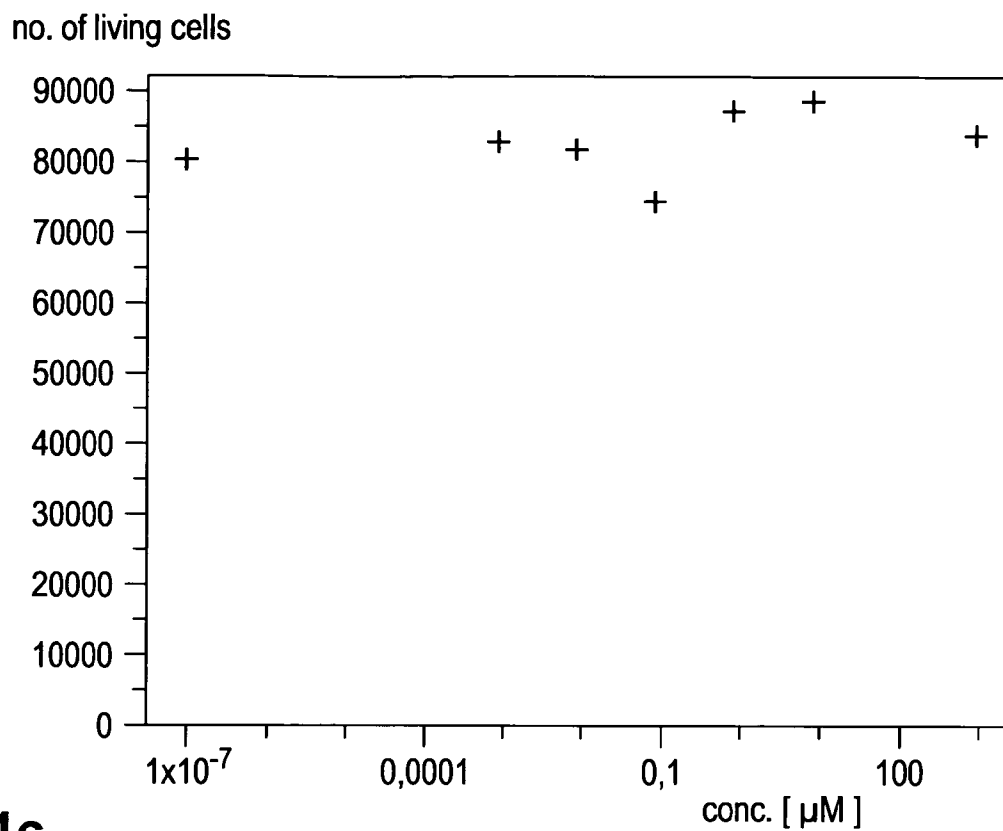
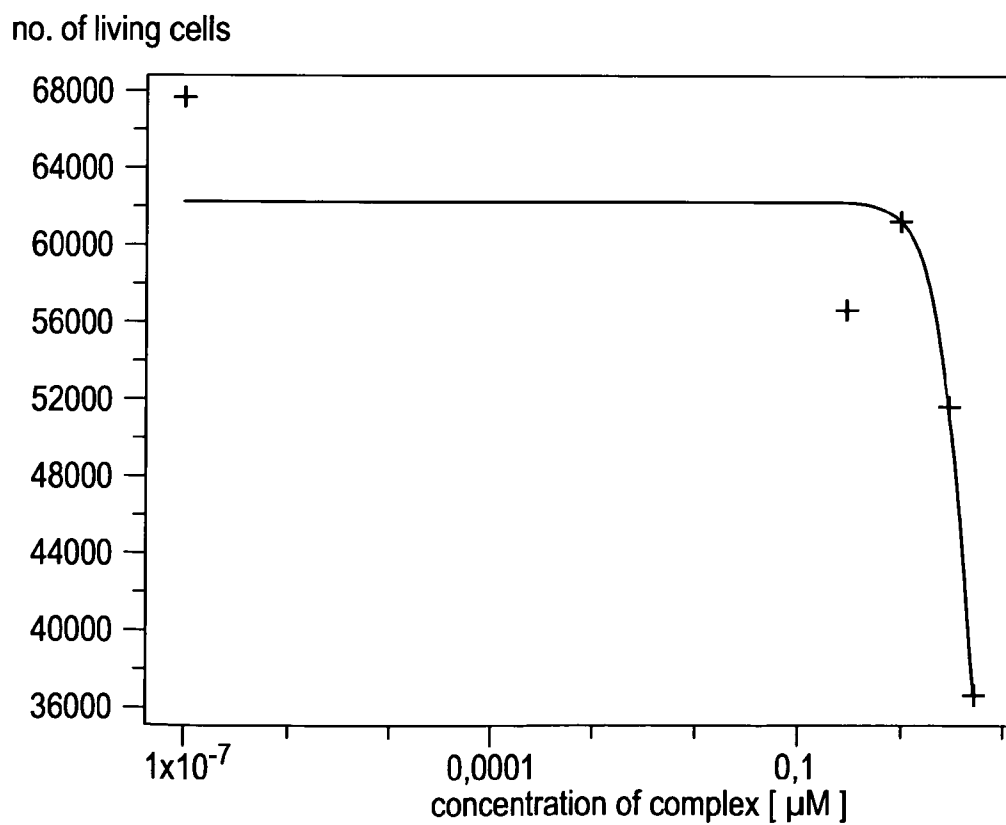
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Fig. 20a**Fig. 20b**

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Fig. 20c**Fig. 21a**

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Fig. 21b**Fig. 21c**

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Fig. 22a

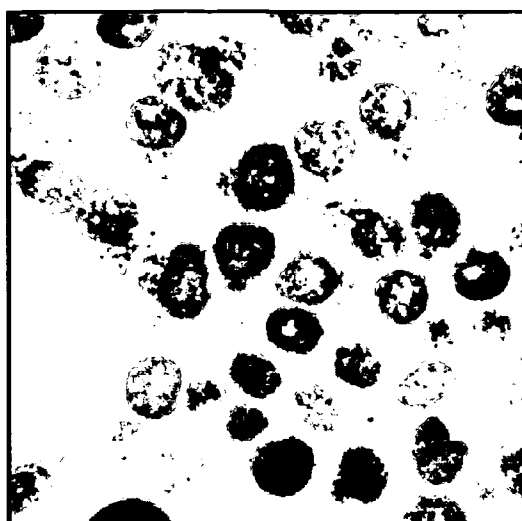


Fig. 22b

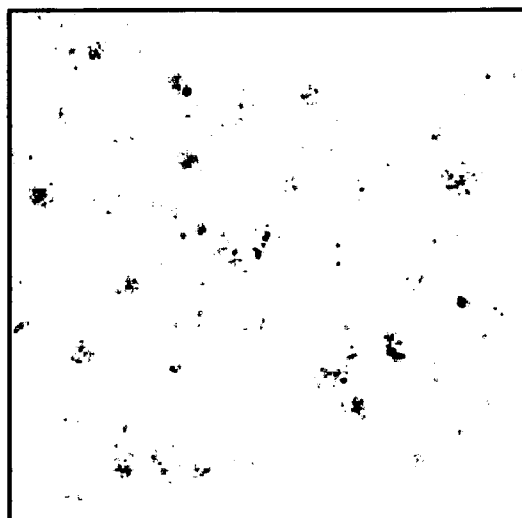


Fig. 22c

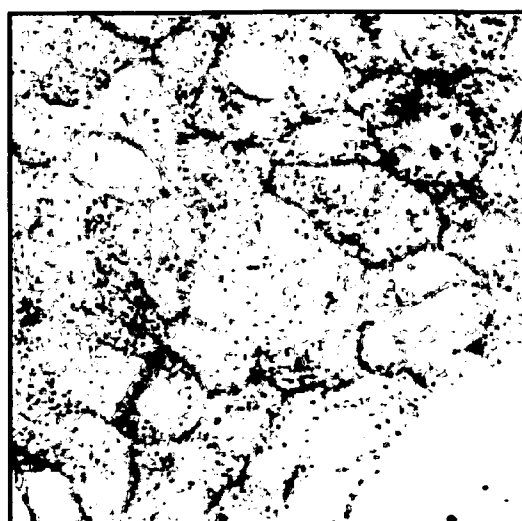
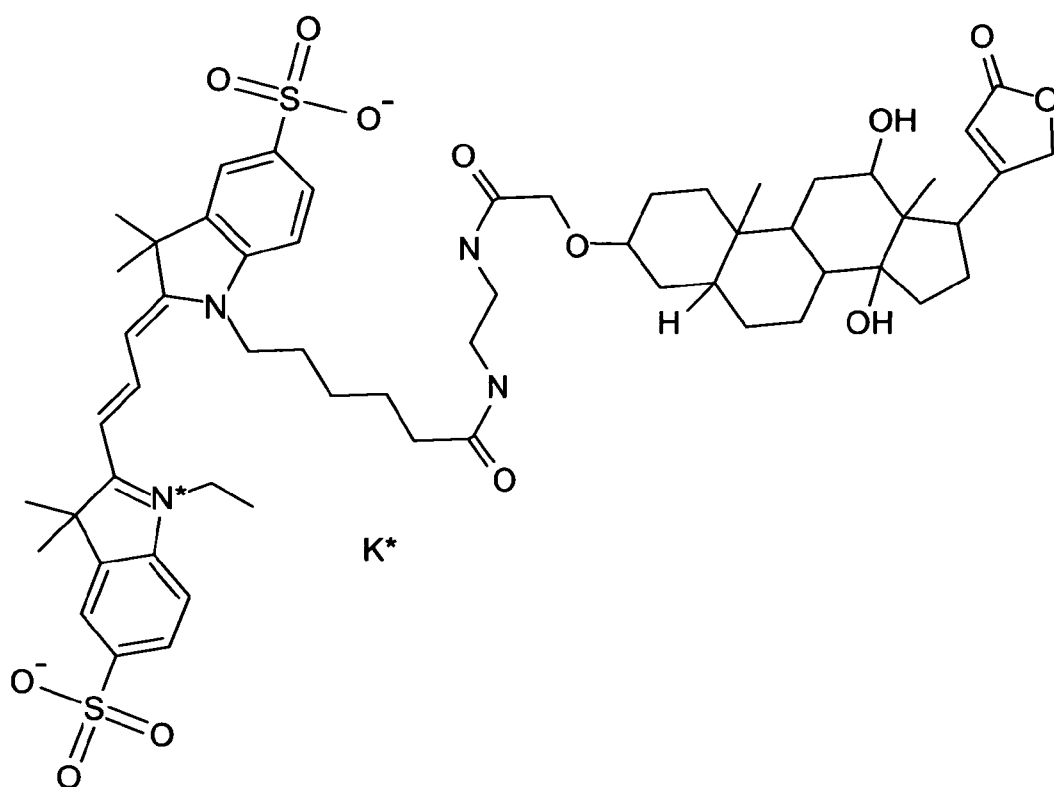
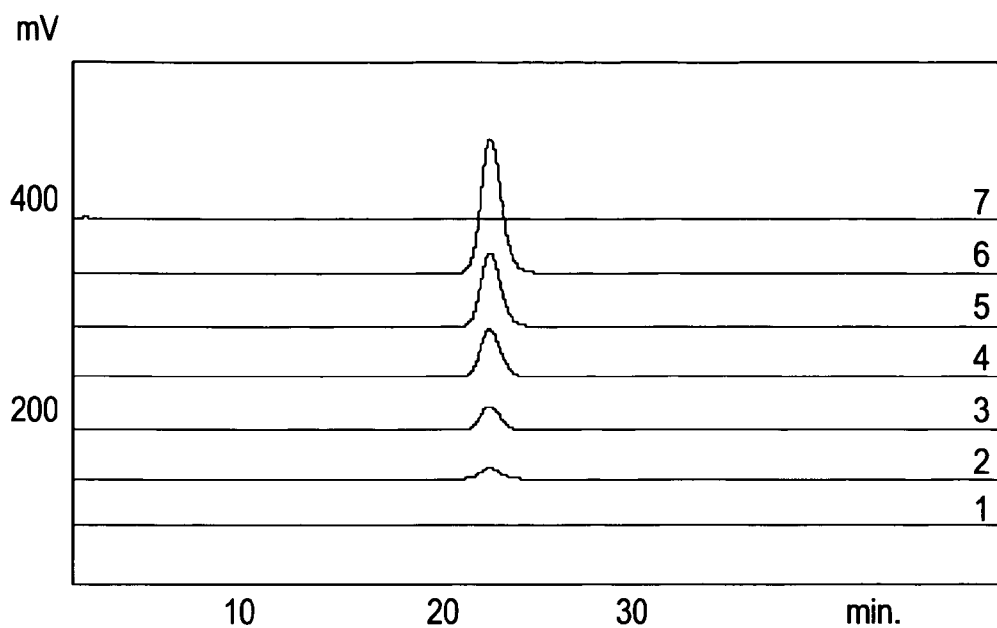


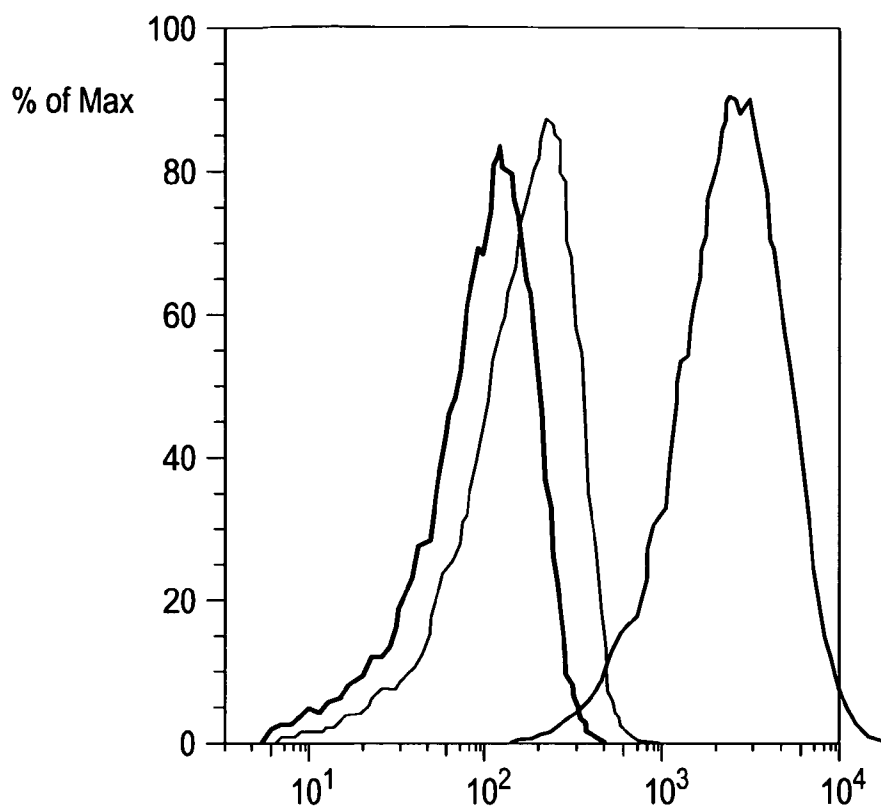
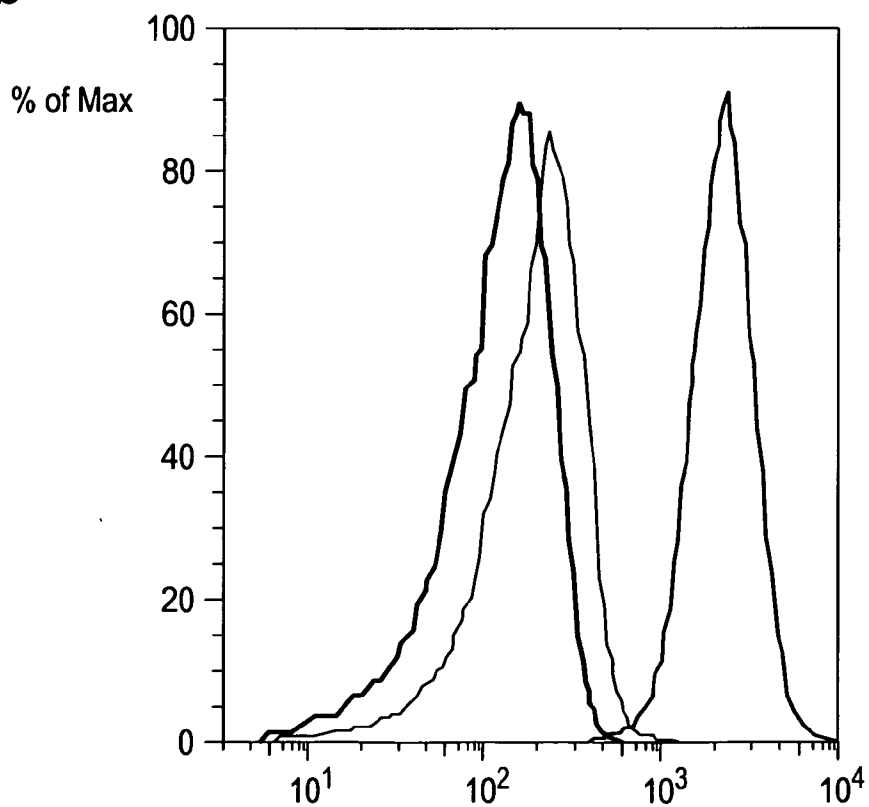
Fig. 23

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Fig. 24a**Fig. 24b**

ratio <Her2- Dig>:Dig- Cy5	Area (Ex: 650 nm / Em: 667 nm) [mAU*min]
1:0	2
1:0,5	30
1:1	68
1:2	135
1:3	209
1:5	381
0:1	0

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Fig. 25a**Fig. 25b**

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Fig. 26a

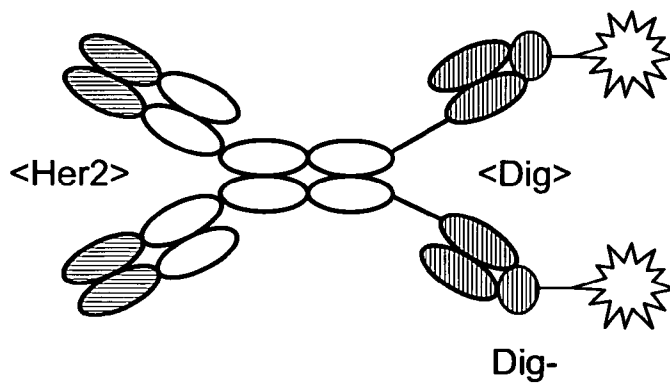


Fig. 26b



Fig. 27a

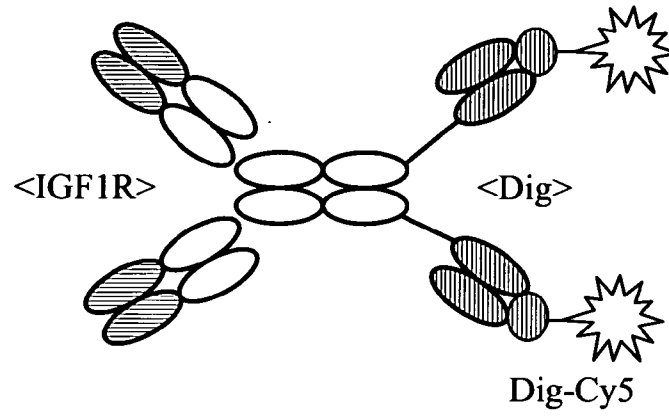


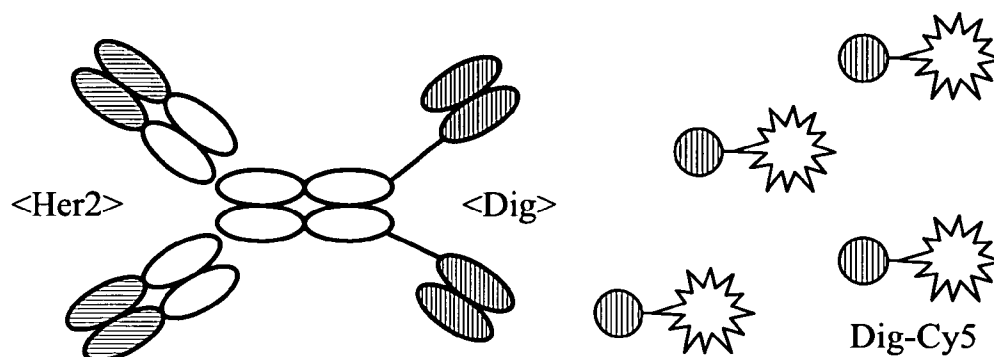
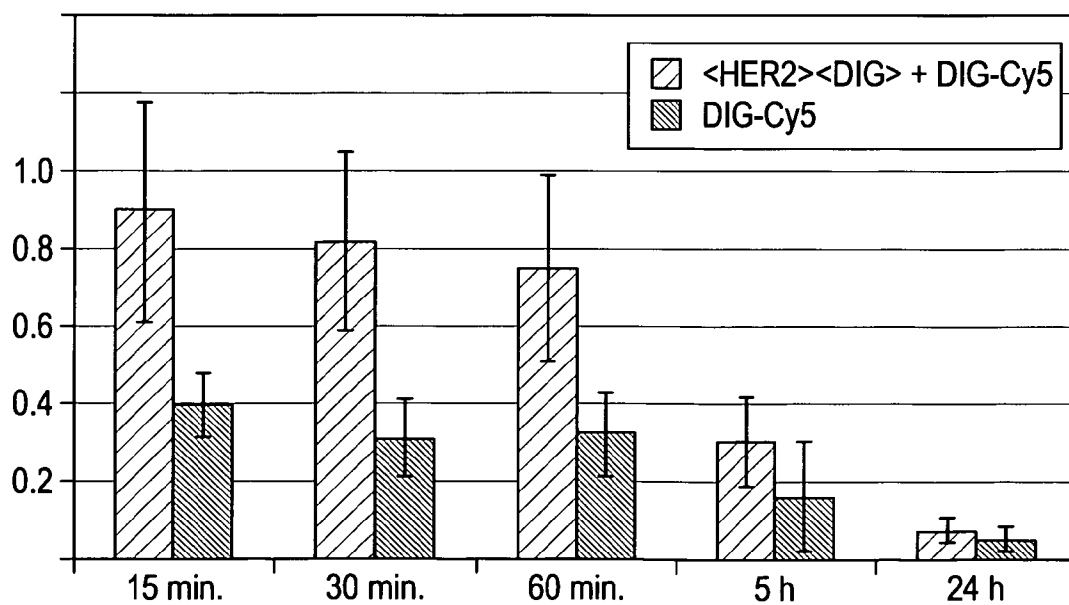
Fig. 27b



Fig. 27c

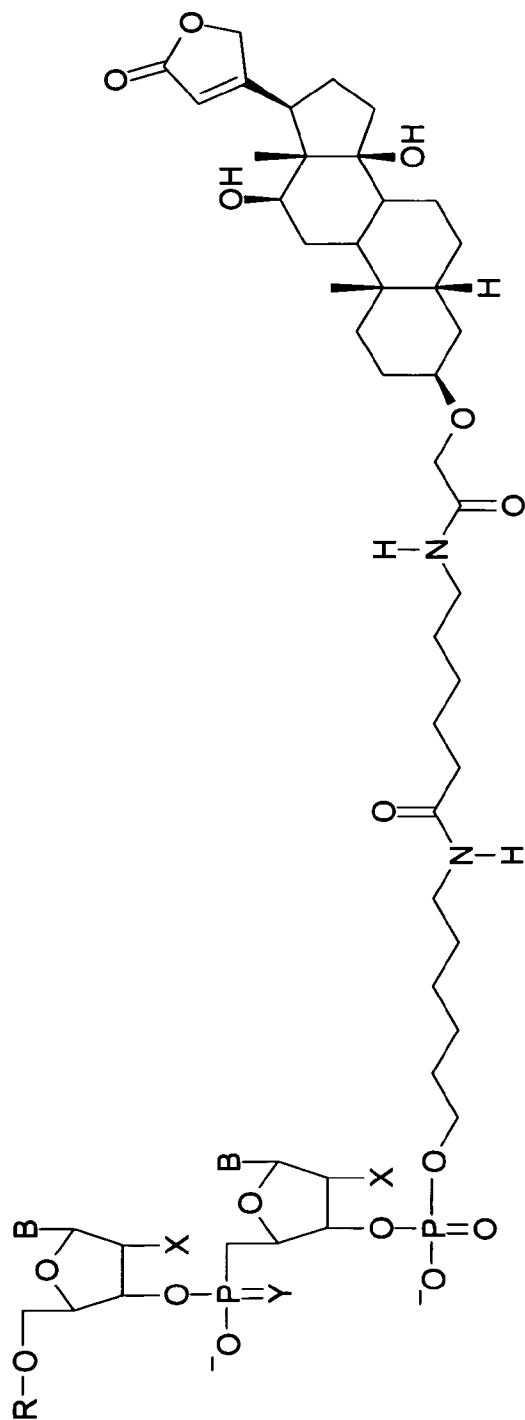


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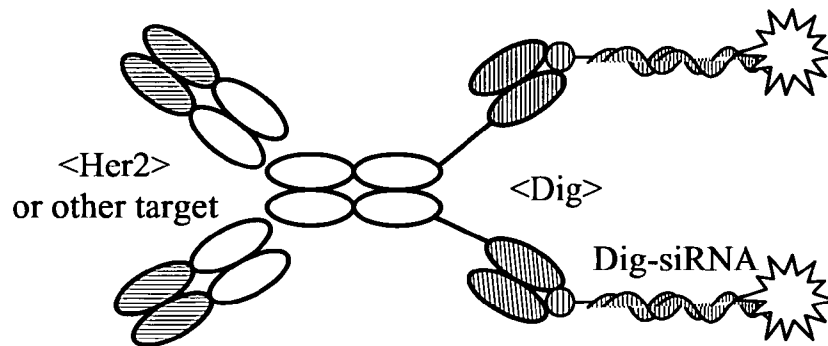
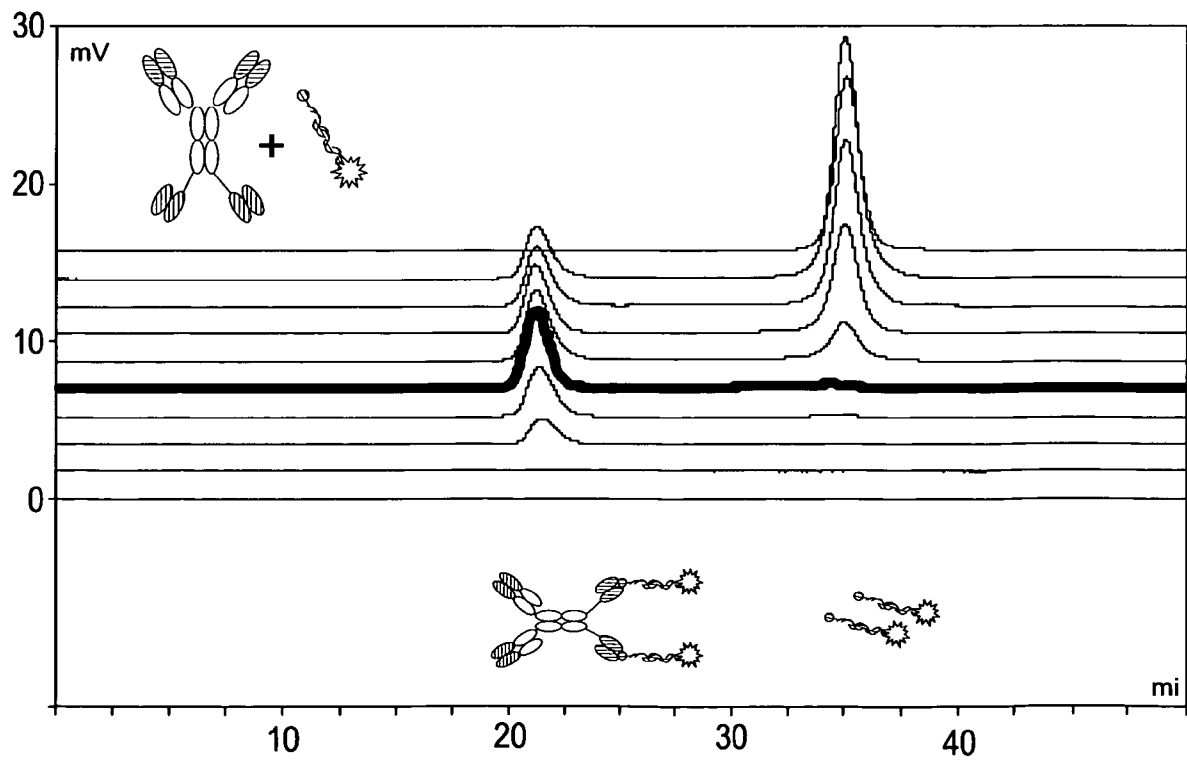
Fig. 28a**Fig. 28b**

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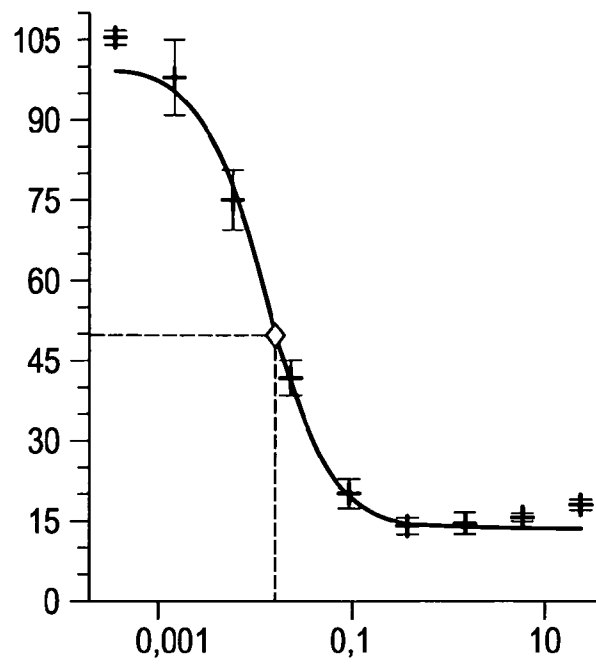
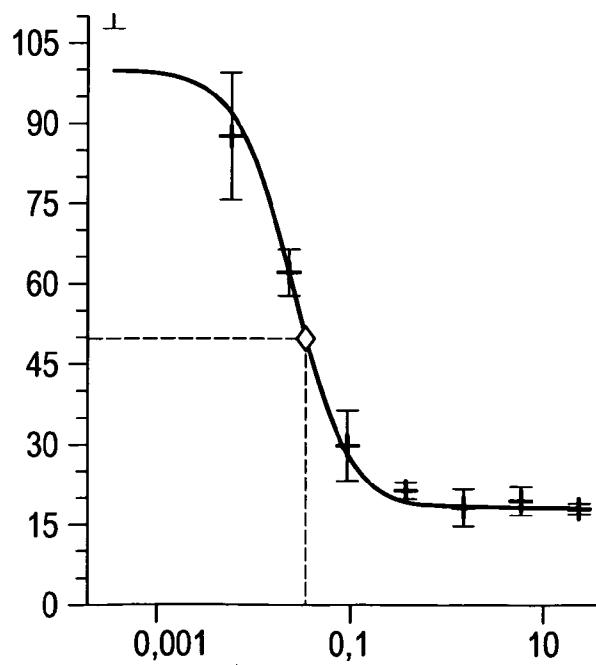
Fig. 29



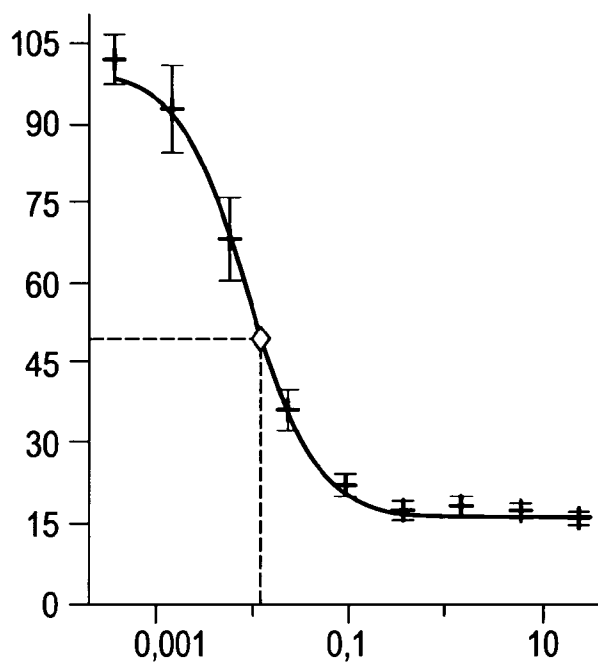
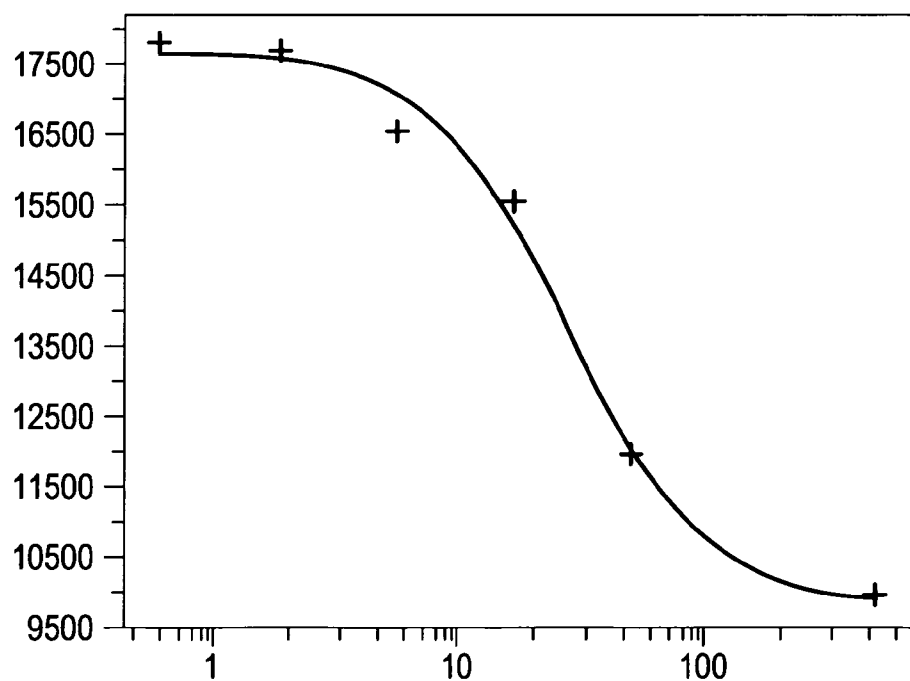
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Fig. 30a**Fig. 30b**

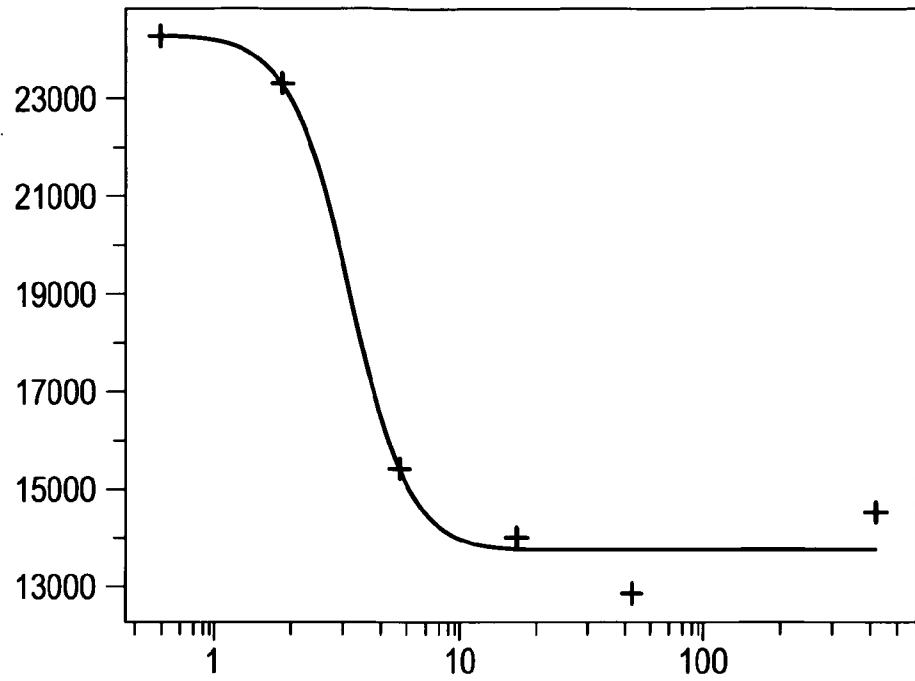
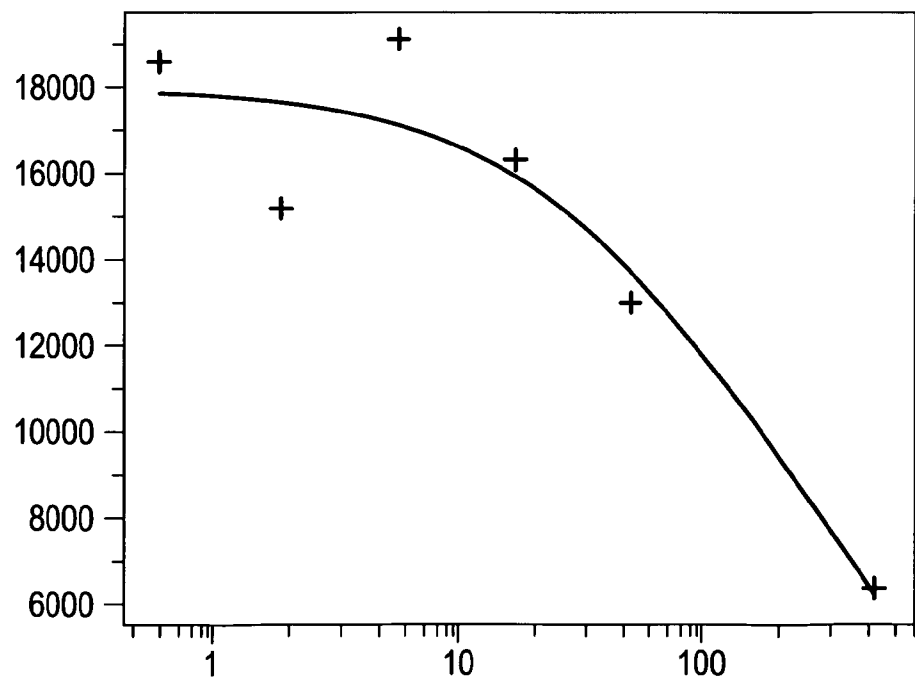
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Fig. 31a**Fig. 31b**

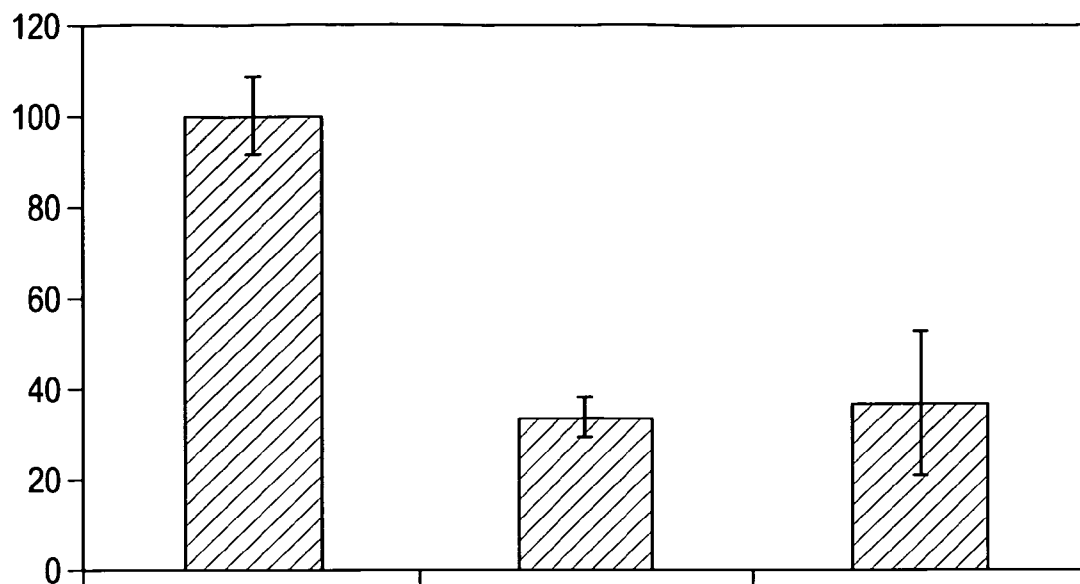
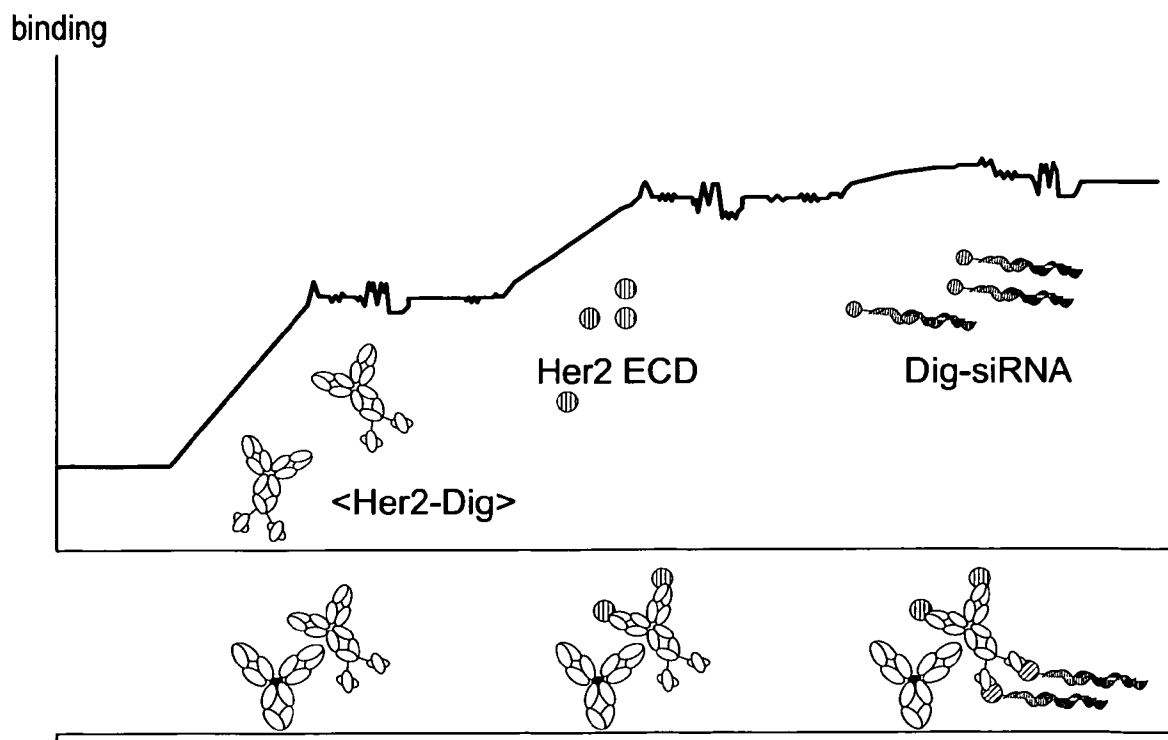
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Fig. 31c**Fig. 31d**

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Fig. 31e**Fig. 31f**

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Fig. 31g**Fig. 32**

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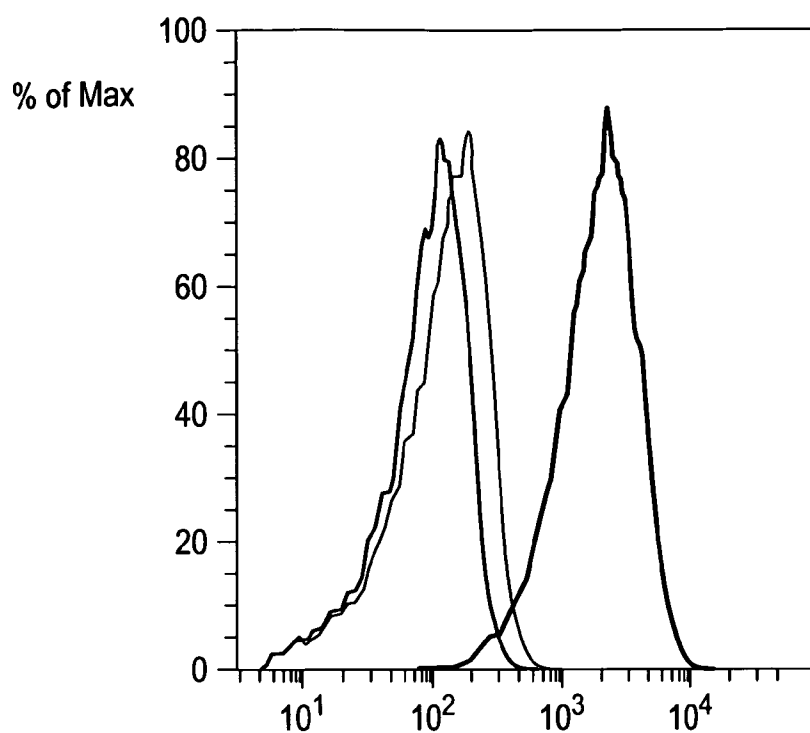
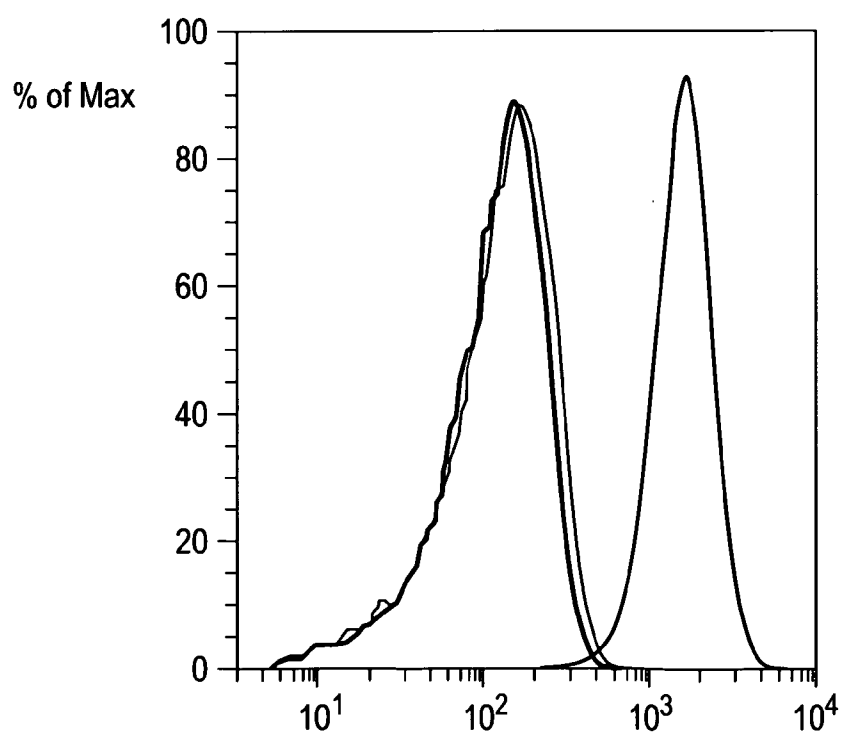
Fig. 33a**Fig. 33b**

Fig. 34a

Fig. 34b

Fig. 34c

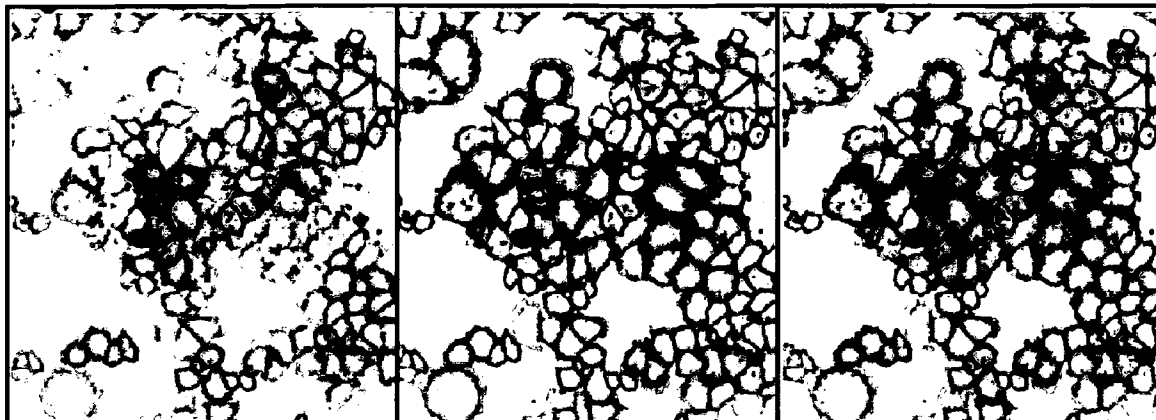


Fig. 34d

Fig. 34e

Fig. 34f

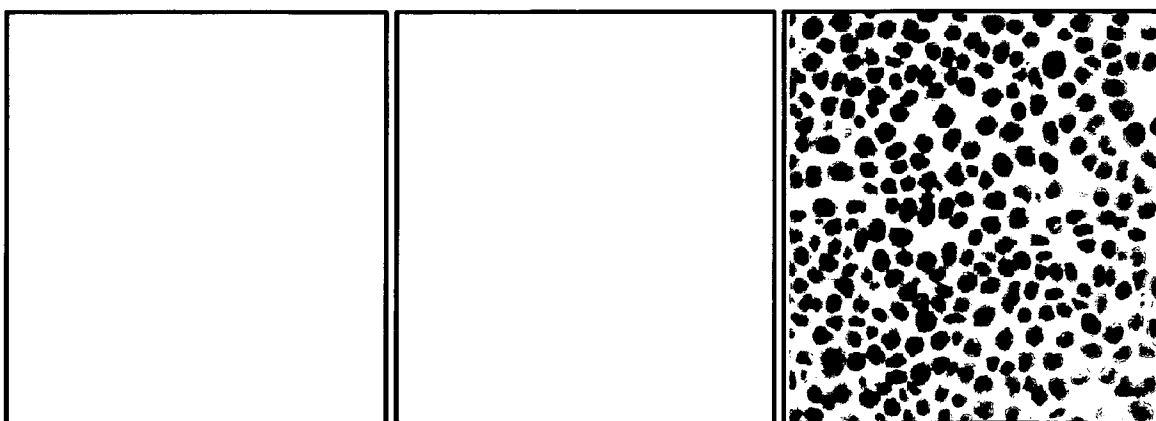


Fig. 34g



Fig. 34h



Fig. 34i

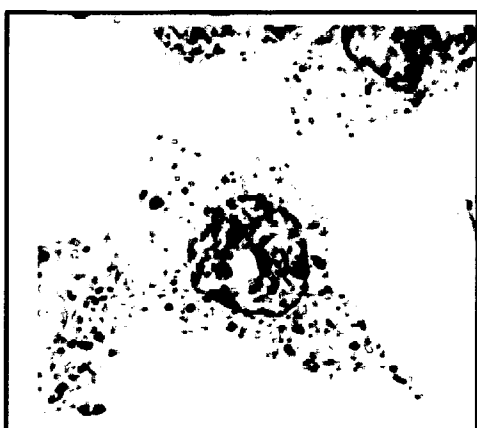


Fig. 34j



Fig. 35a

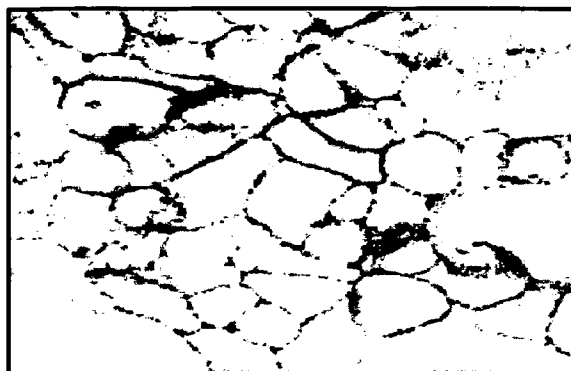


Fig. 35b

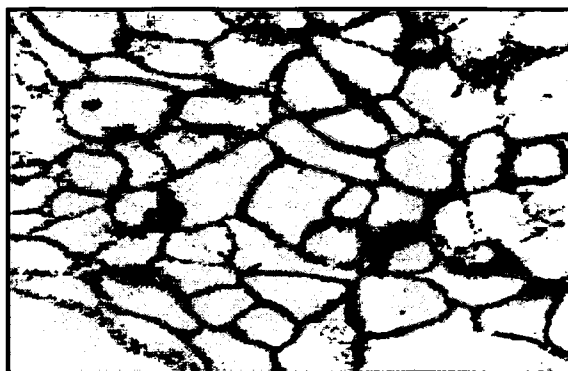


Fig. 35c

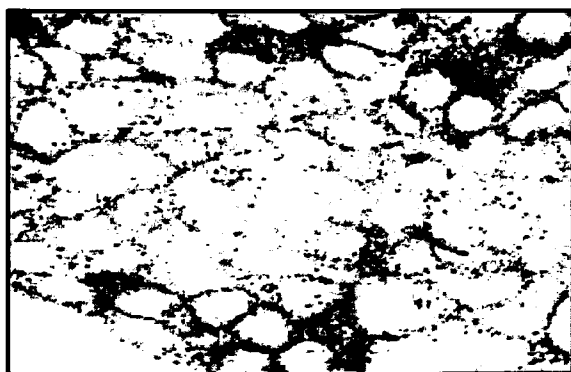


Fig. 35d

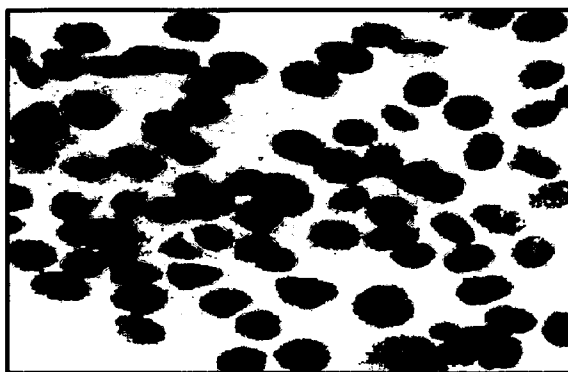


Fig. 35e

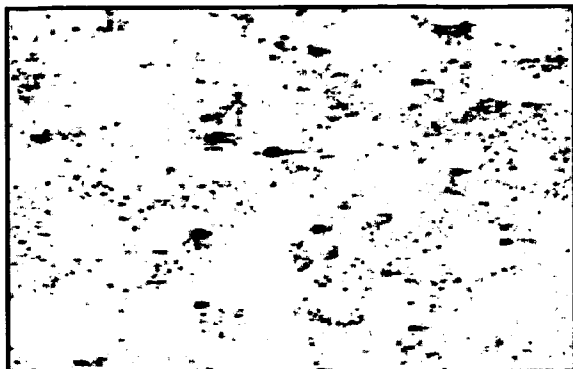


Fig. 35f

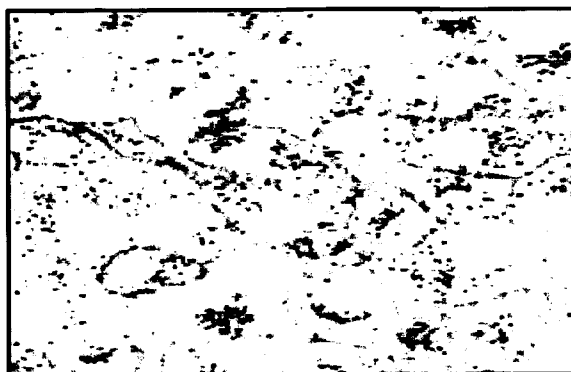


Fig. 35g

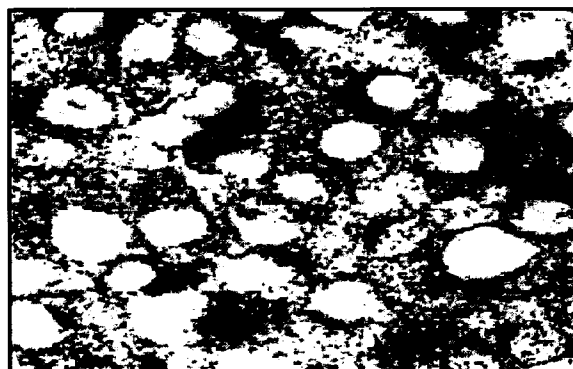
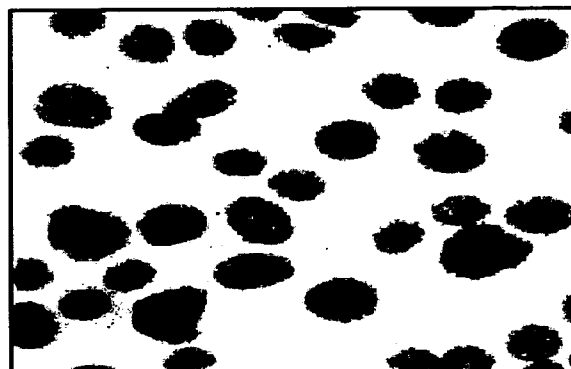
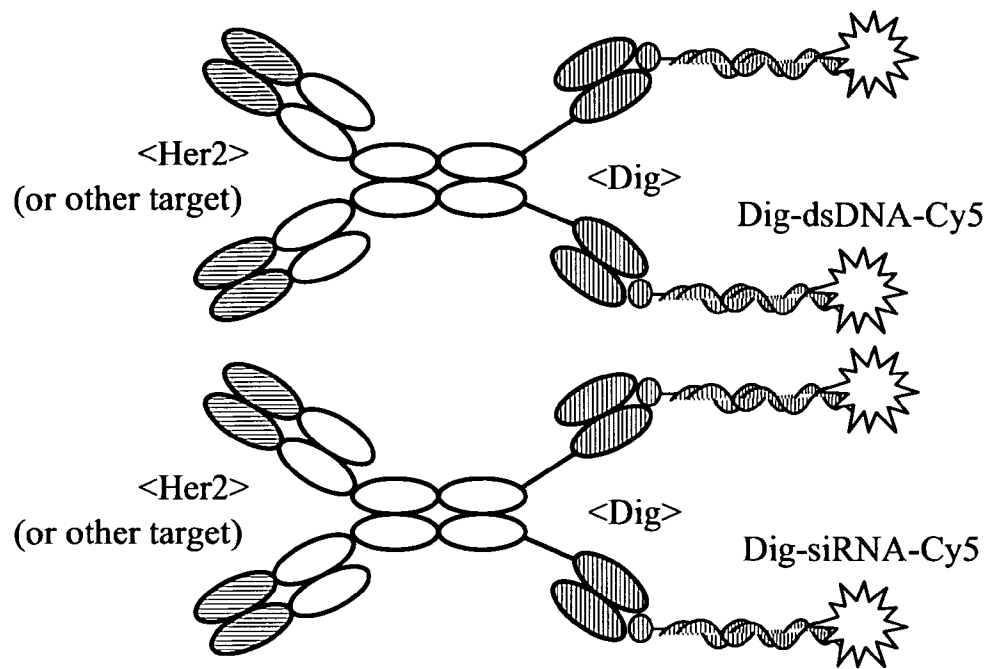
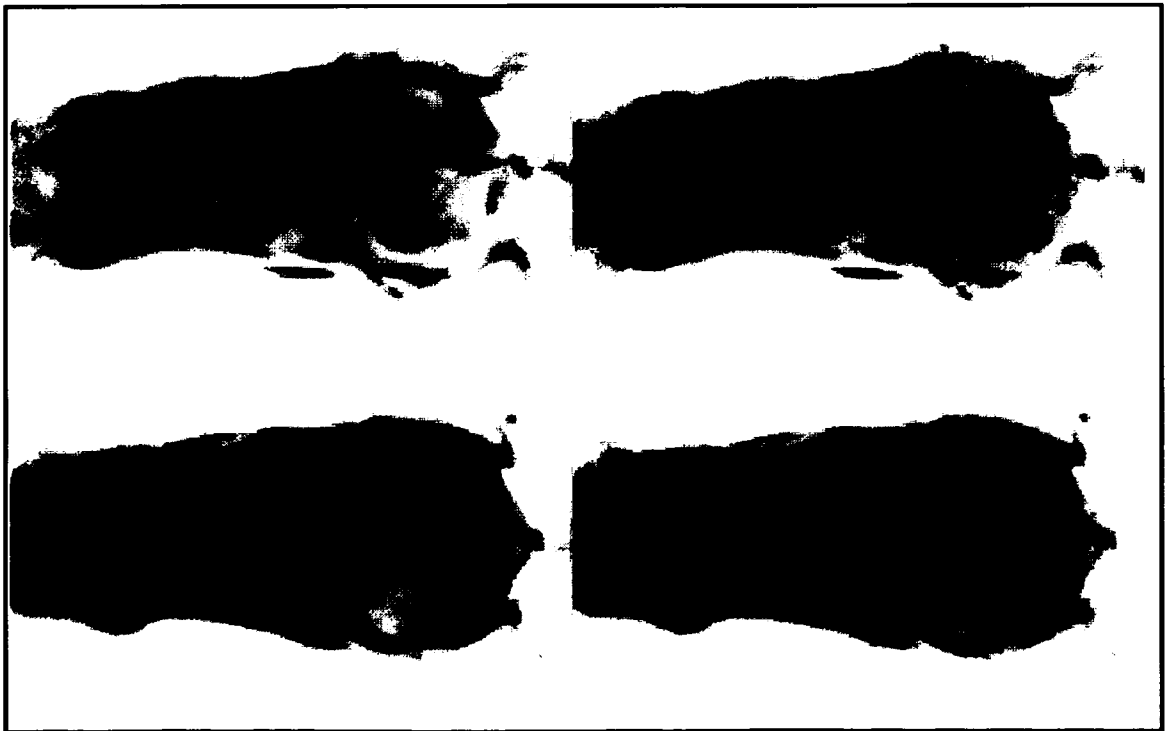


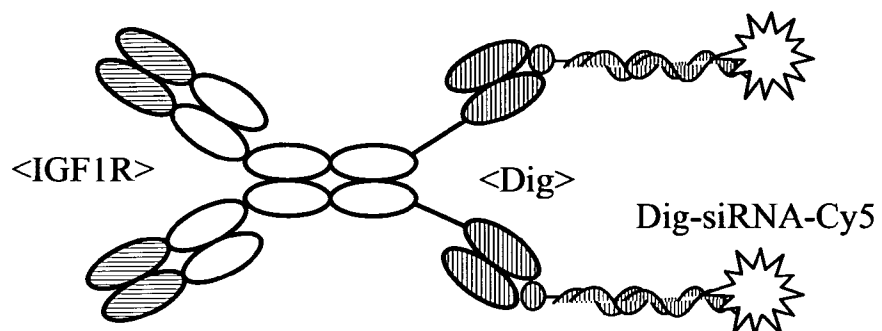
Fig. 35h



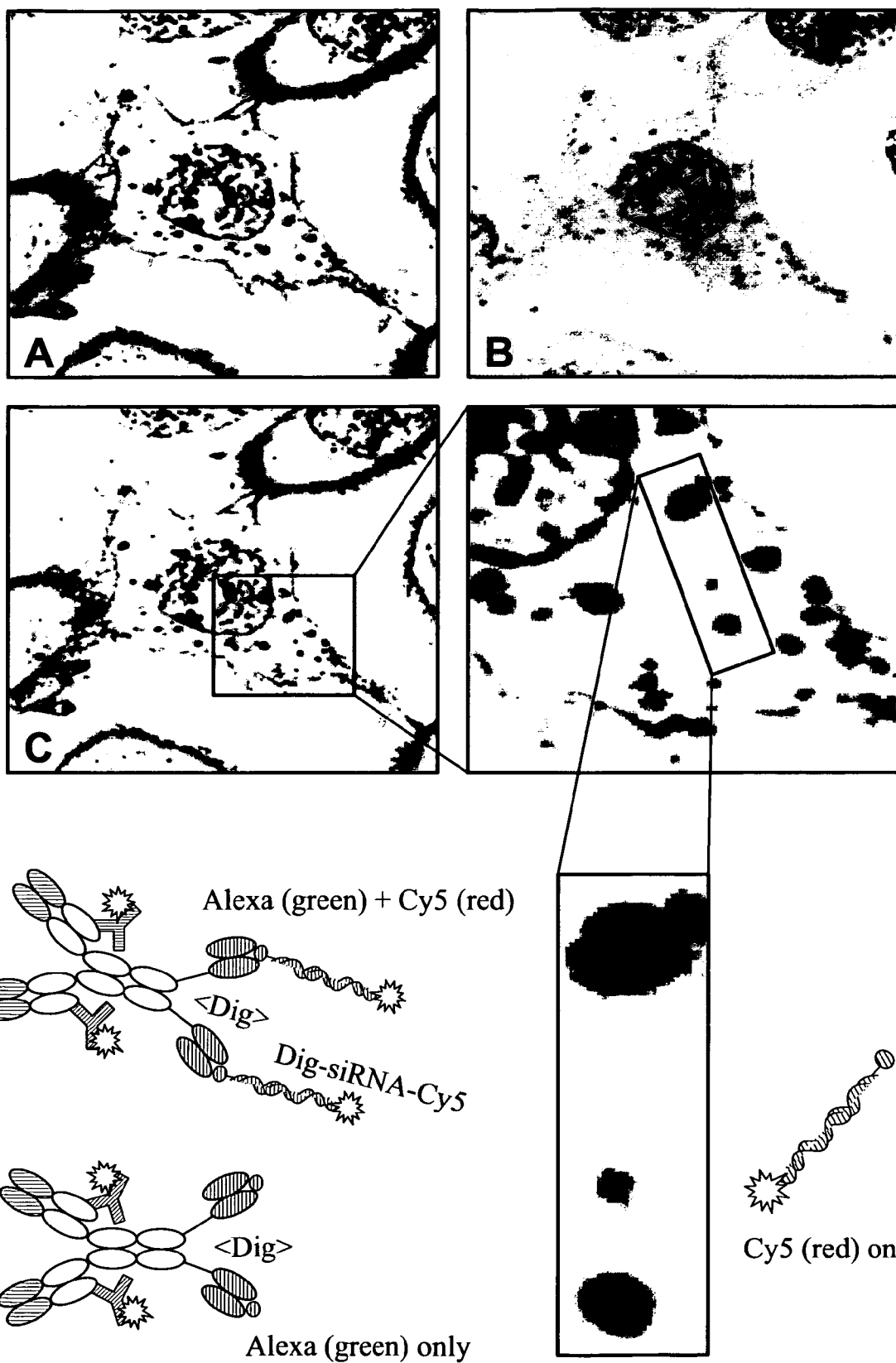
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Fig. 36a**Fig. 36b**

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Fig. 37a**Fig. 37b**

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Fig. 38a

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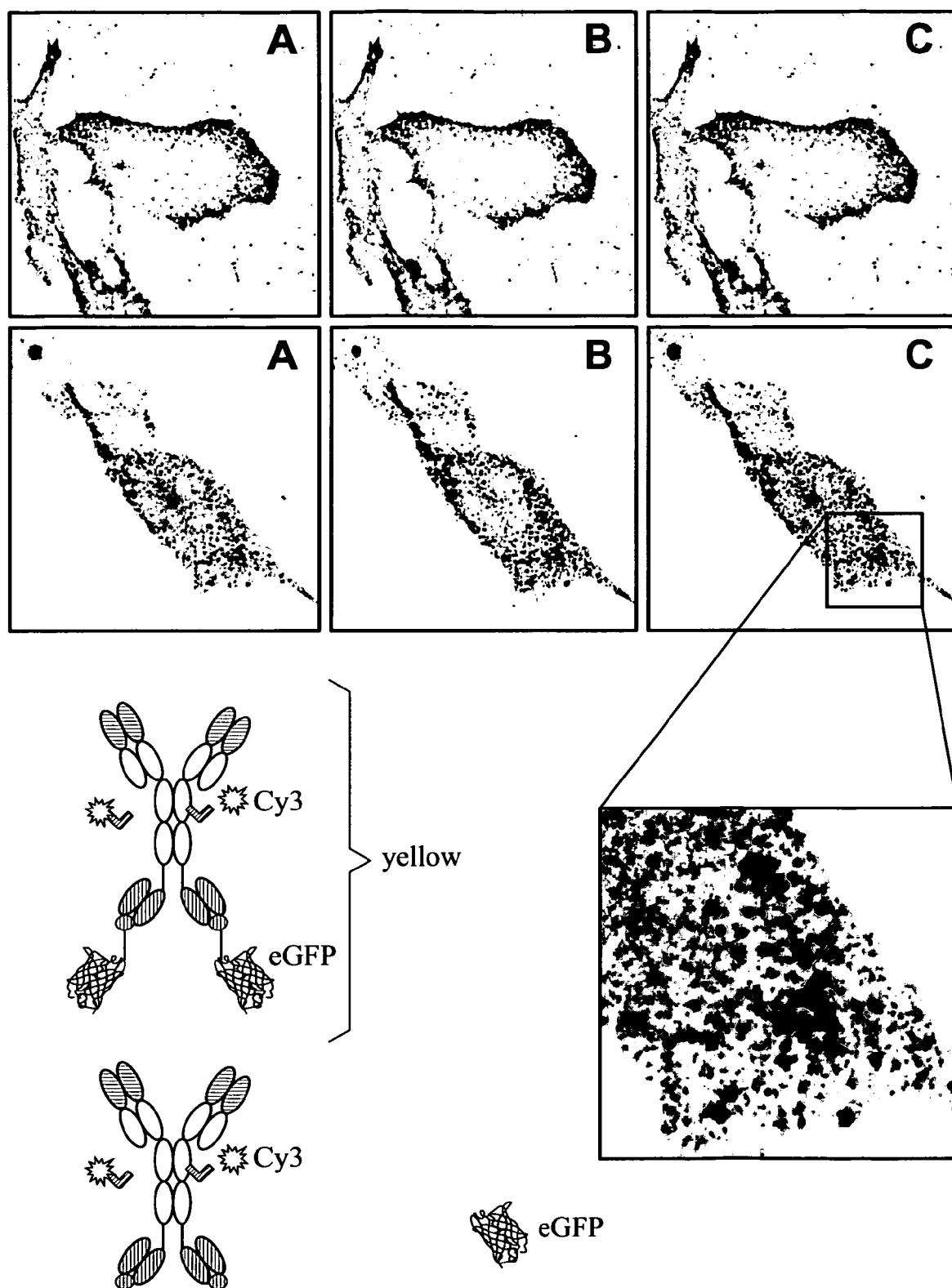
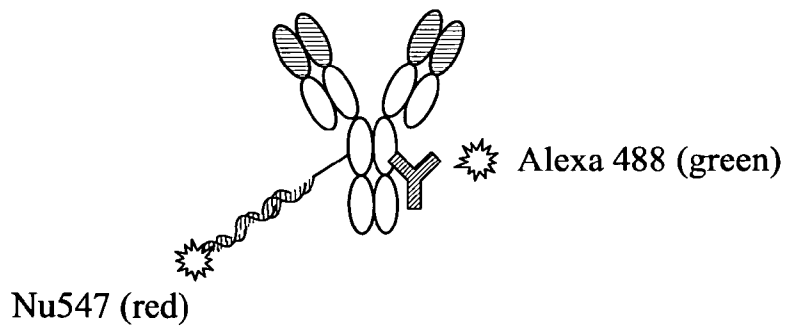
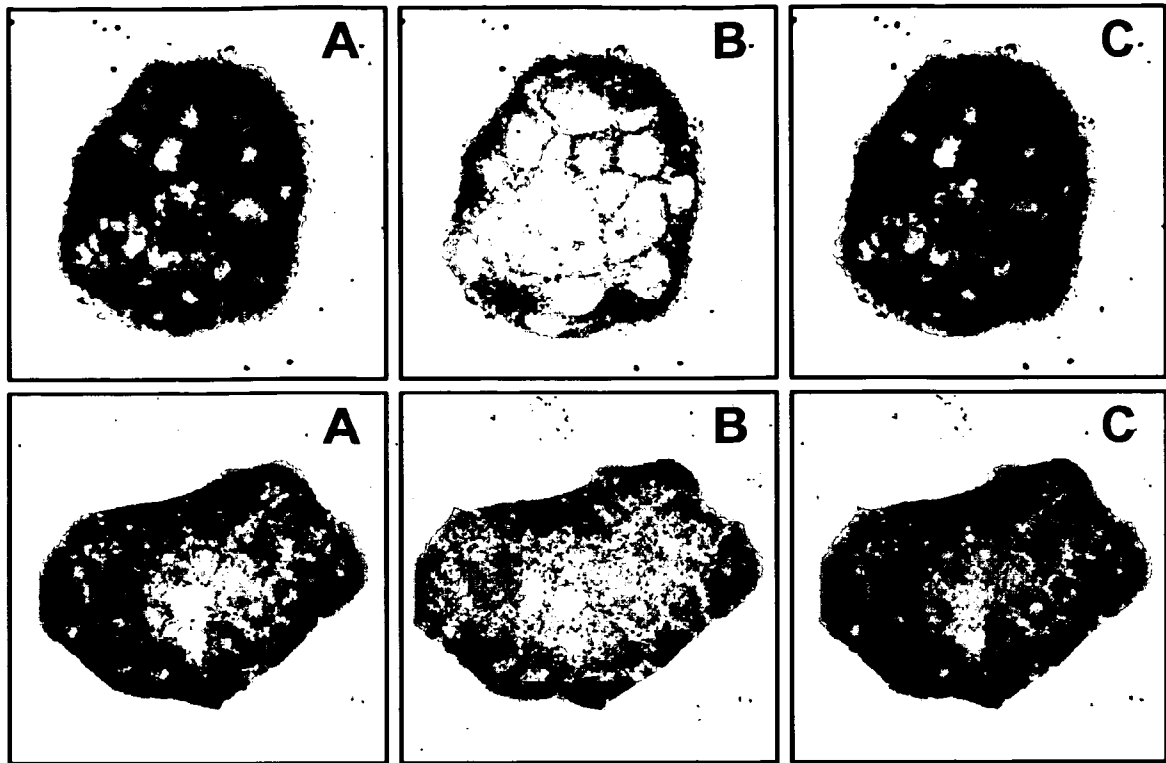
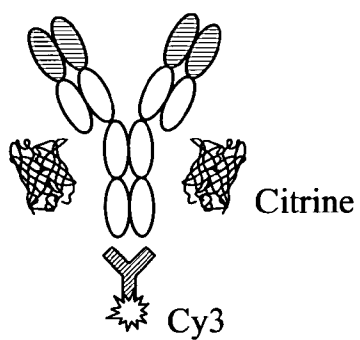
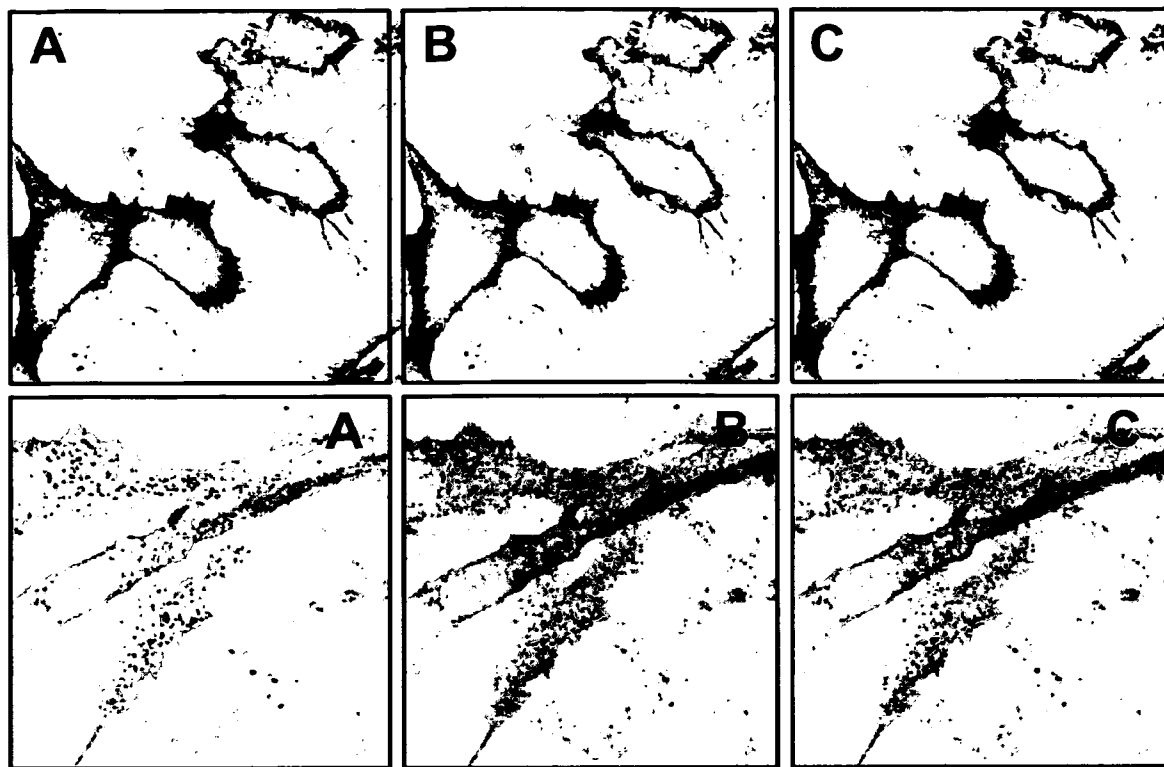
Fig. 38b

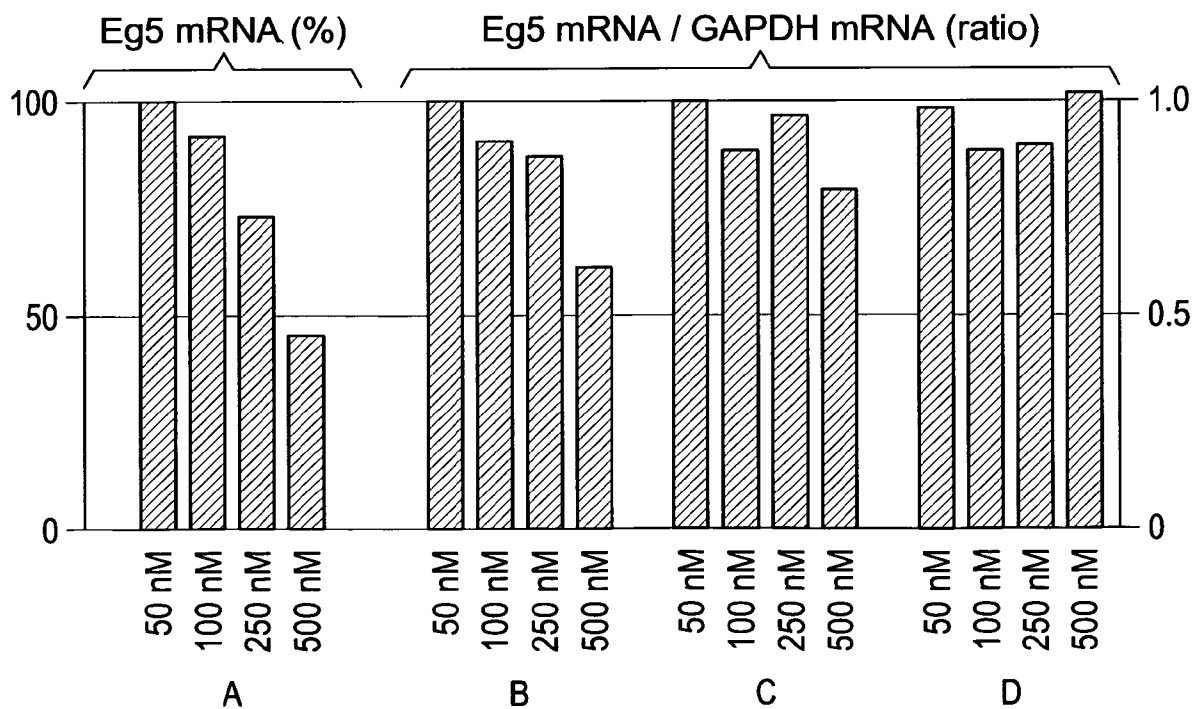
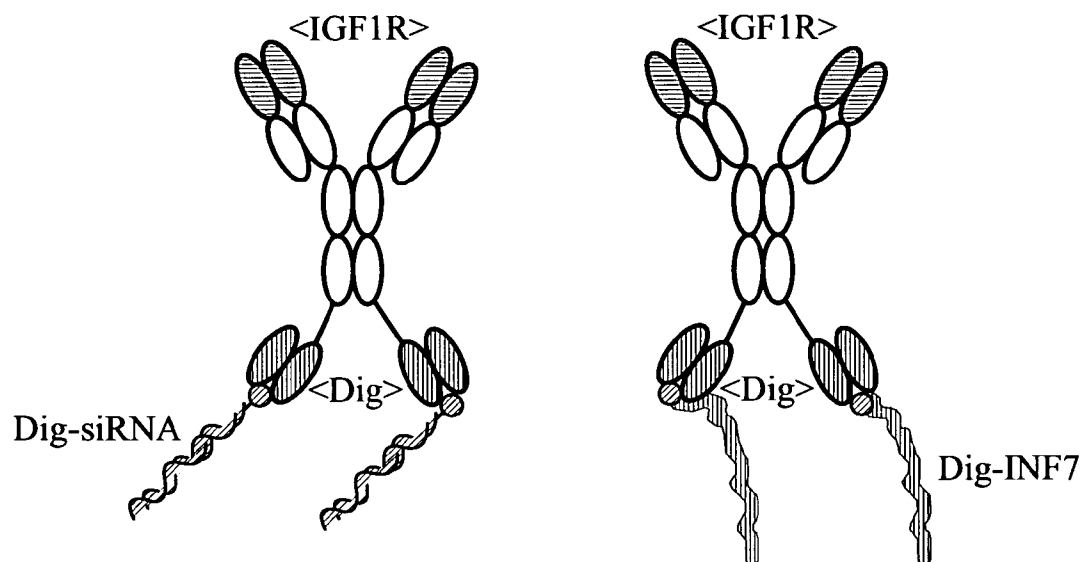
Fig. 38c



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Fig. 38d

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Fig. 39

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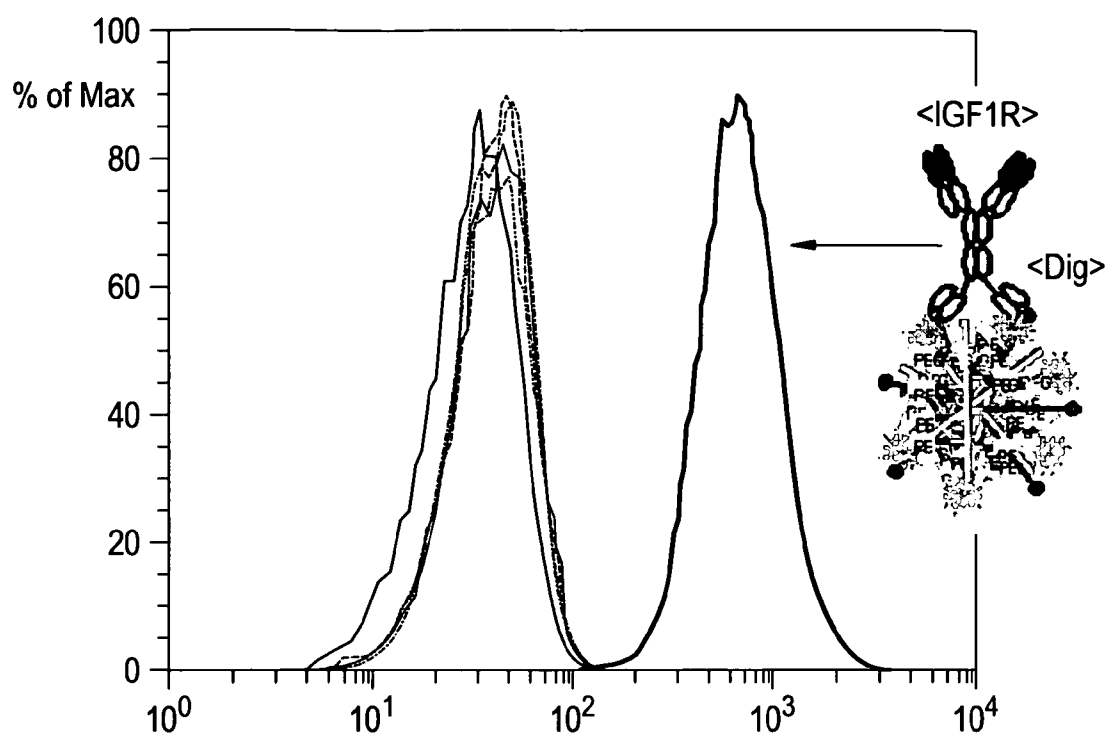
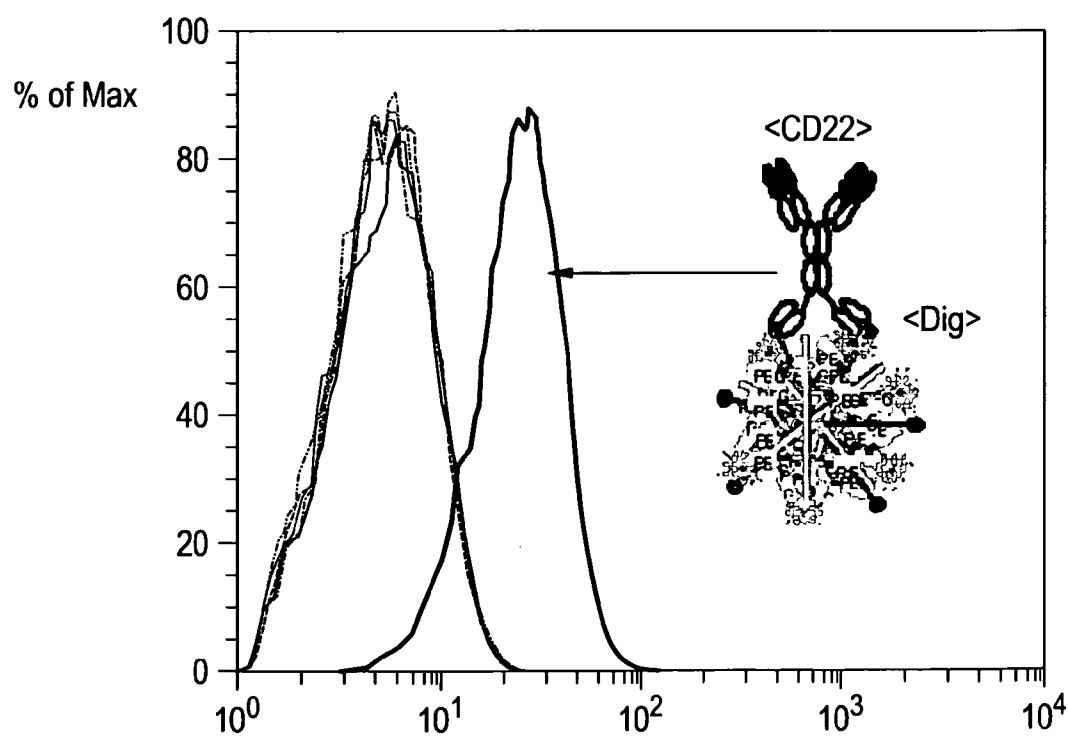
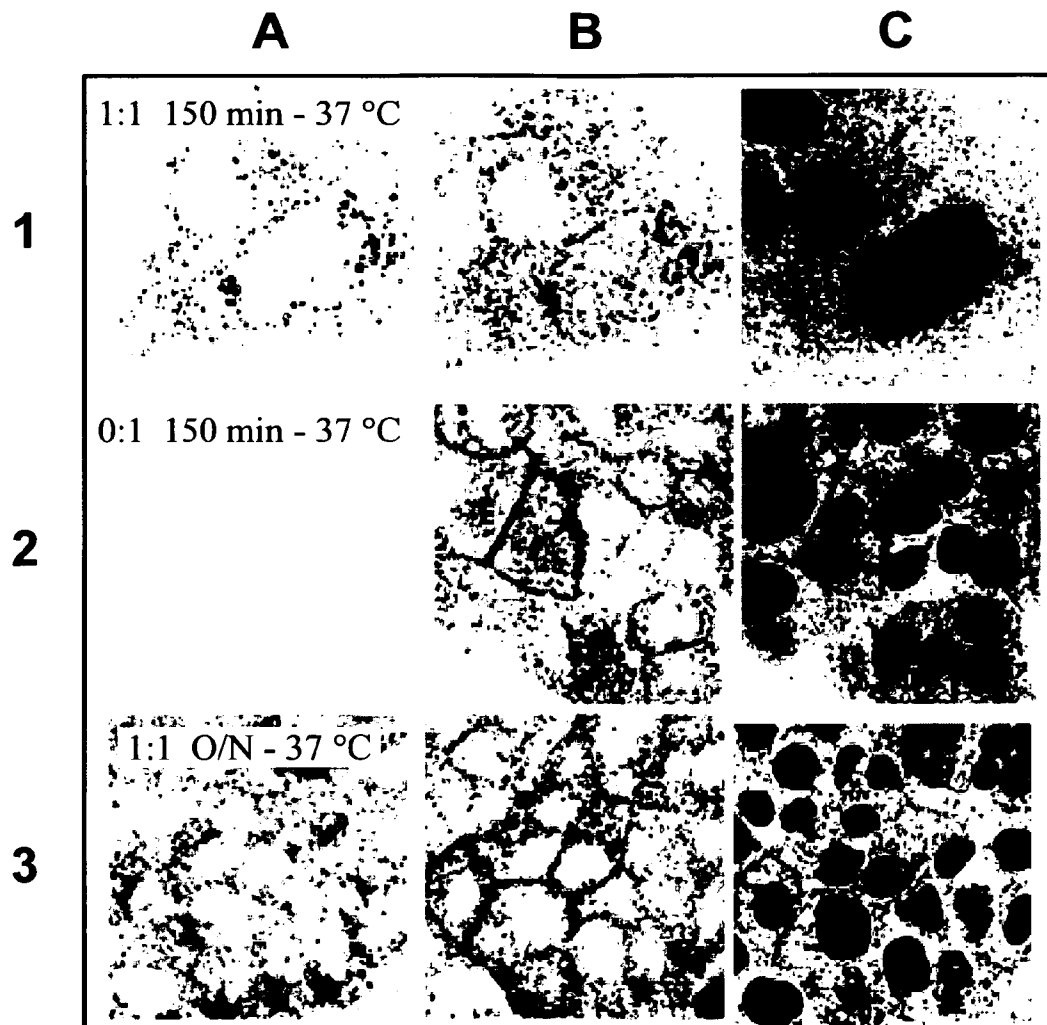
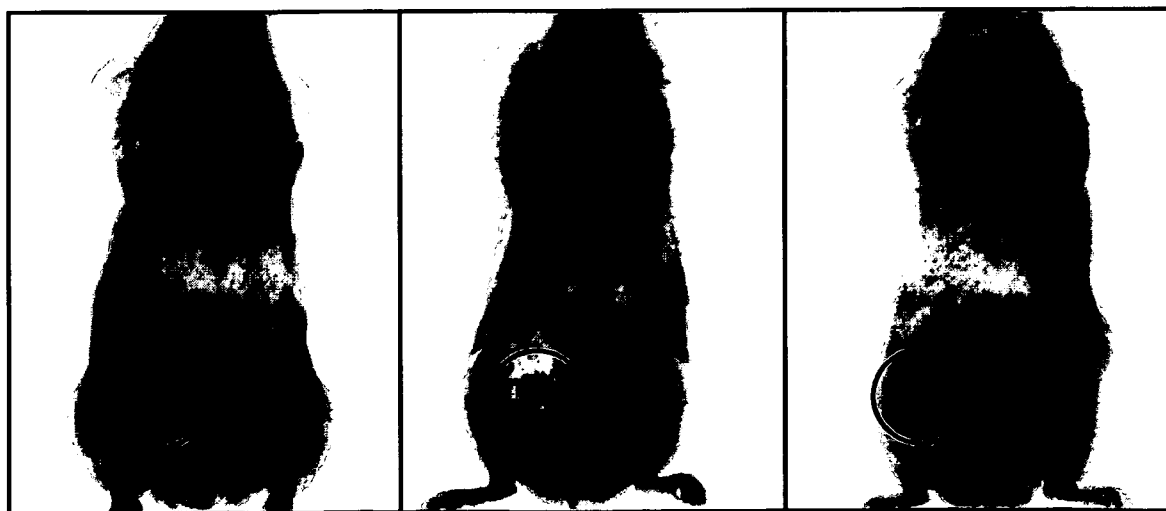
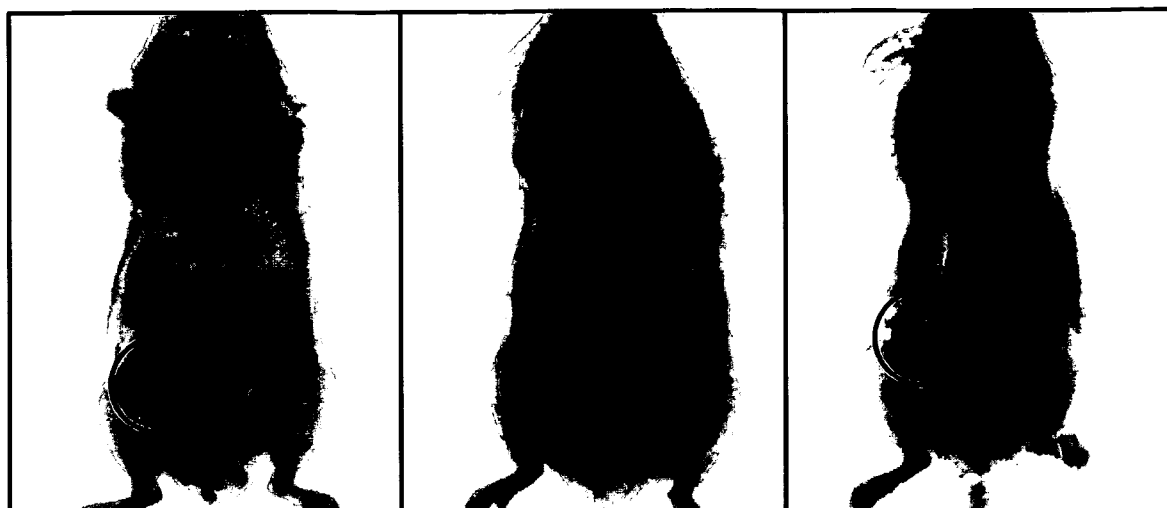
Fig. 40a**Fig. 40b**

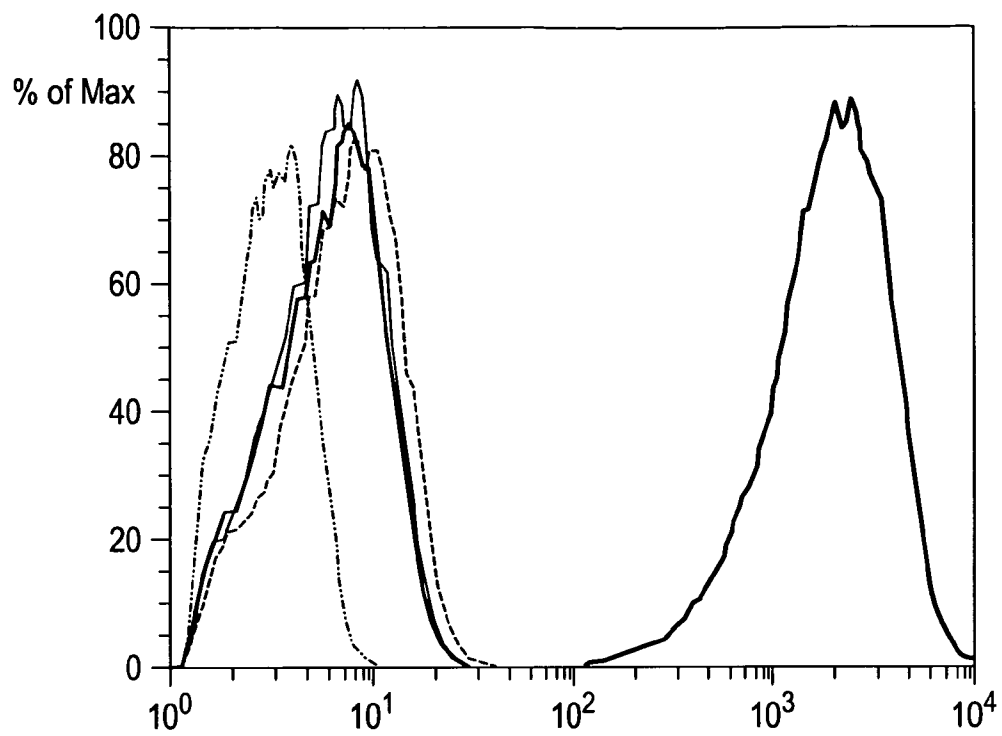
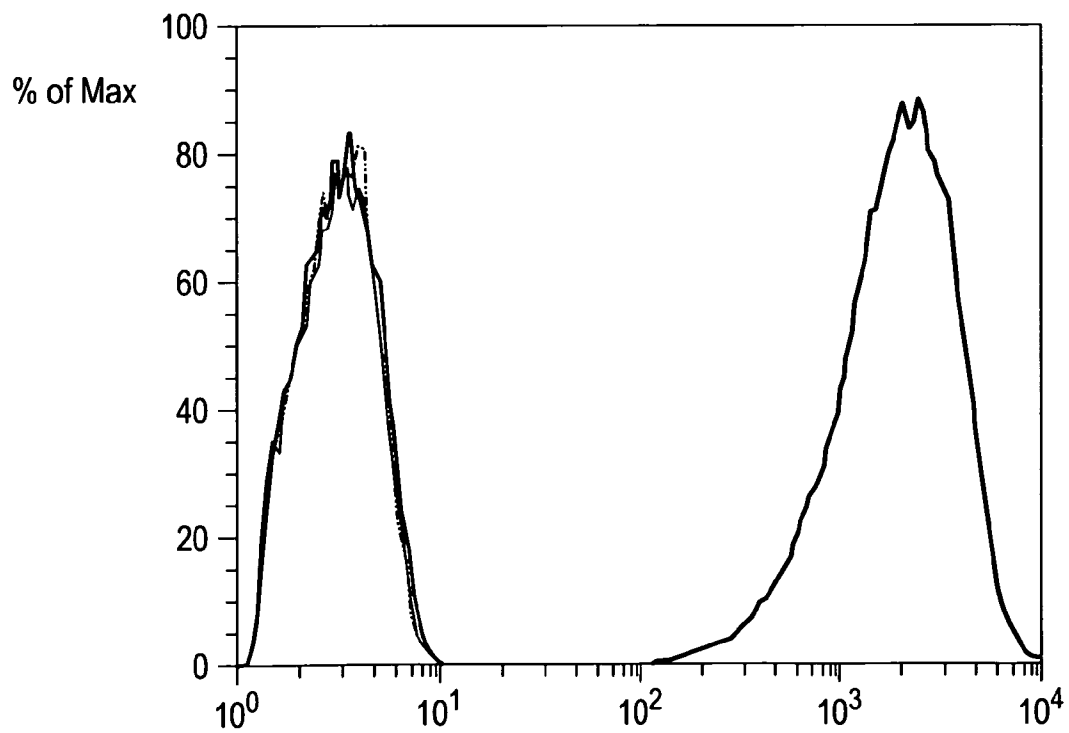
Fig. 41

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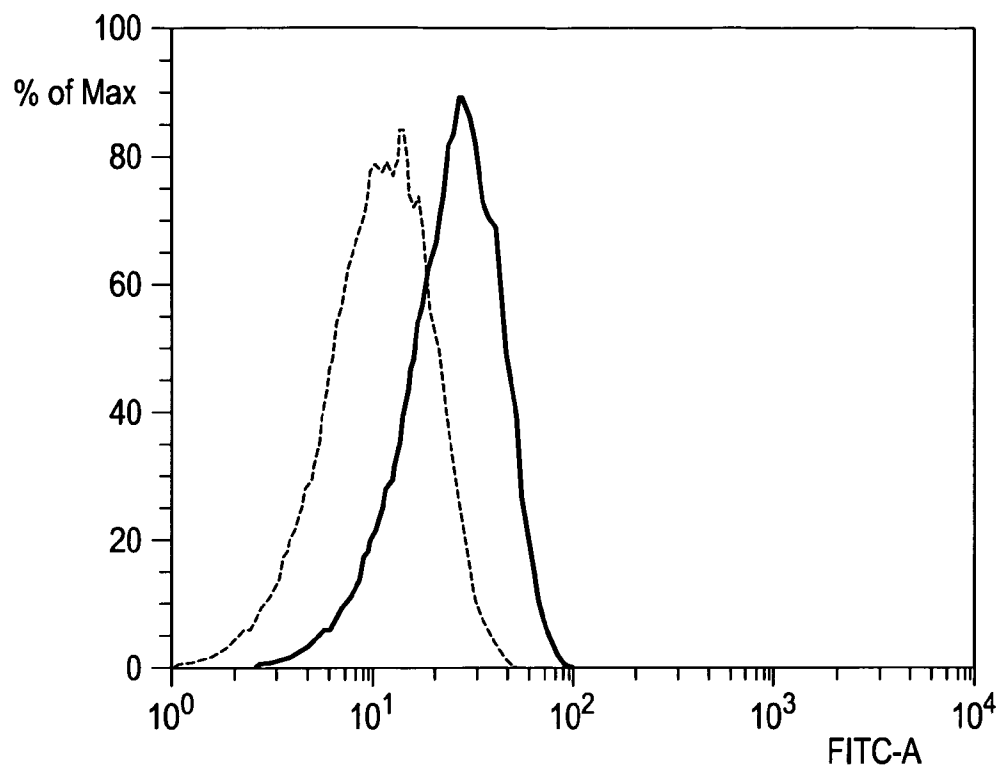
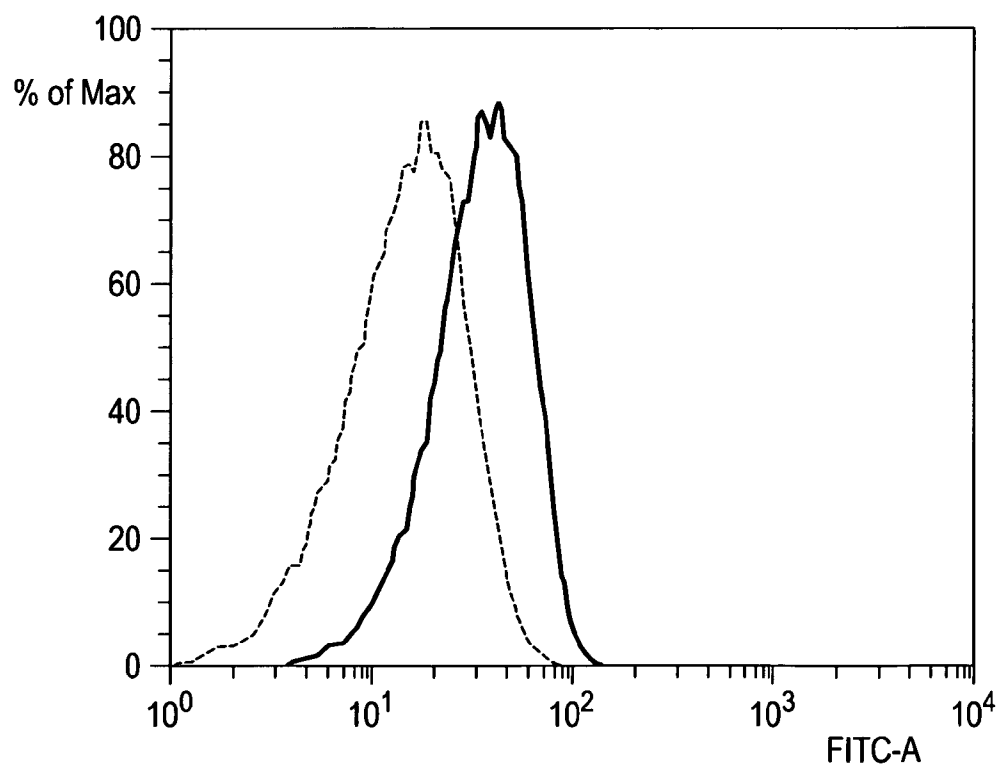
Fig. 42



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Fig. 43a**Fig. 43b**

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Fig. 44a**Fig. 44b**

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Fig. 45a

	complex murine Fab DIG-Cy5
Data collection	
Beamline	X06SA (SLS)
Space group	P 42 21 2
Cell dimensions	
a, b, c (Å)	138.103 138.103 123.696
α, β, γ (°)	90.00 90.00 90.00
Wavelength	0.9795
Resolution (Å)	50.0-2.80
Rsym	10.1 (32.1)
I / s	26.38 (9.11)
Completeness (%)	98.1 (95.0)
Redundancy	14.7
Refinement	
Resolution (Å)	46.040 - 2.798
No. reflections (test)	29999 (1534)
Rwork / Rfree	20.340 / 23.12
No. atoms	
Protein	6660
Ligand	2x28
Water	348
B-factor (Å²)	
Protein	23.65
Ligand	16.00
Water	32.29
R.m.s deviations	
Bonds (Å)	0.006
Angles (°)	1.292
Ramachandran	
Core (%)	87.4
Disallowed (%)	0.4

Fig. 45b

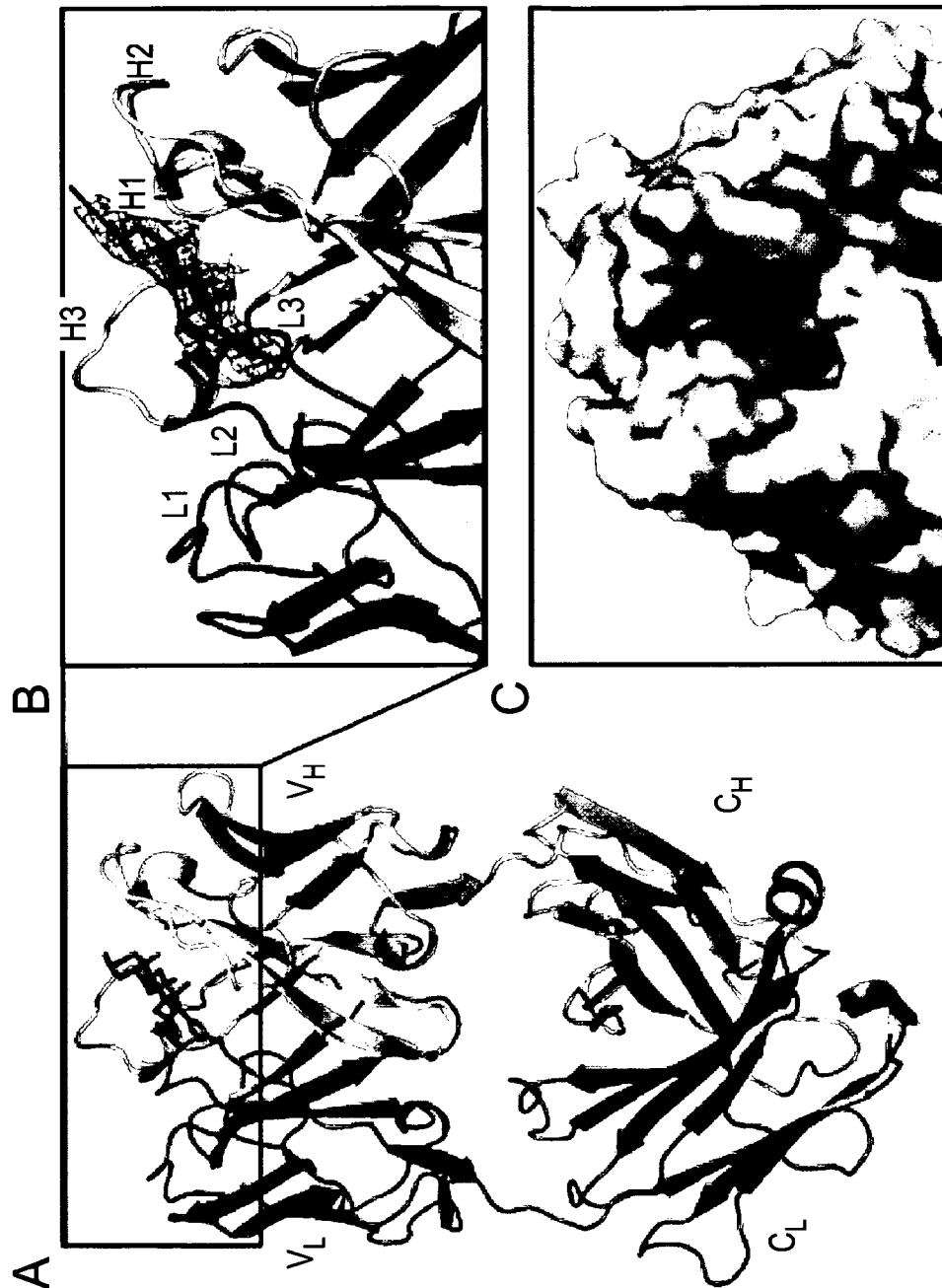


Fig. 45c

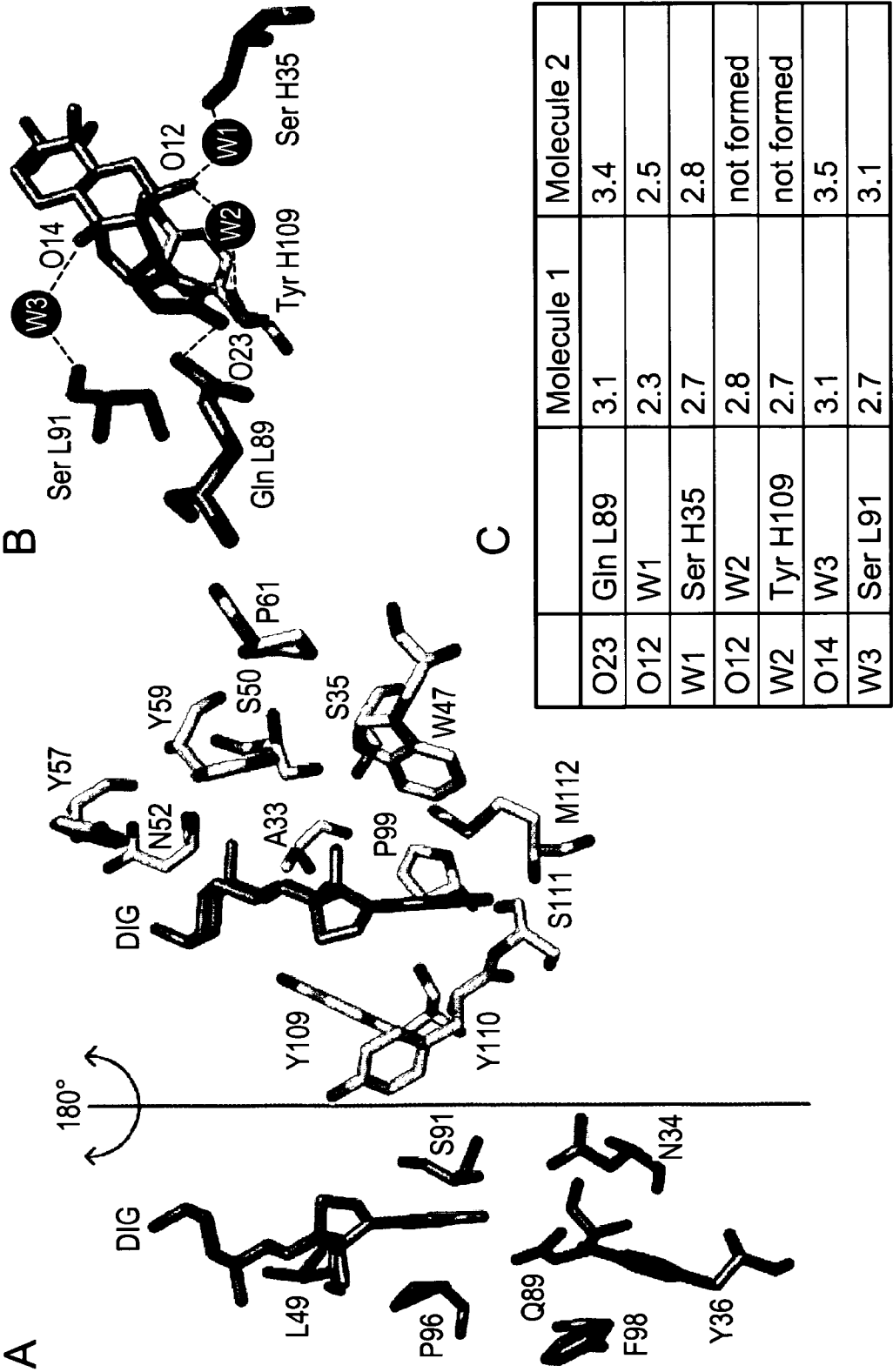
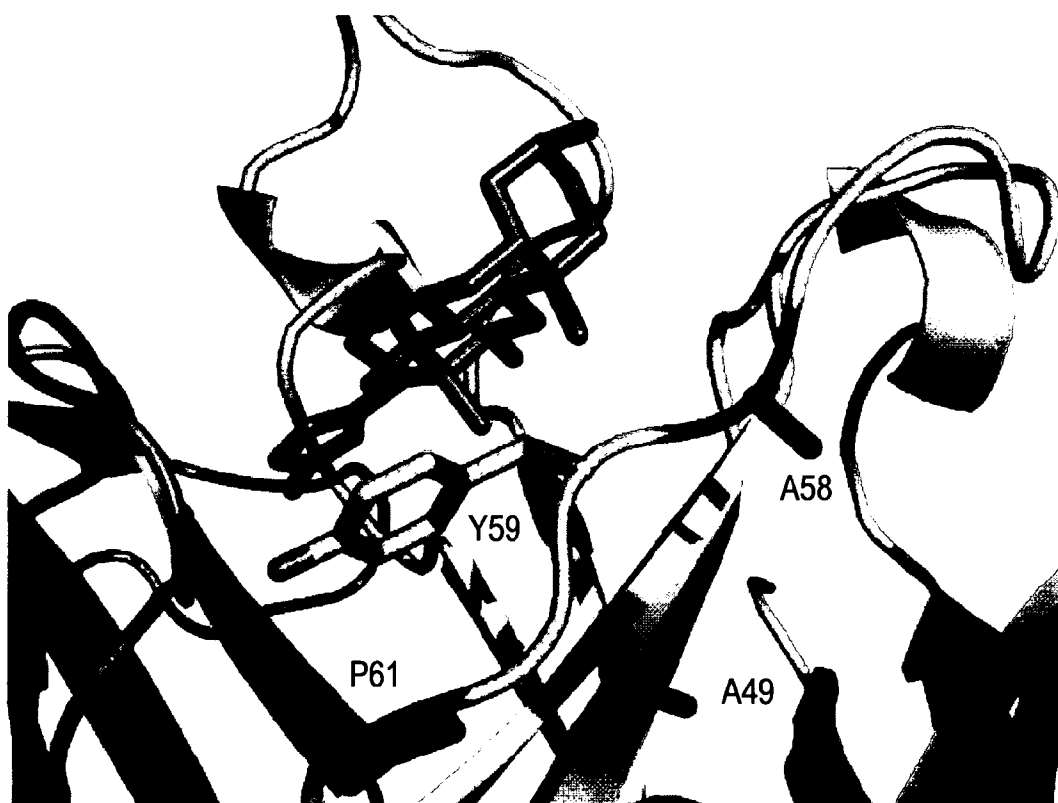


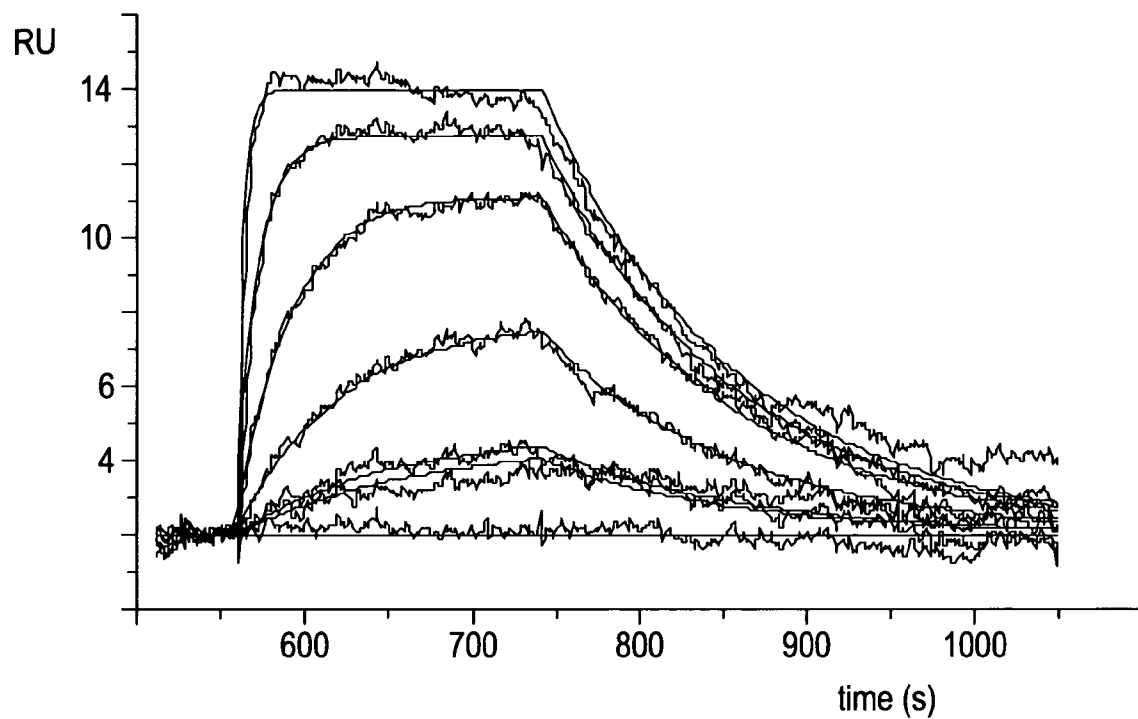
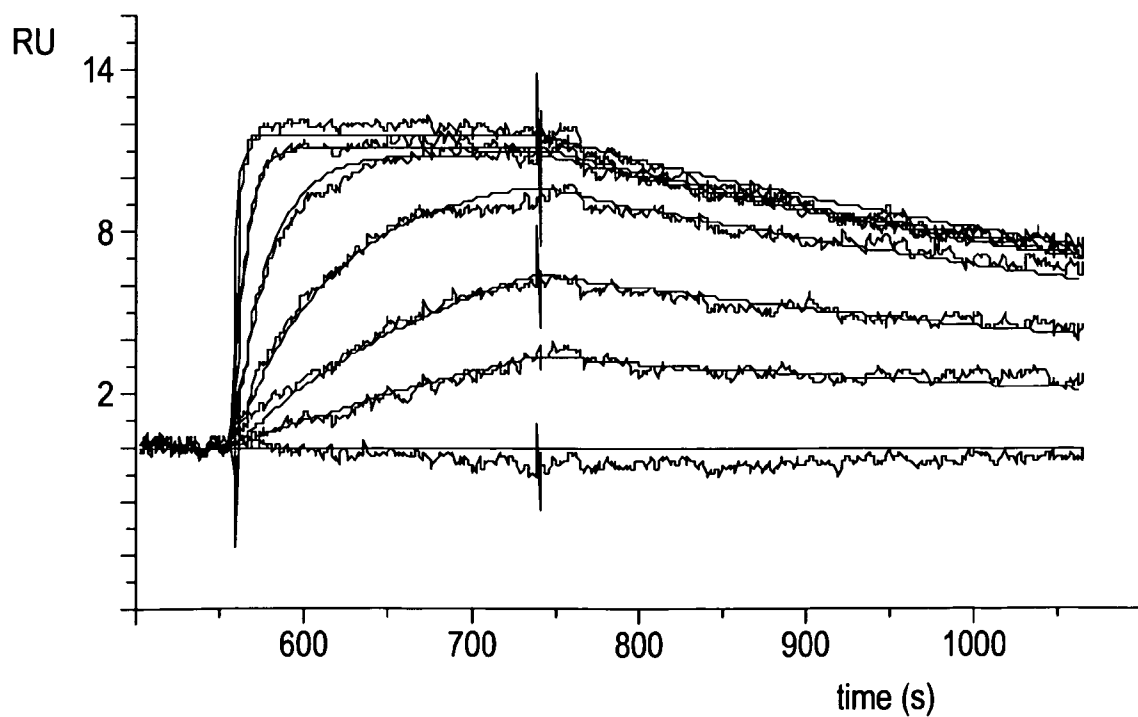


Fig. 46a

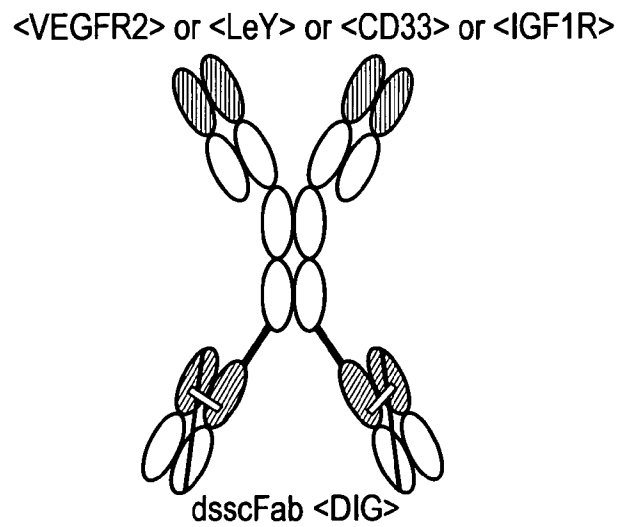
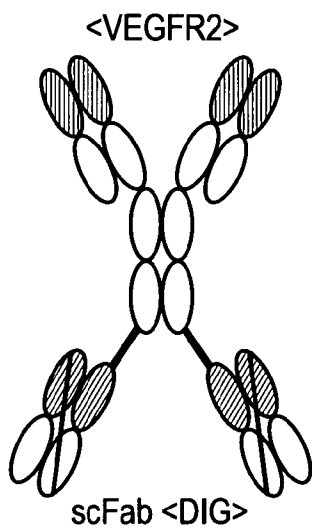
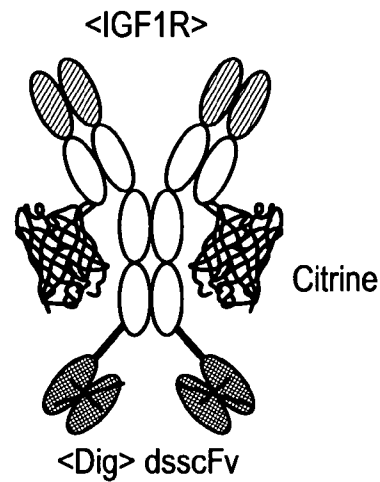
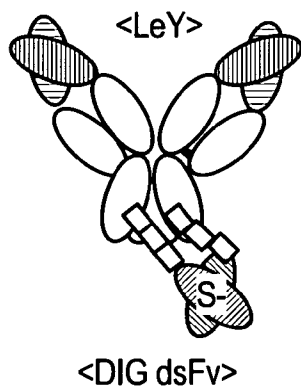
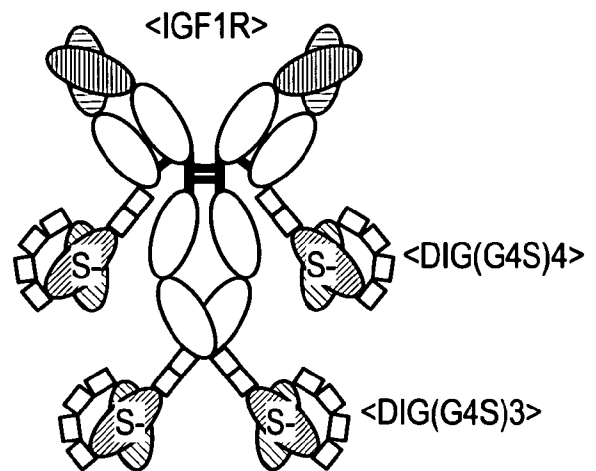
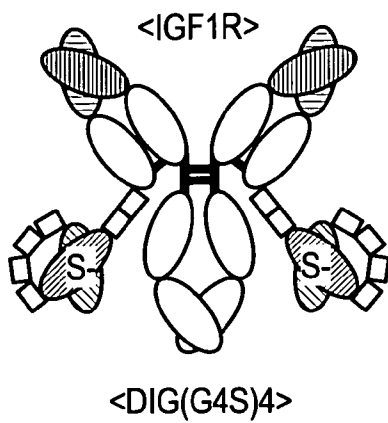
Fig. 46b



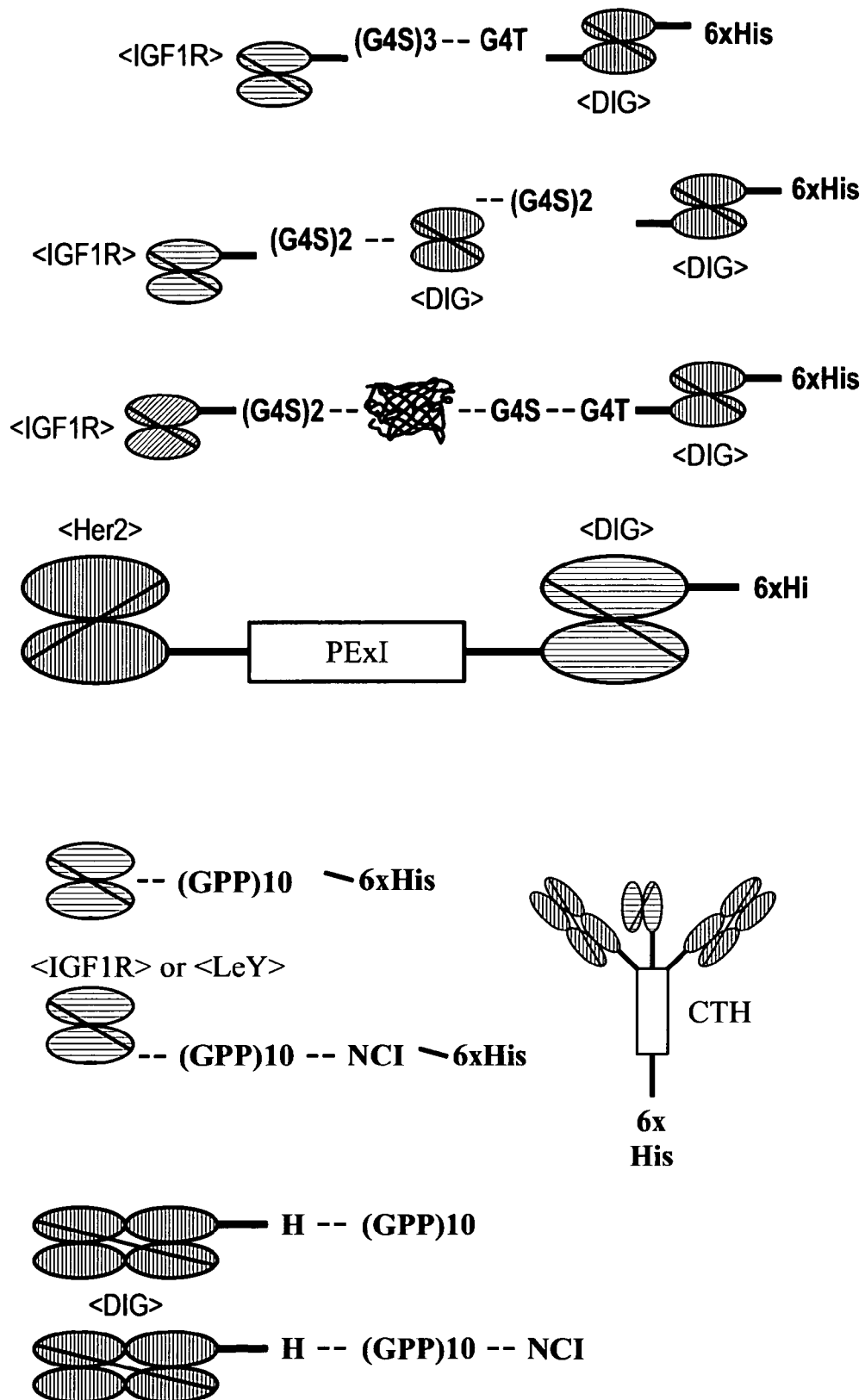
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Fig. 46c**Fig. 46d**

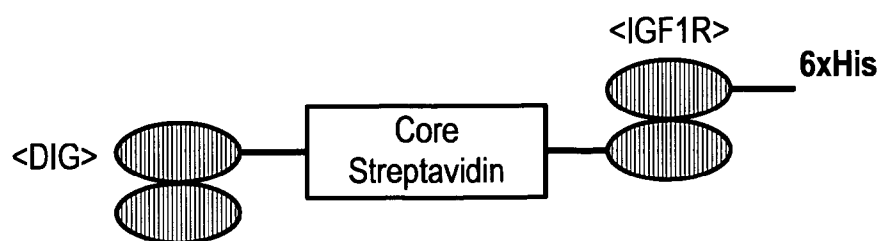
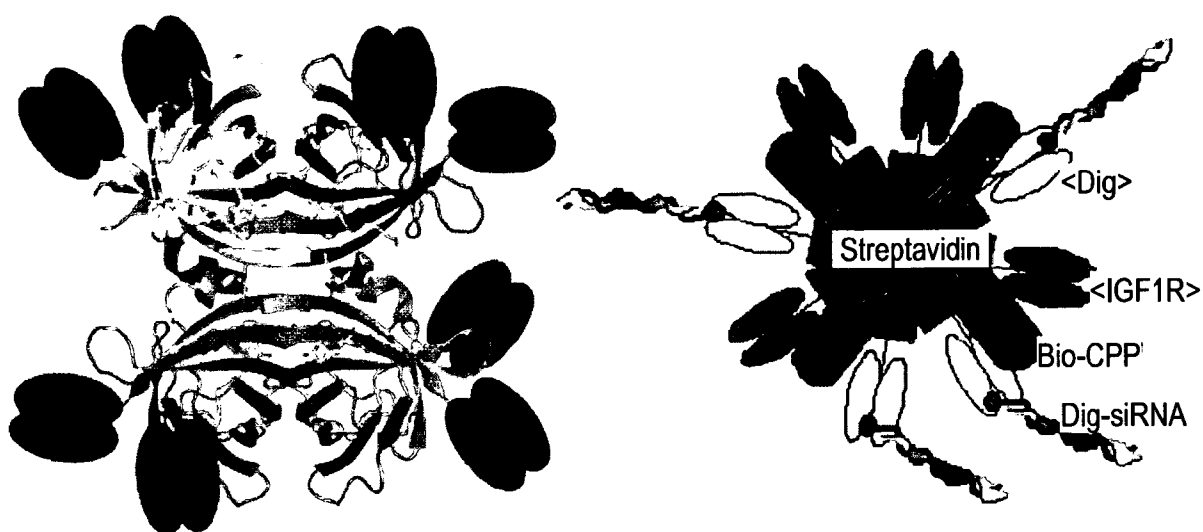
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Fig. 47a

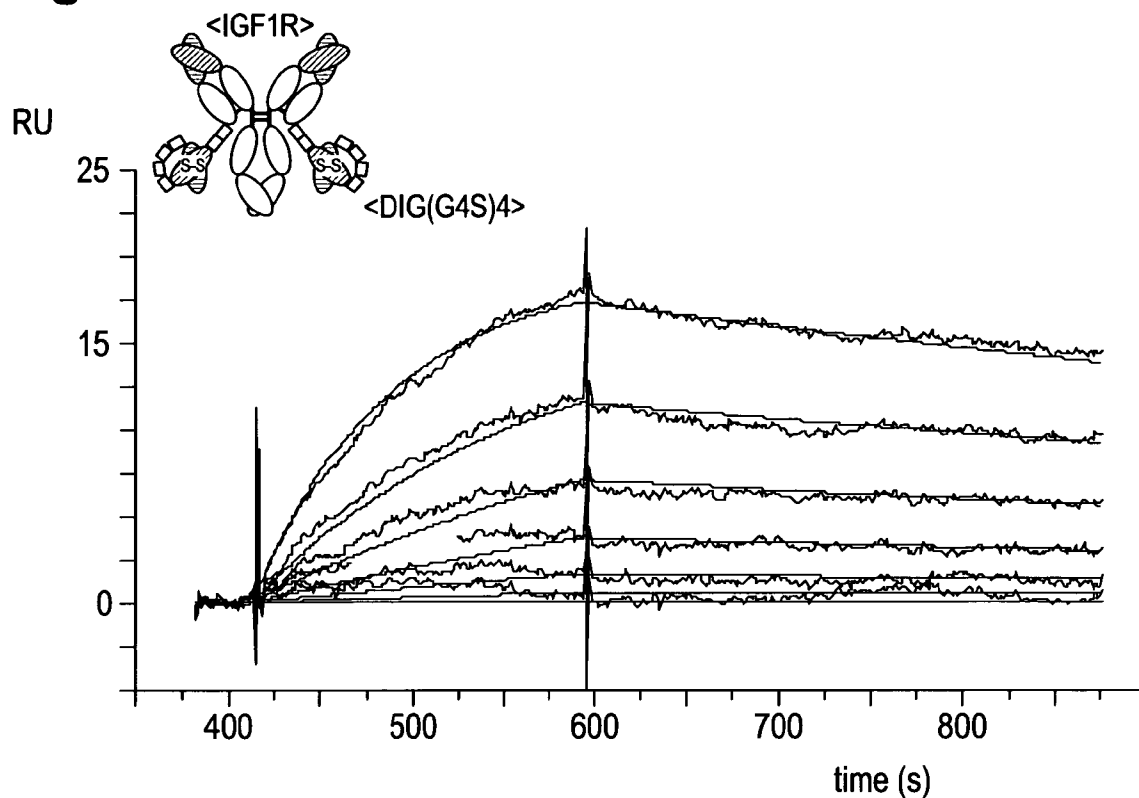
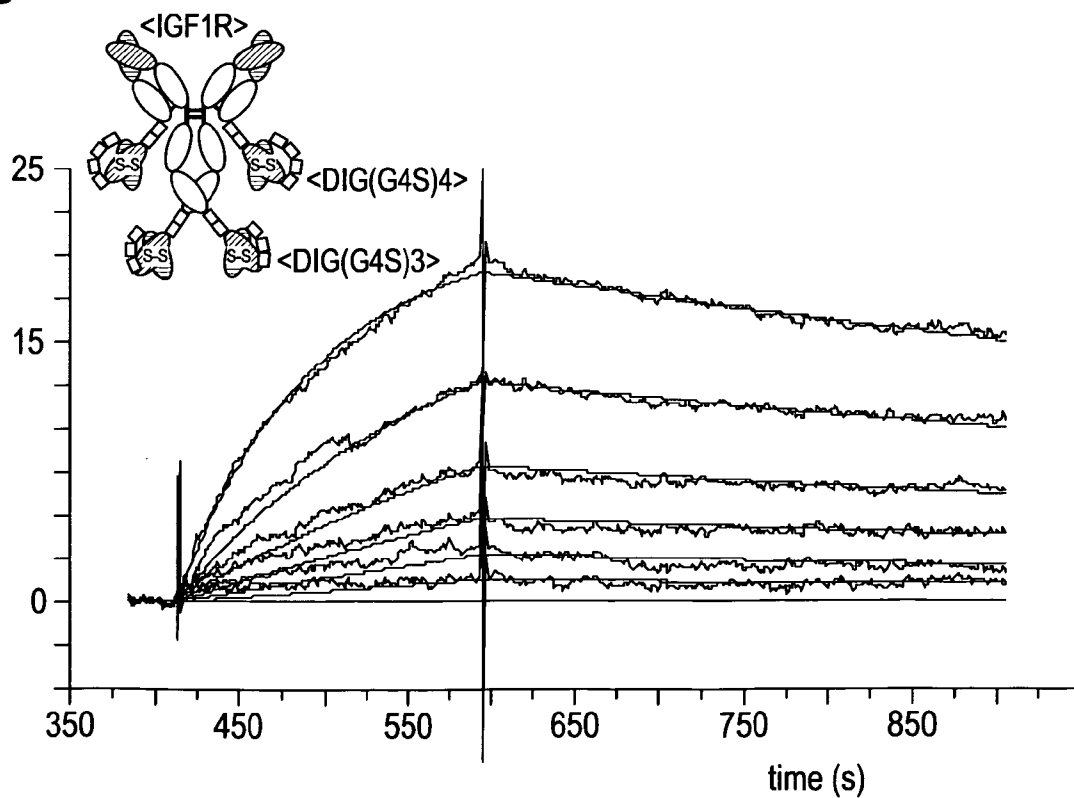
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Fig. 47b

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Fig. 47c

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Fig. 47d**Fig. 47e**

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Fig. 47f

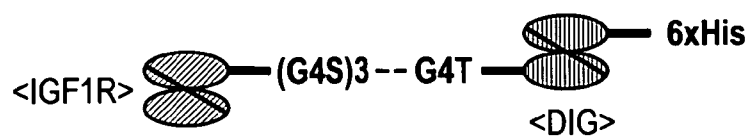
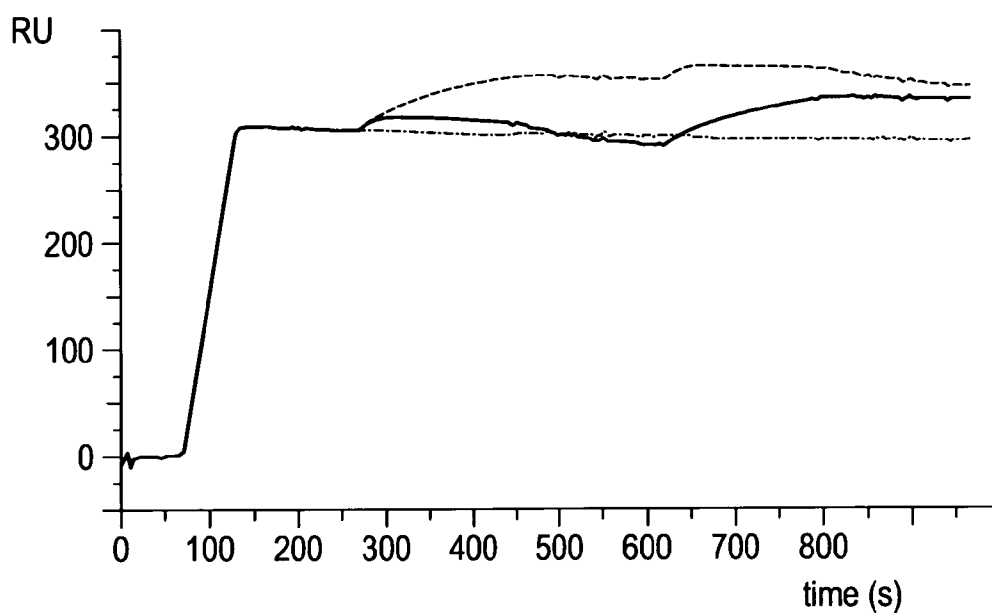
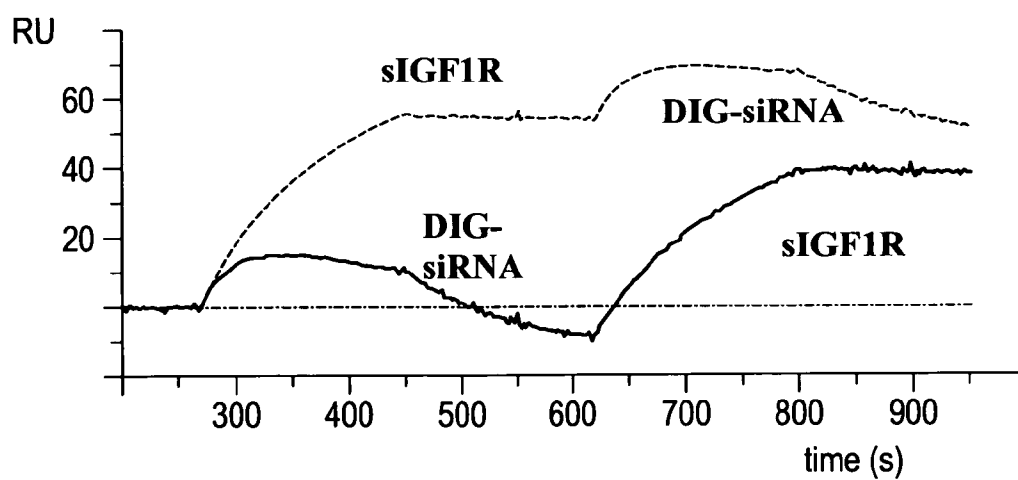
Affinity to siRNA-DIG	kd (1/s)	KD (nM)
<IGF1R-DIG> Dig on CH3	9,81E-03	20
<IGF1R-DIG> Dig on Ckappa	9,71E-03	23
<IGF1R-DIG-DIG> hexavalent	9,17E-03	24
Affinity to IGF-1R	kd (1/s)	KD (nM)
<IGF1R-DIG> Dig on CH3	1,09E-03	3
<IGF1R-DIG> Dig on Ckappa	7,99E-03	3
<IGF1R-DIG-DIG> hexavalent	7,64E-03	3

Affinity for DIG-siRNA		kd (1/s)	KD (nM)
<IGF1R-DIG> 2321	5,03E+0	1,17E-02	23
<IGF1R-scFab-DIG> 2321	8,32E+0	1,12E-02	14
<IGF1R-dsFab-DIG> 2321	5,79E+0	7,82E-02	14

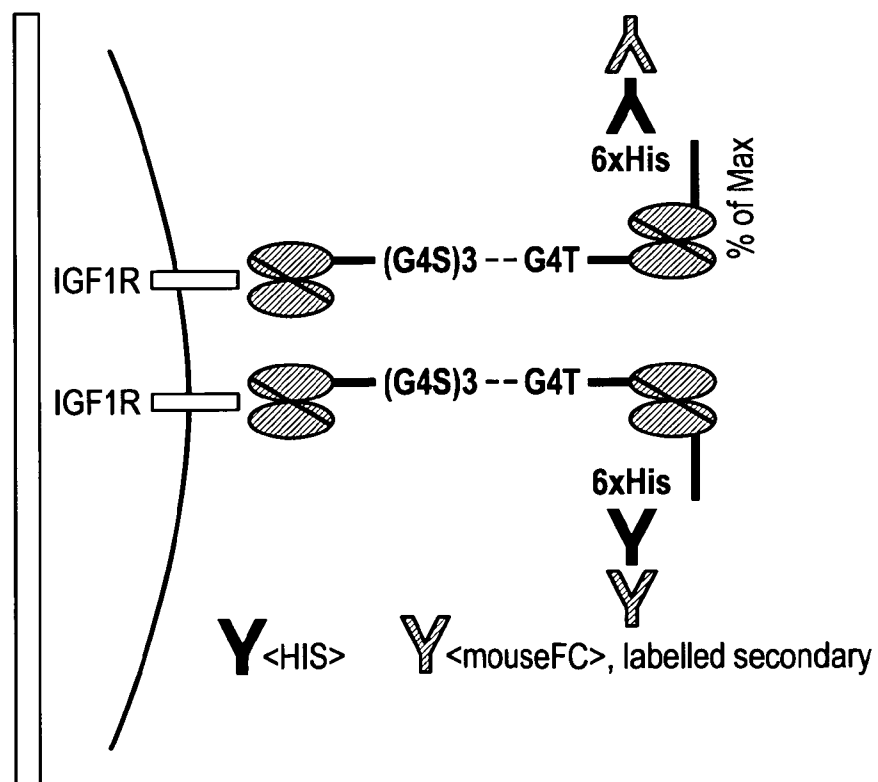
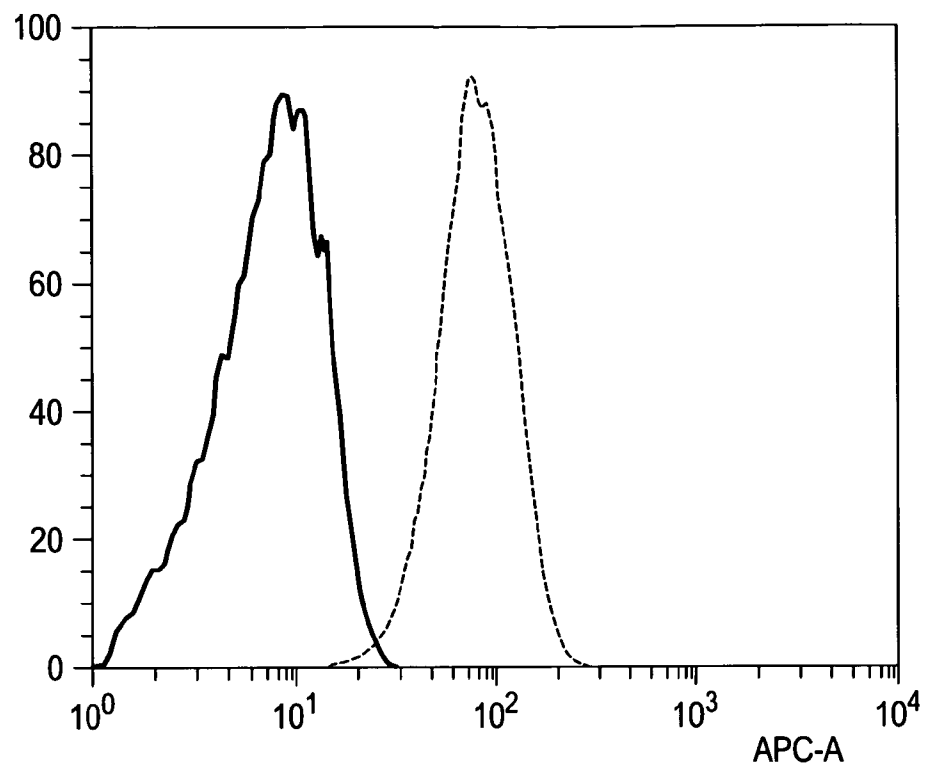
Affinity for DIG-siRNA

Capture	Antibody	ka (1/Ms)	kd (1/s)	KD (M)
human VEGFR2-Fc	<VEGFR2(D1F7)-DIG>_001	3.44E+06	6.54E-03	1.09E-09
	<VEGFR2(D1F7)-scFab-DIG>	4.98E+06	6.70E-03	1.35E-09
	<VEGFR2(D1F7)-dsFab-DIG>	2.49E+06	9.68E-03	3.89E-09
mouse VEGFR2-Fc	<VEGFR2(D1F7)-DIG>_001	3.89E+06	6.56E-03	1.69E-09
	<VEGFR2(D1F7)-scFab-DIG>	3.21E+06	8.92E-03	2.78E-09
	<VEGFR2(D1F7)-dsFab-DIG>	2.01E+06	1.14E-02	5.65E-09

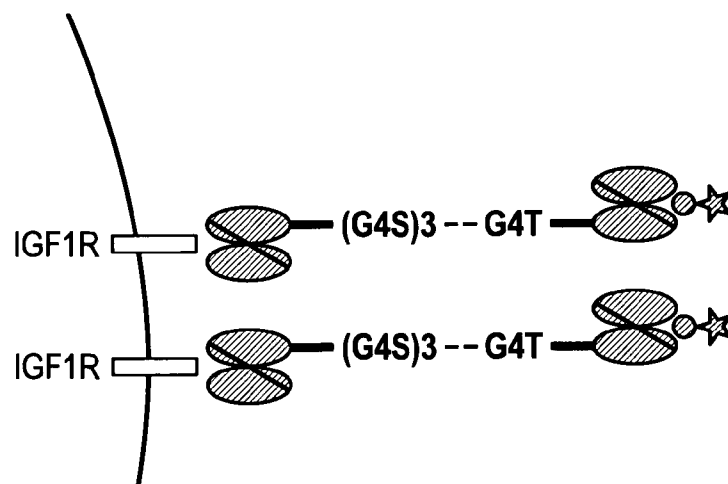
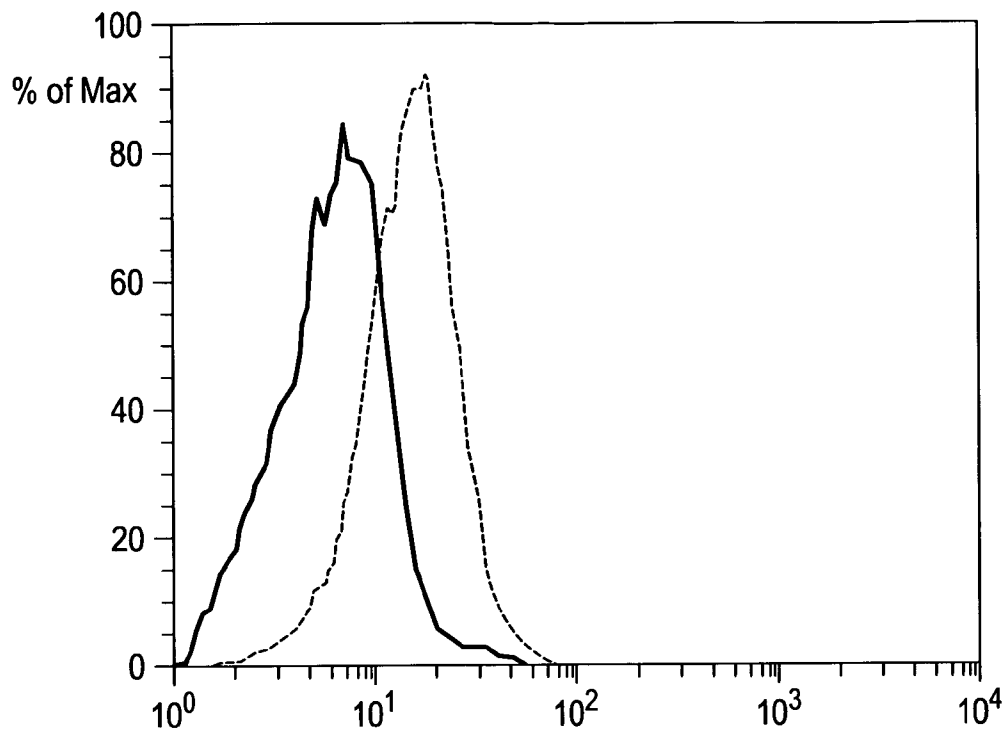
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Fig. 47g**Fig. 47h****Fig. 47i**

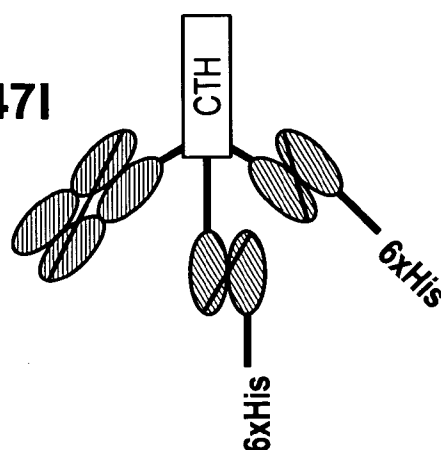
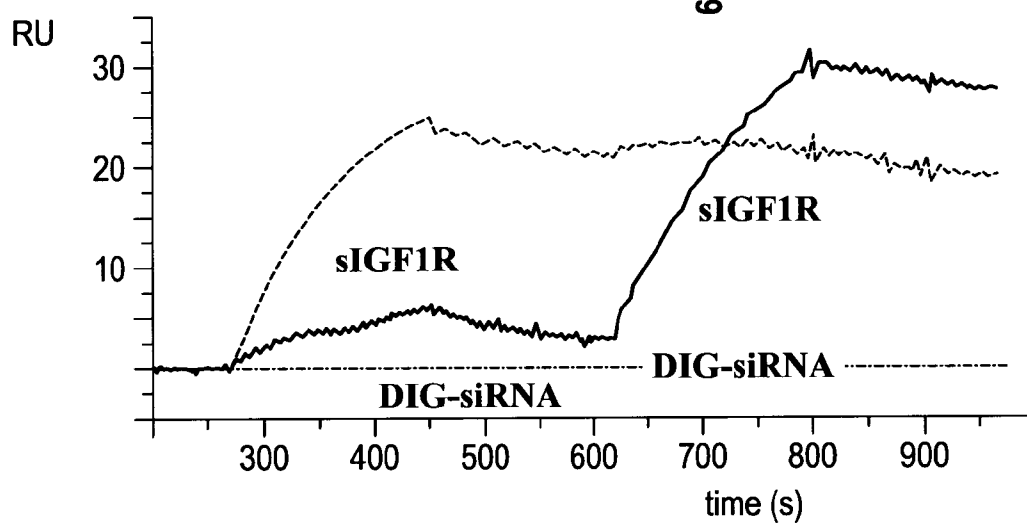
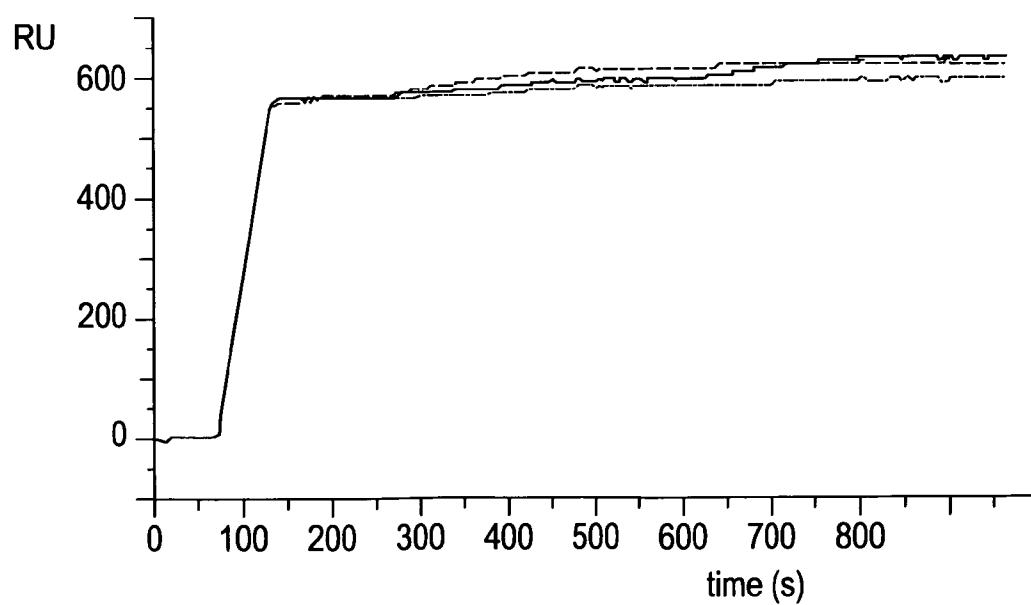
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Fig. 47j

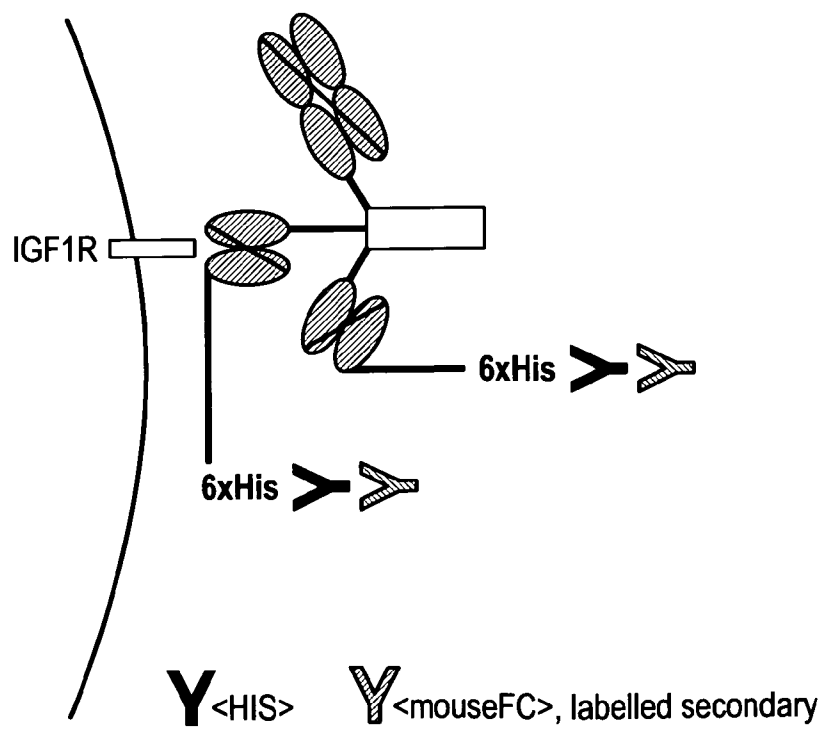
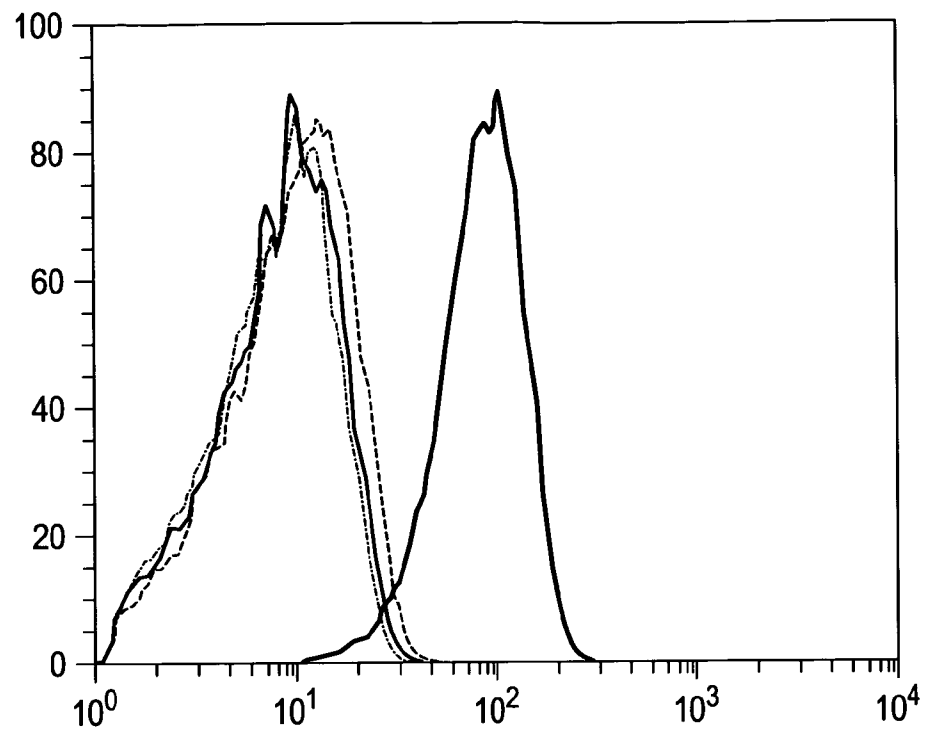
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Fig. 47k

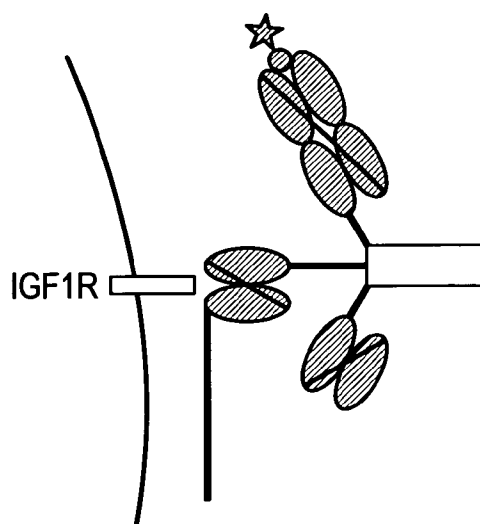
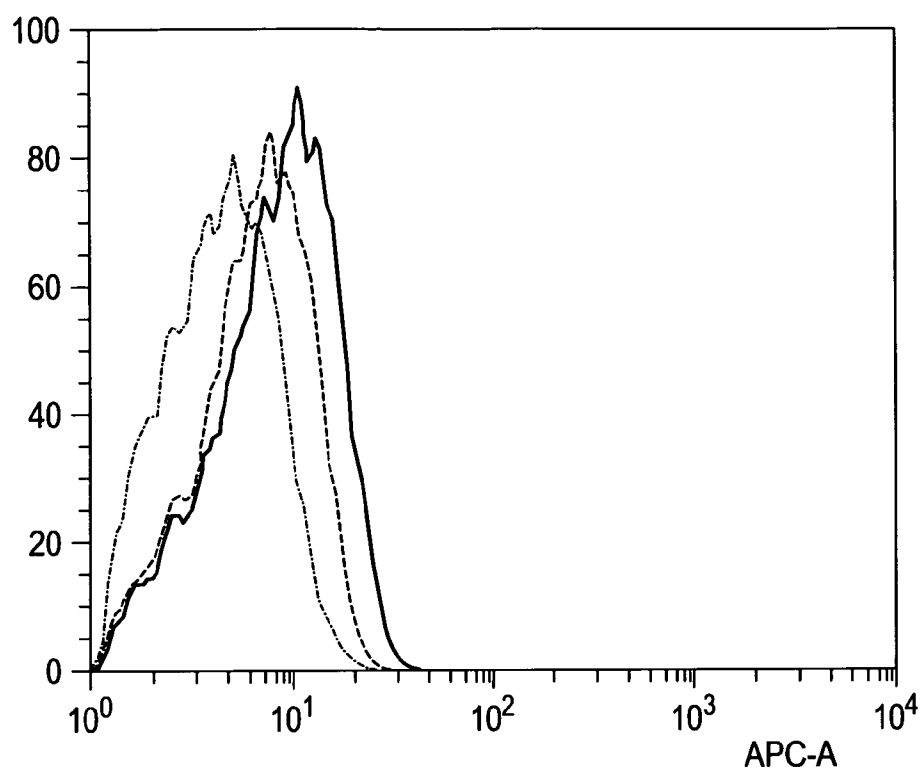
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Fig. 47l**Fig. 47m****Fig. 47n**

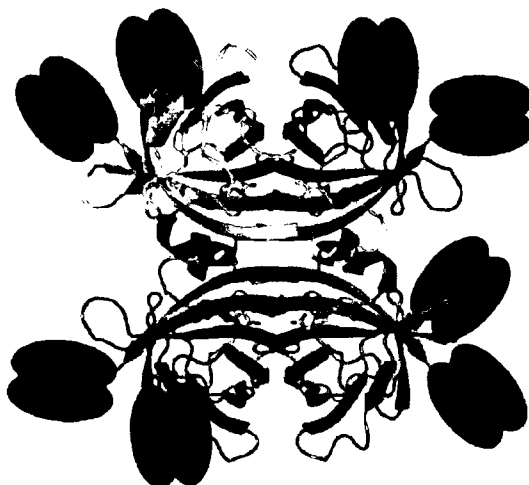
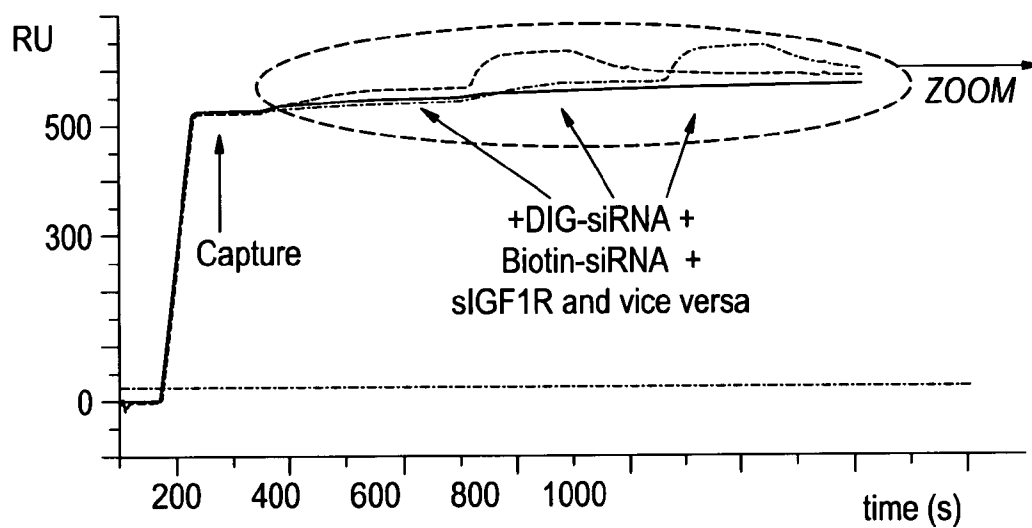
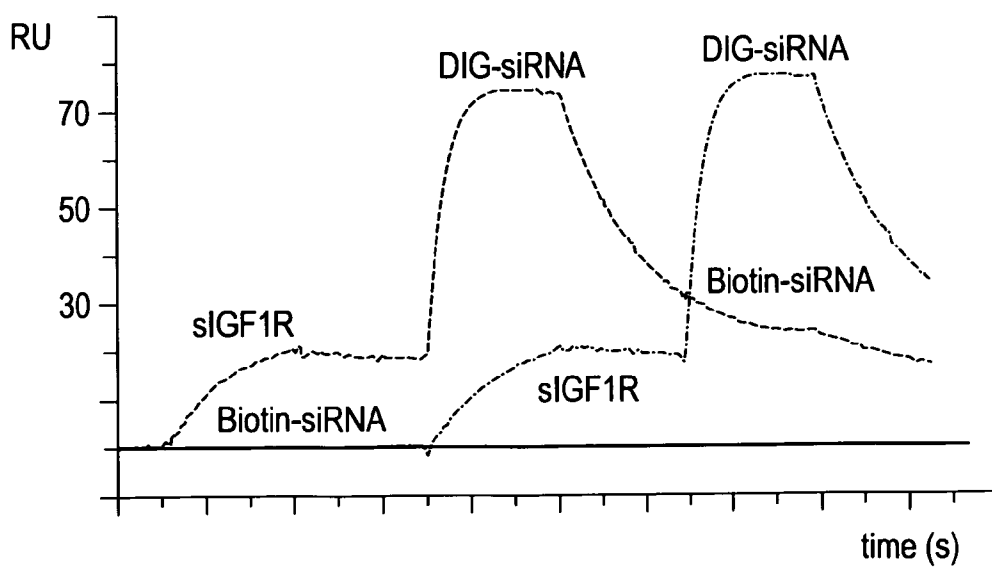
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Fig. 47o

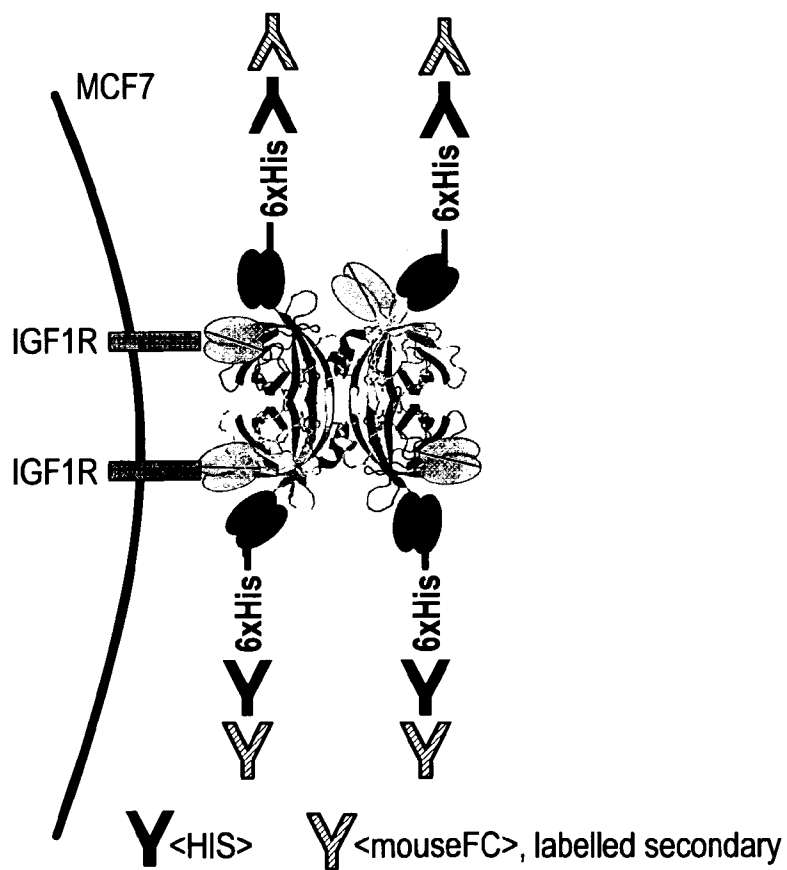
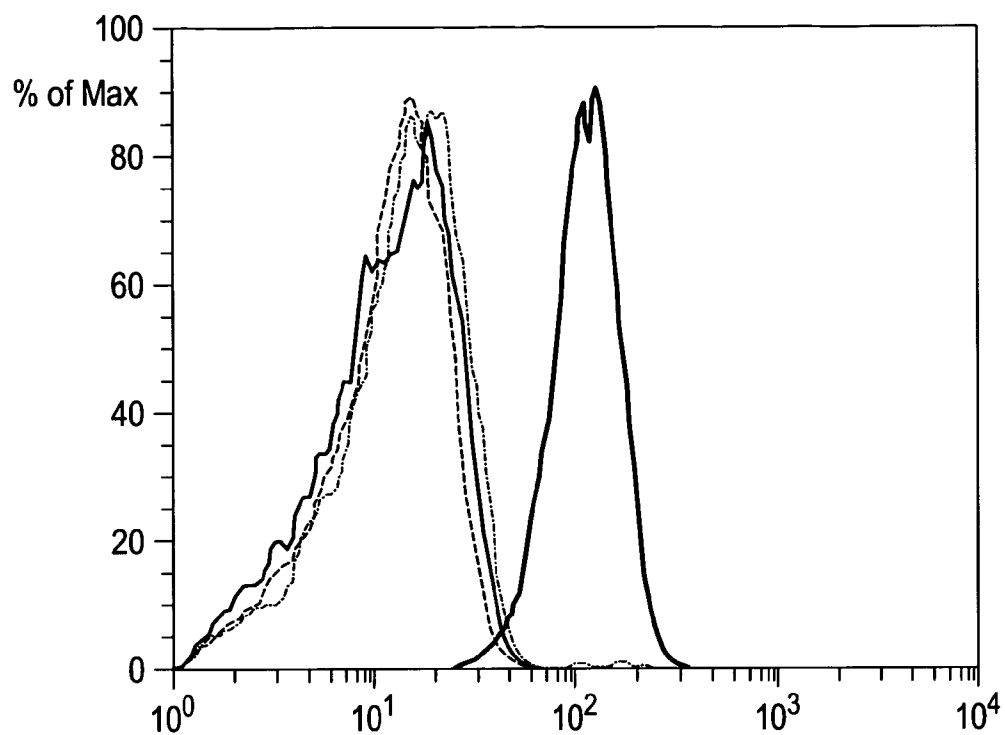
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Fig. 47p

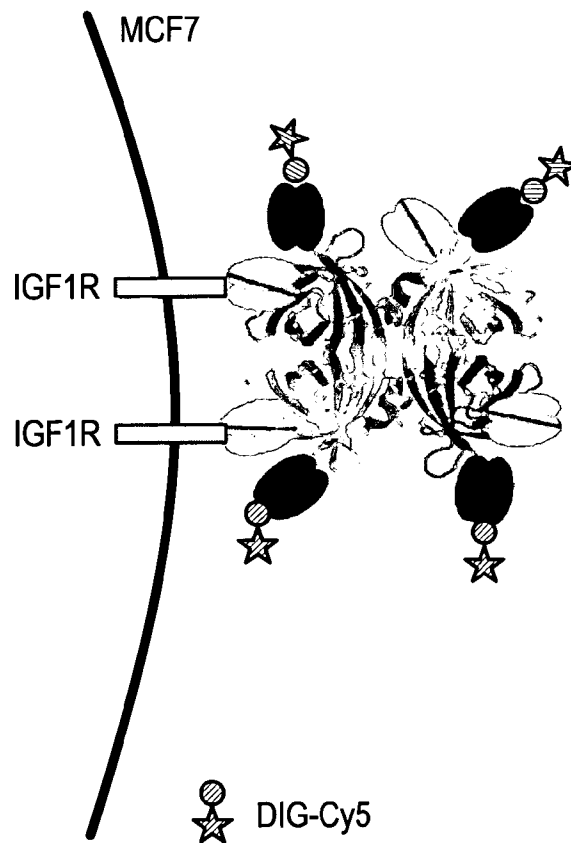
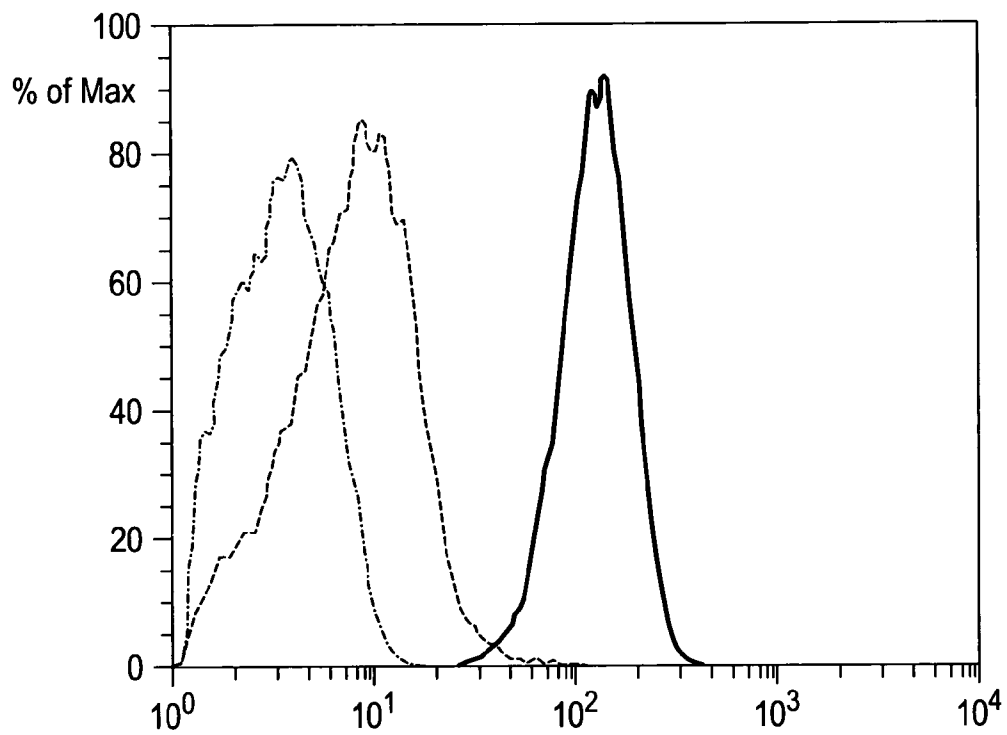
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Fig. 47q**Fig. 47r****Fig. 47s**

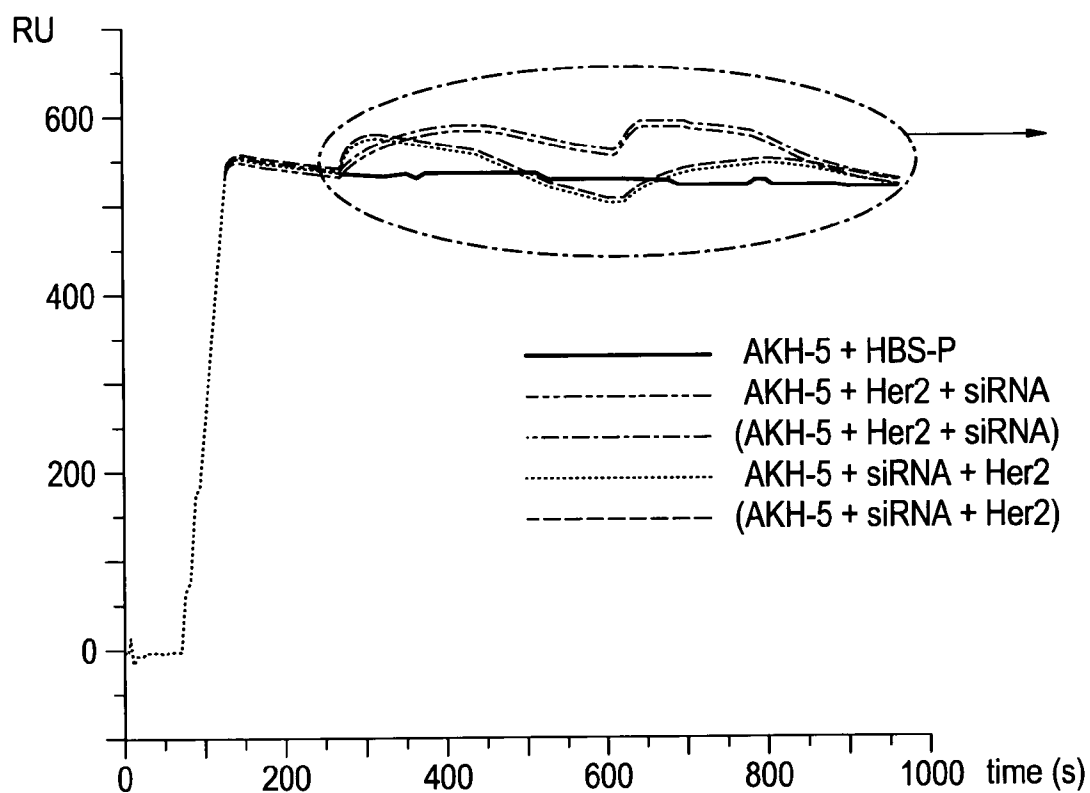
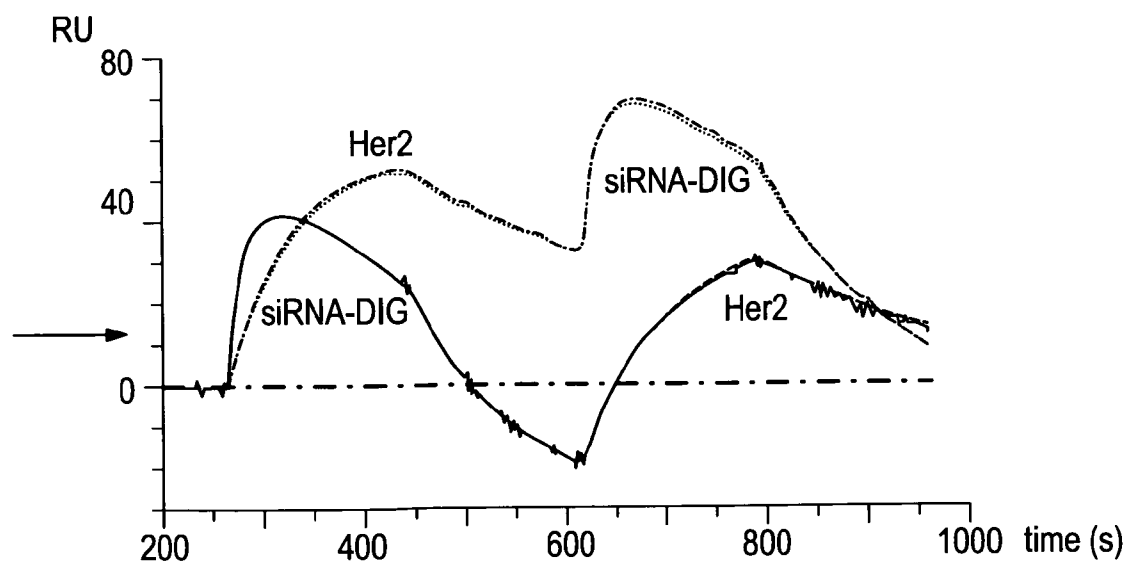
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Fig. 47t

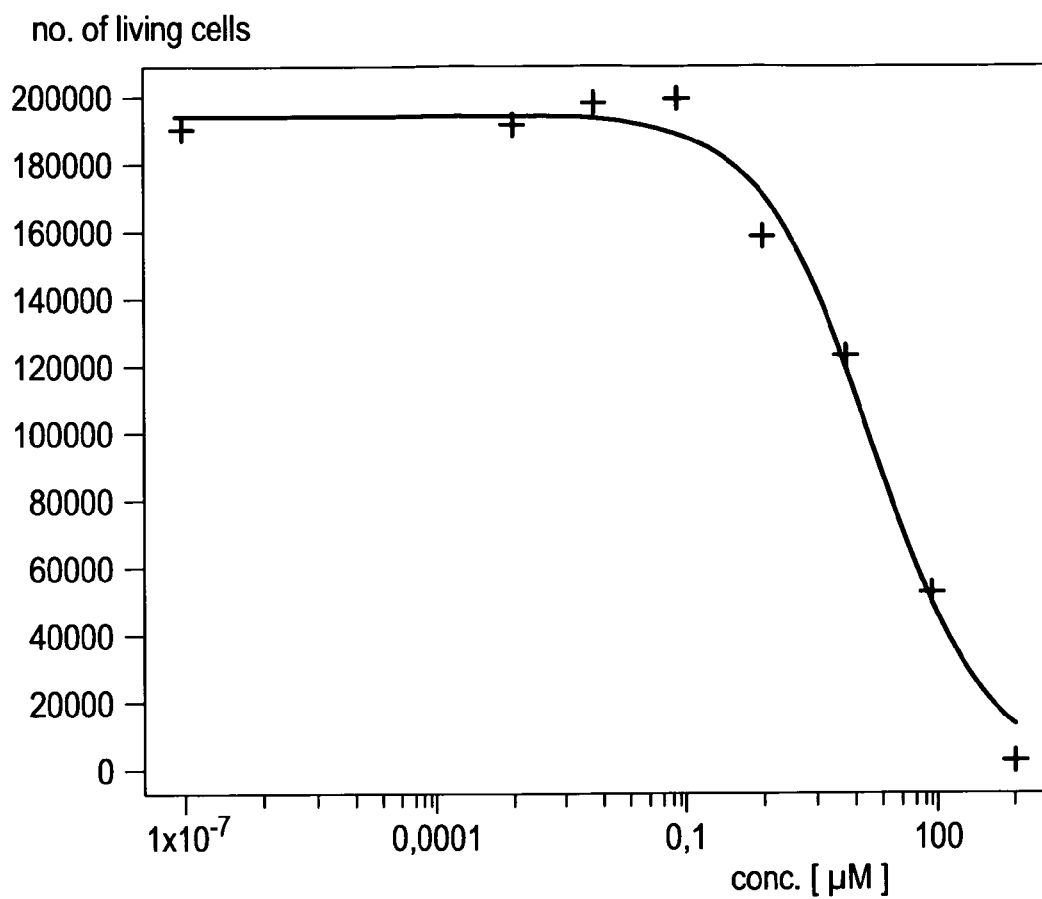
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Fig. 47u

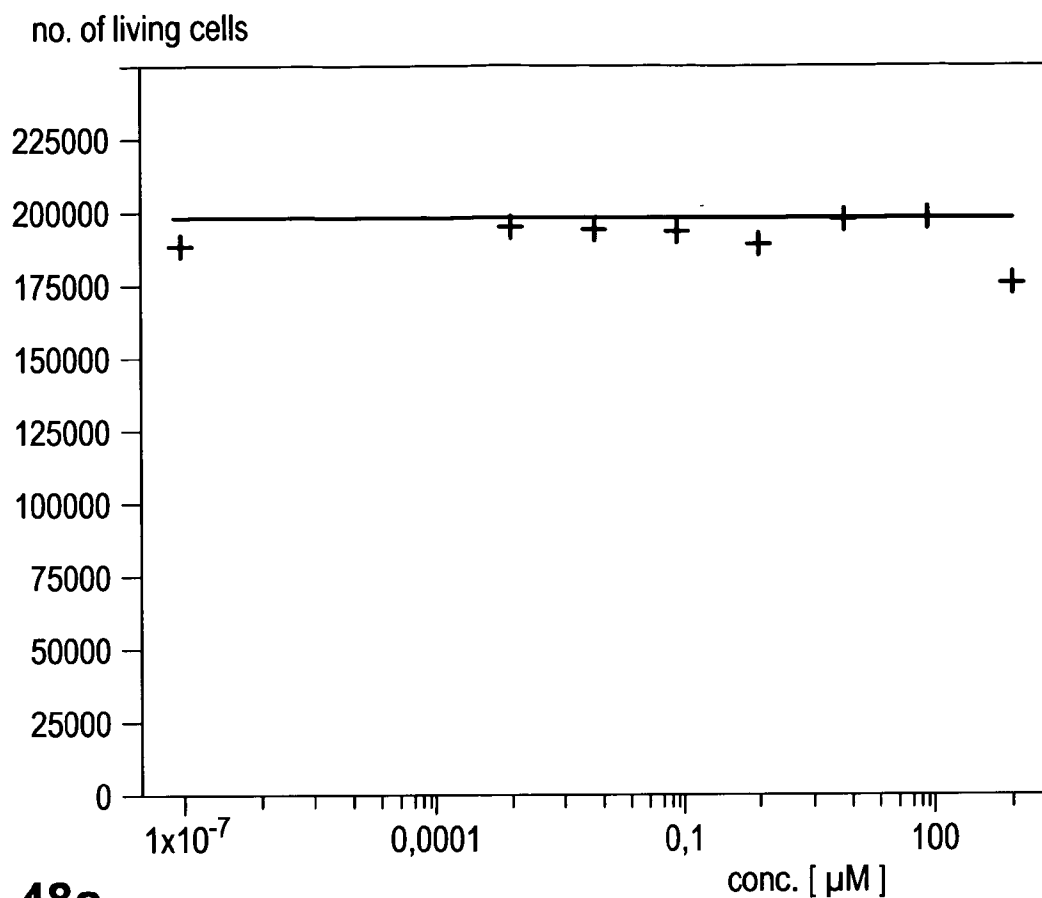
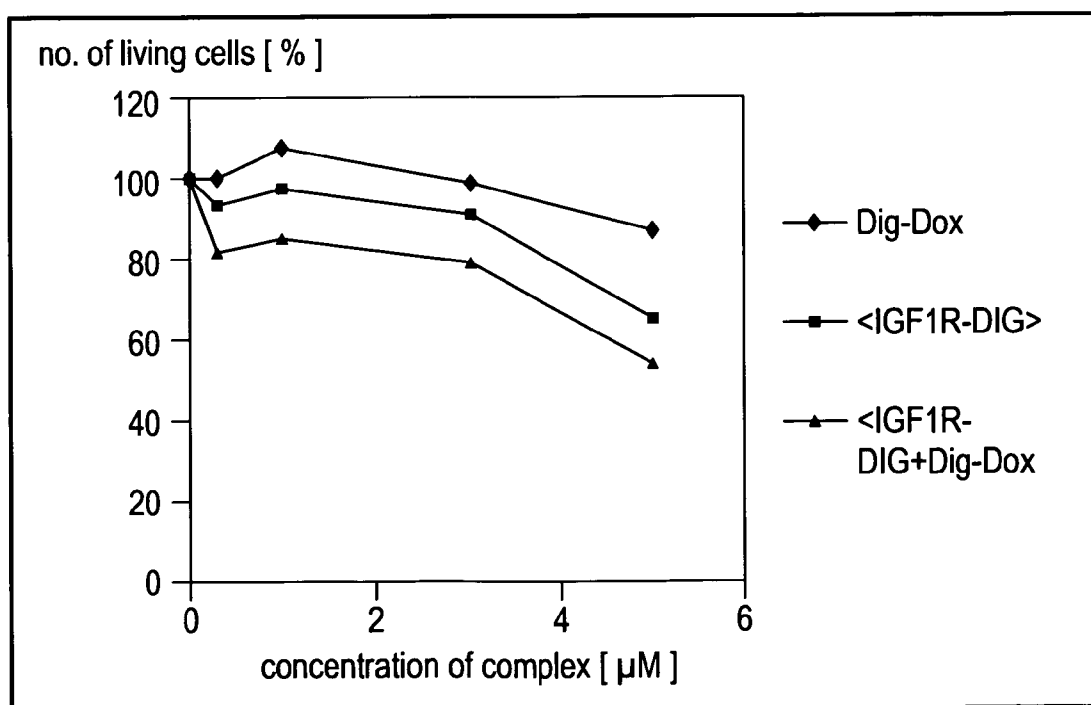
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Fig. 47v**Fig. 47w****Fig. 47x**

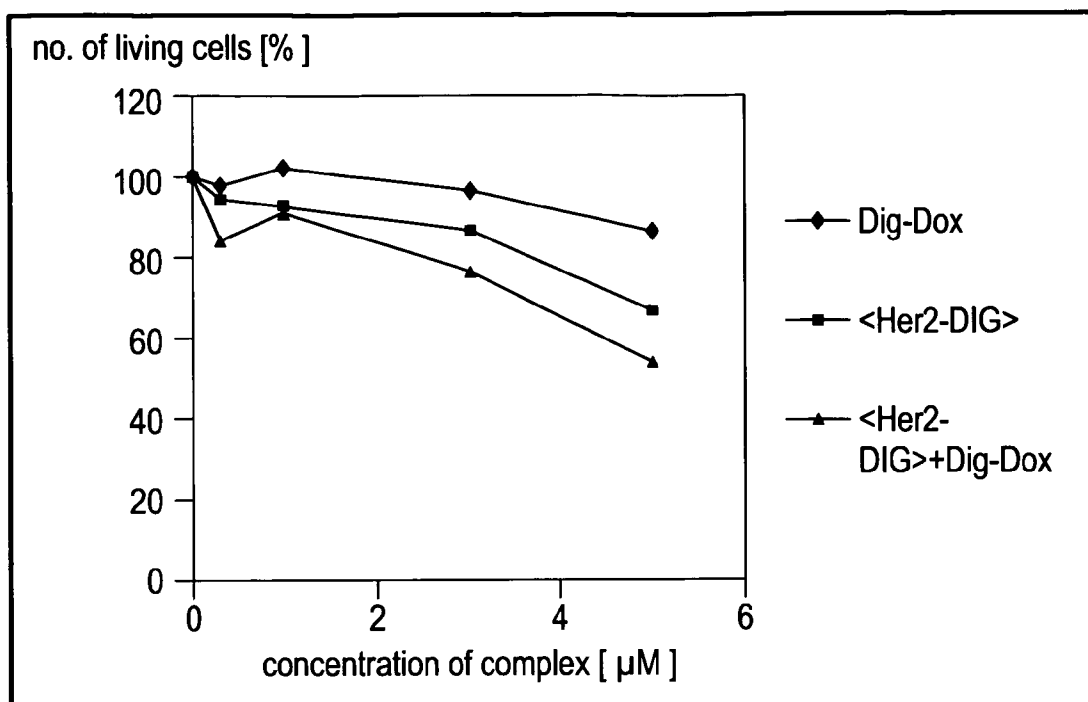
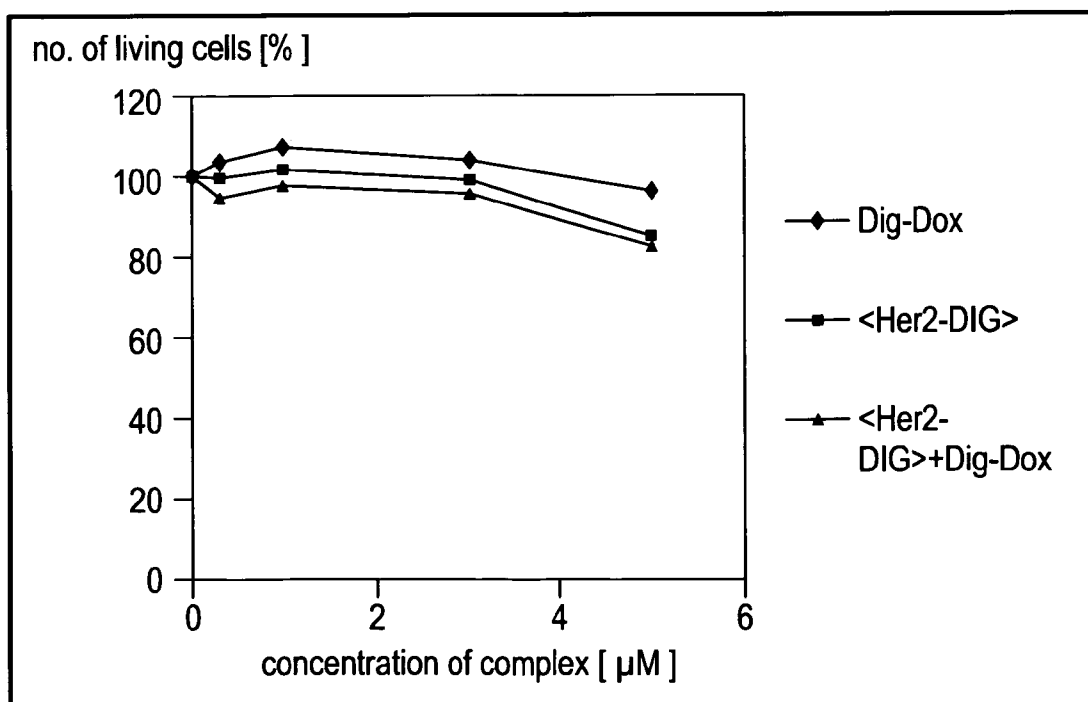
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Fig. 48a

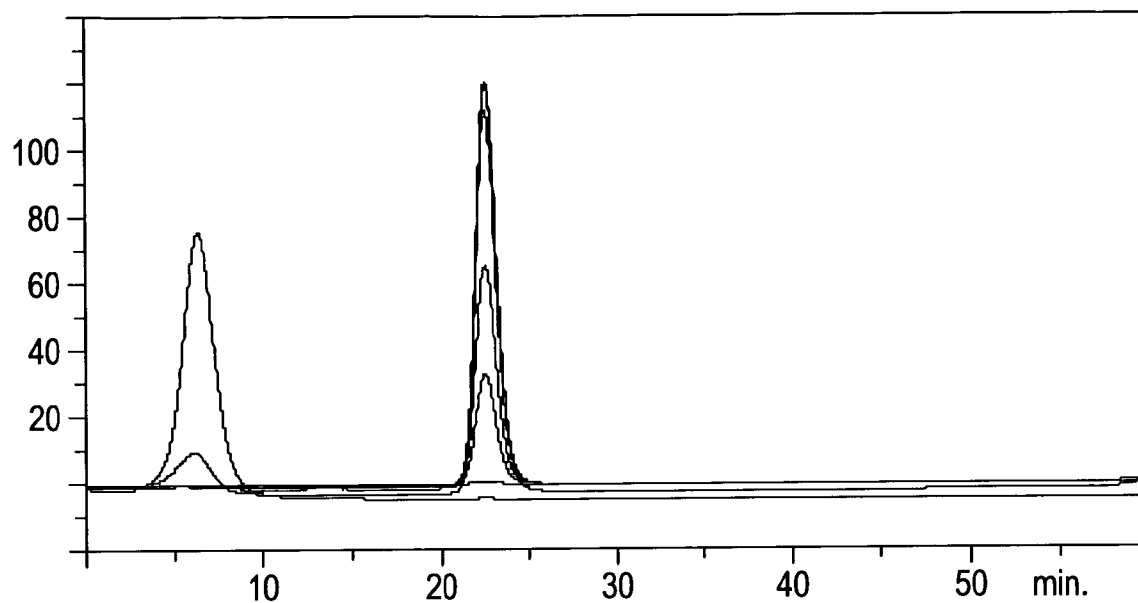
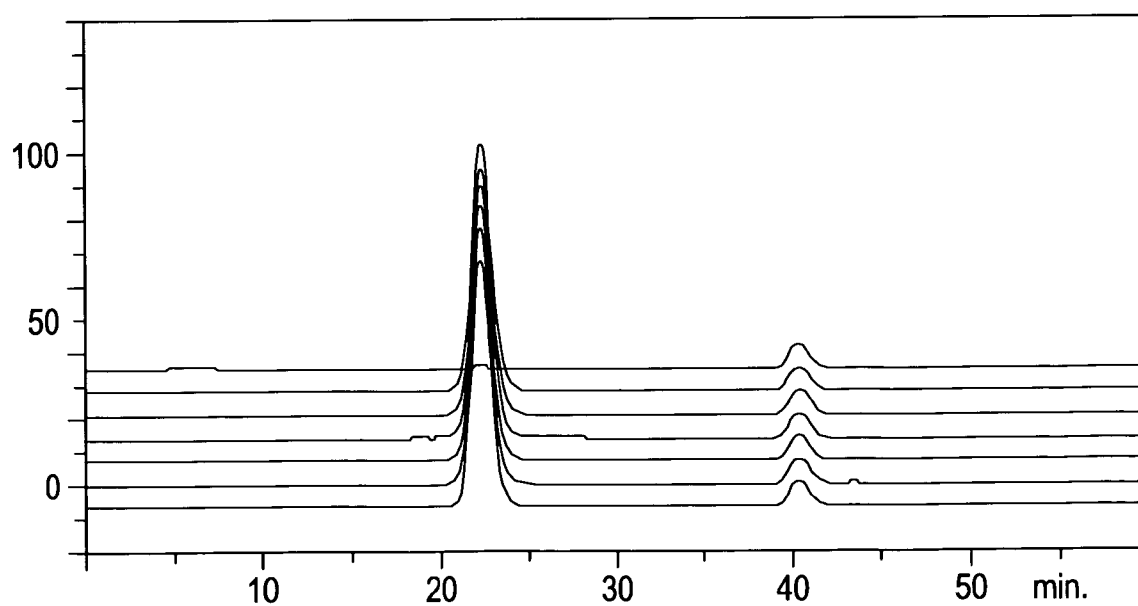
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Fig. 48b**Fig. 48c**

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Fig. 48d**Fig. 48e**

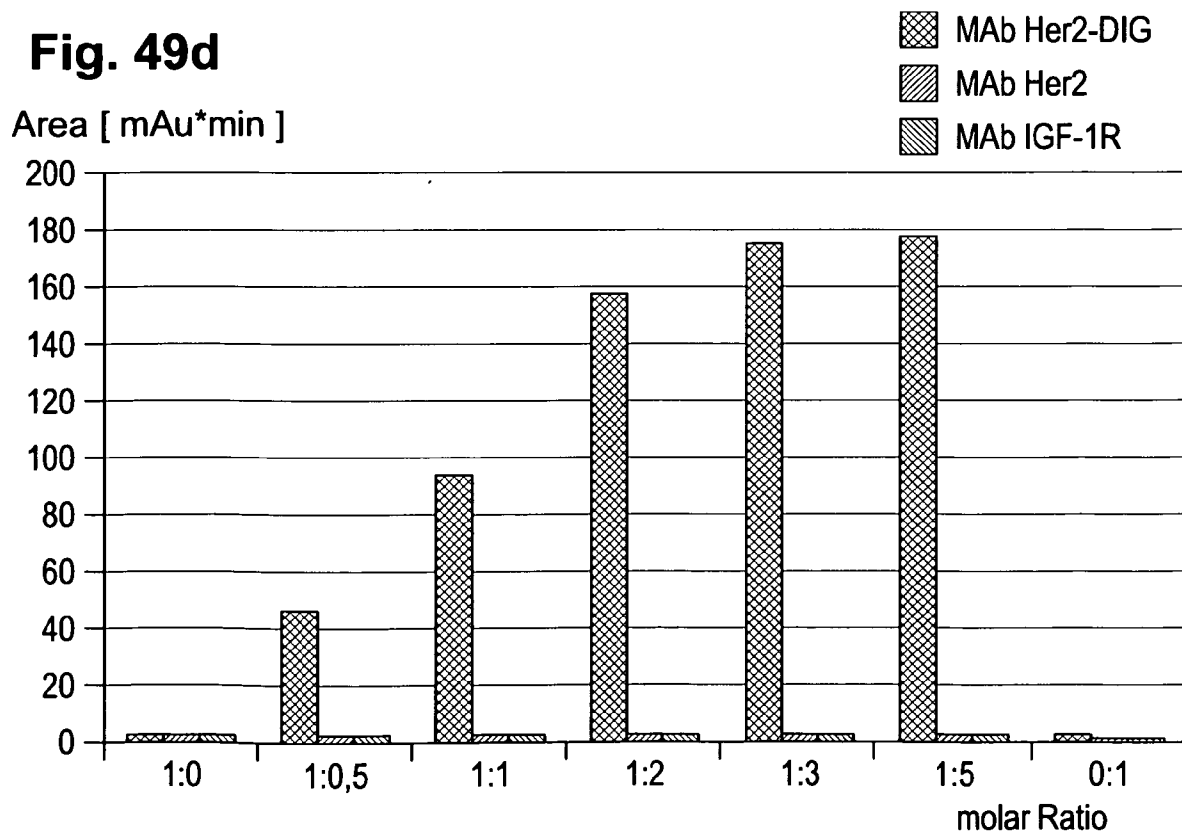
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Fig. 49a**Fig. 49b**

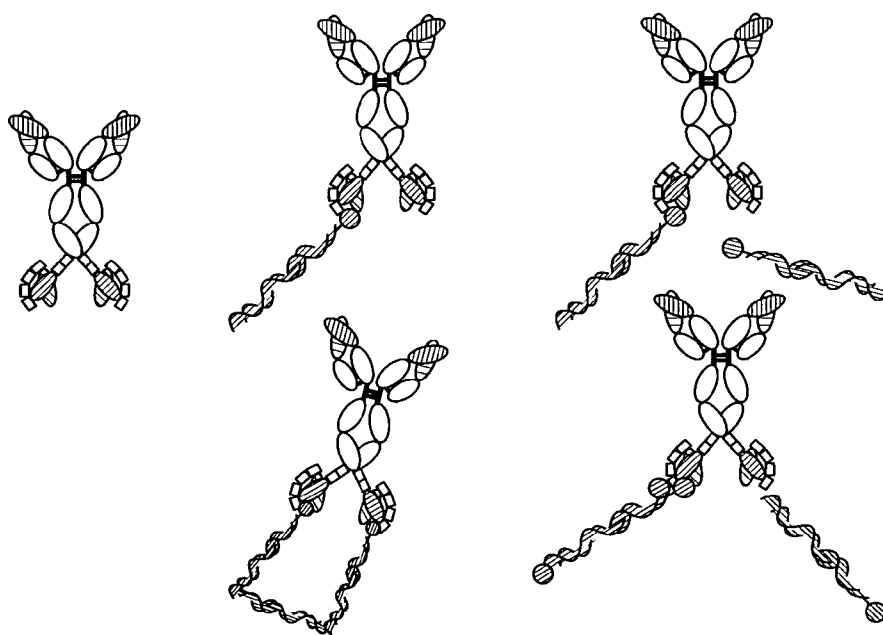
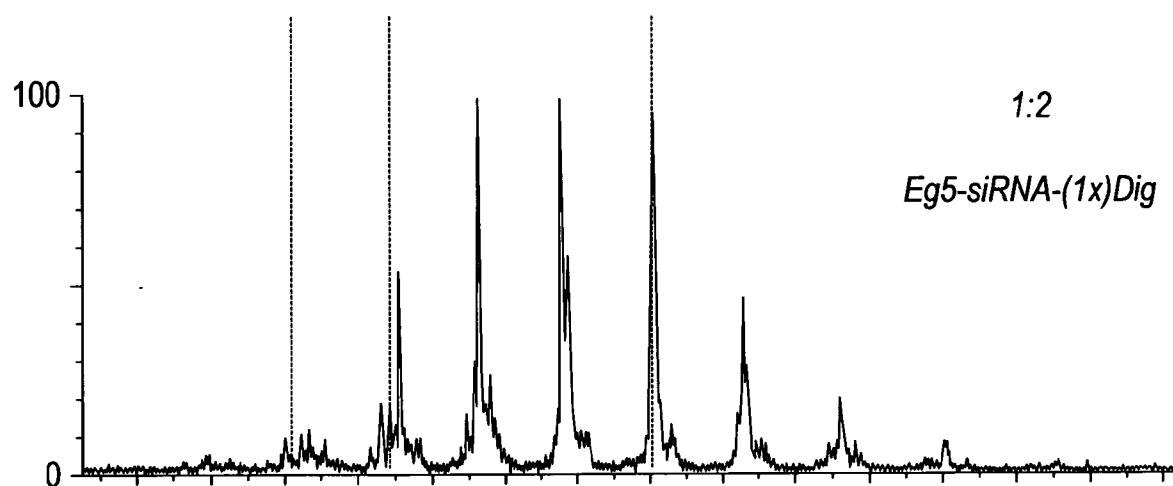
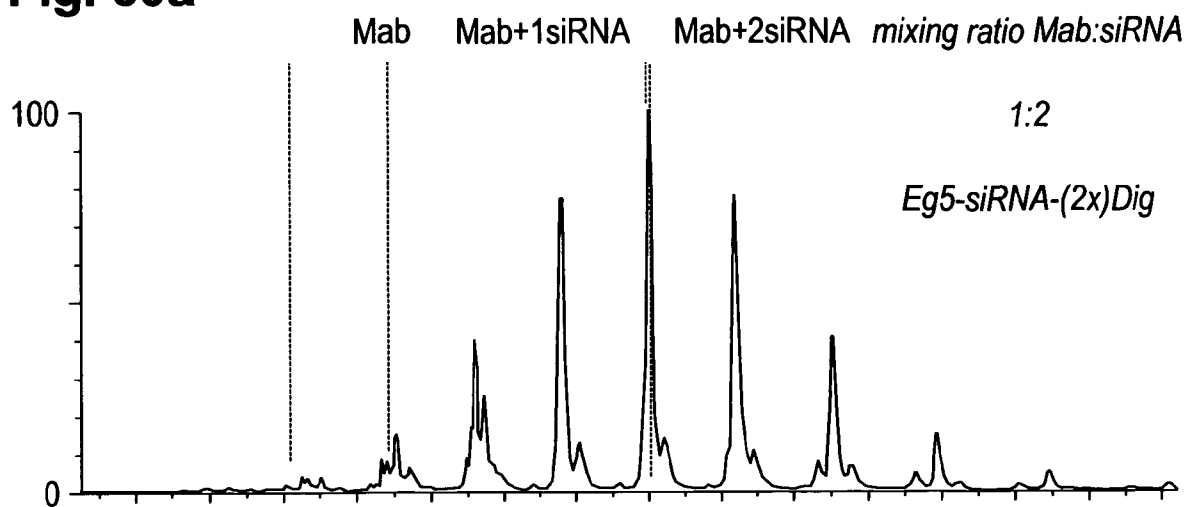
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Fig. 49c

	Area (Ex: 650 nm / Em: 667 nm) [mAU*min]		
Molar ratio AK: Dig-Cy5	MAb Her-DIG	MAb Her2	MAb IGF-1R
1:0	2	2	1
1:0,5	46	2	1
1:1	94	2	1
1:2	159	2	1
1:3	175	2	1
1:5	177	2	1
0:1	1	0	0

Fig. 49d

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Fig. 50a

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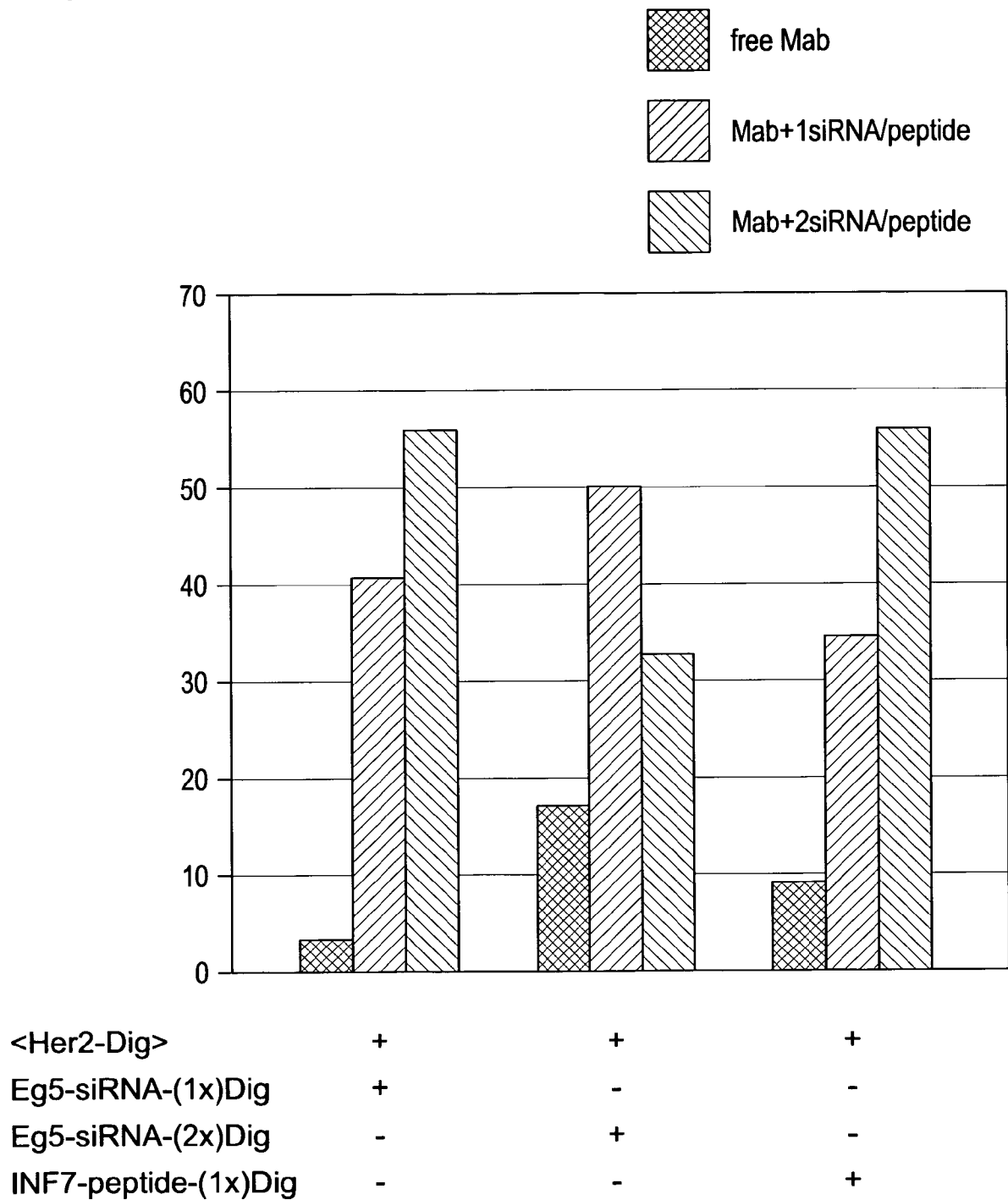
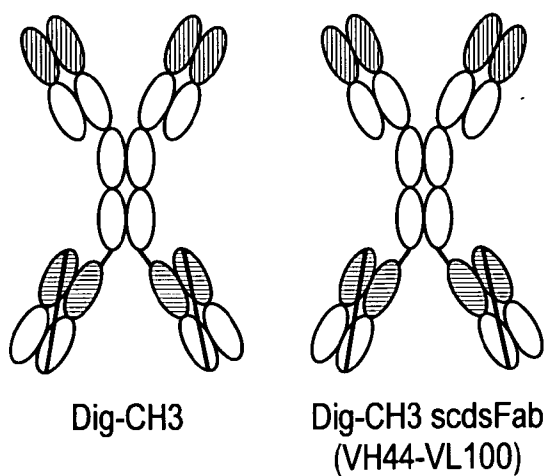
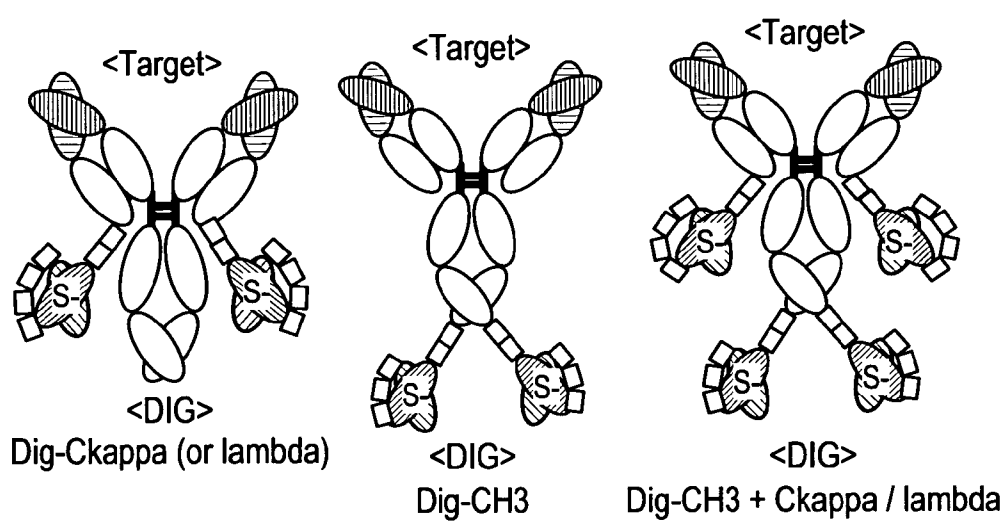
Fig. 50b

Fig. 51a

cell surface antigen	molecule	format
IGF1-Receptor	<IGF1R-DIG> Fv	scFv/dsscFv; Dig - CH3
IGF1-Receptor	<IGF1R-DIG> Fv	scFv/dsscFv; Dig - Ckappa
IGF1-Receptor	<IGF1R-DIG> Fv	dsscFv; Dig - CH3+Ckappa
IGF1-Receptor	<IGF1R-DIG> Fab	scFab; Dig - CH3
IGF1-Receptor	<IGF1R-DIG> Fab	dsscFab; Dig - CH3
VEGF-Receptor 2	<VEGFR2-DIG> Fv	scFv/dsscFv; Dig - CH3
VEGF-Receptor 2	<VEGFR2-DIG> Fab	scFab; Dig - CH3
VEGF-Receptor 2	<VEGFR2-DIG> Fab	dsscFab; Dig - CH3
CD33	<CD33-DIG> Fab	dsscFab; Dig - CH3
CD33	<CD33-DIG> Fv	scFv/dsscFv; Dig - CH3
LeY carbohydrate	<LeY-DIG> Fab	dsscFab; Dig - CH3
LeY carbohydrate	<LeY-DIG> Fv	scFv/dsscFv; Dig - CH3
CD22	<CD22-DIG> Fv	dsscFv; Dig - CH3
Her2	<Her2-DIG> Fv	dsscFv; Dig - CH3
CDCP1	<CDCP1-DIG> Fv	dsscFv; Dig - CH3

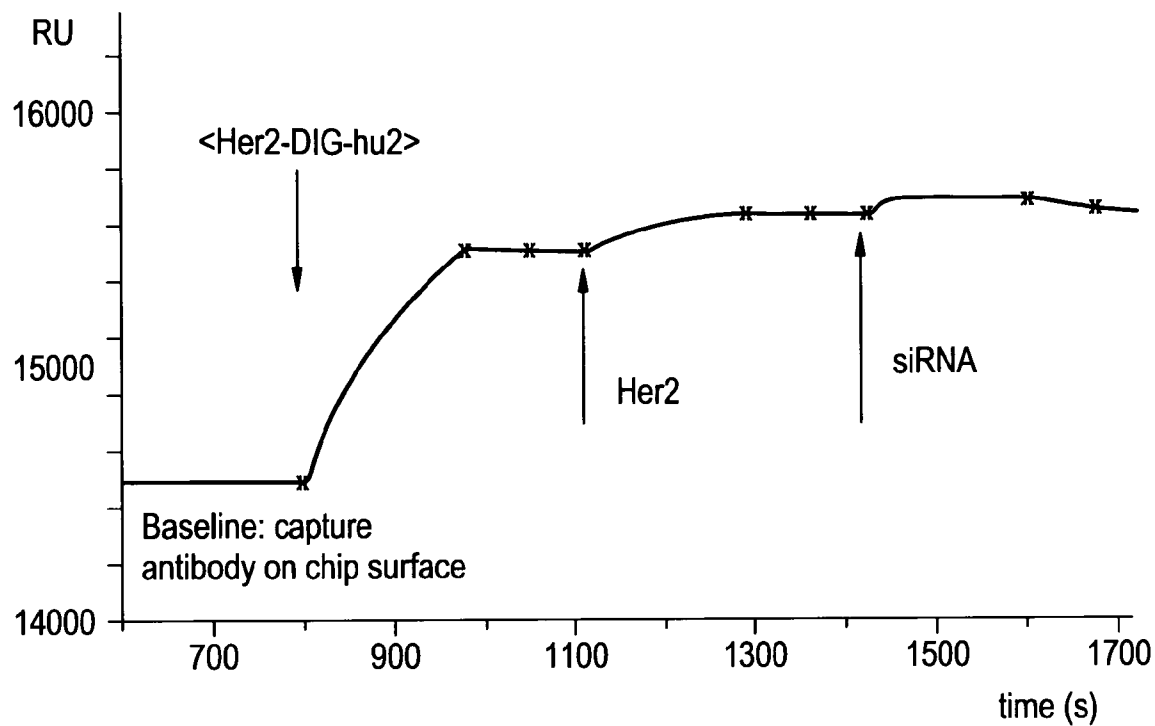
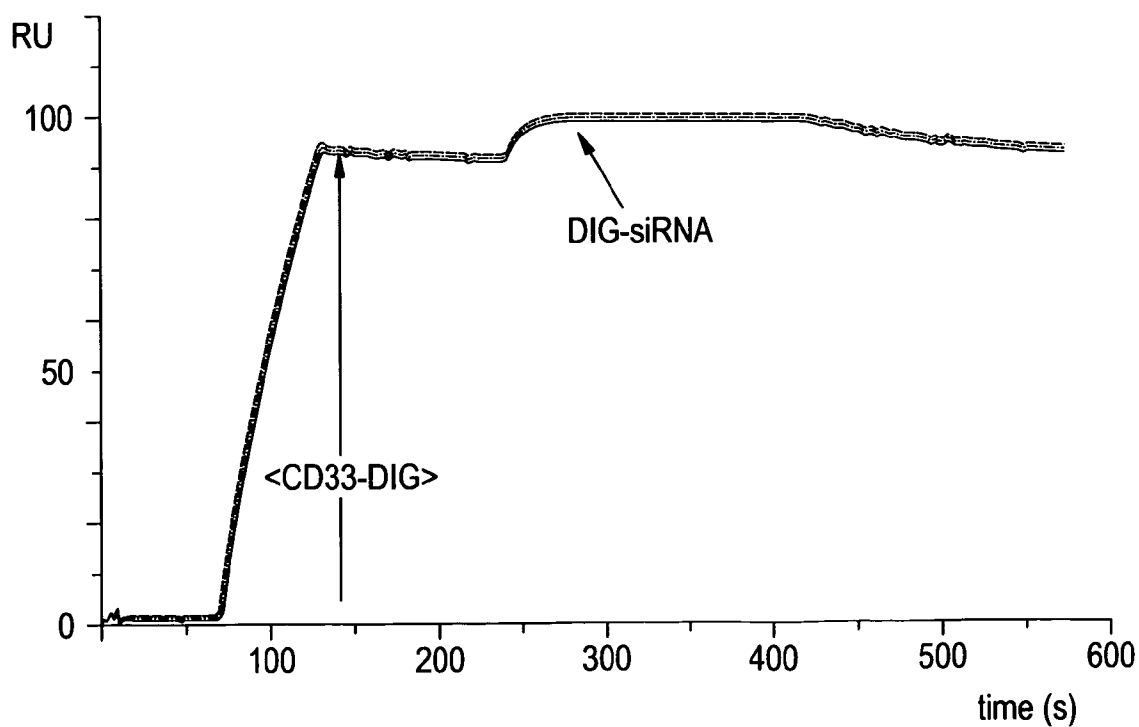
Fig. 51b

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Fig. 51c

Capture	Antibody	ka (1/Ms)	kd (1/s)	KD (M)
human VEGFR2-Fc	<VEGFR2(D1F7)-DIG>_001	3.44E+06	6.54E-03	1.90E-09
	<VEGFR2(D1F7)-scFab-DIG>	4.98E+06	6.70E-03	1.35E-09
	<VEGFR2(D1F7)-dsFab-DIG>	2.49E+06	9.68E-03	3.89E-09
mouse VEGFR2-Fc	<VEGFR2(D1F7)-DIG>_001	3.89E+06	6.56E-03	1.69E-09
	<VEGFR2(D1F7)-scFab-DIG>	3.21E+06	8.92E-03	2.78E-09
	<VEGFR2(D1F7)-dsFab-DIG>	2.01E+06	1.14E-02	5.65E-09

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Fig. 51d**Fig. 51e**

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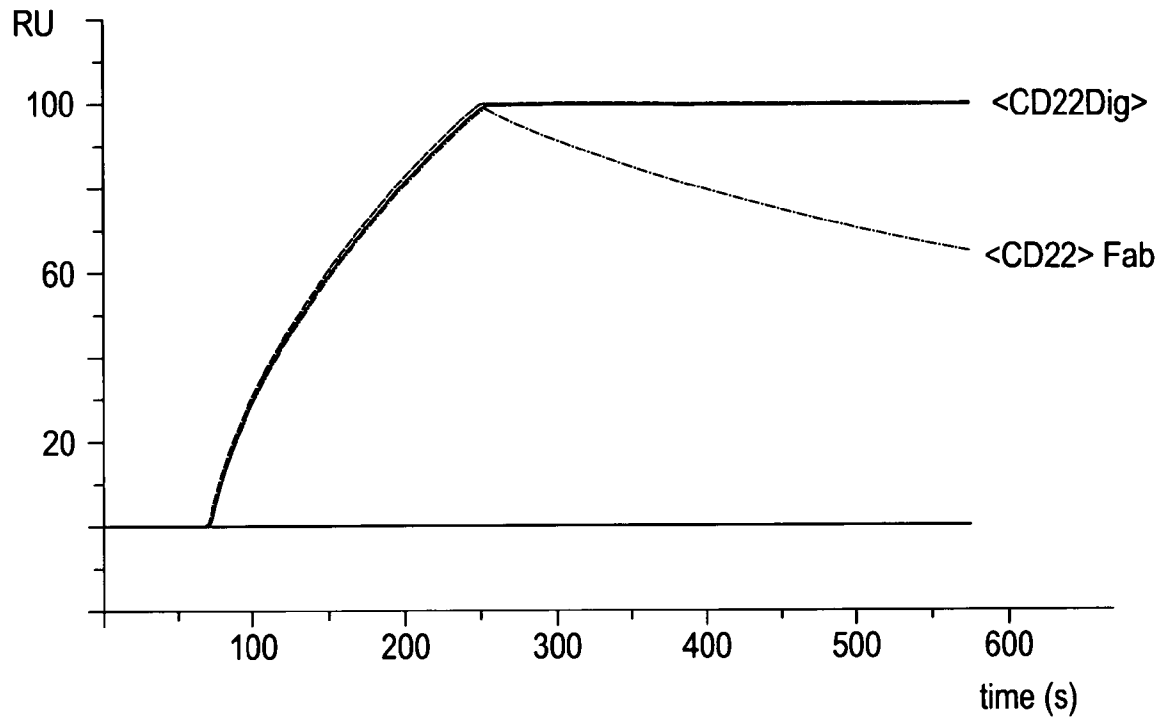
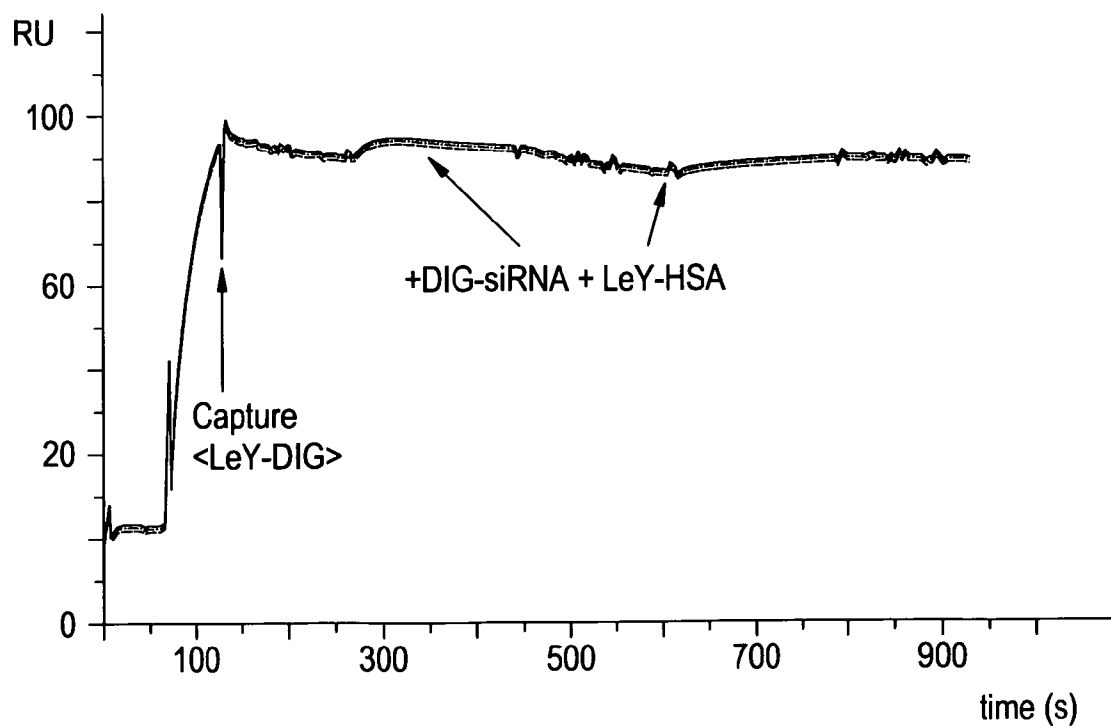
Fig. 51f**Fig. 51g**

Fig. 51h

	ka (1/Ms)	kd (1/s)	KD (nM)
CDCP1-ECD	2.02E+05	1.32E-03	7
	2.02E+05	1.60E-03	8
DIG-siRNA	4.37E+05	0.0097	22
	5.54E+05	0.011	20

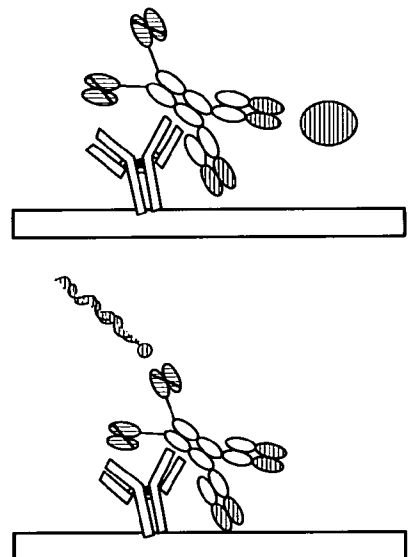


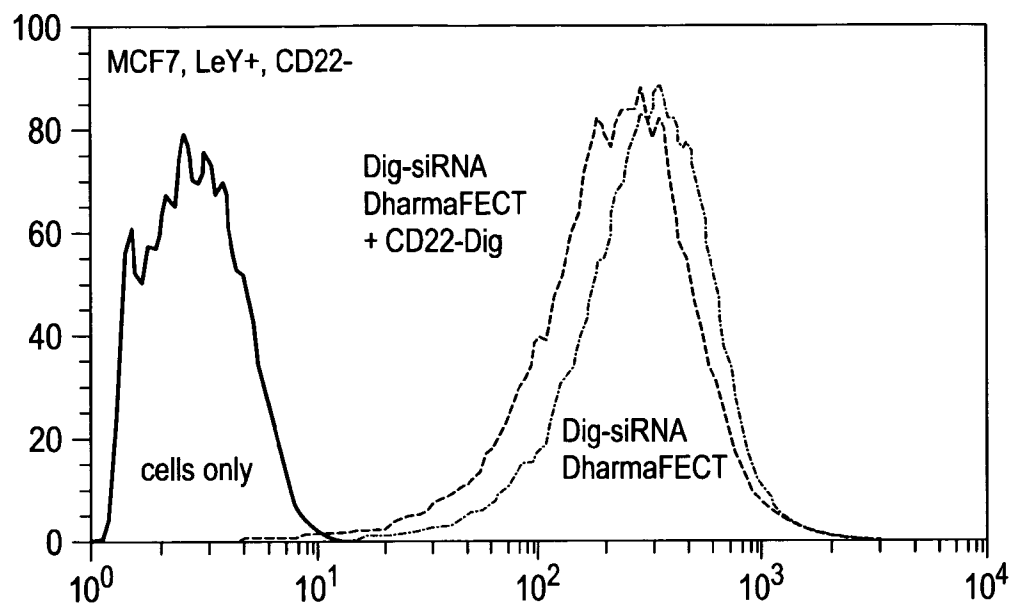
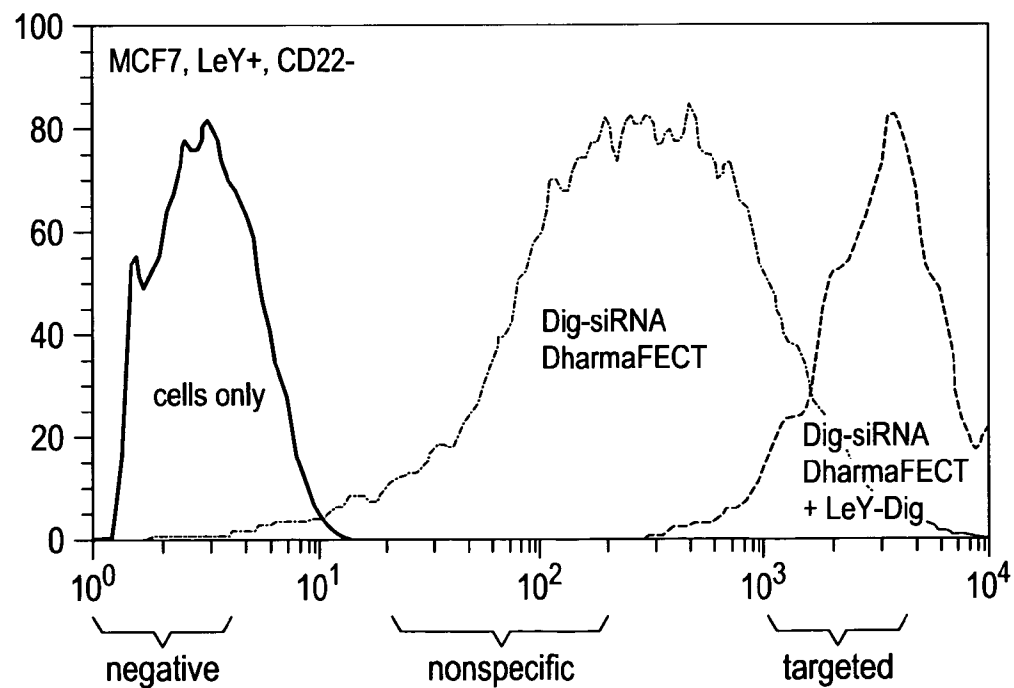
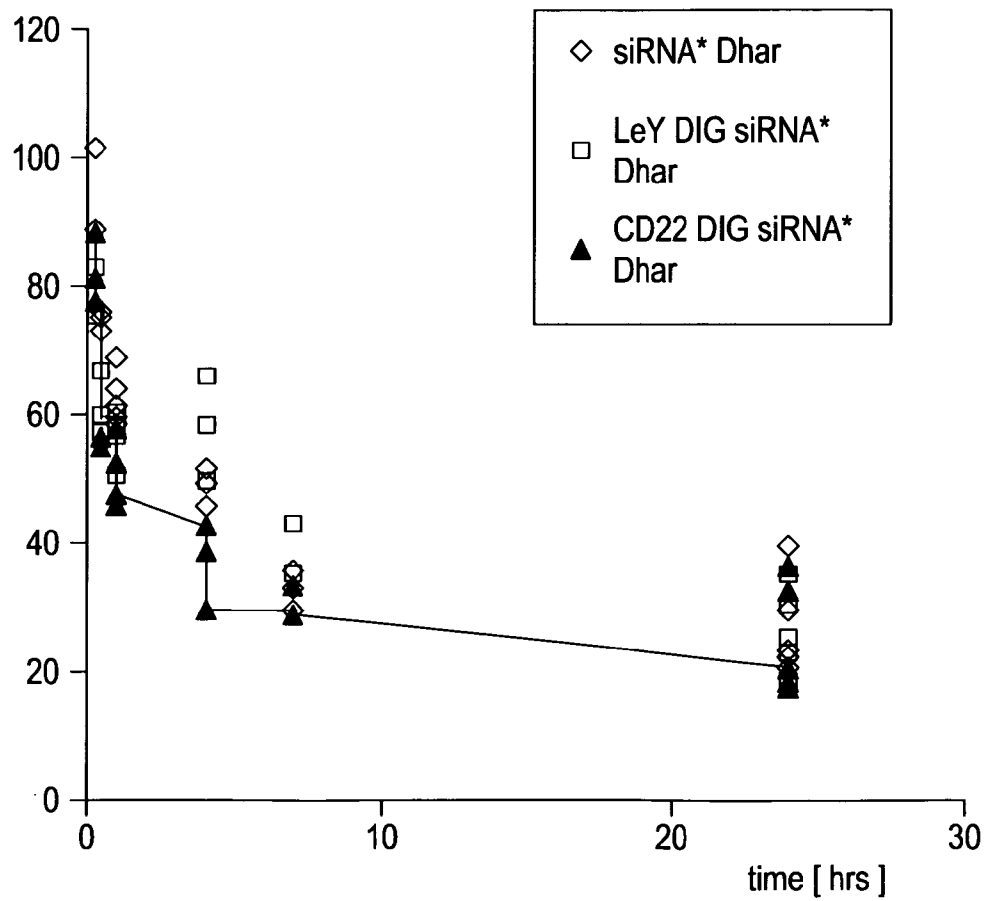
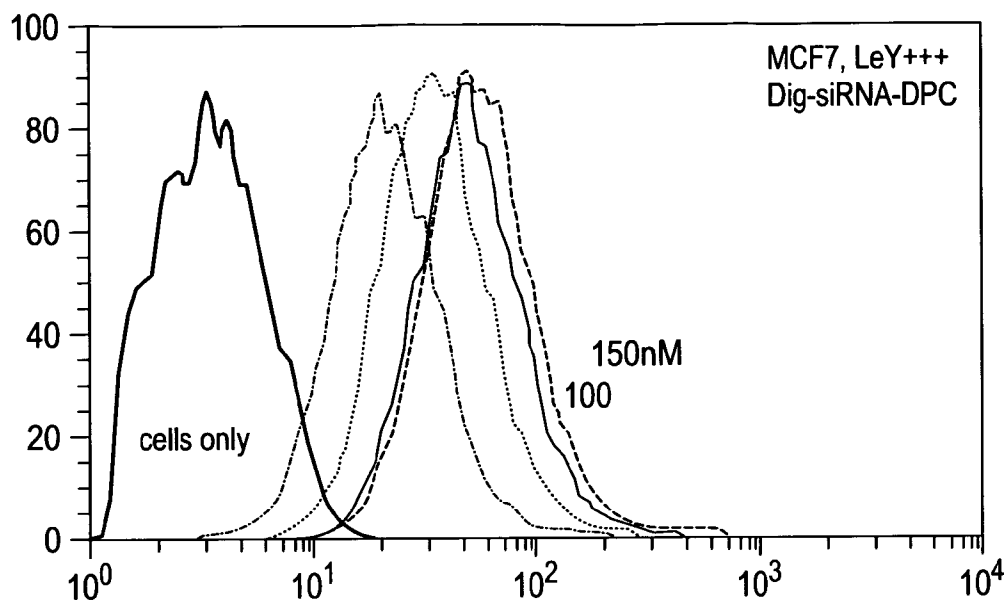
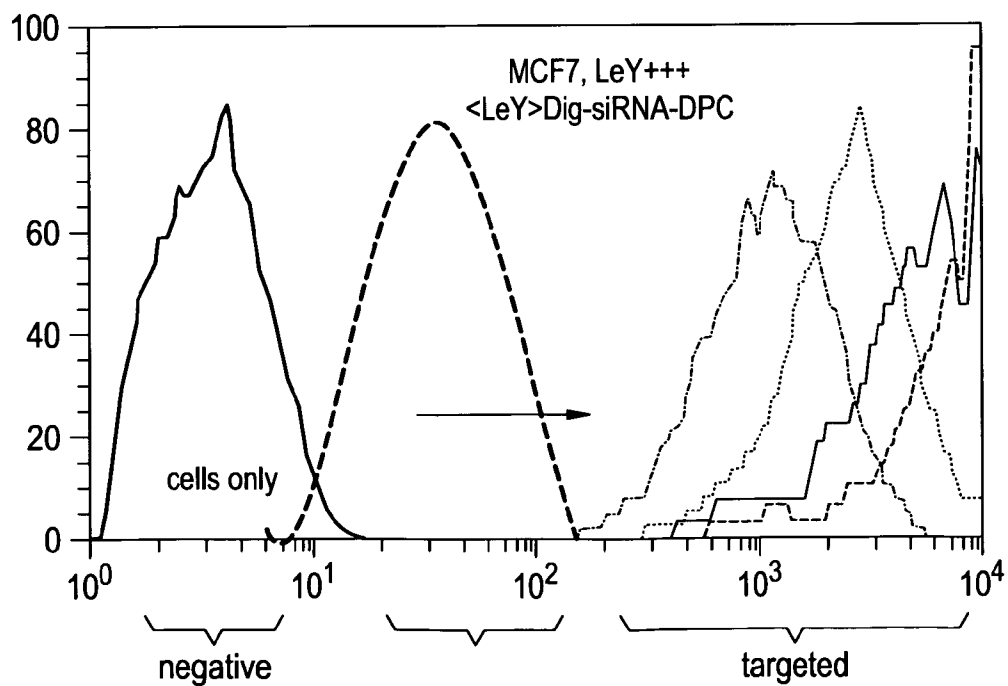
Fig. 52a**Fig. 52b**

Fig. 52c

EG5/GAPDH mRNA level [%]



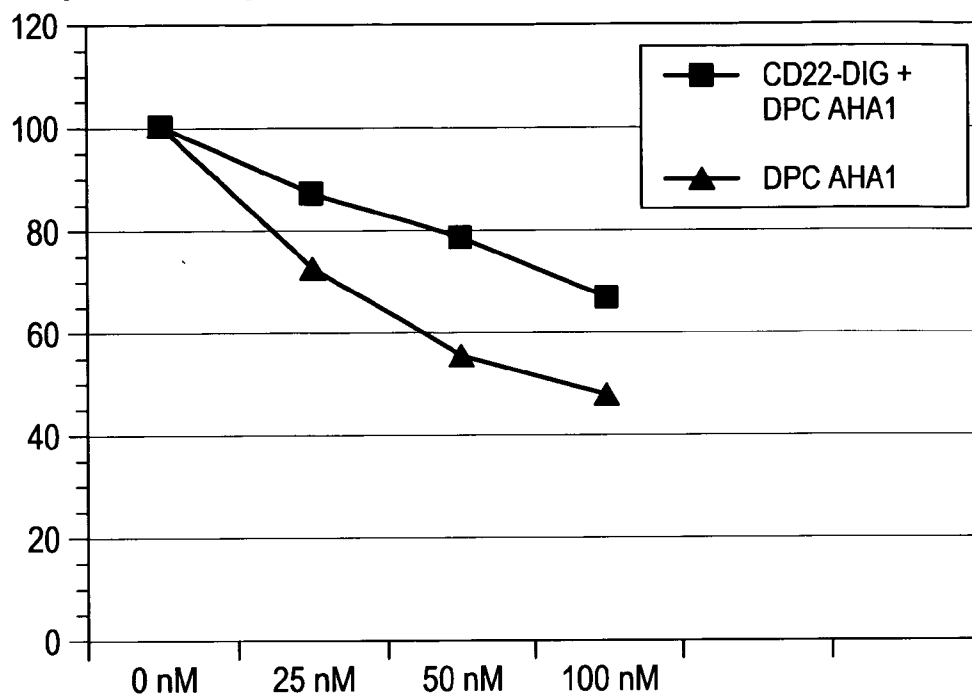
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Fig. 53a**Fig. 53b**

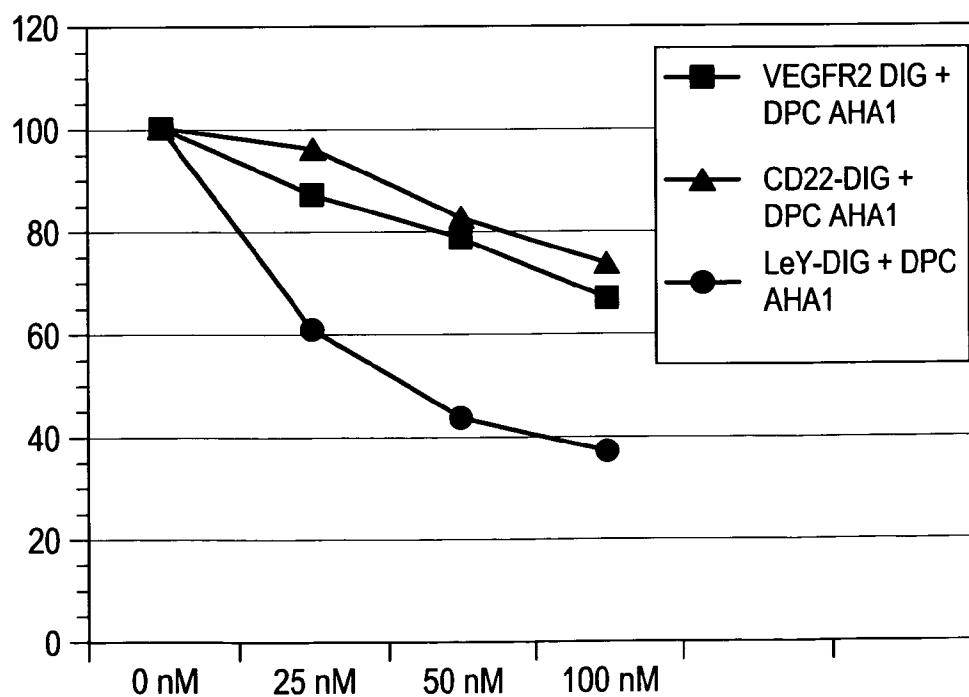
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Fig. 53c

AHA1/GAPDH [% of control]

**Fig. 53d**

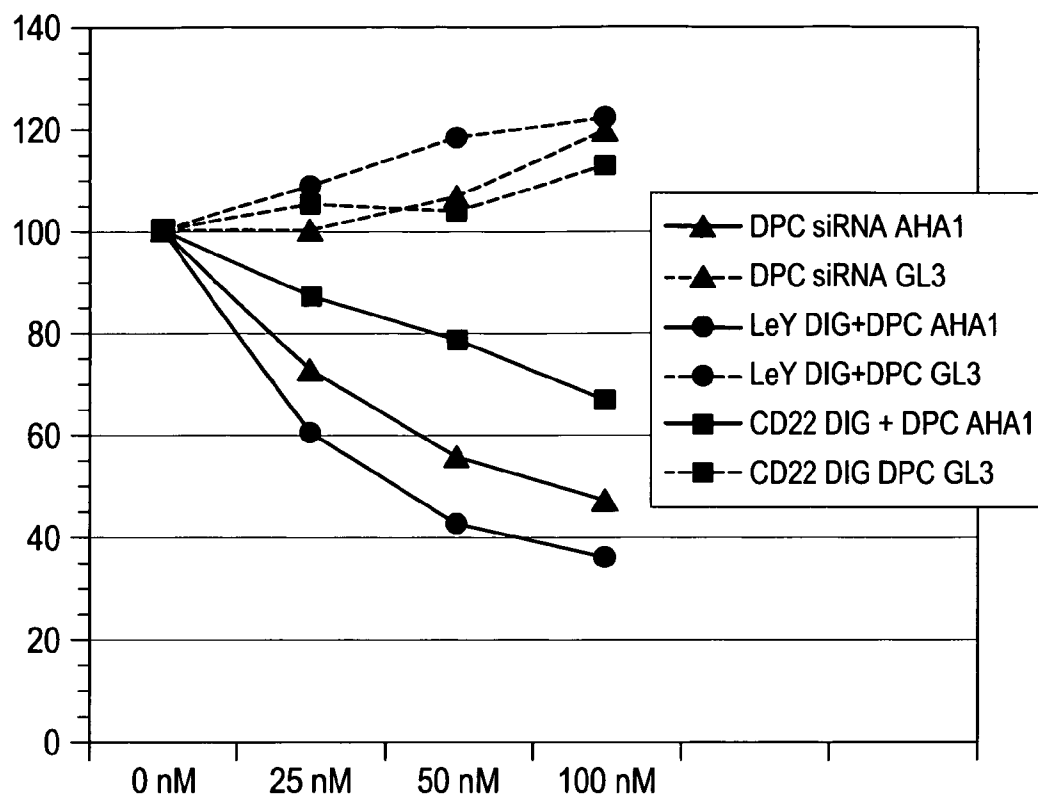
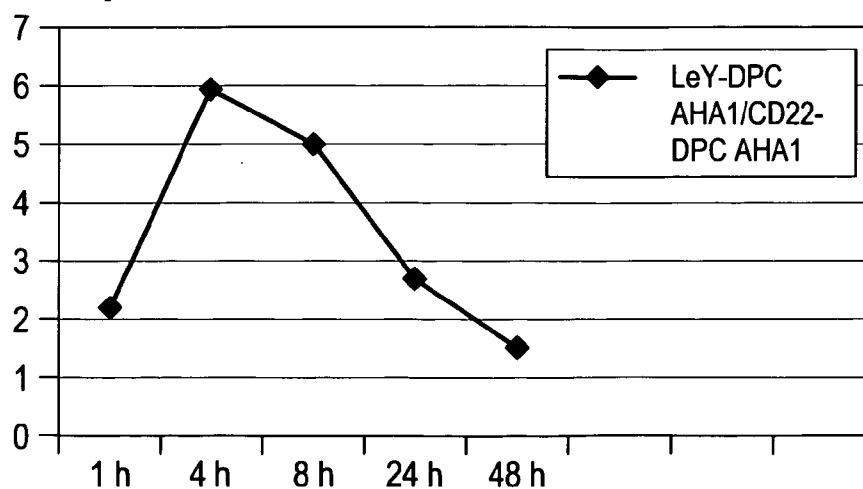
AHA1/GAPDH [% of control]



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Fig. 53e

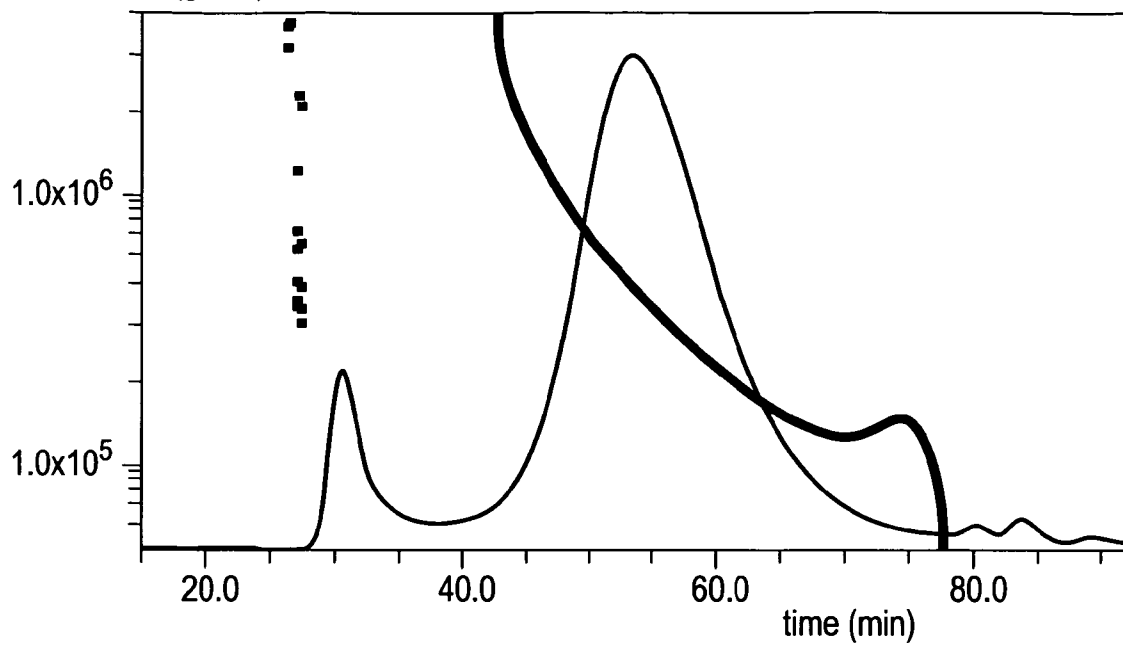
AHA1/GAPDH ratio [% of control]

**Fig. 53f**Targeting specificity factor
[IC40 LeY/CD22]

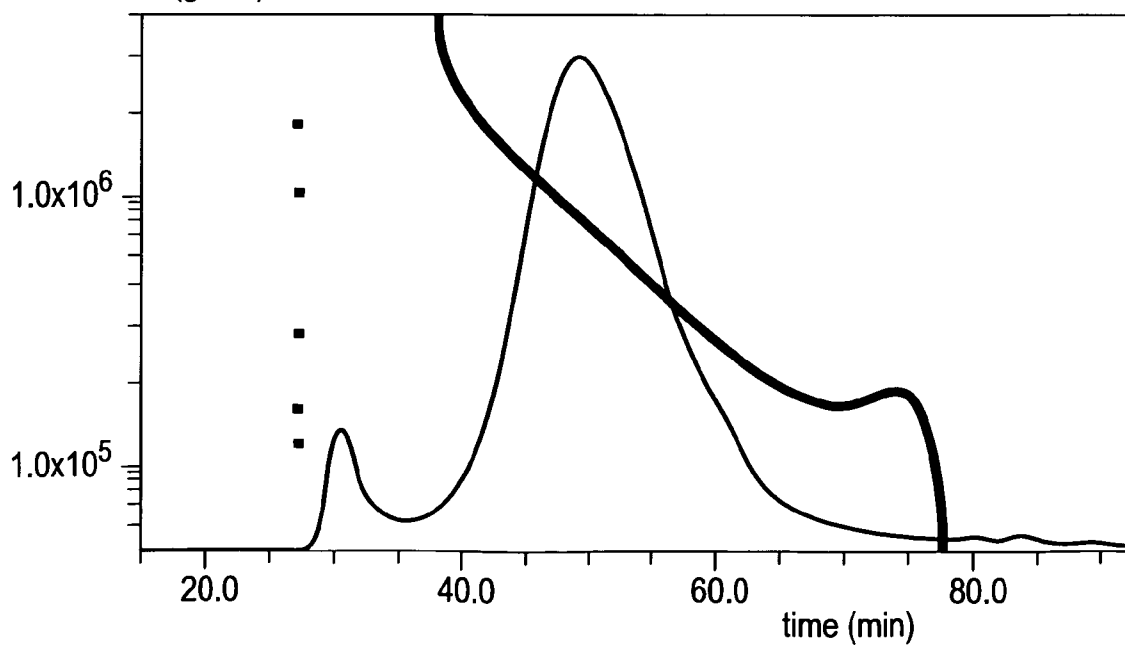
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Fig. 54a

molar mass (g/mol)

**Fig. 54b**

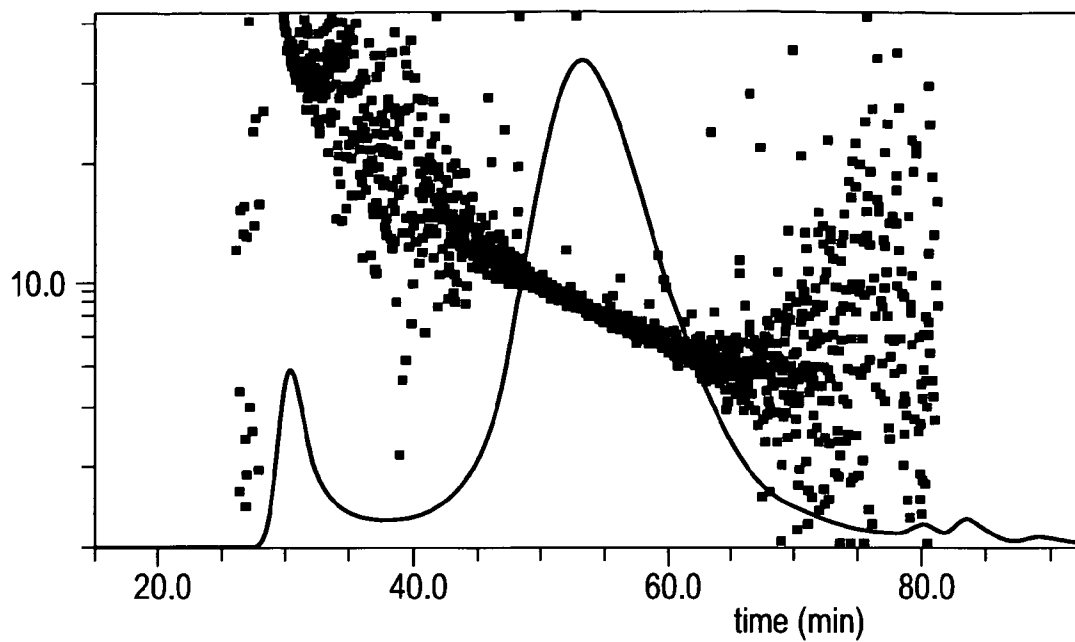
molar mass (g/mol)



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Fig. 54c

hydrodynamic radius (nm)

**Fig. 54d**

hydrodynamic radius (nm)

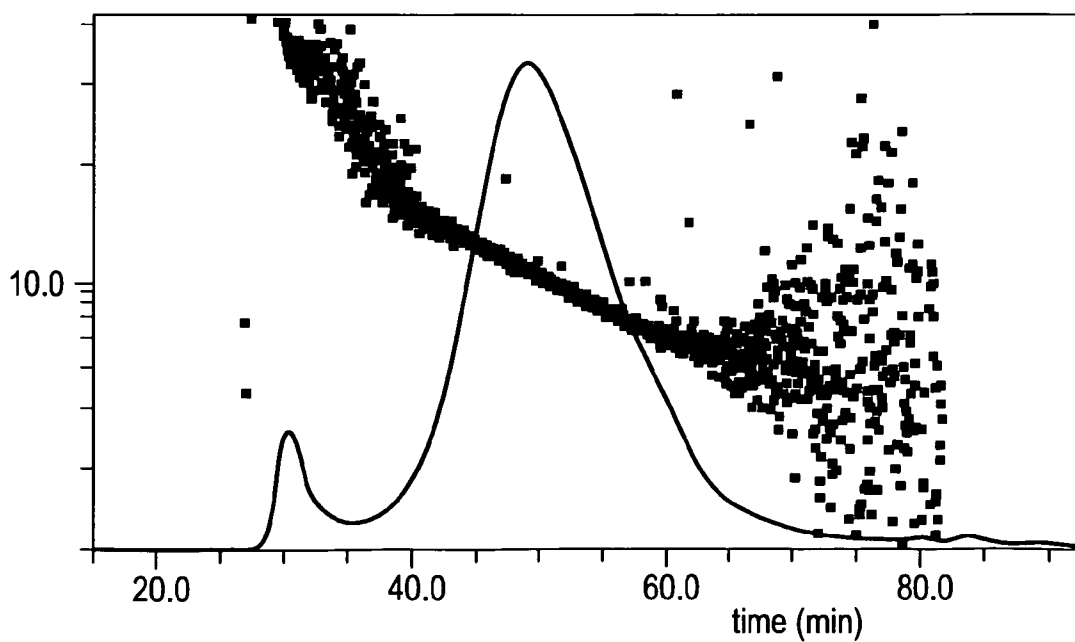


Fig. 55a

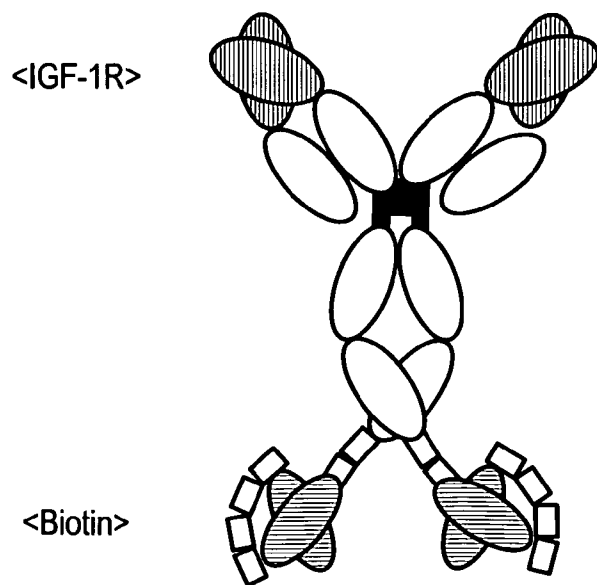
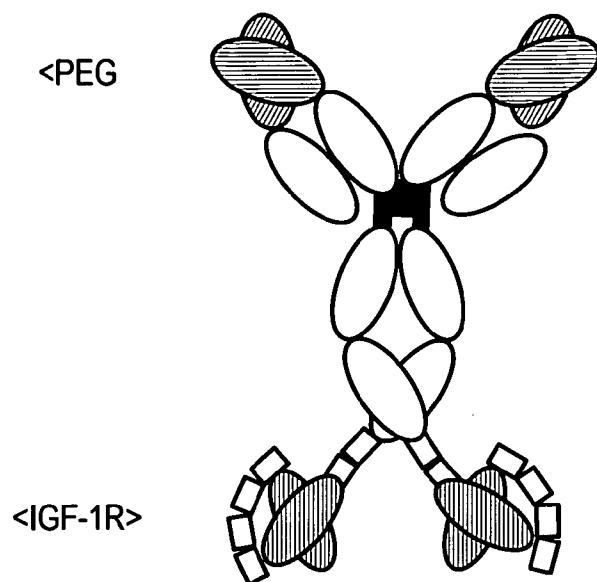
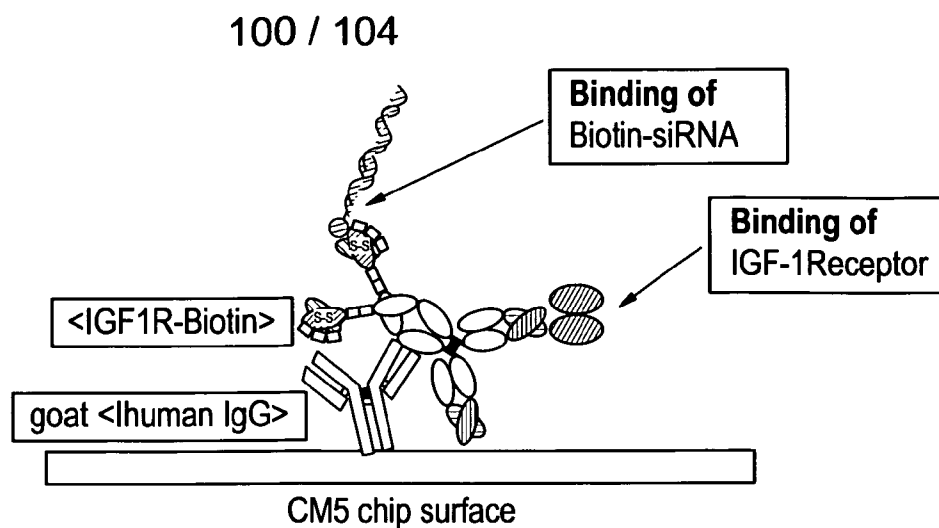
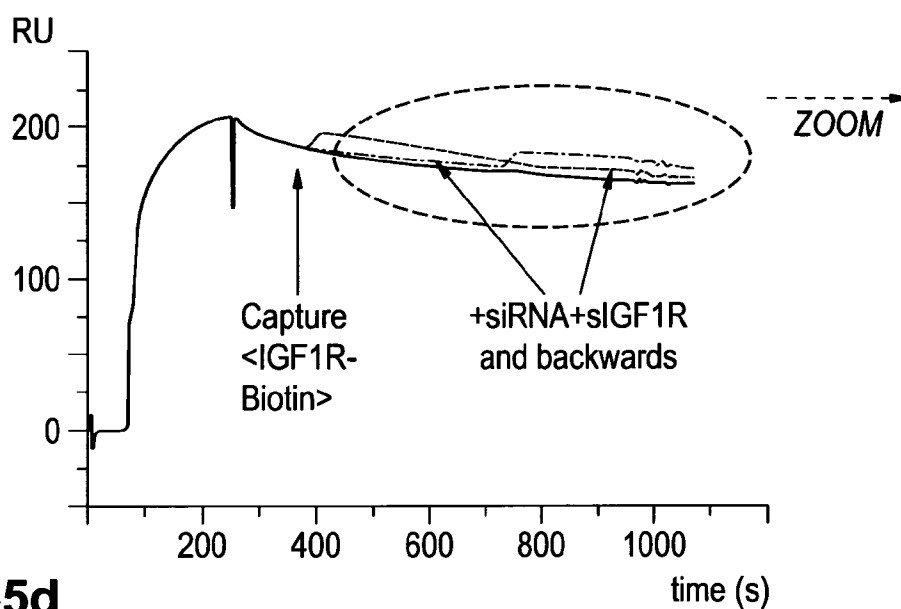
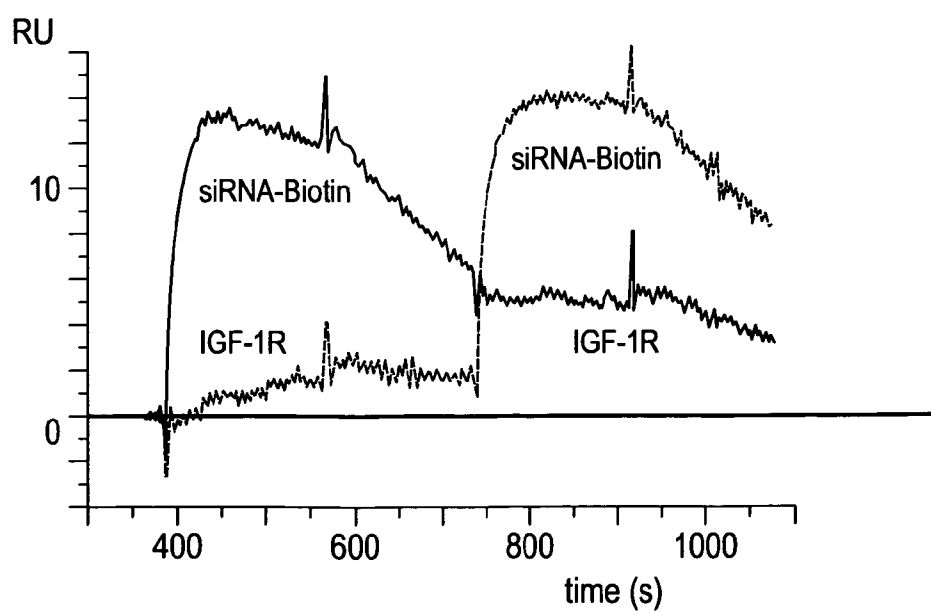


Fig. 55b**Fig. 55c****Fig. 55d**

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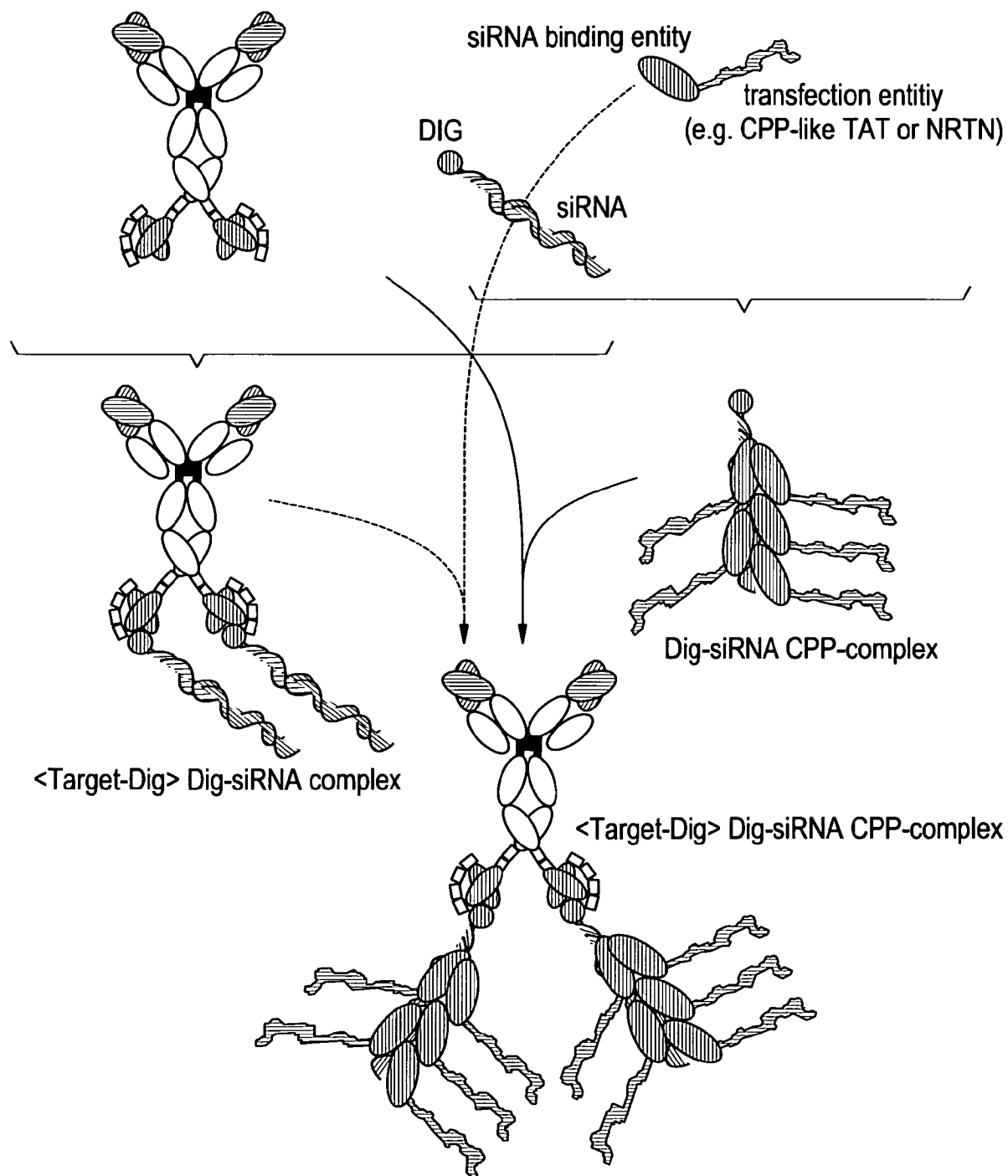
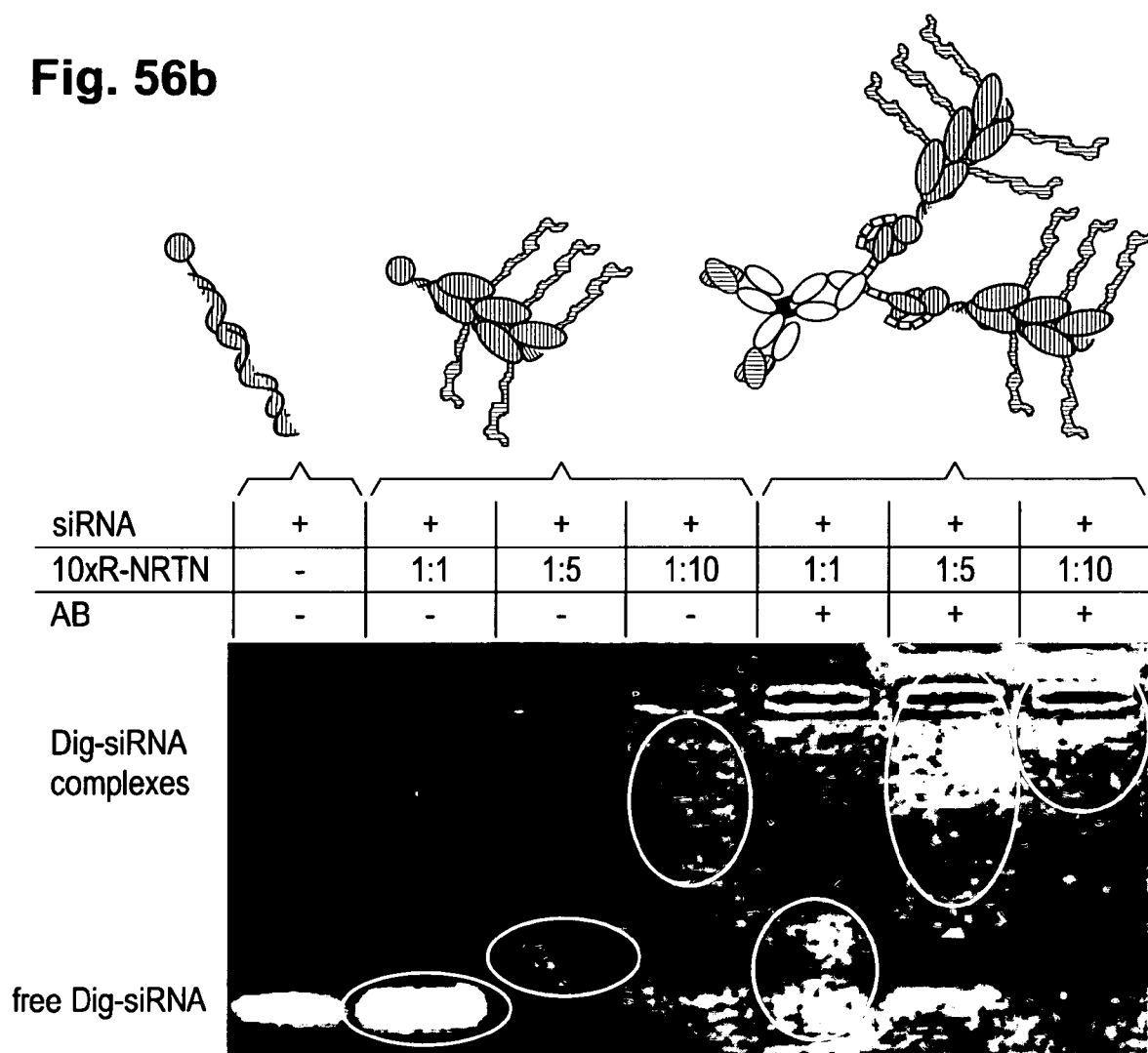
Fig. 56a

Fig. 56b

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Fig. 56c