

## Extended Data for:

# Beyond Natural Antibodies: Scaffold-Based Generation of Novel Anti-3CL<sup>pro</sup> Nanobody Nb01

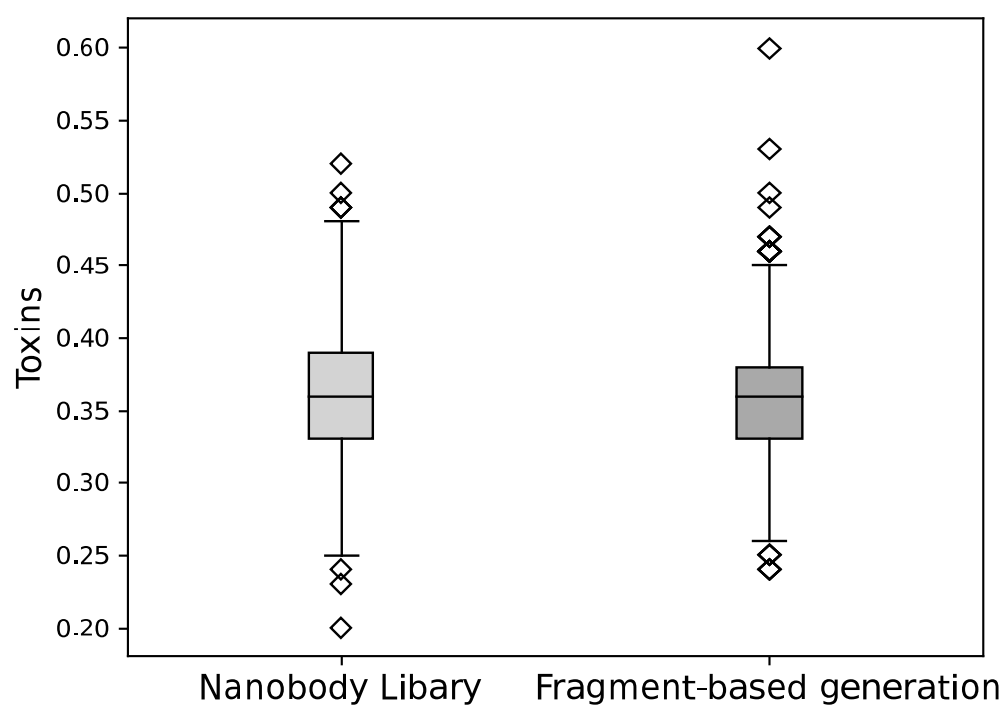
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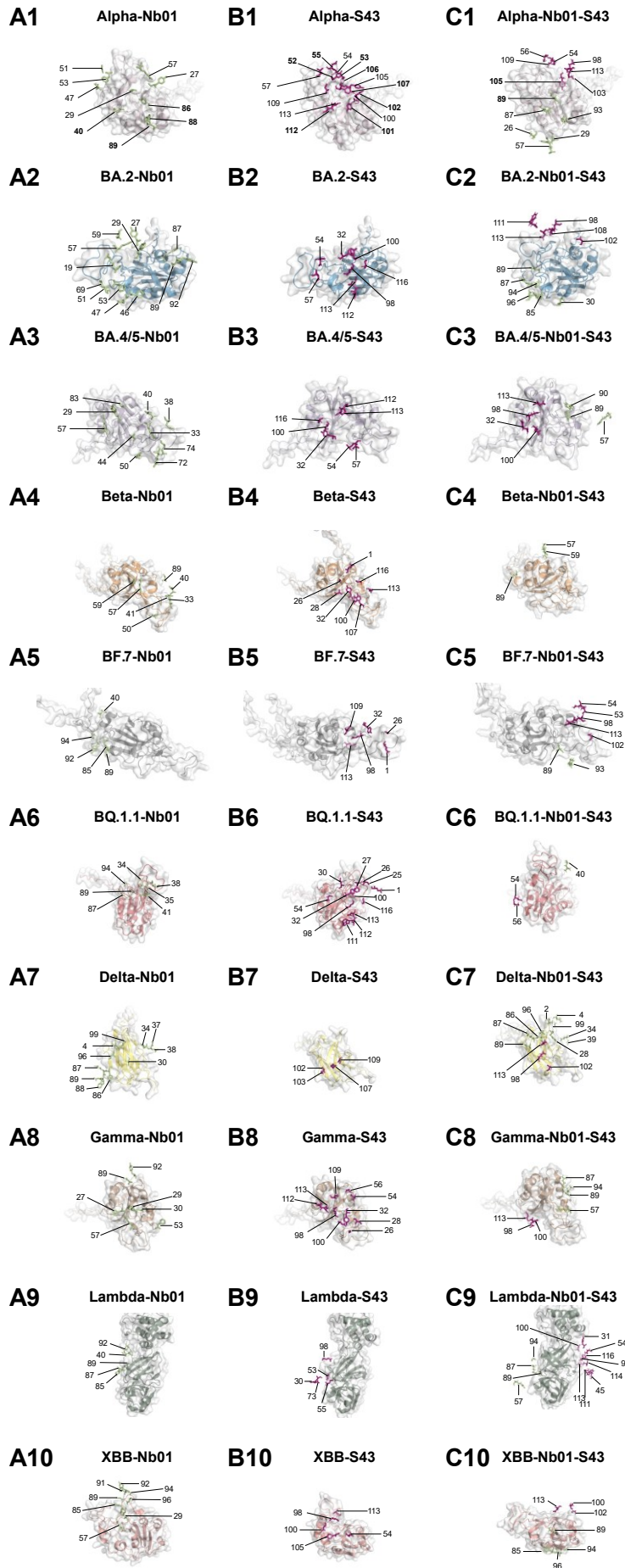
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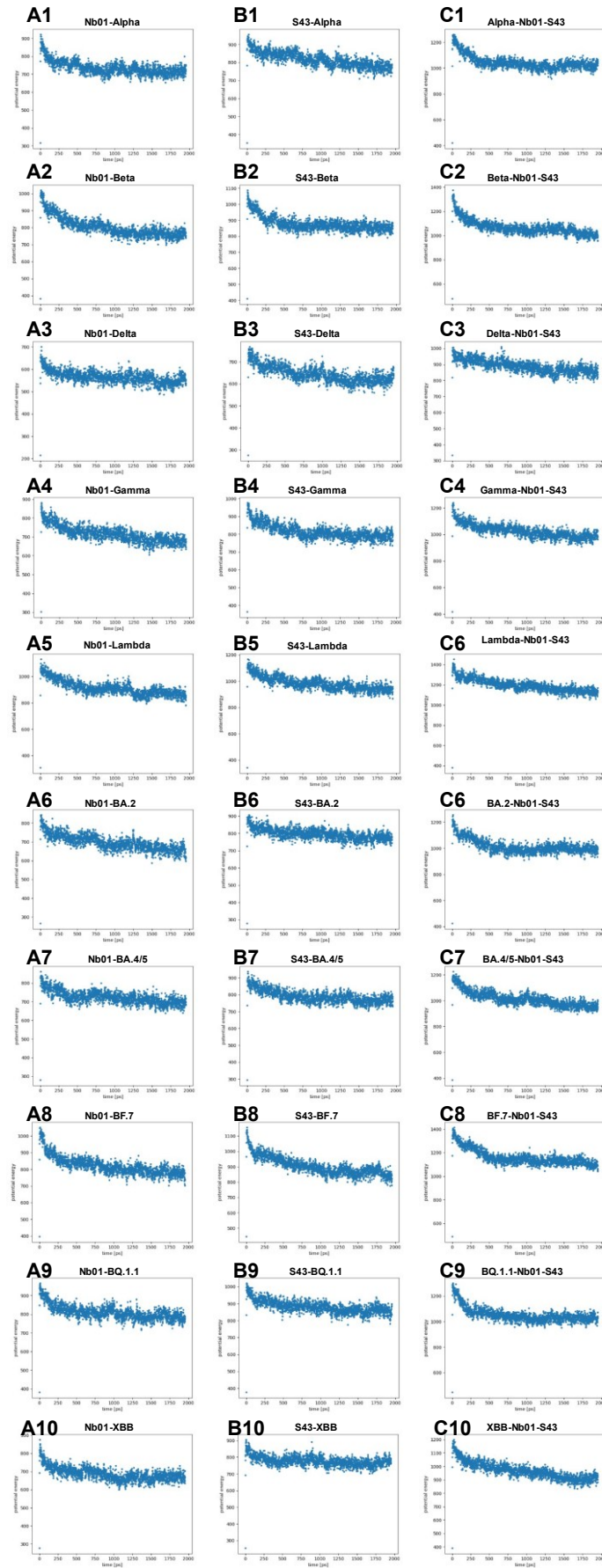
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**Extended Fig. 1 Toxins Prediction of two sets of sequence sets** (Fragment-based generated nanobodies and nanobody library)



**Extended Fig. 2**Details of the Interaction of NB01 and S43 in complex with the SARS-CoV2 variant, as well as of NB01 and S43 after simultaneous binding of the same antigen. Image generated with PyMOL.



**Extended Fig. 3** Potential energy changes when Nb5 and S43 bind to the variants, respectively, and when they compete simultaneously for the same antigen. (A1-10) Potential energy changes when NB01 binds to a variant; (B1-10) Potential energy changes when S43 binds to a variant; (C1-10) Potential energy changes when NB01 and S43 compete to bind the same variant.

**Extended Table. 1 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 ALPHA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR86[ OH ]	TYR128[ O ]	Hydrogen bond	2.53
TRP88[ NE1]	TYR128[ OH ]	Hydrogen bond	3.85
LEU40[ O ]	GLN175[ NE2]	Hydrogen bond	3.85
TRP88[ O ]	VAL180[ N ]	Hydrogen bond	2.31
ASN89[ OD1]	VAL180[ N ]	Hydrogen bond	3.76

**Extended Table. 2 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 BETA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR85[ OH ]	ASP87[ OD2]	Hydrogen bond	3.22
TYR85[ OH ]	GLU88[ OE1]	Hydrogen bond	3.84
ASN99[ N ]	ASN99[ OD1]	Hydrogen bond	3.22
TYR86[ OH ]	TYR135[ O ]	Hydrogen bond	3.73
TRP88[ N ]	TYR135[ OH ]	Hydrogen bond	3.77
ARG33[ NH2]	PHE168[ O ]	Hydrogen bond	3.44
SER48[ N ]	CYS170[ O ]	Hydrogen bond	3.75
ARG57[ NH1]	TYR183[ OH ]	Hydrogen bond	2.10
ALA44[ O ]	GLN175[ NE2]	Hydrogen bond	2.17
ILE45[ O ]	PHE172[ N ]	Hydrogen bond	3.41
GLU47[ OE2]	GLY167[ N ]	Hydrogen bond	2.67
TYR86[ O ]	ASN99[ ND2]	Hydrogen bond	2.63
TRP88[ O ]	TYR103[ OH ]	Hydrogen bond	3.28

**Extended Table. 3 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 DELTA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
GLN100[ N ]	GLU48[ OE1]	Hydrogen bond	3.37
SER30[ OG ]	GLY110[ O ]	Hydrogen bond	3.42
MET95[ N ]	TYR112[ OH ]	Hydrogen bond	2.15
TYR93[ O ]	SER39[ OG ]	Hydrogen bond	3.65
TYR93[ O ]	TYR112[ OH ]	Hydrogen bond	2.84

**Extended Table. 4 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 GAMMA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR28[ OH ]	ASN127[ OD1]	Hydrogen bond	2.04
ASN89[ N ]	PRO176[ O ]	Hydrogen bond	3.10
PHE90[ N ]	PRO176[ O ]	Hydrogen bond	2.31
TYR91[ N ]	THR177[ O ]	Hydrogen bond	3.44
ARG87[ O ]	THR177[ N ]	Hydrogen bond	3.32

**Extended Table. 5 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 LAMBDA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
ALA42[ N ]	THR169[ O ]	Hydrogen bond	3.74
TRP88[ N ]	LEU141[ O ]	Hydrogen bond	2.95
TRP88[ NE1]	CYS145[ SG ]	Hydrogen bond	2.30
ASN89[ N ]	GLY143[ O ]	Hydrogen bond	3.52
TYR91[ N ]	SER139[ OG ]	Hydrogen bond	2.58
TYR91[ N ]	SER139[ O ]	Hydrogen bond	2.45
TYR92[ OH ]	GLU288[ OE1]	Hydrogen bond	2.08
ASN89[ O ]	SER139[ OG ]	Hydrogen bond	3.51
ASN89[ OD1]	GLY143[ N ]	Hydrogen bond	2.20
PHE90[ O ]	PHE140[ N ]	Hydrogen bond	2.89
TYR91[ O ]	SER139[ OG ]	Hydrogen bond	2.15

**Extended Table. 6 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 OMICRON BA.2**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
ASN89[ N ]	GLY121[ O ]	Hydrogen bond	2.40
ARG87[ N ]	ASN124[ OD1]	Hydrogen bond	2.41
TYR93[ OH ]	ASN124[ OD1]	Hydrogen bond	2.42
ASN59[ ND2]	GLY156[ O ]	Hydrogen bond	2.43
ILE55[ N ]	GLY159[ O ]	Hydrogen bond	2.44
THR54[ OG1]	ASN161[ OD1]	Hydrogen bond	2.45
GLY51[ N ]	TYR163[ OH ]	Hydrogen bond	2.46
PHE90[ N ]	PHE171[ O ]	Hydrogen bond	2.47
PHE53[ O ]	TYR163[ OH ]	Hydrogen bond	2.48
ILE55[ O ]	TYR163[ N ]	Hydrogen bond	2.49
TYR86[ OH ]	TYR127[ N ]	Hydrogen bond	2.50
ARG87[ O ]	PHE171[ N ]	Hydrogen bond	2.51
TRP88[ O ]	ARG172[ N ]	Hydrogen bond	2.52
PHE90[ O ]	TYR175[ OH ]	Hydrogen bond	2.53
TYR92[ O ]	ASN122[ ND2]	Hydrogen bond	2.54

**Extended Table. 7 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 OMICRON BA.4/5**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TRP88[ NE1]	TYR127[ OH ]	Hydrogen bond	3.03
GLU47[ N ]	CYS162[ O ]	Hydrogen bond	3.60
SER26[ OG ]	ASN122[ ND2]	Hydrogen bond	3.80
LEU40[ O ]	TYR163[ OH ]	Hydrogen bond	3.66
GLU41[ OE2]	ASN161[ N ]	Hydrogen bond	2.04
GLU41[ OE2]	CYS162[ N ]	Hydrogen bond	3.61
ILE45[ O ]	PHE164[ N ]	Hydrogen bond	2.78
GLU47[ OE2]	ALA158[ N ]	Hydrogen bond	3.23
SER48[ OG ]	VAL160[ N ]	Hydrogen bond	3.07
ILE55[ O ]	ARG172[ NH1]	Hydrogen bond	2.98
ILE55[ O ]	ARG172[ NH2]	Hydrogen bond	3.13

**Extended Table. 8 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 OMICRON BF.7**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
ARG87[ N ]	ASN70[ O ]	Hydrogen bond	2.70
TYR93[ N ]	ASP64[ OD2]	Hydrogen bond	3.72
TYR93[ N ]	SER66[ OG ]	Hydrogen bond	3.39
TRP88[ O ]	GLU40[ N ]	Hydrogen bond	3.77
TYR92[ O ]	ASN70[ ND2]	Hydrogen bond	2.58
TYR92[ O ]	SER66[ OG ]	Hydrogen bond	3.04

**Extended Table. 9 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 OMICRON BQ.1.1**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
GLY39[ N ]	VAL162[ O ]	Hydrogen bond	3.38
LEU40[ N ]	TYR152[ O ]	Hydrogen bond	3.65
GLU41[ N ]	GLY164[ O ]	Hydrogen bond	3.64
GLU41[ N ]	CYS167[ O ]	Hydrogen bond	2.79
TYR86[ OH ]	GLN172[ OE1]	Hydrogen bond	3.68
ARG87[ NH1]	ASP99[ OD2]	Hydrogen bond	2.65
ASN89[ ND2]	GLY95[ O ]	Hydrogen bond	2.43
TYR91[ OH ]	GLU144[ OE2]	Hydrogen bond	3.46
TYR92[ N ]	ASP99[ O ]	Hydrogen bond	2.53
GLN34[ OE1]	TYR168[ OH ]	Hydrogen bond	3.33
ALA35[ O ]	VAL165[ N ]	Hydrogen bond	2.53
ALA35[ O ]	ASN166[ N ]	Hydrogen bond	3.29
GLN38[ OE1]	ALA163[ N ]	Hydrogen bond	3.69
GLY39[ O ]	VAL165[ N ]	Hydrogen bond	3.08
LEU40[ O ]	PHE169[ N ]	Hydrogen bond	2.95
ARG87[ NH1]	ASP99[ OD2]	Salt bridge	2.65
ARG87[ NH1]	ASP99[ OD1]	Salt bridge	3.43

**Extended Table. 10 THE INTERACTION BINDING SITE BETWEEN NB01 AND SARS-COV-2 OMICRON XBB**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR28[ N ]	THR167[ O ]	Hydrogen bond	3.86
TYR28[ OH ]	ARG165[ O ]	Hydrogen bond	3.35
TYR86[ OH ]	HIS172[ O ]	Hydrogen bond	3.45
ASN89[ N ]	ASN115[ O ]	Hydrogen bond	3.55
GLY94[ N ]	SER113[ O ]	Hydrogen bond	3.74
GLY84[ O ]	GLY171[ N ]	Hydrogen bond	3.71
TYR85[ O ]	TYR116[ N ]	Hydrogen bond	2.67
ASN89[ O ]	SER113[ OG ]	Hydrogen bond	2.76
ASN89[ O ]	GLY114[ N ]	Hydrogen bond	3.57
TYR92[ O ]	GLY114[ N ]	Hydrogen bond	3.11

**Extended Table. 11 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 ALPHA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
SER102[ N ]	ASN125[ O ]	Hydrogen bond	3.19
TYR106[ OH ]	GLY159[ O ]	Hydrogen bond	3.21
ASN55[ N ]	GLU161[ O ]	Hydrogen bond	3.59
SER52[ OG ]	GLU161[ O ]	Hydrogen bond	2.55
SER53[ N ]	GLU161[ O ]	Hydrogen bond	3.77
SER53[ OG ]	GLU161[ OE2]	Hydrogen bond	2.56
THR112[ OG1]	GLN170[ OE1]	Hydrogen bond	3.22
TYR107[ OH ]	ASN127[ ND2]	Hydrogen bond	3.55
ASP100[ OD1]	ASN127[ ND2]	Hydrogen bond	3.82

**Extended Table. 12 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 BETA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
SER102[ OG ]	SER176[ O ]	Hydrogen bond	2.51
SER102[ OG ]	SER176[ OG ]	Hydrogen bond	3.44
TYR101[ OH ]	PRO181[ O ]	Hydrogen bond	3.20
TYR32[ OH ]	ASN130[ ND2]	Hydrogen bond	3.49
TYR105[ O ]	LYS166[ NZ ]	Hydrogen bond	3.22
TYR106[ OH ]	GLN175[ NE2]	Hydrogen bond	2.53
VAL104[ O ]	GLY178[ N ]	Hydrogen bond	3.15
SER102[ O ]	PHE179[ N ]	Hydrogen bond	3.22
ASP100[ O ]	PHE179[ N ]	Hydrogen bond	2.23
TYR101[ OH ]	TYR183[ N ]	Hydrogen bond	3.34

**Extended Table. 13 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 DELTA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR105[ N ]	GLY61[ O ]	Hydrogen bond	3.74
SER102[ O ]	SER58[ OG ]	Hydrogen bond	3.43
GLY103[ O ]	GLY59[ N ]	Hydrogen bond	3.76
GLY103[ O ]	ASP60[ N ]	Hydrogen bond	3.39
VAL104[ O ]	ARG57[ N ]	Hydrogen bond	2.04
VAL104[ O ]	SER58[ N ]	Hydrogen bond	3.12
TYR105[ OH ]	VAL54[ N ]	Hydrogen bond	3.60

**Extended Table. 14 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 GAMMA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR105[ OH ]	GLY162[ O ]	Hydrogen bond	3.25
TYR31[ OH ]	ASN164[ OD1]	Hydrogen bond	2.36
VAL104[ N ]	PHE167[ O ]	Hydrogen bond	3.55
CYS109[ O ]	TYR126[ OH ]	Hydrogen bond	3.45
TYR105[ OH ]	TYR166[ N ]	Hydrogen bond	2.56
TYR105[ OH ]	PHE167[ N ]	Hydrogen bond	3.49

**Extended Table. 15 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 LAMBDA**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
SER53[ OG ]	GLN189[ O ]	Hydrogen bond	3.89
ASN54[ ND2]	THR190[ OG1]	Hydrogen bond	3.63
THR108[ N ]	ALA191[ O ]	Hydrogen bond	2.14
GLY103[ O ]	GLY170[ N ]	Hydrogen bond	2.96
GLY103[ O ]	VAL171[ N ]	Hydrogen bond	2.98
ASN54[ OD1]	ARG188[ NH1]	Hydrogen bond	3.86
TYR106[ O ]	ALA193[ N ]	Hydrogen bond	3.52



**Extended Table. 16 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 OMICRON BA.2**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
ASN54[ ND2]	GLY159[ O ]	Hydrogen bond	2.10
ASN54[ ND2]	CYS162[ O ]	Hydrogen bond	3.33
TYR105[ N ]	SER168[ OG ]	Hydrogen bond	3.46
SER102[ OG ]	TYR169[ O ]	Hydrogen bond	2.01
SER102[ N ]	PHE171[ O ]	Hydrogen bond	3.74
ASP100[ O ]	ASN122[ ND2]	Hydrogen bond	2.12
TYR105[ O ]	ARG167[ NH2]	Hydrogen bond	3.53
SER102[ OG ]	TYR169[ N ]	Hydrogen bond	2.94
SER102[ OG ]	GLY170[ N ]	Hydrogen bond	3.36
PHE114[ O ]	ARG172[ NH1]	Hydrogen bond	3.54
ASP113[ OD1]	ARG172[ NE ]	Salt bridge	2.79
ASP113[ OD1]	ARG172[ NH2]	Salt bridge	3.05
ASP113[ OD2]	ARG172[ NH2]	Salt bridge	3.89

**Extended Table. 17 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 OMICRON BA.4/5**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
VAL104[ N ]	TRP27[ O ]	Hydrogen bond	3.79
TYR105[ OH ]	ARG126[ O ]	Hydrogen bond	2.56
TYR106[ OH ]	ILE142[ O ]	Hydrogen bond	3.83
TYR32[ OH ]	ARG20[ NH1]	Hydrogen bond	3.16
SER56[ OG ]	GLY156[ N ]	Hydrogen bond	3.44
ASP100[ O ]	ARG20[ NH1]	Hydrogen bond	3.37
SER102[ O ]	SER23[ N ]	Hydrogen bond	2.36
SER102[ OG ]	SER23[ N ]	Hydrogen bond	3.05
VAL104[ O ]	ARG128[ NE ]	Hydrogen bond	3.33
ASP113[ OD1]	ARG126[ NH2]	Hydrogen bond	2.70
ASP113[ OD2]	ARG126[ NH1]	Hydrogen bond	3.01
ASP100[ OD2]	ARG20[ NH1]	Salt bridge	3.70
ASP113[ OD1]	ARG126[ NE ]	Salt bridge	3.79
ASP113[ OD1]	ARG126[ NH1]	Salt bridge	3.28
ASP113[ OD1]	ARG126[ NH2]	Salt bridge	2.70
ASP113[ OD2]	ARG126[ NH1]	Salt bridge	3.01
ASP113[ OD2]	ARG126[ NH2]	Salt bridge	3.92

**Extended Table. 18 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 OMICRON BF.7**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR107[ OH ]	TYR201[ OH ]	Hydrogen bond	3.19
TRP111[ N ]	THR200[ OG1]	Hydrogen bond	3.01
GLY26[ O ]	ASN187[ N ]	Hydrogen bond	3.26
GLU98[ OE2]	TYR201[ OH ]	Hydrogen bond	2.51
PRO99[ O ]	ARG103[ NH1]	Hydrogen bond	3.48
PRO99[ O ]	ARG103[ NH2]	Hydrogen bond	3.90
TYR101[ O ]	ASN117[ ND2]	Hydrogen bond	2.82
SER102[ OG ]	HIS205[ NE2]	Hydrogen bond	3.20
VAL104[ O ]	ASN105[ ND2]	Hydrogen bond	2.70
VAL104[ O ]	HIS205[ NE2]	Hydrogen bond	3.43
GLY110[ O ]	ARG198[ NH1]	Hydrogen bond	2.14
GLY110[ O ]	TYR201[ OH ]	Hydrogen bond	3.09
ASP113[ OD1]	ARG198[ NE ]	Salt bridge	2.10
ASP113[ OD1]	ARG198[ NH2]	Salt bridge	3.44
ASP113[ OD2]	ARG198[ NE ]	Salt bridge	2.83

**Extended Table. 19 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 OMICRON BQ.1.1**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance(Å)
SER102[ OG ]	TYR132[ O ]	Hydrogen bond	2.05
VAL104[ N ]	TYR132[ O ]	Hydrogen bond	3.85
THR28[ OG1]	ALA154[ O ]	Hydrogen bond	3.59
TYR31[ N ]	ASN166[ OD1]	Hydrogen bond	3.51
VAL104[ N ]	TYR168[ O ]	Hydrogen bond	3.22
THR112[ OG1]	ASN127[ ND2]	Hydrogen bond	3.31
SER102[ OG ]	TYR132[ N ]	Hydrogen bond	3.59
PHE27[ O ]	LYS157[ NZ ]	Hydrogen bond	3.43
TYR101[ O ]	GLY164[ N ]	Hydrogen bond	3.17
TYR107[ OH ]	VAL165[ N ]	Hydrogen bond	2.04
ASP100[ OD2]	ASN166[ N ]	Hydrogen bond	2.02
THR28[ O ]	ASN166[ ND2]	Hydrogen bond	2.62
THR28[ OG1]	ASN166[ ND2]	Hydrogen bond	2.28
ASP100[ OD1]	TYR168[ N ]	Hydrogen bond	3.49
ASP100[ OD2]	TYR168[ N ]	Hydrogen bond	3.85
GLY103[ O ]	PHE169[ N ]	Hydrogen bond	2.53

**Extended Table. 20 THE INTERACTION BINDING SITE BETWEEN S43 AND SARS-COV-2 OMICRON XBB**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
ASN54[ ND2]	ASN115[ OD1]	Hydrogen bond	2.16
TYR101[ OH ]	VAL150[ O ]	Hydrogen bond	2.99
VAL104[ N ]	ARG165[ O ]	Hydrogen bond	2.75
TYR105[ N ]	PRO166[ O ]	Hydrogen bond	3.37
THR112[ OG1]	ASN148[ O ]	Hydrogen bond	2.88
SER102[ O ]	THR167[ N ]	Hydrogen bond	2.41

**Extended Table. 21 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
ASN89[HD22]	GLY162[ O ]	Hydrogen bond	2.13
ASN89[HD21]	GLU161[ O ]	Hydrogen bond	2.04

**Extended Table. 22 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
ARG57[HH11]	ASN122[ OD1]	Hydrogen bond	2.17
ARG57[HH21]	ASN122[ OD1]	Hydrogen bond	2.50

**Extended Table. 23 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
GLN34[ OE1]	ARG49[HH22]	Hydrogen bond	2.23
TYR93[ O ]	TYR112[ HH ]	Hydrogen bond	1.83
GLN100[HE21]	GLY46[ O ]	Hydrogen bond	1.88
TRP98[ H ]	ARG49[ O ]	Hydrogen bond	2.42
ARG87[HH12]	ASP66[ OD1]	Hydrogen bond	1.72
ARG87[HH22]	ASP66[ OD2]	Hydrogen bond	1.73
TYR28[ HH ]	TYR108[ O ]	Hydrogen bond	1.84
ARG87[ NH1]	ASP66[ OD1]	Salt bridge	2.71
ARG87[ NH2]	ASP66[ OD1]	Salt bridge	3.43
ARG87[ NH1]	ASP66[ OD2]	Salt bridge	3.54
ARG87[ NH2]	ASP66[ OD2]	Salt bridge	2.72

**Extended Table. 24 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
LYS50[ HZ1]	SER154[ OG ]	Hydrogen bond	1.98
ASN89[HD22]	ASP82[ OD2]	Hydrogen bond	2.24
PHE90[ H ]	TYR130[ OH ]	Hydrogen bond	2.31

**Extended Table. 25 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
LYS50[ HZ1]	SER154[ OG ]	Hydrogen bond	1.98
ASN89[HD22]	ASP82[ OD2]	Hydrogen bond	2.24
PHE90[ H ]	TYR130[ OH ]	Hydrogen bond	2.31

**Extended Table. 26 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR28[ OH ]	TYR175[ HH ]	Hydrogen bond	1.99
PHE90[ O ]	ARG167[HH22]	Hydrogen bond	1.94
PHE90[ H ]	ASN161[ OD1]	Hydrogen bond	1.81
TYR91[ HH ]	VAL157[ O ]	Hydrogen bond	1.78
TYR92[ H ]	ASN161[ OD1]	Hydrogen bond	1.72

**Extended Table. 27 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR91[ HH ]	A:ASN 124[ OD1]	Hydrogen bond	2.28

**Extended Table. 28 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR85[ OH ]	GLY146[ H ]	Hydrogen bond	1.92
TYR86[ O ]	ASN150[HD21]	Hydrogen bond	2.29
TYR93[ OH ]	ARG152[HH22]	Hydrogen bond	2.36
TRP88[ H ]	GLY147[ O ]	Hydrogen bond	2.37

**Extended Table. 29 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR86[ OH ]	ARG131[HH11]	Hydrogen bond	1.91

**Extended Table. 30 THE INTERACTION BINDING SITE OF NB01 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR91[ OH ]	LYS111[ H ]	Hydrogen bond	2.23
TYR86[ HH ]	TYR168[ O ]	Hydrogen bond	2.32
ASN89[ H ]	GLY163[ O ]	Hydrogen bond	1.66
TYR91[ H ]	GLY114[ O ]	Hydrogen bond	2.47

**Extended Table. 31 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR105[ OH ]	ALA25[ H ]	Hydrogen bond	2.22
TYR105[ HH ]	ARG23[ O ]	Hydrogen bond	1.78

**Extended Table. 32 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR101[ O ]	ASN163[HD22]	Hydrogen bond	1.76
SER102[ OG ]	ARG28[ HE ]	Hydrogen bond	2.32
SER102[ OG ]	ARG28[HH21]	Hydrogen bond	1.95
THR108[ OG1]	GLY167[ H ]	Hydrogen bond	1.98
ASP113[ OD2]	THR160[ H ]	Hydrogen bond	1.76
TYR106[ HH ]	GLU22[ OE1]	Hydrogen bond	1.71
GLY110[ H ]	SER159[ O ]	Hydrogen bond	2.47
TYR107[ H ]	CYS162[ O ]	Hydrogen bond	2.32
GLY103[ H ]	ASN163[ OD1]	Hydrogen bond	2.48
SER53[ H ]	GLY164[ O ]	Hydrogen bond	2.42
THR108[ H ]	CYS170[ SG ]	Hydrogen bond	2.38

**Extended Table. 33 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
GLU98[ OE2]	TYR108[ HH ]	Hydrogen bond	1.68
VAL104[ O ]	THR106[ H ]	Hydrogen bond	2.18
TYR106[ O ]	PHE107[ H ]	Hydrogen bond	2.08
TYR106[ H ]	ASP105[ O ]	Hydrogen bond	1.77

**Extended Table. 34 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
ASP113[ OD1]	ARG34[ H ]	Hydrogen bond	1.82

**Extended Table. 35 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
GLU98[ OE1]	LYS102[ HZ2]	Hydrogen bond	2.03
GLU98[ OE1]	LYS102[ HZ3]	Hydrogen bond	2.33
GLU98[ OE2]	LYS102[ HZ3]	Hydrogen bond	2.29
ASP100[ O ]	ARG298[HH22]	Hydrogen bond	2.20
VAL104[ O ]	GLN110[HE22]	Hydrogen bond	2.27
THR108[ O ]	LYS102[ HZ3]	Hydrogen bond	2.46
THR108[ OG1]	ARG105[ H ]	Hydrogen bond	1.96
GLY110[ O ]	LYS102[ HZ1]	Hydrogen bond	2.22
THR112[ O ]	LYS100[ HZ2]	Hydrogen bond	1.74
ASP113[ OD1]	CYS156[ HG ]	Hydrogen bond	1.76
VAL104[ H ]	GLY109[ O ]	Hydrogen bond	2.41
THR108[ OG1]	ARG105[ O ]	Hydrogen bond	3.46
GLU98[ OE1]	LYS102[ NZ ]	Salt bridge	2.71
GLU98[ OE2]	LYS102[ NZ ]	Salt bridge	2.78
ASP113[ OD2]	LYS102[ NZ ]	Salt bridge	3.28

**Extended Table. 36 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
GLU98[ OE1]	ASN155[HD22]	Hydrogen bond	1.74
TYR101[ O ]	ASN122[HD22]	Hydrogen bond	1.79
SER102[ O ]	ASN122[ H ]	Hydrogen bond	2.07
VAL104[ O ]	ARG20[HH21]	Hydrogen bond	1.84
VAL104[ O ]	ARG20[ HE ]	Hydrogen bond	2.12
ASP113[ OD1]	ASN155[ H ]	Hydrogen bond	1.85
ASP113[ OD2]	GLN148[HE22]	Hydrogen bond	2.05

**Extended Table. 37 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR32[ OH ]	ARG20[HH11]	Hydrogen bond	2.06
TYR101[ O ]	ALA158[ H ]	Hydrogen bond	1.70
VAL104[ H ]	ALA158[ O ]	Hydrogen bond	2.07
TYR105[ H ]	ALA158[ O ]	Hydrogen bond	1.82

**Extended Table. 38 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
TYR105[ O ]	GLN193[HE22]	Hydrogen bond	1.75
TYR106[ O ]	ARG198[ HE ]	Hydrogen bond	1.84
GLU98[ OE1]	ARG198[HH11]	Hydrogen bond	1.87
TYR105[ O ]	ARG198[HH22]	Hydrogen bond	1.76
GLU98[ OE1]	TYR201[ HH ]	Hydrogen bond	1.74
GLU98[ OE1]	ARG198[ NH1]	Salt bridge	2.68
GLU98[ OE1]	ARG198[ NH2]	Salt bridge	3.77
GLU98[ OE2]	ARG198[ NH2]	Salt bridge	3.94

**Extended Table. 39 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
VAL104[ O ]	ASN96[HD21]	Hydrogen bond	1.77
TYR105[ HH ]	LEU134[ O ]	Hydrogen bond	2.17

**Extended Table. 40 THE INTERACTION BINDING SITE OF S43 WHEN THE COMPLEX WITH THE VARIANT**

Nanobody Res. Info.	Antigen Res. Info.	Interaction Info.	Distance (Å)
ASP100[ O ]	LYS111[ HZ2]	Hydrogen bond	2.45
VAL104[ O ]	ASN21[HD22]	Hydrogen bond	1.84