

1/45

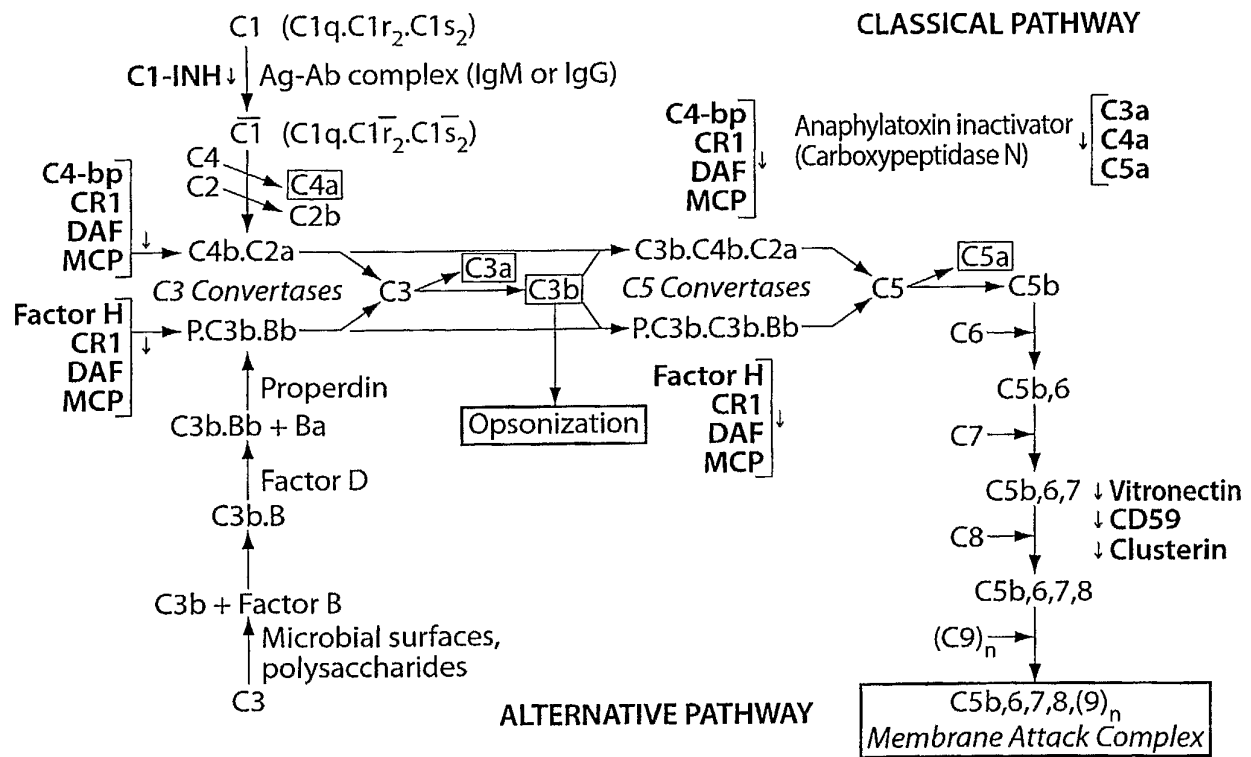


Fig. 1

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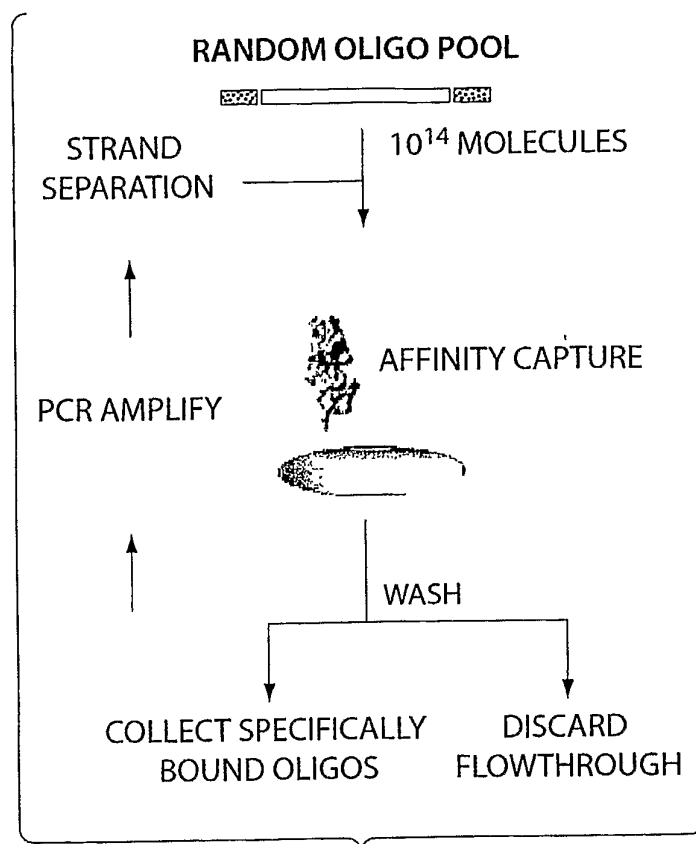


Fig. 2

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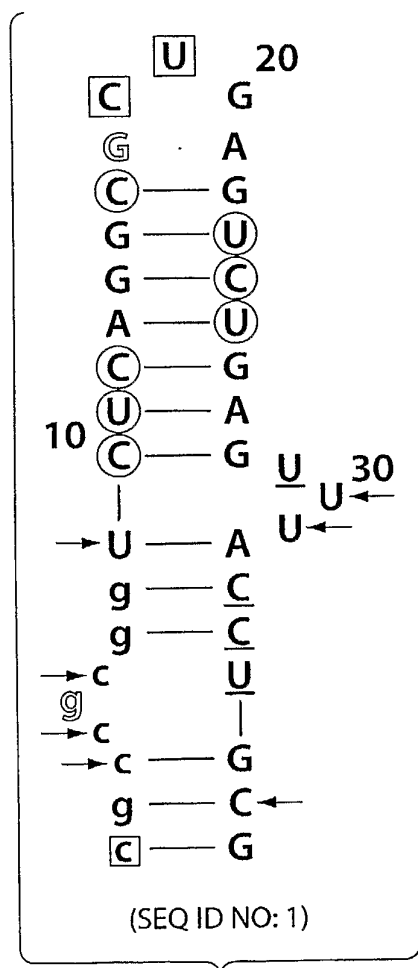


Fig. 3A

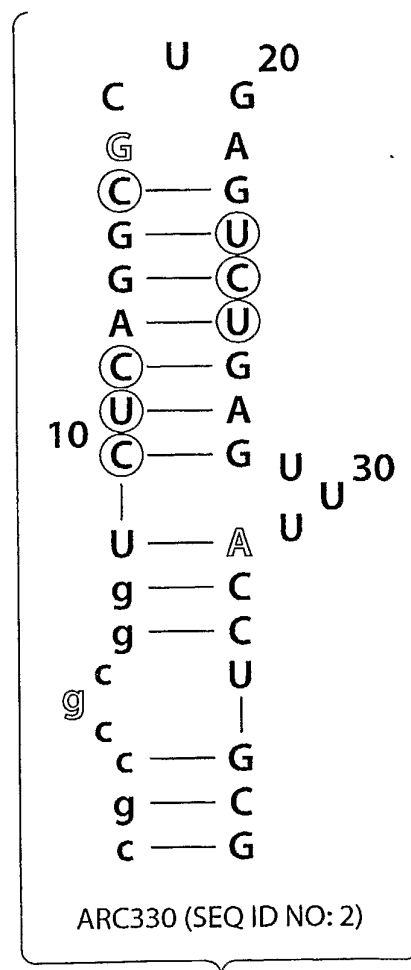


Fig. 3B

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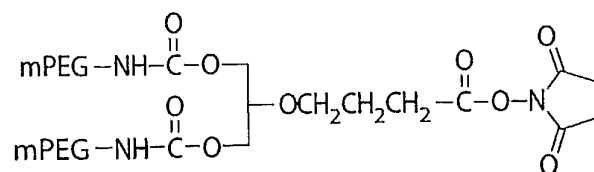


Fig. 4

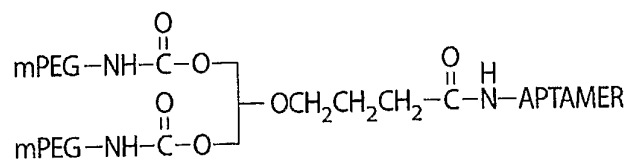


Fig. 5

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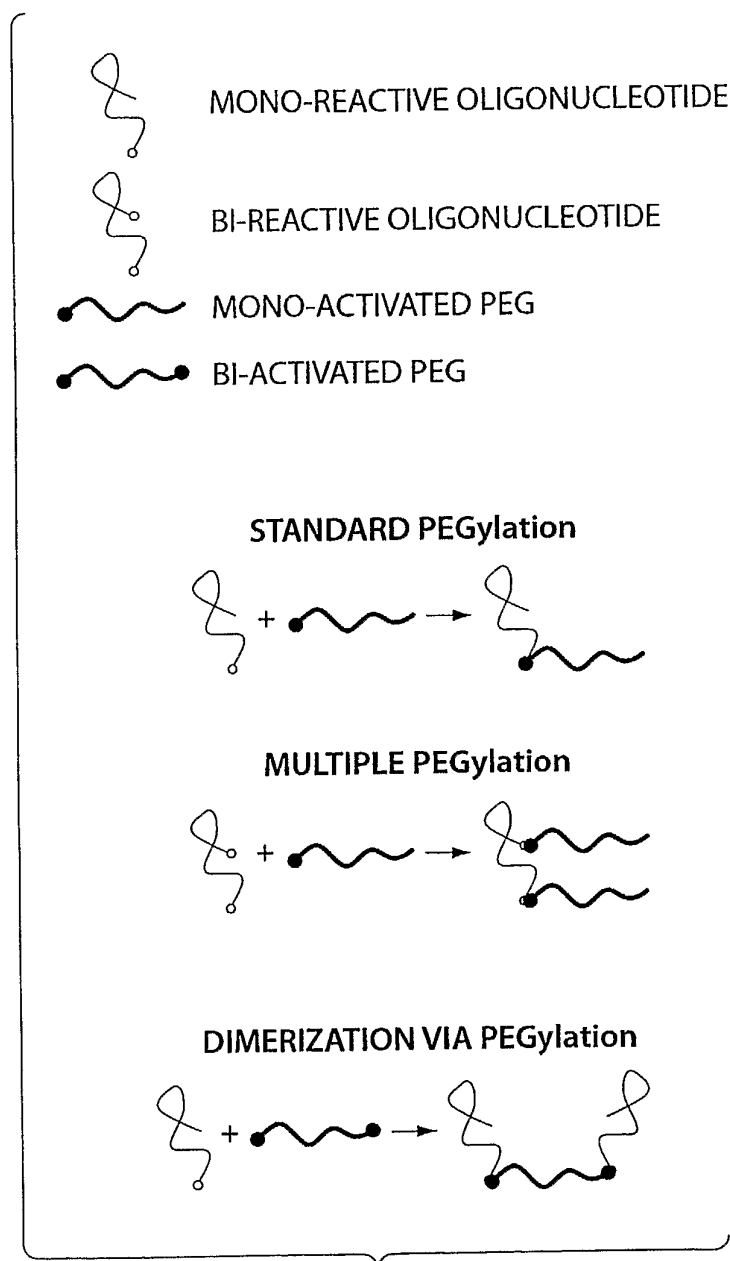


Fig. 6

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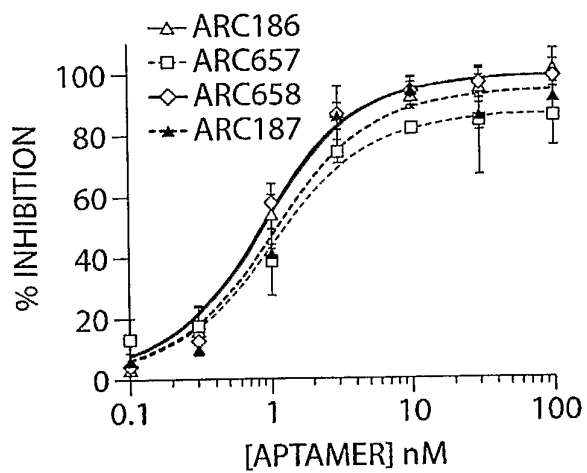


Fig. 7A

ARC#	PEG MODIFICATION	IC50 (nM)
186	NO PEG	0.5 ± 0.1
657	ARC186+20 kDa	0.6 ± 0.1
658	ARC186+30 kDa	0.5 ± 0.1
187	40 kDa BRANCHED 1,3-BIS (mPEG-[20 kDa])-PROPYL- 2-(4'-BUTAMIDE)	0.6 ± 0.2

Fig. 7B

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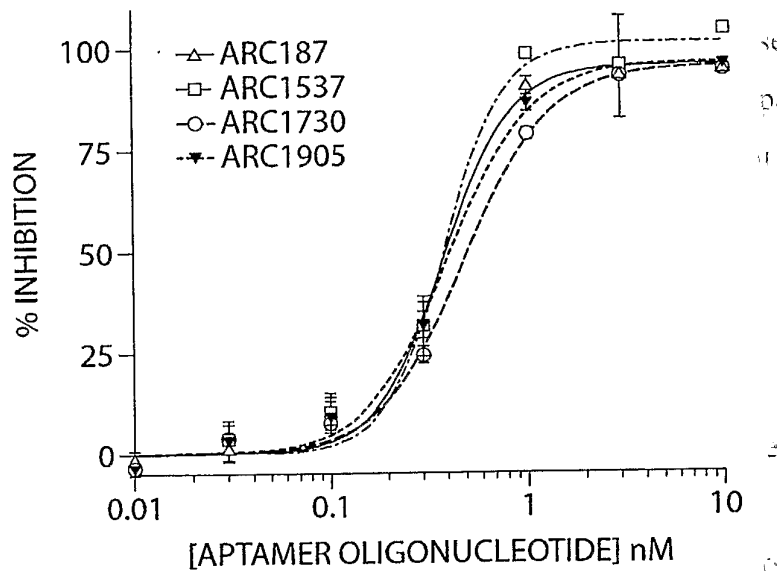


Fig. 7C

ARC#	PEG MODIFICATION	IC50 (nM)
187	40K BRANCHED 1,3-BIS(mPEG-[20 kDa])-PROPYL-2-(4'-BUTAMIDE)	0.38 ± 0.03
1537	40K DOW LINEAR	0.39 ± 0.06
1730	2 x 20K LINEAR	0.48 ± 0.04
1905	40K BRANCHED 2,3-BIS(mPEG-[20 kDa])-PROPYL-1-CARBAMOYL	0.40 ± 0.03

Fig. 7D

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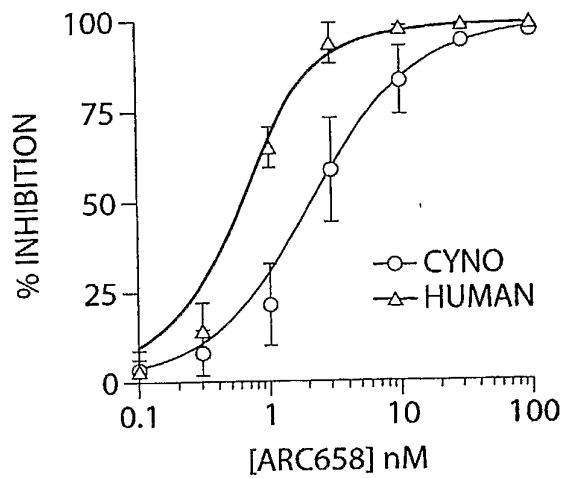


Fig. 8

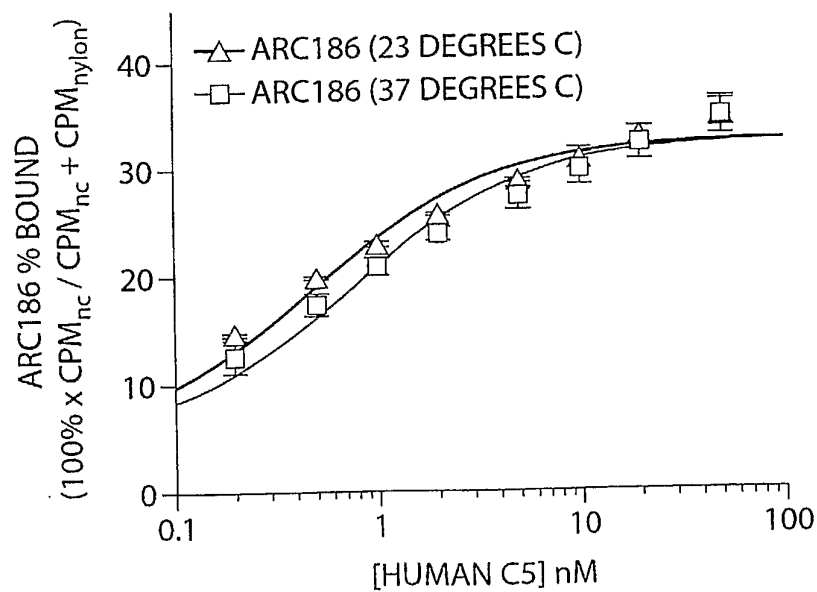


Fig. 9

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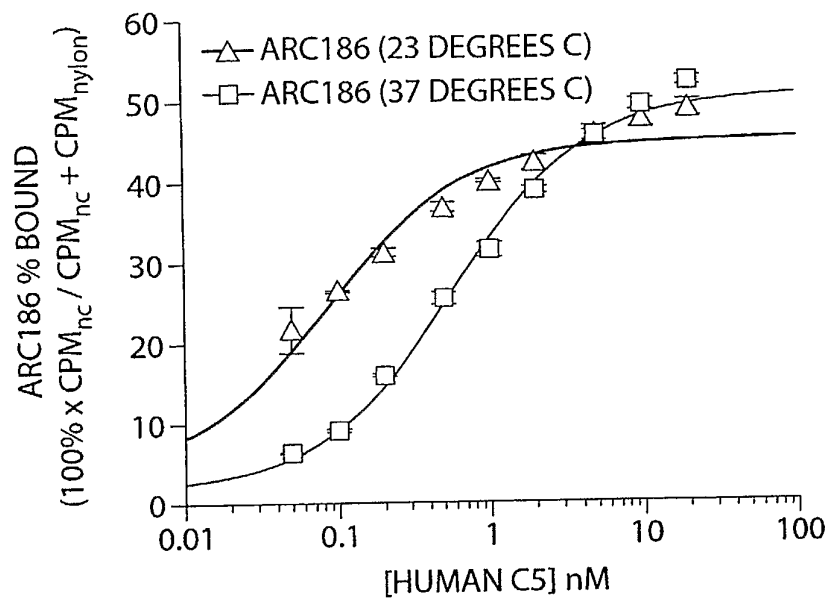


Fig. 10

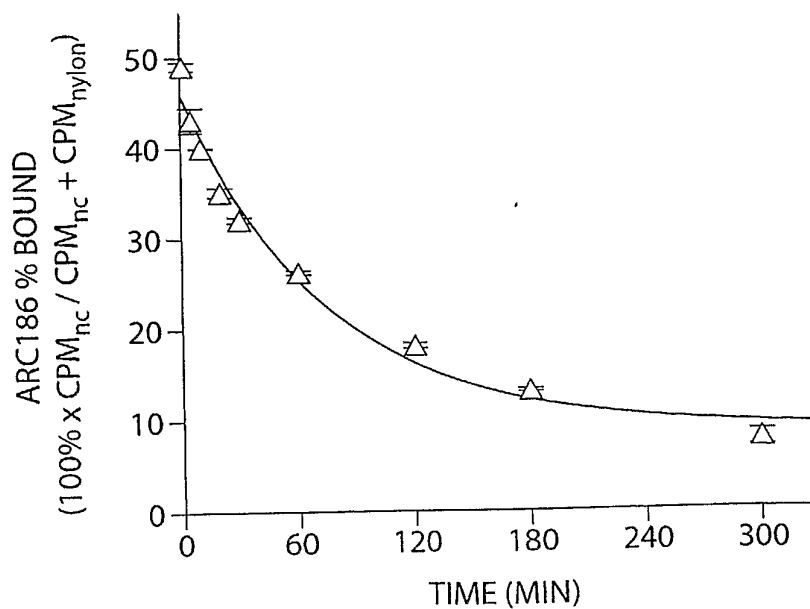


Fig. 11

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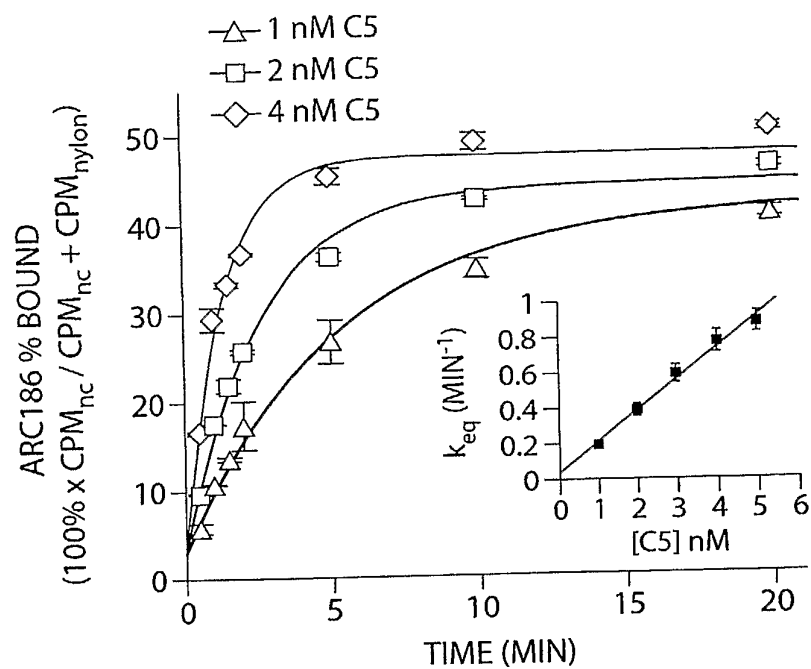


Fig. 12

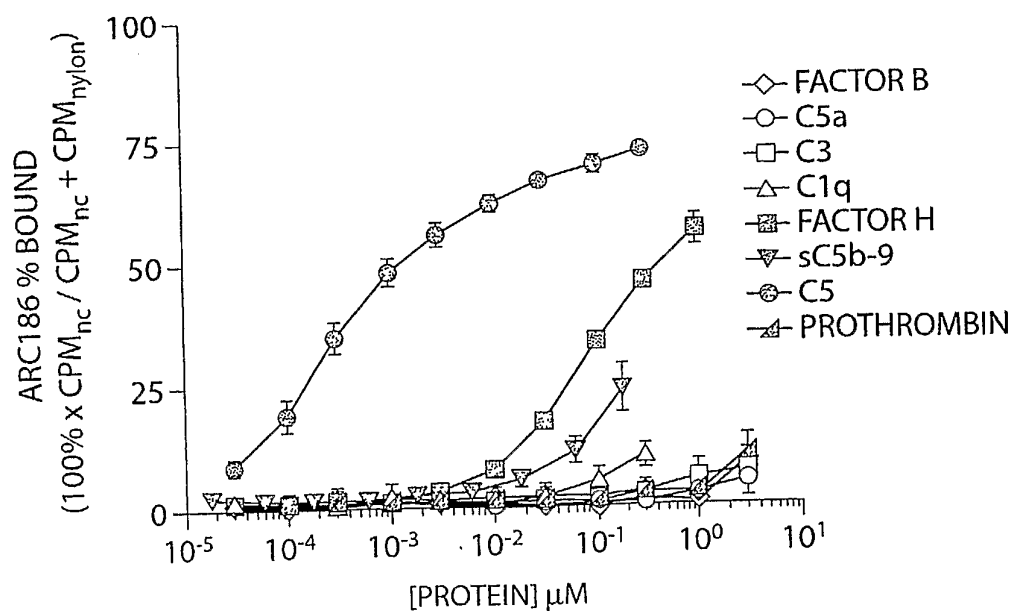


Fig. 13

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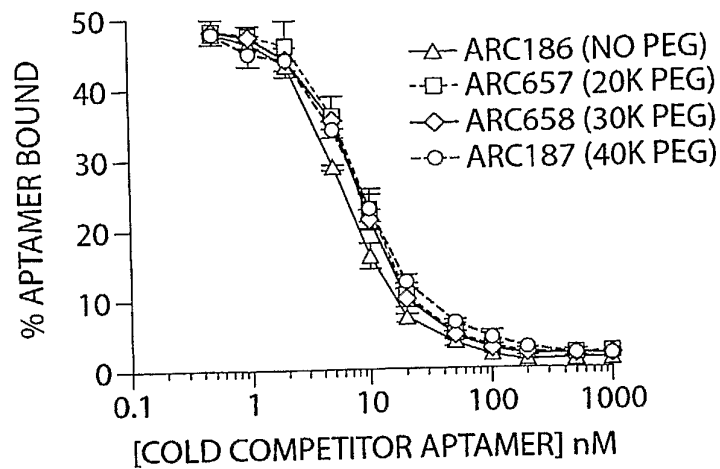


Fig. 14

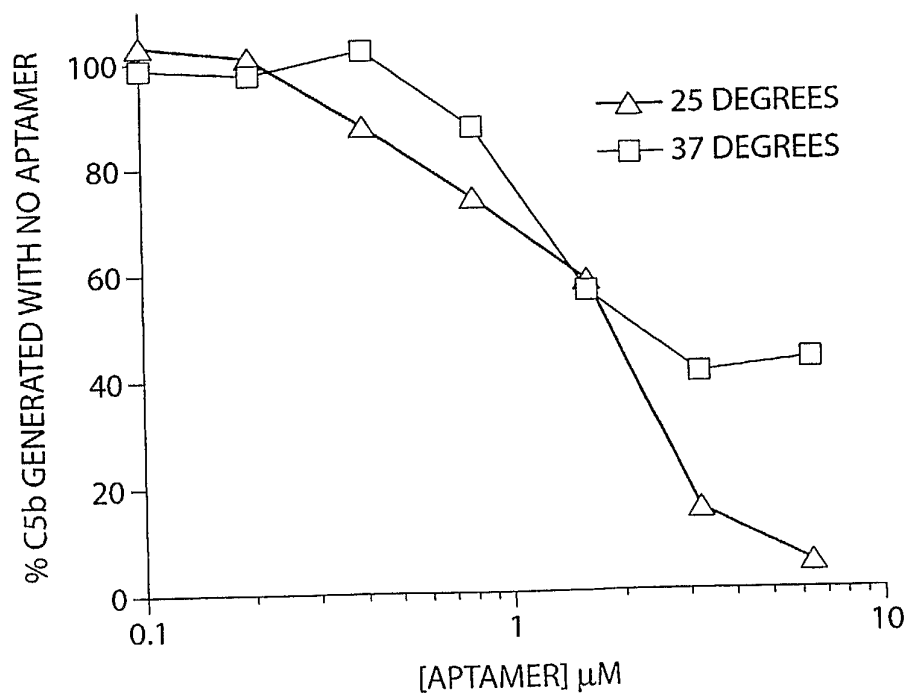


Fig. 15

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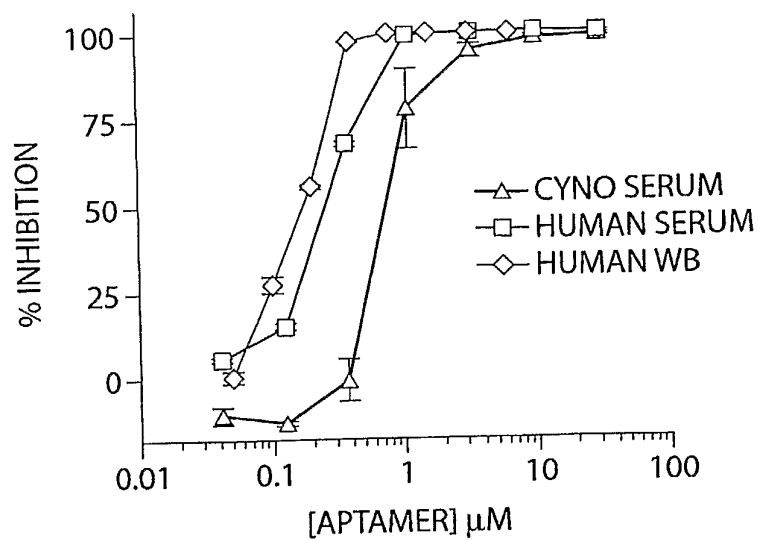


Fig. 16

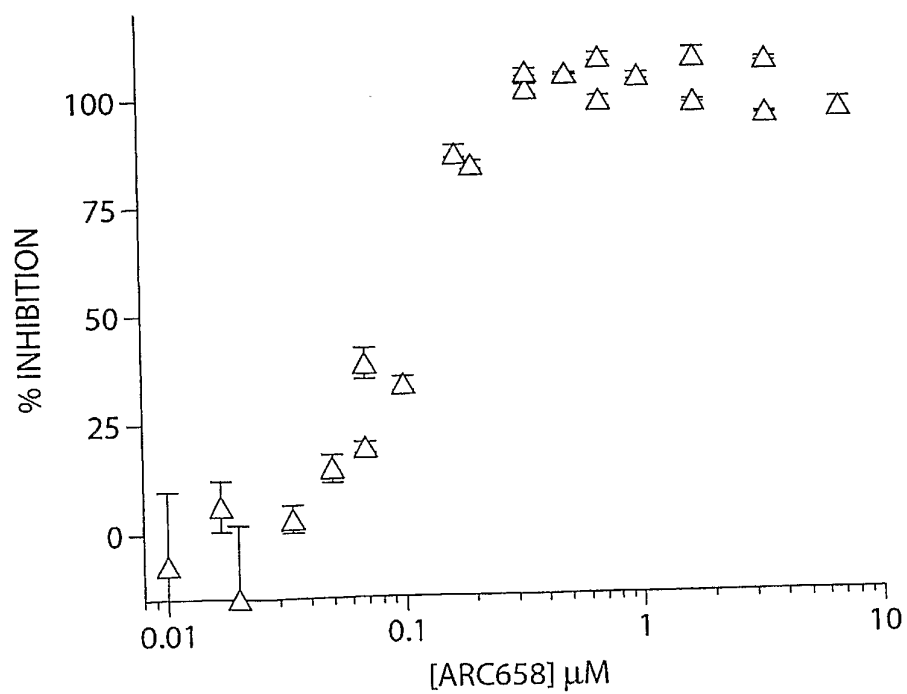


Fig. 17

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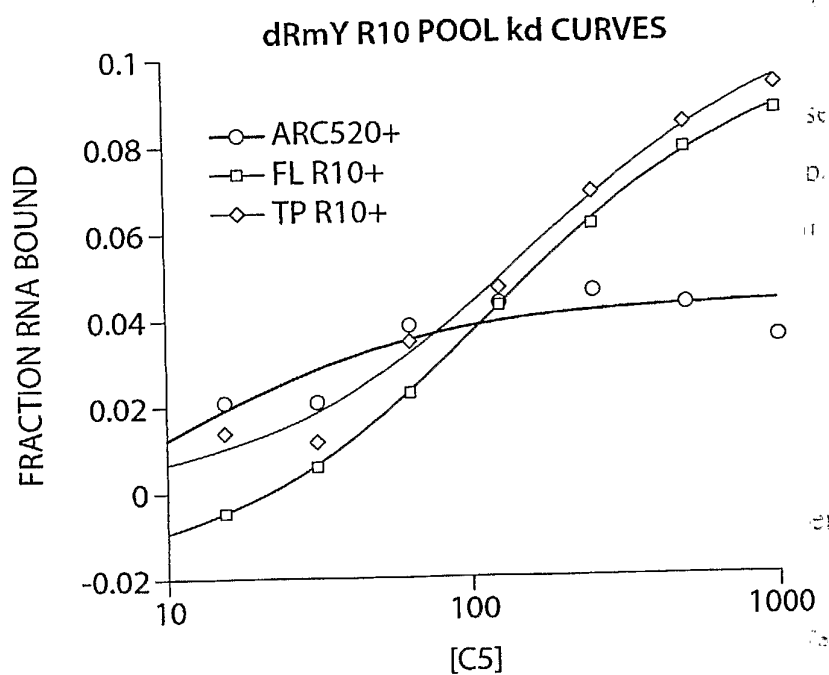


Fig. 18

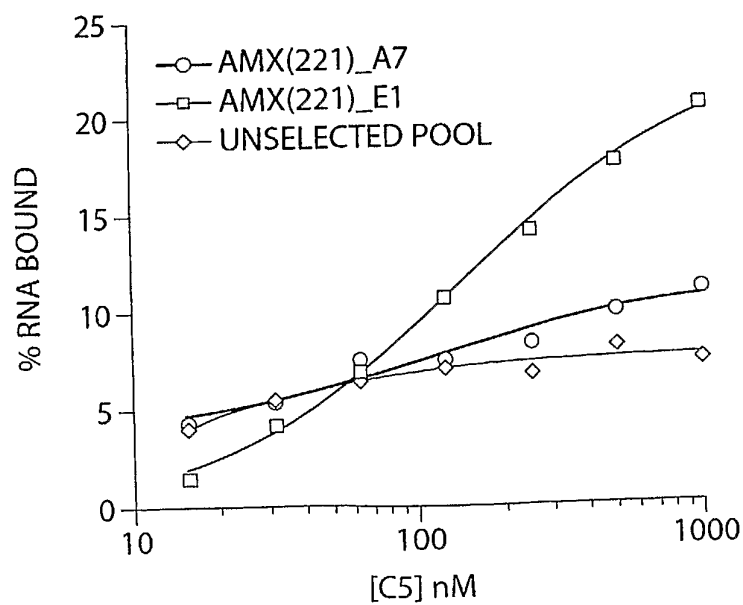


Fig. 19

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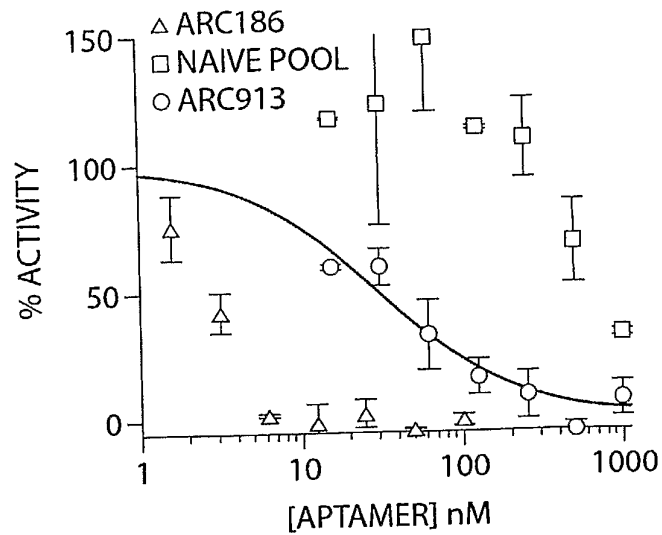


Fig. 20

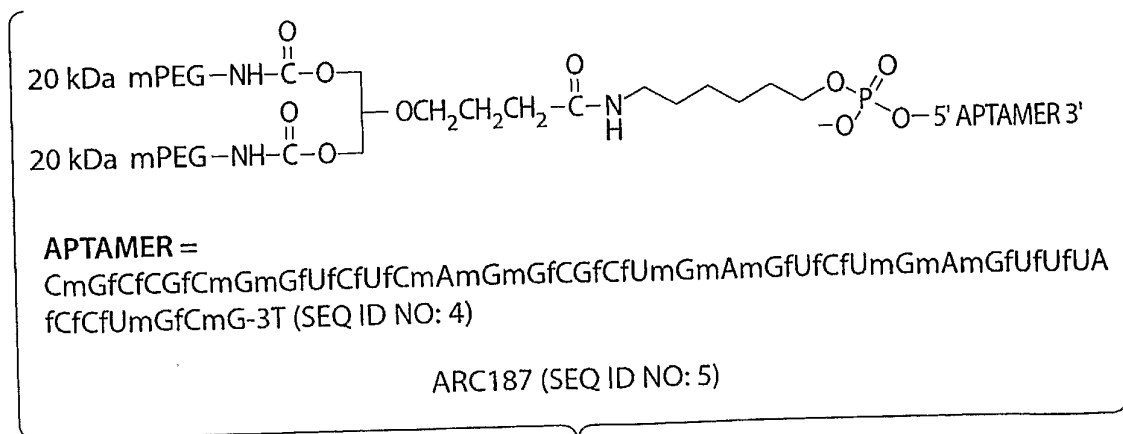
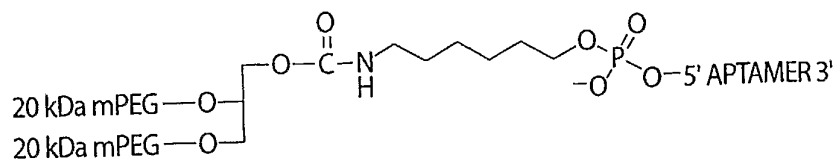


Fig. 21

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APTAMER =

CmGfCfCGfCmGmGfUfCfUfCmAmGmGfCGfCfUmGmAmGfUfCfUmGmAmGfUfUfUA
fCfCfUmGfCmG-3T (SEQ ID NO: 4)

ARC1905 (SEQ ID NO: 67)

Fig. 22

GROUP	# MICE	TEST ARTICLE	DOSE		MEASUREMENTS
			CONC (nM)	PERFUSION RATE mL/MIN	
1	5	NO APTAMER	0	3	HEART RATE, RHYTHM, LEFT VENTRICULAR PRESSURE
3	3	IRRELEVANT APTAMER AT 50X MOLAR RATIO	1500	3	HEART RATE, RHYTHM, LEFT VENTRICULAR PRESSURE
4	3	ARC186 AT MOLAR EQUIVALENCE	30	3	HEART RATE, RHYTHM, LEFT VENTRICULAR PRESSURE
5	5	ARC186 AT 10X MOLAR RATIO	300	3	HEART RATE, RHYTHM, LEFT VENTRICULAR PRESSURE
6	4	ARC186 AT 50X MOLAR RATIO	1500	3	HEART RATE, RHYTHM, LEFT VENTRICULAR PRESSURE

Fig. 23

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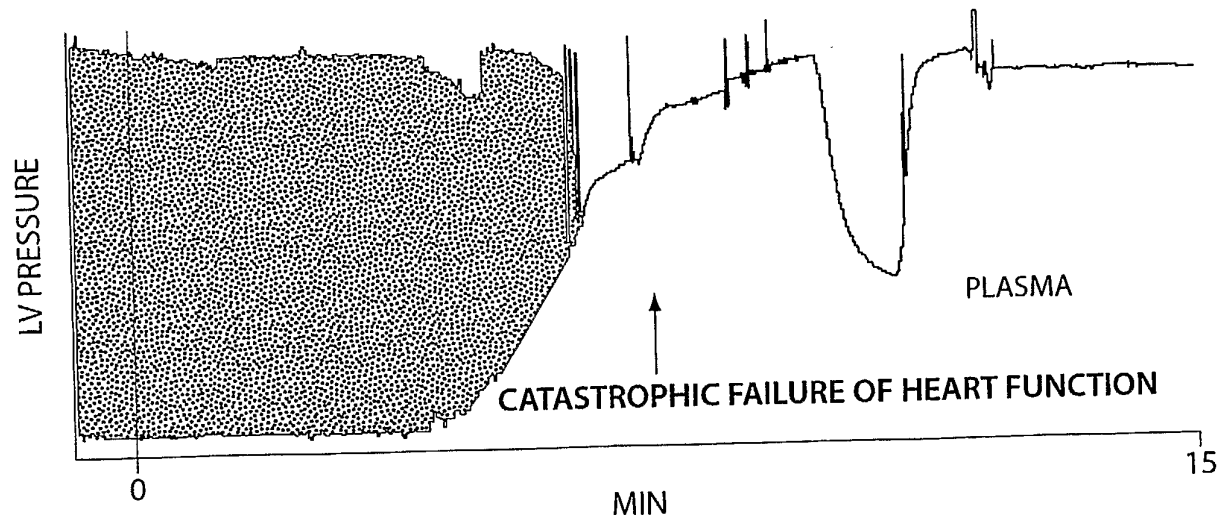


Fig. 24A

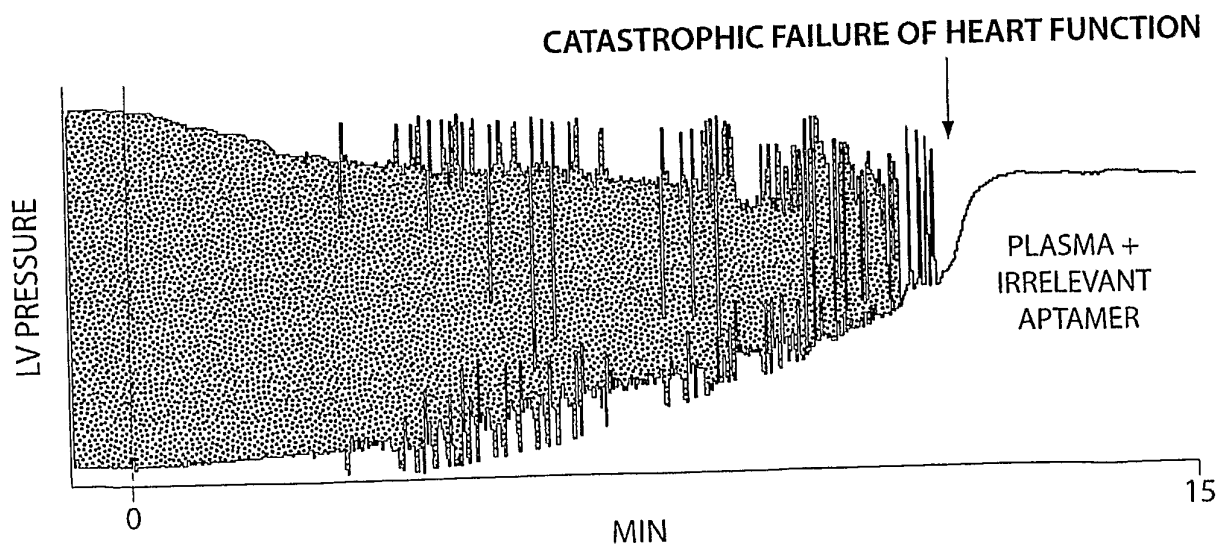


Fig. 24B

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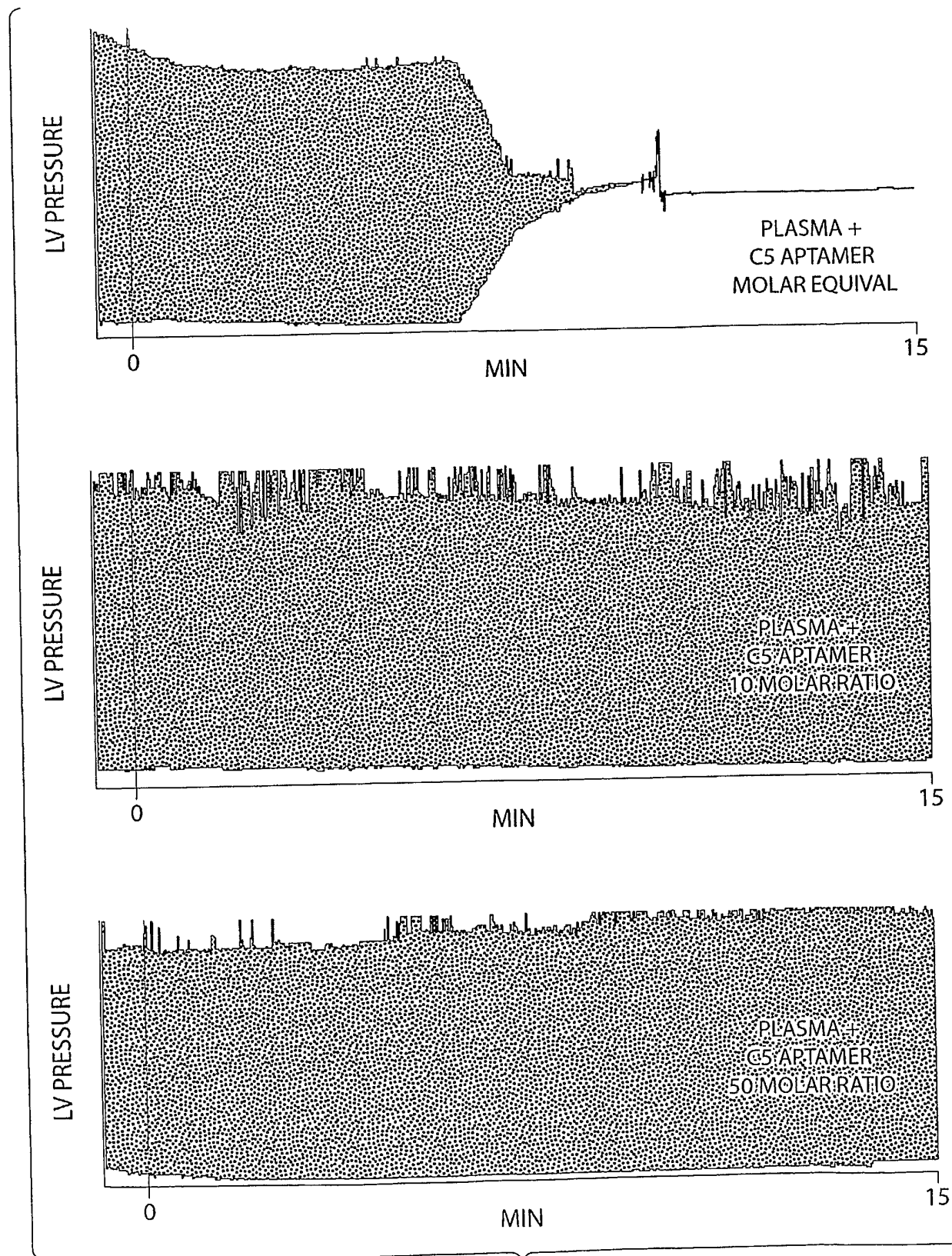


Fig. 25

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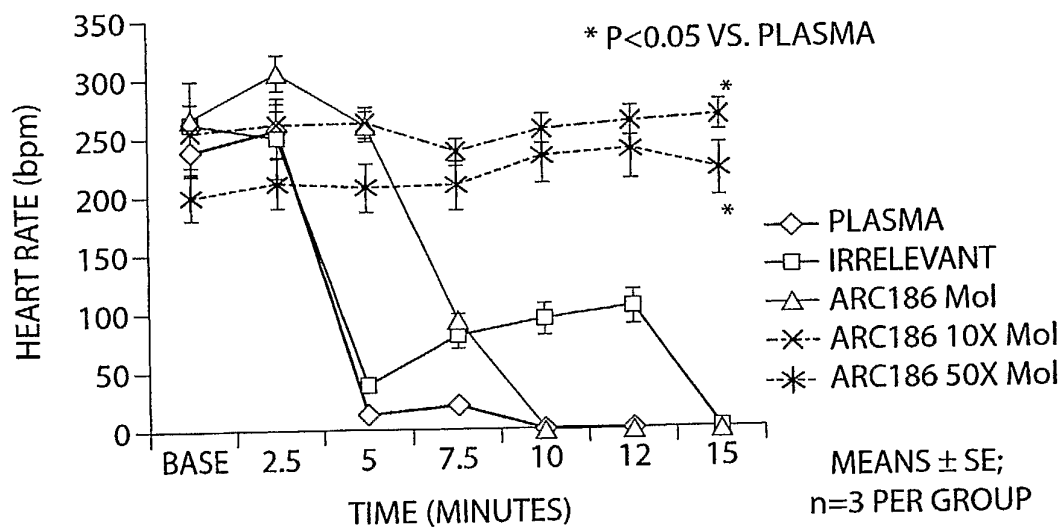


Fig. 26

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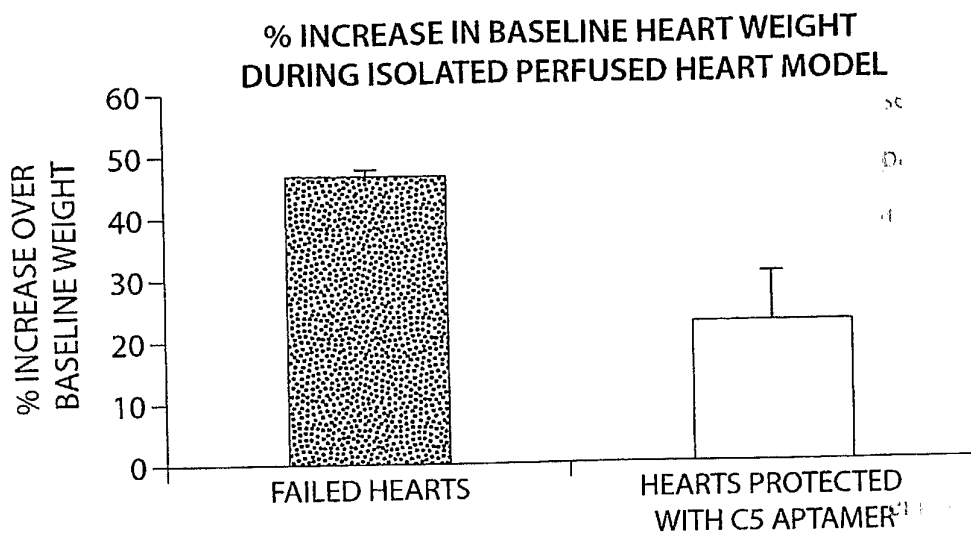


Fig. 27

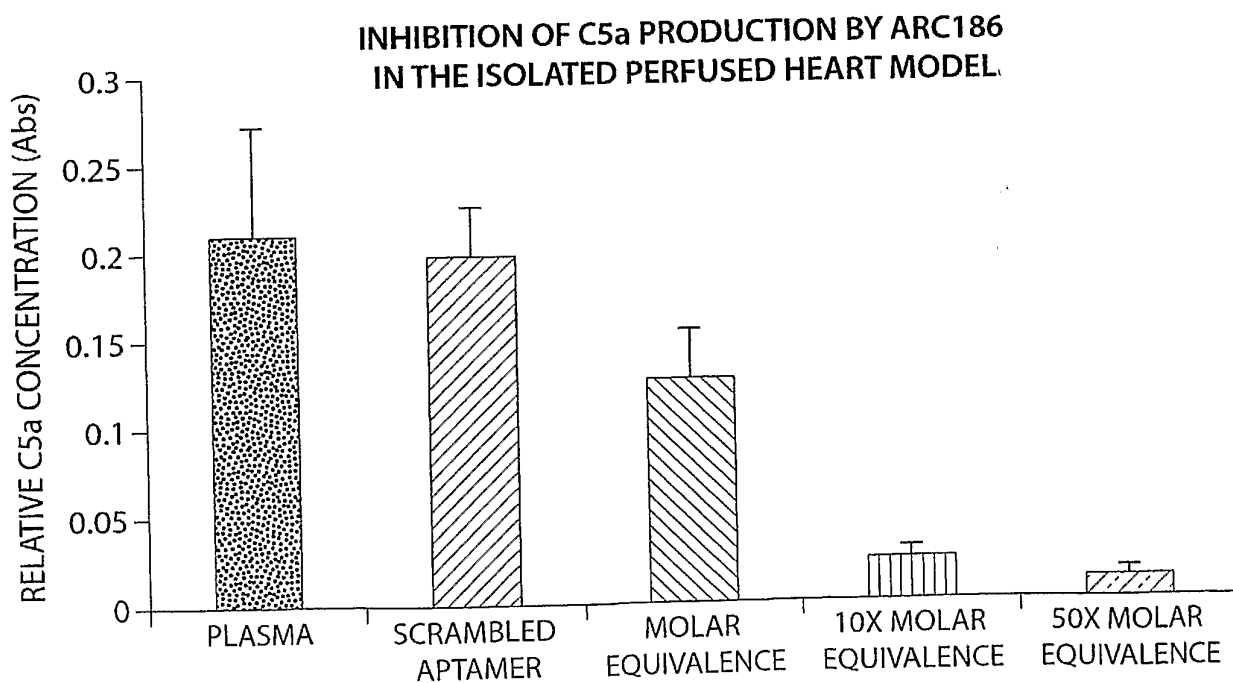


Fig. 28

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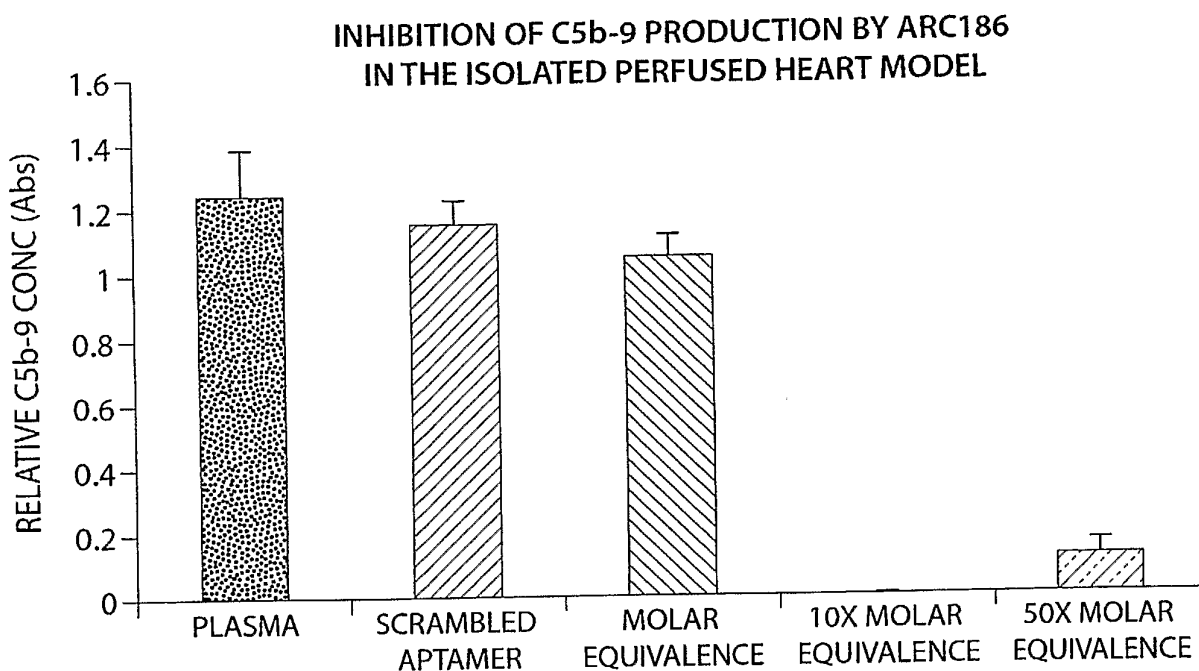


Fig. 29

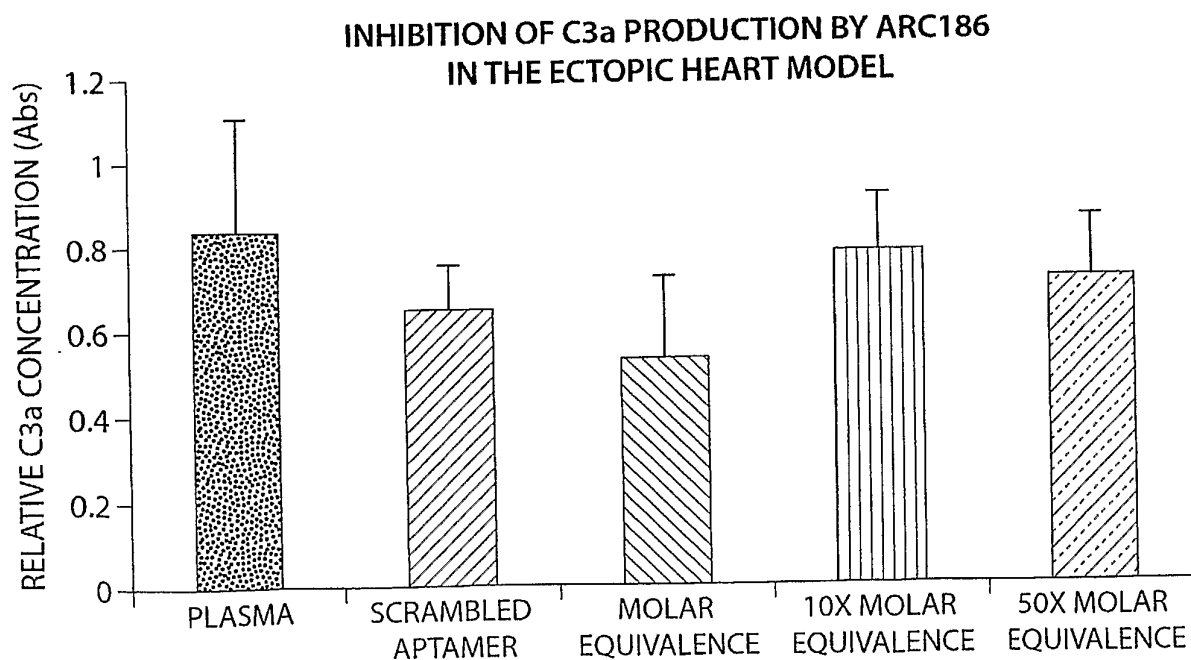


Fig. 30

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ANIMAL	TREATMENT	IRRELEVANT	C3b	C5b-9
1-001 (1/26)	NONE	NEG	POS	POS
1-002 (1-26)	NONE	NEG	POS	POS
1-001	NONE	NEG	POS	POS
1-002	NONE	NEG	POS	POS
1-003	NONE	NEG	POS	POS
3-001	IRRELEVANT APTAMER 50X MOLAR	NEG	POS	POS
3-002	IRRELEVANT APTAMER 50X MOLAR	NEG	POS	POS
3-003	IRRELEVANT APTAMER 50X MOLAR	NEG	POS	POS
4-001	C5 APTAMER MOLAR EQUIVALENCE	NEG	POS	POS
4-002	C5 APTAMER MOLAR EQUIVALENCE	NEG	POS	POS
4-003	C5 APTAMER MOLAR EQUIVALENCE	NEG	POS	POS
5-001	C5 APTAMER 10X MOLAR EQUIVALENCE	NEG	POS	NEG
5-002	C5 APTAMER 10X MOLAR EQUIVALENCE	NEG	POS	NEG
5-003	C5 APTAMER 10X MOLAR EQUIVALENCE	NEG	POS	NEG
5-004	C5 APTAMER 10X MOLAR EQUIVALENCE	NEG	POS	NEG
5-005	C5 APTAMER 10X MOLAR EQUIVALENCE	NEG	POS	NEG
6-001	C5 APTAMER 50X MOLAR EQUIVALENCE	NEG	POS	NEG
6-002	C5 APTAMER 50X MOLAR EQUIVALENCE	NEG	POS	NEG
6-003	C5 APTAMER 50X MOLAR EQUIVALENCE	NEG	POS	NEG
6-004	C5 APTAMER 50X MOLAR EQUIVALENCE	NEG	POS	NEG

Fig. 31

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ANIMAL	COMPOUND	SERUM	MOLAR RATIO	INCREASED EDP	FAILURE (Y OR NO)	TIME TO FAILURE
1-001	ARC658	HUMAN	0	Y	Y	4 MIN 30 SEC
1-002	ARC658	HUMAN	0	Y	Y	4 MIN 38 SEC
1-003	ARC658	HUMAN	0	Y	Y	3 MIN 20 SEC
1-004	ARC658	HUMAN	0	Y	Y	12 MIN 24 SEC
1-005	ARC658	HUMAN	0	Y	N	NA
1-006	ARC658	HUMAN	0	Y	Y	8 MIN 30 SEC
1a-001	ARC658	HUMAN	0.5	Y	Y	7 MIN 22 SEC
1a-002	ARC658	HUMAN	0.5	Y	Y	7 MIN 30 SEC
1a-003	ARC658	HUMAN	0.5	Y	Y	8 MIN 13 SEC
2-001	ARC658	HUMAN	1	N	N	NA
2-002	ARC658	HUMAN	1	N	N	NA
2-003	ARC658	HUMAN	1	N	N	NA
2-004	ARC658	HUMAN	1	N	N	NA
3-001	ARC658	HUMAN	3	N	N	NA
3-002	ARC658	HUMAN	3	N	N	NA
3-003	ARC658	HUMAN	3	N	N	NA
6-001	ARC658	PRIMATE	0	Y	Y	2 MIN 30 SEC
6-002	ARC658	PRIMATE	0	Y	Y	2 MIN 47 SEC
6-003	ARC658	PRIMATE	0	Y	Y	3 MIN 30 SEC
6-004	ARC658	PRIMATE	0	Y	Y	1 MIN 28 SEC
6a-001	ARC658	PRIMATE	3	Y	Y	5 MIN 2 SEC
6a-002	ARC658	PRIMATE	3	Y	Y	4 MIN 30 SEC
6a-003	ARC658	PRIMATE	3	Y	Y	3 MIN 43 SEC
6a-004	ARC658	PRIMATE	3	Y	Y	8 MIN 0 SEC
7-001	ARC658	PRIMATE	10	Y	N	NA
7-002	ARC658	PRIMATE	10	Y	N	NA
7-003	ARC658	PRIMATE	10	Y	Y	9 MIN 15 SEC
7-004	ARC658	PRIMATE	10	Y	N	NA
9-001	ARC658	PRIMATE	20	Y	Y	12 MIN 50 SEC
11-001	ARC658	PRIMATE	30	Y	N	NA
11-002	ARC658	PRIMATE	30	Y	Y	10 MIN 0 SEC
11-003	ARC658	PRIMATE	30	Y	N	NA
13-001	ARC658	PRIMATE	50	N	N	NA
13-002	ARC658	PRIMATE	50	N	N	NA
13-003	ARC658	PRIMATE	50	N	N	NA

Fig. 32

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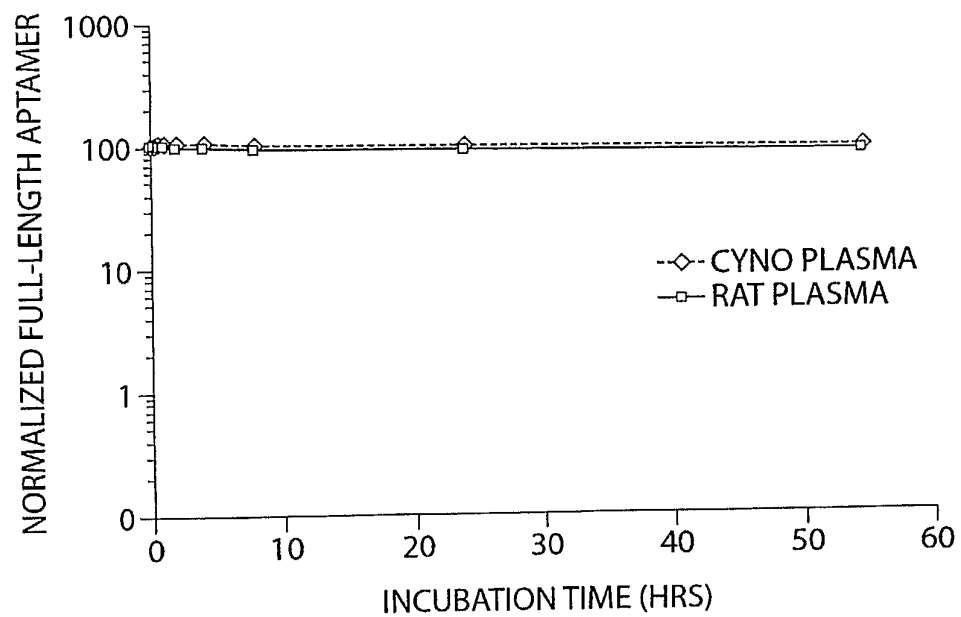


Fig. 33

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GROUP NUMBER	NUMBER OF ANIMALS	TEST ARTICLE	DOSAGE LEVEL (mg/kg)	DOSAGE VOLUME (mL/kg)	DOSING REGIMEN	SAMPLE COLLECTION
1	3	ARC657 20 kDa PEG	10	1	INTRAVENOUS BOLUS ON DAY 1	t=PRE-DOSE, 0.5, 1, 2, 4, 8, 16, 24, 32, 48 HRS
2	3	ARC658 30 kDa PEG	10	1	INTRAVENOUS BOLUS ON DAY 1	t=PRE-DOSE, 0.5, 1, 2, 4, 8, 16, 24, 32, 48 HRS
3	3	ARC187 40 kDa PEG	10	1	INTRAVENOUS BOLUS ON DAY 1	t=PRE-DOSE, 0.5, 1, 2, 4, 8, 16, 24, 32, 48 HRS

Fig. 34

PK OF ANTI-C5 APTAMER-PEG CONJUGATES IN SPRAGUE-DAWLEY RAT						
APTAMER	ARC657		ARC658		ARC187	
PEG GROUP	20 kDa		30 kDa		40 kDa	
	MEAN	STDEV	MEAN	STDEV	MEAN	STDEV
TIME (HRS)	Cp (μ M)	Cp (μ M)	Cp (μ M)	Cp (μ M)	Cp (μ M)	Cp (μ M)
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	12.77	2.67	2.97	0.62	6.52	1.77
1	13.38	2.08	4.09	1.44	7.94	1.08
2	6.63	1.87	3.40	0.66	6.57	1.56
4	2.38	0.87	2.22	0.39	4.56	0.54
8	0.72	0.18	2.87	1.84	1.53	0.57
12	0.31	0.03	0.60	0.09	1.45	0.17
24	<LLOQ	<LLOQ	0.47	0.17	0.73	0.03
32	<LLOQ	<LLOQ	<LLOQ	<LLOQ	0.49	0.01
48	<LLOQ	<LLOQ	<LLOQ	<LLOQ	0.27	0.02

Fig. 35

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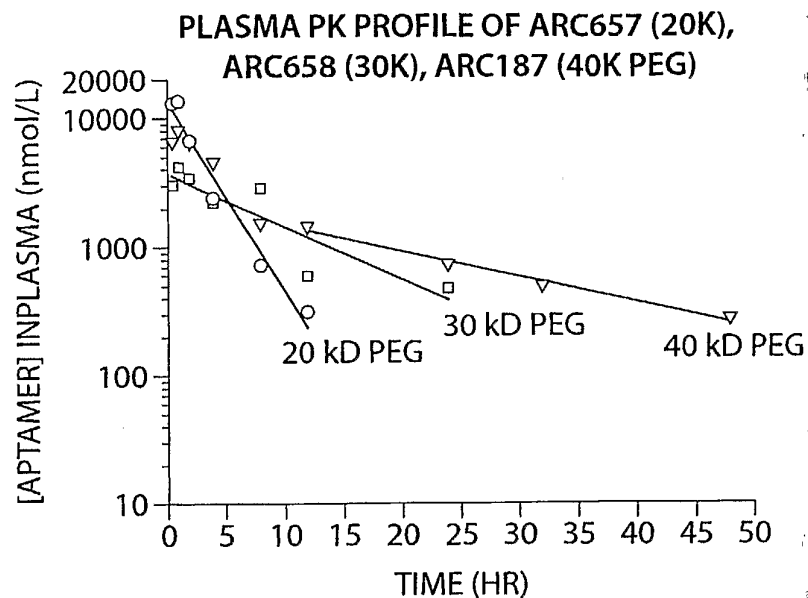


Fig. 36

SPECIES	DOSE (mg/kg)	ADMIN ROUTE	PEG GROUP	C _{max} (μg/ml)	AUC _{0-∞} (μg_hr/mL)	t _{1/2} (α) (HR)	t _{1/2} (β) (HR)	Cl (mL/min_kg)	V _{ss} (mL/kg)
RAT	10	IV	20 kD	169.97	458	-	2.05	0.36	65
RAT	10	IV	30 kD	52.00	497	-	7.40	0.34	220
RAT	10	IV	40 kD	100.85	886	-	15.00	0.19	188

Fig. 37

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GROUP NO.	NO. ANIMALS	TEST ARTICLE	DOSE		DOSE ROUTE	SAMPLE COLLECTION
			(mg/kg)	(mL/kg)		
1	33F	ARC187	10	4	IV	t=PRE-DOSE, 0.5, 1, 2, 4, 8, 16, 24, 32, 48, 72 HRS
2	33F	ARC1905	10	4	IV	t=PRE-DOSE, 0.5, 1, 2, 4, 8, 16, 24, 32, 48, 72 HRS

Fig. 38A

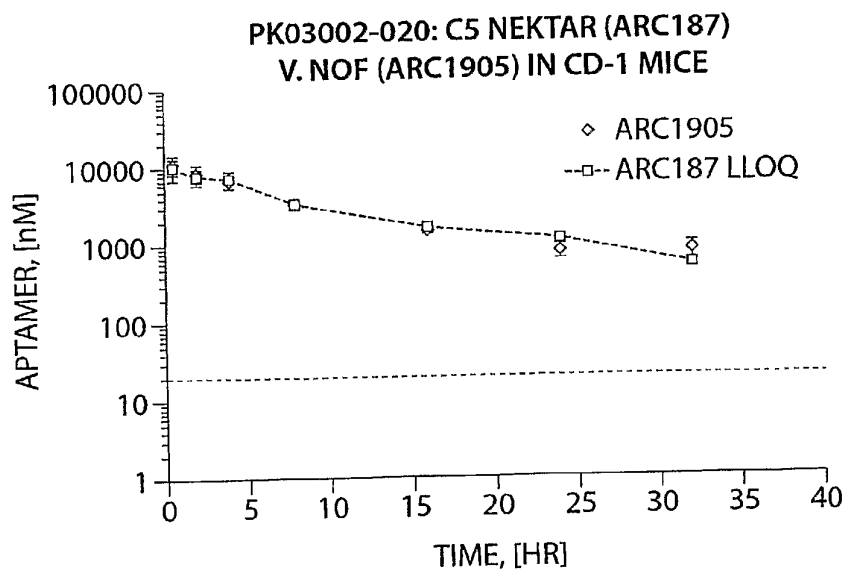


Fig. 38B

NONCOMPARTMENTAL PK ANALYSIS (NCA)			
ATTRIBUTE	UNIT	ARC1905	ARC187
C _{max}	μM	12	10
AUC _{0-∞}	μM-HR	88	89
MRT _{0-∞}	HR	11	11
CL	mL/min.kg	0.15	0.15
V _{ss}	mL/kg	95	96
K ₁₀	1/HR	0.151	0.121
t _{1/2} (K ₁₀)	HR	5	6

Fig. 38C

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APTAMER	PRE	1 HR	3 HR	6 HR
ARC657	NO	YES	YES	YES
ARC658	NO	YES	YES	YES
ARC187	NO	YES	YES	YES

Fig. 39

GROUP NUMBER	NUMBER OF ANIMALS	TEST ARTICLE	DOSAGE LEVEL (mg/kg)	DOSAGE VOLUME (mL/kg)	DOSING REGIMEN	SAMPLE COLLECTION
1	1	ARC657 20 kDa PEG	30	3	INTRAVENOUS BOLUS ON DAY 1	t=PRE-DOSE, 1, 5, 10, 15, AND 30 MINUTES AND AT 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, AND 192 HRS
2	1	ARC658 30 kDa PEG	30	3	INTRAVENOUS BOLUS ON DAY 1	t=PRE-DOSE, 1, 5, 10, 15, AND 30 MINUTES AND AT 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, AND 192 HRS
3	1	ARC187 40 kDa PEG	30	3	INTRAVENOUS BOLUS ON DAY 1	t=PRE-DOSE, 1, 5, 10, 15, AND 30 MINUTES AND AT 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, AND 192 HRS

Fig. 40

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PK OF ANTI-C5 APTAMER -PEG CONJUGATES IN CYNOMOLGUS MACAQUE			
APTAMER	ARC657	ARC658	ARC187
PEG GROUP	20 kDa	30 kDa	40 kDa
	MEAN	MEAN	MEAN
TIME (HRS)	Cp (μ M)	Cp (μ M)	Cp (μ M)
0	0.00	0.00	0.00
0.08	16.41	21.99	18.00
0.25	16.64	22.67	17.26
0.5	19.38	26.16	24.17
1	19.36	27.08	21.79
4	7.73	14.16	21.69
8	2.03	6.02	16.68
12	1.10	3.04	13.11
24	0.36	0.95	7.24
48	0.15	0.42	2.30
72	0.07	0.25	0.96
96	0.03	0.23	0.54
192	0.01	0.04	0.14

Fig. 41

SPECIES	DOSE (mg/kg)	ADMIN ROUTE	PEG GROUP	C _{max} (μ g/ml)	AUC _{0-∞} (μ g _· hr/mL)	t _{1/2} (α) (HR)	t _{1/2} (β) (HR)	Cl (mL/min _· kg)	V _{ss} (mL/kg)
PRIMATE	30	IV	20 kD	293	1191	2.35	31.80	0.41	273
PRIMATE	30	IV	30 kD	385	2484	3.33	40.08	0.20	233
PRIMATE	30	IV	40 kD	316	6752	12.38	60.11	0.07	141

Fig. 42

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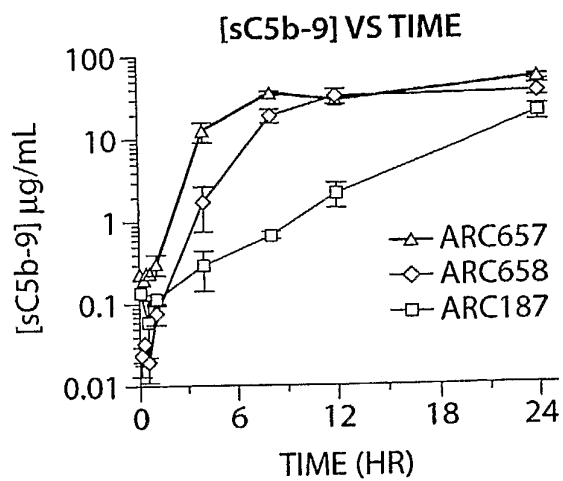


Fig. 43A

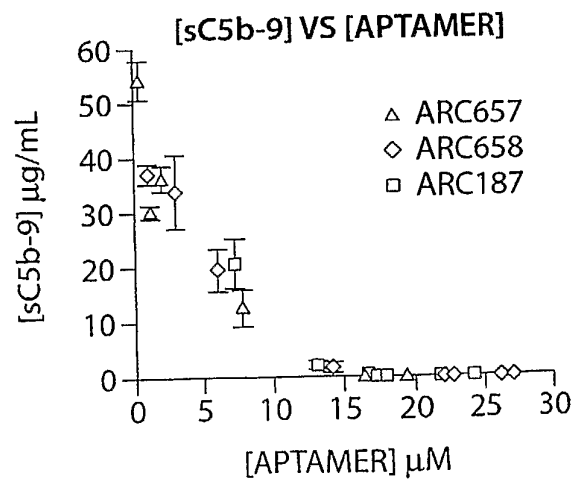


Fig. 43B

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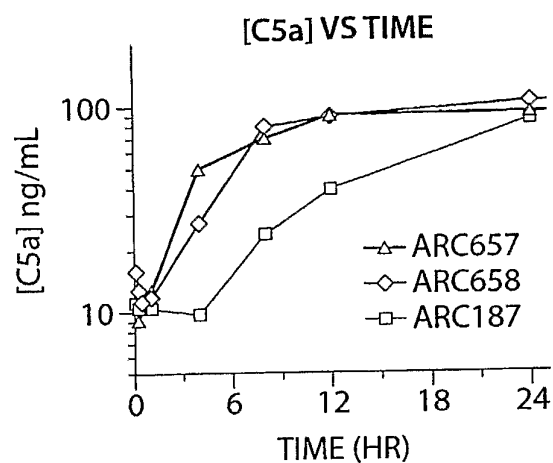


Fig. 43C

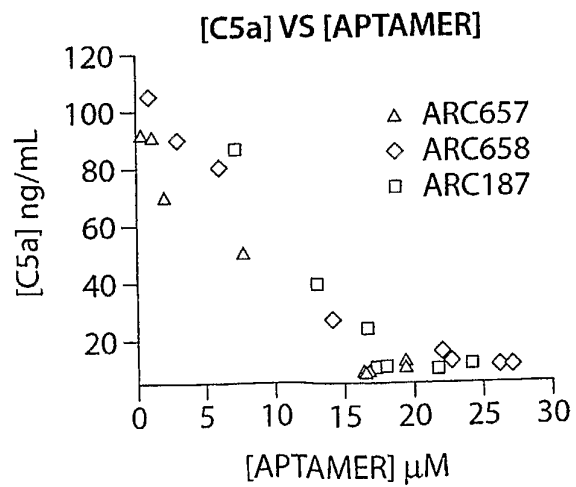


Fig. 43D

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GROUP NUMBER	NUMBER OF ANIMALS	TEST ARTICLE	DOSAGE LEVEL (mg/kg)	DOSE VOLUME (mL/kg)	DOSING REGIMEN	SAMPLE COLLECTION
1	4	ARC658 30 kDa PEG	30	3	INTRAVENOUS BOLUS ON DAY 1	t=PRE-DOSE, 5, 10, 15, AND 30 MINUTES AND AT 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 144 AND 192 HRS
2	4	ARC187 40 kDa PEG	30	3	INTRAVENOUS BOLUS ON DAY 1	t=PRE-DOSE, 5, 10, 15, AND 30 MINUTES AND AT 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 144 AND 192 HRS

Fig. 44

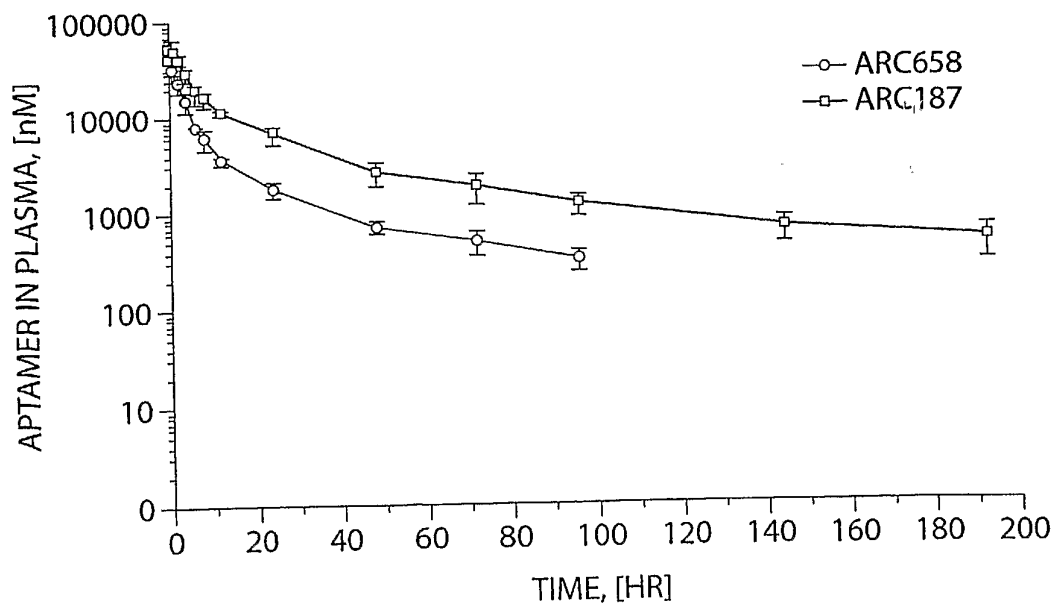


Fig. 45

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SPECIES	DOSE (mg/kg)	ADMIN ROUTE	PEG GROUP	C _{max} (μM)	AUC _{0-∞} (μg_hr/mL)	t _{1/2} (α) (HR)	t _{1/2} (β) (HR)	Cl (mL/min_kg)	V _{ss} (mL/kg)
PRIMATE	30	IV	30 kD	519	3059	2.35	30.45	0.16	213
PRIMATE	30	IV	40 kD	609	8061	4.48	53.13	0.06	168

Fig. 46

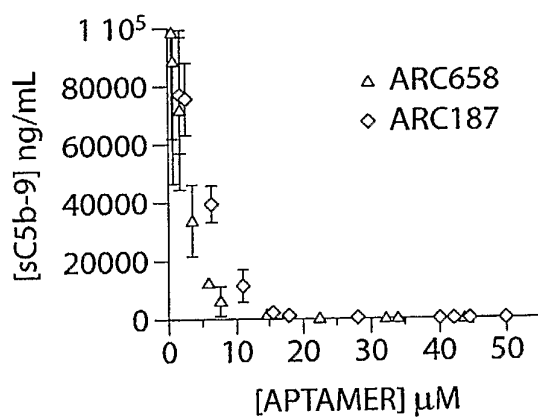


Fig. 47

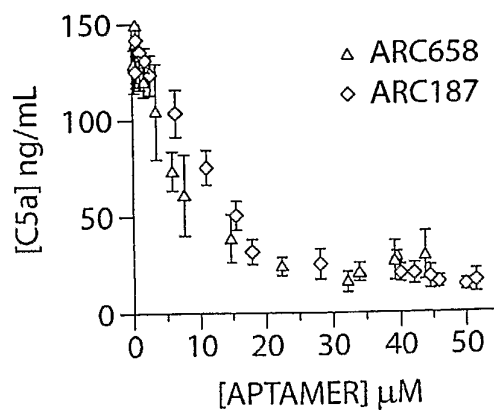


Fig. 48

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GROUP NUMBER	NUMBER OF ANIMALS	TEST ARTICLE	DOSAGE LEVEL (mg/kg)	DOSE CONC. (mg/mL)	DOSE VOLUME (mL/kg)	DOSING REGIMEN	LAST DAY ON TEST
1	3	ARC187	1 mg/kg IV BOLUS AND 0.0013 mg/kg/min IV INFUSION	10	0.1 mL/kg IV BOLUS AND 0.1872 mL/kg/day, IV INFUSION	IV BOLUS AND 48 HOUR INFUSION ON DAY 1	DAY 8

Fig. 49

SPECIES	DOSE (mg/kg)	ADMIN ROUTE	PEG GROUP	C _{max} (μg/mL)	AUC _{0-∞} (μg_hr/mL)	t _{1/2} (α) (HR)	t _{1/2} (β) (HR)	Cl (mL/min_kg)	V _{ss} (mL/kg)
PRIMATE	30	IV	40 kD	610	8061	4.48	53.13	0.06	168

Fig. 50

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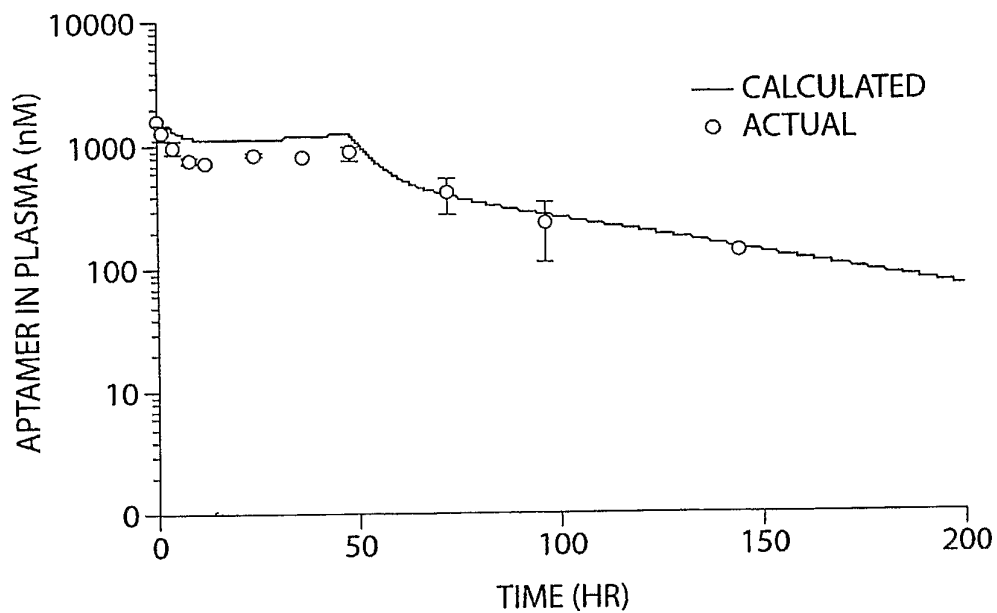


Fig. 51

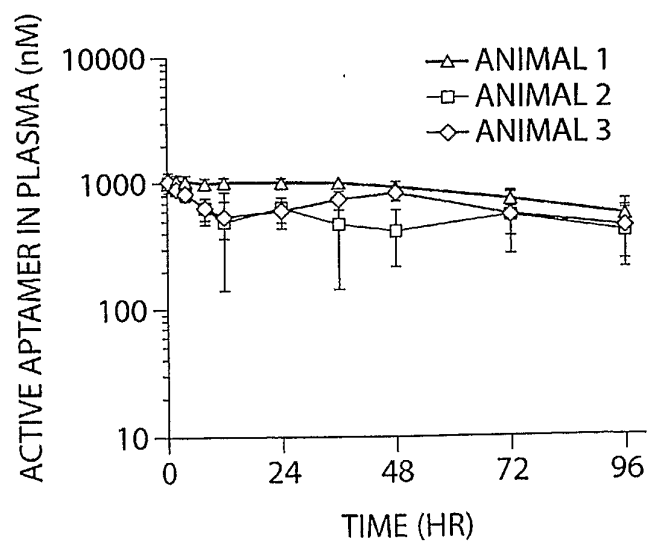


Fig. 52

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APTAMER	PEG GROUP	MOL. WT. (OLIGO)	MOL. WT. (TOTAL)	$t_{1/2}(\alpha)$ (HR)	$t_{1/2}(\beta)$ (HR)	TOTAL (OLIGO) DOSE FOR 1.5 μ M (g)
ARC187	40 kDa	12,703	52,703	4.48	53.13	0.40

Fig. 53

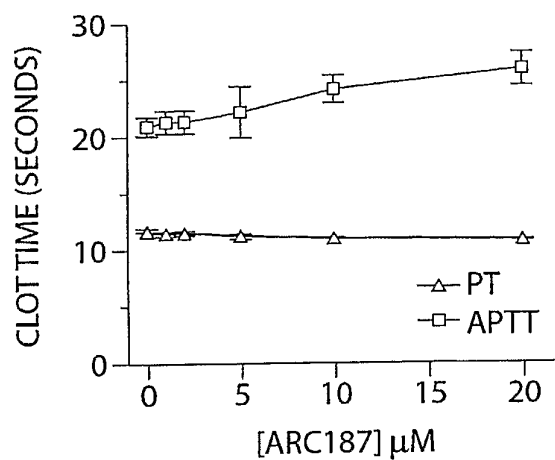


Fig. 54

TREATMENT	ACT (SECONDS)		
	DONOR 1 ^a	DONOR 2 ^b	DONOR 3 ^b
BASELINE	133 $\pm$ 30	145 $\pm$ 12	138 $\pm$ 1
+ HEPARIN	842 $\pm$ 95	519 $\pm$ 16	450 $\pm$ 15
+ HEPARIN & ARC187	nd	618 $\pm$ 55	492 $\pm$ 28
+ HEPARIN & PROTAMINE	160 $\pm$ 11	155 $\pm$ 6	159 $\pm$ 9
+ HEPARIN, PROTAMINE & ARC187	200 $\pm$ 5	172 $\pm$ 1	169 $\pm$ 8

^a5 U/mL HEPARIN; ^b4 U/mL HEPARIN; nd, NOT DETERMINED

Fig. 55

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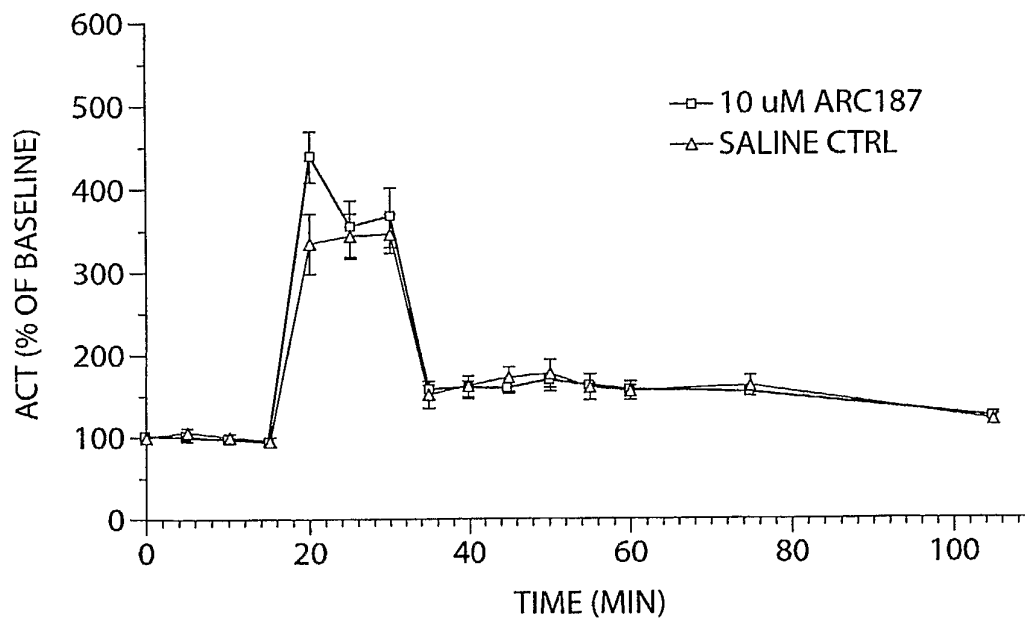


Fig. 56

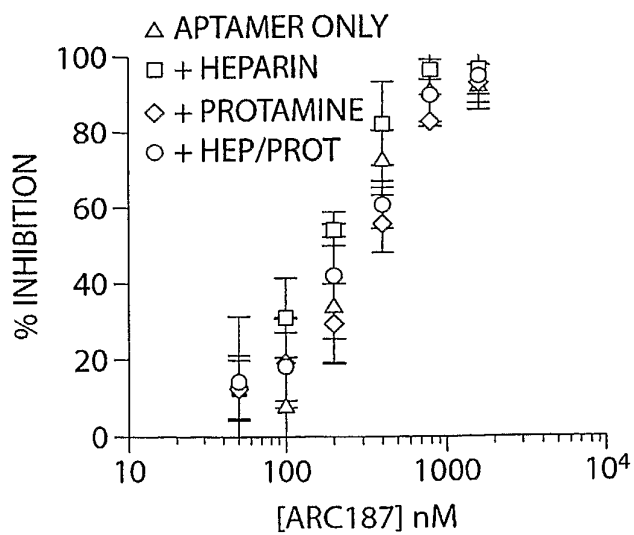


Fig. 57

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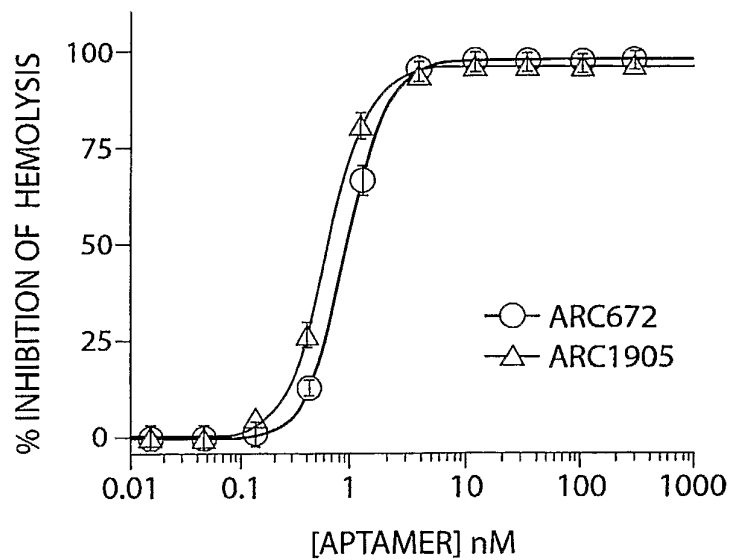


Fig. 58

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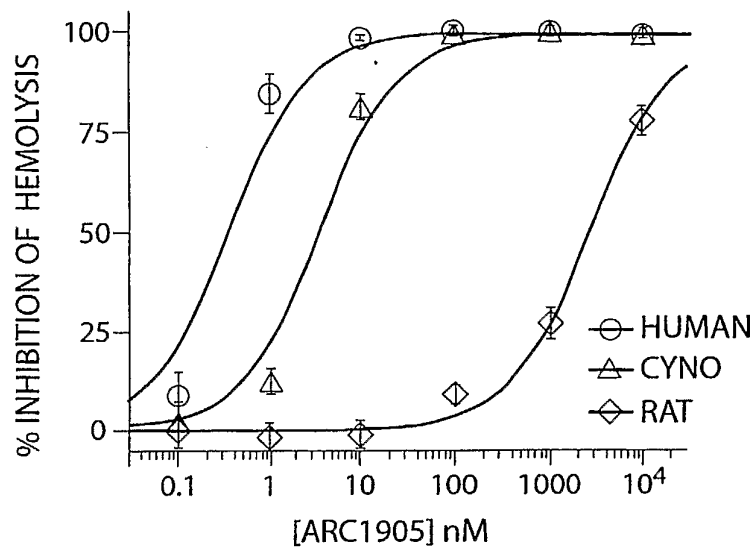


Fig. 59A

Serum Species	ARC1905 IC ₅₀ (nM)	ARC127 IC ₅₀ (nM)
Human	0.349 ±0.0898	>10,000 NA
Cynomolgus Monkey	3.69 ±0.603	>10,000 NA
Rat	2700 ±470	~10,000 NA

Fig. 59B

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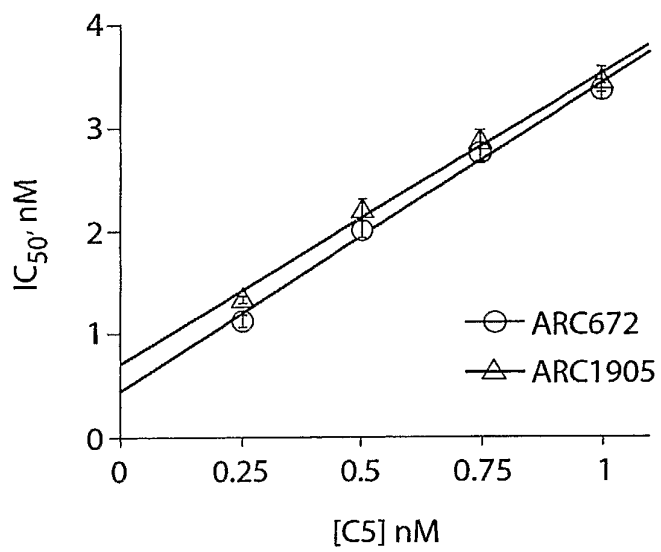


Fig. 60

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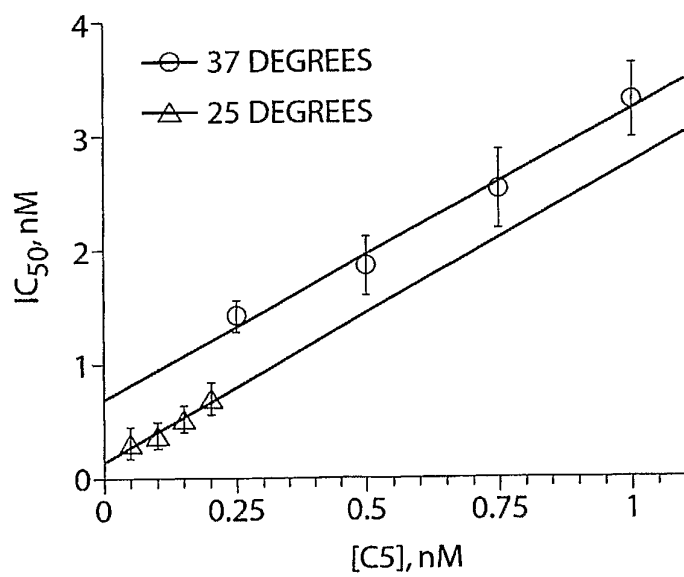


Fig. 61

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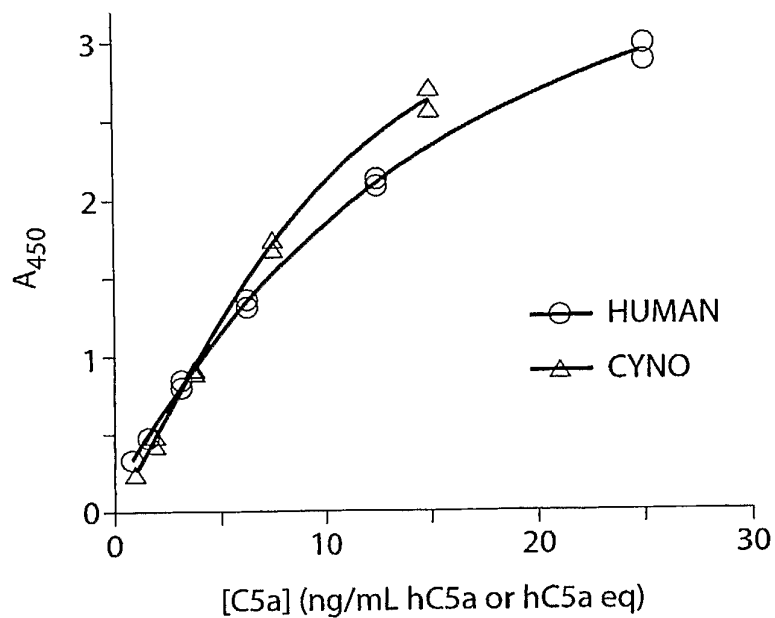


Fig.62

Aptamer	IC ₅₀ (nM)	IC ₉₀ (nM)	IC ₉₉ (nM)
Human	196 ±13.9	442 ±23.2	1090 ±198.0
Cynomolgus Macaque	536 ±54.7	1810 ±405.8	6900 ±2600
cyno/human ratio	2.73 ±0.339	4.1 ±0.94	6.4 ±2.65

Fig.63

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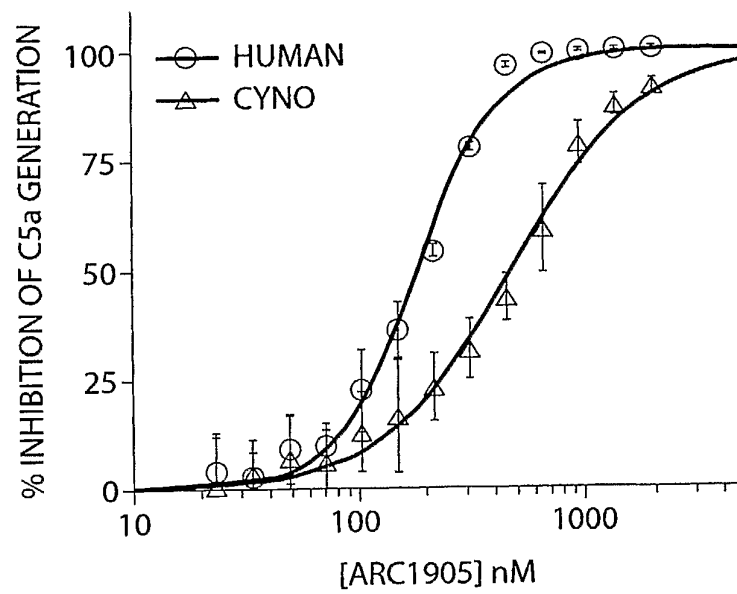


Fig. 64

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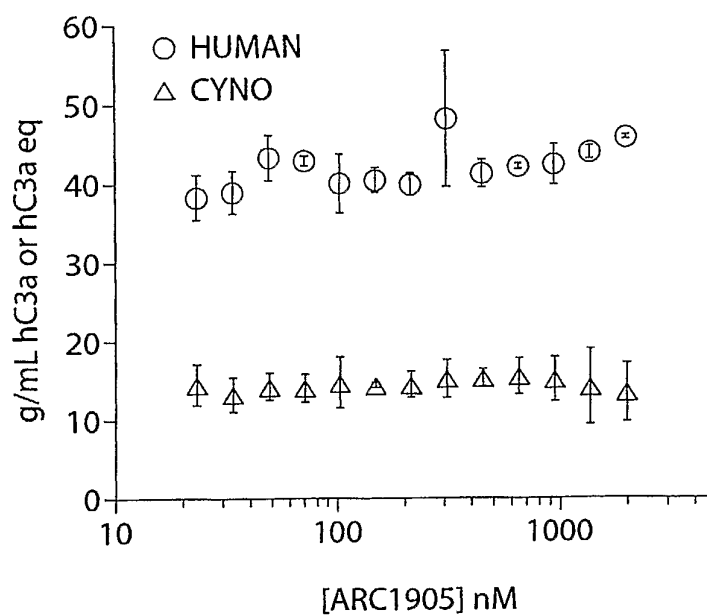


Fig. 65

Donor	IC ₅₀ (nM)	IC ₉₀ (nM)	IC ₉₉ (nM)
Mean of 5 donors	119	268	694
SD	28.6	39.2	240.9

Fig. 66

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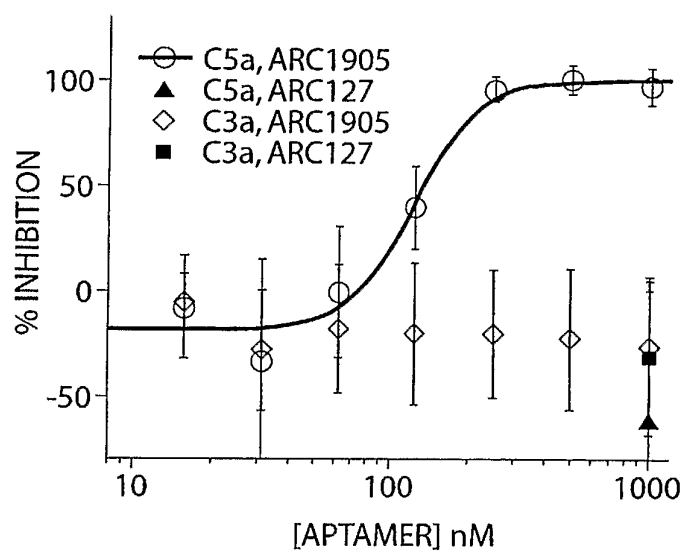


Fig. 67