Name	SEQ ID NO.	nt.	Sequence: 5′-3′	Comp (APM)
212-G1-001	001	48	**CGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACG**	=
226-F2-001	002	50	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	+
212-F1-001	003	48	**CGUG**CUGUUGGAGACUACUUGUUAAGUAGAUAUAGGUUCCCUCC**CACG**	=
224-B2-001	004	50	**GCGUG**CUGUCGGAGACUACGCUUCGCGUAGAGAUAGGUCCCCUCC**CACGC**	=
224–E1-001	005	48	**GCAG**CUGUCGGAGACUCACCGUCGGUGAGAAAUAGGUCCCCUCC**CUGC**	=
226-A2-002	006	48	**CGUG**AUAUCGGAGACUACUCGUGGAGUAGAAAUAGGUCCCCUCC**CACG**	--
226-A3-001	007	50	**CCGUG**CUGUCGGAGACUACUCAUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	+
226-G2-002	008	48	**CGUG**CAGUCGGAGACUACUCAUCGAGUAGAAAUAGGUCCCUUCC**CACG**	--
226-C2-002	009	48	**CGUG**CUGUCGGAGACUACUCGUAGAGUGGAGAUAGGUCCCCUCC**CACG**	--
226-E1-002	010	48	**CGUG**CUGUCGGAGACUACUCGUAGAGUAGAGAUAAGUCCCCUCC**UACG**	--
226-F1-001	011	50	**CCGUG**CUGUCGGAGACUACUCGUAGAGUAGAUAUAGGUCCCCUCC**CACGG**	=
226-C3-001	012	50	**CCGUG**CUGUCGGAGACUACUCGUAGAGUAGAAAUAGGUCCCCUCC**CACGG**	+

nt.: number of nucleotides; any of G, C, U and A is a ribonucleotide;
nucleotides edged by ☐ represents a CGRP-binding motif;
Comp(APM): Molecules of the indicated sequence were tested as aptamers (D-nucleic acid) in pull-down competition binding assay vs. 212-G1-001 as reference;
+: better binding affinity than 212-G1-001; =: similar binding affinity as 212-G1-001; --: much weaker binding affinity than 212-G1-001

Fig. 1A

Name	SEQ ID NO.	nt.	Sequence: 5′-3′	Comp (APM)
231-A1-001	**013**	**52**	**GUCAUG**CUGUCGGAGACUACUCAUCGAGUAGAAAUAGGUCCCCUCC**CACGGC**	+
231-G2-001	**014**	**52**	**GCCAUG**CUGUCGGAGACUACUCAUCGAGUAGAAAUAGAUCCCCUCC**CAUGGC**	--
231-C1-001	**015**	**52**	**GCCGUG**CUGUCGGAGACUACUCAUCGAGUAGAAAUAGGUCCCCUCC**CACGGC**	+
231-C2-001	**016**	**52**	**GCCGUG**CUGUCGGAGACUACUCGUUGAGUAGAAAUAGGUCCCCUCC**CACGGC**	+
231-D1-001	**017**	**52**	**GCCGUG**CUGUCGGAGACUACUCGUUGAGUAGAAAUAGGUCCCGUCC**CACGGC**	--
231-F1-001	**018**	**52**	**GCCGUG**CUGUCGGAGACUACUCGCCGAGUAGAAAUAGGUCCCCUCC**CACGGC**	+
231-E1-001	**019**	**52**	**CCCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGGG**	+
231-B3-001	**020**	**54**	**CACCGUG**CUGUCGGAUACUACUCGCCGAGUAGAAAUAGGUCCCCUCC**CACGGUG**	--
231-A2-001	**021**	**54**	**GGCCGUG**CUGUCGGAGACUACUCGCCGAGUAGAAAUAGGUCCCCUCC**CACGGCU**	+
231-E2-001	**022**	**52**	**CCCGUG**CUGUCGGAGACUACUCGUAGGGUAGAAAUAGGUCCCCUCC**CACGGG**	+
231-H2-001	**023**	**52**	**GCCGUG**UUGUCGGAGACUACCCCCAGGGUAGAAAUAGGUCCCCUCC**CACGGC**	--

nt.: number of nucleotides; any of G, C, U and A is a ribonucleotide;
nucleotides edged by [ ] represents a CGRP-binding motif;
Comp(APM): Molecules of the indicated sequence were tested as aptamers (D-nucleic acid) in pull-down competition binding assay vs. 212-G1-001 as reference;
+: better binding affinity than 212-G1-001; =: similar binding affinity as 212-G1-001; --: much weaker binding affinity than 212-G1-001

Fig. 1B

Name	SEQ ID NO.	nt.	Sequence: 5′-3′	Comp (APM)
226-F2-001	002	50	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	=
226-F2-003	024	50	**GCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGC**	+
226-F2-004	025	50	**GGGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACCC**	=
226-F2-005	026	50	**GCCUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CAGGC**	=

nt.: number of nucleotides; any of G, C, U and A is a ribonucleotide;
nucleotides edged by ☐ represents a CGRP-binding motif;
Comp(APM): Molecules of the indicated sequence were tested as aptamers (D-nucleic acid) in pull-down competition binding assay vs. th... 226-F2-001 as reference;
=: similar binding affinity as 226-F2-001; +: better inding affinity than 226-F2-001;

Fig. 2

Derivatives of 226-F2-001

Name	SEQ ID NO.	Sequence: 5'-3'	x-fold improved binding affinity	Biacore (SPM) K_D [nM]
226-F2-001	**002**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	**1.0**	**2.6**
226-F2-001-D03	**027**	**CCdGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	4.06	0.64
226-F2-001-D05	**028**	**CCGUdG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	3.25	0.80
226-F2-001-D08	**029**	**CCGUG**CUdGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	4.64	0.56
226-F2-001-D09	**030**	**CCGUG**CUGdTCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	3.38	0.77
226-F2-001-D14	**031**	**CCGUG**CUGUCGGAdGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	3.21	0.81
226-F2-001-D16	**032**	**CCGUG**CUGUCGGAGAdCUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	1.78	1.46
226-F2-001-D19	**033**	**CCGUG**CUGUCGGAGACUAdCUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	8.39	0.31
226-F2-001-D22	**034**	**CCGUG**CUGUCGGAGACUACUCdGUCGAGUAGAAAUAGGUCCCCUCC**CACGG**	2.11	1.60
226-F2-001-D23	**035**	**CCGUG**CUGUCGGAGACUACUCGdTCGAGUAGAAAUAGGUCCCCUCC**CACGG**	4.48	0.58

nucleotides edged by ☐ represents a CGRP-binding motif; **SPM**: Spiegelmer

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

x-fold improved binding affinity: Improved binding affinity of Spiegelmers relative to 226-F2-001, measured by surface plasmon resonance on Biacore using direct binding to covalently immobilized human L-CGRP.

Biacore(SPM): 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 biotinylated L-CGRP

Fig. 3A

Derivatives of 226-F2-001

Name	SEQ ID NO.	Sequence: 5′-3′	x-fold improved binding affinity	Biacore (SPM) K_D [nM]
226-F2-001-D24	036	**CCGUG**CUGUCGGAGACUACUCGUdCGAGUAGAAAUAGGUCCCCUCC**CACGG**	1.70	1.53
226-F2-001-D25	037	**CCGUG**CUGUCGGAGACUACUCGUCdGAGUAGAAAUAGGUCCCCUCC**CACGG**	1.50	1.73
226-F2-001-D26	038	**CCGUG**CUGUCGGAGACUACUCGUCGdAGUAGAAAUAGGUCCCCUCC**CACGG**	5.65	0.46
226-F2-001-D28	039	**CCGUG**CUGUCGGAGACUACUCGUCGAGdTAGAAAUAGGUCCCCUCC**CACGG**	3.21	0.81
226-F2-001-D30	040	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAdGAAAUAGGUCCCCUCC**CACGG**	1.63	1.60
226-F2-001-D33	041	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAdAUAGGUCCCCUCC**CACGG**	2.30	1.13
226-F2-001-D34	042	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAdTAGGUCCCCUCC**CACGG**	4.41	0.59
226-F2-001-D37	043	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGdGUCCCCUCC**CACGG**	4.06	0.64
226-F2-001-D39	044	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUdCCCCUCC**CACGG**	1.87	1.39

nucleotides edged by ☐ represents a CGRP-binding motif; **SPM**: Spiegelmer

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

x-fold improved binding affinity: Improved binding affinity of Spiegelmers relative to 226-F2-001, measured by surface plasmon resonance on Biacore using direct binding to covalently immobilized human L-CGRP.

Biacore(SPM): 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 biotinylated L-CGRP

Fig. 3B

Derivatives of 226-F2-001

Name	SEQ ID NO.	Sequence: 5′-3′	x-fold improved binding affinity	Biacore (SPM) K_D [nM]
226-F2-001-D41	**045**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCdCCUCC**CACGG**	5.2	0.50
226-F2-001-D42	**046**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCdCUCC**CACGG**	5.00	0.52
226-F2-001-D44	**047**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUdCC**CACGG**	6.34	0.41
226-F2-001-D45	**048**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCdC**CACGG**	5.00	0.52
226-F2-001-D46	**049**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**dCACGG**	4.06	0.64
226-F2-001-D47	**050**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CdACGG**	3.77	0.69
226-F2-001-D48	**051**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CAdCGG**	4.64	0.56
226-F2-001-D49	**052**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACdGG**	4.00	0.65
226-F2-001-D50	**053**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCCCUCC**CACGdG**	3.17	0.82
226-F2-001-D41/D44	**054**	**CCGUG**CUGUCGGAGACUACUCGUCGAGUAGAAAUAGGUCCdCCUdCC**CACGG**	13.00	0.20

nucleotides edged by ☐ represents a CGRP-binding motif; **SPM**: Spiegelmer

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

x-fold improved binding affinity: Improved binding affinity of Spiegelmers relative to 226-F2-001, measured by surface plasmon resonance on Biacore using direct binding to covalently immobilized human L-CGRP.

Biacore(SPM): 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 biotinylated L-CGRP

Fig. 3C

Derivatives of 226-F2-001

Name	SEQ ID NO.	Sequence: 5′-3′	x-fold improved binding affinity	Biacore (SPM) K_D [nM]
226-F2-001-D41-dU20	126	**CCGUG**CUGUCGGAGACUACdUCGUCGAGUAGAAAUAGGUCCdCCUCC**CACGG**	37.14	0.07
226-F2-001-D41-dU28	127	**CCGUG**CUGUCGGAGACUACUCGUCGAGdUAGAAAUAGGUCCdCCUCC**CACGG**	12.38	0.21
226-F2-001-D41-dU20-28	128	**CCGUG**CUGUCGGAGACUACdUCGUCGAGdUAGAAAUAGGUCCdCCUCC**CACGG**	4.19	0.62
226-F2-001-D41/D44-dU20	129	**CCGUG**CUGUCGGAGACUACdUCGUCGAGUAGAAAUAGGUCCdCCUdCC**CACGG**	6.34	0.41
226-F2-001-D41/D44-dU28	130	**CCGUG**CUGUCGGAGACUACUCGUCGAGdUAGAAAUAGGUCCdCCUdCC**CACGG**	7.03	0.37
226-F2-001-D41/D44-dU20-28	131	**CCGUG**CUGUCGGAGACUACdUCGUCGAGdUAGAAAUAGGUCCdCCUdCC**CACG G**	7.88	0.33

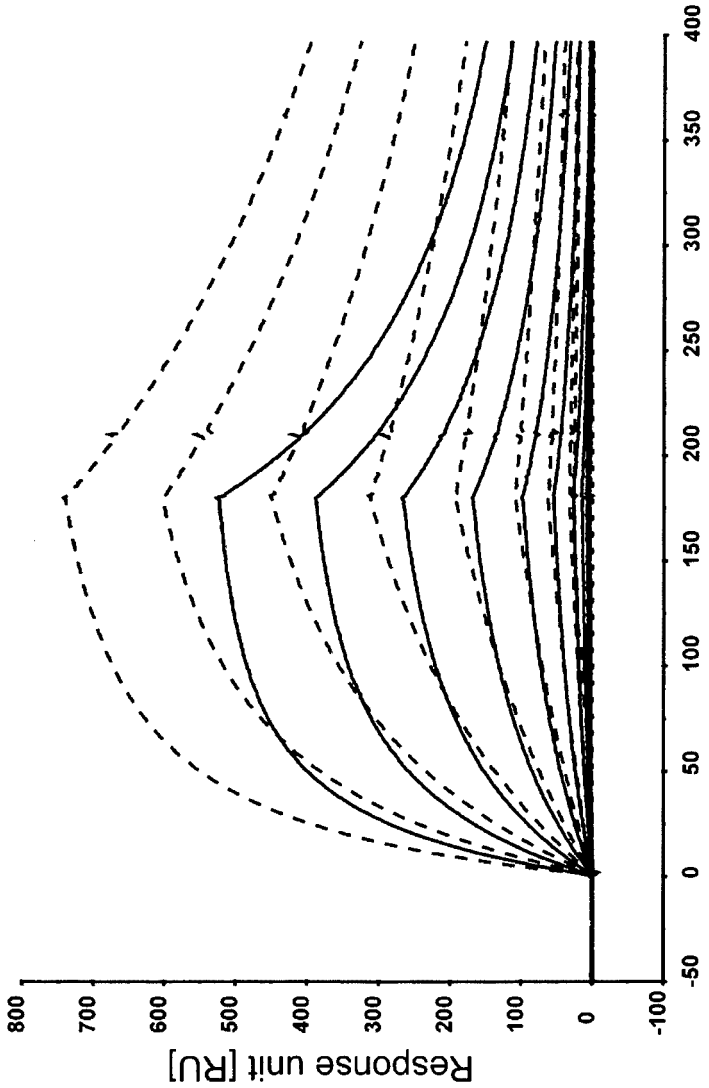
nucleotides edged by ☐ represents a CGRP-binding motif; **SPM**: Spiegelmer

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

x-fold improved binding affinity: Improved binding affinity of Spiegelmers relative to 226-F2-001, measured by surface plasmon resonance on Biacore using direct binding to covalently immobilized human L-CGRP.

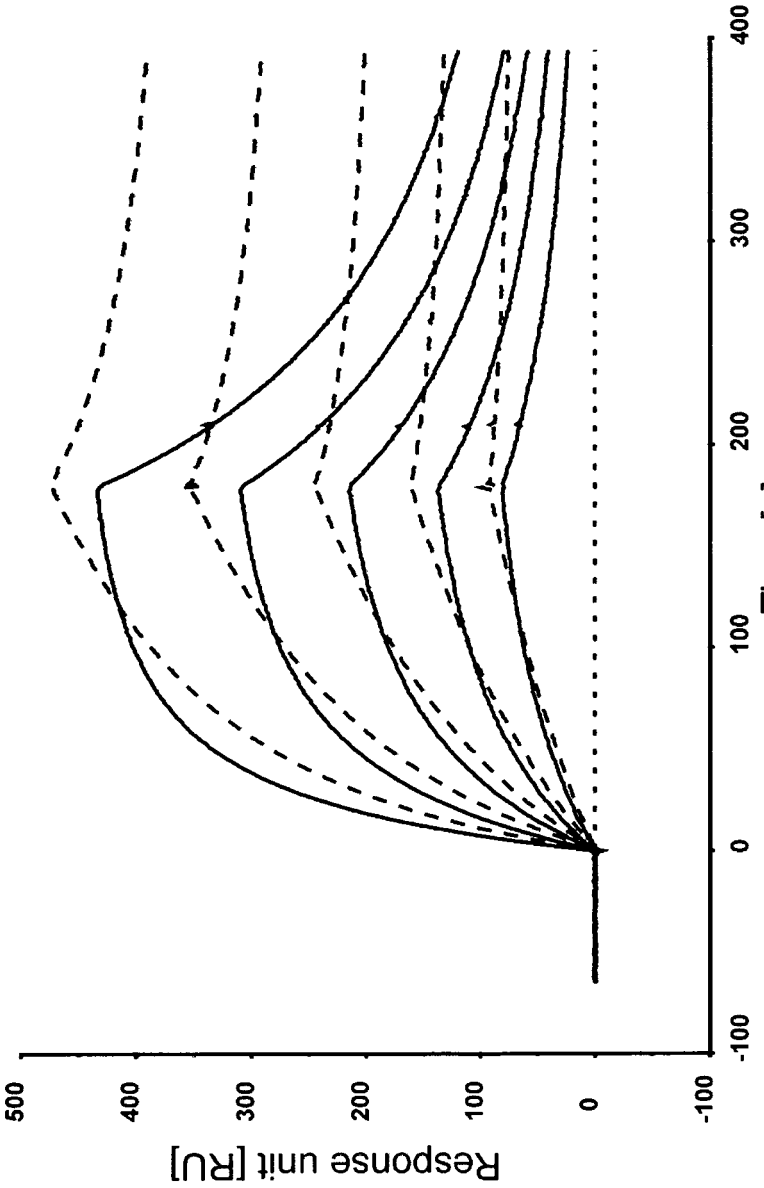
Biacore(SPM): Dissociation constant K_D of Spiegelmers (L-nucleic acid), molecules of the indicated sequence were tested as Spiegelmers (L-nucleic acid) measured as surface plasmon resonance on Biacore using direct binding to biotinylated L-CGRP

Fig. 3D



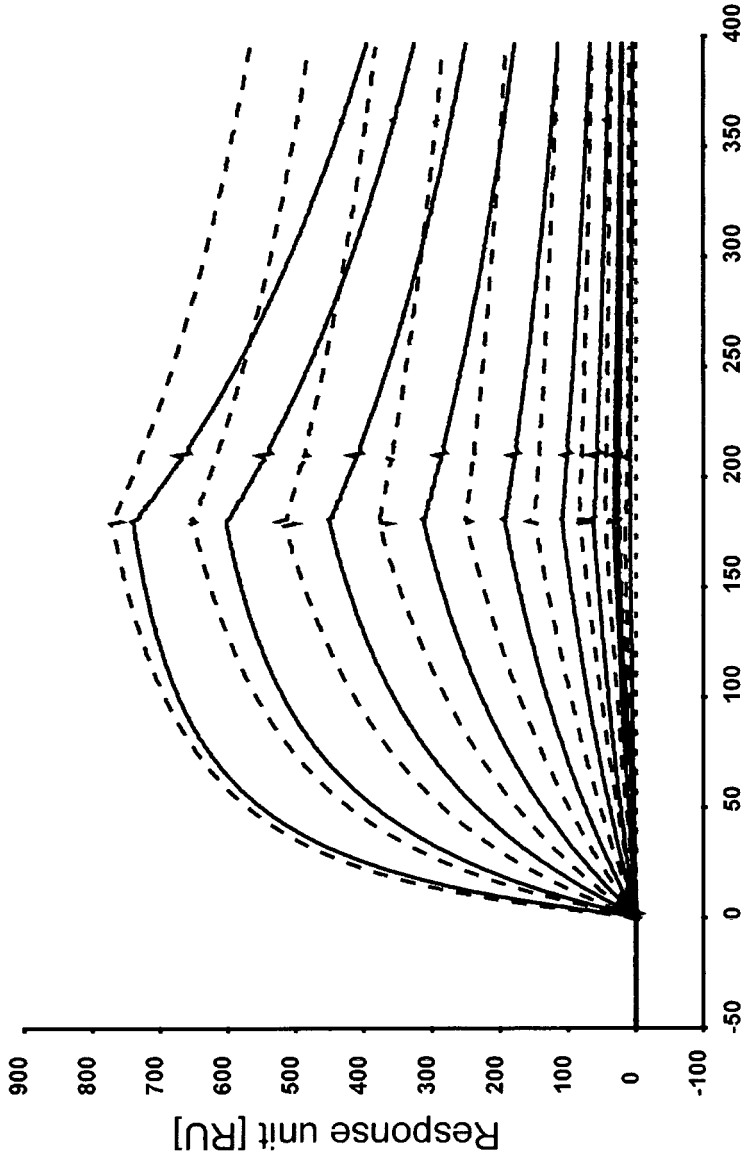
	K_D [nM]
226-F2-001 (solid lines)	2.6
226-F2-001-D41 (dashed lines)	0.50

Fig. 4



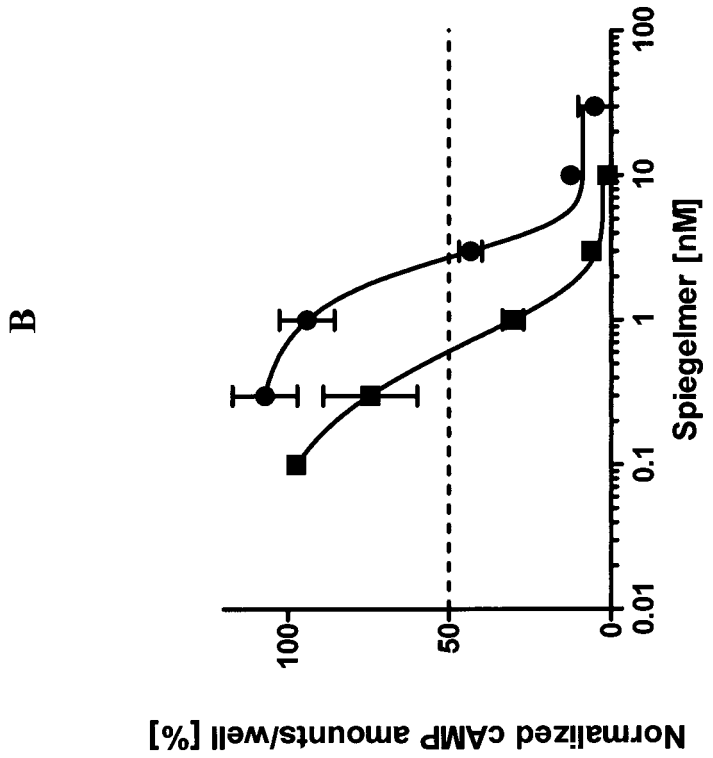
	K_D [nM]
226-F2-001 (solid lines)	2.6
226-F2-001-D44 (dashed line)	0.52

Fig. 5



	K_D [nM]
226-F2-001-D41 (solid line)	0.5
226-F2-001-D41/D44 (dashed line)	0.20

Fig. 6


B
Normalized cAMP amounts/well [%]
100
50
0
0.01
0.1
1
10
100
Spiegelmer [nM]

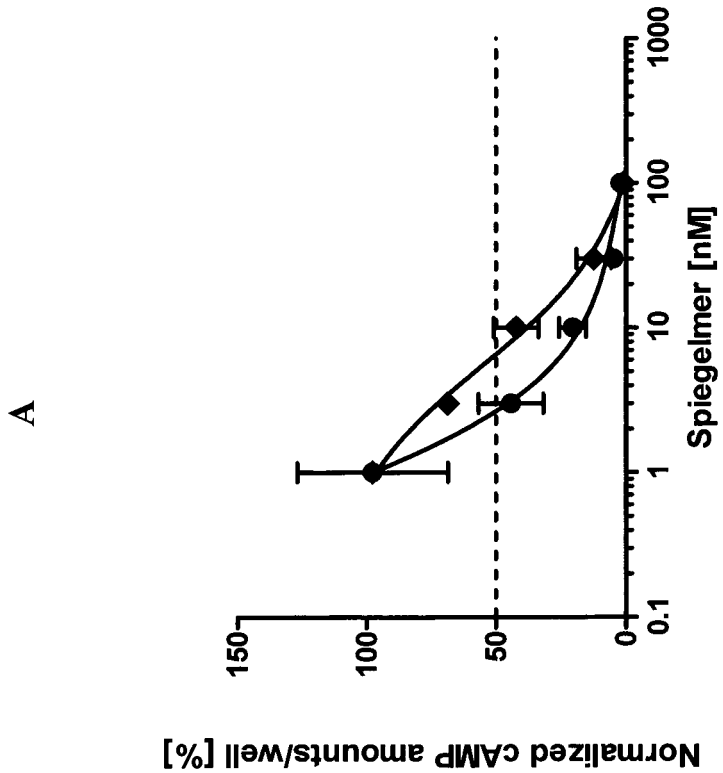

A
Normalized cAMP amounts/well [%]
150
100
50
0
0.1
1
10
100
1000
Spiegelmer [nM]

Fig. 7

A

```
Human alpha-CGRP:                    AC-DTATCV THRLAGLLSR SGGVVKNNFV PTNVGSKAF [SEQ ID NO: 82]
Human beta-CGRP:                     AC-NTATCV THRLAGLLSR SGGMVKSNFV PTNVGSKAF [SEQ ID NO: 83]
Human amylin:                        KC-NTATCA TQRLANFLVH SSNNFGAILS STNVGSNTY [SEQ ID NO: 84]
Human calcitonin:                    -CGNLSTCM LGTYTQDFNK FHT-----FP QTAIGVGAP [SEQ ID NO: 85]
Human adrenomedullin: YRQSMNNFQGLRSFGC-RFGTCT VQKLAHQIYQ FTDKDKDNVA PRSKISPQGY [SEQ ID NO: 86]
Human intermedin:           TQAQLLRVGC-VLGTCQ VQNLSHRLWQ LMGPAGRQDS APVDPSSPHSY [SEQ ID NO: 87]
```

B

```
Alpha-CGRP from
human:           ACDTATCV THRLAGLLSR SGGVVKNNFV PTNVGSKAF [SEQ ID NO: 82]
macaca mulatta*: ACDTATCV THRLAGLLSR SGGVVKNNFV PTNVGSKAF [SEQ ID NO: 82]
rat:             SCNTATCV THRLAGLLSR SGGVVKDNFV PTNVGSEAF [SEQ ID NO: 89]
mouse:           SCNTATCV THRLAGLLSR SGGVVKDNFV PTNVGSEAF [SEQ ID NO: 89]
sus scorfa:      SCNTATCV THRLAGLLSR SGGMVKSNFV PTDVGSEAF [SEQ ID NO: 91]
sheep:           SCNTATCV THRLAGLLSR SGGVVKSNFV PTNVGSQAF [SEQ ID NO: 92]
dog:             SCNTATCV THRLAGLLSR SGGVVKNNFV PTNVGSEAF [SEQ ID NO: 93]
```

Fig. 8

		IC_{50} (NOX-L41)	K_D (226-F2-001-D41)
h-αCGRP	ACDTATCVTHRLAGLLSRSGGVVKNNFVPTNVGSKAF [SEQ ID NO: 82]	0.39 nM	0.55 nM
r-αCGRP	SCNTATCVTHRLAGLLSRSGGVVKDNFVPTNVGSEAF [SEQ ID NO: 89]	3.6 nM	0.57 nM
r-Amylin	KCNTATCATQRLANFLVRSSNNFGAILSPTNVGSNTY [SEQ ID NO: 94]	283 nM	n.d.
h-Amylin	KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY [SEQ ID NO: 84]	>1000 nM	no binding

Fig. 9

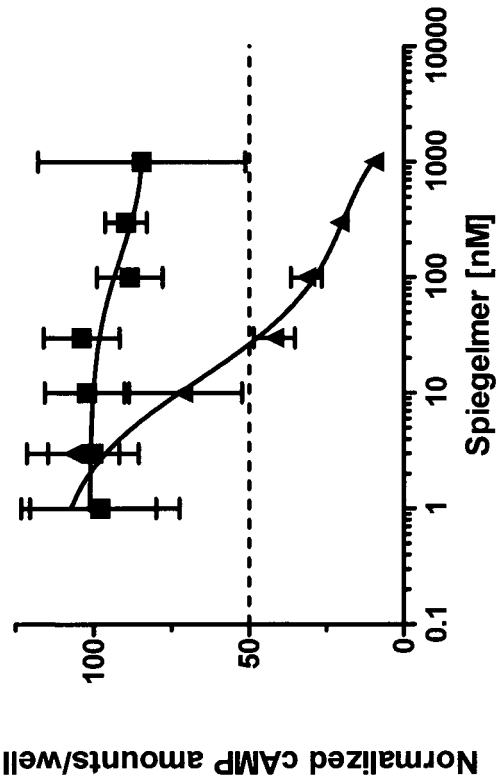

Normalized cAMP amounts/well [%]
100
50
0
0.1
1
10
100
1000
10000
Spiegelmer [nM]

Fig. 10

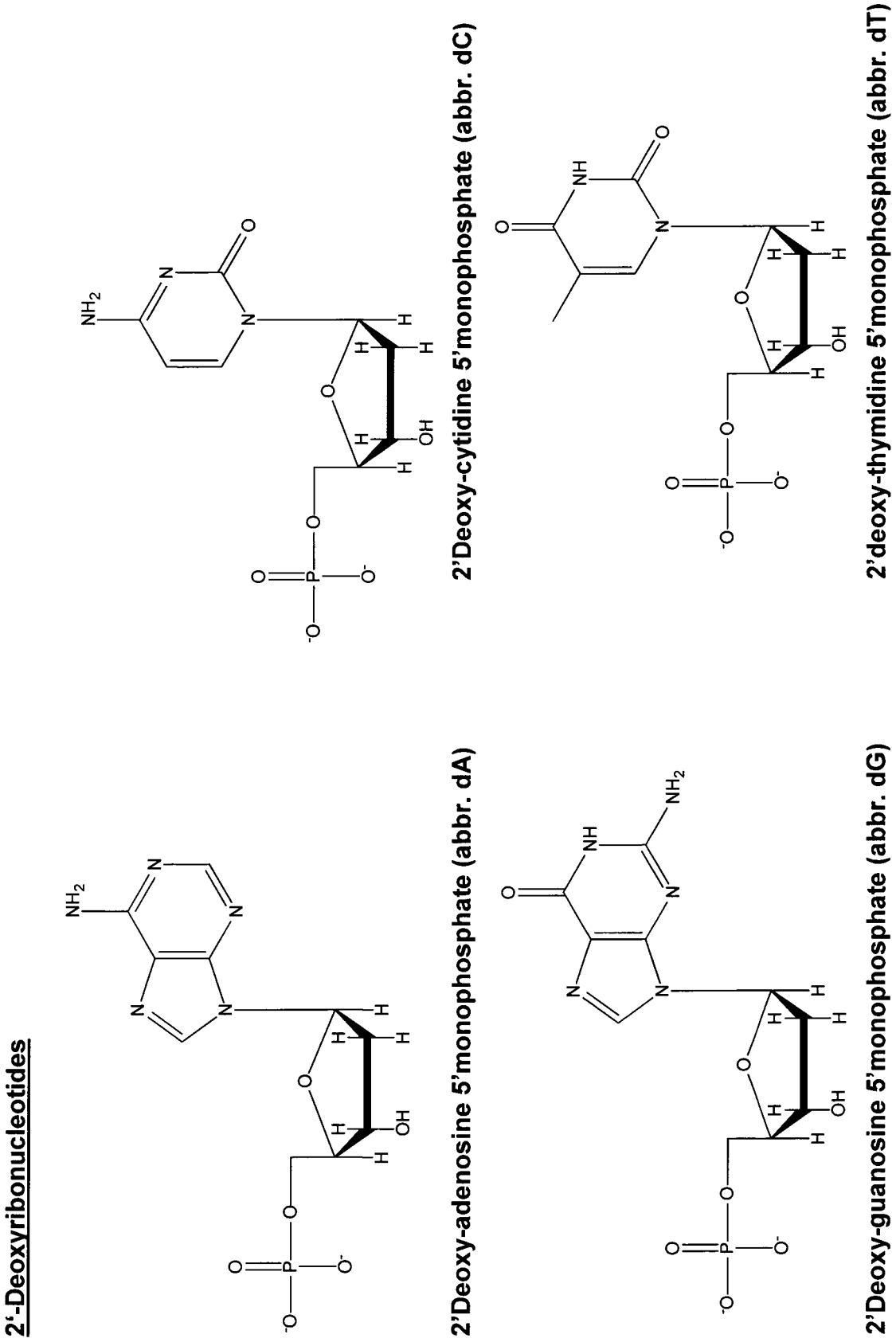
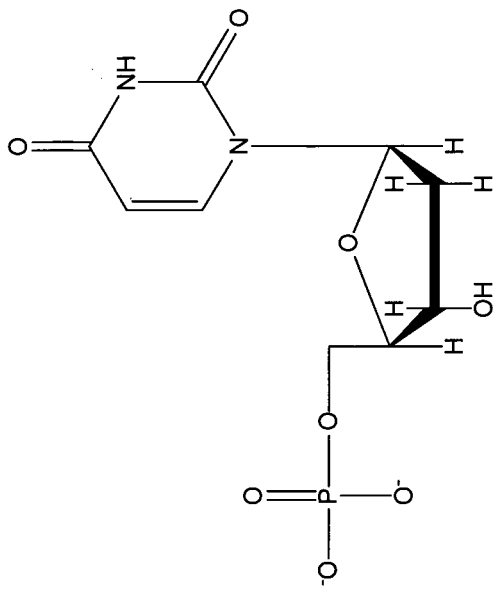

2'-Deoxyribonucleotides
2'Deoxy-adenosine 5'monophosphate (abbr. dA)
2'Deoxy-cytidine 5'monophosphate (abbr. dC)
2'Deoxy-guanosine 5'monophosphate (abbr. dG)
2'deoxy-thymidine 5'monophosphate (abbr. dT)

Fig. 11A

2'-Deoxyribonucleotides



2'Deoxy Uridine 5'monophosphate (abbr. dU)

Fig. 11B

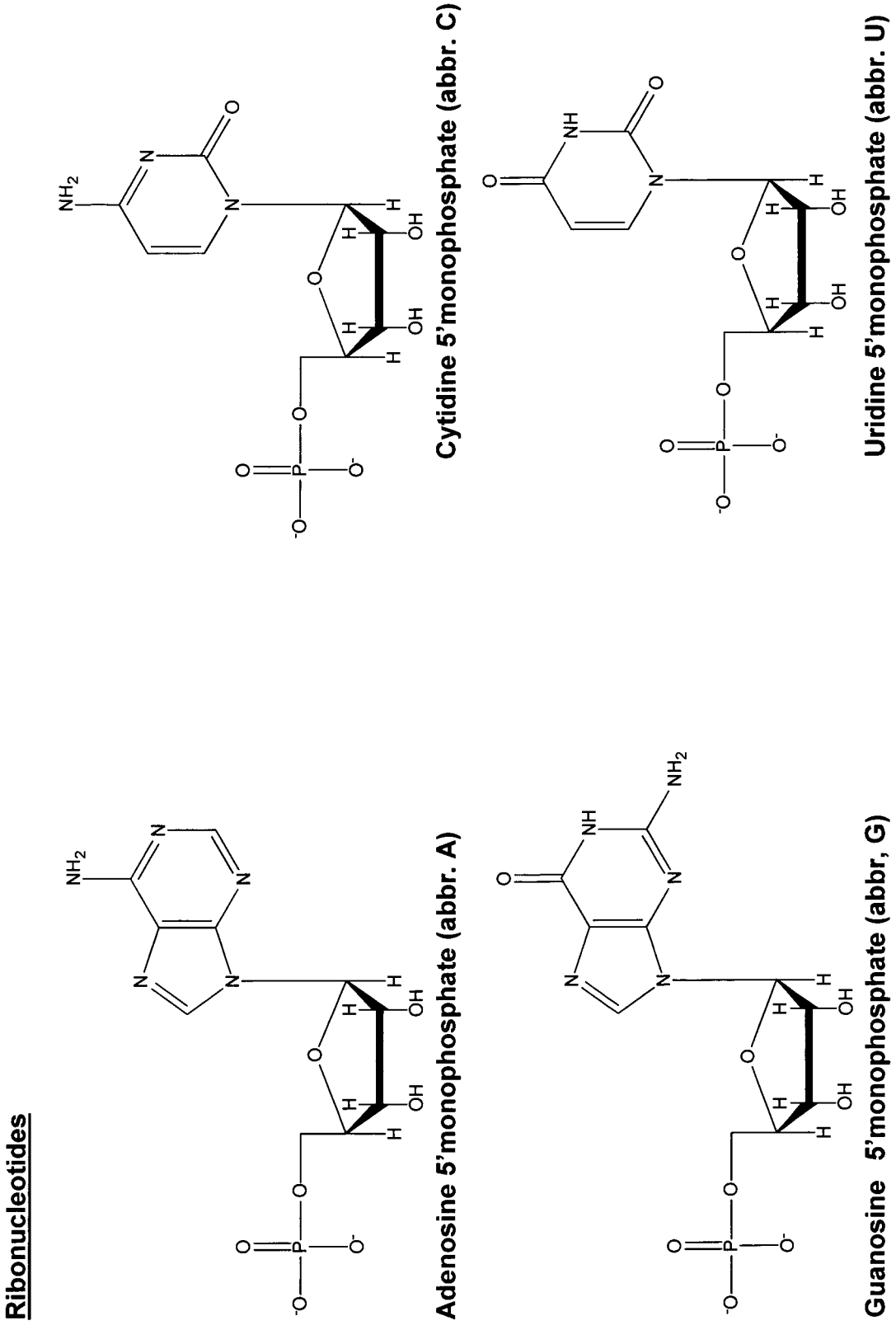
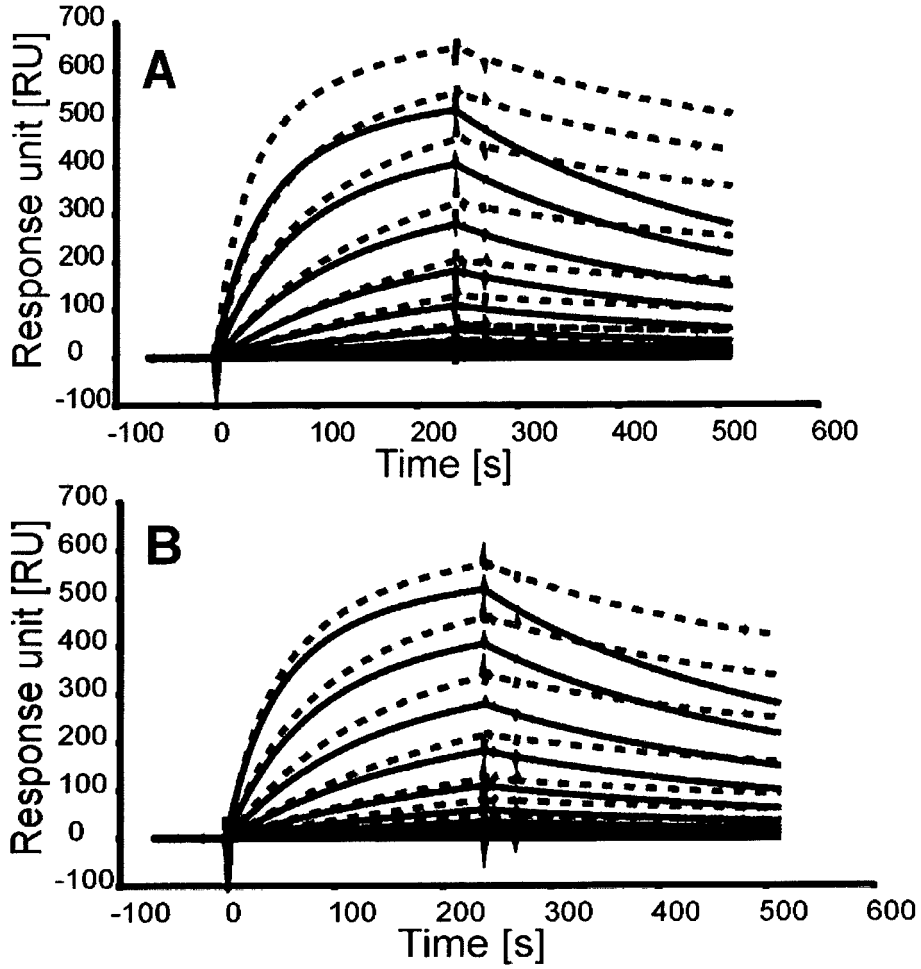

Ribonucleotides
Adenosine 5'monophosphate (abbr. A)
Cytidine 5'monophosphate (abbr. C)
Guanosine 5'monophosphate (abbr, G)
Uridine 5'monophosphate (abbr. U)

Fig. 12



	K_D [nM]
226-F2-001-D41 (A and B, solid line)	0.5
226-F2-001-D41-dU20 (A, dashed line)	0.07
226-F2-001-D41-dU28 (B, dashed line)	0.21

Fig. 13