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	**GCCUG**AUGUGGUGGUGAAGGGUUGUUGGGUGUCGACGCA**CAGGC**	1.38
NOX-D19001-D09	008	**GCCUG**AUGdUGGUGGUGAAGGGUUGUUGGGUGUCGACGCA**CAGGC**	0.71
NOX-D19001-D16	009	**GCCUG**AUGUGGUGGUdGAAGGGUUGUUGGGUGUCGACGCA**CAGGC**	1.03
NOX-D19001-D17	010	**GCCUG**AUGUGGUGGUGdAAGGGUUGUUGGGUGUCGACGCA**CAGGC**	0.91
NOX-D19001-D30	011	**GCCUG**AUGUGGUGGUGAAGGGUUGUUGGGdUGUCGACGCA**CAGGC**	0.77
NOX-D19001-D32	012	**GCCUG**AUGUGGUGGUGAAGGGUUGUUGGGUGdUCGACGCA**CAGGC**	0.92
NOX-D19001-D40	013	**GCCUG**AUGUGGUGGUGAAGGGUUGUUGGGUGUCGACGCA**dCAGGC**	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**AUGdUGGUGGUdGAAGGGUUGUUGGGdUGdUCGACGCA**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**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**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**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGGC**	44	0.42
NOX-D19001-6xDNA-023	040	**CG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGC**	40	9.38
NOX-D19001-6xDNA-024	041	**G**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAGC**	39	8.29
NOX-D19001-6xDNA-025	042	**GCUG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCAC**	41	5.01
NOX-D19001-6xDNA-026	043	**GCUG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCC**	40	16.8
NOX-D19001-6xDNA-027	044	**GCUG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCA**	40	4.71
NOX-D19001-6xDNA-028	045	**CG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCGC**	39	3.36
NOX-D19001-6xDNA-029	046	**G**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCGC**	38	6.89
NOX-D19001-6xDNA-030	047	**GCG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dCC**	39	16.1
NOX-D19001-6xDNA-032	048	**GCG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**dC**	38	5.58
NOX-D19001-6xDNA-033	049	**GG**AUGdUGGUGGUdGdAAGGGUUGUUGGGdUGdUCGACGCA**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;

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

Name	SEQ ID NO.	Sequence: 5′-3′	KD [nM]	IC_{50} [nM]
NOX-D19001-020	55	**GCG**AUGUGGUGGUGAAGGGUUGUUGGGUGUCGACGCA**CGC**	11.3	9.4
1 RNA-to-DNA substitutions:				
NOX-D19001-1xDNA-020	56	**GCG**AUGdUGGUGGUGAAGGGUUGUUGGGUGUCGACGCA**CGC**	1.34	3
2 RNA-to-DNA substitutions:				
NOX-D19001-2xDNA-020	57	**GCG**AUGdUGGUGGUGAAGGGUUGUUGGGdUGUCGACGCA**CGC**	0.73	2.2
3 RNA-to-DNA substitutions:				
NOX-D19001-3xDNA-020	58	**GCG**AUGdUGGUGGUGAAGGGUUGUUGGGdUGdUCGACGCA**CGC**	0.91	3.7
NOX-D19001-2dU-1dC-020 (=NOX-D21001)	59	**GCG**AUGdUGGUGGUGAAGGGUUGUUGGGdUGUCGACGCA**dCGC**	0.82	0.6
4 RNA-to-DNA substitutions:				
NOX-D19001-3dU-1dC-020	60	**GCG**AUGdUGGUGGUGAAGGGUUGUUGGGdUGdUCGACGCA**dCGC**	0.87	0.6

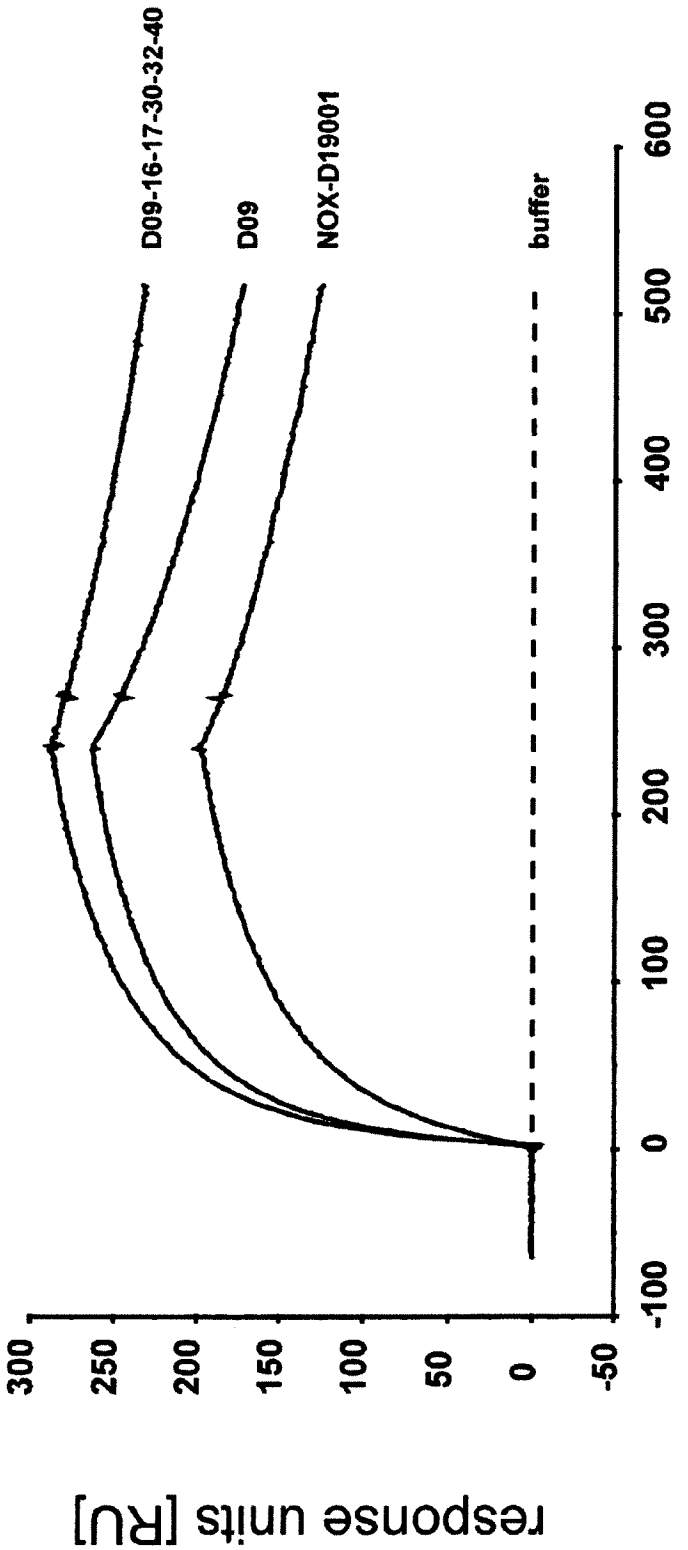
any of G, C, U and A is a ribonucleotide; any of dG, dC, dU and dA is a 2'-desoxyribonucleotide;

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* taxis assy 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

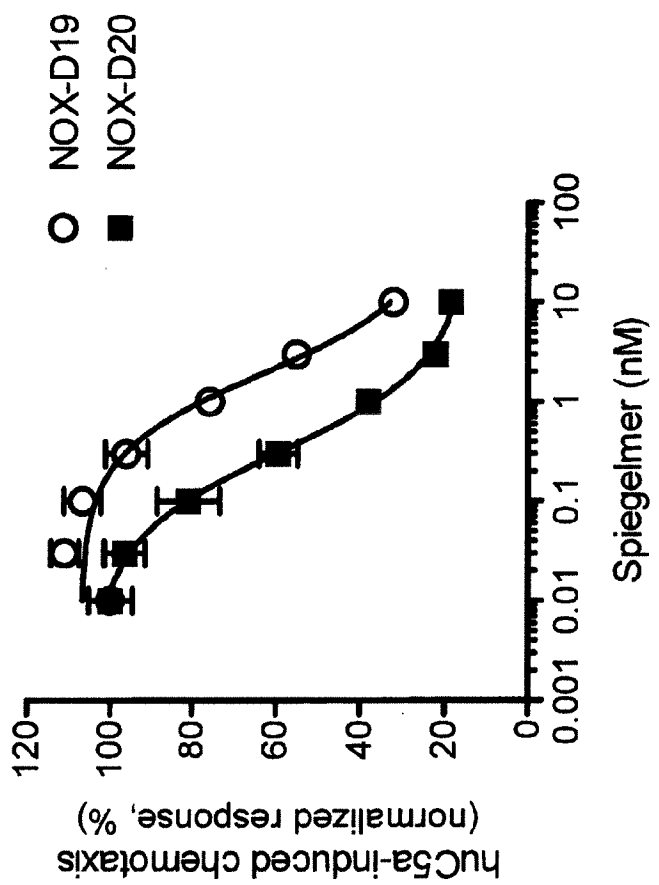

NOX-D19
NOX-D20
huC5a-induced chemotaxis
(normalized response, %)
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
Spiegelmer (nM)

Fig. 7

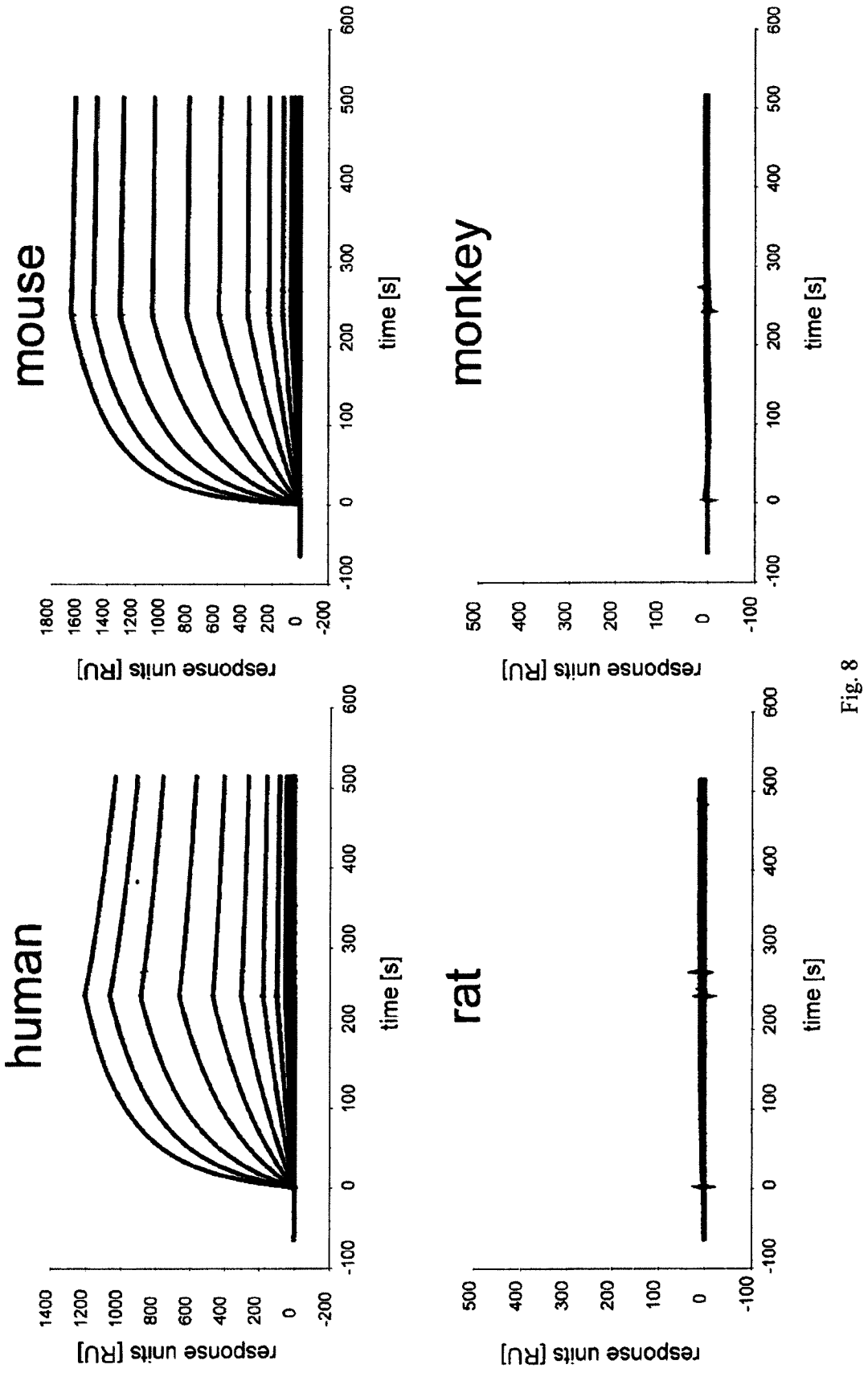
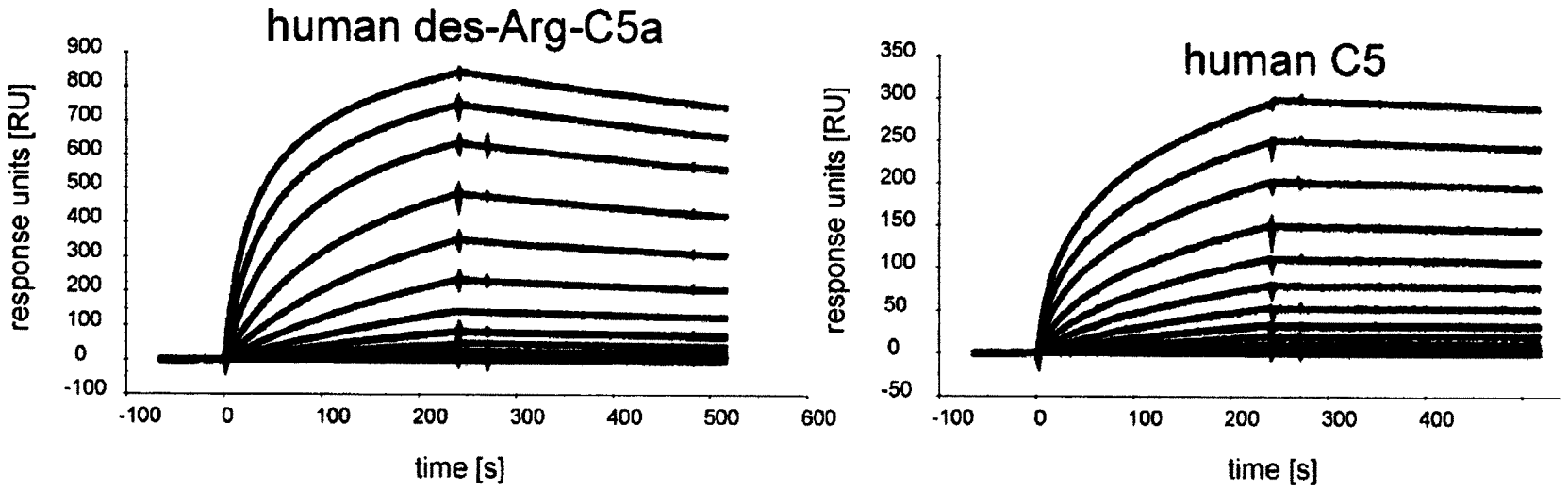

mouse
response units [RU]
time [s]
monkey
response units [RU]
time [s]
human
response units [RU]
time [s]
rat
response units [RU]
time [s]

Fig. 8

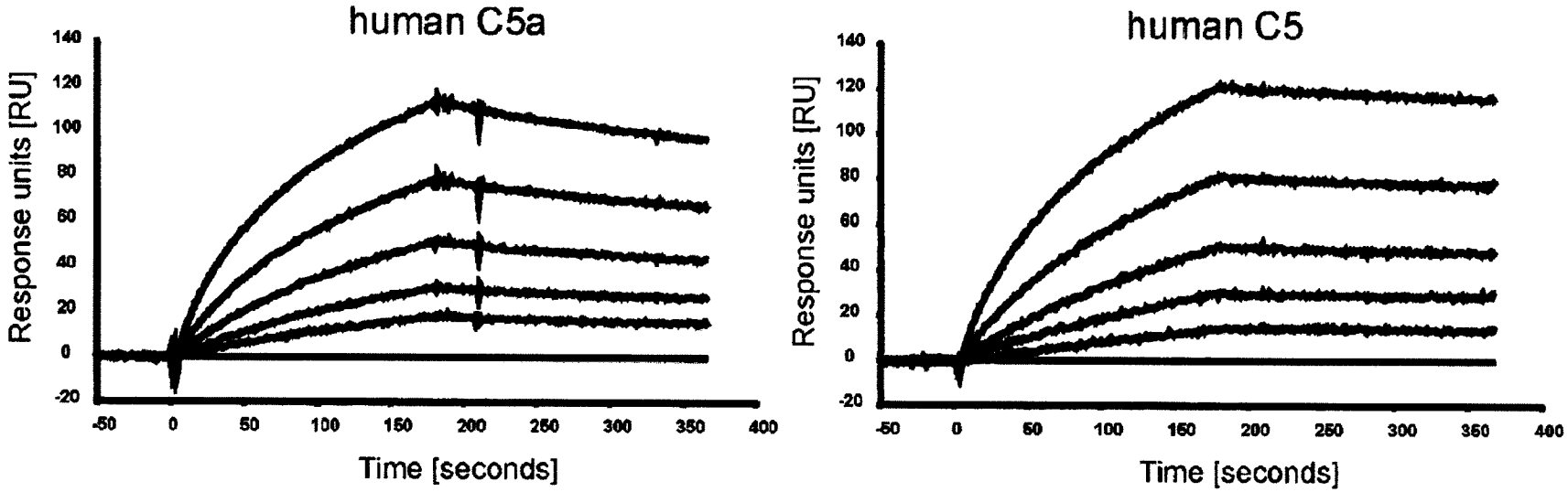
NOX-D20 binding to:	K_D [pM]
mouse C5a	19.1
human C5a	299
rat C5a	--
rhesus monkey C5a	--

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]

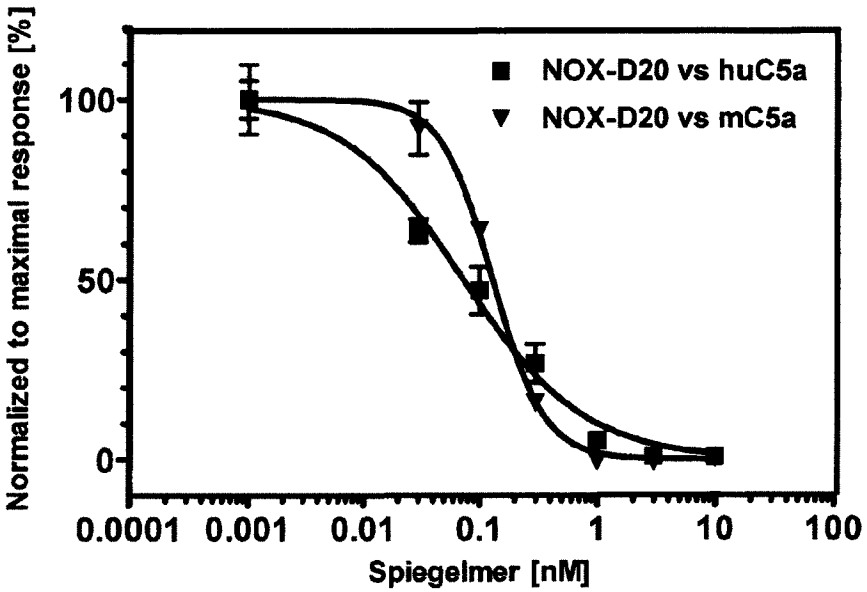
rhesus: MLQEKIEEIAAKYKHLVVKKCCYDGVRINHDETCEQRAARISVGPRCVKAFTECCVVASQLRANNSHKDLQLGR
[SEQ ID NO: 054]

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

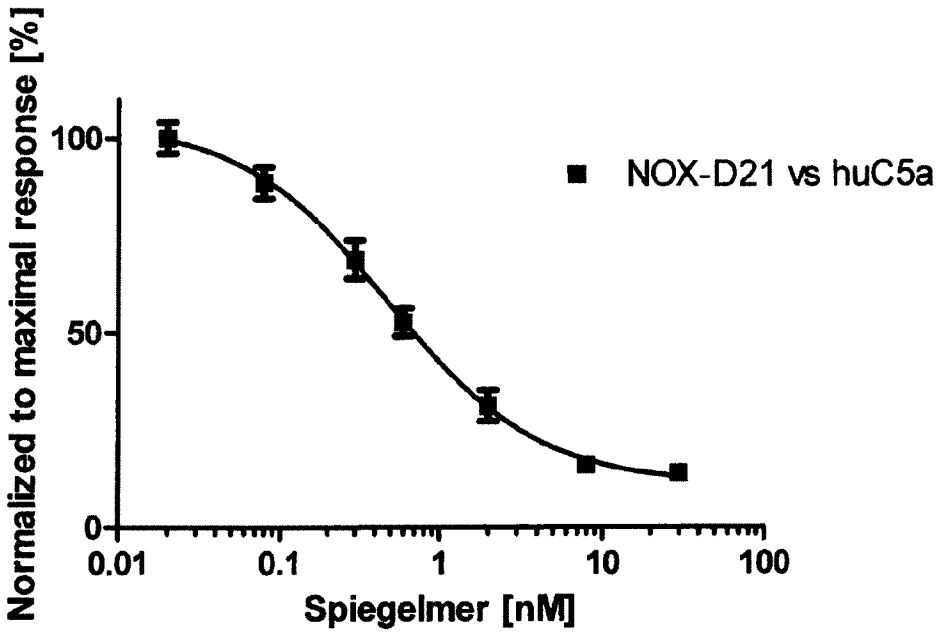

Normalized to maximal response [%]
100
50
0
NOX-D21 vs huC5a
0.01
0.1
1
10
100
Spiegelmer [nM]

Fig. 12

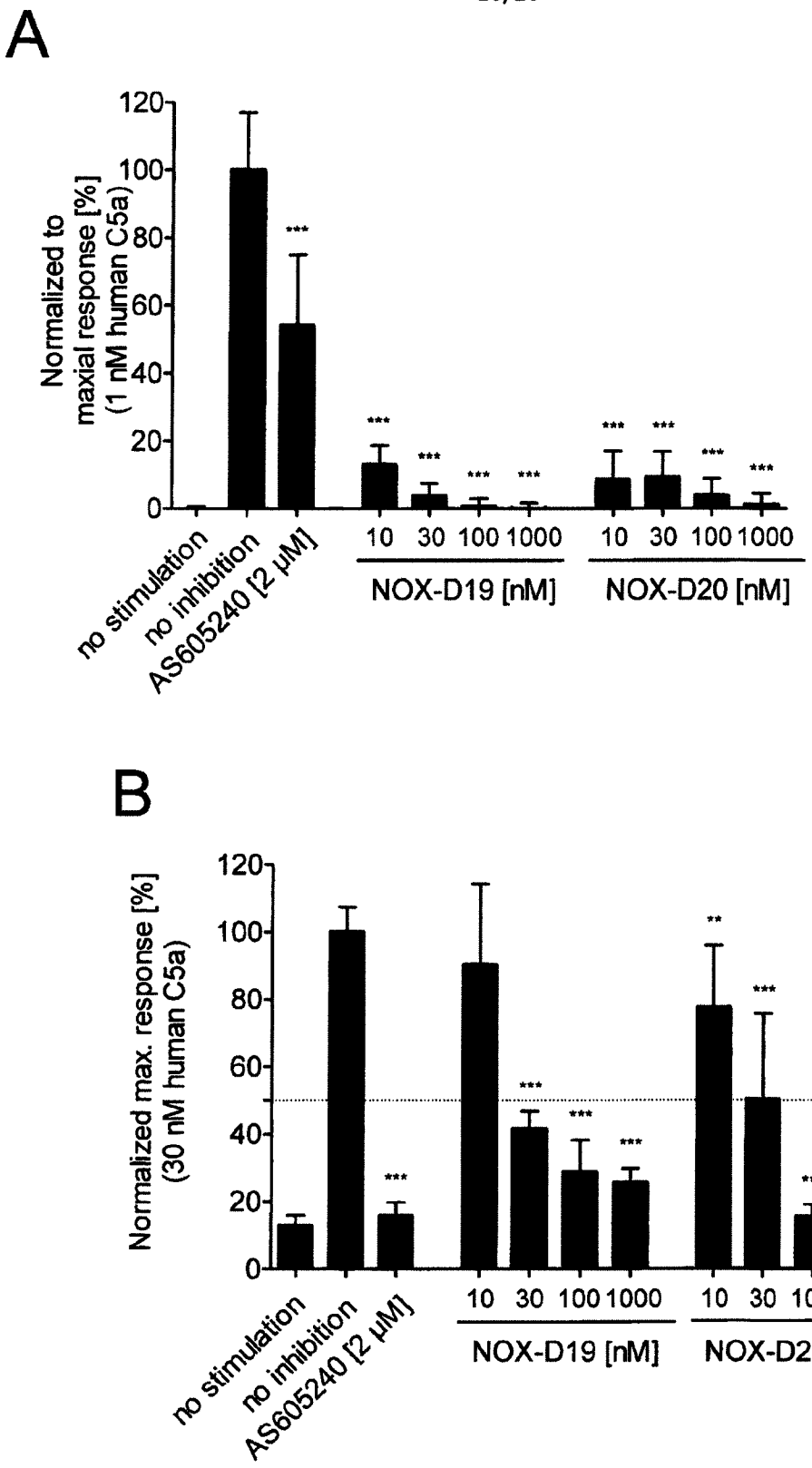

A
Normalized to maxial response [%] (1 nM human C5a)
120
100
80
60
40
20
0
***
***
***
***
***
***
***
***
***
no stimulation
no inhibition
AS605240 [2 µM]
10 30 100 1000
NOX-D19 [nM]
10 30 100 1000
NOX-D20 [nM]
B
Normalized max. response [%] (30 nM human C5a)
120
100
80
60
40
20
0
**
***
***
***
***
***
***
***
***
no stimulation
no inhibition
AS605240 [2 µM]
10 30 100 1000
NOX-D19 [nM]
10 30 100 1000
NOX-D20 [nM]

Fig. 13

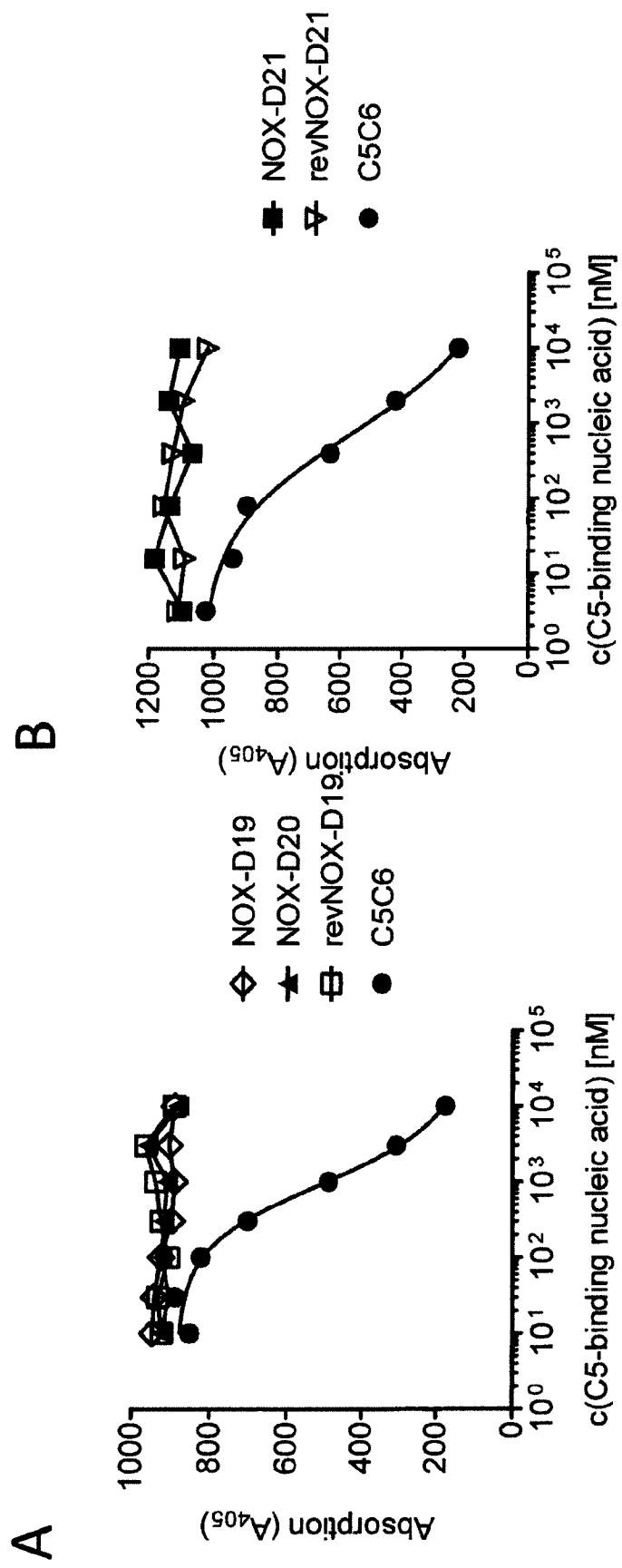

A
Absorption (A_{405})
1000
800
600
400
200
0
10^0 10^1 10^2 10^3 10^4 10^5
c(C5-binding nucleic acid) [nM]
NOX-D19
NOX-D20
revNOX-D19
C5C6
B
Absorption (A_{405})
1200
1000
800
600
400
200
0
10^0 10^1 10^2 10^3 10^4 10^5
c(C5-binding nucleic acid) [nM]
NOX-D21
revNOX-D21
C5C6

Fig. 14

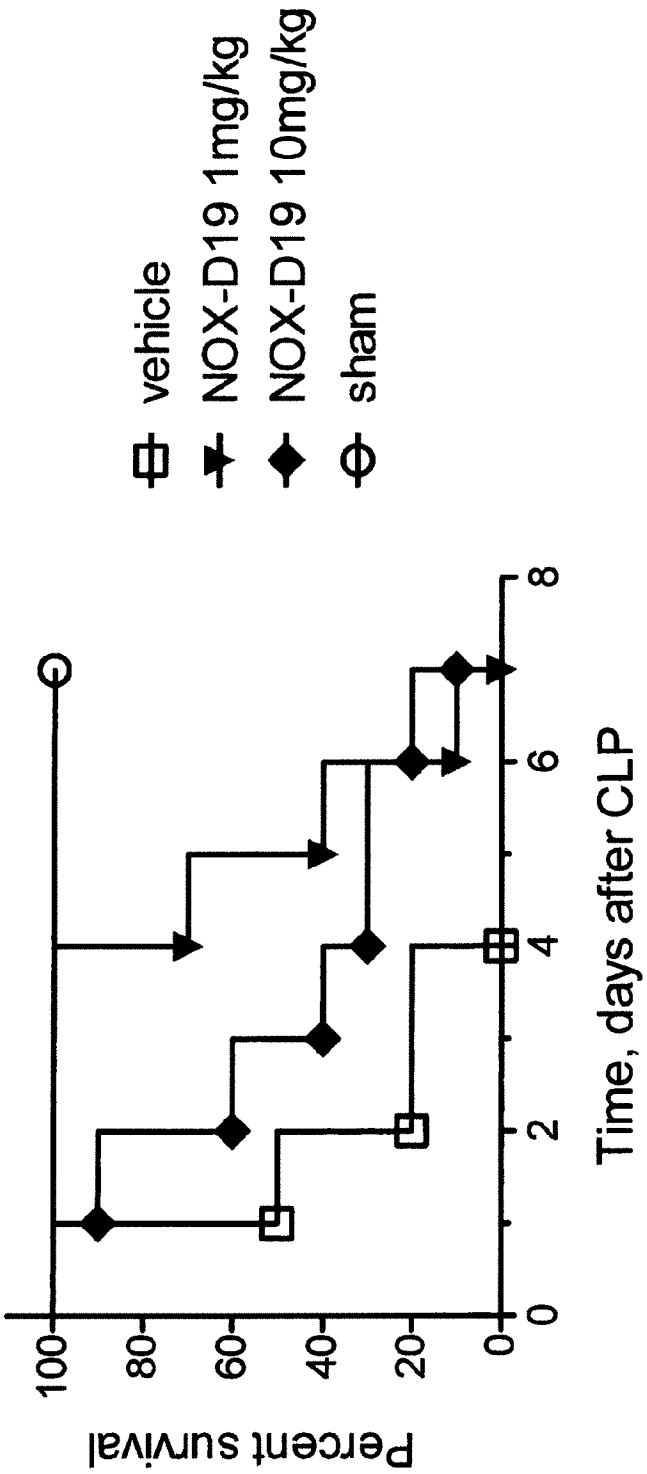

vehicle
NOX-D19 1mg/kg
NOX-D19 10mg/kg
sham
Percent survival
100
80
60
40
20
0
0
2
4
6
8
Time, days after CLP

Fig. 15

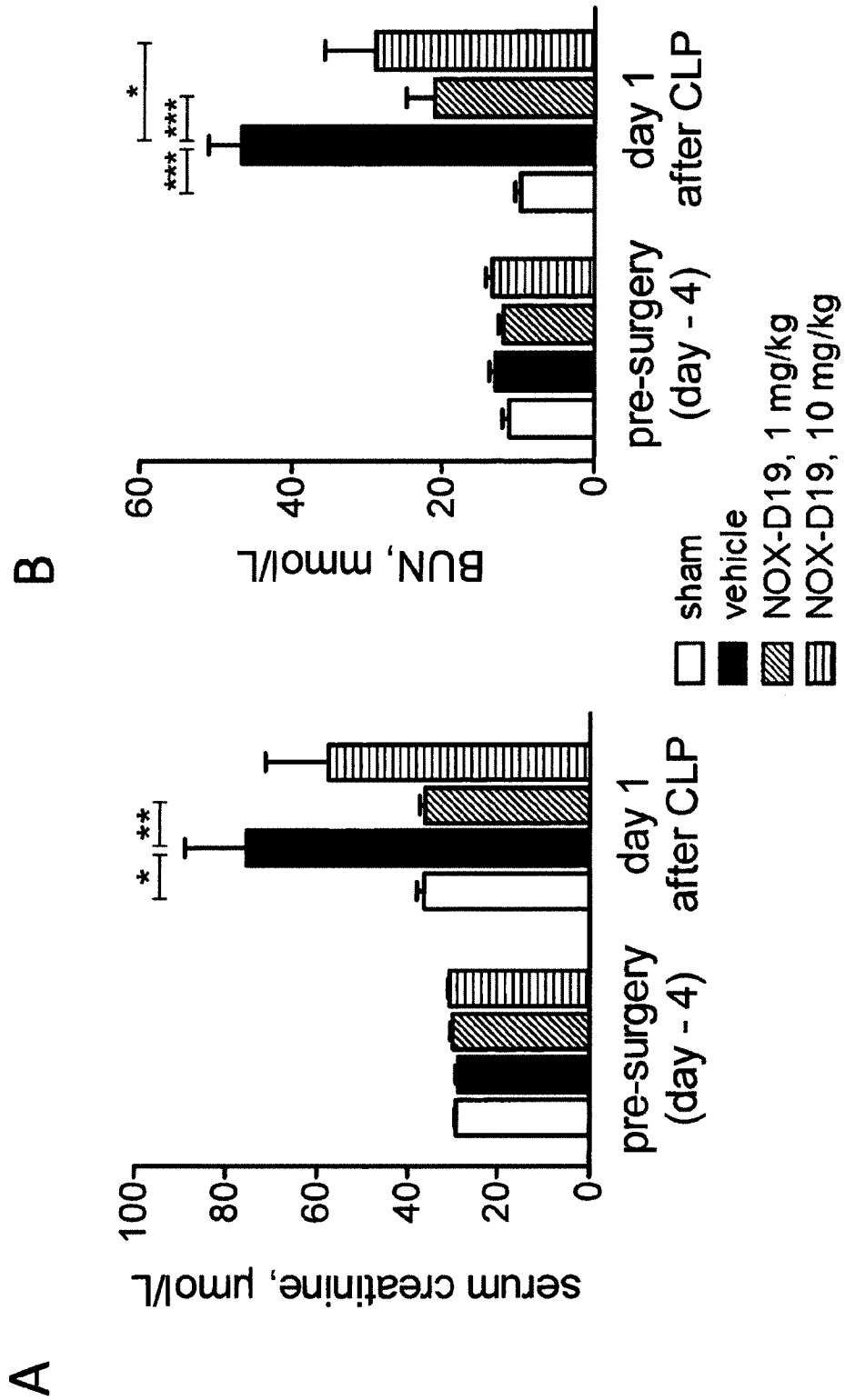

A
serum creatinine, µmol/L
100
80
60
40
20
0
* **
pre-surgery (day - 4)
day 1 after CLP
B
BUN, mmol/L
60
40
20
0
*
*** ***
pre-surgery (day - 4)
day 1 after CLP
sham
vehicle
NOX-D19, 1 mg/kg
NOX-D19, 10 mg/kg

Fig. 16

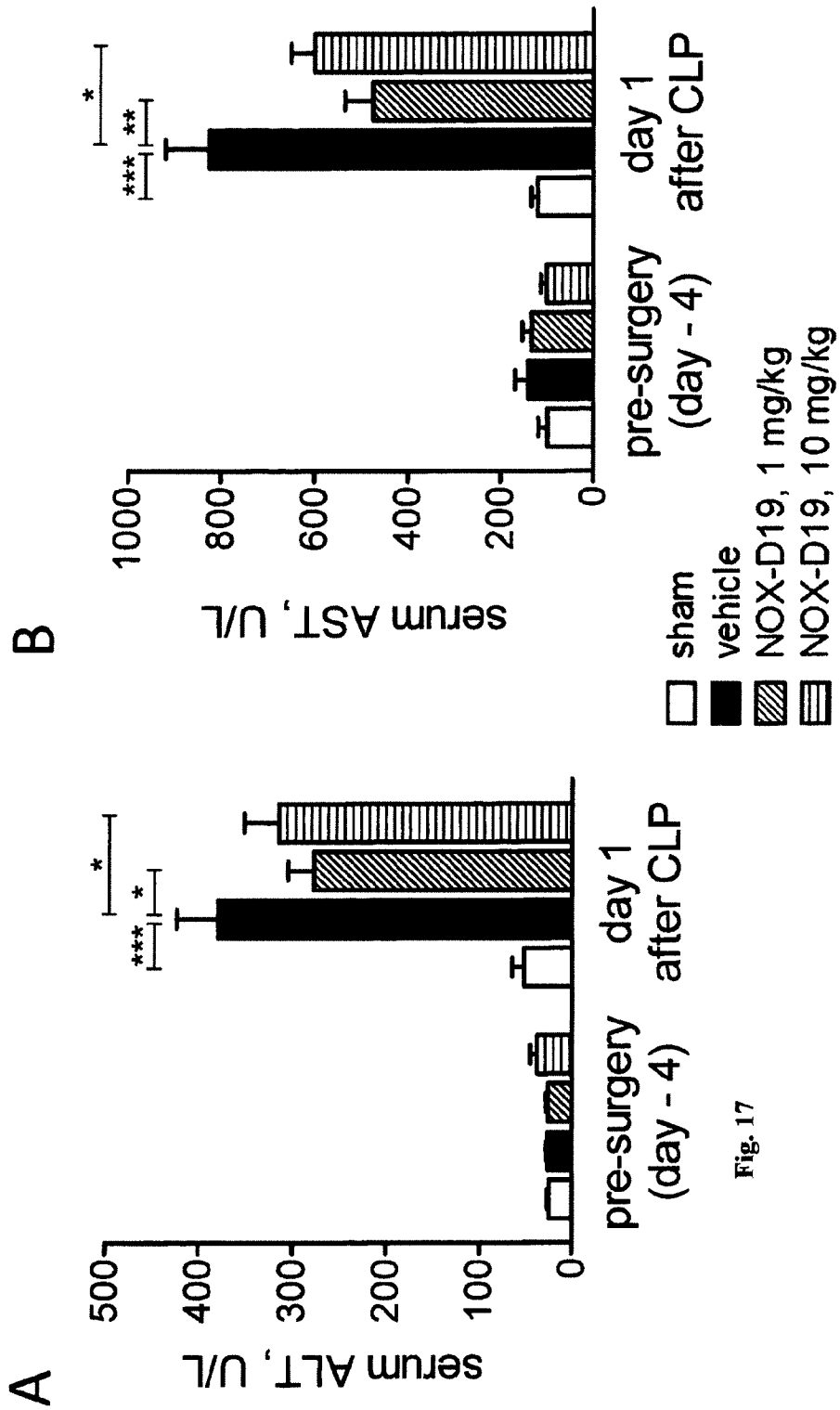

A
serum ALT, U/L
500
400
300
200
100
0
***
*
*
pre-surgery (day - 4)
day 1 after CLP
B
serum AST, U/L
1000
800
600
400
200
0
***
**
*
pre-surgery (day - 4)
day 1 after CLP
sham
vehicle
NOX-D19, 1 mg/kg
NOX-D19, 10 mg/kg

Fig. 17

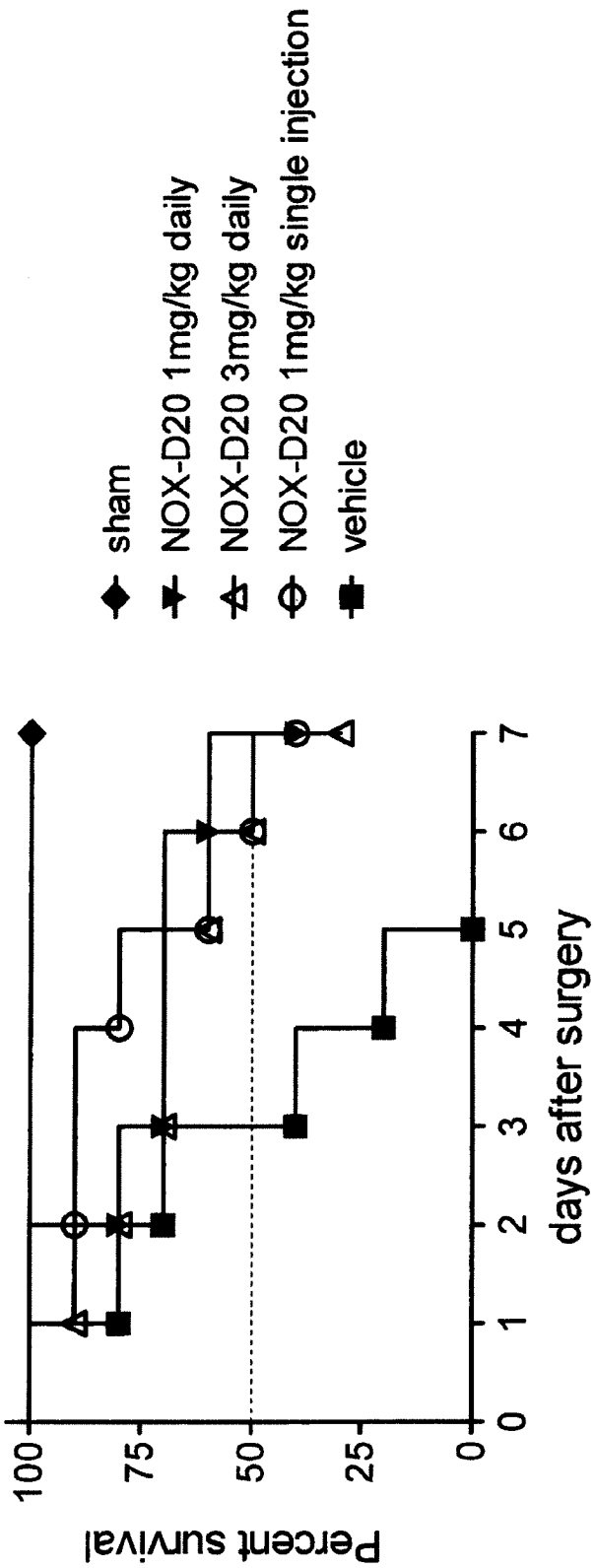

sham
NOX-D20 1mg/kg daily
NOX-D20 3mg/kg daily
NOX-D20 1mg/kg single injection
vehicle
Percent survival
100
75
50
25
0
0
1
2
3
4
5
6
7
days after surgery

Fig. 18

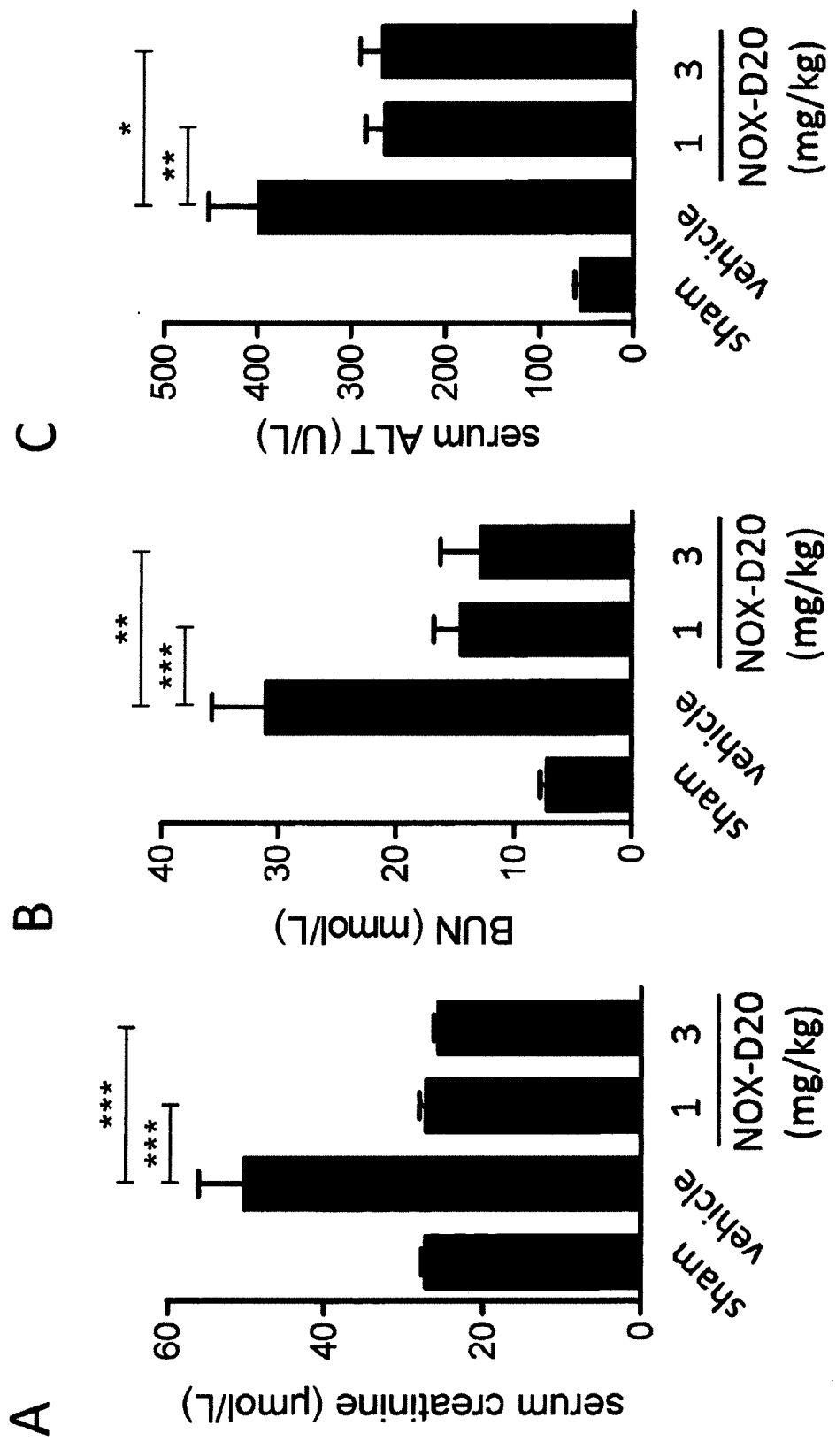

A
serum creatinine (µmol/L)
60
40
20
0
***
***
sham
vehicle
1
3
NOX-D20
(mg/kg)
B
BUN (mmol/L)
40
30
20
10
0
**
***
sham
vehicle
1
3
NOX-D20
(mg/kg)
C
serum ALT (U/L)
500
400
300
200
100
0
*
**
sham
vehicle
1
3
NOX-D20
(mg/kg)

Fig. 19

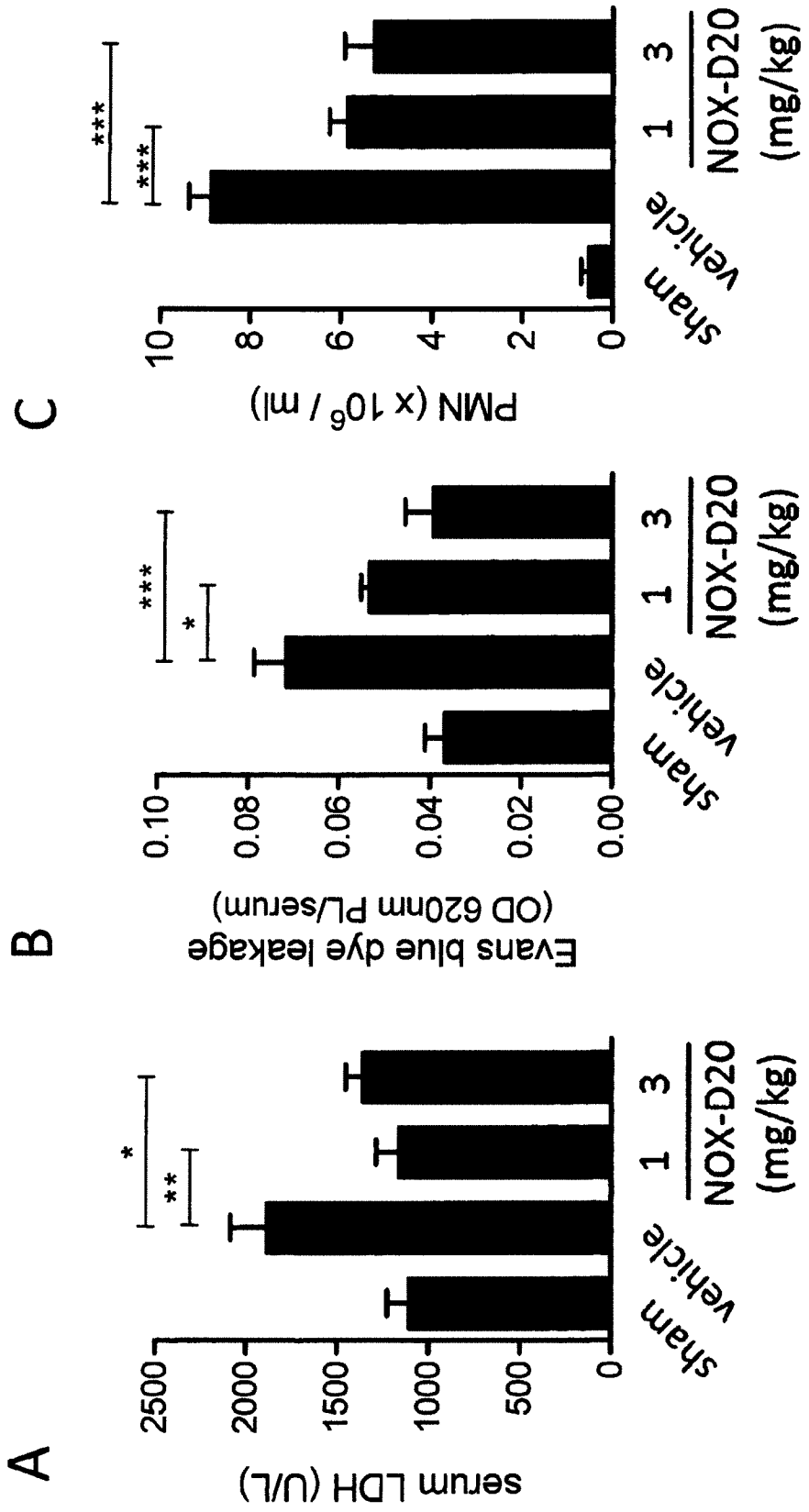

A
serum LDH (U/L)
2500
2000
1500
1000
500
0
*
**
sham
vehicle
1
3
NOX-D20
(mg/kg)
B
Evans blue dye leakage
(OD 620nm PL/serum)
0.10
0.08
0.06
0.04
0.02
0.00
***
*
sham
vehicle
1
3
NOX-D20
(mg/kg)
C
PMN (x 10^6 / ml)
10
8
6
4
2
0
***
***
sham
vehicle
1
3
NOX-D20
(mg/kg)

Fig. 20

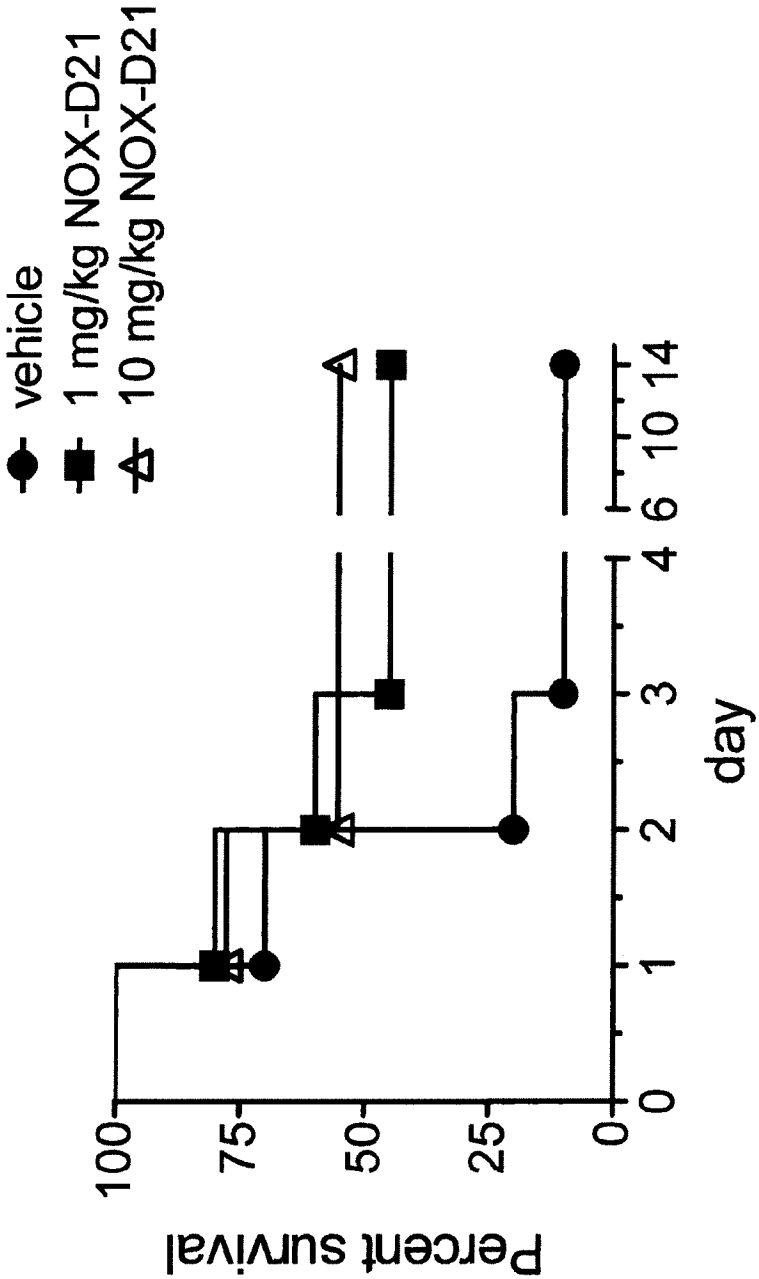

vehicle
1 mg/kg NOX-D21
10 mg/kg NOX-D21
Percent survival
100
75
50
25
0
0
1
2
3
4
6
10
14
day

Fig. 21

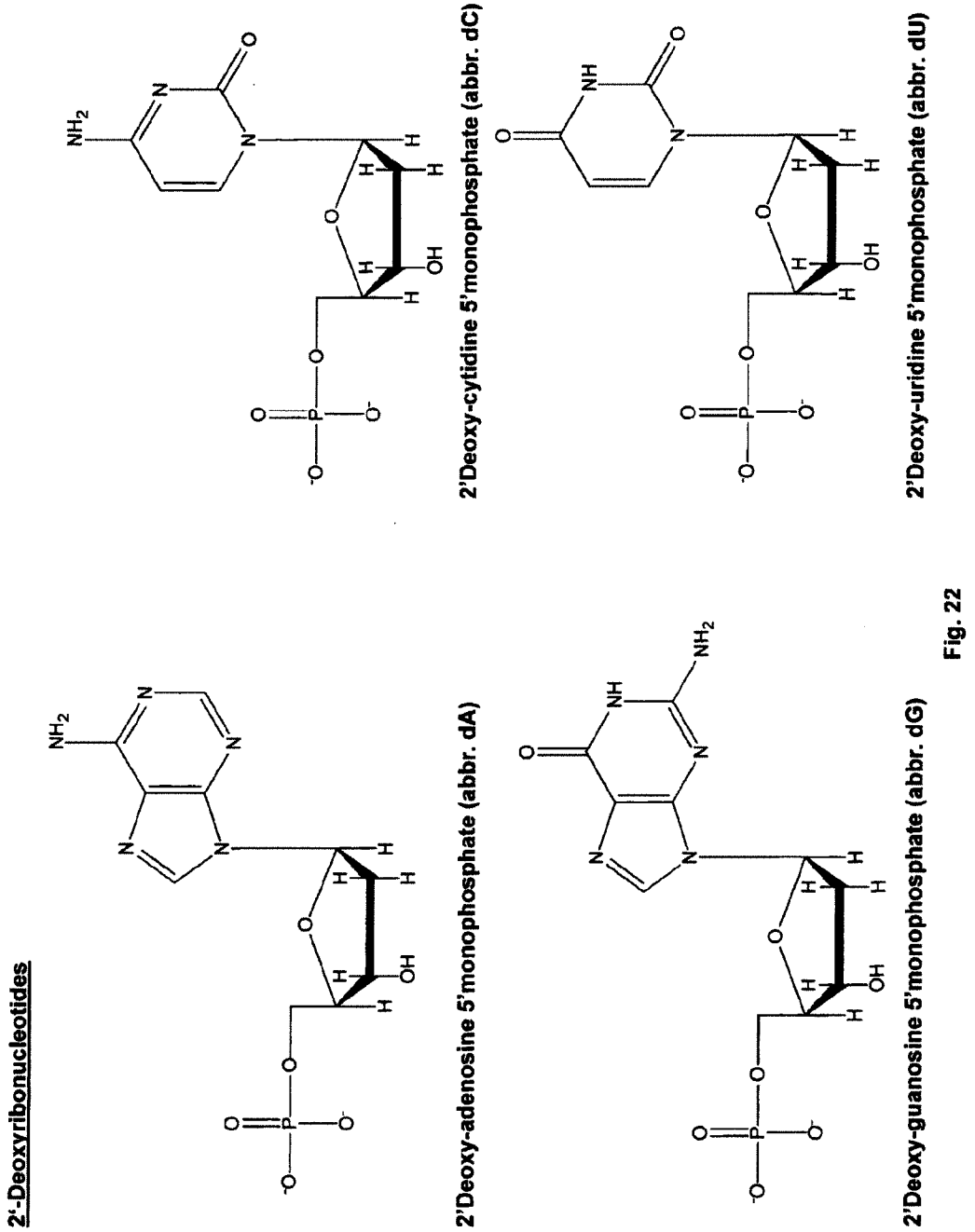
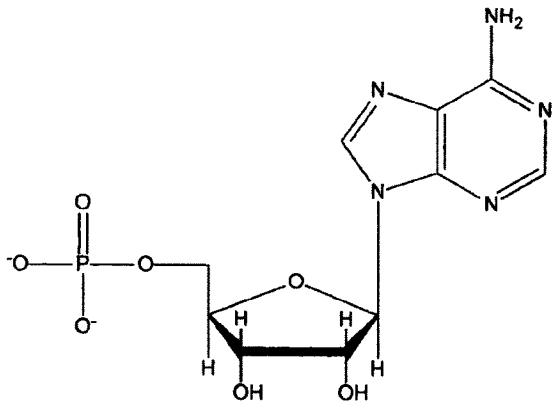
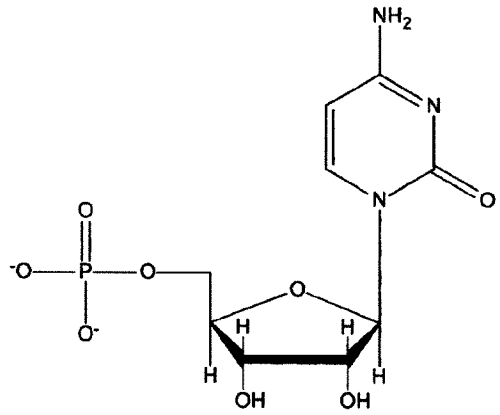

2'-Deoxyribonucleotides
2'Deoxy-adenosine 5'monophosphate (abbr. dA)
2'Deoxy-cytidine 5'monophosphate (abbr. dC)
2'Deoxy-guanosine 5'monophosphate (abbr. dG)
2'Deoxy-uridine 5'monophosphate (abbr. dU)

Fig. 22

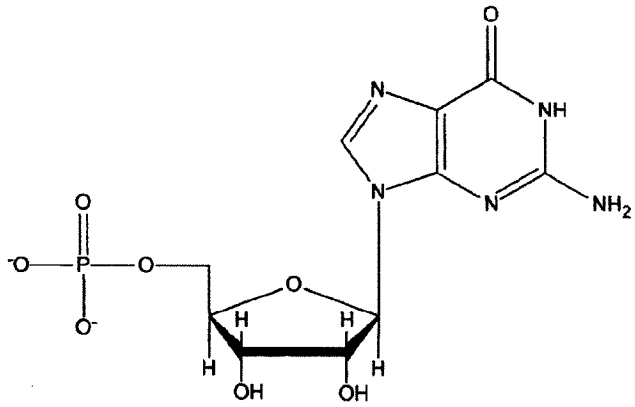
Ribonucleotides



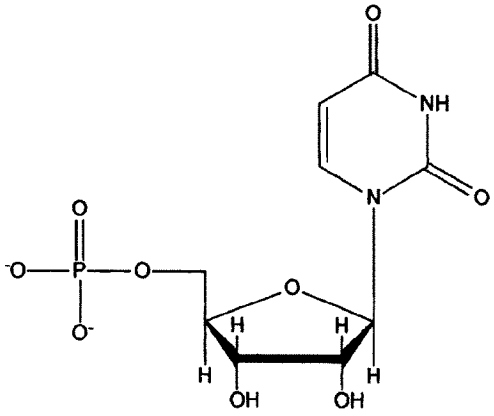
Adenosine 5'monophosphate (abbr. A)



Cytidine 5'monophosphate (abbr. C)



Guanosine 5'monophosphate (abbr, G)



Uridine 5'monophosphate (abbr. U)

Fig. 23