Name	SEQ ID NO.	Sequence: 5′-3′	KD [nM]	
			mC5a	huC5a
274-B5-002	001	**GCCUG**AUGUGGUGUUGAAGGGUUGUGGGGUGUCGACGCA**CAGGC**	3.5	12.1
274-D5-002	002	**GCCUG**AUGUGGUGUUGAGGGGUUGUGGGGUGUCGACGCA**CAGGC**	2.2	7.8
274-C8-002	003	**GCCUG**AUGUGGUGUUGAAGGGUUGUUGGGUGUCGACGCA**CAGGC**	0.9	5.1
274-C8-002-G14 (=NOX-D19001)	004	**GCCUG**AUGUGGUGGUGAAGGGUUGUUGGGUGUCGACGCA**CAGGC**	0.3	1.4
274-C5-002	005	**GCCUG**AUGUGGUGGUGAGGGGUUGUGGGGUGUCGACGCA**CAGGC**	0.3	1.6
274-G6-002	006	**GCCUG**AUGUGGUGGUGAGGGGAUGUGGGGUGUCGACGCA**CAGGC**	1.0	4.8
274-H6-002	007	**GCCUG**AUGUGGUGUUGAGGGGCUGUGGGGUGUCGACGCA**CAGGC**	n.d.	n.d.

any of G, C, U and A is a ribonucleotide; nucleotides edged by ☐ represent a C5a-binding motif;

KD: Dissociation constant K_D of Spiegelmers (L-nucleic acid), molecules of the indicated sequence were tested as Spiegelmers (L-nucleic acid) measured as surface plasmon resonance on Biacore using direct binding to covalently immobilized human C5a (huC5a) or mouse C5a (mC5a)

Fig.1

Name	SEQ ID NO.	Sequence: 5'-3'	KD [nM] huC5a
NOX-D19001	004	GCCUGAUGUGGUGGUGAAGGGUUGUUGGGUGUCGACGCACAGGC	1.38
NOX-D19001-D09	008	GCCUGAUGdUGGUGGUGAAGGGUUGUUGGGUGUCGACGCACAGGC	0.71
NOX-D19001-D16	009	GCCUGAUGUGGUGGUdGAAGGGUUGUUGGGUGUCGACGCACAGGC	1.03
NOX-D19001-D17	010	GCCUGAUGUGGUGGUGdAAGGGUUGUUGGGUGUCGACGCACAGGC	0.91
NOX-D19001-D30	011	GCCUGAUGUGGUGGUGAAGGGUUGUUGGGdUGUCGACGCACAGGC	0.77
NOX-D19001-D32	012	GCCUGAUGUGGUGGUGAAGGGUUGUUGGGUGdUCGACGCACAGGC	0.92
NOX-D19001-D40	013	GCCUGAUGUGGUGGUGAAGGGUUGUUGGGUGUCGACGCAdCAGGC	0.88

any of G, C, U and A is a ribonucleotide; any of dG, dC, dU and dA is a 2'-desoxyribonucleotide;

nucleotides edged by ☐ represent a C5a-binding motif;

KD: Dissociation constant K_D of Spiegelmers (L-nucleic acid), molecules of the indicated sequence were tested as Spiegelmers (L-nucleic acid) measured as surface plasmon resonance on Biacore using direct binding to covalently immobilized human C5a (huC5a)

Fig. 2

Name	SEQ ID NO.	Sequence: 5′-3′	KD [nM]
2 RNA-to-DNA substitutions:			
NOX-D19001-D09-30	014	**GCCUG**AUGdUGGUGGUGAAGGGUUGUUGGGdUGUCGACGCA**CAGGC**	0.461
NOX-D19001-D09-32	015	**GCCUG**AUGdUGGUGGUGAAGGGUUGUUGGGUGdUCGACGCA**CAGGC**	0.566
NOX-D19001-D09-40	016	**GCCUG**AUGdUGGUGGUGAAGGGUUGUUGGGUGUCGACGCA**dCAGGC**	0.570
NOX-D19001-D30-32	017	**GCCUG**AUGUGGUGGUGAAGGGUUGUUGGGdUGdUCGACGCA**CAGGC**	0.855
NOX-D19001-D30-40	018	**GCCUG**AUGUGGUGGUGAAGGGUUGUUGGGdUGUCGACGCA**dCAGGC**	0.624
NOX-D19001-D32-40	019	**GCCUG**AUGUGGUGGUGAAGGGUUGUUGGGUGdUCGACGCA**dCAGGC**	0.652
3 RNA-to-DNA substitutions:			
NOX-D19001-D09-30-32	020	**GCCUG**AUGdUGGUGGUGAAGGGUUGUUGGGdUGdUCGACGCA**CAGGC**	0.526
NOX-D19001-D09-30-40	021	**GCCUG**AUGdUGGUGGUGAAGGGUUGUUGGGdUGUCGACGCA**dCAGGC**	0.400
NOX-D19001-D09-32-40	022	**GCCUG**AUGdUGGUGGUGAAGGGUUGUUGGGUGdUCGACGCA**dCAGGC**	0.448
NOX-D19001-D30-32-40	023	**GCCUG**AUGUGGUGGUGAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	0.880
4 RNA-to-DNA substitutions:			
NOX-D19001-D09-30-32-40	024	**GCCUG**AUGdUGGUGGUGAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	0.385
5 RNA-to-DNA substitutions:			
NOX-D19001-D09-16-30-32-40	025	**GCCUG**AUGdUGGUGGUGdGAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	0.351
NOX-D19001-D09-17-30-32-40	026	**GCCUG**AUGdUGGUGGUGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	0.308
6 RNA-to-DNA substitutions:			
NOX-D19001-D09-16-17-30-32-40 (= NOX-D19001-6xDNA)	027	**GCCUG**AUGdUGGUGGUGdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	0.36

Fig. 3

any of G, C, U and A is a ribonucleotide; any of dG, dC, dU and dA is a 2'-desoxyribonucleotide;

nucleotides edged by ☐ represent a C5a-binding motif;

KD: Dissociation constant K_D of Spiegelmers (L-nucleic acid), molecules of the indicated sequence were tested as Spiegelmers (L-nucleic acid) measured as surface plasmon resonance on Biacore using direct binding to covalently immobilized human C5a (huC5a)

Fig. 3 continuation

Name	SEQ ID NO.	Sequence: 5′-3′	nt	KD [nM] huC5a
NOX-D19001-6xDNA	**027**	**GCCUG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	44	0.36
NOX-D19001-6xDNA-007	028	**CCUG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	43	0.46
NOX-D19001-6xDNA-008	029	**CUG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	42	0.57
NOX-D19001-6xDNA-009	030	**UG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	41	3.51
NOX-D19001-6xDNA-010	031	**G**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	40	6.89
NOX-D19001-6xDNA-011	032	**GCUG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGC**	42	0.34
NOX-D19001-6xDNA-012	033	**GUG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAC**	40	0.81
NOX-D19001-6xDNA-013	034	**UG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCA**	38	8.22
NOX-D19001-6xDNA-018	035	**GCCG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCGGC**	42	0.30
NOX-D19001-6xDNA-019	036	**GGCG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCGCC**	42	0.24
NOX-D19001-6xDNA-020 (=NOX-D20001)	037	**GCG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCGC**	40	0.42
NOX-D19001-6xDNA-021	038	**CUG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGC**	41	0.70
NOX-D19001-6xDNA-022	039	**UG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGC**	40	3.27

any of G, C, U and A is a ribonucleotide; any of dG, dC, dU and dA is a 2'-desoxyribonucleotide;

nucleotides edged by ☐ represent a C5a-binding motif; **nt**.: number of nucleotides;

KD: Dissociation constant K_D of Spiegelmers (L-nucleic acid), molecules of the indicated sequence were tested as Spiegelmers (L-nucleic acid) measured as surface plasmon resonance on Biacore using direct binding to covalently immobilized human C5a (huC5a)

Fig. 4A

Name	SEQ ID NO.	Sequence: 5′-3′	nt	KD [nM] huC5a
NOX-D19001-6xDNA	**027**	**GCCUG**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	44	0.42
NOX-D19001-6xDNA-023	040	**CG**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCAGC**	40	9.38
NOX-D19001-6xDNA-024	041	**G**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCAGC**	39	8.29
NOX-D19001-6xDNA-025	042	**GCUG**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCAC**	41	5.01
NOX-D19001-6xDNA-026	043	**GCUG**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCC**	40	16.8
NOX-D19001-6xDNA-027	044	**GCUG**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCA**	40	4.71
NOX-D19001-6xDNA-028	045	**CG**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCGC**	39	3.36
NOX-D19001-6xDNA-029	046	**G**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCGC**	38	6.89
NOX-D19001-6xDNA-030	047	**GCG**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCC**	39	16.1
NOX-D19001-6xDNA-032	048	**GCG**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dC**	38	5.58
NOX-D19001-6xDNA-033	049	**GG**AUGdUGGUGGUdGdAAGGUUGUUGGGdUGdUCGACGCA**dCC**	38	5.47

any of G, C, U and A is a ribonucleotide; any of dG, dC, dU and dA is a 2'-desoxyribonucleotide;

Fig. 4B

nucleotides edged by ☐ represent a C5a-binding motif; **nt.**: number of nucleotides;

KD: Dissociation constant K_D of Spiegelmers (L-nucleic acid), molecules of the indicated sequence were tested as Spiegelmers (L-nucleic acid) measured as surface plasmon resonance on Biacore using direct binding to covalently immobilized human C5a (huC5a)

Fig. 4B (continuation)

Name	SEQ ID NO.	Sequence: 5′-3′	KD [nM]	IC_{50} [nM]
NOX-D19001-020	55	GCGAUGUGGUGGUGAAGGGUUGUUGGGUGUCGACGCACGC	11.3	9.4
1 RNA-to-DNA substitutions:				
NOX-D19001-1xDNA-020	56	GCGAUGdUGGUGGUGAAGGGUUGUUGGGUGUCGACGCACGC	1.34	3
2 RNA-to-DNA substitutions:				
NOX-D19001-2xDNA-020	57	GCGAUGdUGGUGGUGAAGGGUUGUUGGGdUGUCGACGCACGC	0.73	2.2
3 RNA-to-DNA substitutions:				
NOX-D19001-3xDNA-020	58	GCGAUGdUGGUGGUGAAGGGUUGUUGGGdUGdUCGACGCACGC	0.91	3.7
NOX-D19001-2dU-1dC-020 (=NOX-D21001)	59	GCGAUGdUGGUGGUGAAGGGUUGUUGGGdUGUCGACGCAdCGC	0.82	0.6
4 RNA-to-DNA substitutions:				
NOX-D19001-3dU-1dC-020	60	GCGAUGdUGGUGGUGAAGGGUUGUUGGGdUGdUCGACGCAdCGC	0.87	0.6

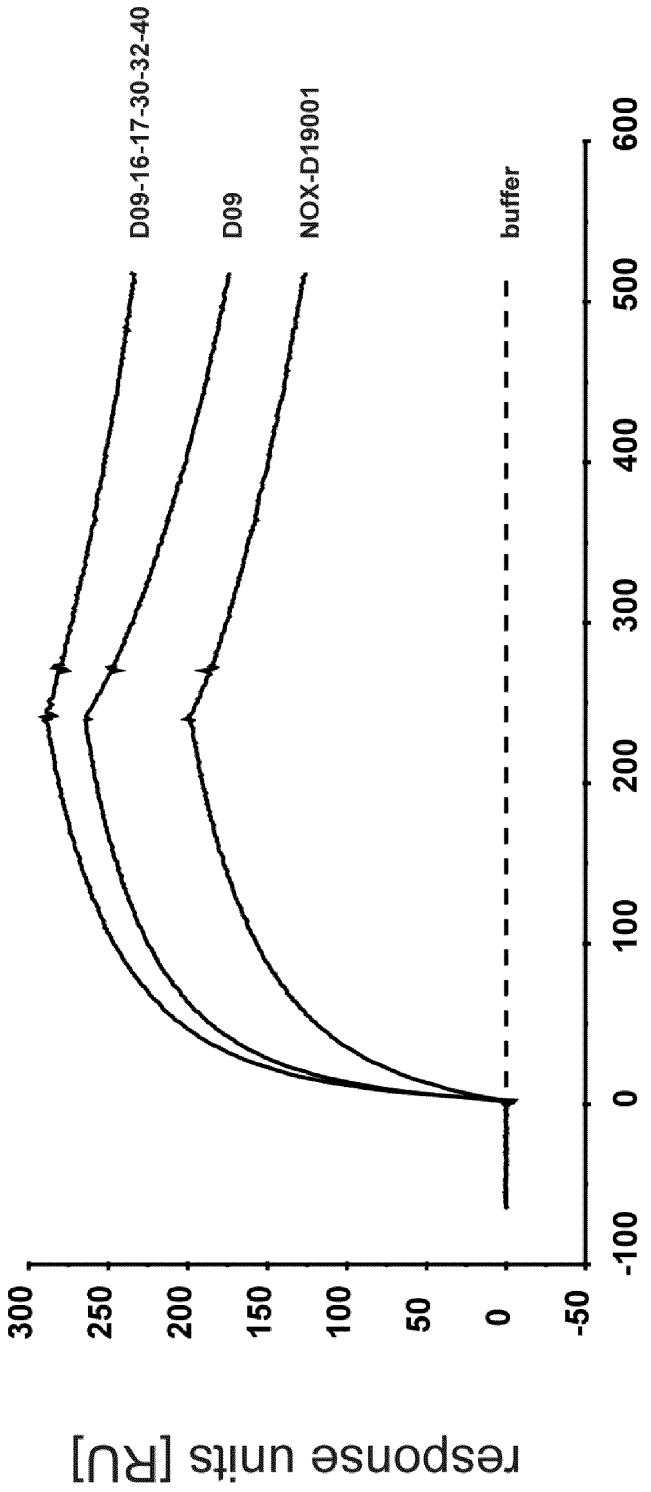
any of G, C, U and A is a ribonucleotide; any of dG, dC, dU and dA is a 2'-desoxyribonucleotide;

nucleotides edged by ☐ represent a C5a-binding motif;

KD: Dissociation constant K_D of Spiegelmers (L-nucleic acid), molecules of the indicated sequence were tested as Spiegelmers (L-nucleic acid) measured as surface plasmon resonance on Biacore using direct binding to covalently immobilized human C5a (huC5a)

IC_{50}: Half maximal inhibitory concentration (IC50) of Spiegelmers (L-nucleic acid), molecules of the indicated sequence were tested as Spiegelmers in a cell culture *in vitro* chemotaxis assay to inhibit C5a

Fig. 5



	K_D [nM]
NOX-D19001	1.38
NOX-D19001-D09	0.71
NOX-D19001-D09-16-17-30-32-40	0.36

Fig. 6

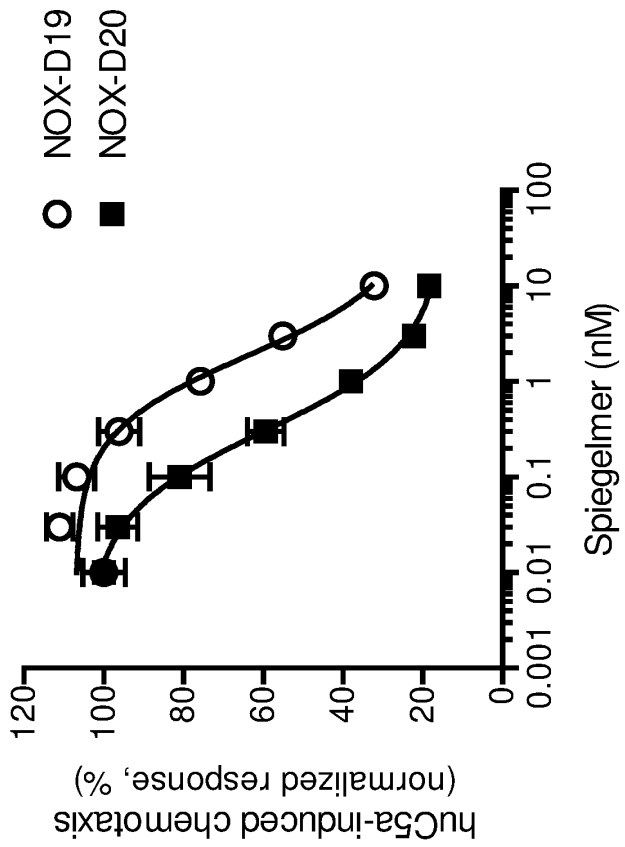

NOX-D19
NOX-D20
huC5a-induced chemotaxis
(normalized response, %)
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
Spiegelmer (nM)

Fig. 7

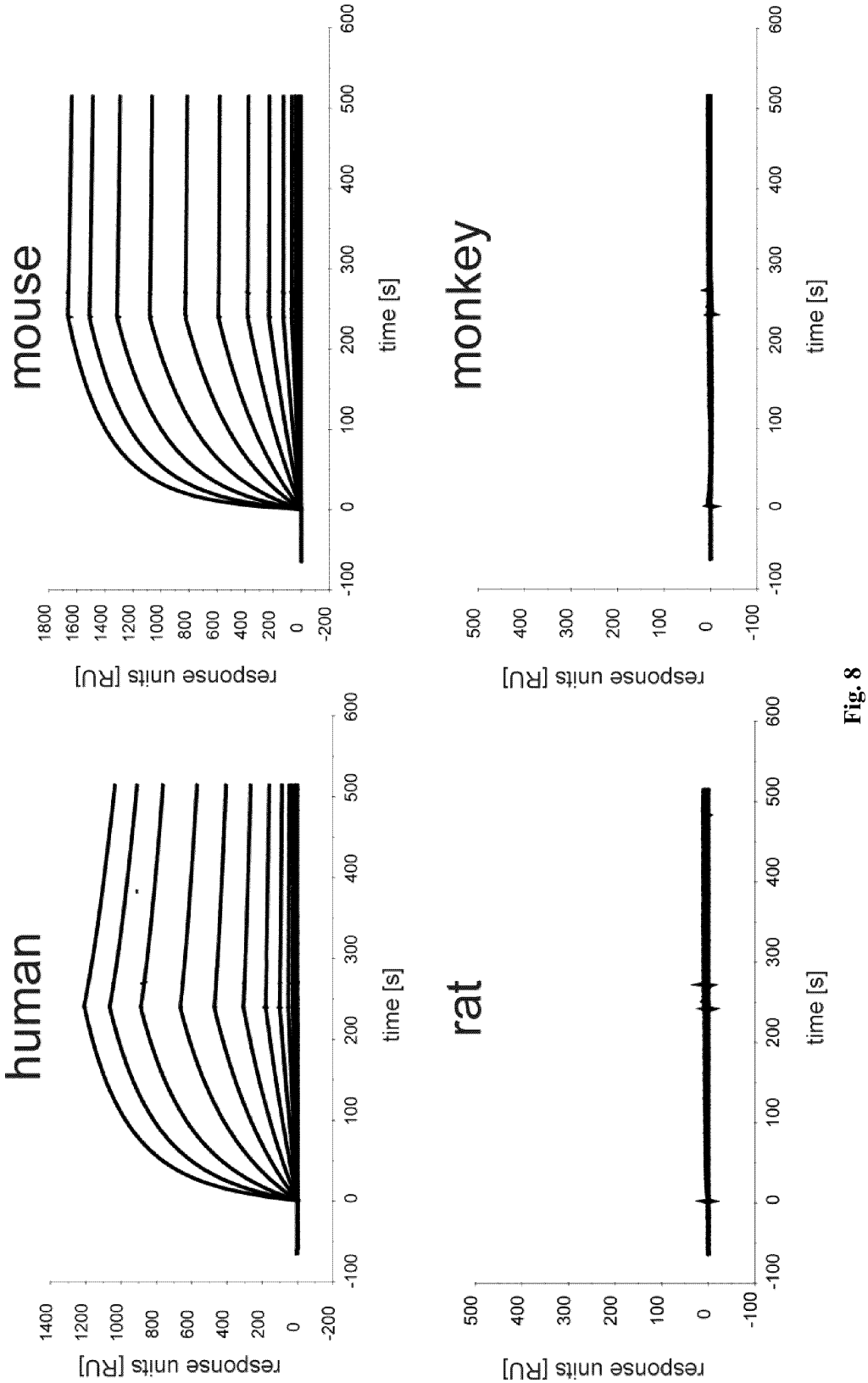
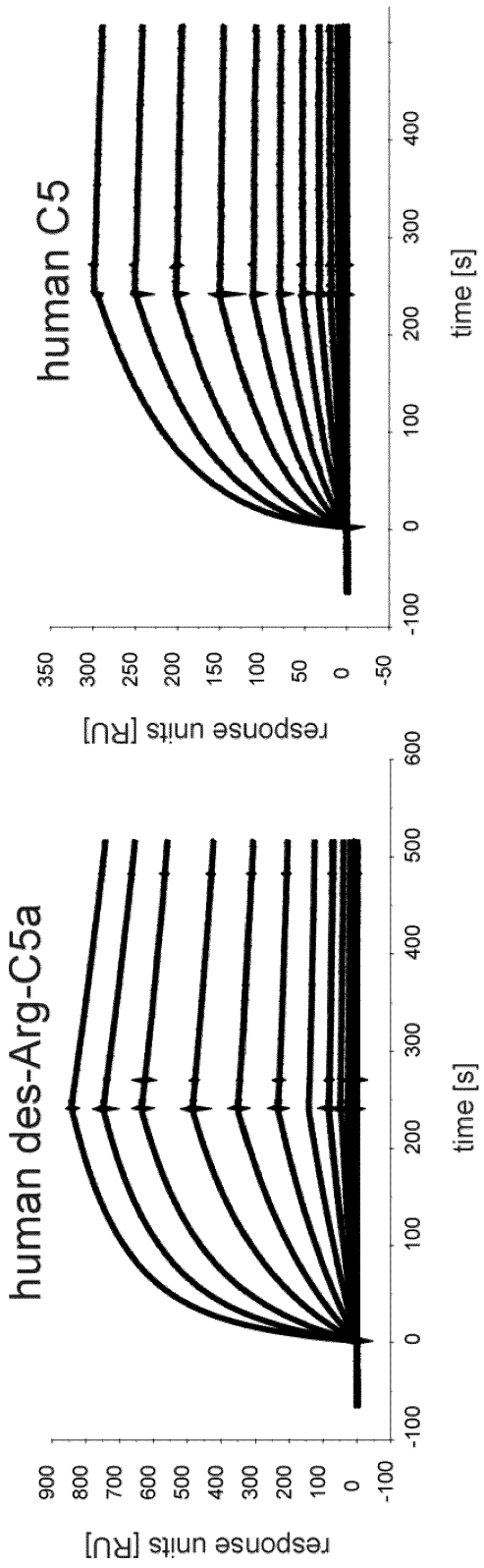

mouse
monkey
human
rat
response units [RU]
time [s]
1800
1600
1400
1200
1000
800
600
400
200
0
-200
500
400
300
200
100
-100
-100
0
100
200
300
400
500
600

Fig. 8

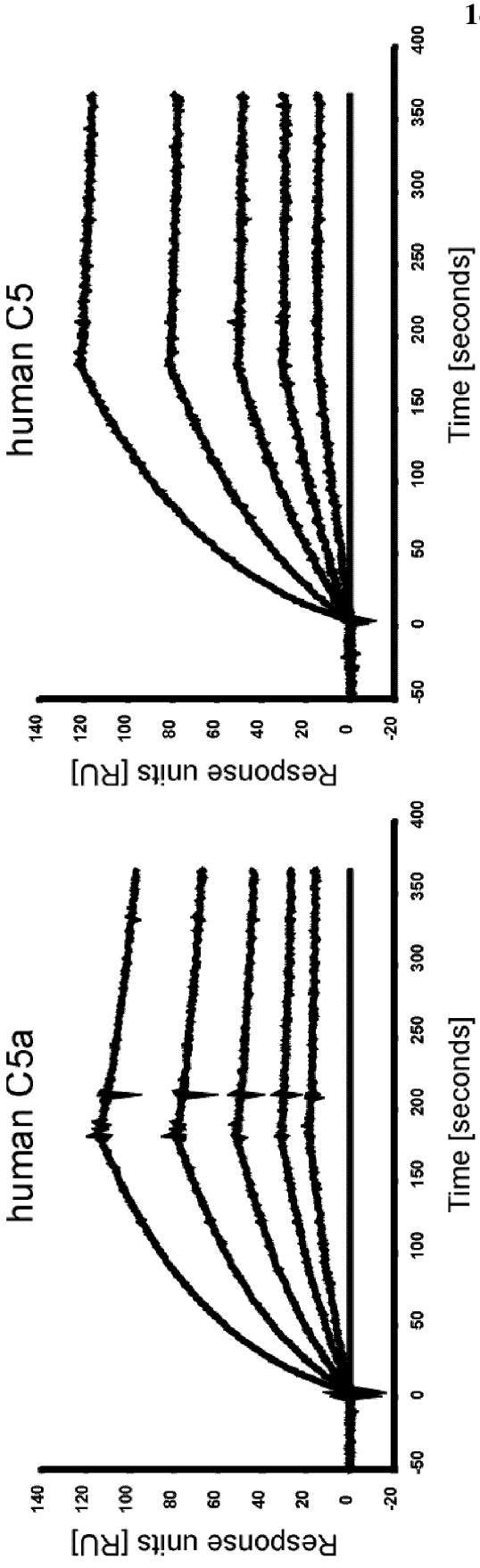
NOX-D20 binding to:	K_D [pM]
mouse C5a	19.1
human C5a	299
rat C5a	--
rhesus monkey C5a	--

Fig. 8 continuation



NOX-D20 binding to:	K_D [pM]
human desArg-C5a	316
human C5	164

Fig. 9



NOX-D21 binding to:	K_D [pM]
human C5a	815
human C5	413
human des-ArgC5a	854
mouseC5a	29.4
mouse des-ArgC5a	27.6

Fig. 10

Alignment of C5a from selected species

human: TLQKKIEEIAAKYKHSVVKKCCYDGACVNNDETCEQRAARISLGPRCIKAFTECCVVASQLRANISHKDMQLGR
[SEQ ID NO: 050]

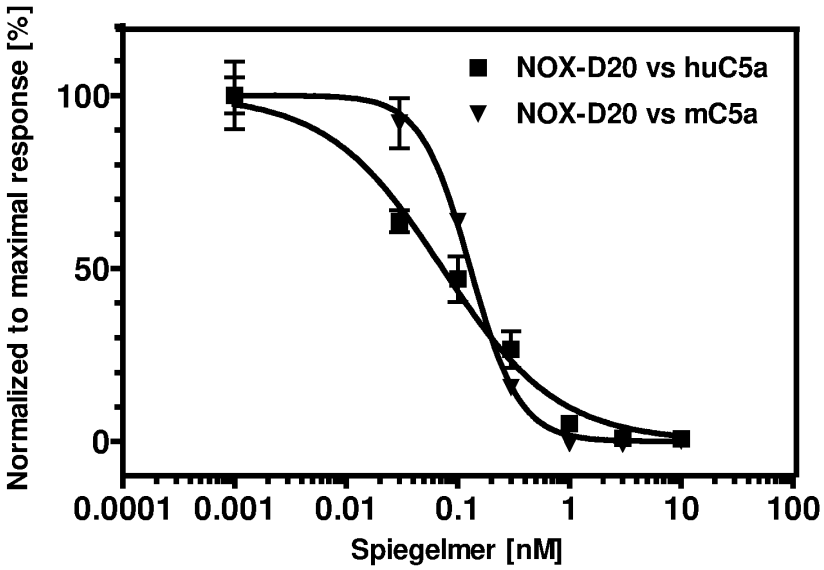
rhesus: MLQEKIEEIAAKYKHLVVKKCCYDGVRINHDETCEQRAARISVGPRCVKAFTECCVVASQLRANNSHKDLQLGR
[SEQ ID NO: 054]

mouse: NLHLLRQKIEEQAAKYKHSVPKKCCYDGARVNFYETCEERVARVTIGPLCIRAFNECCTIANKIRKESPHKPVQLGR
[SEQ ID NO: 052]

rat: DLQLLHQKVEEQAAKYKHRVPKKCCYDGARENKYETCEQRVARVTIGPHCIRAFNECCTIADKIRKESHHKGMLLGR
[SEQ ID NO: 051]

Fig. 11

A


Normalized to maximal response [%]
100
50
0
NOX-D20 vs huC5a
NOX-D20 vs mC5a
0.0001 0.001 0.01 0.1 1 10 100
Spiegelmer [nM]

B

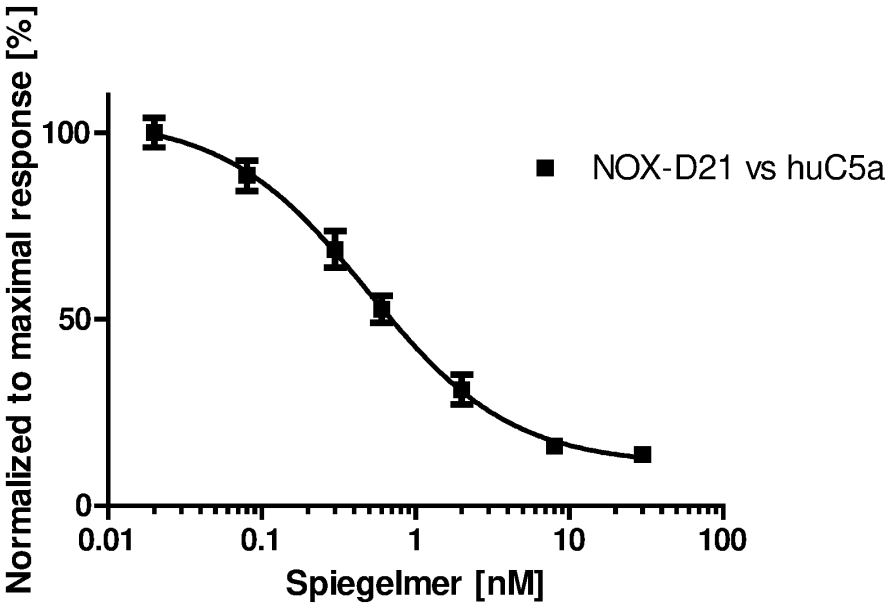

Normalized to maximal response [%]
100
50
0
NOX-D21 vs huC5a
0.01 0.1 1 10 100
Spiegelmer [nM]

Fig. 12

Name	Sequence: 5′-3′	Binding (KD) Human C5a	Inhibition (IC50) Human C5a
AON-D21$_{VD19}$	GCCUGAUGUGGUGGUGAAGGGUUGUUGGGUGUCGACGCAcAGGC	1.38 nM	1.9 nM
AON-D21$_{VD20}$	GCGAUGdUGGUGGUGdGdAAGGGUUGUUGGGdUGdUCGACGCAdCGC	0.299 nM	0.28 nM
AON-D21	GCGAUGdUGGUGGUGAAGGGUUGUUGGGdUGdUCGACGCAdCGC	0.815 nM	0.476 nM

Fig. 13

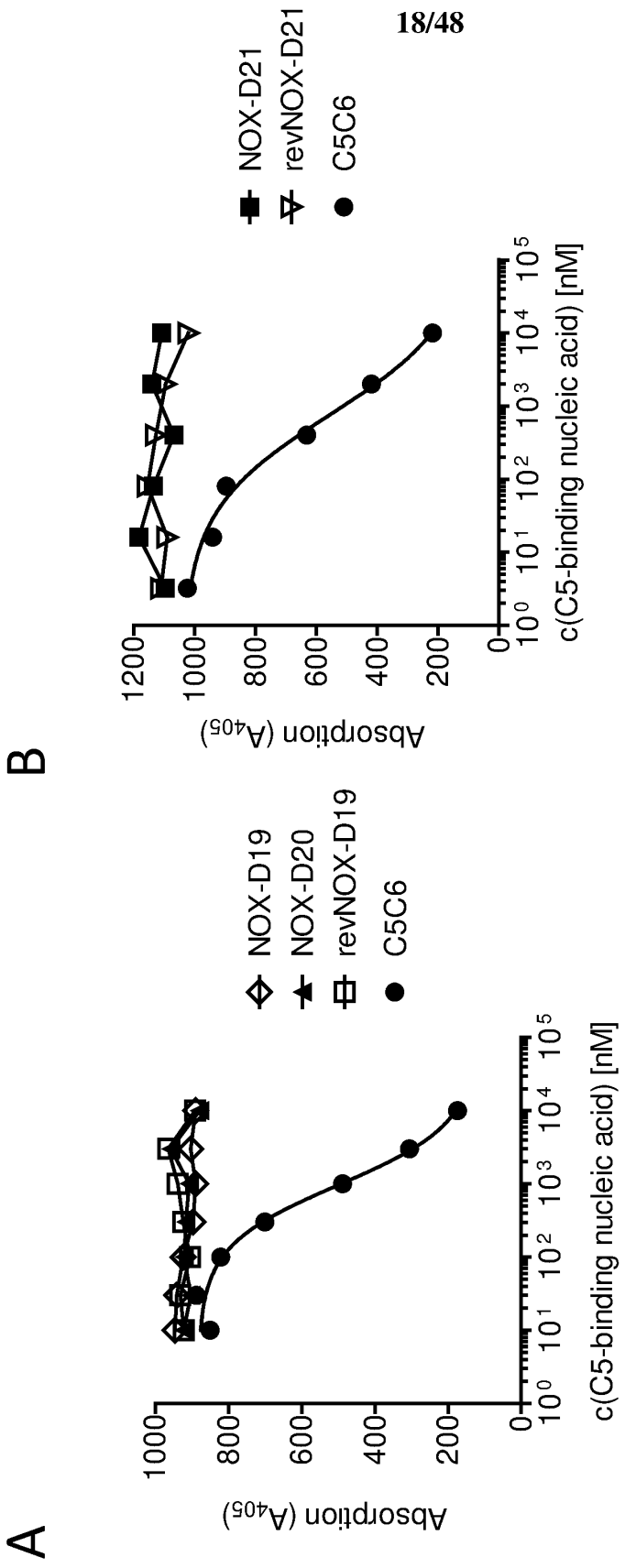

A
B
Absorption (A_{405})
c(C5-binding nucleic acid) [nM]
NOX-D19
NOX-D20
revNOX-D19
C5C6
NOX-D21
revNOX-D21
C5C6

Fig. 14

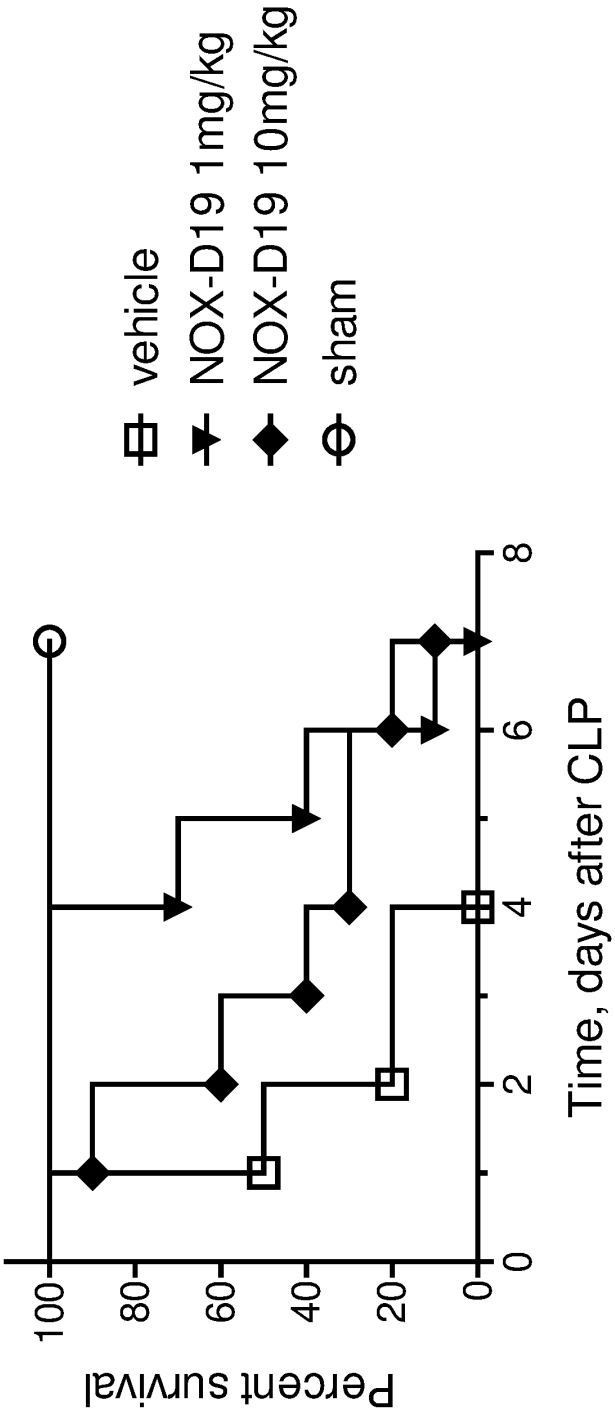

vehicle
NOX-D19 1mg/kg
NOX-D19 10mg/kg
sham
Percent survival
100
80
60
40
20
0
0
2
4
6
8
Time, days after CLP

Fig. 15

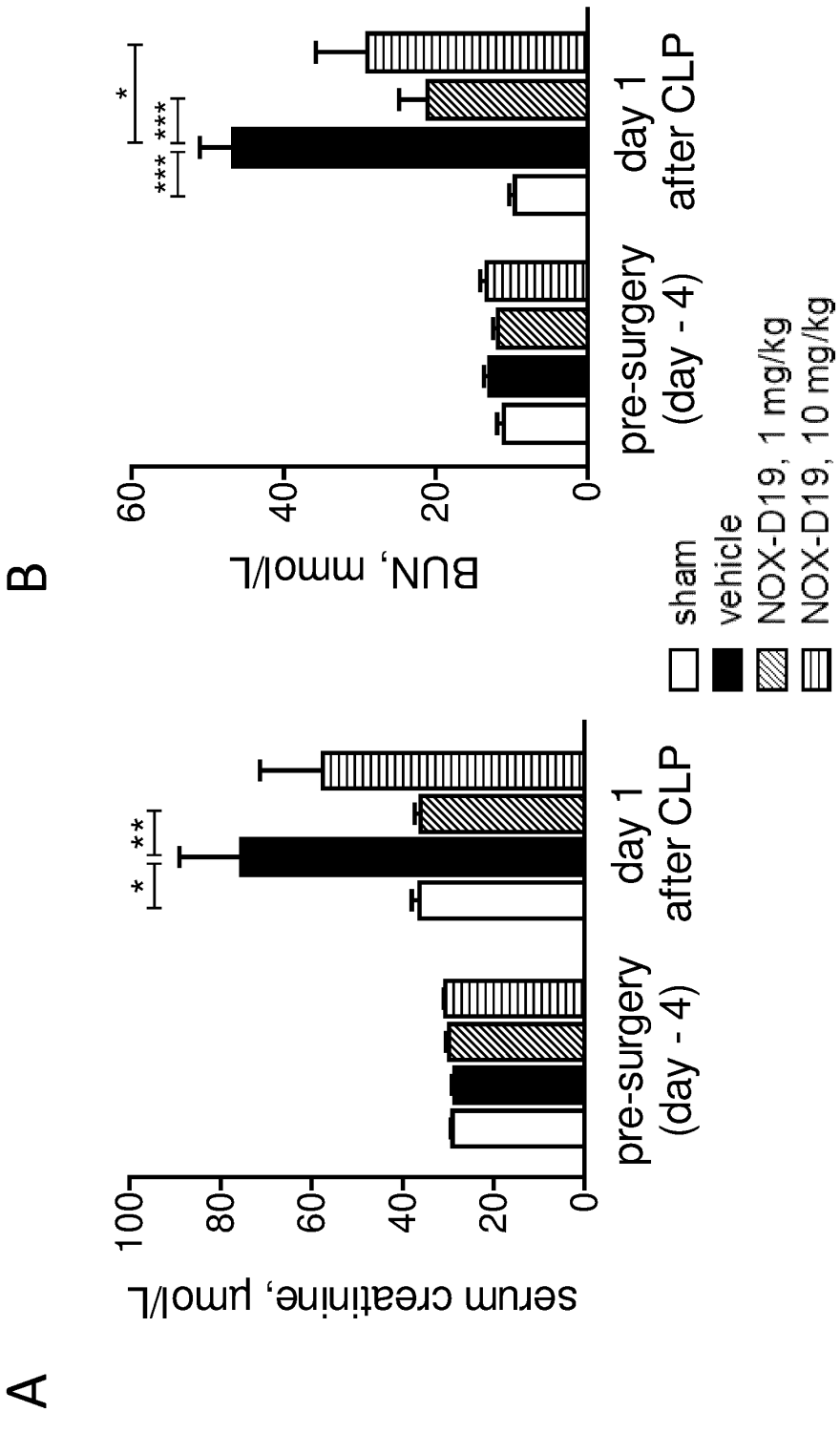

A
serum creatinine, µmol/L
100
80
60
40
20
0
* **
pre-surgery (day - 4)
day 1 after CLP
B
BUN, mmol/L
60
40
20
0
*** ***
*
pre-surgery (day - 4)
day 1 after CLP
sham
vehicle
NOX-D19, 1 mg/kg
NOX-D19, 10 mg/kg

Fig. 16

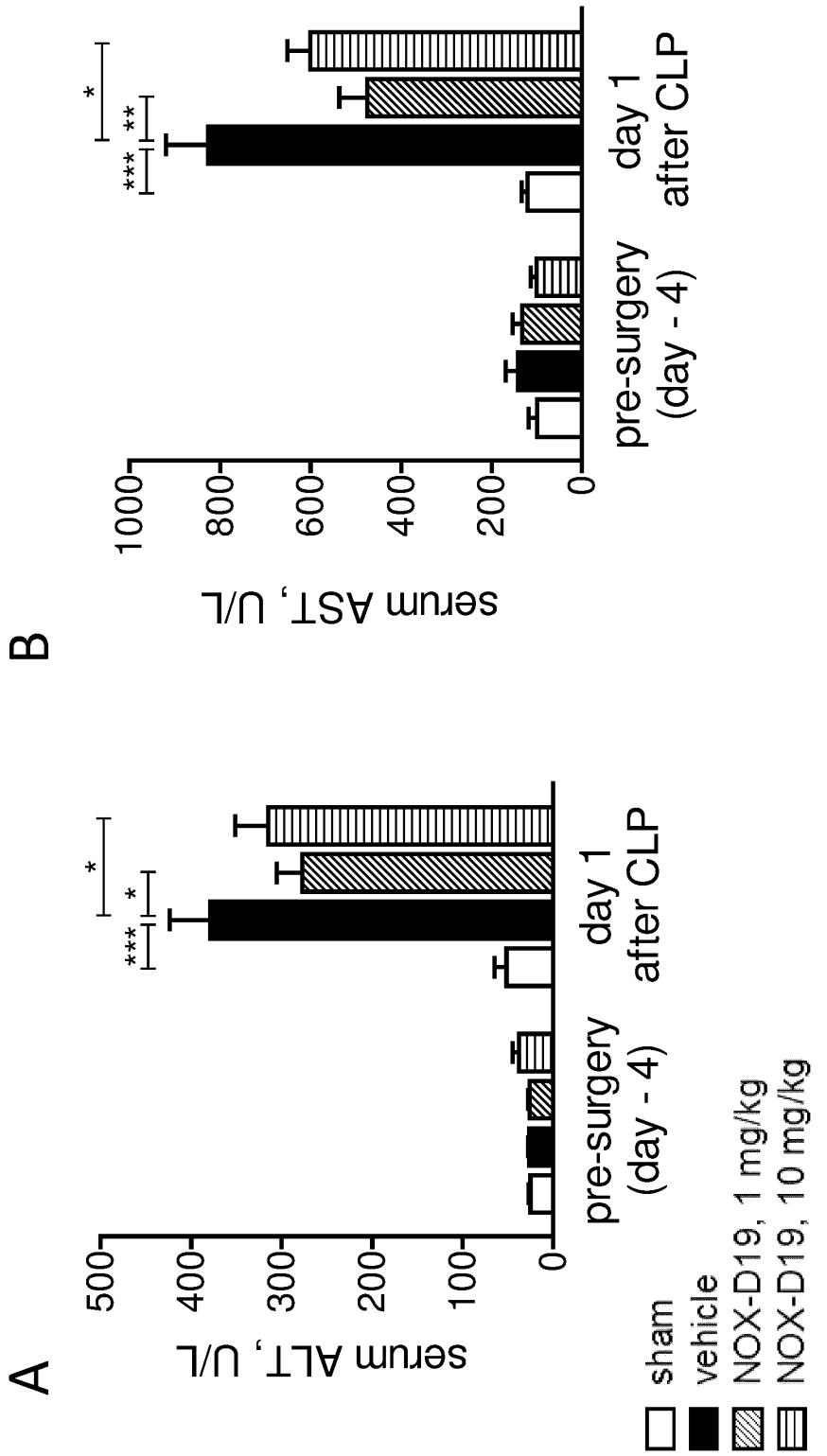

A
serum ALT, U/L
500
400
300
200
100
0
*
***
*
pre-surgery (day - 4)
day 1 after CLP
sham
vehicle
NOX-D19, 1 mg/kg
NOX-D19, 10 mg/kg
B
serum AST, U/L
1000
800
600
400
200
0
*
***
**
pre-surgery (day - 4)
day 1 after CLP

Fig. 17

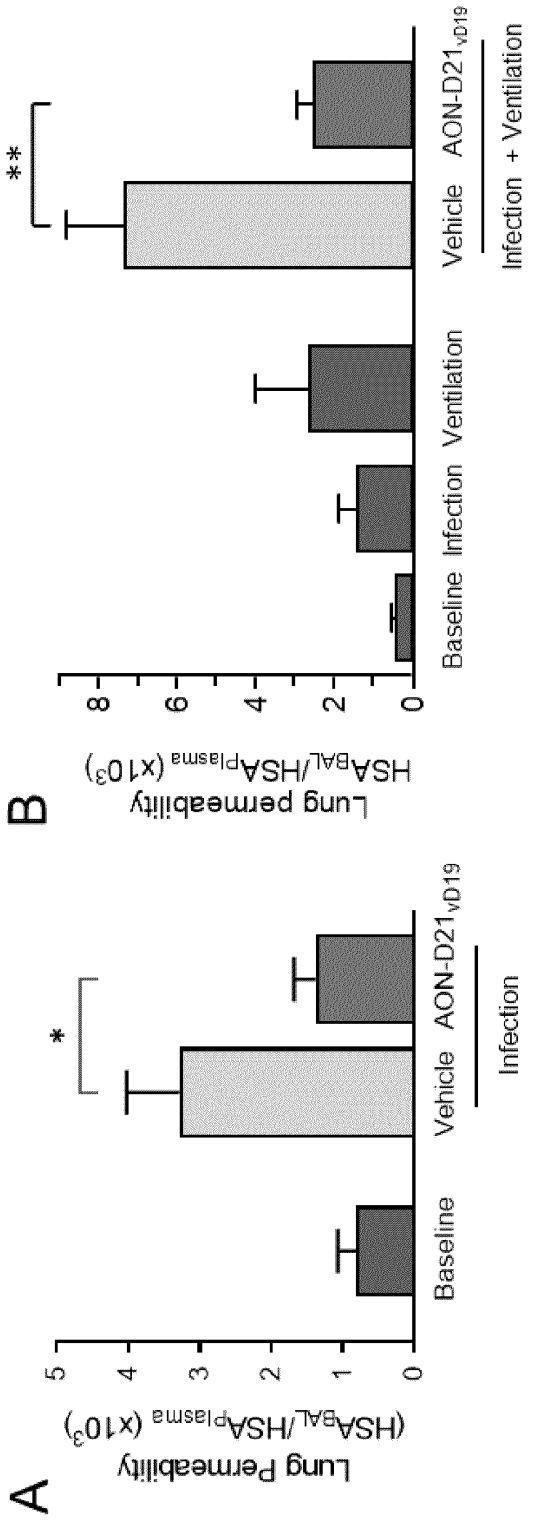

A
Lung Permeability
(HSA$_{BAL}$/HSA$_{Plasma}$ (x10^3))
0
1
2
3
4
5
*
Baseline
Vehicle
AON-D21$_{vD19}$
Infection
B
Lung permeability
HSA$_{BAL}$/HSA$_{Plasma}$ (x10^3)
0
2
4
6
8
**
Baseline
Infection
Ventilation
Vehicle
AON-D21$_{vD19}$
Infection + Ventilation

Fig. 18

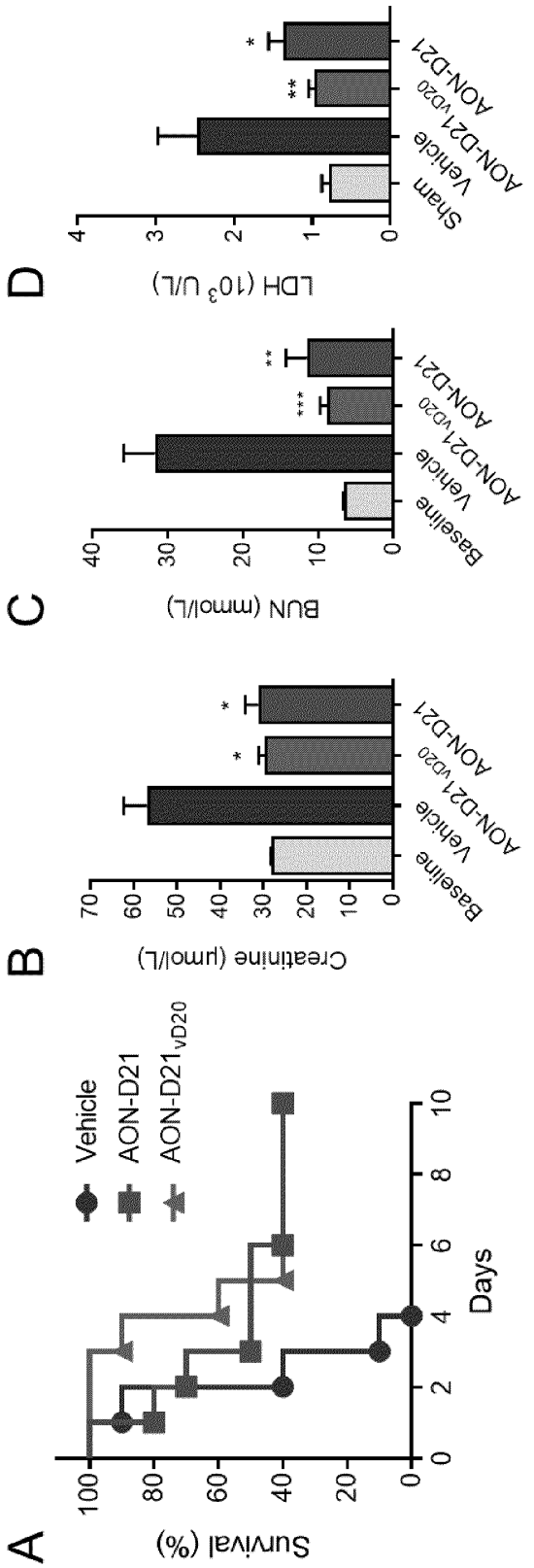

A
Survival (%)
Days
Vehicle
AON-D21
AON-D21vD20
B
Creatinine (μmol/L)
C
BUN (mmol/L)
D
LDH (10³ U/L)
Baseline
Vehicle
AON-D21vD20
AON-D21
Sham

Fig. 19

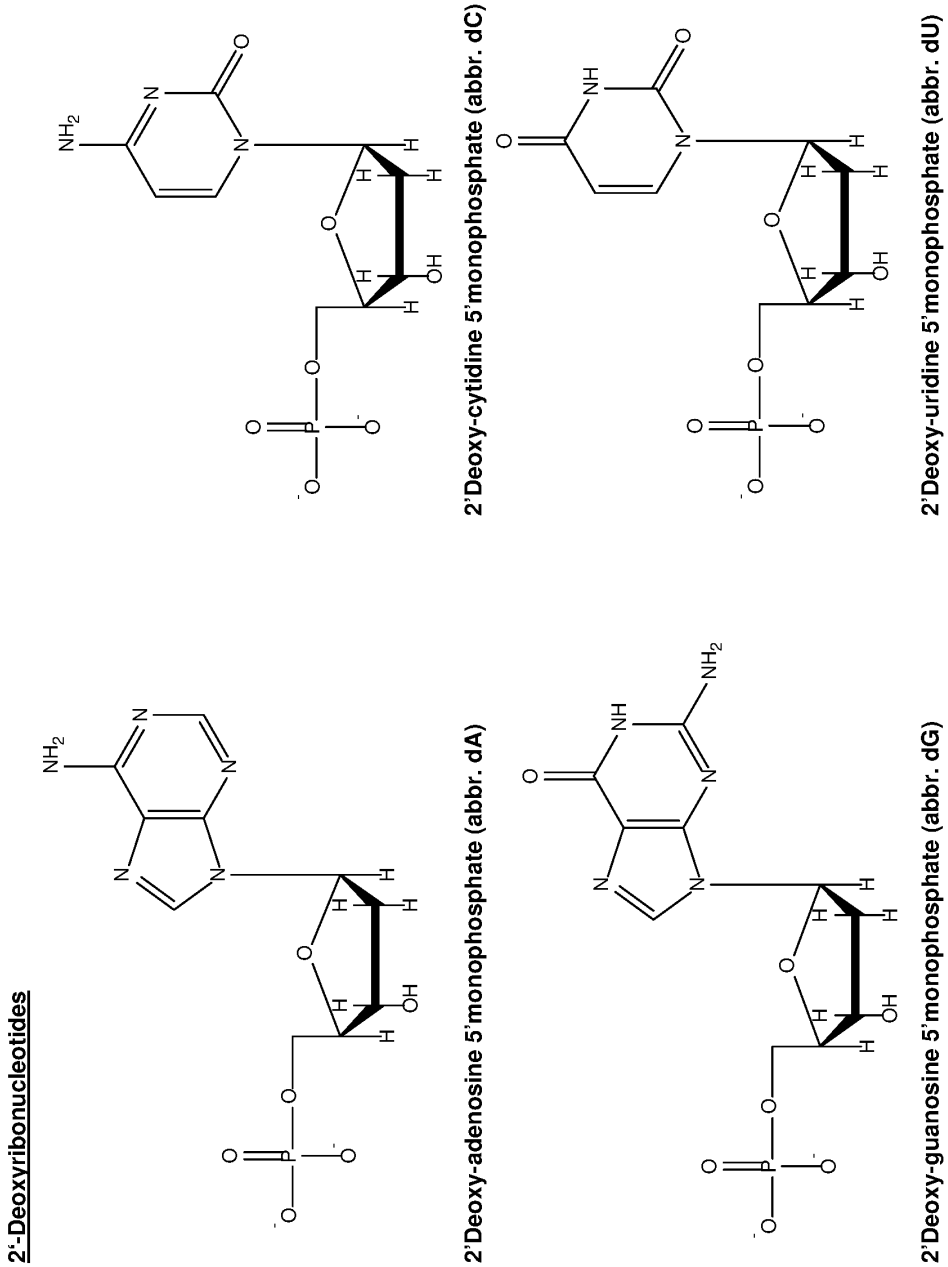

2'-Deoxyribonucleotides
2'Deoxy-adenosine 5'monophosphate (abbr. dA)
2'Deoxy-cytidine 5'monophosphate (abbr. dC)
2'Deoxy-guanosine 5'monophosphate (abbr. dG)
2'Deoxy-uridine 5'monophosphate (abbr. dU)

Fig. 20

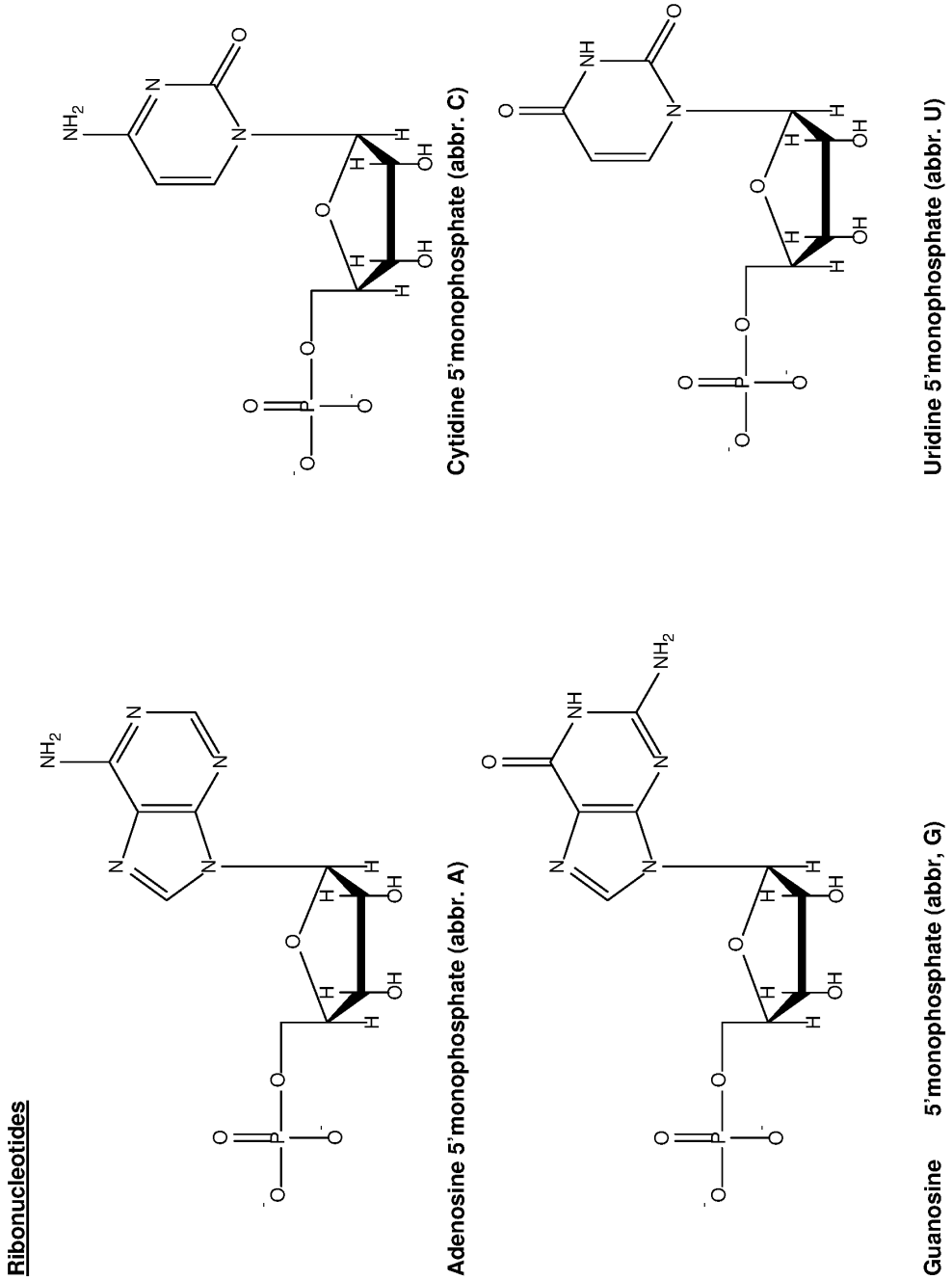

Ribonucleotides
Cytidine 5'monophosphate (abbr. C)
Uridine 5'monophosphate (abbr. U)
Adenosine 5'monophosphate (abbr. A)
Guanosine 5'monophosphate (abbr, G)

Fig. 21

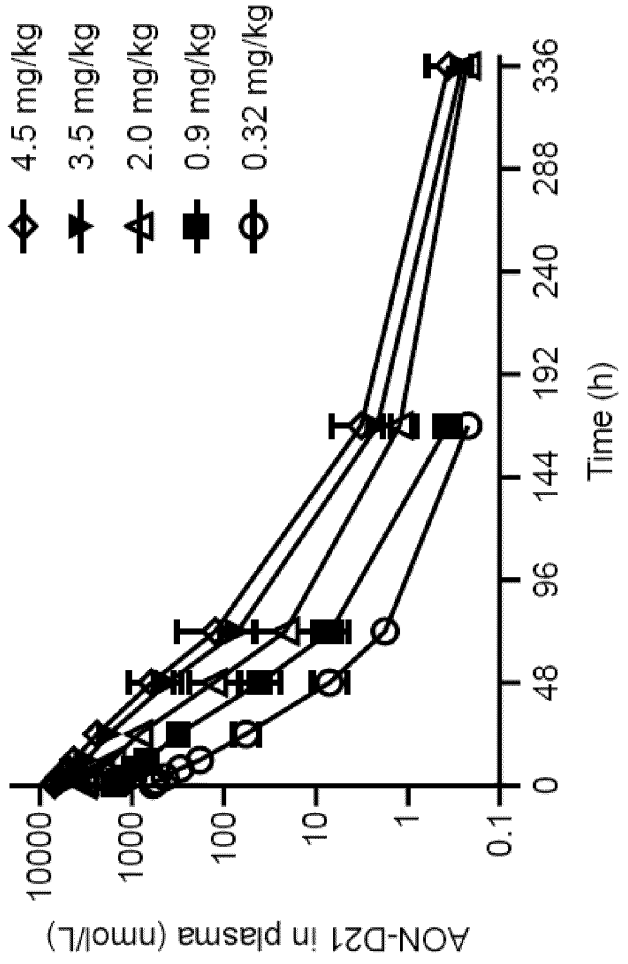

4.5 mg/kg
3.5 mg/kg
2.0 mg/kg
0.9 mg/kg
0.32 mg/kg
AON-D21 in plasma (nmol/L)
10000
1000
100
10
1
0.1
0
48
96
144
192
240
288
336
Time (h)

Fig. 22

Parameter	Statistics	Treatment				
		0.32 mg/kg SD (n=6)	0.9 mg/kg SD (n=5)	2.0 mg/kg SD (n=6)	3.5 mg/kg SD (n=6)	4.5 mg/kg SD (n=6)
C_{max}	Mean	601	1,580	3,440	5,480	7,280
(nmol/L)	SD	96.3	228	389	941	1,040
	CV%	16.0	14.4	11.3	17.2	14.3
	Minimum	412	1,270	2,800	4,300	6,060
	Median	631	1,670	450	5,580	7,260
	Maximum	671	1,850	3,950	6,470	8,540
DN C_{max}	Mean	1,880	1,760	1,720	1,570	1,620
(nmol/L)/(mg/kg)	SD	301	253	194	269	231
$t_{½}$	Mean	7.56	9.13	10.2	12.7	14.3
0-48h	SD	0.893	1.28	1.55	1.84	3.20
(h)	CV%	11.8	14.0	15.2	14.5	22.4
	Minimum	6.29	7.20	8.47	10.3	10.5
	Median	7.39	9.43	10.2	13.4	13.1
	Maximum	8.76	10.7	11.9	14.3	19.2

C_{max}: Maximum observed plasma concentration over the sampling interval

DN C_{max}: Dose-normalized C_{max} calculated as C_{max} divided by the applied dose (in mg AON-D21/kg body weight)

t½ 0-48h: Elimination half-life with the first 48 hours after dosing.

Fig. 23

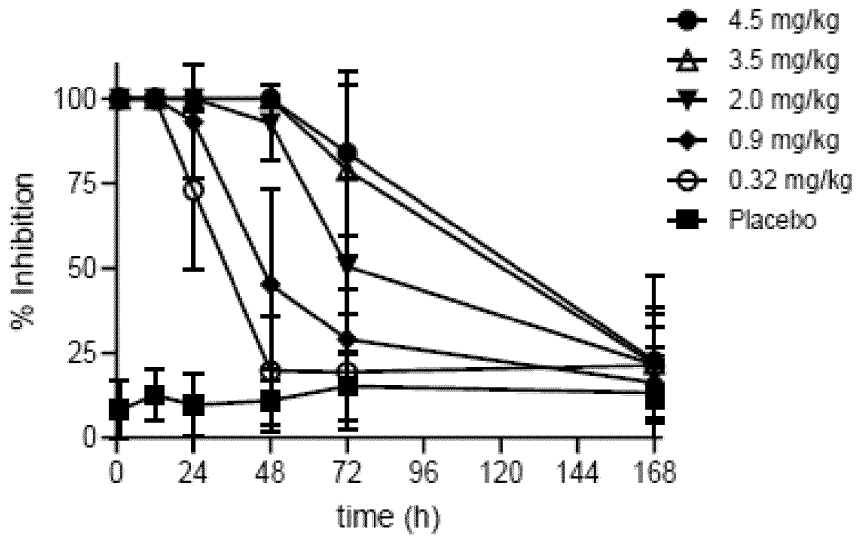

4.5 mg/kg
3.5 mg/kg
2.0 mg/kg
0.9 mg/kg
0.32 mg/kg
Placebo
% Inhibition
100
75
50
25
0
0
24
48
72
96
120
144
168
time (h)

Fig. 24

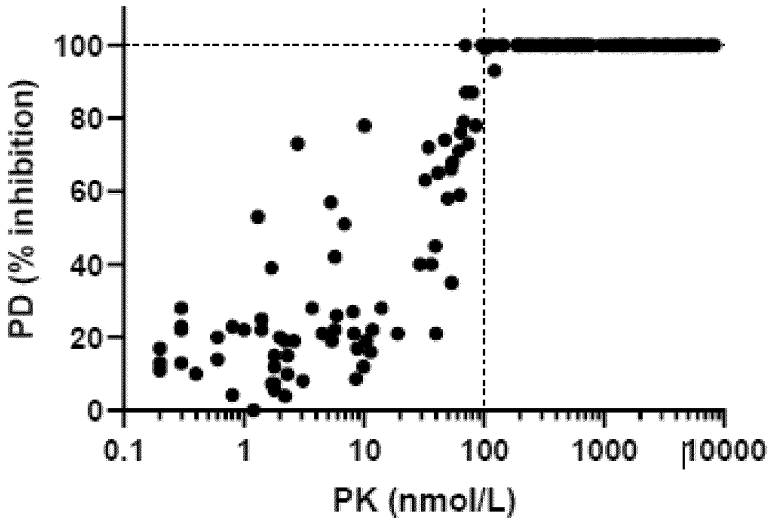


Fig. 25 A

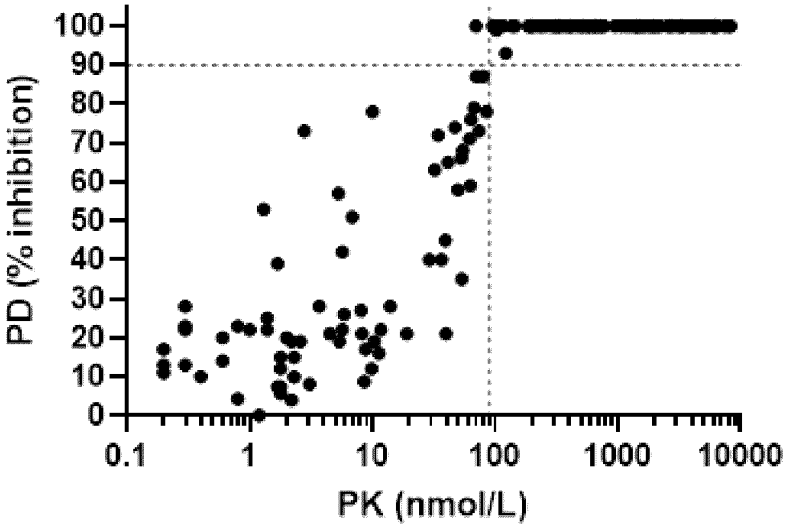


Fig. 25 B

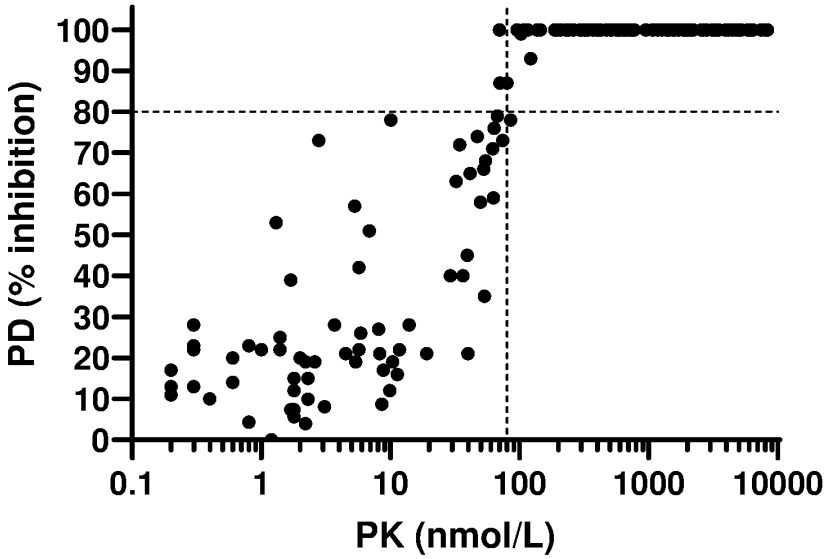


Fig. 25 C

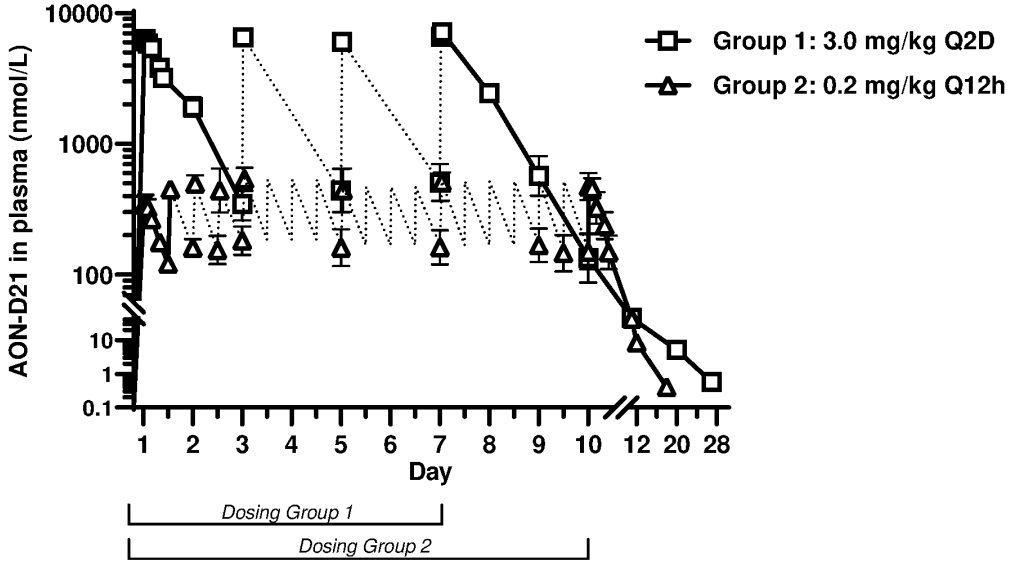


Fig. 26

Parameter	Statistics	Treatment			
		3.0 mg/kg Q2D (n=6)		0.2 mg/kg Q12h (n=6)	
		1st Dose (Day 1)	4th Dose (Day 7)	1st Dose (Day 1)	19st Dose (Day 10)
C_{max} (nmol/L)	Mean	6,420	7,300	364	504
	SD	673	835	58	79
	CV%	10.5	11.4	15.9	15.6
	Minimum	5,510	5,970	280	402
	Median	6,580	7,540	392	527
	Maximum	7,270	7,990	412	602
DN C_{max} (nmol/L)/(mg/kg)	Mean	2,139	N.A.	1,820	N.A.
	SD	224		290	
t_{max} (h)	Minimum	0,92	0.52	0.25	0.25
	Median	1	1	0.625	0.625
	Maximum	2	1	1	1
$t_{½}$ 0-tau (h)	Mean	11.5	No data	6.95	6.82
	SD	1.4		1.28	0.87
	CV%	12.2		18.3	12.7
	Minimum	9.53		5.73	6.05
	Median	11.6		6.55	6.58
	Maximum	13.6		9.34	8.28
		Day 3 (pre 2nd dose)	Day 7 (pre 4th dose)	Day 1 (pre 2nd dose)	Day 10 (pre 19th dose)
C_{trough} (nmol/L)	Mean	356	525	122	155
	SD	87	142	13.7	49.2
	CV%	24.5	27.0	11.2	31.7
	Minimum	205	276	105	95
	Median	383	554	121	154
	Maximum	443	677	138	242

C_{max}: Maximum observed plasma concentration over the sampling interval

DN C_{max}: Dose-normalized C_{max} calculated as Cmax divided by the applied dose (in mg/kg)

t_{max}: Time corresponding to occurrence of C_{max}

t½ 0-tau: Elimination half-life with the dosing interval (48h for dose group 1, 12h for dose group 2).

C_{trough}: Measured concentration at the end of a dosing interval (taken directly before next administration)

Fig. 27

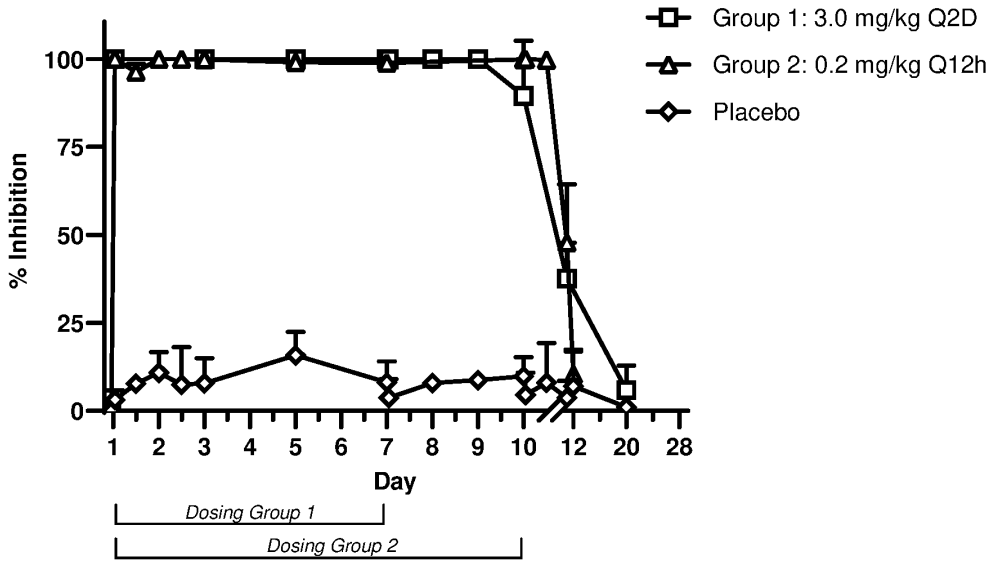


Fig. 28

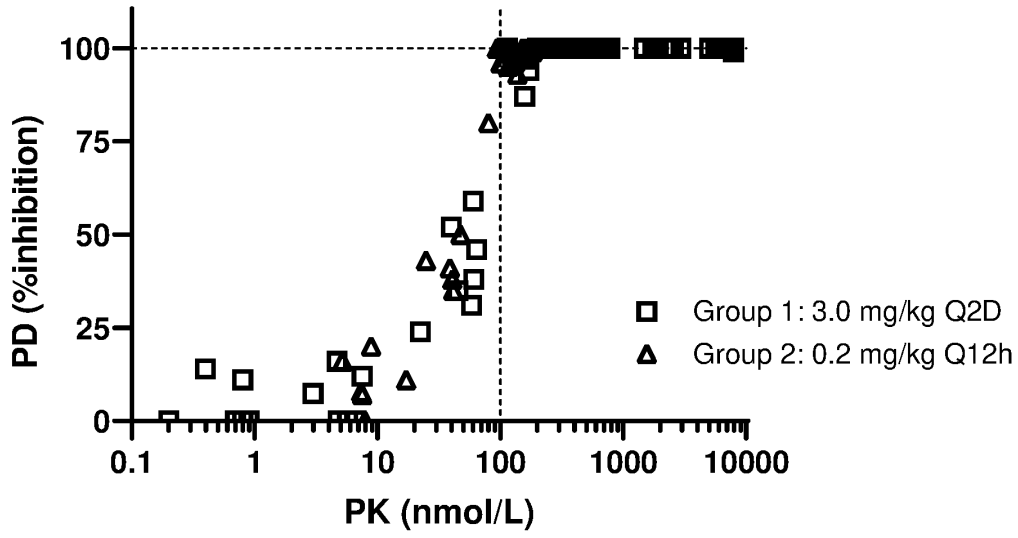


Fig. 29 A

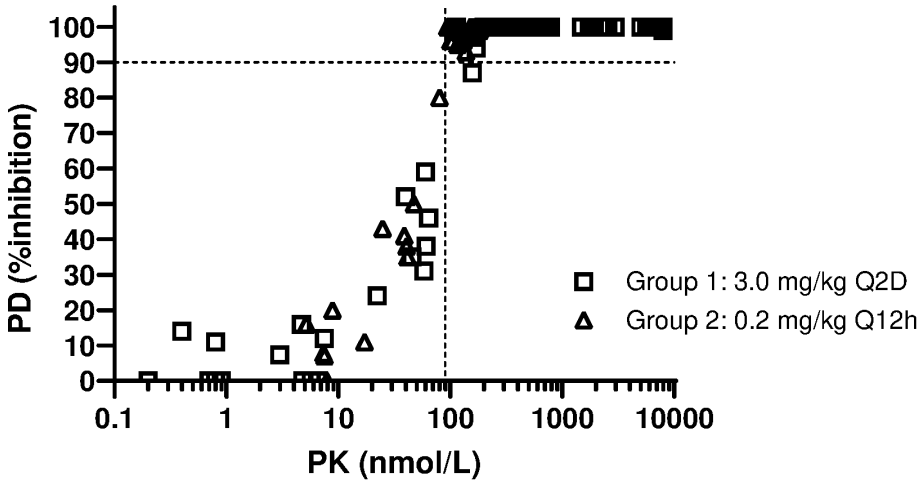


Fig. 29 B

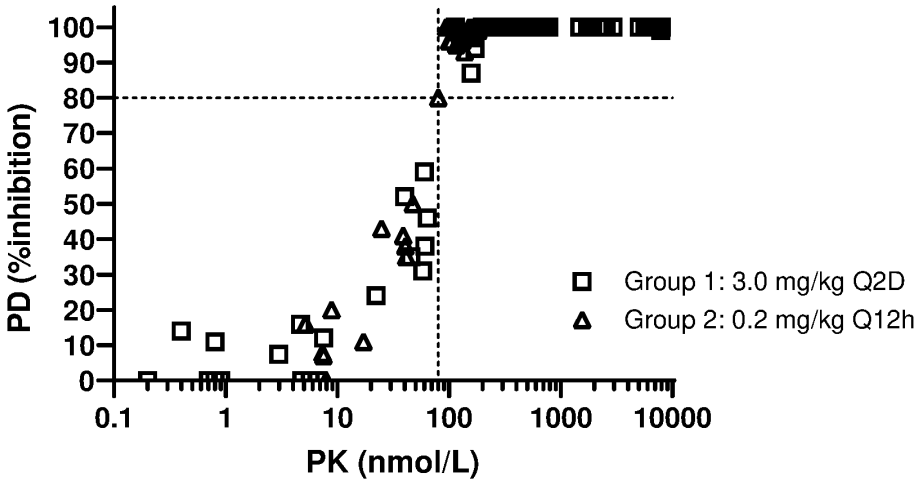


Fig. 29 C

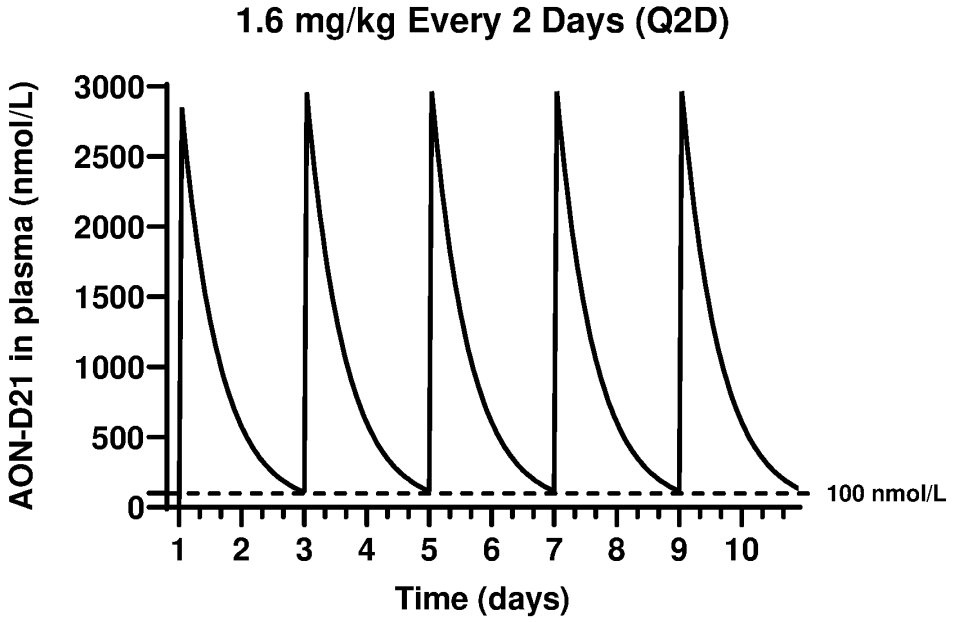

1.6 mg/kg Every 2 Days (Q2D)
AON-D21 in plasma (nmol/L)
3000
2500
2000
1500
1000
500
0
100 nmol/L
1 2 3 4 5 6 7 8 9 10
Time (days)

Fig. 30

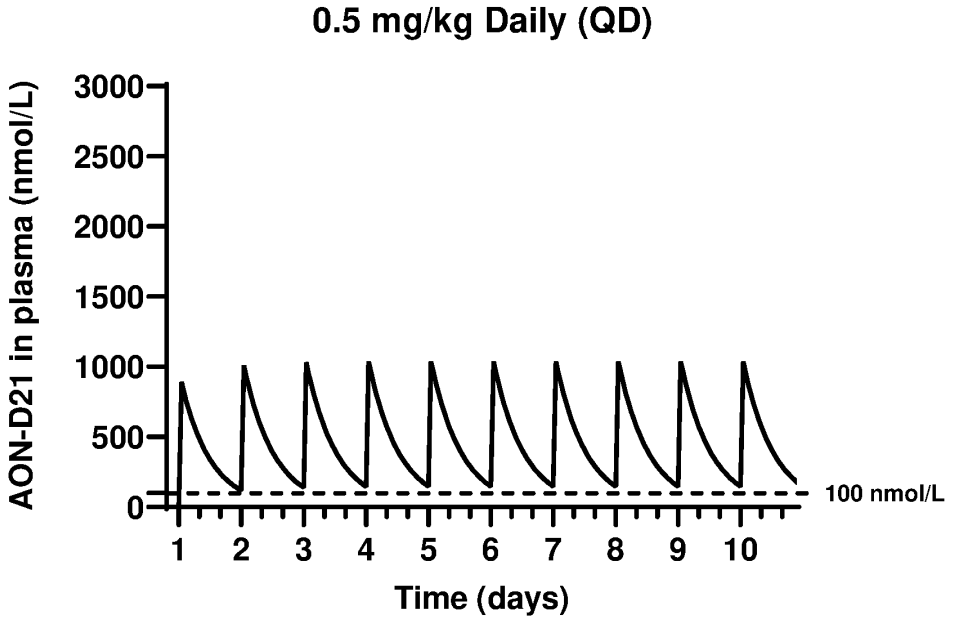

0.5 mg/kg Daily (QD)
AON-D21 in plasma (nmol/L)
3000
2500
2000
1500
1000
500
0
100 nmol/L
1 2 3 4 5 6 7 8 9 10
Time (days)

Fig. 31

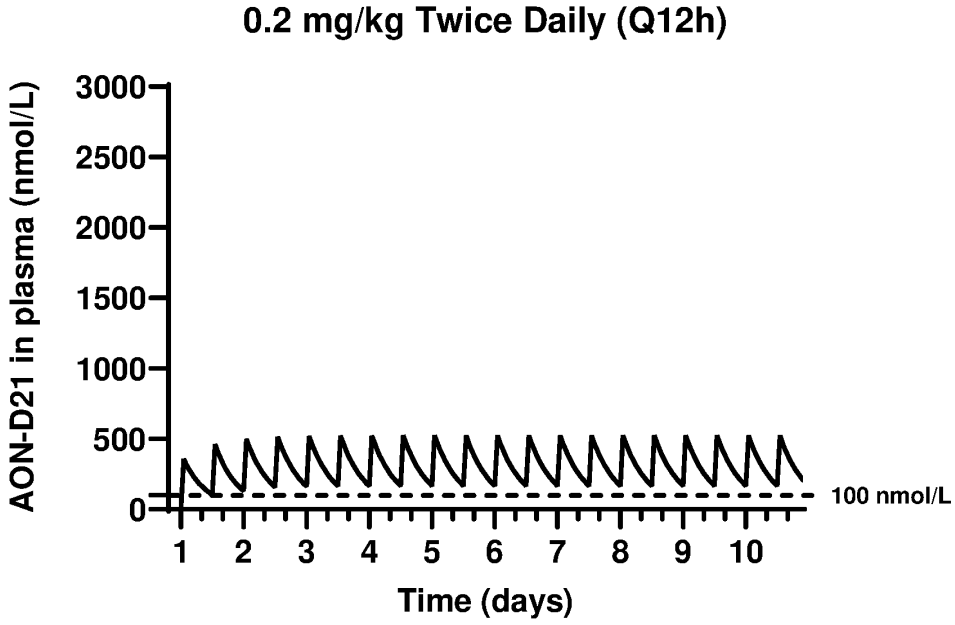

0.2 mg/kg Twice Daily (Q12h)
AON-D21 in plasma (nmol/L)
3000
2500
2000
1500
1000
500
0
100 nmol/L
1 2 3 4 5 6 7 8 9 10
Time (days)

Fig. 32

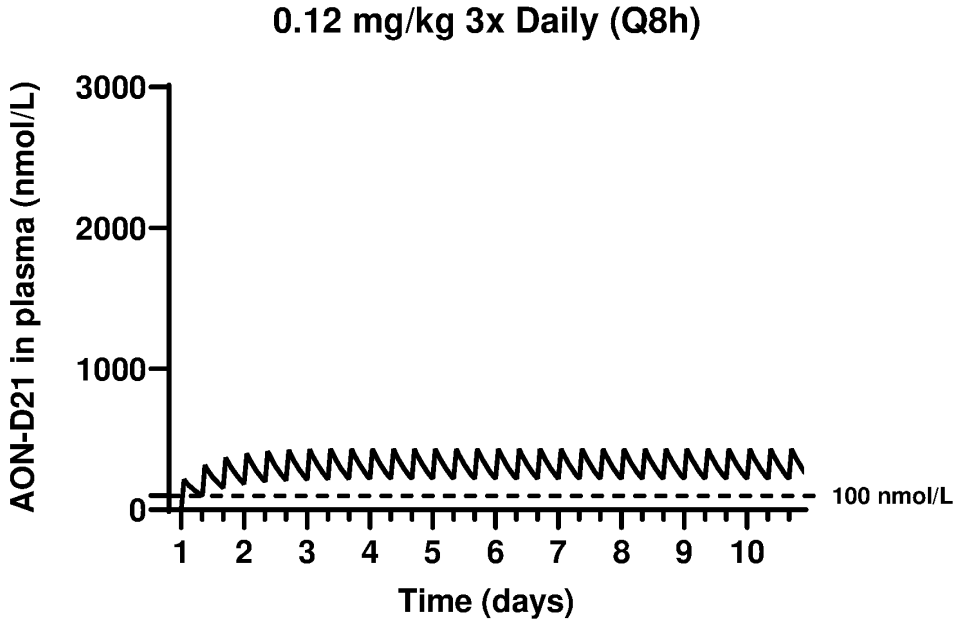
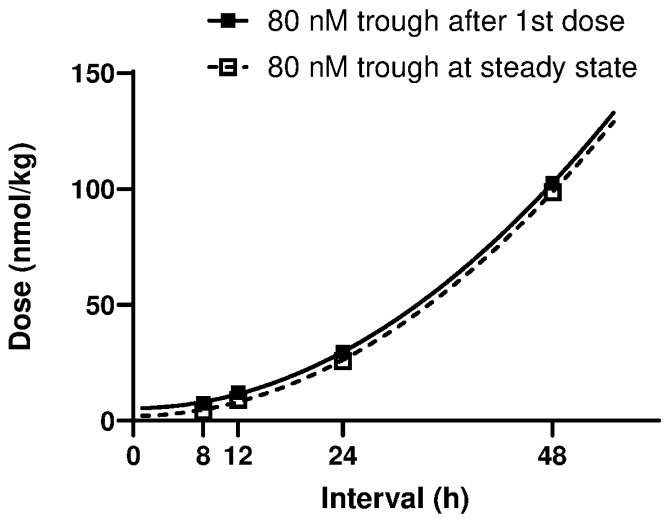

0.12 mg/kg 3x Daily (Q8h)
AON-D21 in plasma (nmol/L)
3000
2000
1000
0
100 nmol/L
1 2 3 4 5 6 7 8 9 10
Time (days)

Fig. 33

A


80 nM trough after 1st dose
80 nM trough at steady state
Dose (nmol/kg)
150
100
50
0
0
8
12
24
48
Interval (h)

B

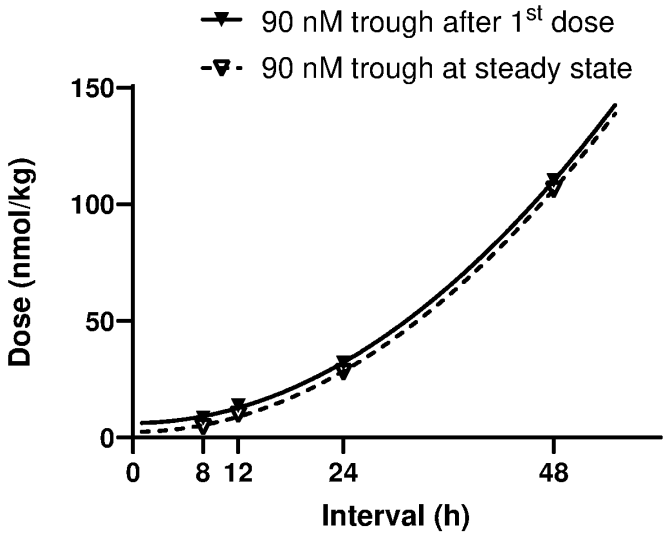
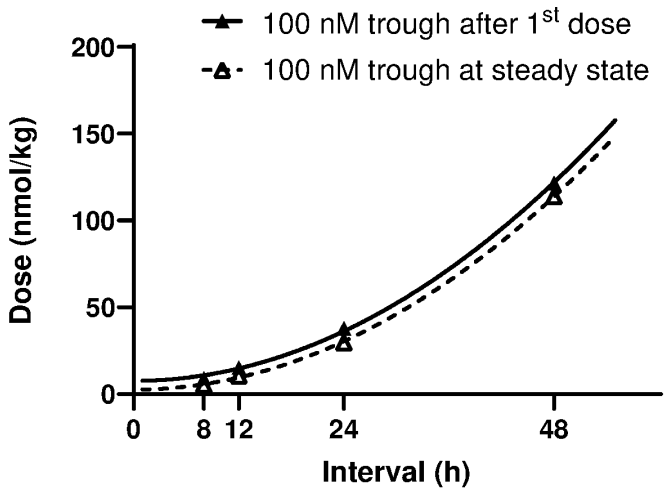

90 nM trough after 1st dose
90 nM trough at steady state
Dose (nmol/kg)
150
100
50
0
0
8
12
24
48
Interval (h)

Fig. 34

C



D

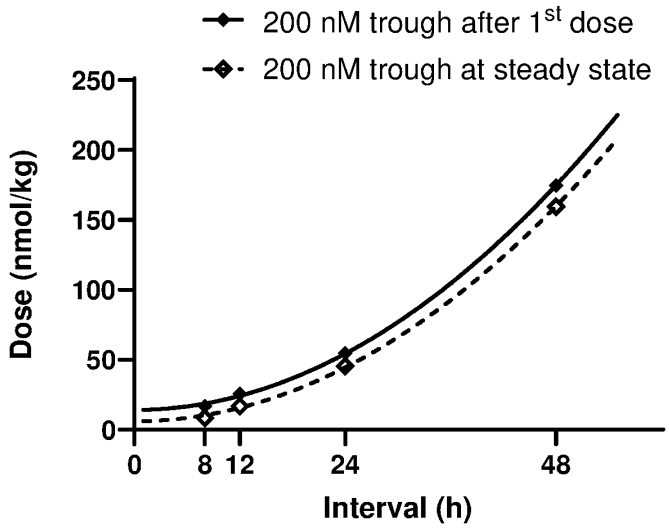


Fig. 34 (continuation)

E

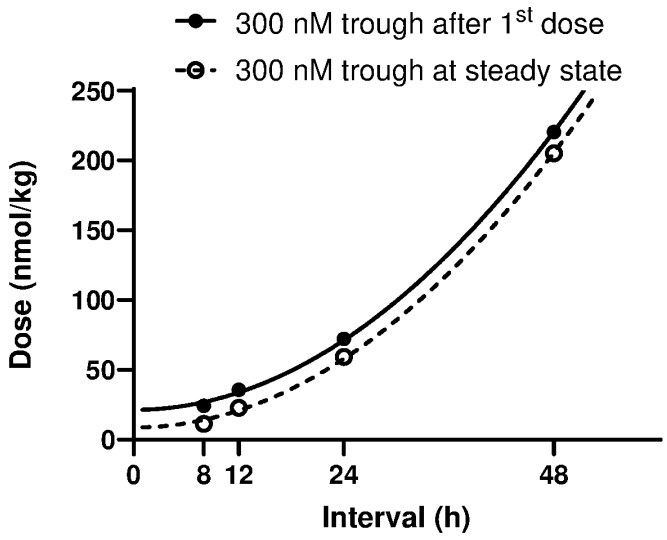


Fig. 34 (continuation)

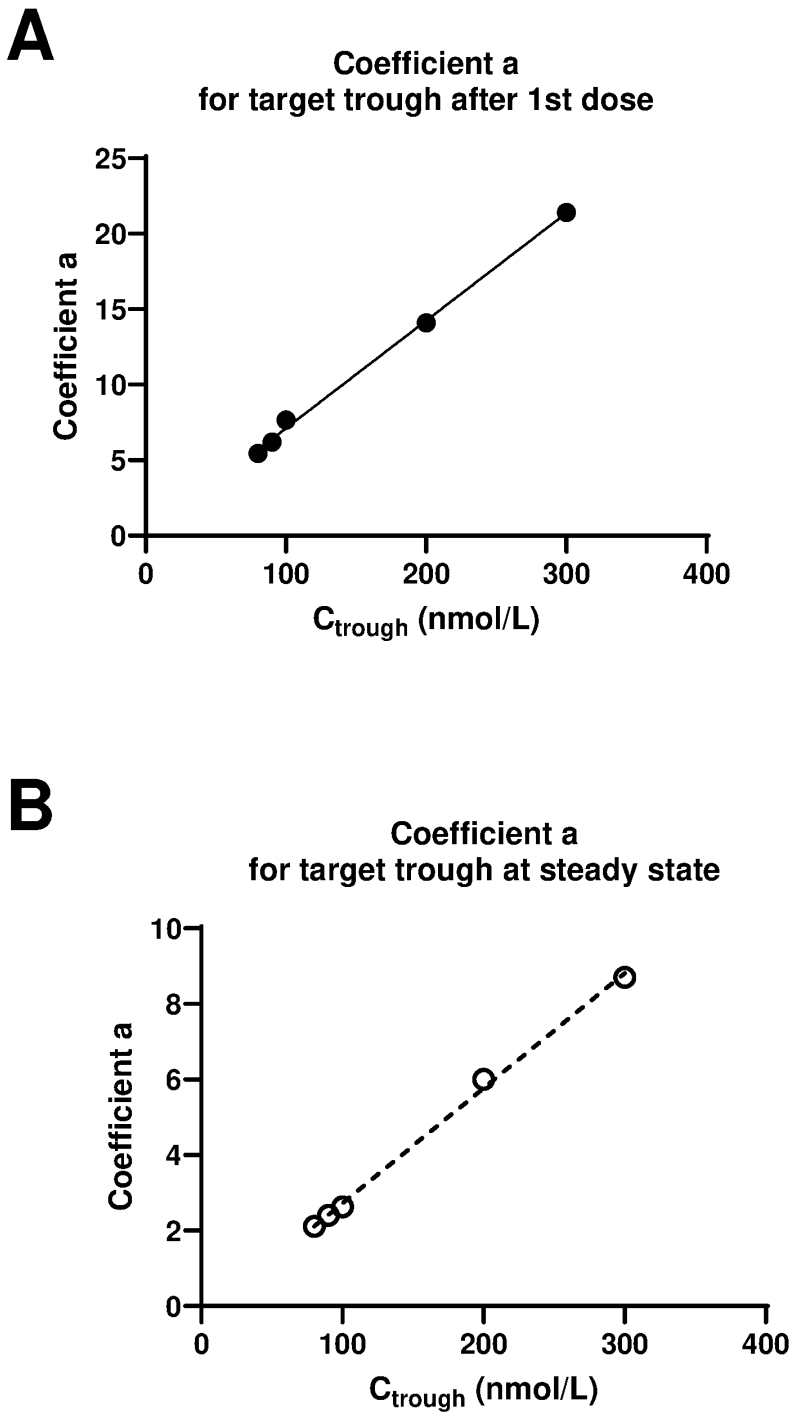
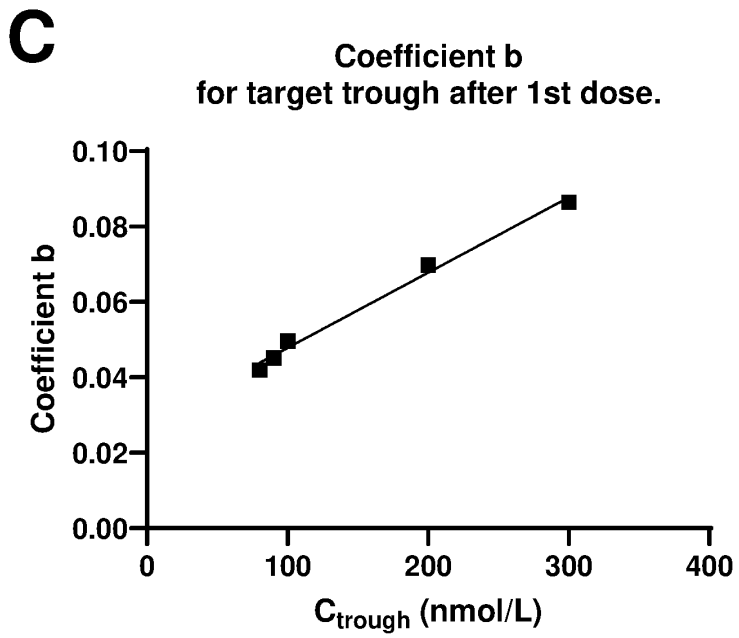

A
Coefficient a
for target trough after 1st dose
Coefficient a
25
20
15
10
5
0
0
100
200
300
400
Ctrough (nmol/L)
B
Coefficient a
for target trough at steady state
Coefficient a
10
8
6
4
2
0
0
100
200
300
400
Ctrough (nmol/L)

Fig. 35



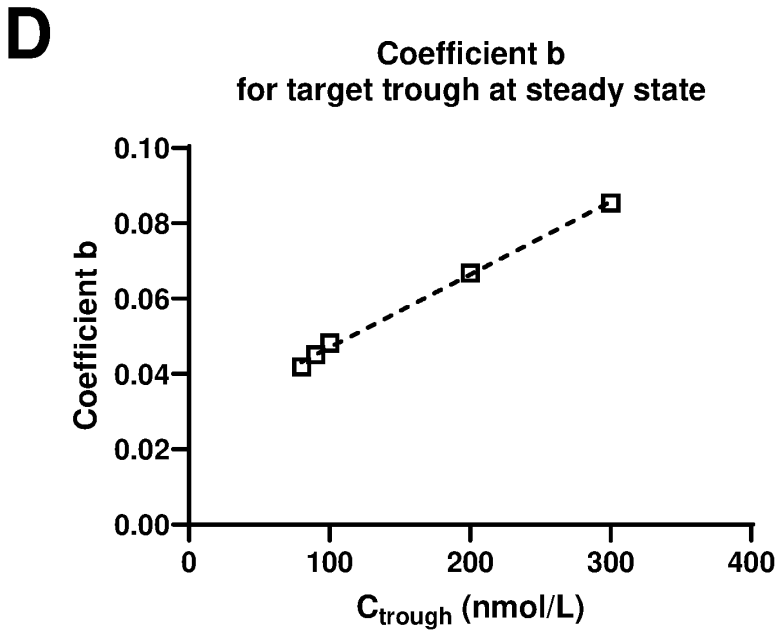


Fig. 35 (continuation)

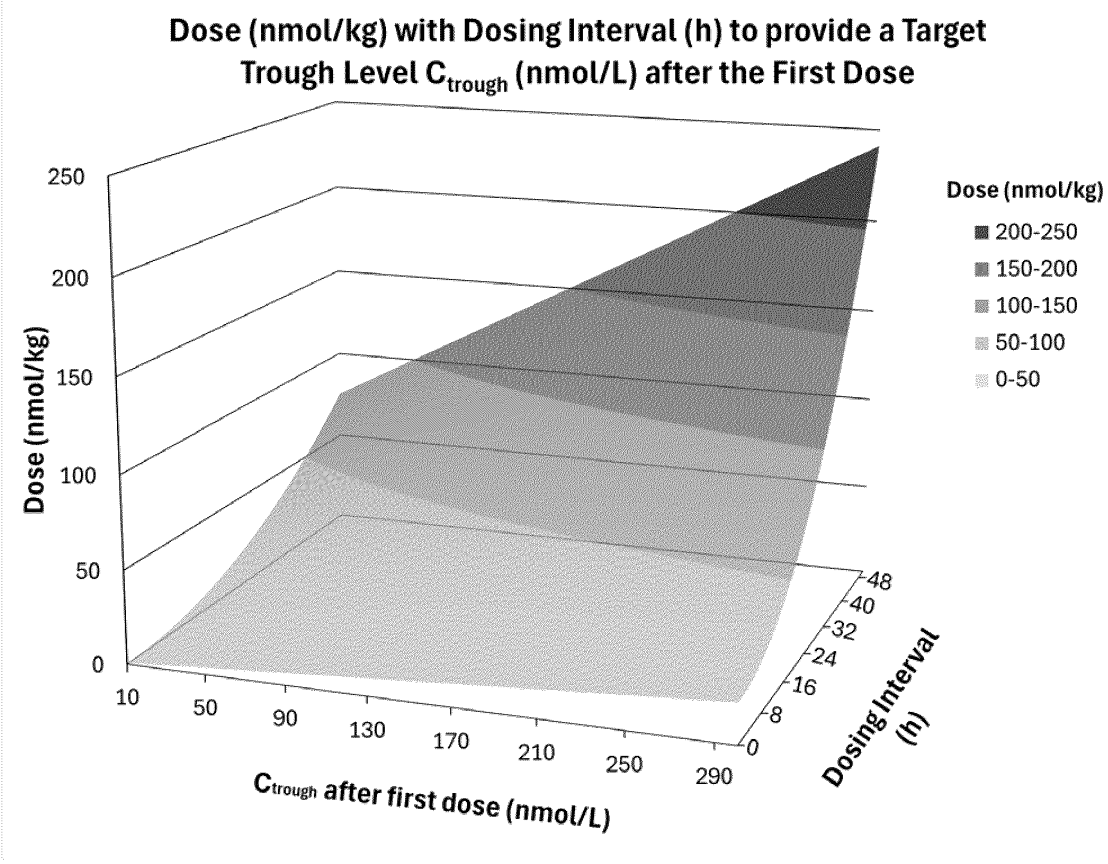

Dose (nmol/kg) with Dosing Interval (h) to provide a Target Trough Level C_{trough} (nmol/L) after the First Dose
Dose (nmol/kg)
250
200
150
100
50
0
10
50
90
130
170
210
250
290
C_{trough} after first dose (nmol/L)
48
40
32
24
16
8
0
Dosing Interval (h)
Dose (nmol/kg)
200-250
150-200
100-150
50-100
0-50

Fig. 36

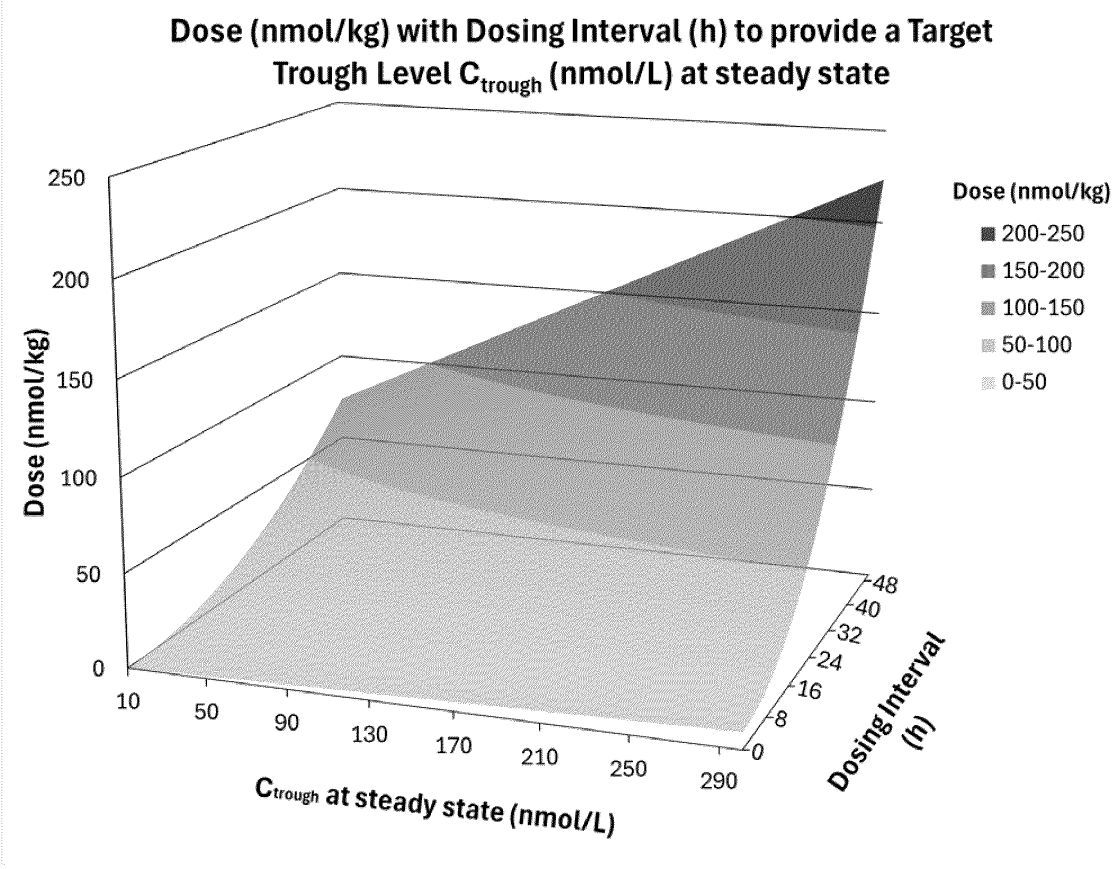

Dose (nmol/kg) with Dosing Interval (h) to provide a Target Trough Level C_{trough} (nmol/L) at steady state
Dose (nmol/kg)
250
200
150
100
50
0
Dose (nmol/kg)
200-250
150-200
100-150
50-100
0-50
10
50
90
130
170
210
250
290
C_{trough} at steady state (nmol/L)
48
40
32
24
16
8
0
Dosing Interval (h)

Fig. 37

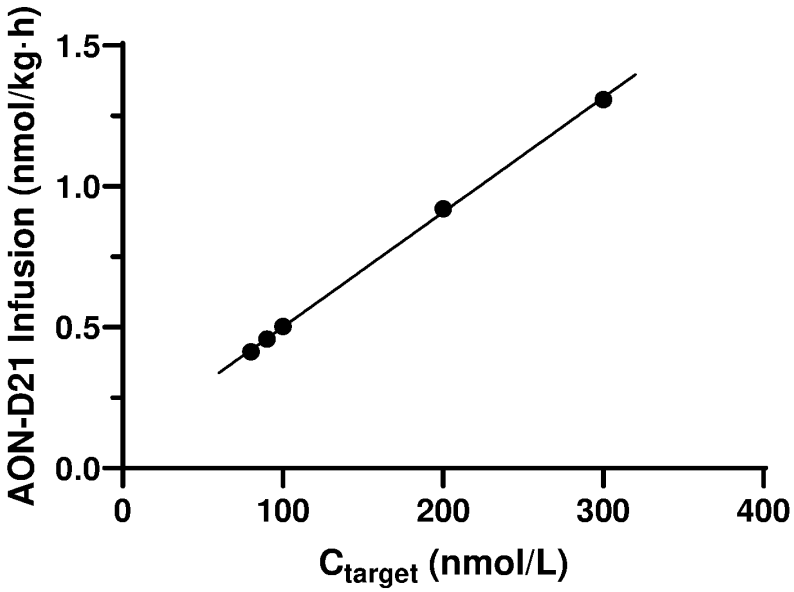

AON-D21 Infusion (nmol/kg·h)
1.5
1.0
0.5
0.0
0
100
200
300
400
Ctarget (nmol/L)

Fig. 38

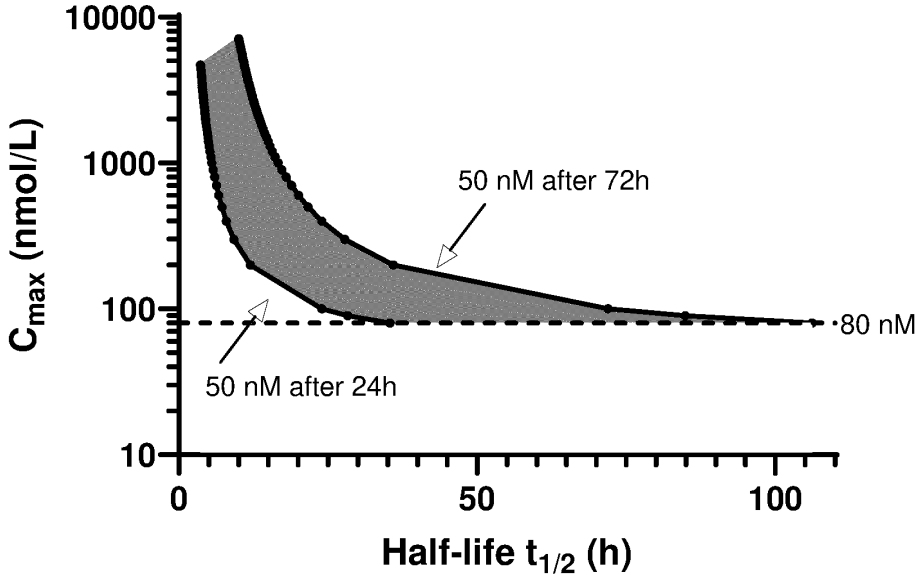

10000
1000
100
10
C_{max} (nmol/L)
50 nM after 72h
80 nM
50 nM after 24h
0
50
100
Half-life $t_{1/2}$ (h)

Fig. 39

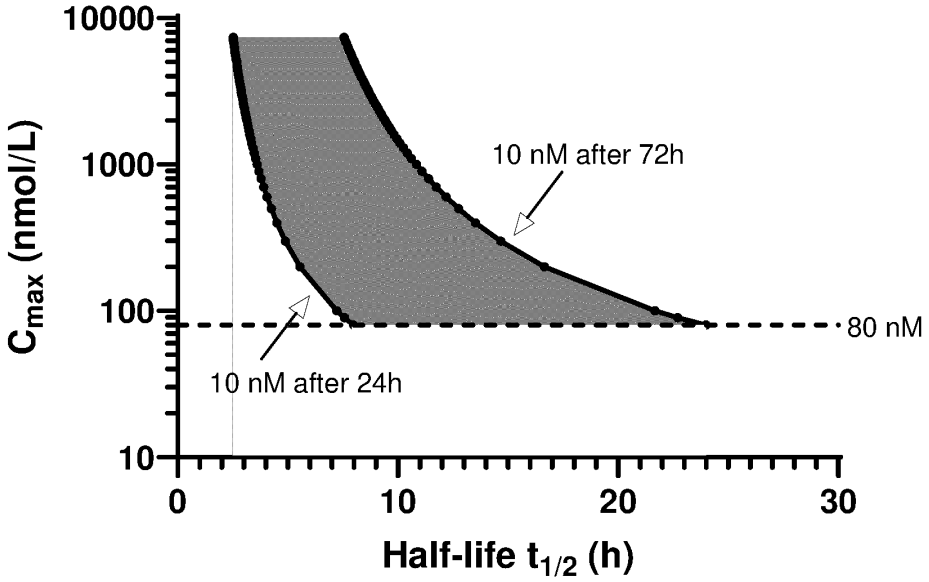

10000
1000
100
10
C_{max} (nmol/L)
10 nM after 72h
80 nM
10 nM after 24h
0
10
20
30
Half-life $t_{1/2}$ (h)

Fig. 40

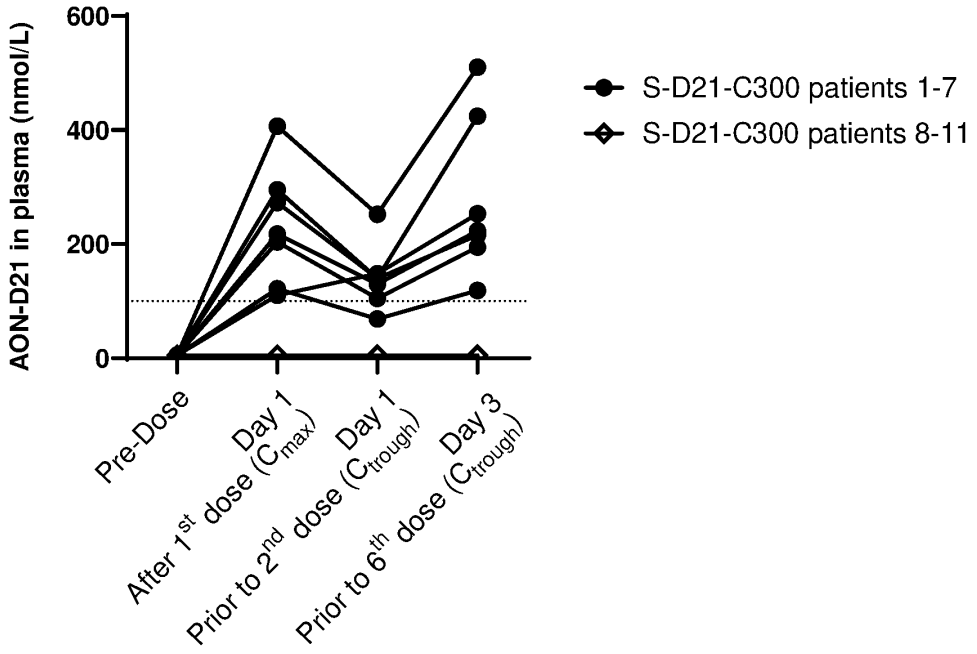

AON-D21 in plasma (nmol/L)
600
400
200
0
Pre-Dose
Day 1
After 1st dose (Cmax)
Day 1
Prior to 2nd dose (Ctrough)
Day 3
Prior to 6th dose (Ctrough)
S-D21-C300 patients 1-7
S-D21-C300 patients 8-11

Fig. 41

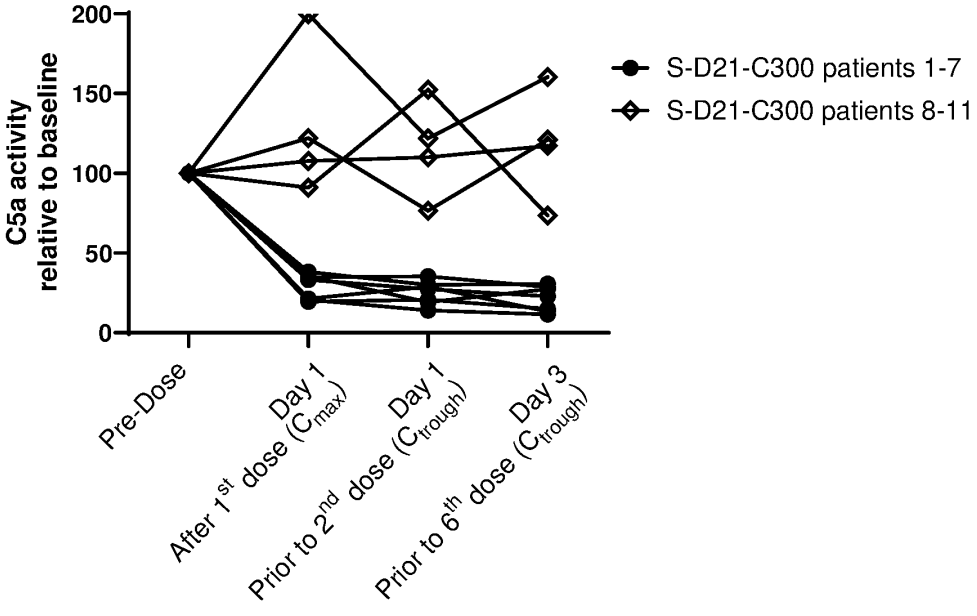
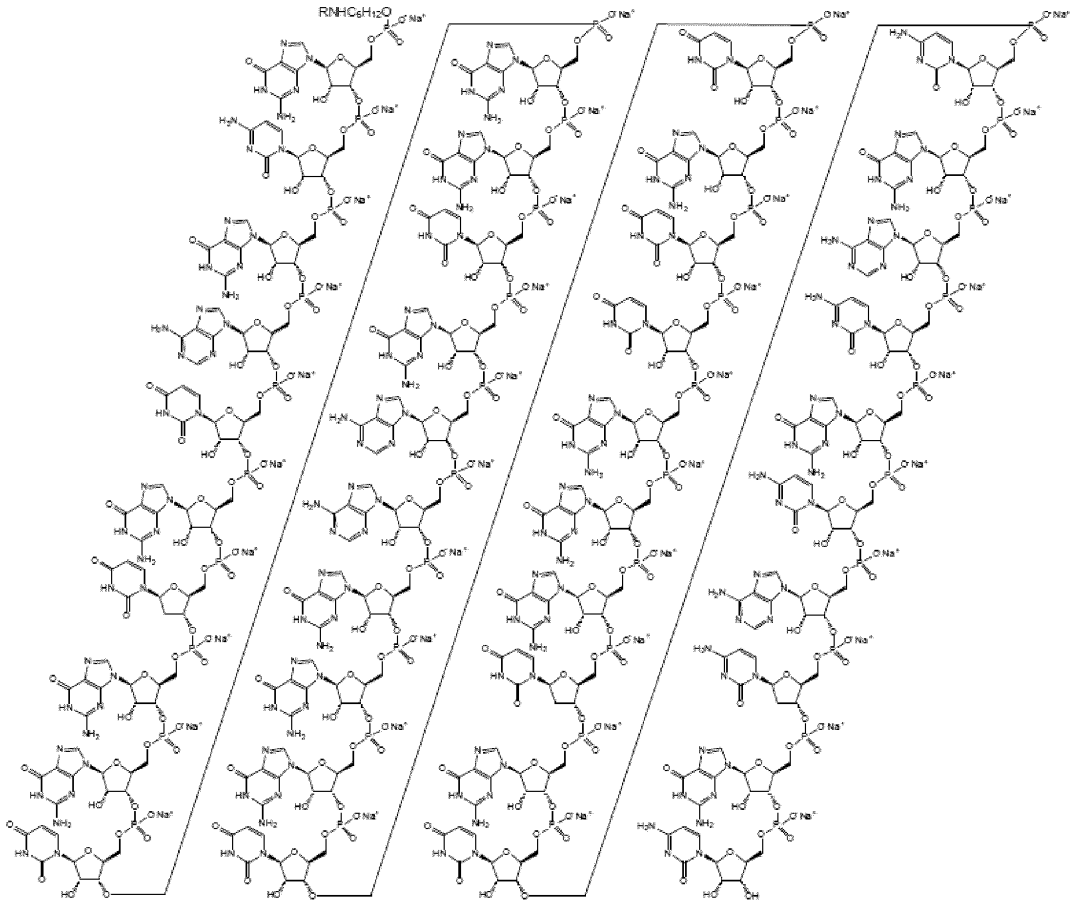
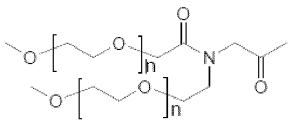

C5a activity relative to baseline
200
150
100
50
0
Pre-Dose
Day 1
After 1st dose (Cmax)
Day 1
Prior to 2nd dose (Ctrough)
Day 3
Prior to 6th dose (Ctrough)
S-D21-C300 patients 1-7
S-D21-C300 patients 8-11

Fig. 42

AON-D21 is represented by the following structural formula:



wherein $NHC_6H_{12}O$ is a hexylamino linker and R is



and n is approximately 450.

Fig. 43

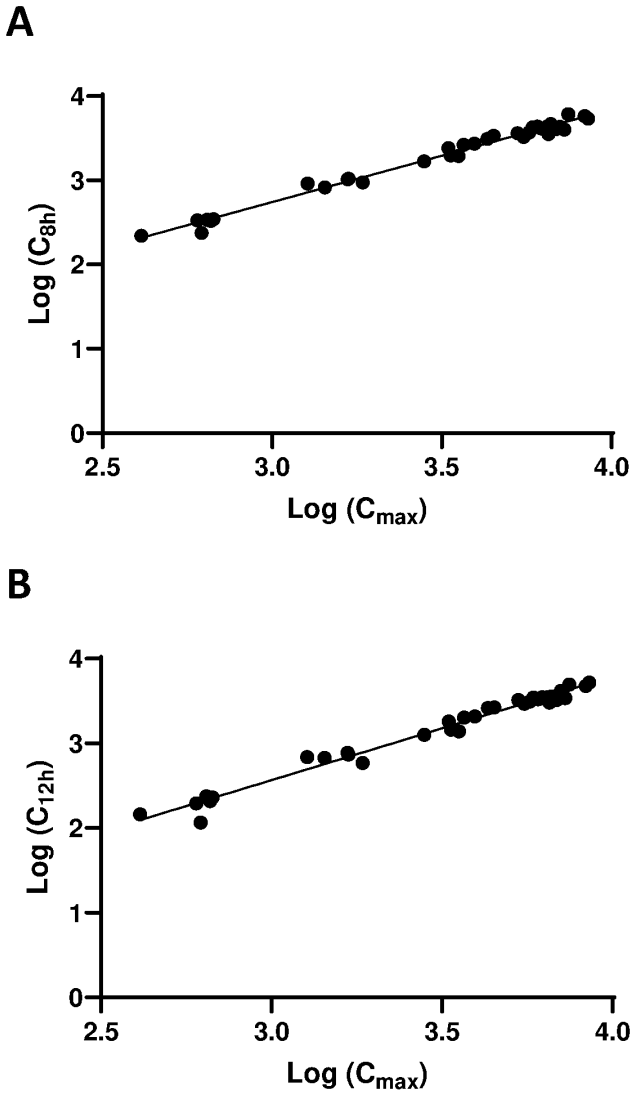
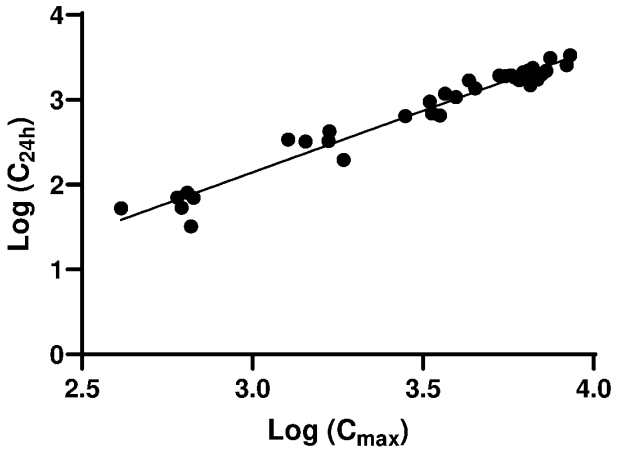


Fig. 44

C



D

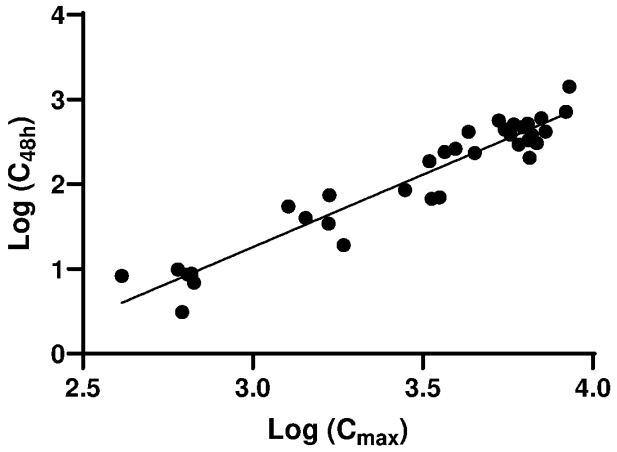


Fig. 44 (continuation)