Supporting Information

Quantitative Structure Activity Relationship (QSAR) study predicts small molecule binding to RNA structure

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Table of Contents

Section A. Supplementary table and figures

Parameter	Input
Rejection limit	100
Iteration limit	10000
RMS gradient	0.005
MM iteration limit	500
RMSD limit	0.15
Energy window	3
Conformation limit	10000

Table S1. Parameters used for conformation search

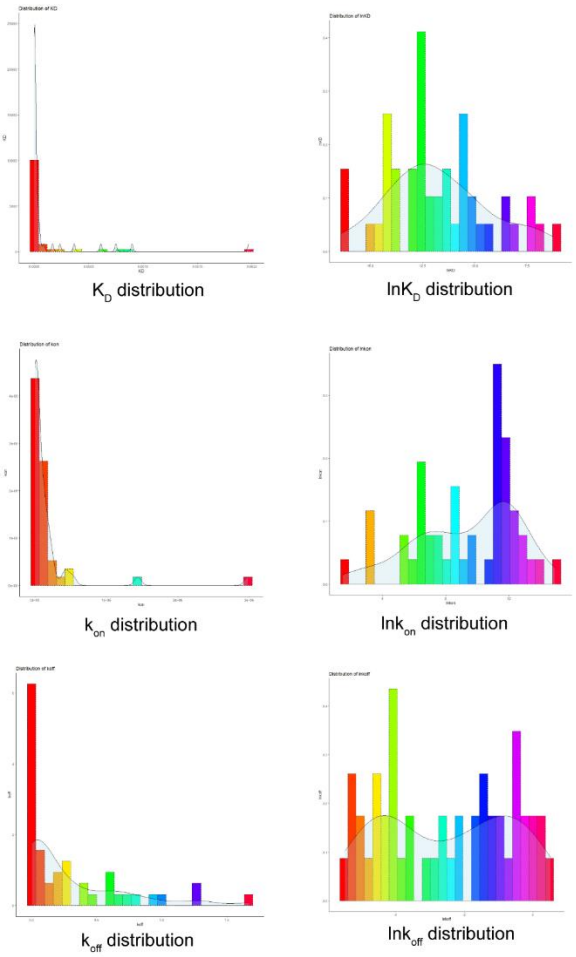


Figure S1 Natural log transformation was taken for each response variable to shift the skewed distribution close to a normal distribution.

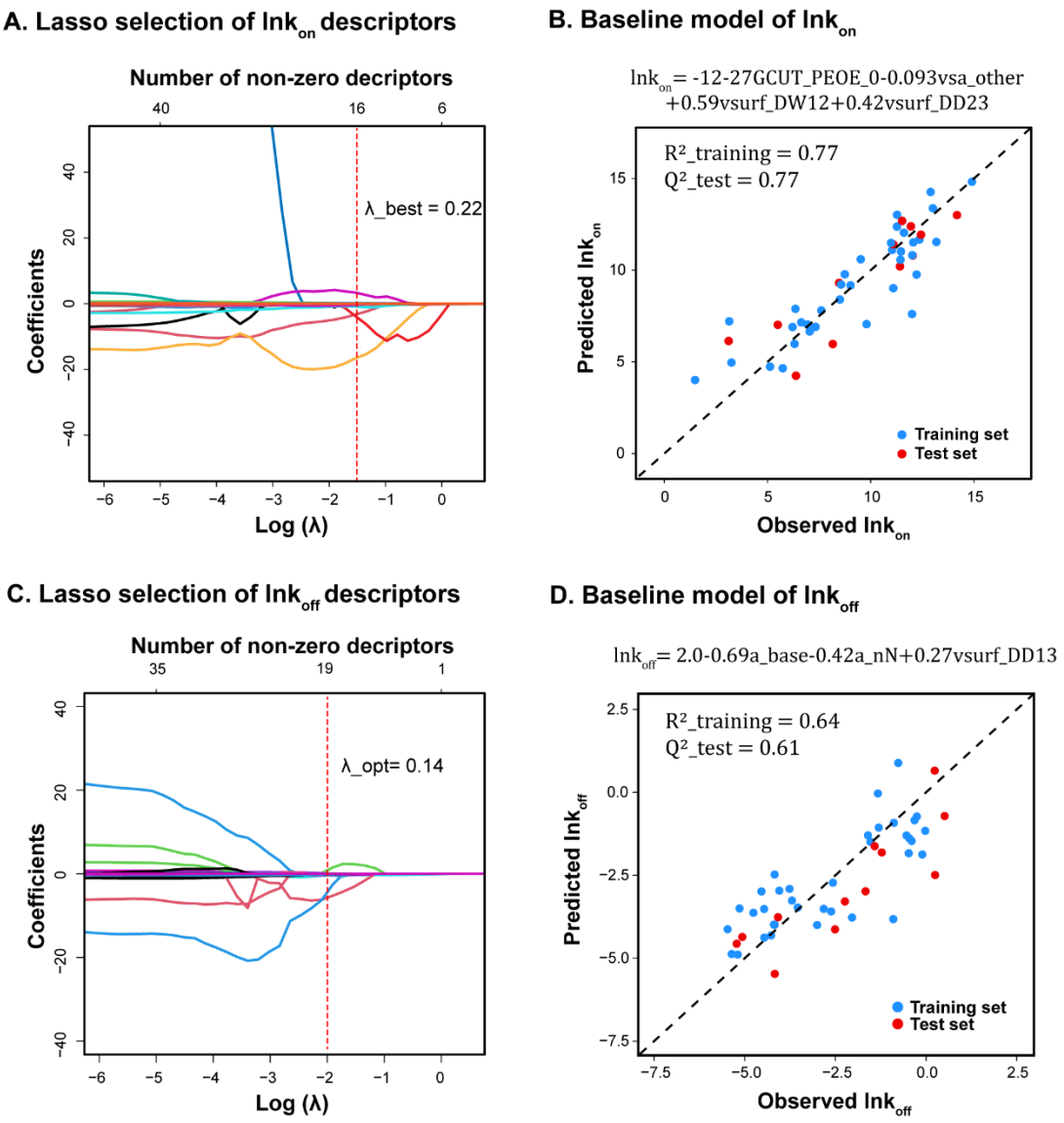


Figure S2 A. Lasso selection of lnk_{on} descriptors, the best λ was determined as 0.22 from 5-fold cross validation. **B** Observed lnk_{on} was plotted with the value predicted by the MLR baseline model shown at top. **C** Lasso selection of lnk_{off} descriptors, the optimized λ was determined as 0.14 to ensure the inclusion of a decisive descriptor: vsurf_DD13. **D** Observed lnk_{off} was plotted with the value predicted by the MLR baseline model shown at top.

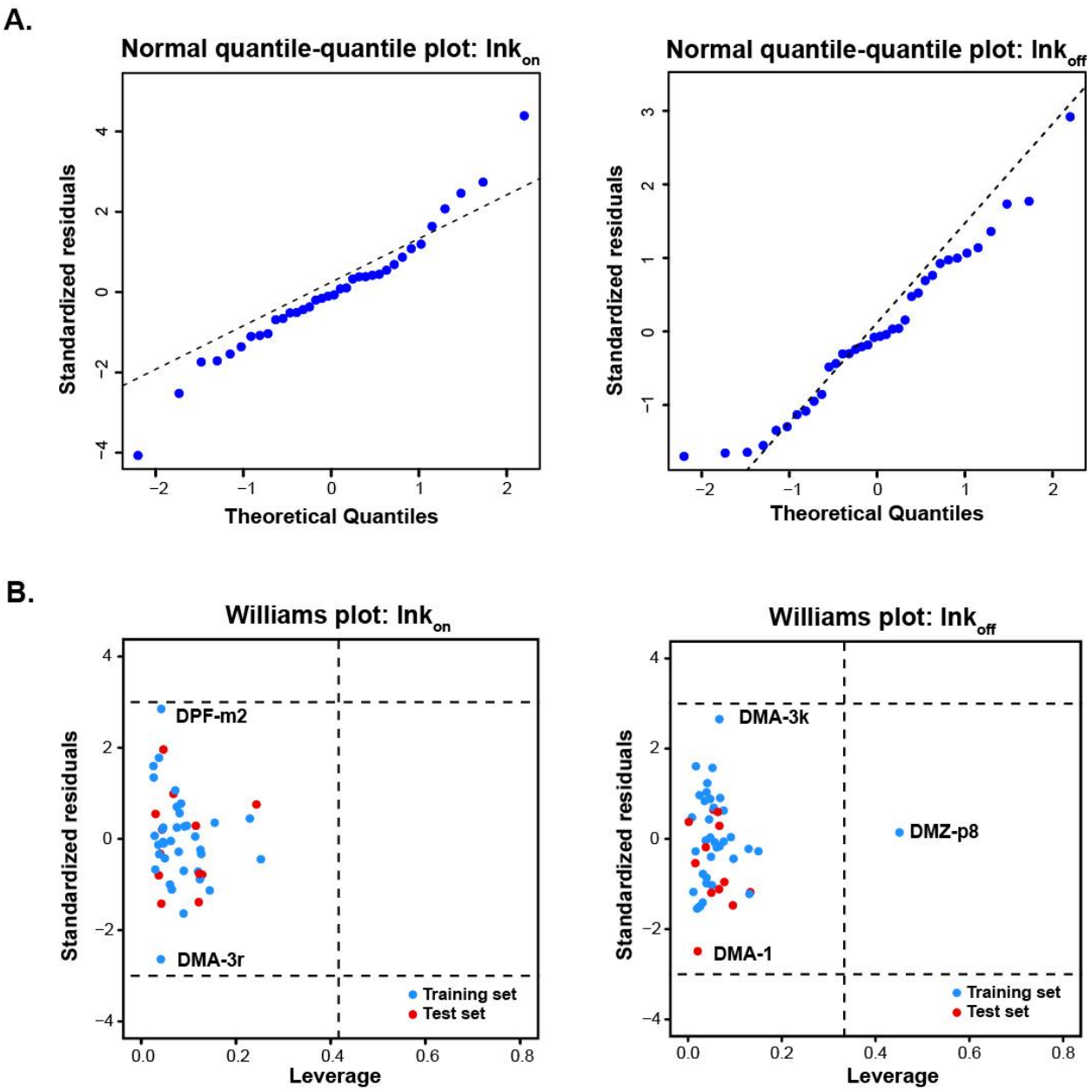


Figure S3 A. Normal quantile-quantile plots of lnk_{on} and lnk_{off} models. **B.** Williams plot showed applicable domain of lnk_{on} and lnk_{off} models with training and test sets.

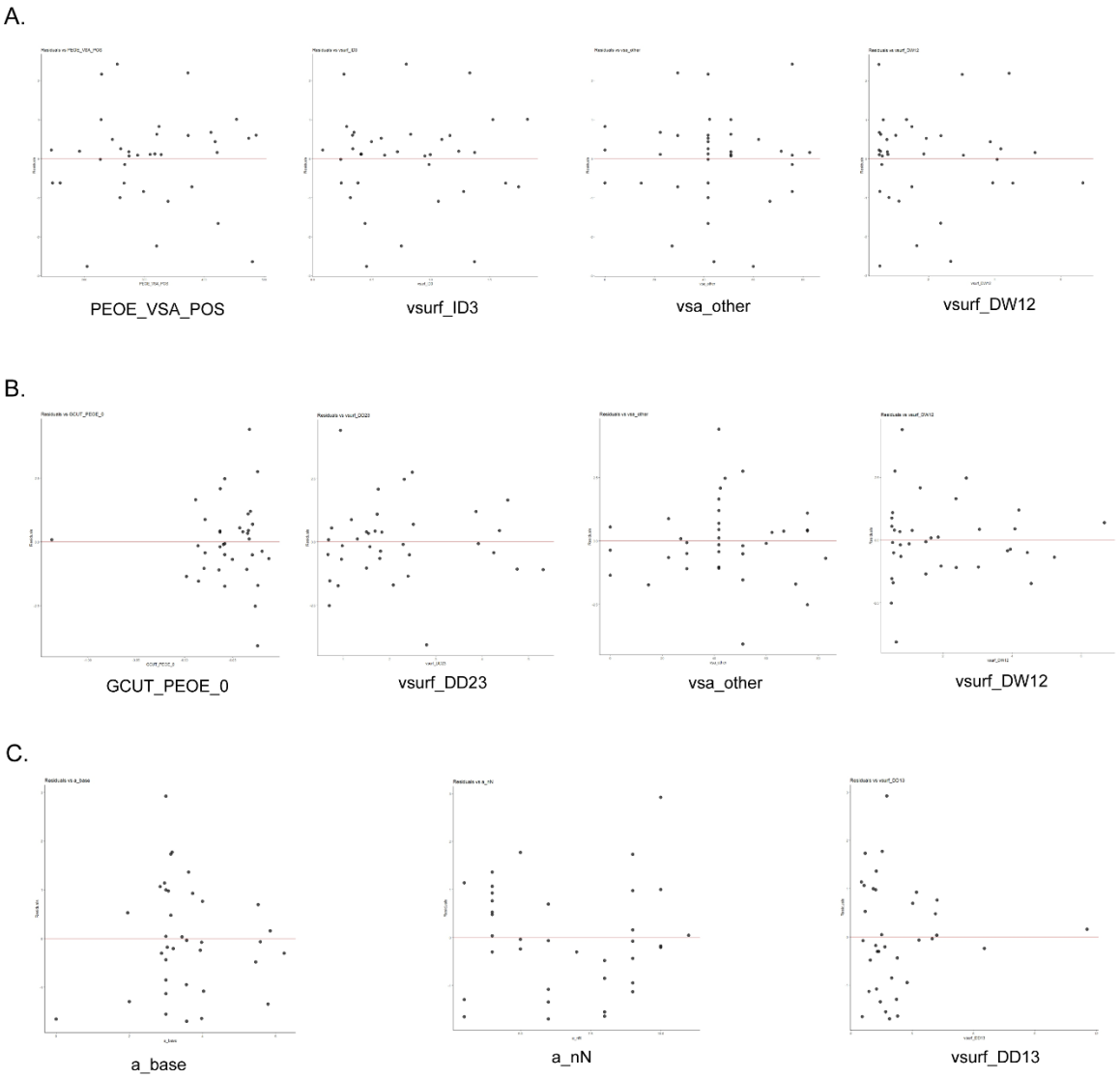
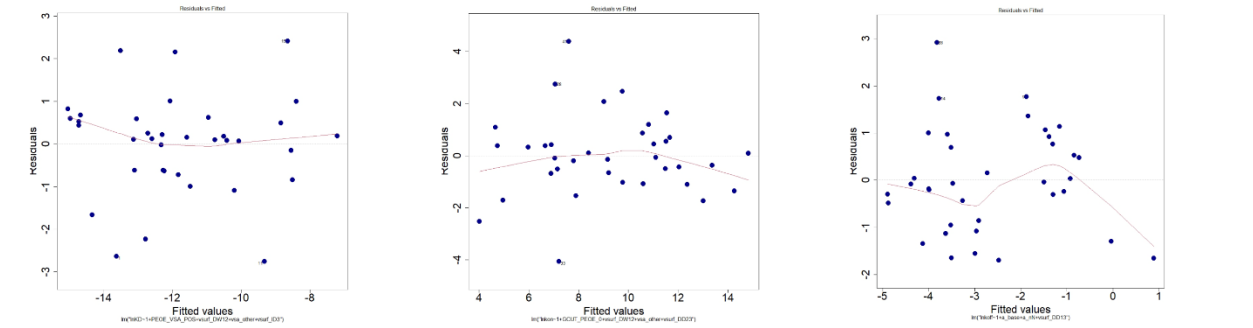


Figure S4 Plots of fitting residuals against each descriptor from 3 MLR models (**A.** lnK_D model. **B.** lnk_{on} model. **C.** lnk_{off} model) to check linearity assumption.



$\ln K_D = -10 - 0.015 PEOE\_VSA\_POS + 0.054 vsa\_other - 0.37 vsurf\_DW12 + 1.7 vsurf\_ID3$

$\ln k_{on} = -12 - 27 GCUT\_PEOE\_0 - 0.093 vsa\_other + 0.59 vsurf\_DW12 + 0.42 vsurf\_DD23$

$\ln k_{off} = 2.0 - 0.69 a\_base - 0.42 a\_nN + 0.27 vsurf\_DD13$

Figure S5 Plots of fitting residuals against the fitted values for 3 MLR models to check independence and equal variance assumption.

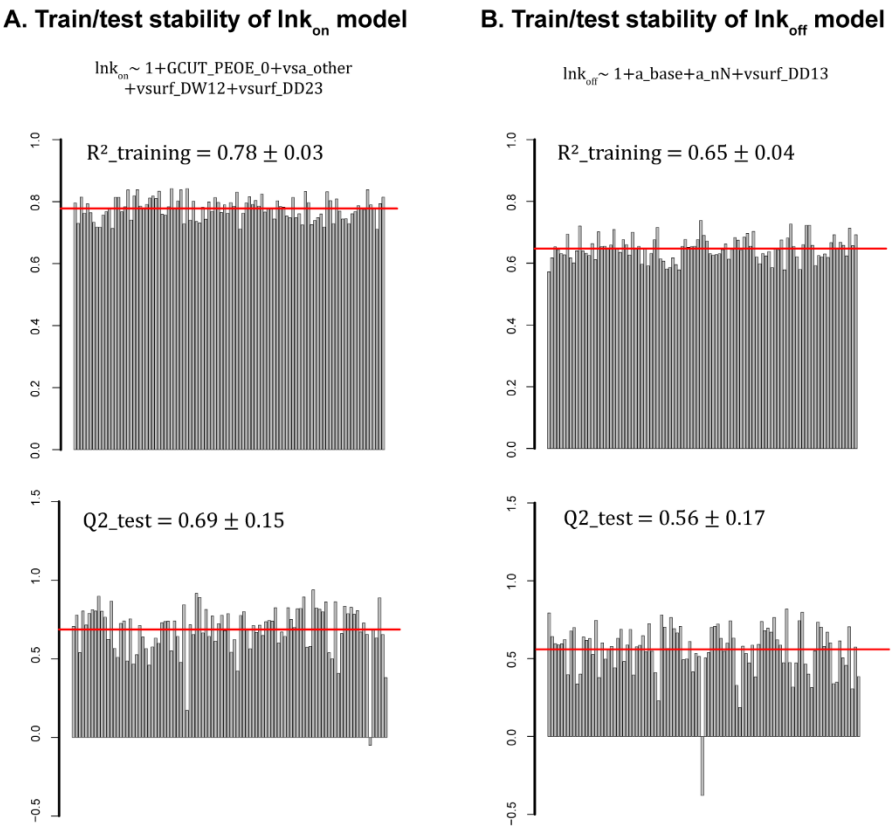


Figure S6 A. Model stability test on lnk_{on} data using formula: lnk_{on}~1 + GCUT_PEOE_0 + vsa_other + vsurf_DW12 + vsruf_DD23. **B.** Model stability test on lnk_{off} data using formula: lnk_{off} ~1 + a_base + a_nN + vsurf_DD13.

Section B. Chemistry

1. Chemical structures of molecules for model training

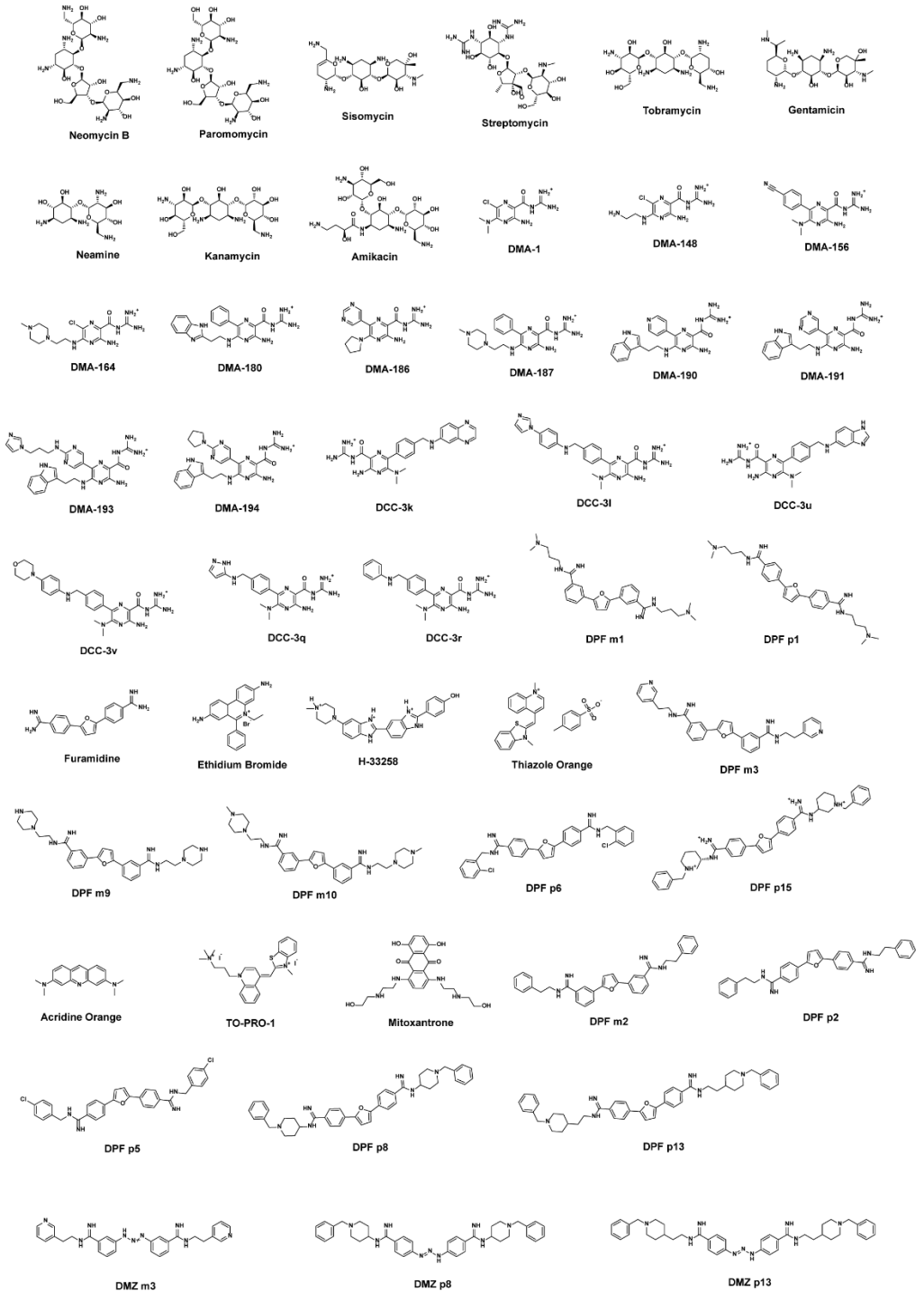
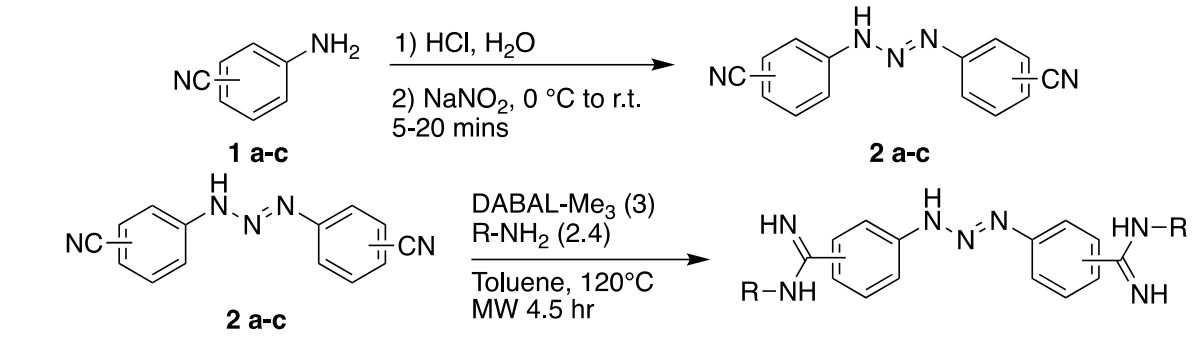


Figure S7. Chemical structures of molecules for model training: DMA-1~DMA-164 are from ref 1[1], DMA-180~DMA-194 from ref 2[2], DMA compounds from ref 3[3], DPF x1~DPF x10 from ref 4[4] (x = m or p), DPF p13, p15 from ref 5[5]. DMZs were synthesized as below. The rest of compounds are commercially available.

2. Synthesis and characterization of diminazenes (DMZ)

Reaction schemes and DMZ structures



Scheme S1. Synthetic routes for DMZ compounds

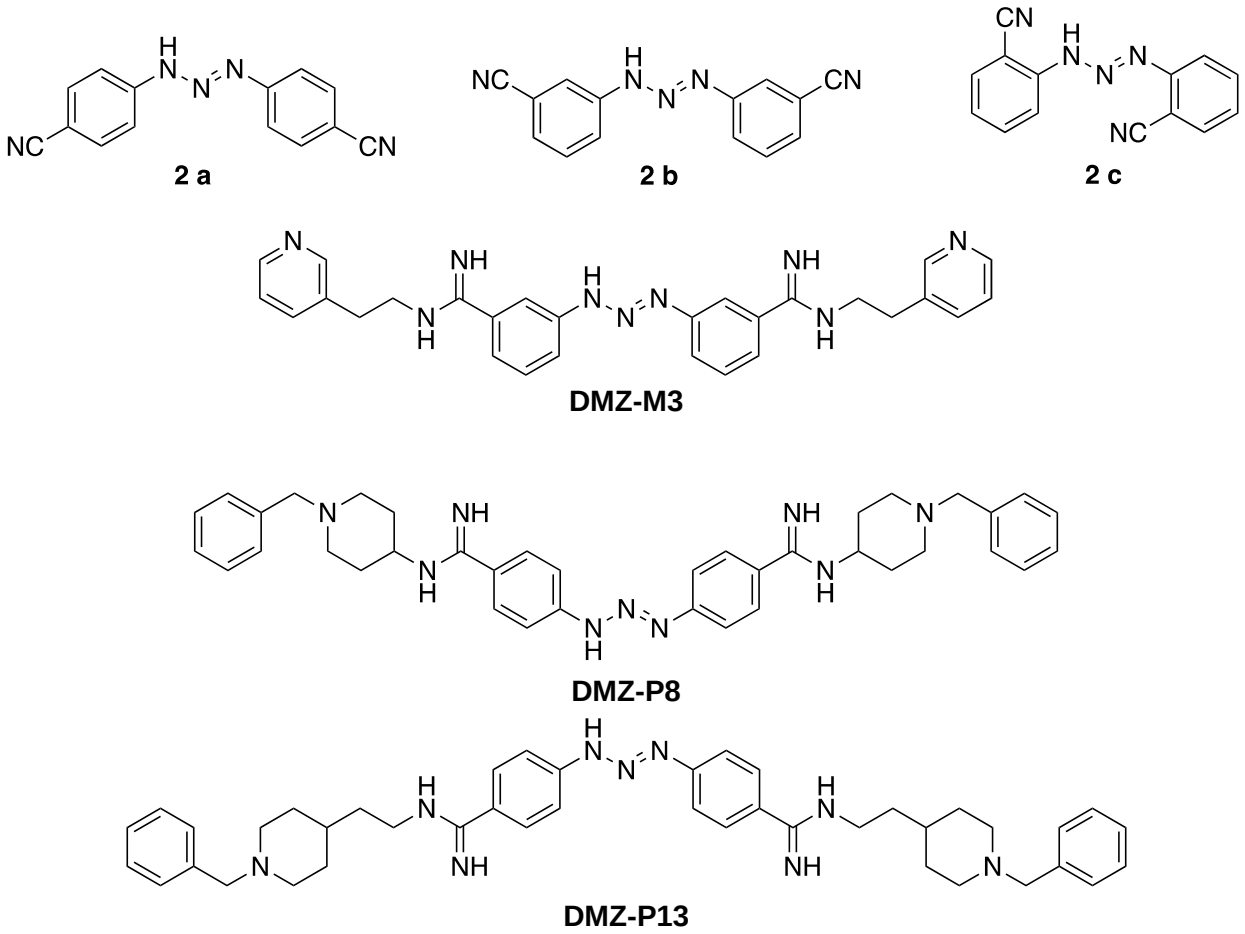


Figure S8. Chemical structures of DMZ synthetic intermediates and three DMZs used in this work

Characterization spectra

- **DMZ M3**

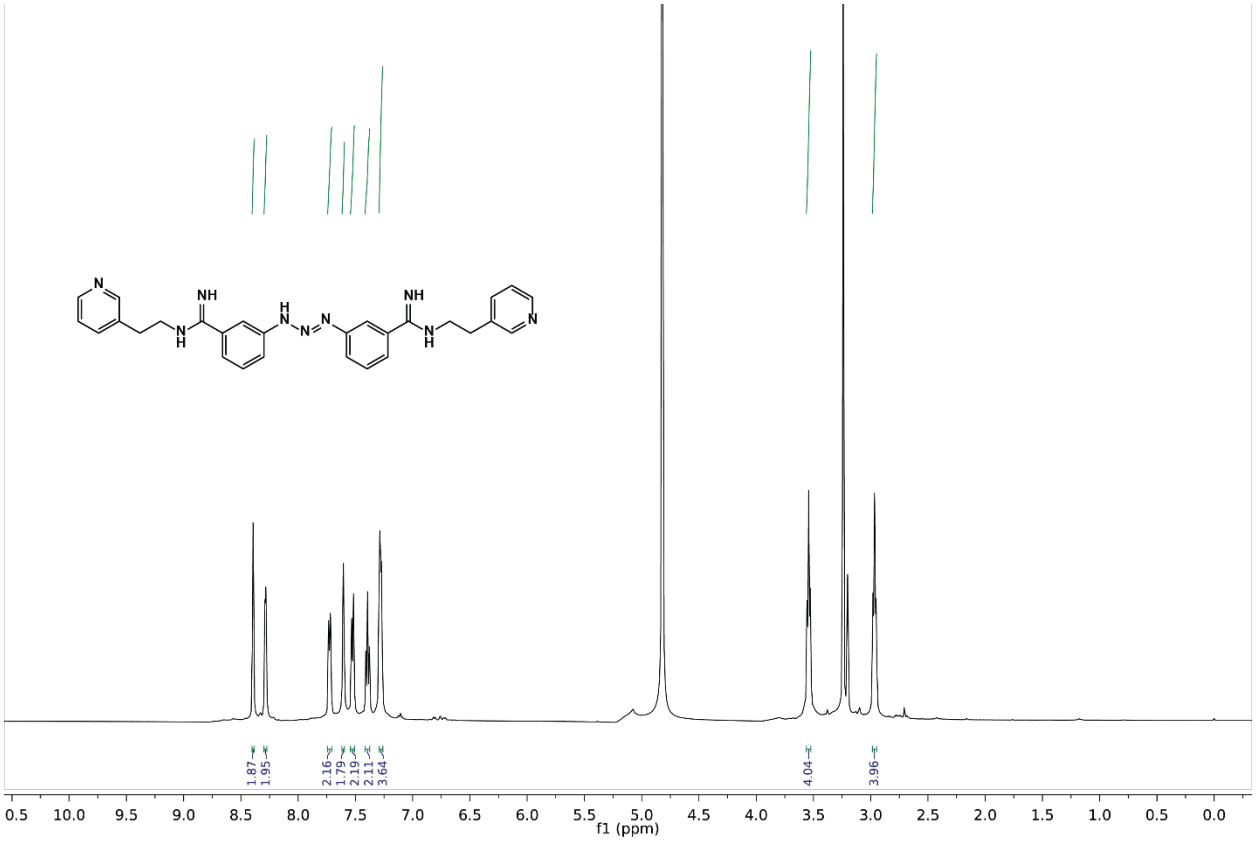


Figure S9 A. The ^{1}H-NMR spectrum of DMZ m3

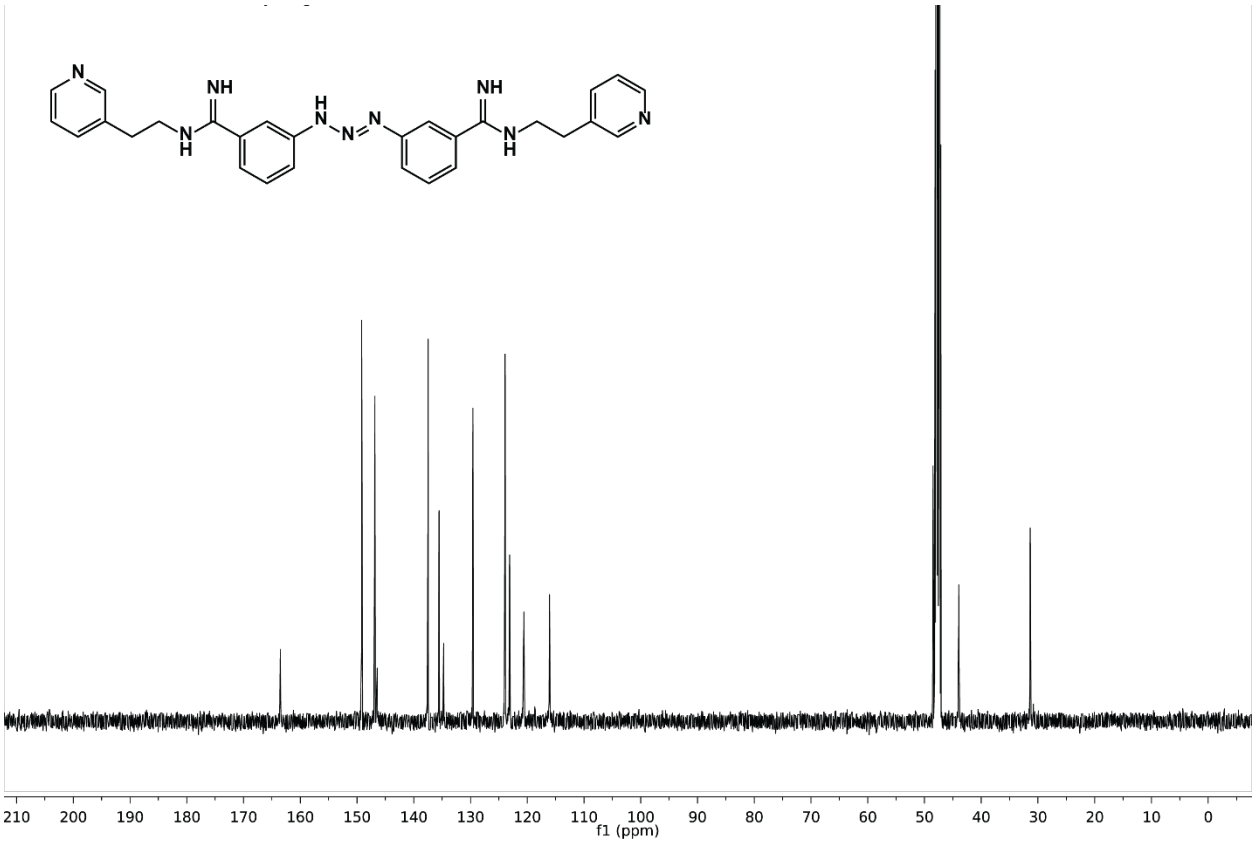
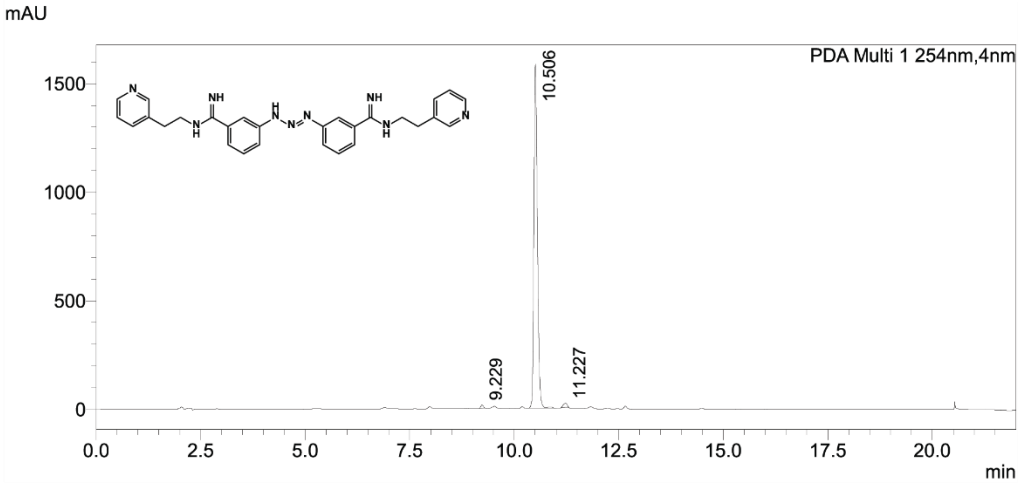


Figure S9 B. The ^{13}C-NMR spectrum of DMZ m3

<Sample Information>

Sample Name	: DMZ-M3		
Sample ID	: DMZ-M3		
Data Filename	: DMZ-M3.lcd		
Method Filename	: GP short-Grd10-90_22min_PDA.lcm		
Batch Filename	: 10282020_MSCHECK.lcb		
Vial #	: 1-8	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 10/28/2020 10:06:30 PM	Acquired by	: chemist
Date Processed	: 10/28/2020 10:28:33 PM	Processed by	: chemist

<Chromatogram>



<Peak Table>

RF-20A Ex:350nm,Em:450nm

Peak#	Ret. Time	Area%
Total		

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	9.229	0.653
2	10.506	98.114
3	11.227	1.234
Total		100.000

Figure S9 C. The HPLC spectrum of DMZ m3

- **DMZ P8**

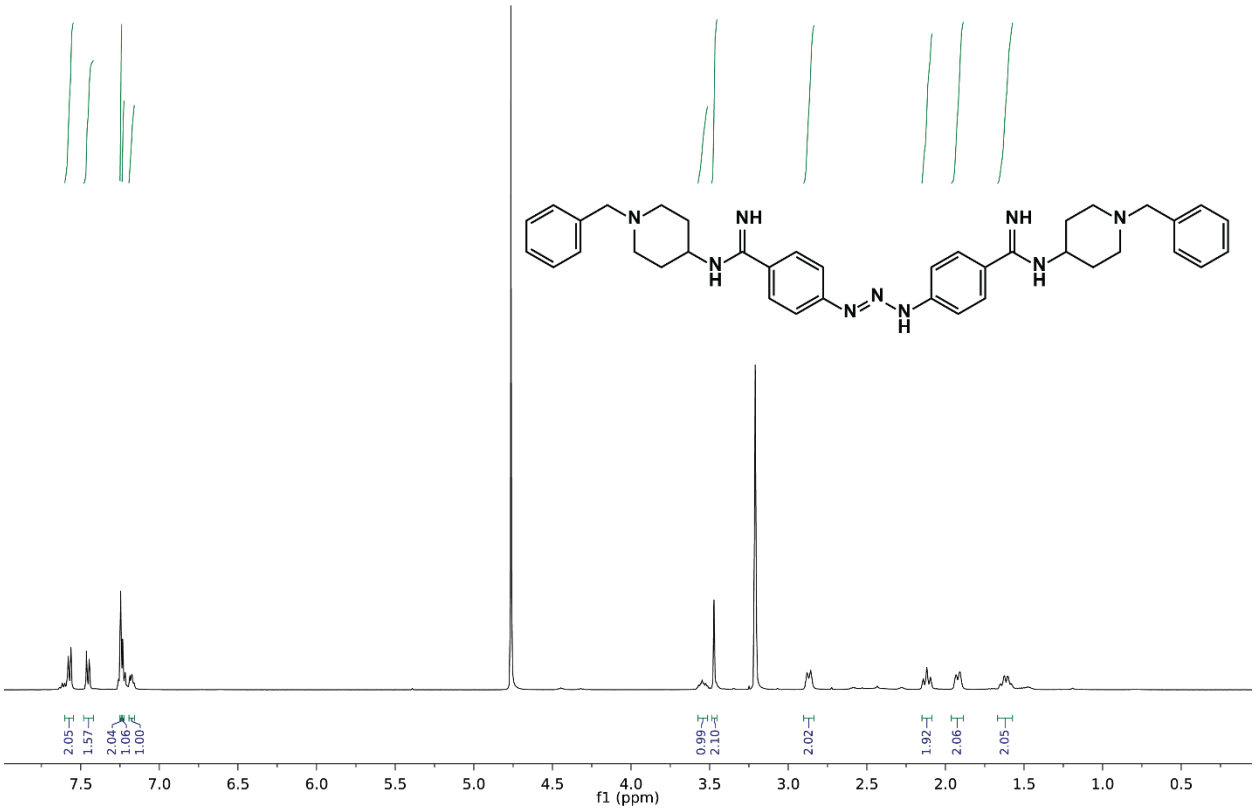


Figure S10 A. The ^{1}H-NMR spectrum of DMZ p8

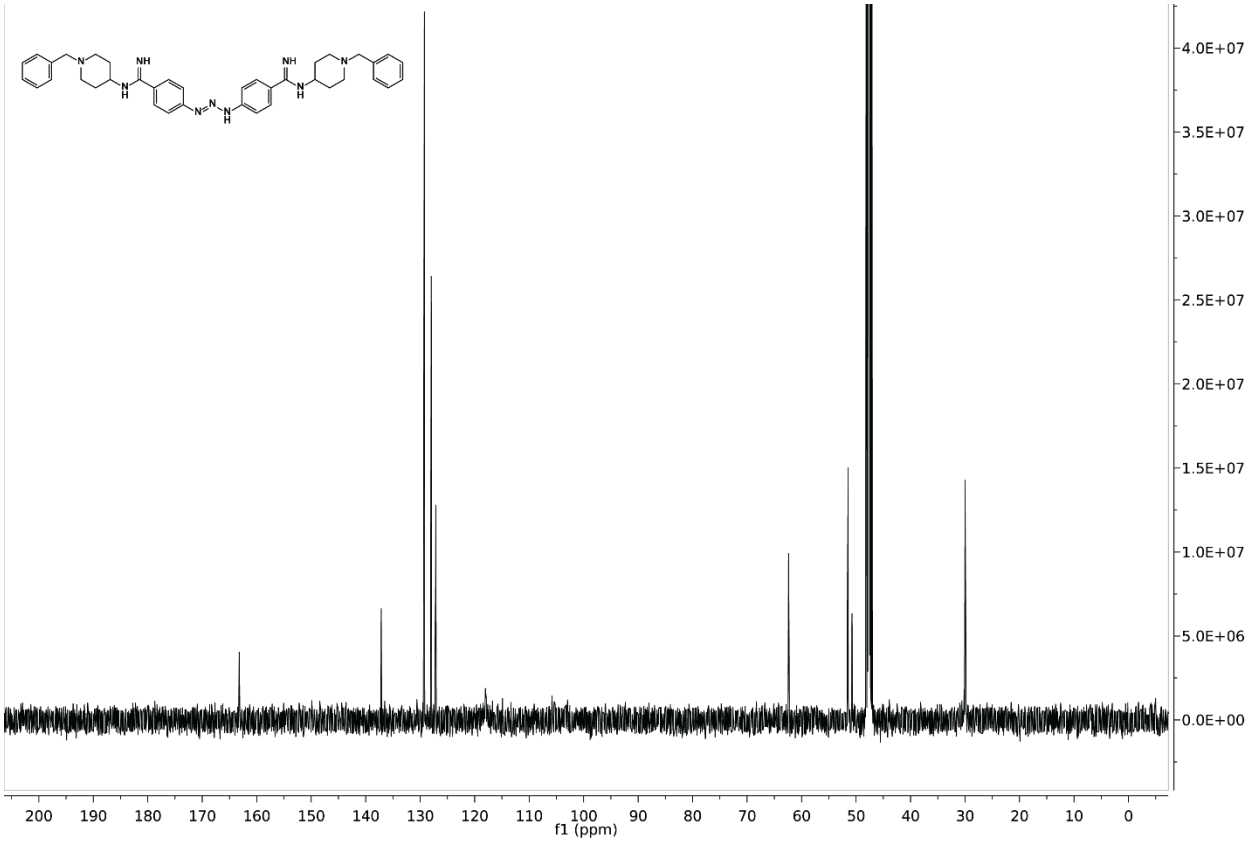
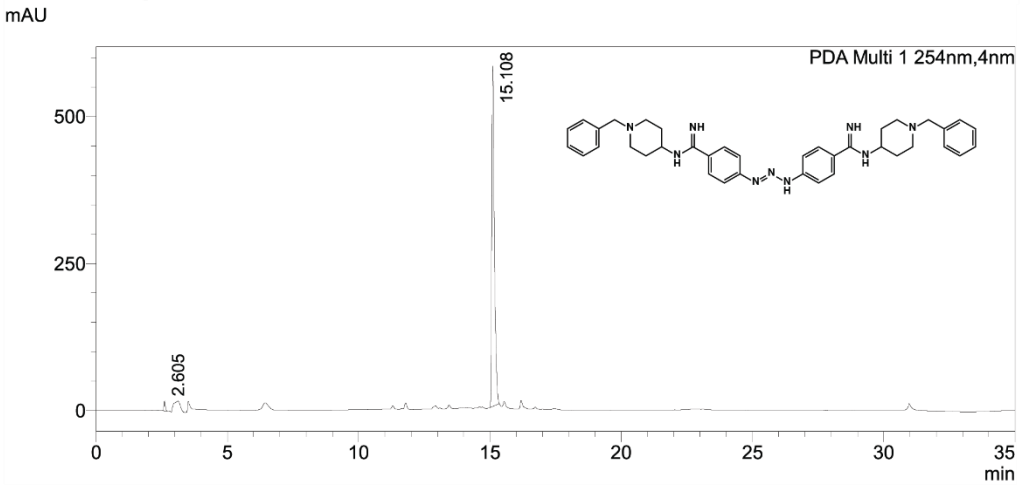


Figure S10 B. The ^{13}C-NMR spectrum of DMZ p8

<Sample Information>

Sample Name	: MZ-06-14-19_48_p8		
Sample ID	: MZ-06-14-19_48_p8		
Data Filename	: MZ-06-14-19_48_p8.lcd		
Method Filename	: GP-MZ_90ACN_gradient.lcm		
Batch Filename	: 06-14-19_Berenilrun1.lcb		
Vial #	: 1-91	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 6/14/2019 2:42:06 PM	Acquired by	: chemist
Date Processed	: 6/14/2019 3:17:10 PM	Processed by	: chemist

<Chromatogram>



<Peak Table>

RF-20A Ex:350nm,Em:450nm

Peak#	Ret. Time	Area%	Height%
Total			

PDA Ch1 254nm

Peak#	Ret. Time	Area%	Height%
1	2.605	1.497	2.875
2	15.108	98.503	97.125
Total		100.000	100.000

Figure S10 C. The HPLC spectrum of DMZ p8

- **DMZ P13**

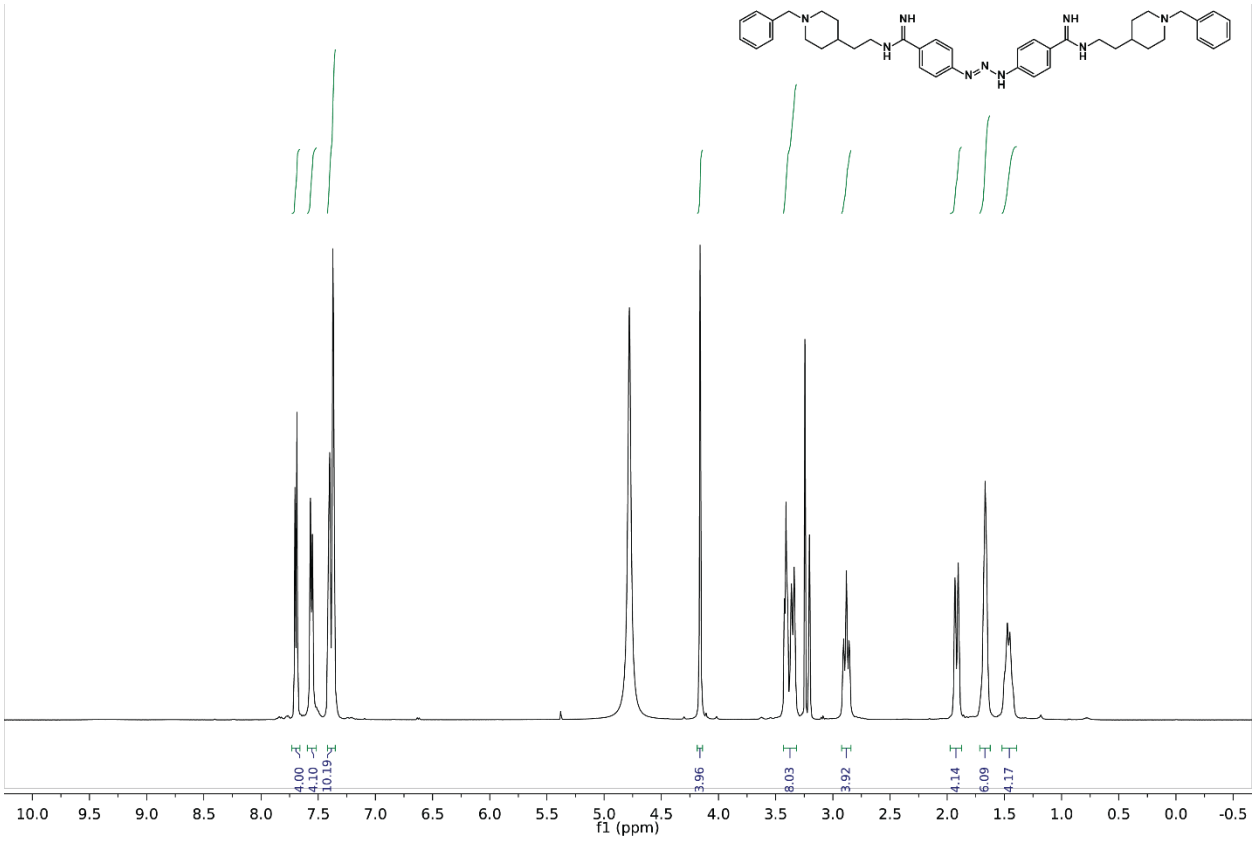


Figure S11 A. The ^{1}H-NMR spectrum of DMZ p13

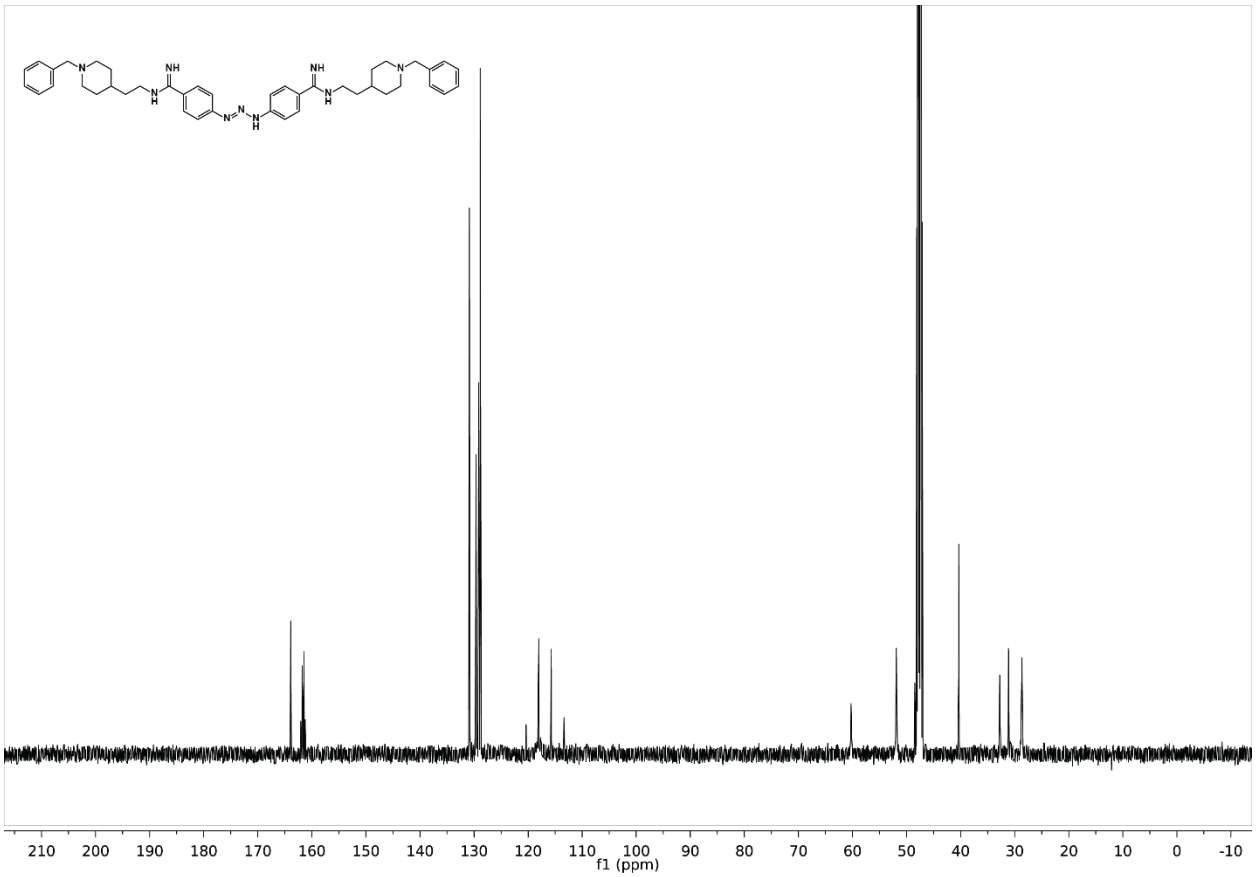
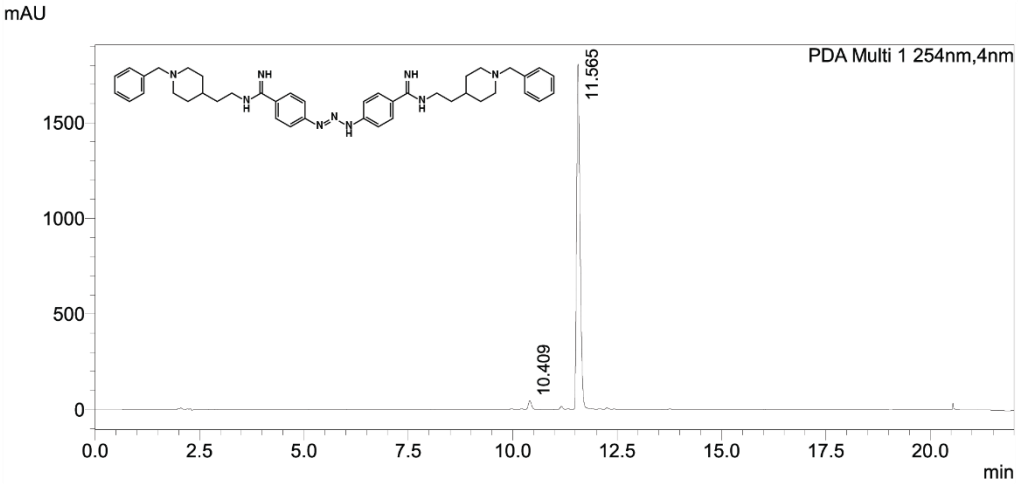


Figure S11 B. The ^{13}C-NMR spectrum of DMZ p13

<Sample Information>

Sample Name	: DMZ-P13		
Sample ID	: DMZ-P13		
Data Filename	: DMZ-P13.lcd		
Method Filename	: GP short-Grd10-90_22min_PDA.lcm		
Batch Filename	: 10282020_MSCHECK.lcb		
Vial #	: 1-17	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 10/29/2020 1:29:27 AM	Acquired by	: chemist
Date Processed	: 10/29/2020 1:51:30 AM	Processed by	: chemist

<Chromatogram>



<Peak Table>

RF-20A Ex:350nm,Em:450nm

Peak#	Ret. Time	Area%
Total		

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	10.409	1.689
2	11.565	98.311
Total		100.000

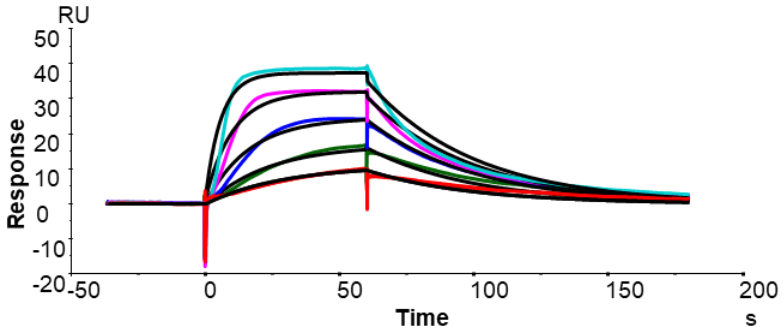
Figure S11 C. The HPLC spectrum of DMZ p13

Section C. Surface plasmon resonance

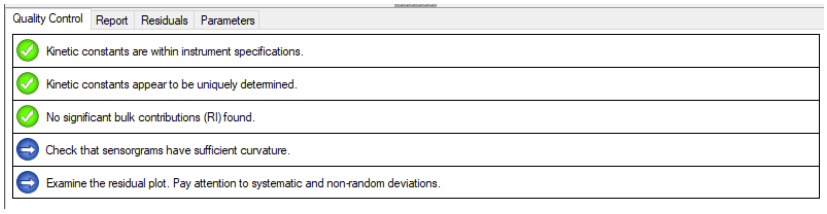
Sensorgrams, fitting parameters and quality control table

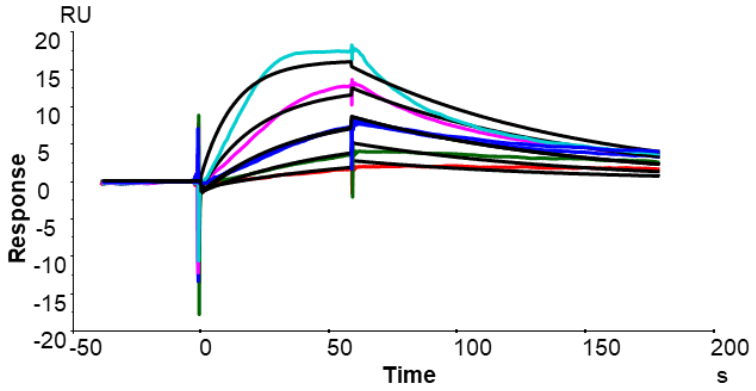
The units for k_{on}, k_{off} and K_D are $M^{-1}•s^{-1}$, s^{-1}, and M, respectively.

- Neomycin

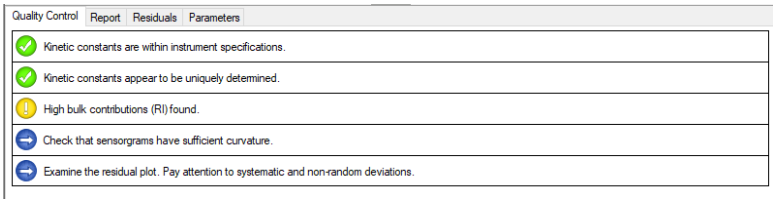


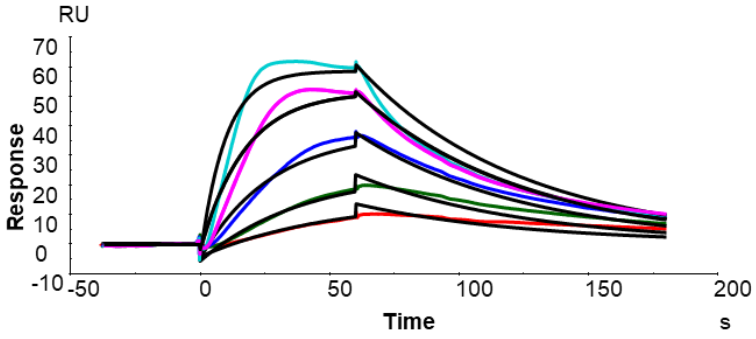
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2.944E+5	0.02529	8.589E-8	41.22	
Cycle: 39 0.03125 µM					3.125E-8
Cycle: 40 0.0625 µM					6.250E-8
Cycle: 41 0.125 µM					1.250E-7
Cycle: 42 0.25 µM					2.500E-7
Cycle: 43 0.5 µM					5.000E-7
Cycle: 44 0.03125 µM					3.125E-8





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.857E+5	0.01606	8.646E-8	71.39	
Cycle: 2 0.03125 µM					3.125E-8
Cycle: 3 0.0625 µM					6.250E-8
Cycle: 4 0.125 µM					1.250E-7
Cycle: 5 0.25 µM					2.500E-7
Cycle: 6 0.5 µM					5.000E-7
Cycle: 7 0.25 µM					2.500E-7





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.307E+5	0.01117	8.545E-8	18.20	
Cycle: 2 0.03125 µM					3.125E-8
Cycle: 3 0.0625 µM					6.250E-8
Cycle: 4 0.125 µM					1.250E-7
Cycle: 5 0.25 µM					2.500E-7
Cycle: 6 0.5 µM					5.000E-7
Cycle: 7 0.125 µM					1.250E-7

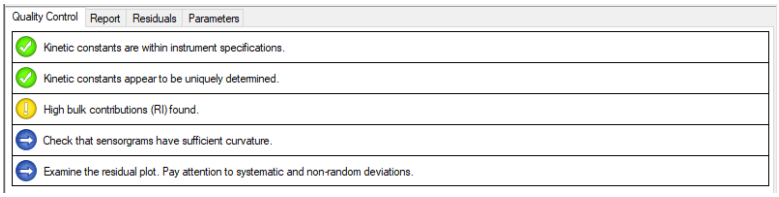
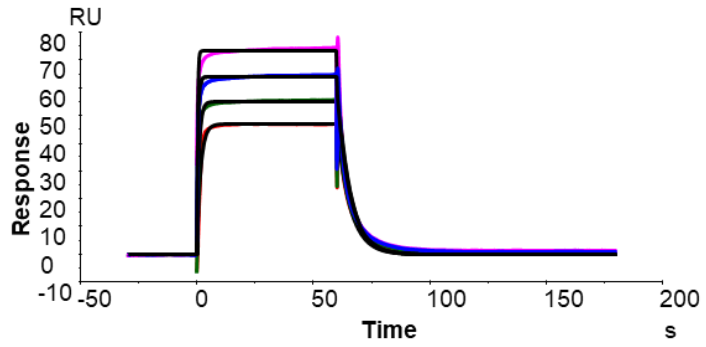
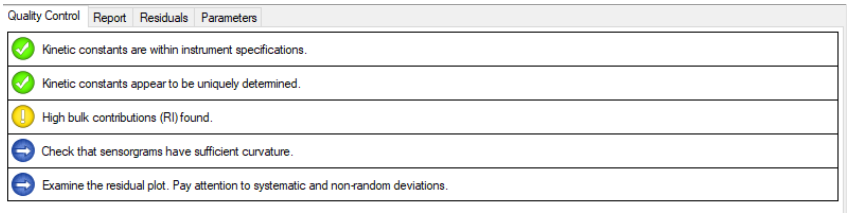


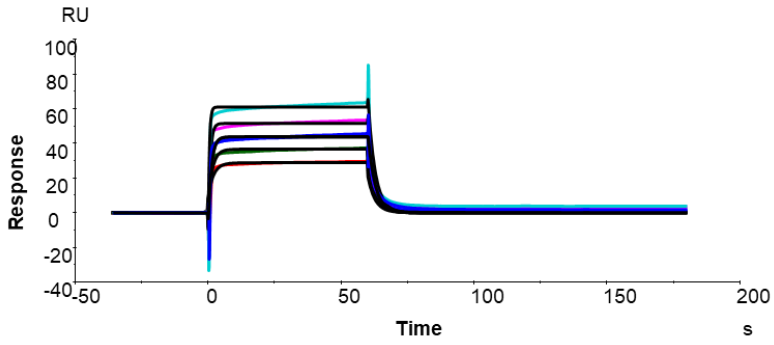
Figure S12. The SPR sensorgrams, fitting parameters and quality control table of neomycin (3 replicates)

- Paromomycin

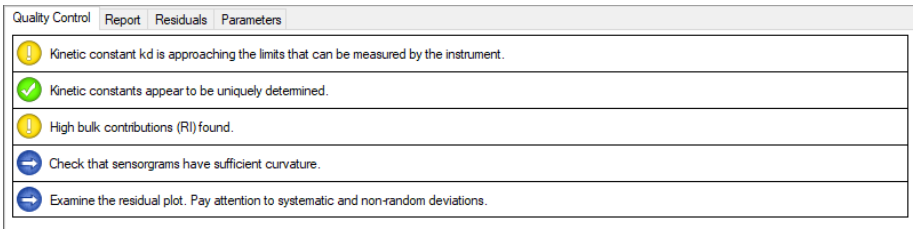


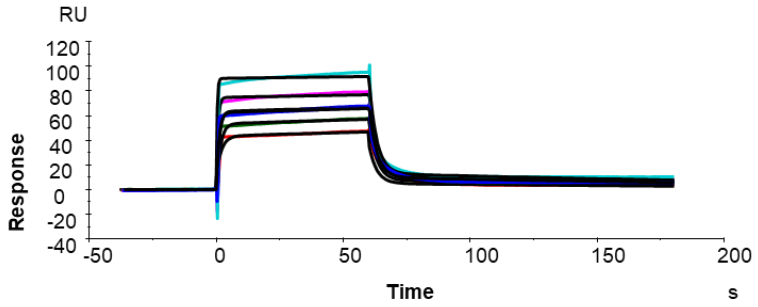
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.160E+5	0.1787	1.540E-6	65.55	
Cycle: 41 3.75 µM					3.750E-6
Cycle: 42 7.5 µM					7.500E-6
Cycle: 43 15 µM					1.500E-5
Cycle: 44 30 µM					3.000E-5
Cycle: 45 15 µM					1.500E-5





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	6.385E+4	0.3724	5.833E-6	83.83	
Cycle: 9 1.875 µM					1.875E-6
Cycle: 10 3.75 µM					3.750E-6
Cycle: 11 7.5 µM					7.500E-6
Cycle: 12 15 µM					1.500E-5
Cycle: 13 30 µM					3.000E-5
Cycle: 14 7.5 µM					7.500E-6



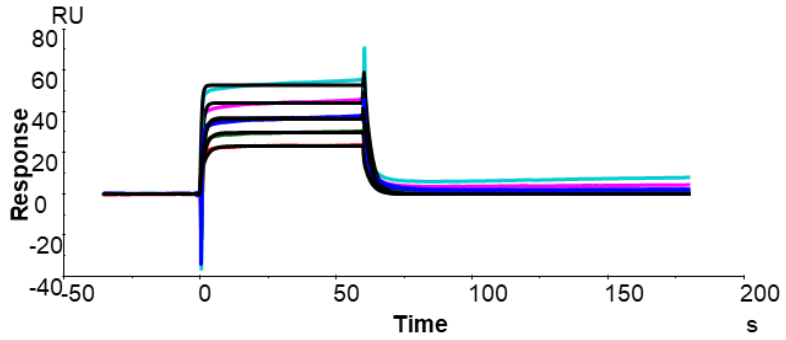


(Two state fitting, 1:1 binding fitting is poor)

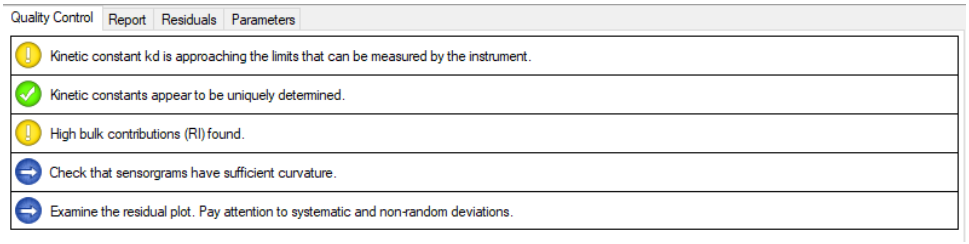
Curve	ka1 (1/Ms)	SE(ka1)	kd1 (1/s)	SE(kd1)	ka2 (1/s)	SE(ka2)	kd2 (1/s)	SE(kd2)
	9.248E+4	1.0E+3	0.3348	0.0023	0.002836	3.3E-5	0.004446	1.2E-4
Cycle: 2 1.875 µM								
Cycle: 3 3.75 µM								
Cycle: 4 7.5 µM								
Cycle: 5 15 µM								
Cycle: 6 30 µM								
Cycle: 7 7.5 µM								

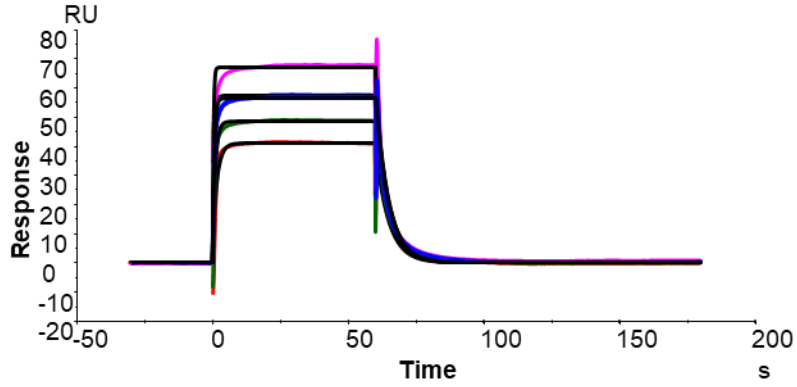
Figure S13. The SPR sensorgrams, fitting parameters and quality control table of paromomycin (3 replicates)

- Sisomycin



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	5.869E+4	0.3859	6.576E-6	77.62	
Cycle: 16 1.875 µM					1.875E-6
Cycle: 17 3.75 µM					3.750E-6
Cycle: 18 7.5 µM					7.500E-6
Cycle: 19 15 µM					1.500E-5
Cycle: 20 30 µM					3.000E-5
Cycle: 21 7.5 µM					7.500E-6

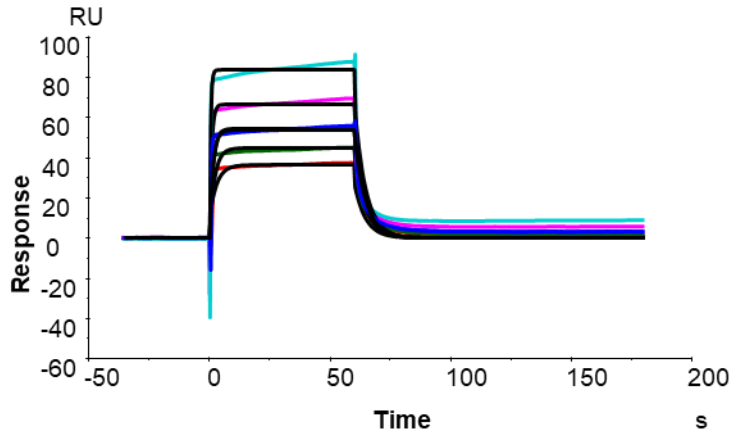




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.099E+5	0.2097	1.908E-6	62.84	
Cycle: 23 3.75 µM					3.750E-6
Cycle: 24 7.5 µM					7.500E-6
Cycle: 25 15 µM					1.500E-5
Cycle: 26 30 µM					3.000E-5
Cycle: 27 15 µM					1.500E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Quality Control | Report | Residuals | Parameters

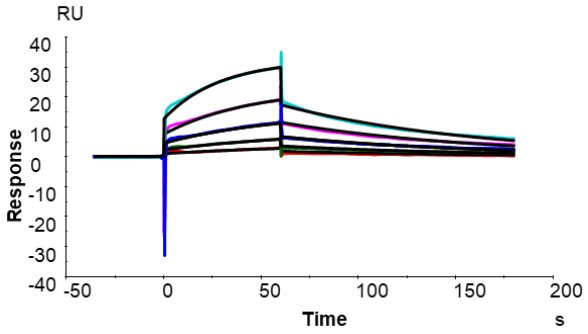
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	6.700E+4	0.2181	3.255E-6	73.86	
Cycle: 9 1.875 µM					1.875E-6
Cycle: 10 3.75 µM					3.750E-6
Cycle: 11 7.5 µM					7.500E-6
Cycle: 12 15 µM					1.500E-5
Cycle: 13 30 µM					3.000E-5
Cycle: 14 7.5 µM					7.500E-6

Quality Control | Report | Residuals | Parameters

- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

Figure S14. The SPR sensorgrams, fitting parameters and quality control table of sisomycin (3 replicates)

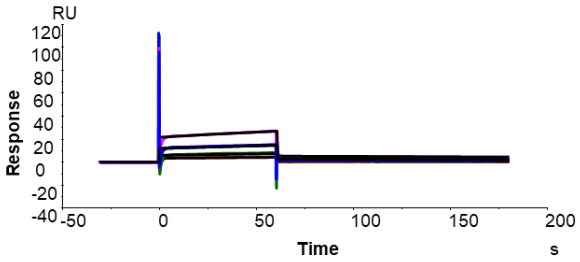
- Streptomycin



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	845.9	0.009834	1.163E-5	27.48	
Cycle: 23 1.875 µM					1.875E-6
Cycle: 24 3.75 µM					3.750E-6
Cycle: 25 7.5 µM					7.500E-6
Cycle: 26 15 µM					1.500E-5
Cycle: 27 30 µM					3.000E-5
Cycle: 28 7.5 µM					7.500E-6

Quality Control | Report | Residuals | Parameters

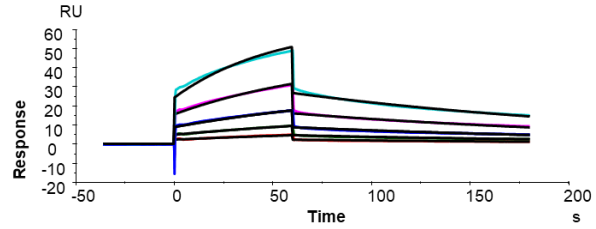
- Kinetic constant ka is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	158.4	0.001721	1.086E-5	22.30	
Cycle: 35 3.75 µM					3.750E-6
Cycle: 36 7.5 µM					7.500E-6
Cycle: 37 15 µM					1.500E-5
Cycle: 38 30 µM					3.000E-5
Cycle: 39 15 µM					1.500E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants cannot be uniquely determined. Try to extend the dissociation time.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



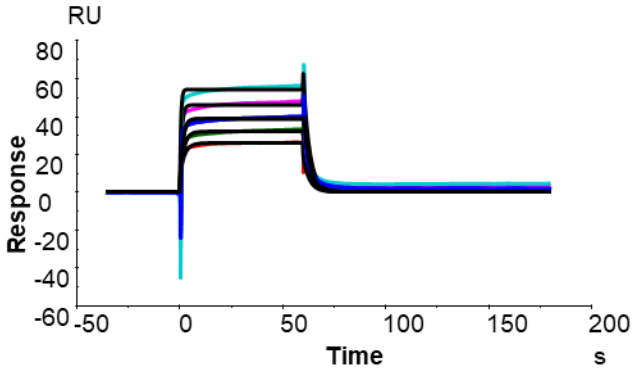
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	491.7	0.005133	1.044E-5	51.78	
Cycle: 16 1.875 µM					1.875E-6
Cycle: 17 3.75 µM					3.750E-6
Cycle: 18 7.5 µM					7.500E-6
Cycle: 19 15 µM					1.500E-5
Cycle: 20 30 µM					3.000E-5
Cycle: 21 7.5 µM					7.500E-6

Quality Control | Report | Residuals | Parameters

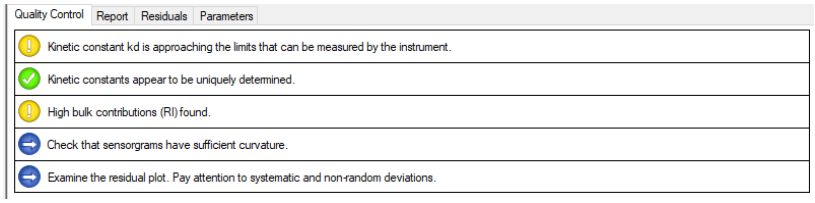
- Kinetic constant ka is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

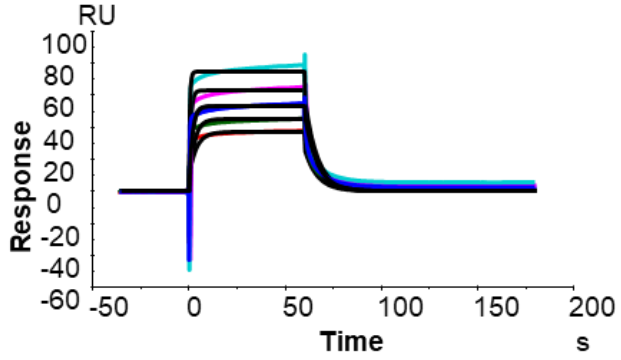
Figure S15. The SPR sensorgrams, fitting parameters and quality control table of streptomycin (3 replicates)

- Tobramycin



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	5.855E+4	0.3347	5.717E-6	74.82	
Cycle: 30 1.875 µM					1.875E-6
Cycle: 31 3.75 µM					3.750E-6
Cycle: 32 7.5 µM					7.500E-6
Cycle: 33 15 µM					1.500E-5
Cycle: 34 30 µM					3.000E-5
Cycle: 35 7.5 µM					7.500E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	5.772E+4	0.1532	2.654E-6	63.32	
Cycle: 23 1.875 µM					1.875E-6
Cycle: 24 3.75 µM					3.750E-6
Cycle: 25 7.5 µM					7.500E-6
Cycle: 26 15 µM					1.500E-5
Cycle: 27 30 µM					3.000E-5
Cycle: 28 7.5 µM					7.500E-6

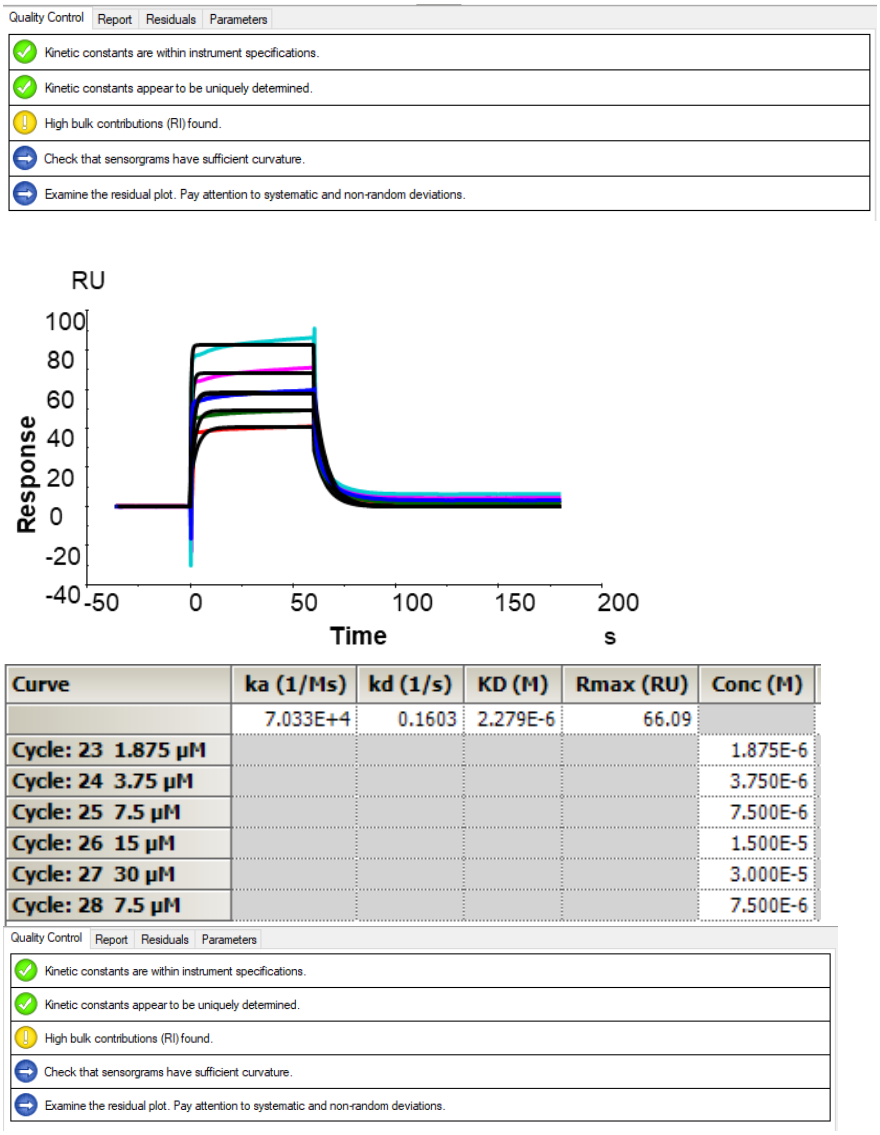
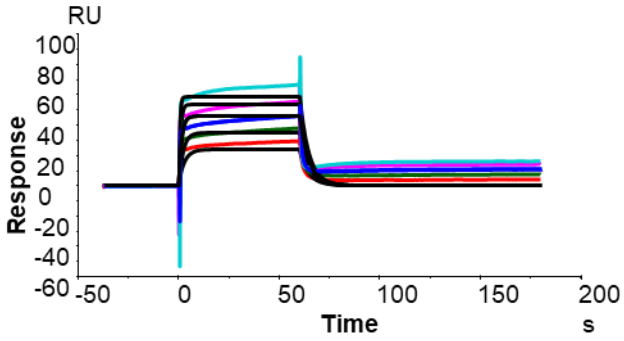
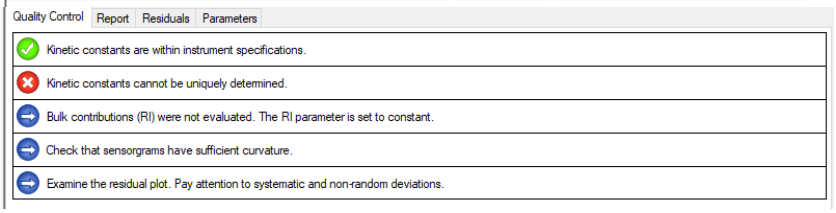


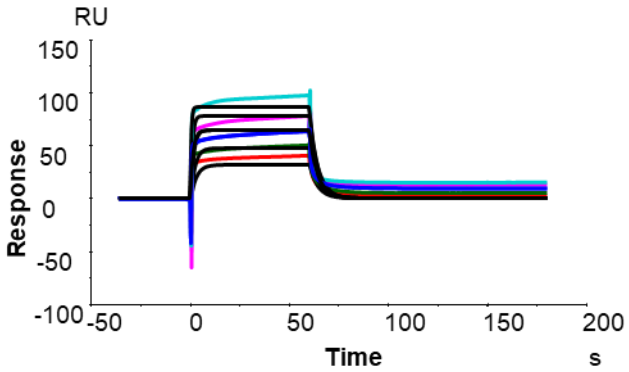
Figure S16. The SPR sensorgrams, fitting parameters and quality control table of tobramycin (3 replicates)

- Gentamycin

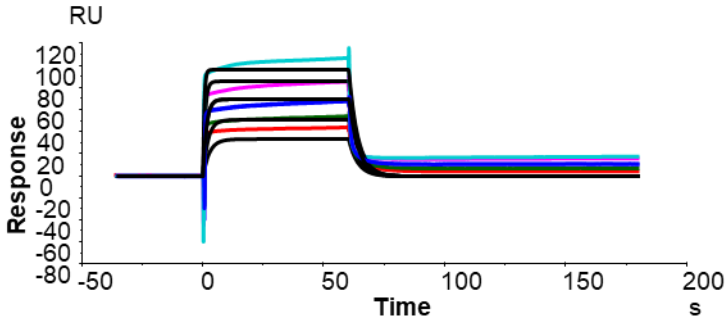


Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	6.898E+4	0.2231	3.235E-6	65.40	
Cycle: 2 1.875 µM					1.875E-6
Cycle: 3 3.75 µM					3.750E-6
Cycle: 4 7.5 µM					7.500E-6
Cycle: 5 15 µM					1.500E-5
Cycle: 6 30 µM					3.000E-5
Cycle: 7 7.5 µM					7.500E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	6.148E+4	0.2648	4.307E-6	109.5	
Cycle: 37 1.875 µM					1.875E-6
Cycle: 38 3.75 µM					3.750E-6
Cycle: 39 7.5 µM					7.500E-6
Cycle: 40 15 µM					1.500E-5
Cycle: 41 30 µM					3.000E-5
Cycle: 42 7.5 µM					7.500E-6



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	6.226E+4	0.2394	3.845E-6	97.49	
Cycle: 37 1.875 µM					1.875E-6
Cycle: 38 3.75 µM					3.750E-6
Cycle: 39 7.5 µM					7.500E-6
Cycle: 40 15 µM					1.500E-5
Cycle: 41 30 µM					3.000E-5
Cycle: 42 7.5 µM					7.500E-6

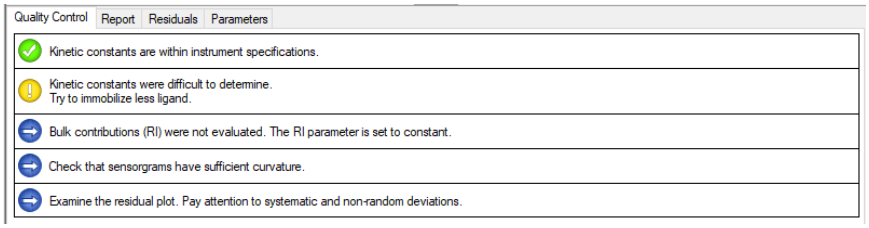
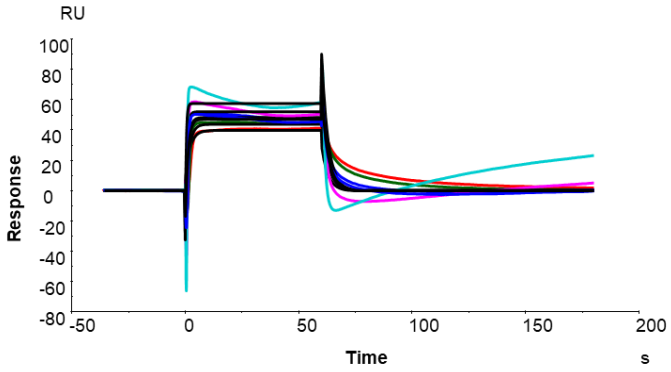
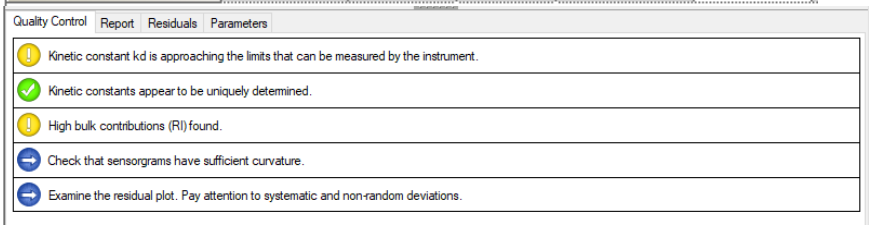


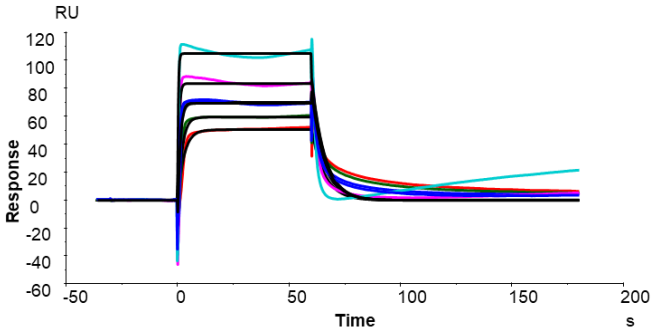
Figure S17. The SPR sensorgrams, fitting parameters and quality control table of gentamycin (3 replicates)

- Neamine



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	7.407E+4	0.3503	4.729E-6	104.5	
Cycle: 9 1.875 µM					1.875E-6
Cycle: 10 3.75 µM					3.750E-6
Cycle: 11 7.5 µM					7.500E-6
Cycle: 12 15 µM					1.500E-5
Cycle: 13 30 µM					3.000E-5
Cycle: 14 7.5 µM					7.500E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	9.967E+4	0.1711	1.716E-6	95.37	
Cycle: 23 1.875 µM					1.875E-6
Cycle: 24 3.75 µM					3.750E-6
Cycle: 25 7.5 µM					7.500E-6
Cycle: 26 15 µM					1.500E-5
Cycle: 27 30 µM					3.000E-5
Cycle: 28 7.5 µM					7.500E-6

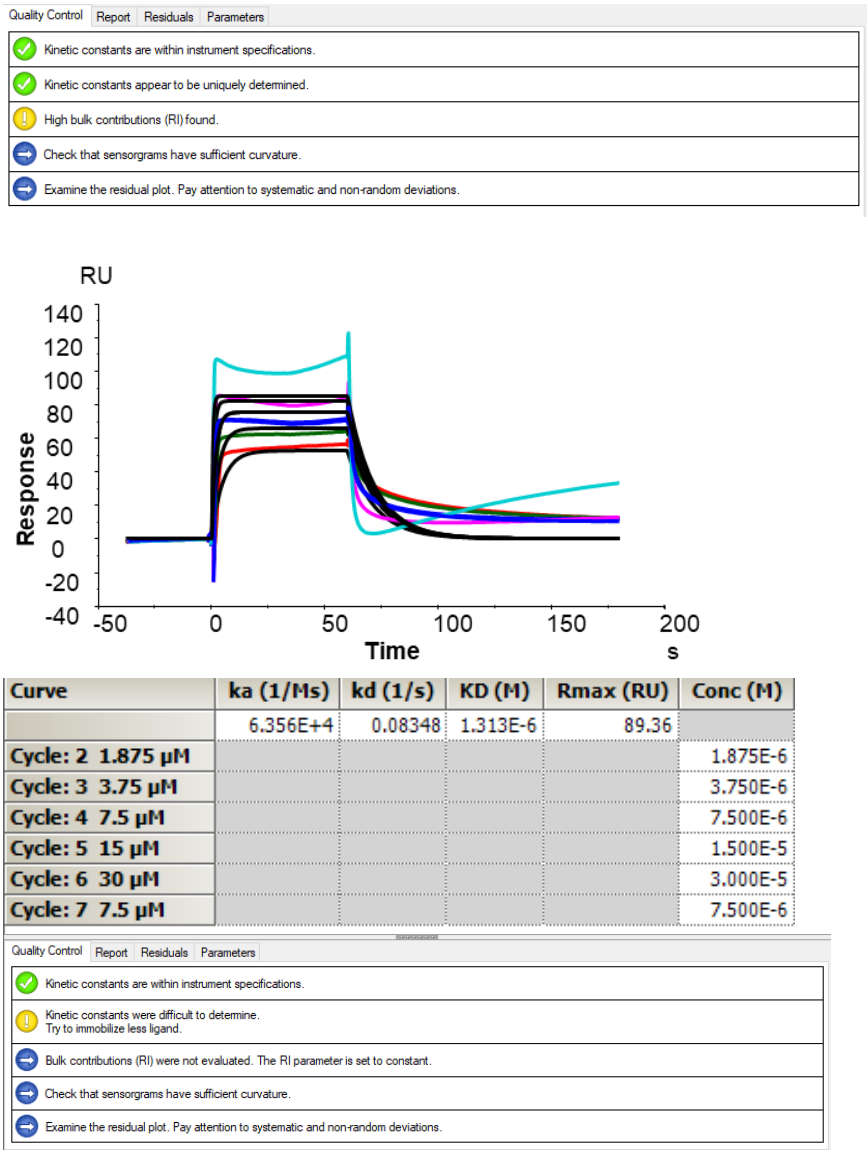
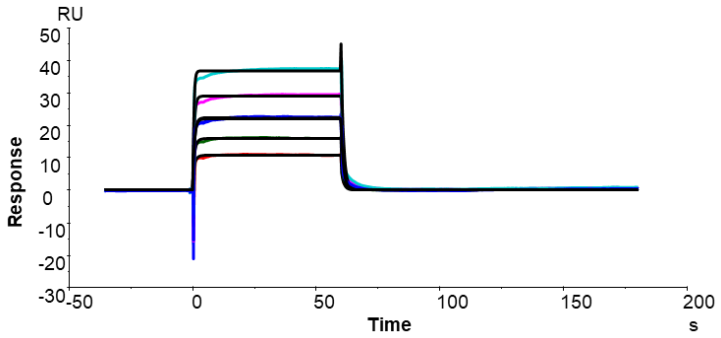


Figure S18. The SPR sensorgrams, fitting parameters and quality control table of neamine (3 replicates)

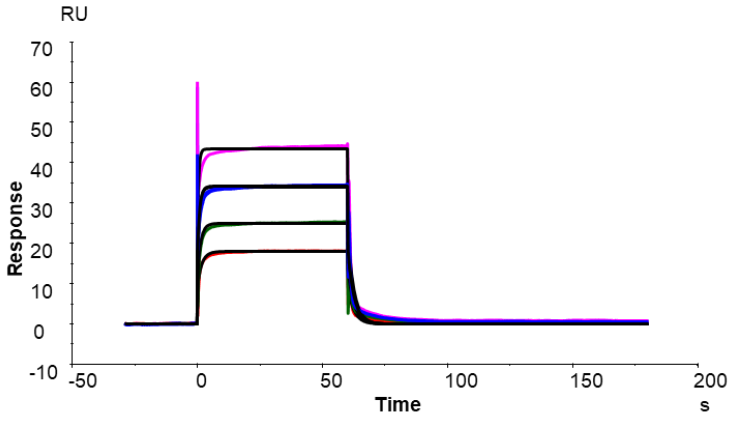
- Kanamycin



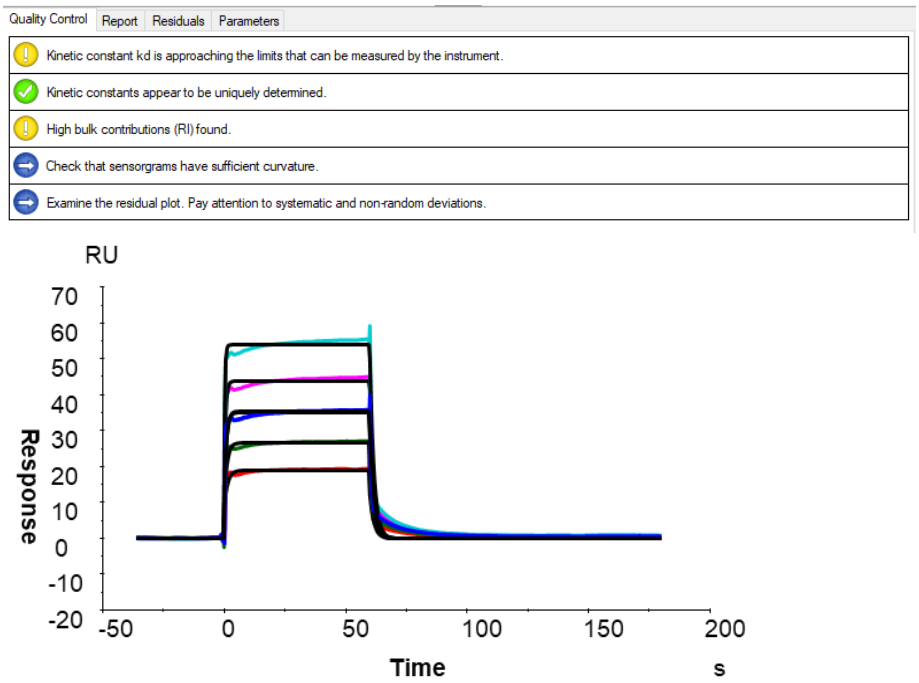
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	5.029E+4	1.015	2.018E-5	75.66	
Cycle: 16 1.875 µM					1.875E-6
Cycle: 17 3.75 µM					3.750E-6
Cycle: 18 7.5 µM					7.500E-6
Cycle: 19 15 µM					1.500E-5
Cycle: 20 30 µM					3.000E-5
Cycle: 21 7.5 µM					7.500E-6

Quality Control | Report | Residuals | Parameters

- Kinetic constant kd is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	4.892E+4	0.4012	8.202E-6	30.24	
Cycle: 17 3.75 µM					3.750E-6
Cycle: 18 7.5 µM					7.500E-6
Cycle: 19 15 µM					1.500E-5
Cycle: 20 30 µM					3.000E-5
Cycle: 21 15 µM					1.500E-5

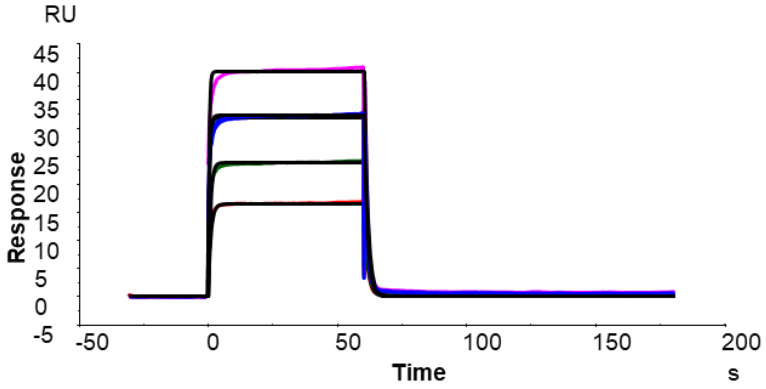


Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	7.717E+4	0.5993	7.765E-6	63.22	
Cycle: 16 1.875 µM					1.875E-6
Cycle: 17 3.75 µM					3.750E-6
Cycle: 18 7.5 µM					7.500E-6
Cycle: 19 15 µM					1.500E-5
Cycle: 20 30 µM					3.000E-5
Cycle: 21 7.5 µM					7.500E-6

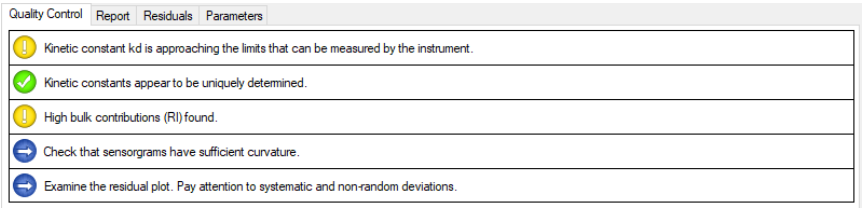
Quality Control
Report
Residuals
Parameters
Kinetic constant kd is approaching the limits that can be measured by the instrument.
Kinetic constants appear to be uniquely determined.
High bulk contributions (RI) found.
Check that sensorgrams have sufficient curvature.
Examine the residual plot. Pay attention to systematic and non-random deviations.

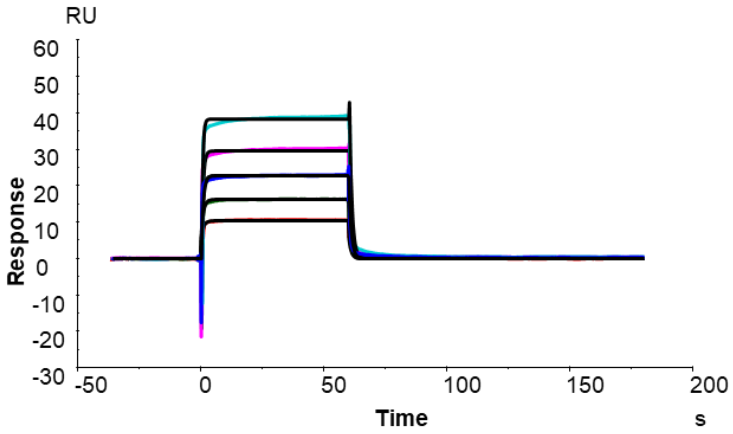
Figure S19. The SPR sensorgrams, fitting parameters and quality control table of kanamycin (3 replicates)

- Amikacin



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	7.498E+4	0.5820	7.762E-6	39.65	
Cycle: 5 3.75 µM					3.750E-6
Cycle: 6 7.5 µM					7.500E-6
Cycle: 7 15 µM					1.500E-5
Cycle: 8 30 µM					3.000E-5
Cycle: 9 15 µM					1.500E-5

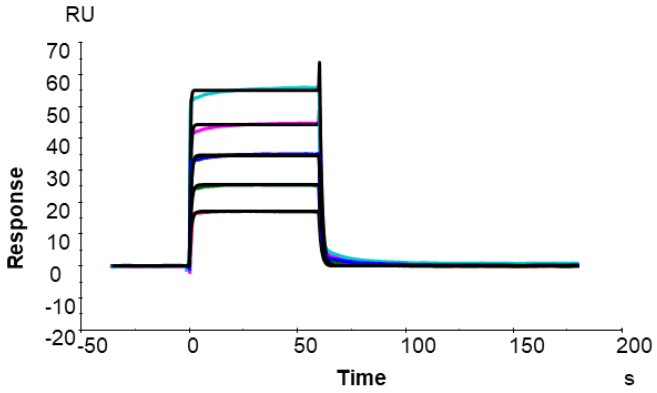




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	3.987E+4	1.025	2.570E-5	97.03	
Cycle: 23 1.875 µM					1.875E-6
Cycle: 24 3.75 µM					3.750E-6
Cycle: 25 7.5 µM					7.500E-6
Cycle: 26 15 µM					1.500E-5
Cycle: 27 30 µM					3.000E-5
Cycle: 28 7.5 µM					7.500E-6

Quality Control | Report | Residuals | Parameters

- Kinetic constant kd is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



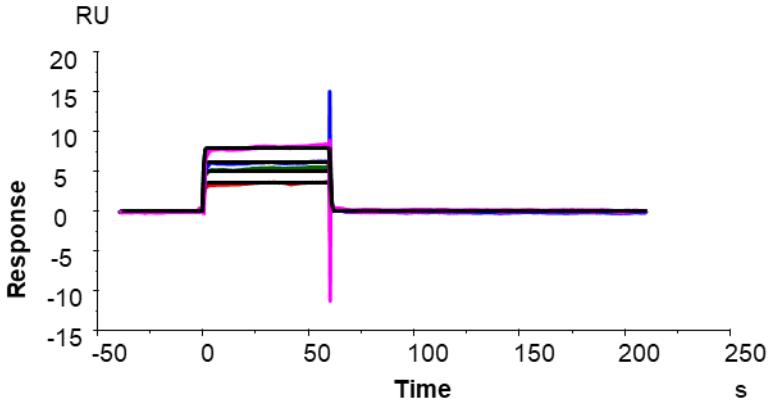
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	8.442E+4	0.9436	1.118E-5	87.68	
Cycle: 9 1.875 µM					1.875E-6
Cycle: 10 3.75 µM					3.750E-6
Cycle: 11 7.5 µM					7.500E-6
Cycle: 12 15 µM					1.500E-5
Cycle: 13 30 µM					3.000E-5
Cycle: 14 7.5 µM					7.500E-6

Quality Control | Report | Residuals | Parameters

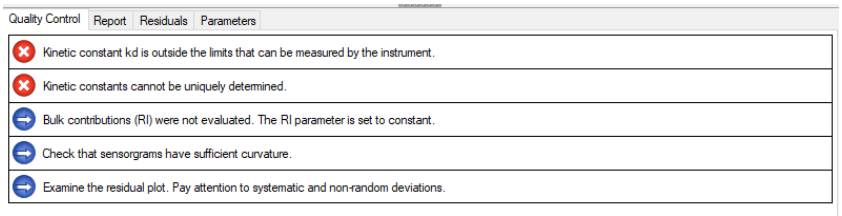
- Kinetic constant kd is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

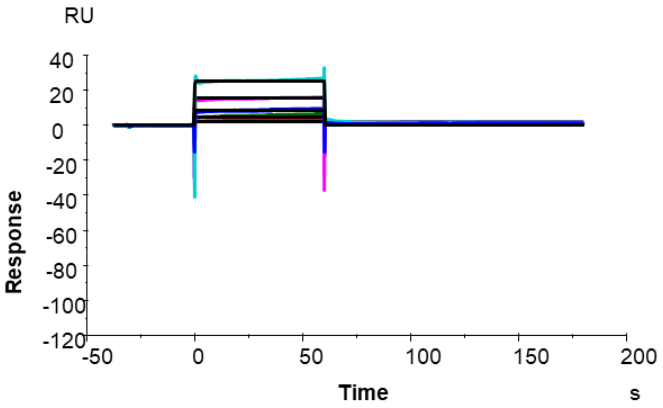
Figure S20. The SPR sensorgrams, fitting parameters and quality control table of amikacin (3 replicates)

- DMA-1

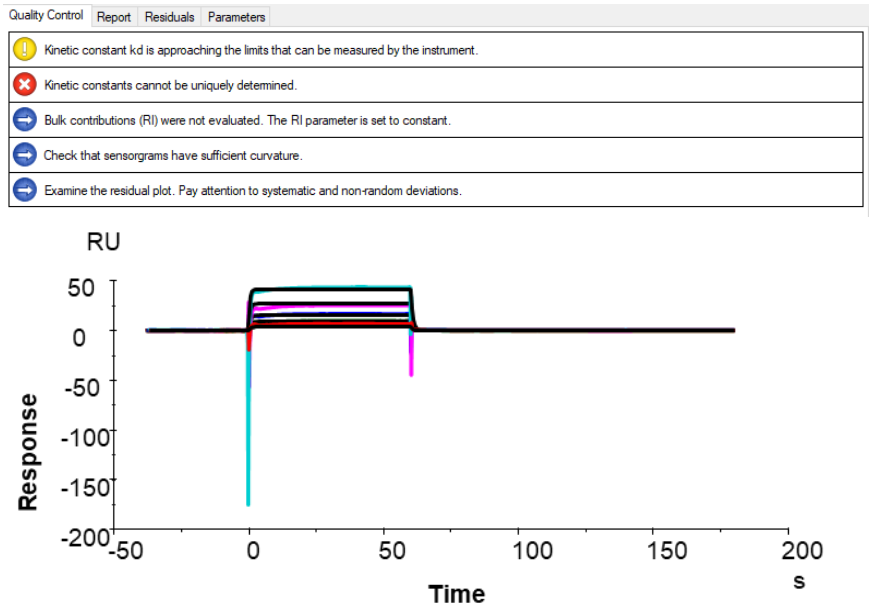


Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2.108E+4	2.427	1.151E-4	20.46	
Cycle: 23 25 µM					2.500E-5
Cycle: 24 37.5 µM					3.750E-5
Cycle: 25 50 µM					5.000E-5
Cycle: 26 75 µM					7.500E-5
Cycle: 27 75 µM					7.500E-5





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.549E+4	7.764	5.012E-4	68.27	
Cycle: 2 18.75 µM					1.875E-5
Cycle: 3 37.5 µM					3.750E-5
Cycle: 4 75 µM					7.500E-5
Cycle: 5 150 µM					1.500E-4
Cycle: 6 300 µM					3.000E-4
Cycle: 7 75 µM					7.500E-5

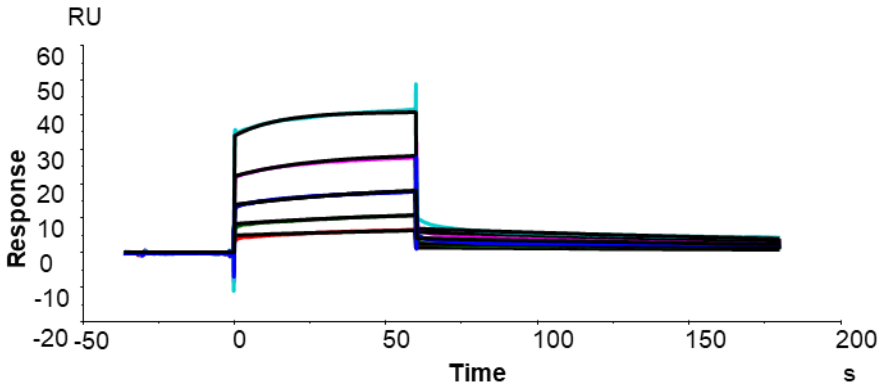


Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	3505	1.284	3.664E-4	91.98	
Cycle: 3 18.75 µM					1.875E-5
Cycle: 4 37.5 µM					3.750E-5
Cycle: 5 75 µM					7.500E-5
Cycle: 6 150 µM					1.500E-4
Cycle: 7 300 µM					3.000E-4
Cycle: 8 18.75 µM					1.875E-5

Quality Control
Report
Residuals
Parameters
Kinetic constant kd is approaching the limits that can be measured by the instrument.
Kinetic constants cannot be uniquely determined.
Bulk contributions (RI) were not evaluated. The RI parameter is set to constant.
Check that sensorgrams have sufficient curvature.
Examine the residual plot. Pay attention to systematic and non-random deviations.

Figure S21. The SPR sensorgrams, fitting parameters and quality control table of DMA-1 (3 replicates)

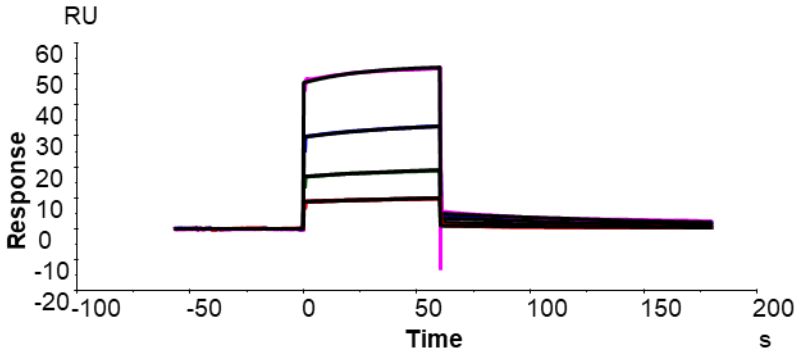
- DMA-148



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1064	0.004564	4.289E-6	7.568	
Cycle: 16 3.75 µM					3.750E-6
Cycle: 17 7.5 µM					7.500E-6
Cycle: 18 15 µM					1.500E-5
Cycle: 19 30 µM					3.000E-5
Cycle: 20 60 µM					6.000E-5
Cycle: 21 15 µM					1.500E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Quality Control | Report | Residuals | Parameters

Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1004	0.007115	7.085E-6	6.920	
Cycle: 10 3.75 µM					3.750E-6
Cycle: 11 7.5 µM					7.500E-6
Cycle: 12 15 µM					1.500E-5
Cycle: 13 30 µM					3.000E-5
Cycle: 14 3.75 µM					3.750E-6

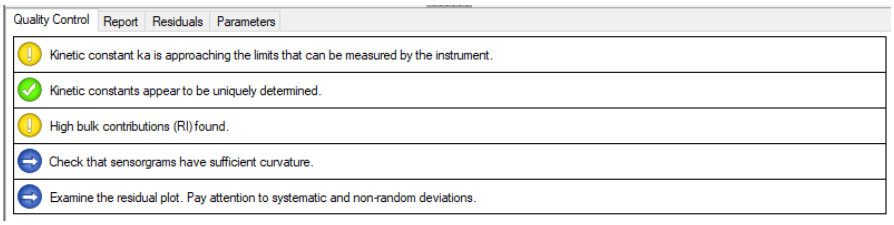
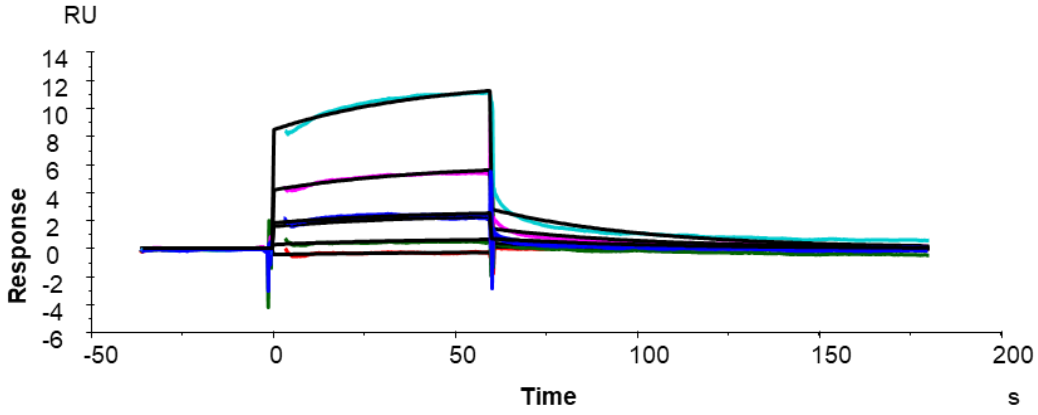


Figure S22. The SPR sensorgrams, fitting parameters and quality control table of DMA-148 (2 replicates)

- DMA-156



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	25.82	0.02319	8.981E-4	114.3	
Cycle: 9 1.875 µM					1.875E-6
Cycle: 10 3.75 µM					3.750E-6
Cycle: 11 7.5 µM					7.500E-6
Cycle: 12 15 µM					1.500E-5
Cycle: 13 30 µM					3.000E-5
Cycle: 14 7.5 µM					7.500E-6

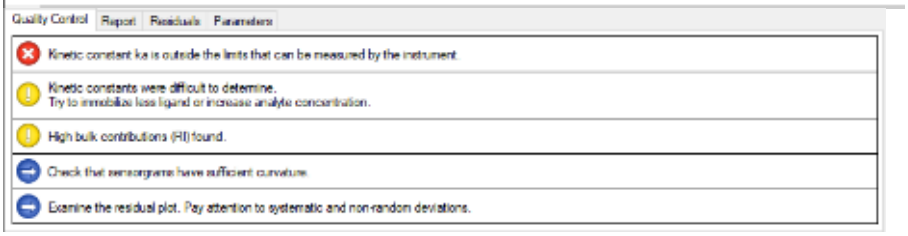
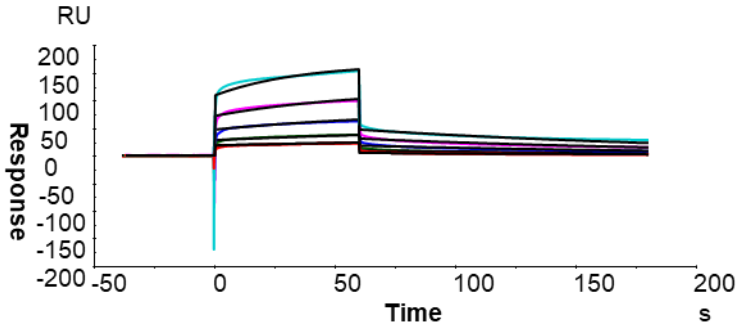
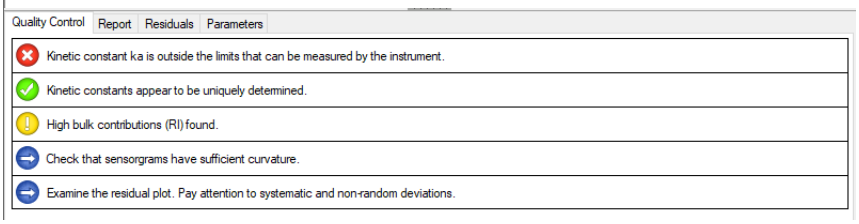


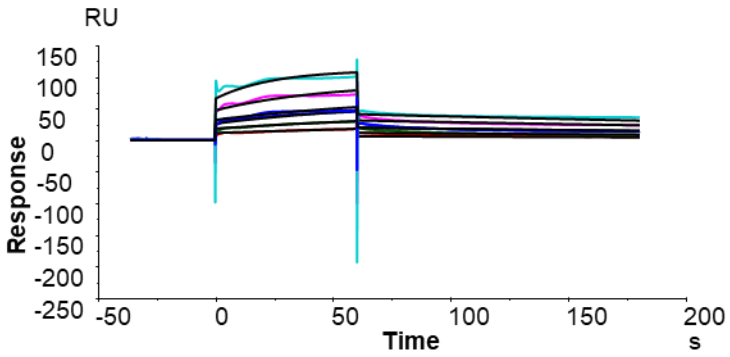
Figure S23. The SPR sensorgrams, fitting parameters and quality control table of DMA-156 (1 replicate)

- DMA-164



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	75.61	0.006060	8.015E-5	73.42	
Cycle: 4 18.75 µM					1.875E-5
Cycle: 5 37.5 µM					3.750E-5
Cycle: 6 75 µM					7.500E-5
Cycle: 7 150 µM					1.500E-4
Cycle: 8 300 µM					3.000E-4
Cycle: 9 18.75 µM					1.875E-5

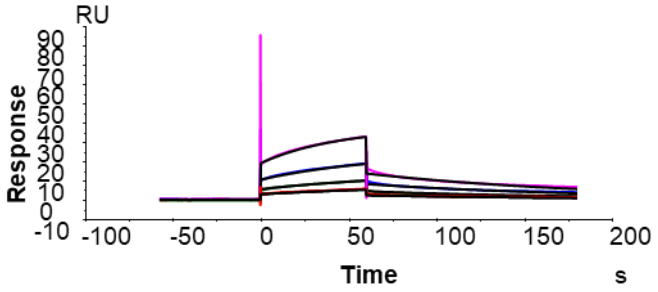




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	131.1	0.002328	1.776E-5	47.74	
Cycle: 30 18.75 µM					1.875E-5
Cycle: 31 37.5 µM					3.750E-5
Cycle: 32 75 µM					7.500E-5
Cycle: 33 150 µM					1.500E-4
Cycle: 34 300 µM					3.000E-4
Cycle: 35 75 µM					7.500E-5

Quality Control | Report | Residuals | Parameters

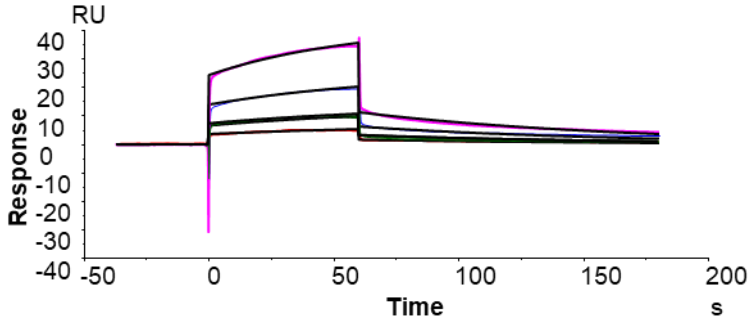
- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	503.2	0.007451	1.481E-5	27.62	
Cycle: 22 3.75 µM					3.750E-6
Cycle: 23 7.5 µM					7.500E-6
Cycle: 24 15 µM					1.500E-5
Cycle: 25 30 µM					3.000E-5
Cycle: 26 3.75 µM					3.750E-6

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	266.6	0.009384	3.520E-5	37.69	
Cycle: 36 3.75 µM					3.750E-6
Cycle: 37 7.5 µM					7.500E-6
Cycle: 38 15 µM					1.500E-5
Cycle: 39 30 µM					3.000E-5
Cycle: 40 7.5 µM					7.500E-6

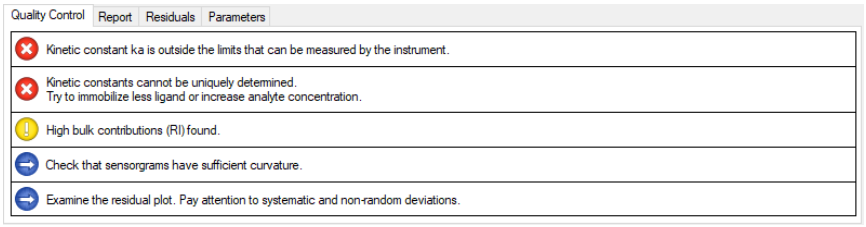
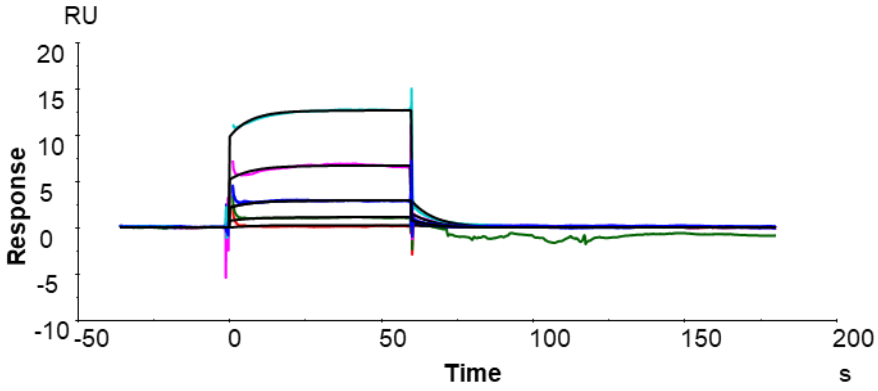


Figure S24. The SPR sensorgrams, fitting parameters and quality control table of DMA-164 (4 replicates)

- DMA-180



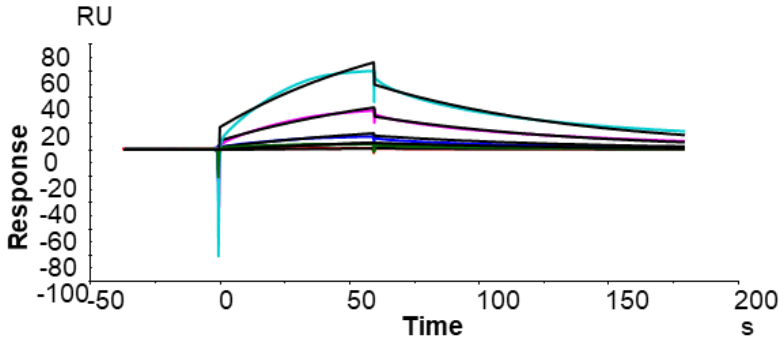
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	549.9	0.1301	2.366E-4	26.03	
Cycle: 16 1.875 µM					1.875E-6
Cycle: 17 3.75 µM					3.750E-6
Cycle: 18 7.5 µM					7.500E-6
Cycle: 19 15 µM					1.500E-5
Cycle: 20 30 µM					3.000E-5
Cycle: 21 7.5 µM					7.500E-6

Quality Control | Report | Residuals | Parameters

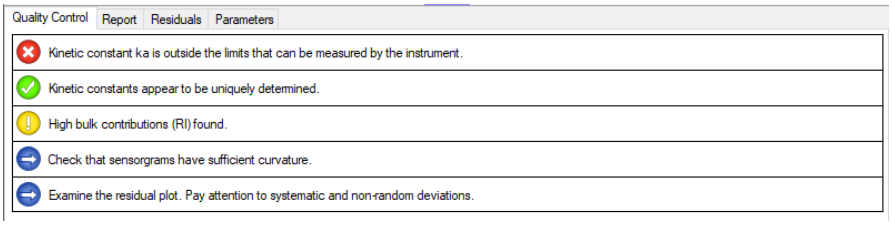
- Kinetic constant ka is approaching the limits that can be measured by the instrument.
- Kinetic constants cannot be uniquely determined. Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

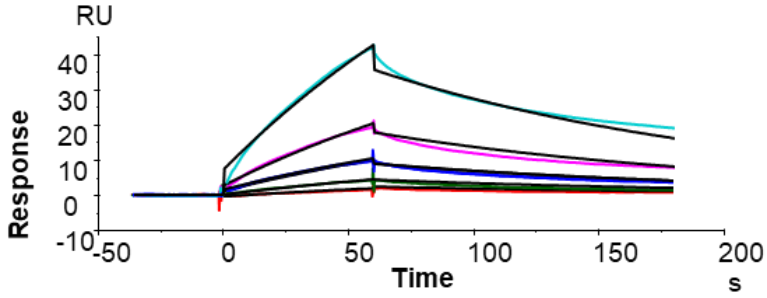
Figure S25. The SPR sensorgrams, fitting parameters and quality control table of DMA-180 (1 replicate)

- DMA-186



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	5.823	0.01247	0.002142	4031	
Cycle: 23 1 µM					1.000E-6
Cycle: 24 5 µM					5.000E-6
Cycle: 25 10 µM					1.000E-5
Cycle: 26 25 µM					2.500E-5
Cycle: 27 50 µM					5.000E-5
Cycle: 28 5 µM					5.000E-6



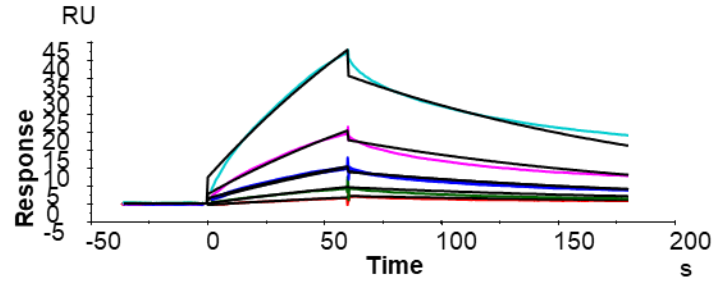


Quality Control | Report | Residuals | Parameters

Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	4.658	0.006616	0.001420	5141	
Cycle: 23 1.875 µM					1.875E-6
Cycle: 24 3.75 µM					3.750E-6
Cycle: 25 7.5 µM					7.500E-6
Cycle: 26 15 µM					1.500E-5
Cycle: 27 30 µM					3.000E-5
Cycle: 28 7.5 µM					7.500E-6

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Quality Control | Report | Residuals | Parameters

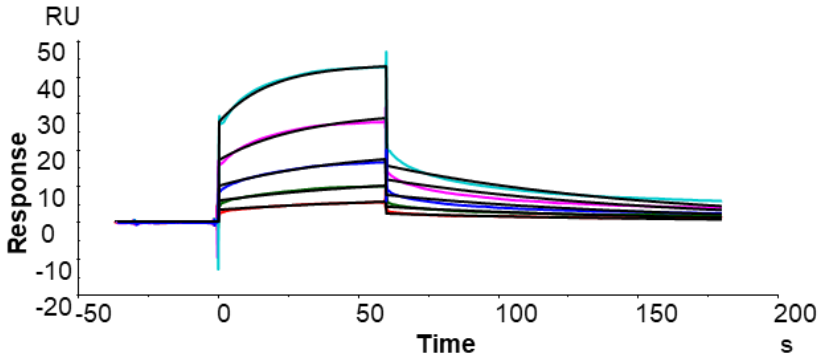
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2.804	0.006597	0.002352	8516	
Cycle: 23 1.875 µM					1.875E-6
Cycle: 24 3.75 µM					3.750E-6
Cycle: 25 7.5 µM					7.500E-6
Cycle: 26 15 µM					1.500E-5
Cycle: 27 30 µM					3.000E-5
Cycle: 28 7.5 µM					7.500E-6

Quality Control | Report | Residuals | Parameters

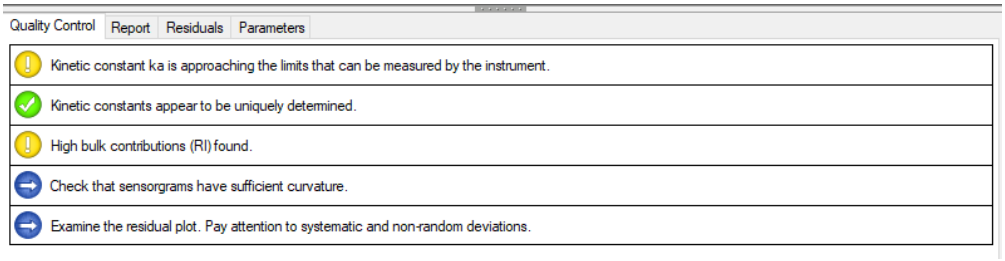
- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

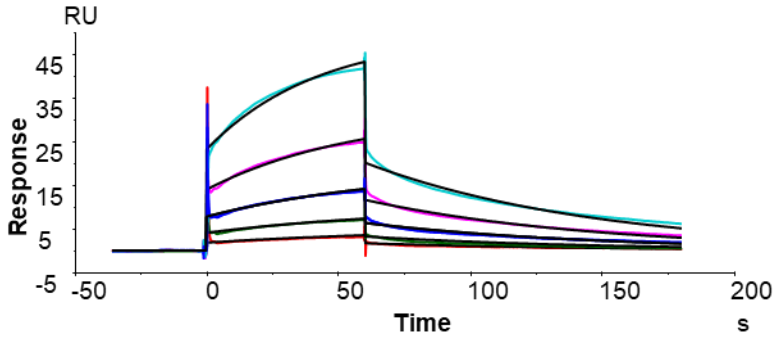
Figure S26. The SPR sensorgrams, fitting parameters and quality control table of DMA-186 (3 replicates)

- DMA-187

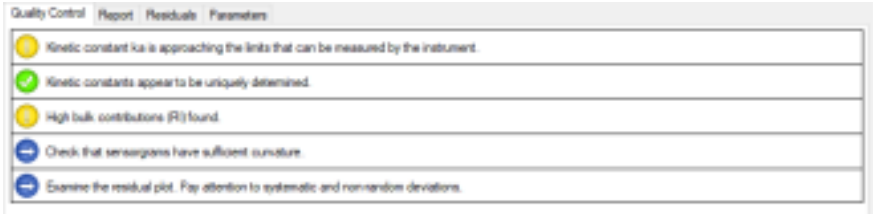


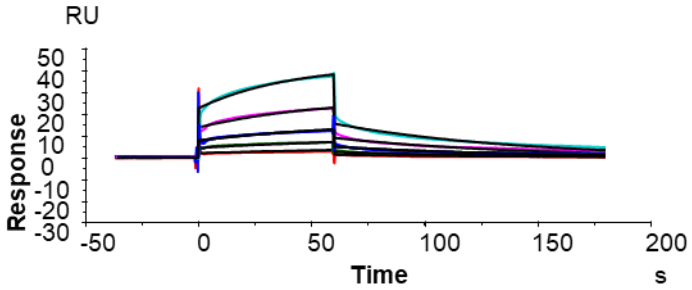
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	887.8	0.01074	1.210E-5	20.02	
Cycle: 23 3.125 µM					3.125E-6
Cycle: 24 6.25 µM					6.250E-6
Cycle: 26 25 µM					2.500E-5
Cycle: 27 50 µM					5.000E-5
Cycle: 28 12.5 µM					1.250E-5





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	413.1	0.01144	2.769E-5	50.99	
Cycle: 30 1.875 µM					1.875E-6
Cycle: 31 3.75 µM					3.750E-6
Cycle: 32 7.5 µM					7.500E-6
Cycle: 33 15 µM					1.500E-5
Cycle: 34 30 µM					3.000E-5
Cycle: 35 7.5 µM					7.500E-6

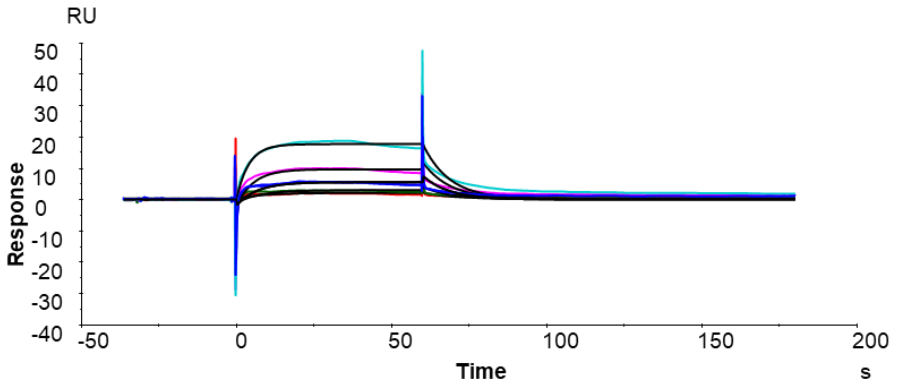




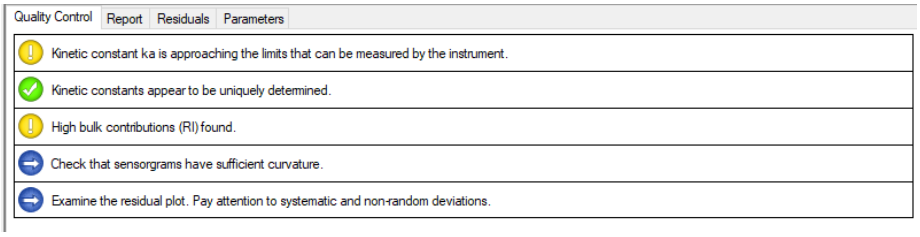
Curve	ka (1/Ms)	SE(ka)	kd (1/s)	SE(kd)	Rmax (RU)	SE(Rmax)	Conc (M)
	420.1	13	0.01251	1.8E-4	40.0	0.87	
Cycle: 37 1.875 µM							1.875E-06
Cycle: 38 3.75 µM							3.75E-06
Cycle: 39 7.5 µM							7.5E-06
Cycle: 40 15 µM							1.5E-05
Cycle: 41 30 µM							3E-05
Cycle: 42 7.5 µM							7.5E-06

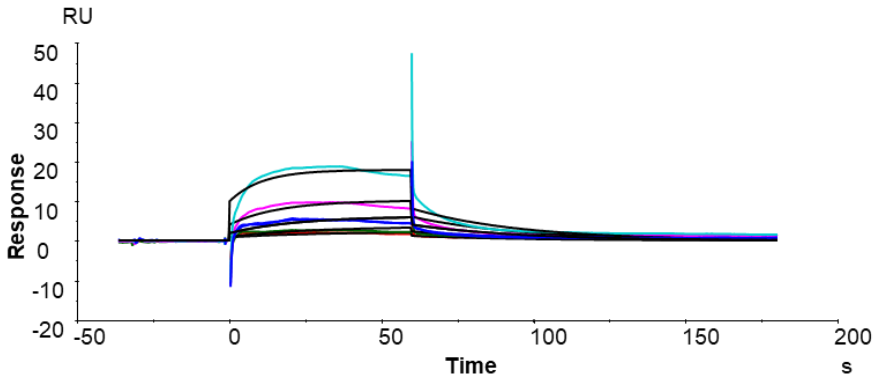
Figure S27. The SPR sensorgrams, fitting parameters and quality control table of DMA-187 (3 replicates)

DMA-190



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2691	0.1180	4.386E-5	33.27	
Cycle: 30 3.125 µM					3.125E-6
Cycle: 31 6.25 µM					6.250E-6
Cycle: 32 12.5 µM					1.250E-5
Cycle: 33 25 µM					2.500E-5
Cycle: 34 50 µM					5.000E-5
Cycle: 35 12.5 µM					1.250E-5





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1331	0.02812	2.113E-5	11.67	
Cycle: 30 3.125 µM					3.125E-6
Cycle: 31 6.25 µM					6.250E-6
Cycle: 32 12.5 µM					1.250E-5
Cycle: 33 25 µM					2.500E-5
Cycle: 34 50 µM					5.000E-5
Cycle: 35 12.5 µM					1.250E-5

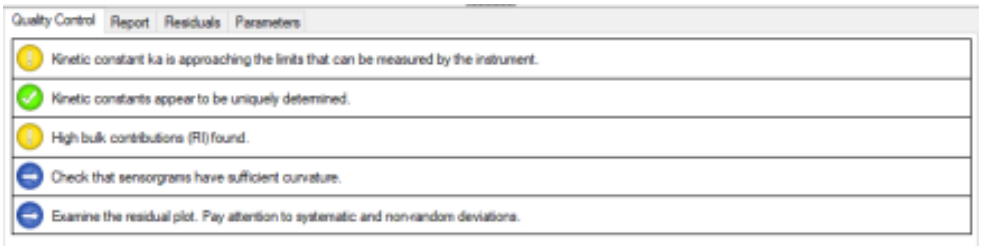
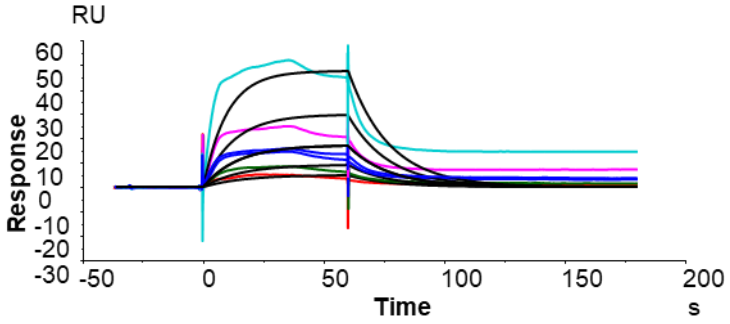
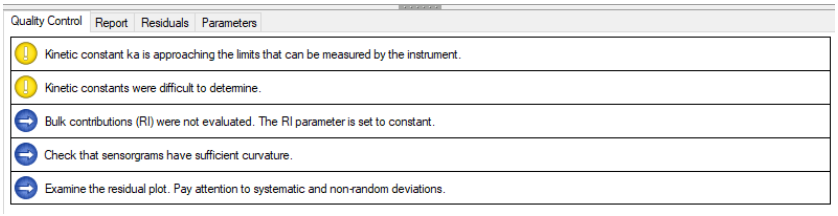


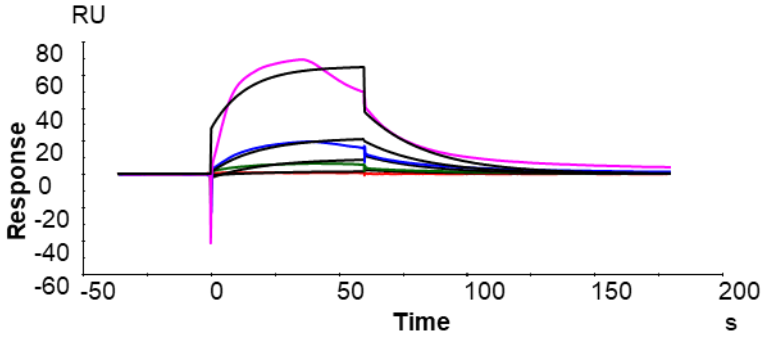
Figure S28. The SPR sensorgrams, fitting parameters and quality control table of DMA-190 (2 replicates)

- DMA-191



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1750	0.05895	3.369E-5	111.2	
Cycle: 37 1.5625 µM					1.563E-6
Cycle: 38 3.125 µM					3.125E-6
Cycle: 39 6.25 µM					6.250E-6
Cycle: 40 12.5 µM					1.250E-5
Cycle: 41 25 µM					2.500E-5
Cycle: 42 6.25 µM					6.250E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1295	0.04046	3.124E-5	85.50	
Cycle: 9 1 µM					1.000E-6
Cycle: 10 5 µM					5.000E-6
Cycle: 11 10 µM					1.000E-5
Cycle: 12 25 µM					2.500E-5

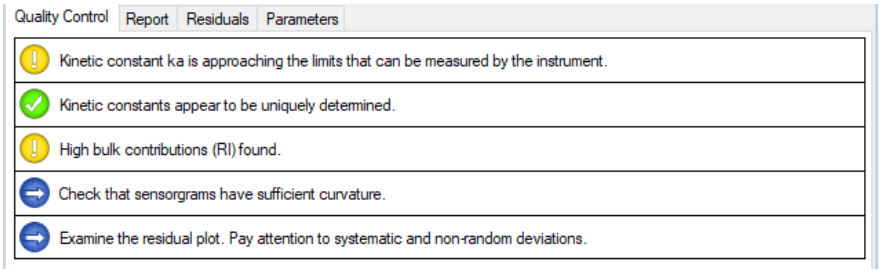
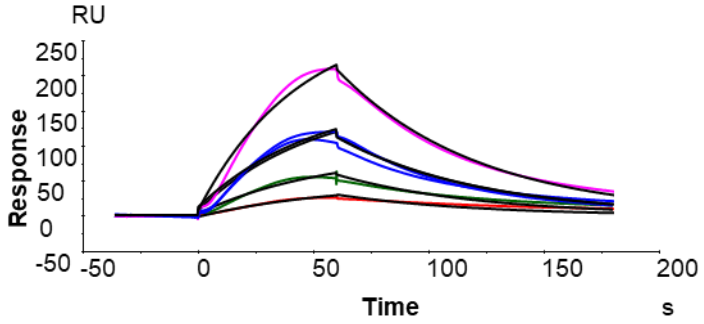
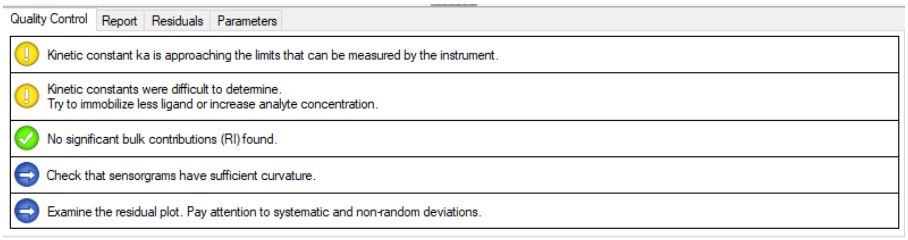


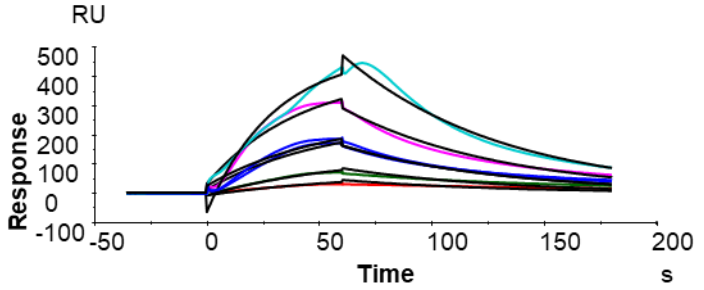
Figure S29. The SPR sensorgrams, fitting parameters and quality control table of DMA-191 (2 replicates)

- DMA-193



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	537.6	0.01667	3.102E-5	963.2	
Cycle: 30 1.5625 µM					1.563E-6
Cycle: 31 3.125 µM					3.125E-6
Cycle: 32 6.25 µM					6.250E-6
Cycle: 33 12.5 µM					1.250E-5
Cycle: 35 6.25 µM					6.250E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	638.9	0.01423	2.227E-5	952.4	
Cycle: 16 1.875 µM					1.875E-6
Cycle: 17 3.75 µM					3.750E-6
Cycle: 18 7.5 µM					7.500E-6
Cycle: 19 15 µM					1.500E-5
Cycle: 20 30 µM					3.000E-5
Cycle: 21 7.5 µM					7.500E-6

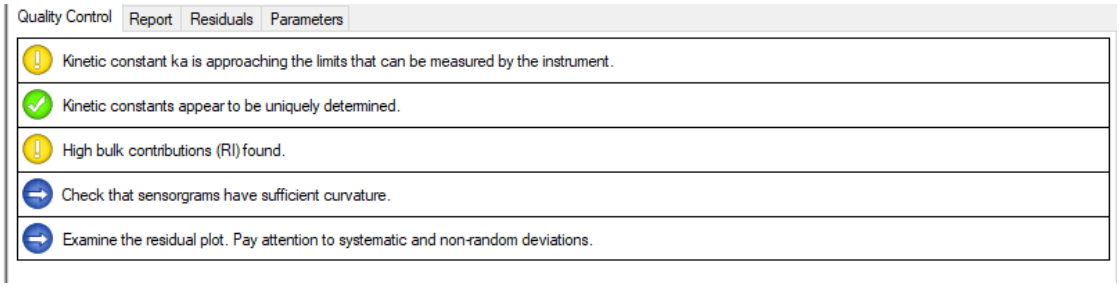
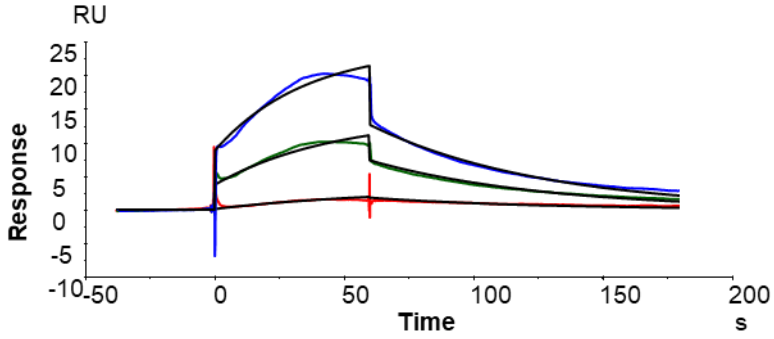


Figure S30. The SPR sensorgrams, fitting parameters and quality control table of DMA-193 (2 replicates)

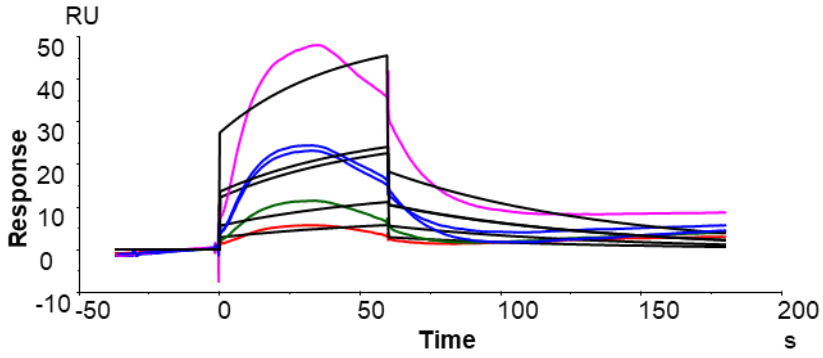
- DMA-194



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1373	0.01491	1.086E-5	32.02	
Cycle: 2 1 µM					1.000E-6
Cycle: 3 5 µM					5.000E-6
Cycle: 4 10 µM					1.000E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	916.8	0.01303	1.421E-5	50.88	
Cycle: 37 1.5625 µM					1.563E-6
Cycle: 38 3.125 µM					3.125E-6
Cycle: 39 6.25 µM					6.250E-6
Cycle: 40 12.5 µM					1.250E-5
Cycle: 42 6.25 µM					6.250E-6

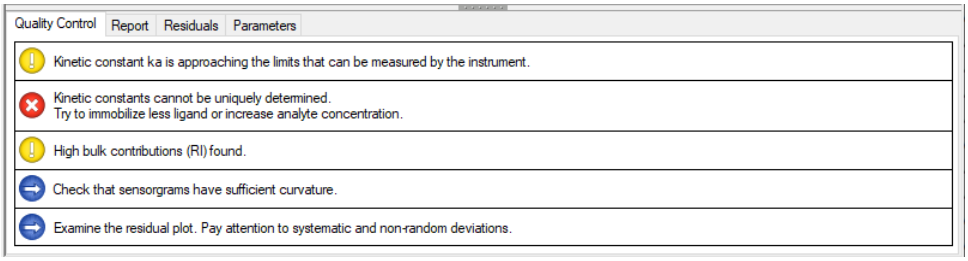
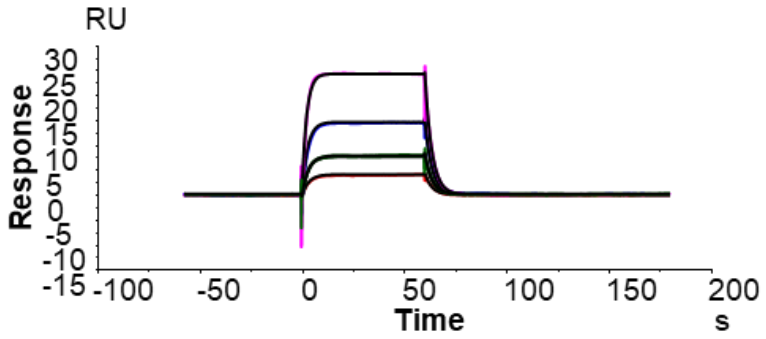
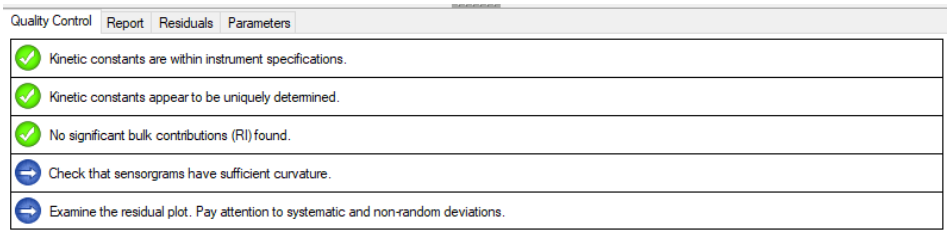


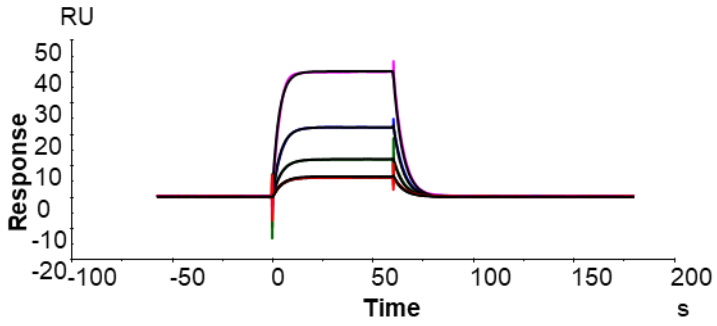
Figure S31. The SPR sensorgrams, fitting parameters and quality control table of DMA-194 (2 replicates)

- TO-PRO-1



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	5.112E+5	0.2935	5.741E-7	76.28	
Cycle: 11 0.0375 µM					3.750E-8
Cycle: 12 0.075 µM					7.500E-8
Cycle: 13 0.15 µM					1.500E-7
Cycle: 14 0.3 µM					3.000E-7
Cycle: 15 0.075 µM					7.500E-8

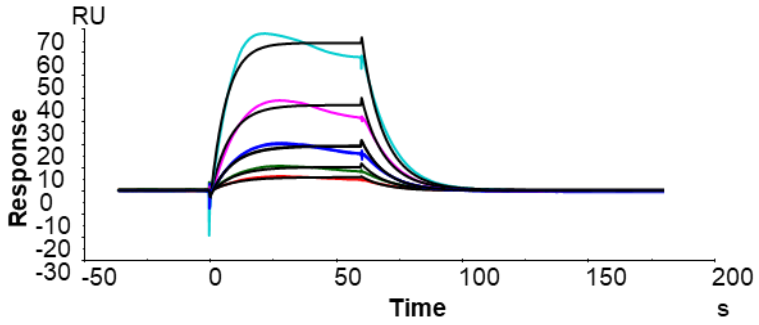




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	3.161E+5	0.2107	6.665E-7	126.8	
Cycle: 34 0.0375 µM					3.750E-8
Cycle: 35 0.075 µM					7.500E-8
Cycle: 36 0.15 µM					1.500E-7
Cycle: 37 0.3 µM					3.000E-7
Cycle: 38 0.0375 µM					3.750E-8

Quality Control | Report | Residuals | Parameters

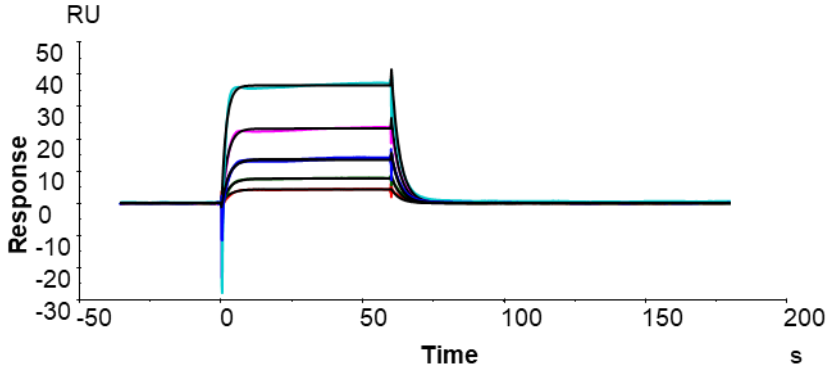
- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- No significant bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	3.229E+5	0.2132	6.605E-7	215.9	
Cycle: 29 0.01875 µM					1.875E-8
Cycle: 30 0.0375 µM					3.750E-8
Cycle: 31 0.075 µM					7.500E-8
Cycle: 32 0.15 µM					1.500E-7
Cycle: 33 0.3 µM					3.000E-7
Cycle: 34 0.075 µM					7.500E-8

Quality Control | Report | Residuals | Parameters

- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	4.566E+5	0.3435	7.523E-7	99.36	
Cycle: 30 0.0375 µM					3.750E-8
Cycle: 31 0.075 µM					7.500E-8
Cycle: 32 0.15 µM					1.500E-7
Cycle: 33 0.3 µM					3.000E-7
Cycle: 34 0.6 µM					6.000E-7
Cycle: 35 0.15 µM					1.500E-7

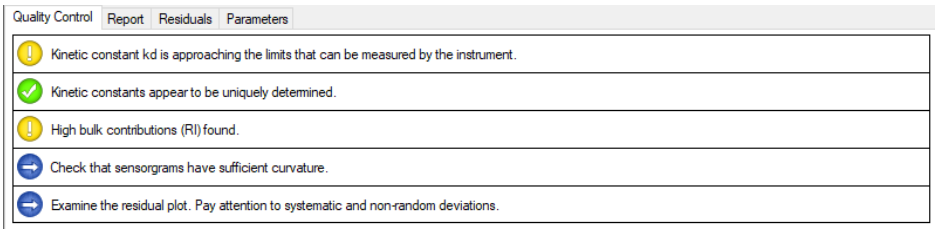
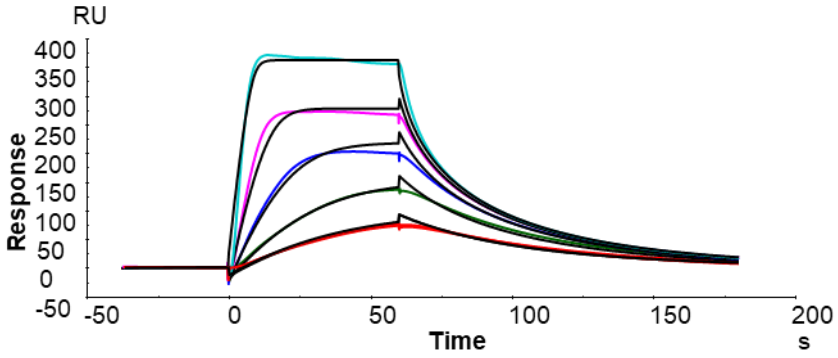
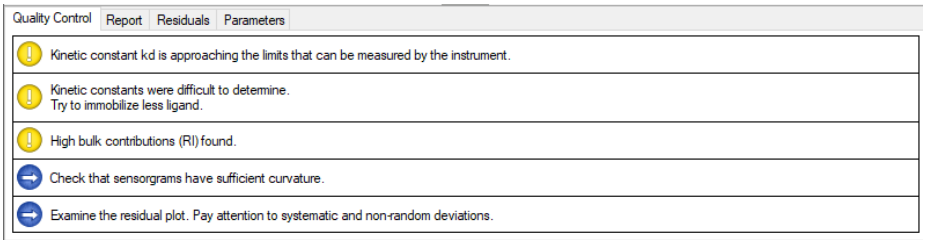


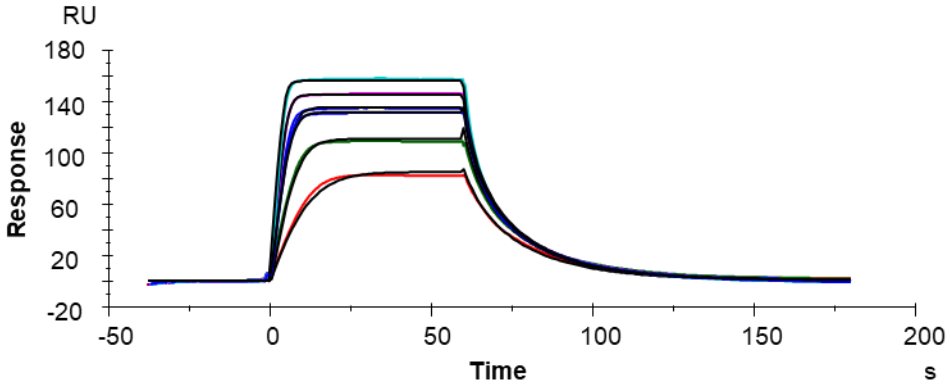
Figure S32. The SPR sensorgrams, fitting parameters and quality control table of TO-PRO-1 (4 replicates)

- Mitoxantrone

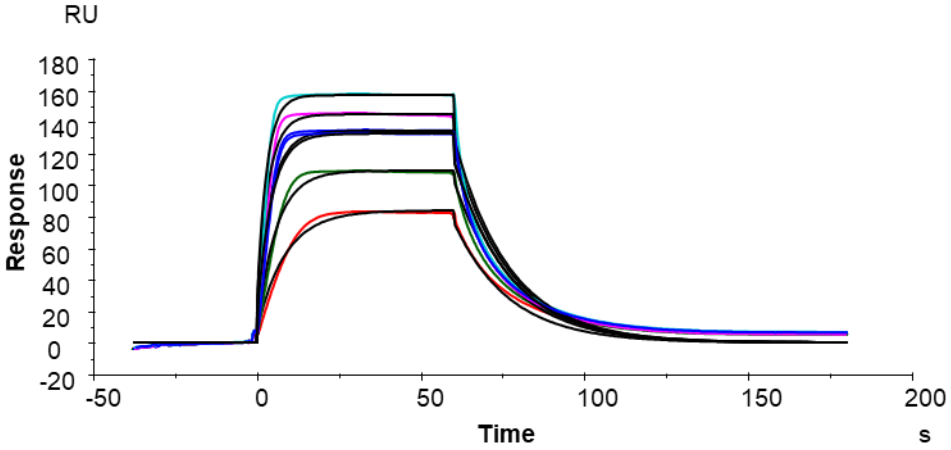


Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	7.568E+5	0.3557	4.700E-7	388.0	
Cycle: 3 0.1875 µM					1.875E-7
Cycle: 4 0.375 µM					3.750E-7
Cycle: 5 0.75 µM					7.500E-7
Cycle: 6 1.5 µM					1.500E-6
Cycle: 7 3 µM					3.000E-6
Cycle: 8 0.1875 µM					1.875E-7





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	7.895E+6	1.770	2.242E-7	185.1	
Cycle: 2 0.2 µM					2.000E-7
Cycle: 3 0.4 µM					4.000E-7
Cycle: 4 0.6 µM					6.000E-7
Cycle: 5 0.8 µM					8.000E-7
Cycle: 6 1 µM					1.000E-6
Cycle: 7 0.6 µM					6.000E-7



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2.851E+5	0.05927	2.079E-7	155.9	
Cycle: 2 0.2 µM					2.000E-7
Cycle: 3 0.4 µM					4.000E-7
Cycle: 4 0.6 µM					6.000E-7
Cycle: 5 0.8 µM					8.000E-7
Cycle: 6 1 µM					1.000E-6
Cycle: 7 0.6 µM					6.000E-7

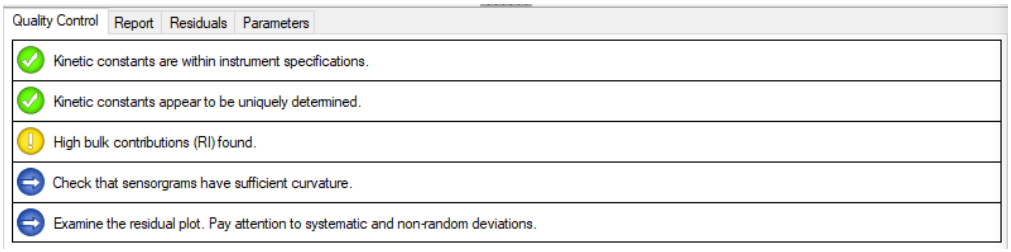
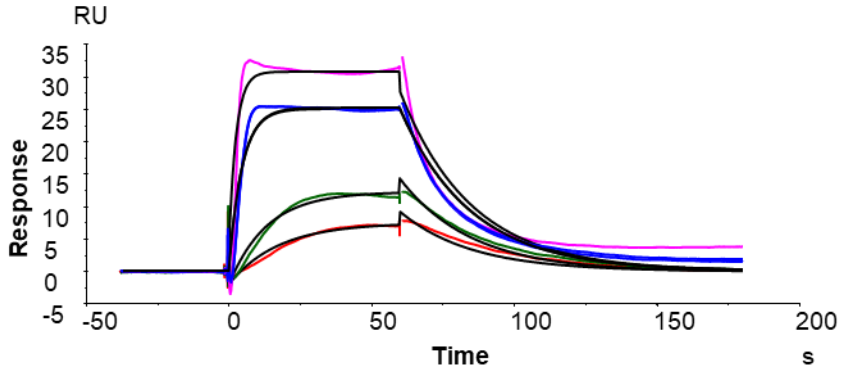
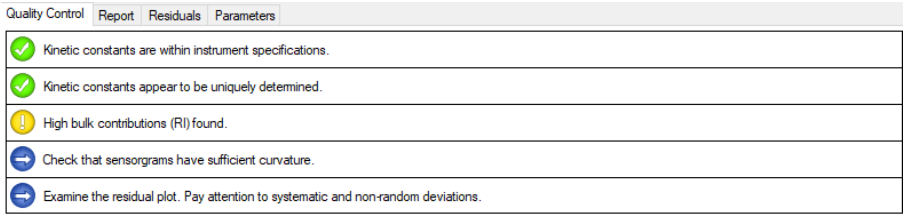


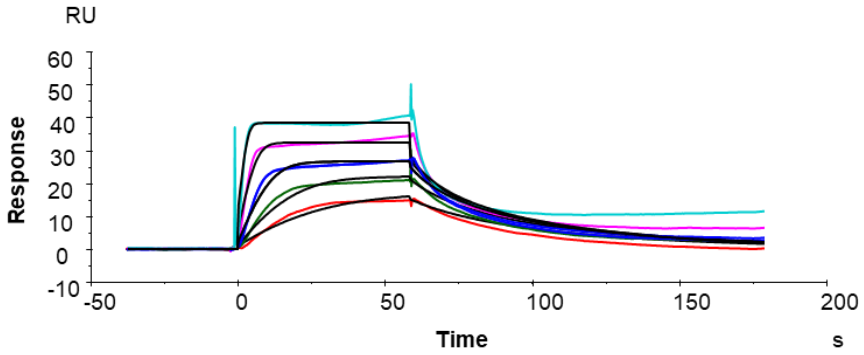
Figure S33. The SPR sensorgrams, fitting parameters and quality control table of mitoxantrone (3 replicates)

- DPF m1



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	3.539E+5	0.04013	1.134E-7	30.70	
Cycle: 3 0.05 µM					5.000E-8
Cycle: 4 0.1 µM					1.000E-7
Cycle: 5 0.5 µM					5.000E-7
Cycle: 6 1 µM					1.000E-6
Cycle: 7 0.5 µM					5.000E-7

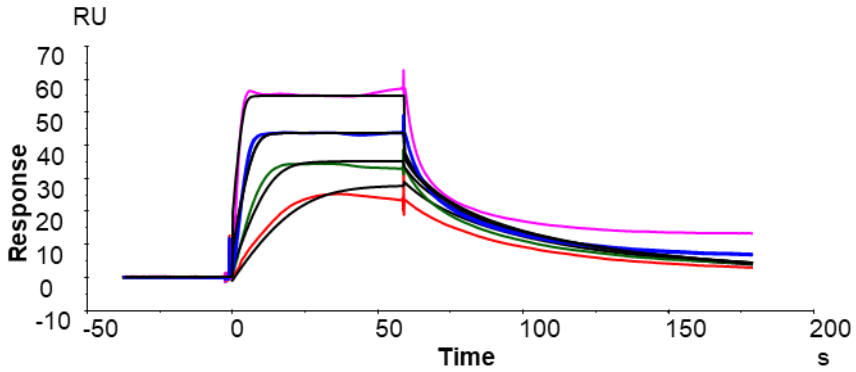




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	6.407E+5	0.06814	1.064E-7	29.98	
Cycle: 9 0.125 µM					1.250E-7
Cycle: 10 0.25 µM					2.500E-7
Cycle: 11 0.5 µM					5.000E-7
Cycle: 12 1 µM					1.000E-6
Cycle: 13 2 µM					2.000E-6
Cycle: 14 0.5 µM					5.000E-7

Quality Control | Report | Residuals | Parameters

- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



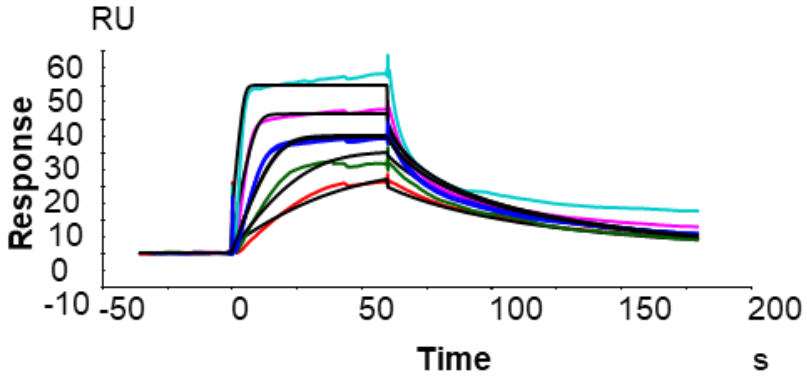
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	5.968E+5	0.07047	1.181E-7	39.79	
Cycle: 23 0.3125 µM					3.125E-7
Cycle: 24 0.625 µM					6.250E-7
Cycle: 25 1.25 µM					1.250E-6
Cycle: 26 2.5 µM					2.500E-6
Cycle: 28 1.25 µM					1.250E-6

Quality Control | Report | Residuals | Parameters

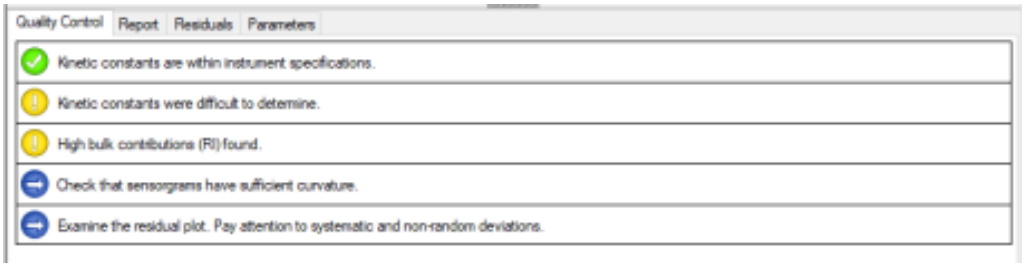
- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

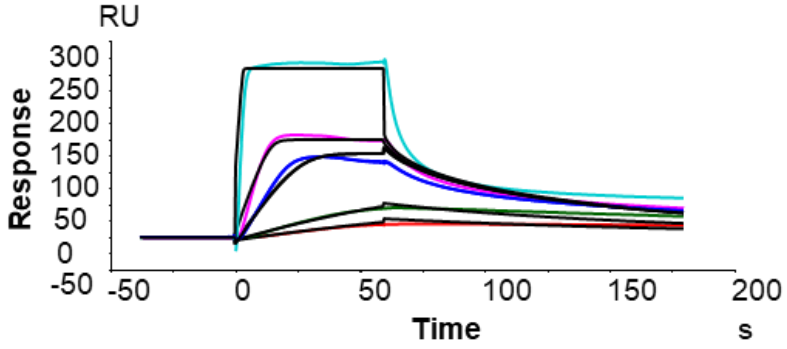
Figure S34. The SPR sensorgrams, fitting parameters and quality control table of DPF m1 (3 replicates)

- DPF p1



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.040E+6	0.1065	1.024E-7	41.86	
Cycle: 16 0.125 µM					1.250E-7
Cycle: 17 0.25 µM					2.500E-7
Cycle: 18 0.5 µM					5.000E-7
Cycle: 19 1 µM					1.000E-6
Cycle: 20 2 µM					2.000E-6
Cycle: 21 0.5 µM					5.000E-7

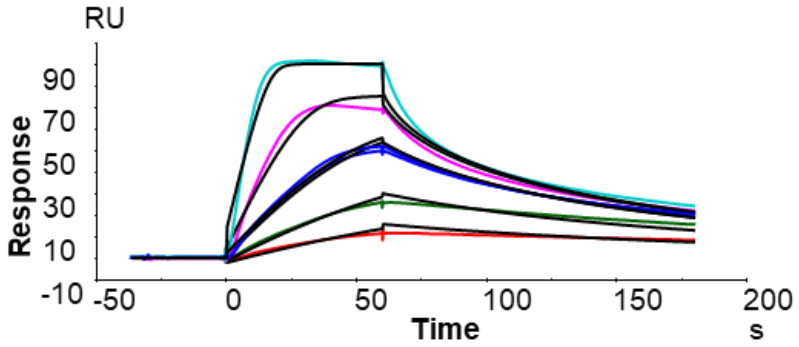




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.300E+6	0.1104	8.492E-8	161.4	
Cycle: 15 0.05 µM					5.000E-8
Cycle: 16 0.1 µM					1.000E-7
Cycle: 17 0.5 µM					5.000E-7
Cycle: 18 1 µM					1.000E-6
Cycle: 19 5 µM					5.000E-6
Cycle: 20 0.5 µM					5.000E-7

Quality Control | Report | Residuals | Parameters

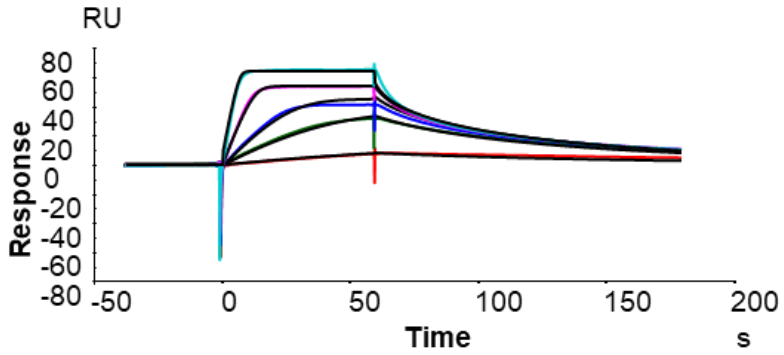
- Kinetic constants are within instrument specifications.
- Kinetic constants cannot be uniquely determined. Try to immobilize less ligand.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.127E+6	0.08319	7.384E-8	84.54	
Cycle: 9 0.05 µM					5.000E-8
Cycle: 10 0.1 µM					1.000E-7
Cycle: 11 0.2 µM					2.000E-7
Cycle: 12 0.4 µM					4.000E-7
Cycle: 13 0.8 µM					8.000E-7
Cycle: 14 0.2 µM					2.000E-7

Quality Control | Report | Residuals | Parameters

- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2.292E+6	0.1273	5.553E-8	59.69	
Cycle: 2 0.02 µM					2.000E-8
Cycle: 3 0.1 µM					1.000E-7
Cycle: 4 0.2 µM					2.000E-7
Cycle: 5 0.5 µM					5.000E-7
Cycle: 6 1 µM					1.000E-6

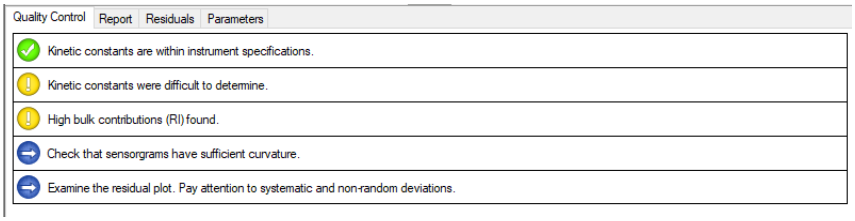
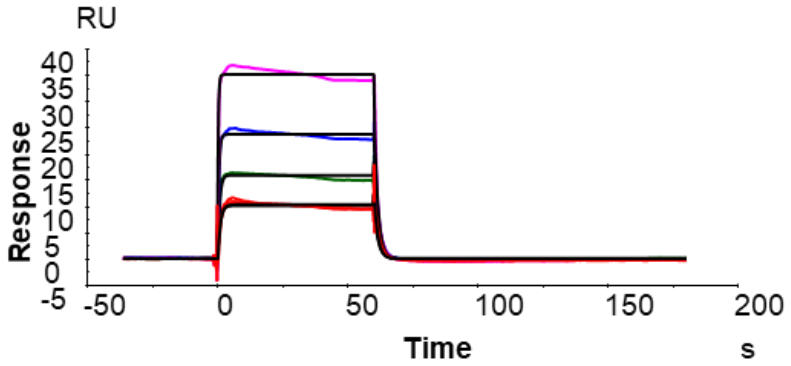
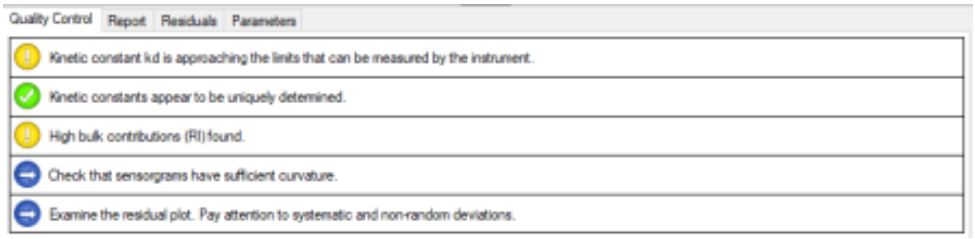


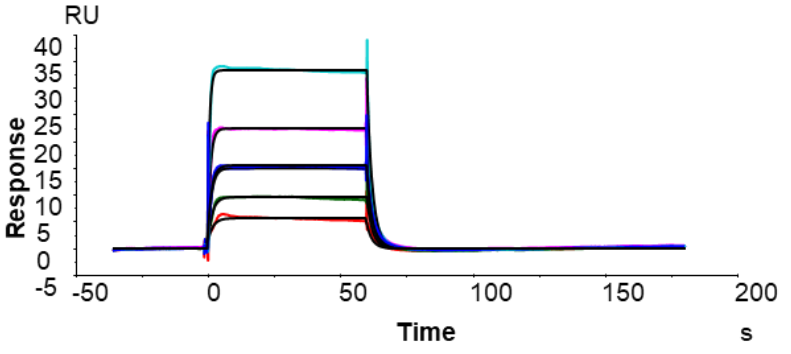
Figure S35. The SPR sensorgrams, fitting parameters and quality control table of DPF p1 (4 replicates)

- Furamidine



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2.838E+5	0.6950	2.449E-6	36.08	
Cycle: 15 1.25 µM					1.250E-6
Cycle: 16 2.5 µM					2.500E-6
Cycle: 17 5 µM					5.000E-6
Cycle: 18 10 µM					1.000E-5
Cycle: 19 1.25 µM					1.250E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.826E+5	0.4720	2.585E-6	46.17	
Cycle: 30 0.3125 µM					3.125E-7
Cycle: 31 0.625 µM					6.250E-7
Cycle: 32 1.25 µM					1.250E-6
Cycle: 33 2.5 µM					2.500E-6
Cycle: 34 5 µM					5.000E-6
Cycle: 35 1.25 µM					1.250E-6

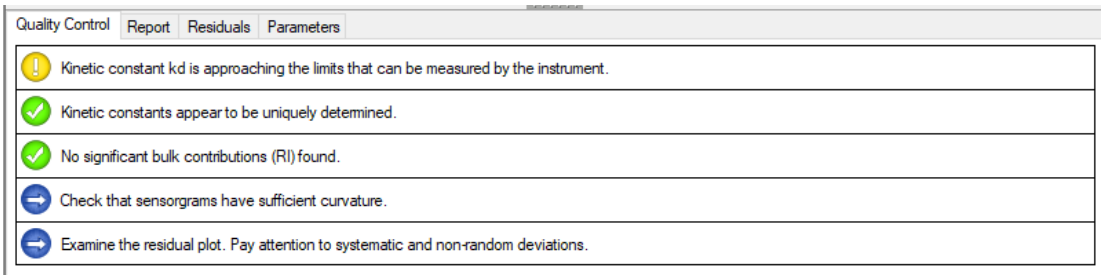
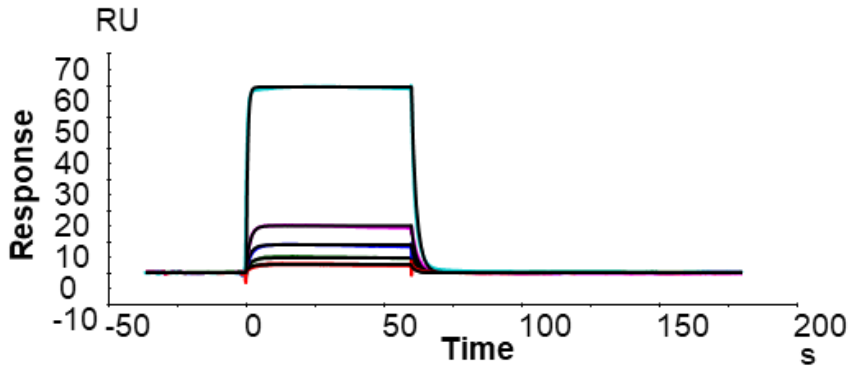


Figure S36. The SPR sensorgrams, fitting parameters and quality control table of furamidine (2 replicates)

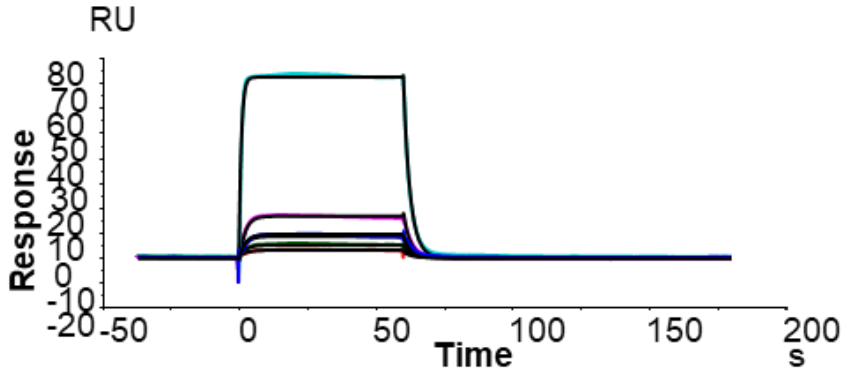
- Ethidium bromide



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	4.513E+5	0.5468	1.212E-6	76.00	
Cycle: 27 0.0375 µM					3.750E-8
Cycle: 28 0.075 µM					7.500E-8
Cycle: 29 0.15 µM					1.500E-7
Cycle: 30 0.3 µM					3.000E-7
Cycle: 31 3 µM					3.000E-6
Cycle: 32 0.0375 µM					3.750E-8

Quality Control | Report | Residuals | Parameters

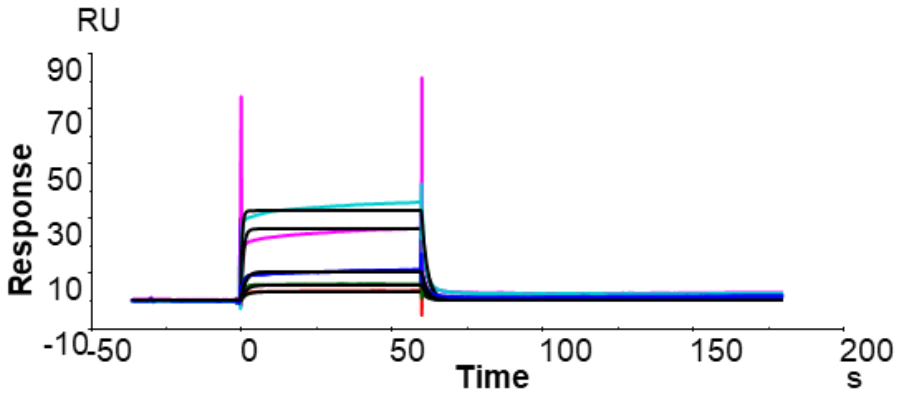
- Kinetic constant kd is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- No significant bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2.541E+5	0.4060	1.598E-6	112.2	
Cycle: 22 0.0375 µM					3.750E-8
Cycle: 23 0.075 µM					7.500E-8
Cycle: 24 0.15 µM					1.500E-7
Cycle: 25 0.3 µM					3.000E-7
Cycle: 26 3 µM					3.000E-6
Cycle: 27 0.15 µM					1.500E-7

Quality Control | Report | Residuals | Parameters

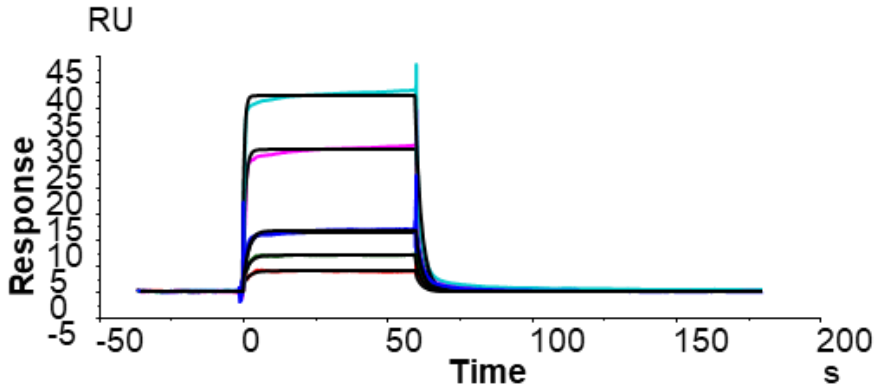
- Kinetic constant kd is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- No significant bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



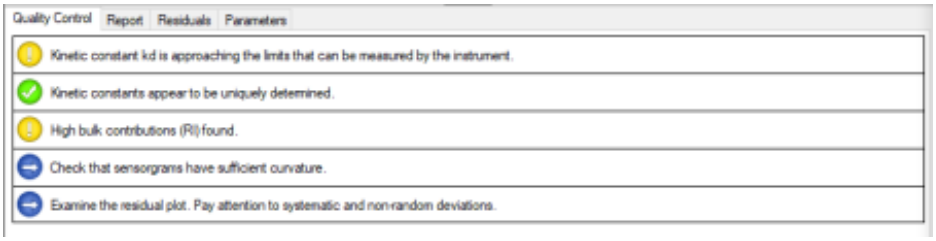
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	5.564E+5	0.5352	9.618E-7	43.22	
Cycle: 9 0.075 µM					7.500E-8
Cycle: 10 0.15 µM					1.500E-7
Cycle: 11 0.3 µM					3.000E-7
Cycle: 12 1.5 µM					1.500E-6
Cycle: 13 3 µM					3.000E-6
Cycle: 14 0.3 µM					3.000E-7

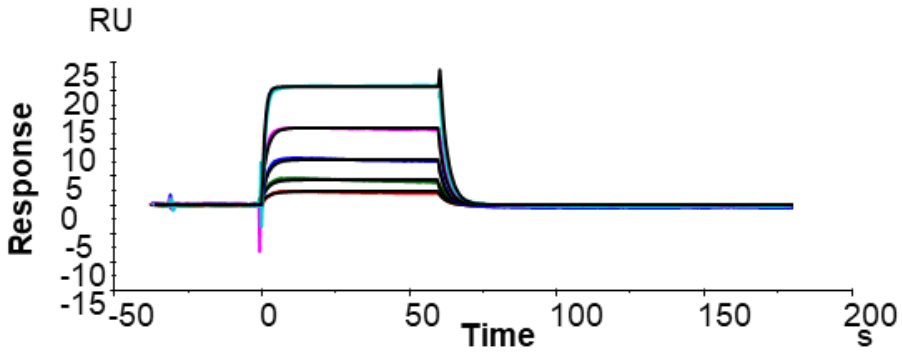
Quality Control | Report | Residuals | Parameters

- Kinetic constant kd is approaching the limits that can be measured by the instrument.
- Kinetic constants were difficult to determine.
- Bulk contributions (RI) were not evaluated. The RI parameter is set to constant.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	4.649E+5	0.4484	9.646E-7	42.01	
Cycle: 37 0.075 µM					7.500E-8
Cycle: 38 0.15 µM					1.500E-7
Cycle: 39 0.3 µM					3.000E-7
Cycle: 40 1.5 µM					1.500E-6
Cycle: 41 3 µM					3.000E-6
Cycle: 42 0.3 µM					3.000E-7





Quality Control | Report | Residuals | Parameters

Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	5.104E+5	0.3871	7.585E-7	40.02	
Cycle: 16 0.0375 µM					3.750E-8
Cycle: 17 0.075 µM					7.500E-8
Cycle: 18 0.15 µM					1.500E-7
Cycle: 19 0.3 µM					3.000E-7
Cycle: 20 1.5 µM					1.500E-6

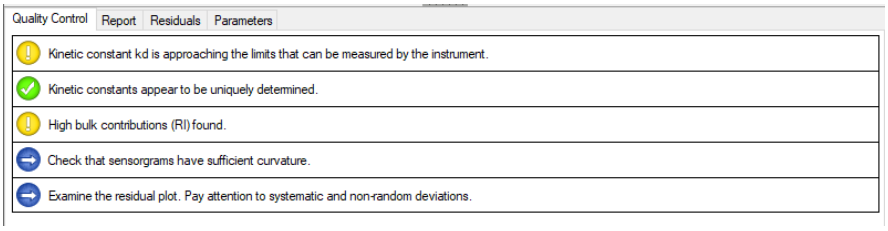
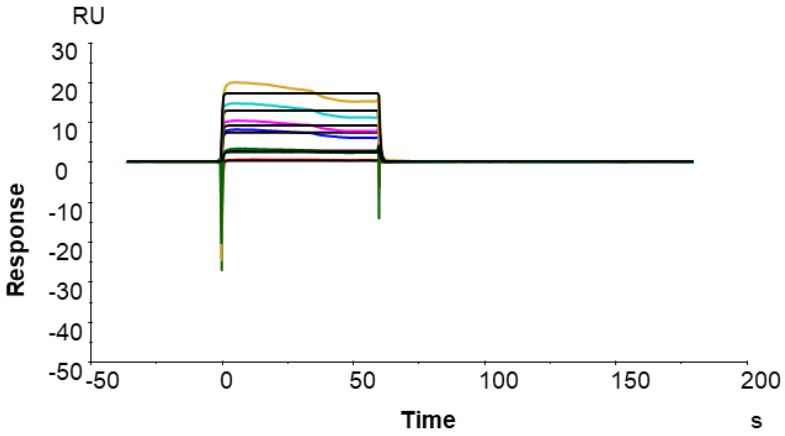
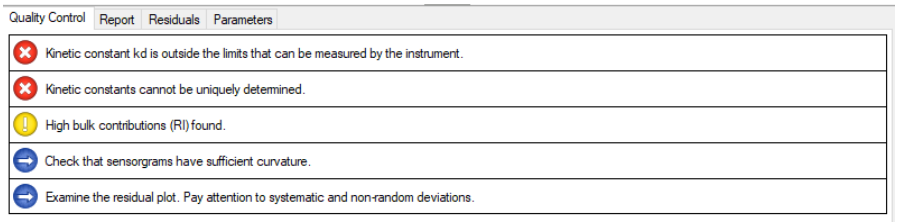


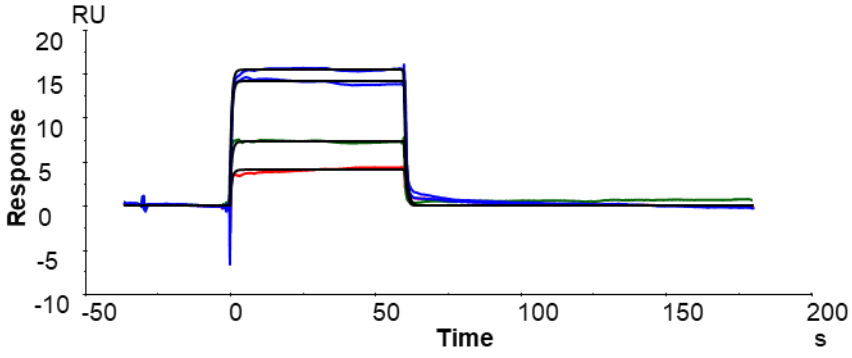
Figure S37. The SPR sensorgrams, fitting parameters and quality control table of ethidium bromide (5 replicates)

- H-33258



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	3.455E+5	1.953	5.652E-6	35.47	
Cycle: 27 0.2 µM					2.000E-7
Cycle: 28 1 µM					1.000E-6
Cycle: 29 2.5 µM					2.500E-6
Cycle: 30 3 µM					3.000E-6
Cycle: 31 4 µM					4.000E-6
Cycle: 32 5 µM					5.000E-6
Cycle: 33 1 µM					1.000E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.578E+5	1.389	8.800E-6	59.36	
Cycle: 9 0.625 µM					6.250E-7
Cycle: 10 1.25 µM					1.250E-6
Cycle: 11 2.5 µM					2.500E-6
Cycle: 14 2.5 µM					2.500E-6

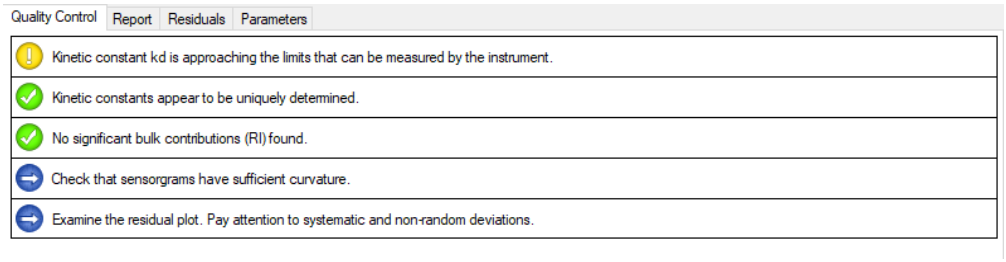
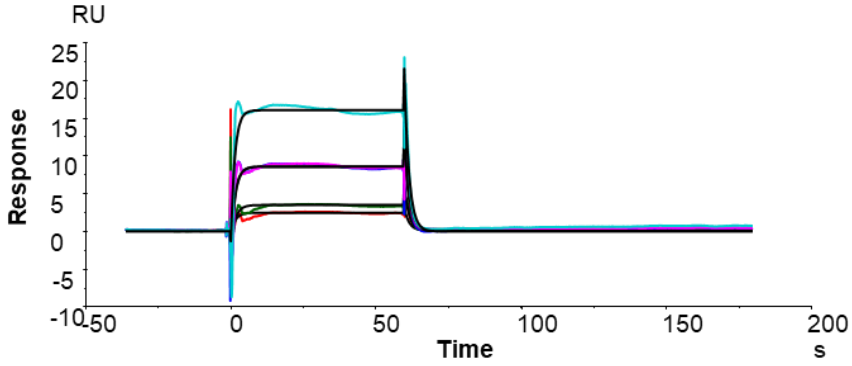
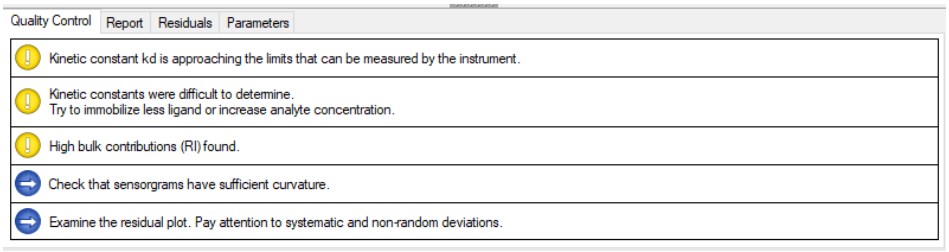


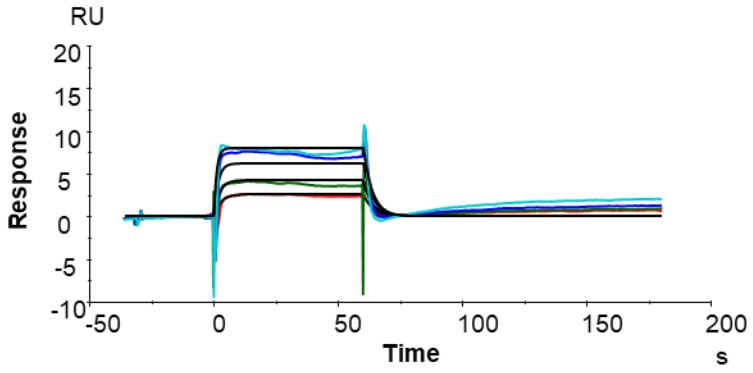
Figure S38. The SPR sensorgrams, fitting parameters and quality control table of H-33258 (2 replicates)

- DMA-3k



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	4975	0.6106	1.227E-4	126.9	
Cycle: 30 3.125 µM					3.125E-6
Cycle: 31 6.25 µM					6.250E-6
Cycle: 32 12.5 µM					1.250E-5
Cycle: 33 15 µM					1.500E-5
Cycle: 34 25 µM					2.500E-5

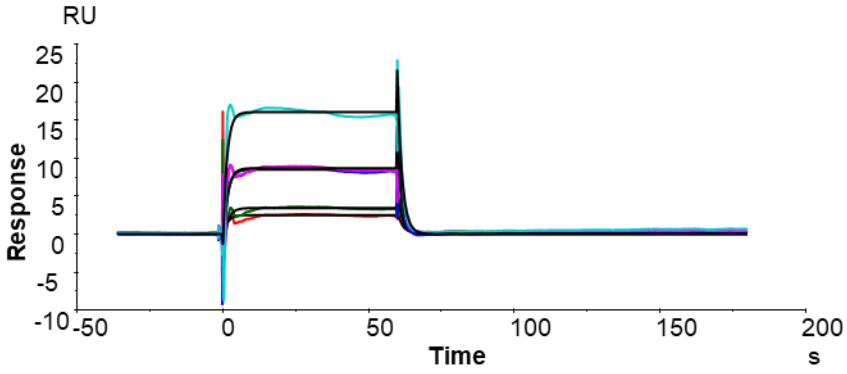




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2.592E+4	0.2797	1.079E-5	11.57	
Cycle: 30 3.125 µM					3.125E-6
Cycle: 31 6.25 µM					6.250E-6
Cycle: 32 12.5 µM					1.250E-5
Cycle: 34 25 µM					2.500E-5

Quality Control | Report | Residuals | Parameters

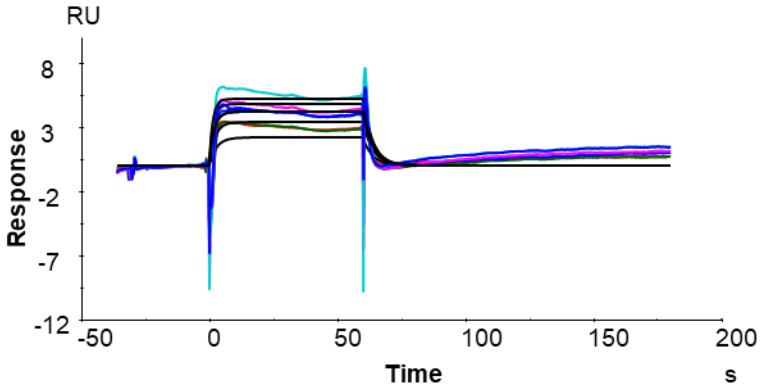
- Kinetic constants are within instrument specifications.
- Kinetic constants were difficult to determine.
- Bulk contributions (RI) were not evaluated. The RI parameter is set to constant.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	8868	0.6373	7.186E-5	81.27	
Cycle: 30 3.125 µM					3.125E-6
Cycle: 31 6.25 µM					6.250E-6
Cycle: 32 12.5 µM					1.250E-5
Cycle: 33 15 µM					1.500E-5
Cycle: 34 25 µM					2.500E-5

Quality Control | Report | Residuals | Parameters

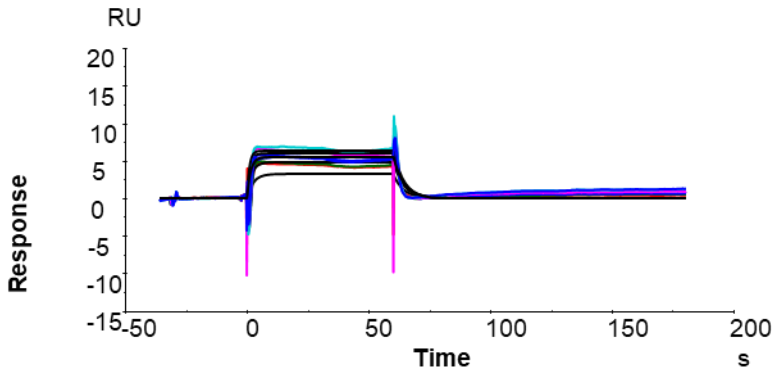
- Kinetic constant kd is approaching the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.898E+4	0.2615	1.378E-5	8.135	
Cycle: 30 5 µM					5.000E-6
Cycle: 31 10 µM					1.000E-5
Cycle: 32 15 µM					1.500E-5
Cycle: 33 20 µM					2.000E-5
Cycle: 34 25 µM					2.500E-5
Cycle: 35 15 µM					1.500E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constants are within instrument specifications.
- Kinetic constants were difficult to determine.
- Bulk contributions (RI) were not evaluated. The RI parameter is set to constant.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	3.125E+4	0.2376	7.605E-6	8.251	
Cycle: 30 5 µM					5.000E-6
Cycle: 31 10 µM					1.000E-5
Cycle: 32 15 µM					1.500E-5
Cycle: 33 20 µM					2.000E-5
Cycle: 34 25 µM					2.500E-5
Cycle: 35 15 µM					1.500E-5

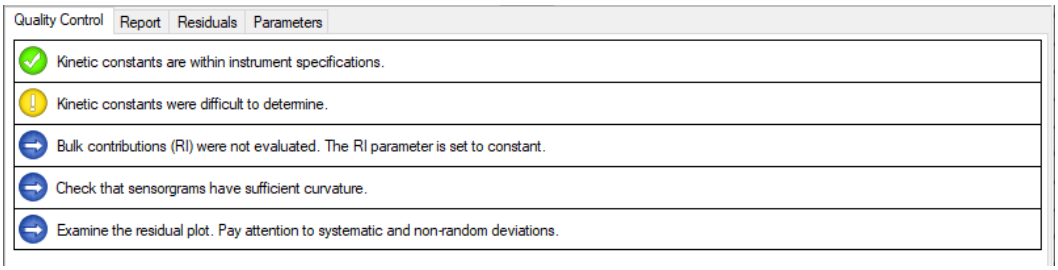
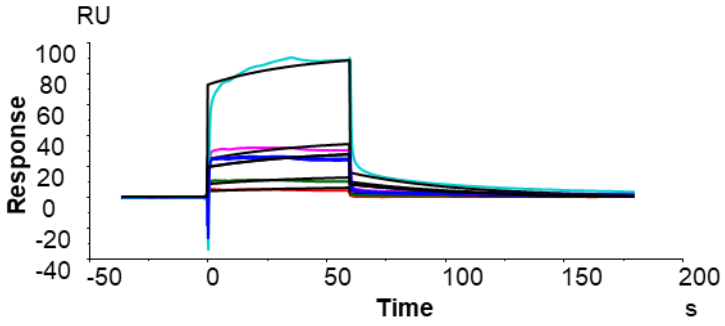
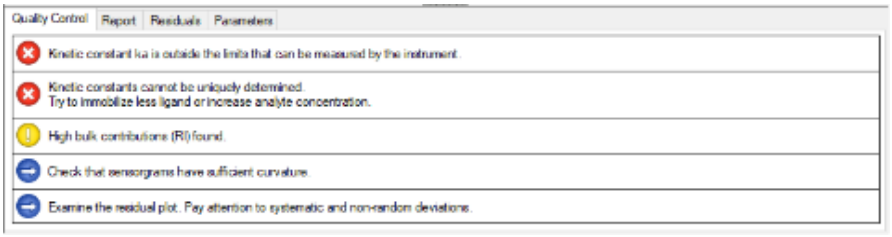


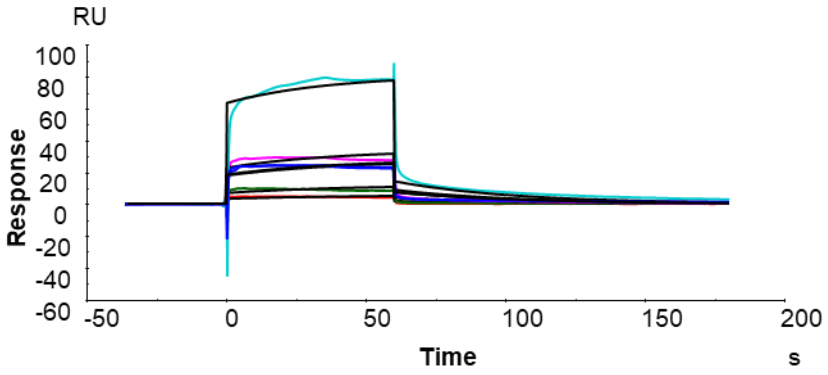
Figure S39. The SPR sensorgrams, fitting parameters and quality control table of DMA-3k (5 replicates)

- DMA-3l



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	139.6	0.02166	1.552E-4	145.9	
Cycle: 9 3.125 µM					3.125E-6
Cycle: 10 6.25 µM					6.250E-6
Cycle: 11 12.5 µM					1.250E-5
Cycle: 12 15 µM					1.500E-5
Cycle: 13 25 µM					2.500E-5
Cycle: 14 12.5 µM					1.250E-5

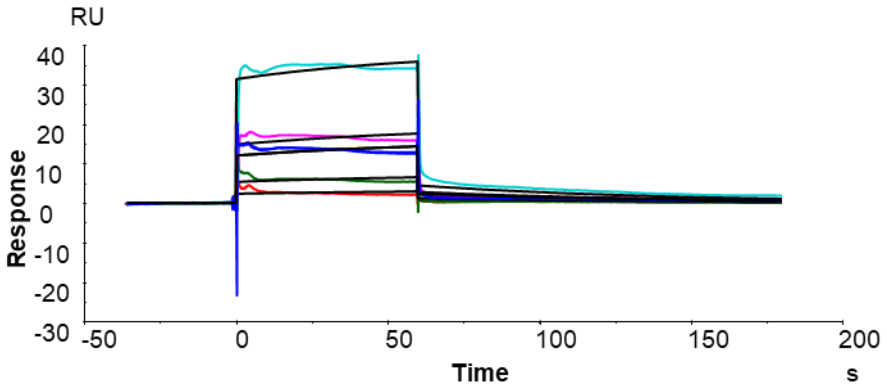




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	177.3	0.02337	1.318E-4	109.9	
Cycle: 9 3.125 µM					3.125E-6
Cycle: 10 6.25 µM					6.250E-6
Cycle: 11 12.5 µM					1.250E-5
Cycle: 12 15 µM					1.500E-5
Cycle: 13 25 µM					2.500E-5
Cycle: 14 12.5 µM					1.250E-5

Quality Control | Report | Residuals | Parameters

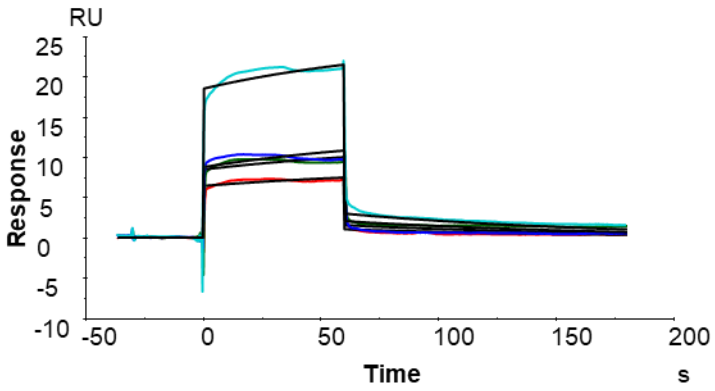
- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants cannot be uniquely determined.
  Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	128.9	0.01214	9.419E-5	35.45	
Cycle: 9 3.125 µM					3.125E-6
Cycle: 10 6.25 µM					6.250E-6
Cycle: 11 12.5 µM					1.250E-5
Cycle: 12 15 µM					1.500E-5
Cycle: 13 25 µM					2.500E-5
Cycle: 14 12.5 µM					1.250E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants cannot be uniquely determined.
  Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

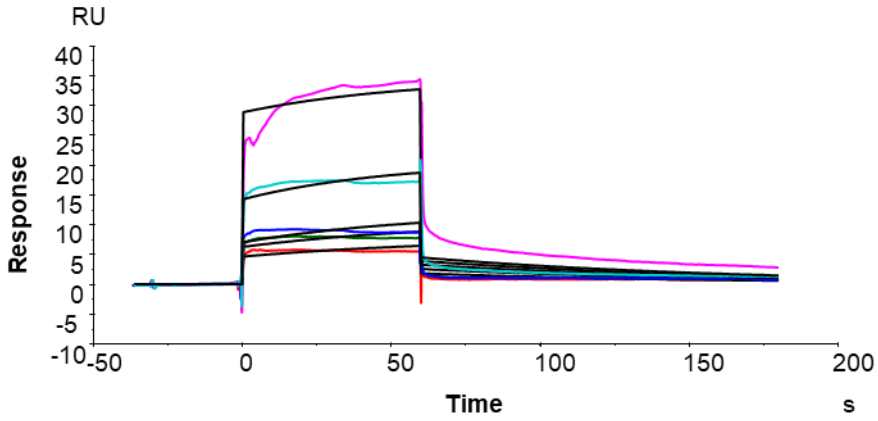


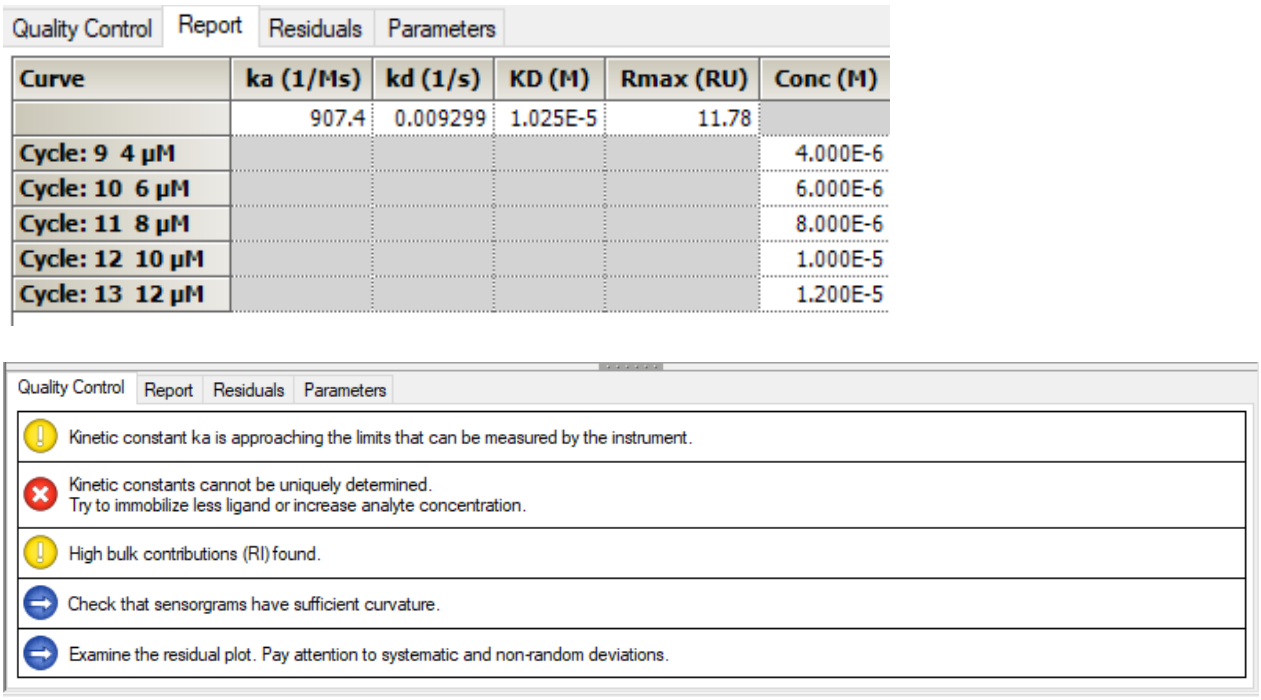
Quality Control | Report | Residuals | Parameters

Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	194.2	0.008890	4.577E-5	29.41	
Cycle: 9 4 µM					4.000E-6
Cycle: 10 6 µM					6.000E-6
Cycle: 11 8 µM					8.000E-6
Cycle: 13 12 µM					1.200E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants cannot be uniquely determined.
  Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



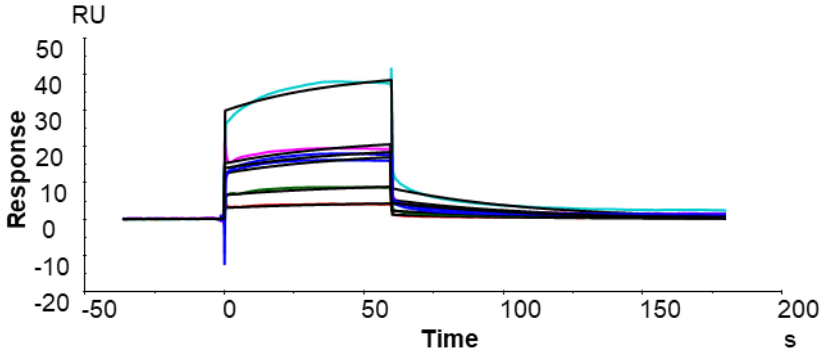


Quality Control | Report | Residuals | Parameters

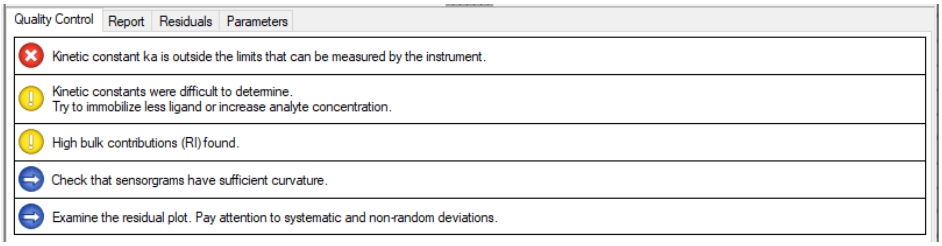
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	907.4	0.009299	1.025E-5	11.78	
Cycle: 9 4 µM					4.000E-6
Cycle: 10 6 µM					6.000E-6
Cycle: 11 8 µM					8.000E-6
Cycle: 12 10 µM					1.000E-5
Cycle: 13 12 µM					1.200E-5

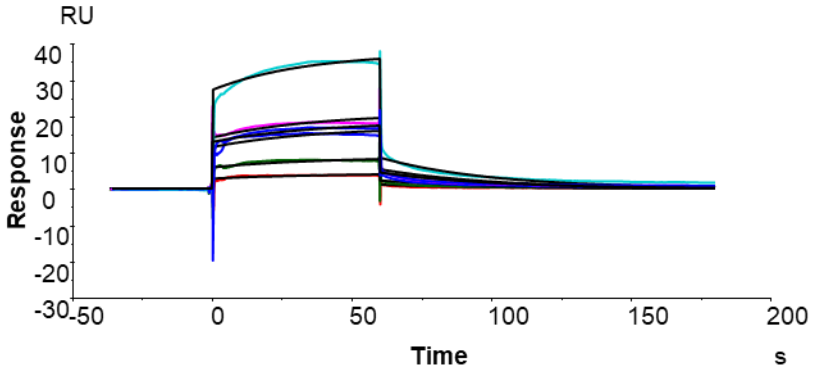
Figure S40. The SPR sensorgrams, fitting parameters and quality control table of DMA-3l (5 replicates)

- DMA-3u



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	184.5	0.01986	1.077E-4	58.46	
Cycle: 23 3.125 µM					3.125E-6
Cycle: 24 6.25 µM					6.250E-6
Cycle: 25 12.5 µM					1.250E-5
Cycle: 26 15 µM					1.500E-5
Cycle: 27 25 µM					2.500E-5
Cycle: 28 12.5 µM					1.250E-5

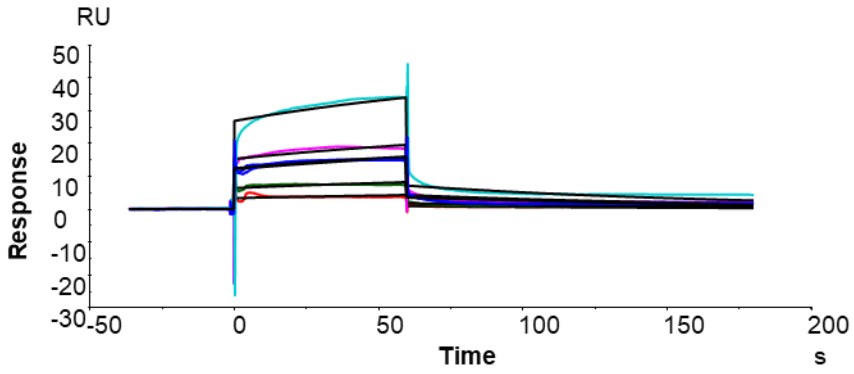




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	197.0	0.02510	1.274E-4	62.50	
Cycle: 23 3.125 µM					3.125E-6
Cycle: 24 6.25 µM					6.250E-6
Cycle: 25 12.5 µM					1.250E-5
Cycle: 26 15 µM					1.500E-5
Cycle: 27 25 µM					2.500E-5
Cycle: 28 12.5 µM					1.250E-5

Quality Control | Report | Residuals | Parameters

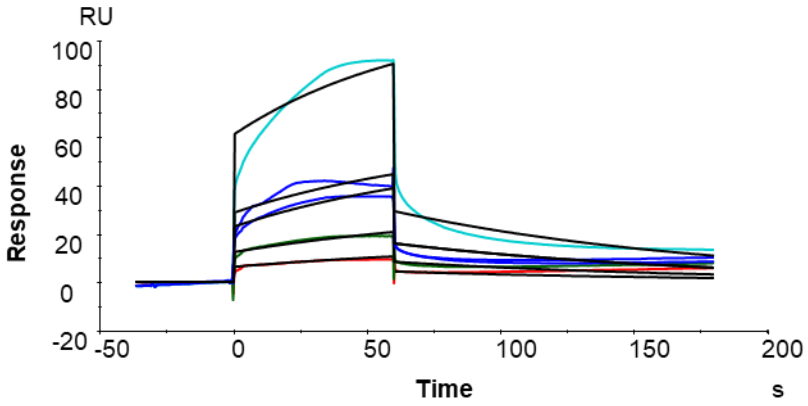
- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants cannot be uniquely determined. Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	20.45	0.008325	4.071E-4	299.2	
Cycle: 23 3.125 µM					3.125E-6
Cycle: 24 6.25 µM					6.250E-6
Cycle: 25 12.5 µM					1.250E-5
Cycle: 26 15 µM					1.500E-5
Cycle: 27 25 µM					2.500E-5
Cycle: 28 12.5 µM					1.250E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants cannot be uniquely determined. Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	268.9	0.008266	3.074E-5	110.5	
Cycle: 23 3.125 µM					3.125E-6
Cycle: 24 6.25 µM					6.250E-6
Cycle: 25 12.5 µM					1.250E-5
Cycle: 27 25 µM					2.500E-5
Cycle: 28 12.5 µM					1.250E-5

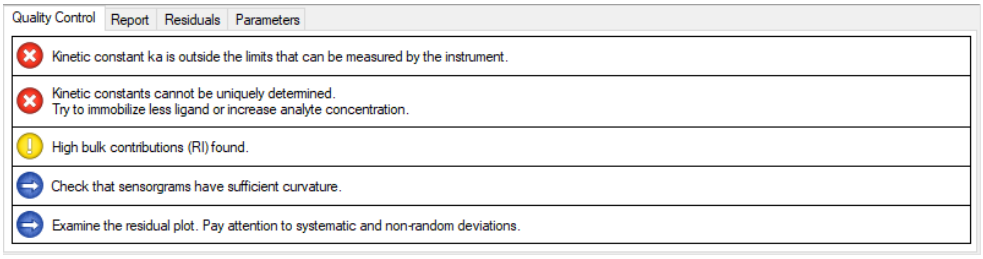
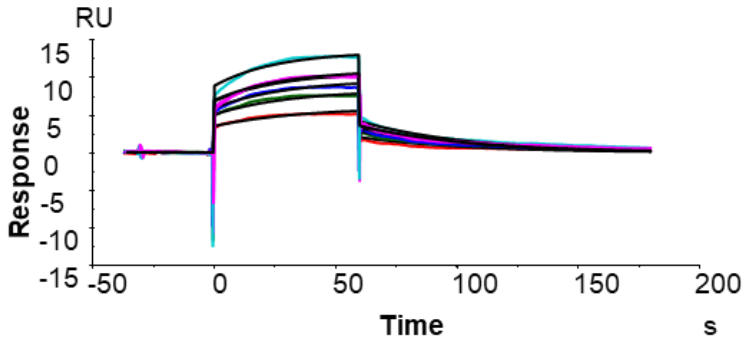
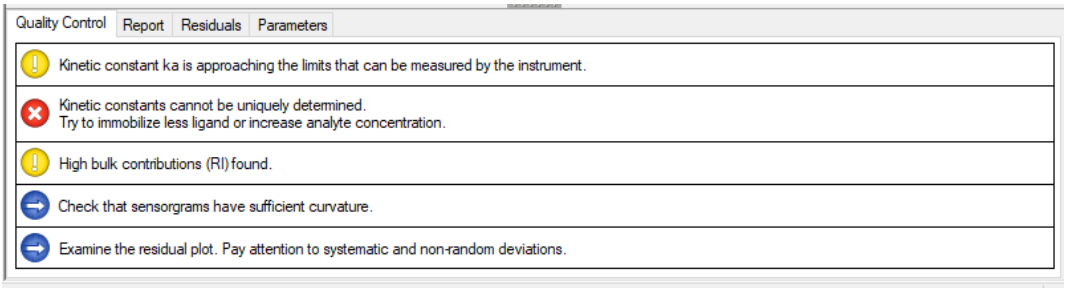


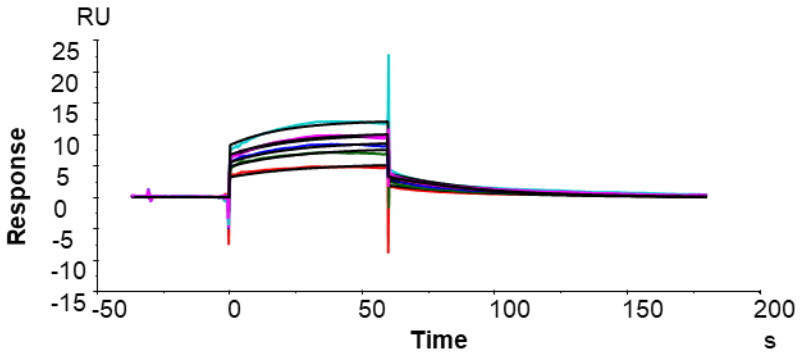
Figure S41. The SPR sensorgrams, fitting parameters and quality control table of DMA-3u (4 replicates)

- DMA-3v



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	681.6	0.02222	3.259E-5	10.62	
Cycle: 37 10 µM					1.000E-5
Cycle: 38 15 µM					1.500E-5
Cycle: 39 17.95 µM					1.795E-5
Cycle: 40 20 µM					2.000E-5
Cycle: 41 25 µM					2.500E-5
Cycle: 42 20 µM					2.000E-5





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	842.2	0.02740	3.253E-5	9.232	
Cycle: 37 10 µM					1.000E-5
Cycle: 38 15 µM					1.500E-5
Cycle: 39 17.95 µM					1.795E-5
Cycle: 40 20 µM					2.000E-5
Cycle: 41 25 µM					2.500E-5
Cycle: 42 20 µM					2.000E-5

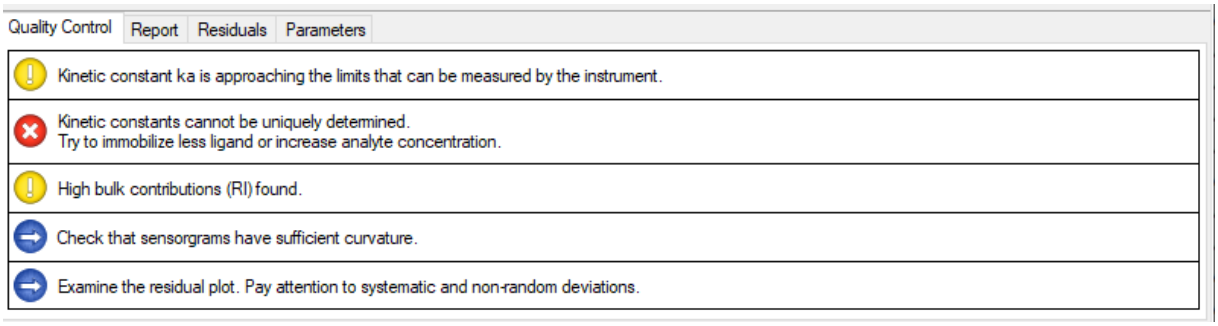
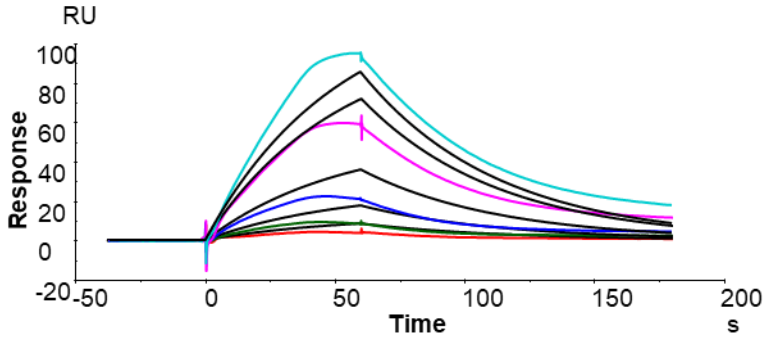
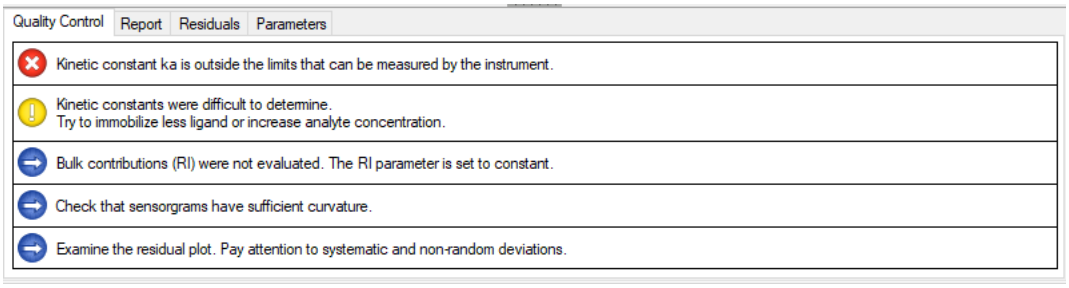


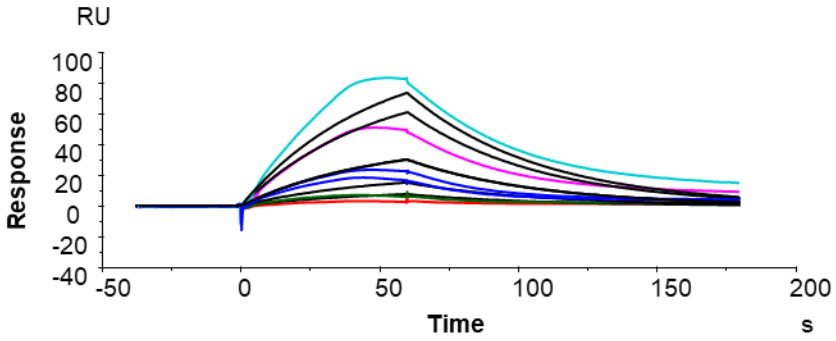
Figure S42. The SPR sensorgrams, fitting parameters and quality control table of DMA-3v (2 replicates)

- DMA-3q



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	24.52	0.01915	7.810E-4	6591	
Cycle: 2 1.5625 µM					1.563E-6
Cycle: 3 3.125 µM					3.125E-6
Cycle: 4 6.25 µM					6.250E-6
Cycle: 5 12.5 µM					1.250E-5
Cycle: 6 15 µM					1.500E-5

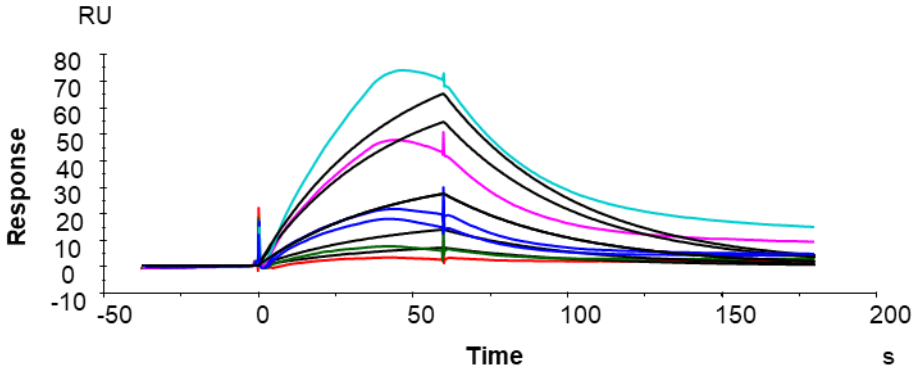




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	27.17	0.01828	6.727E-4	4540	
Cycle: 2 1.5625 µM					1.563E-6
Cycle: 3 3.125 µM					3.125E-6
Cycle: 4 6.25 µM					6.250E-6
Cycle: 5 12.5 µM					1.250E-5
Cycle: 6 15 µM					1.500E-5
Cycle: 7 6.25 µM					6.250E-6

Quality Control | Report | Residuals | Parameters

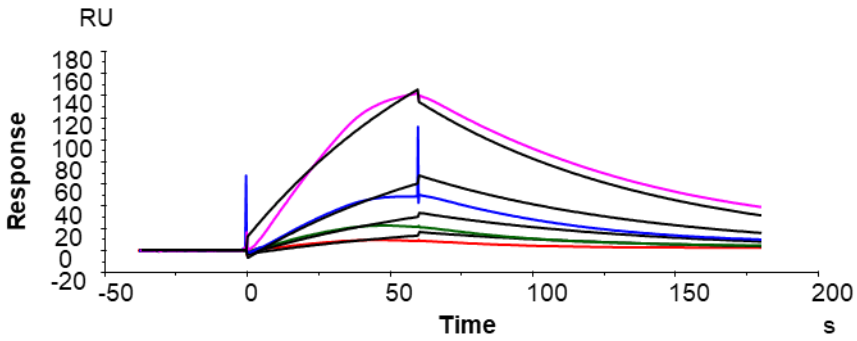
- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants were difficult to determine.
  Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	29.78	0.02342	7.863E-4	4584	
Cycle: 2 1.5625 µM					1.563E-6
Cycle: 3 3.125 µM					3.125E-6
Cycle: 4 6.25 µM					6.250E-6
Cycle: 5 12.5 µM					1.250E-5
Cycle: 6 15 µM					1.500E-5
Cycle: 7 6.25 µM					6.250E-6

Quality Control | Report | Residuals | Parameters

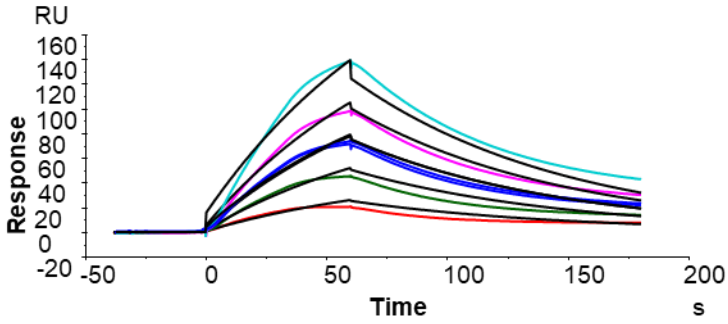
- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants were difficult to determine.
  Try to immobilize less ligand or increase analyte concentration.
- Bulk contributions (RI) were not evaluated. The RI parameter is set to constant.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	16.72	0.01213	7.257E-4	1.509E+4	
Cycle: 2 1.5625 µM					1.563E-6
Cycle: 3 3.125 µM					3.125E-6
Cycle: 4 6.25 µM					6.250E-6
Cycle: 5 12.5 µM					1.250E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	14.68	0.01146	7.811E-4	1.987E+4	
Cycle: 2 2 µM					2.000E-6
Cycle: 3 4 µM					4.000E-6
Cycle: 4 6 µM					6.000E-6
Cycle: 5 8 µM					8.000E-6
Cycle: 6 10 µM					1.000E-5
Cycle: 7 6 µM					6.000E-6

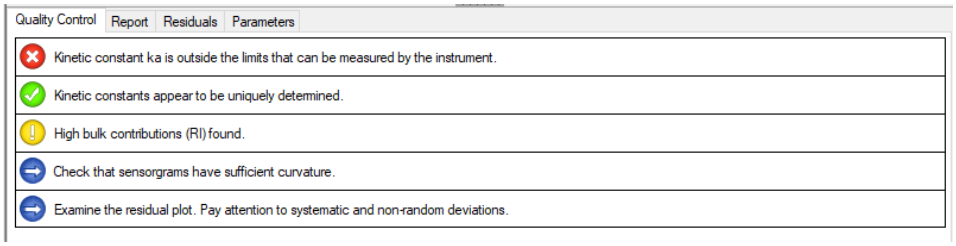
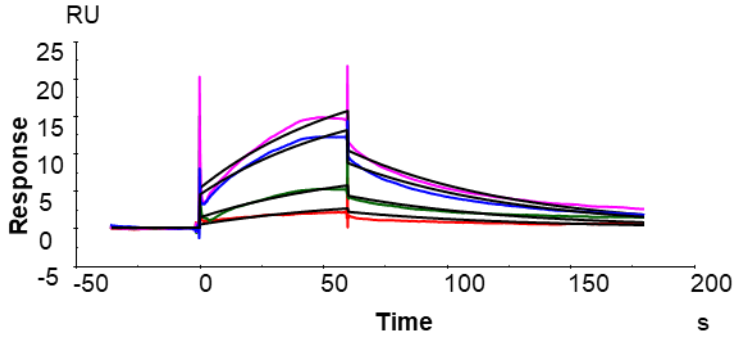
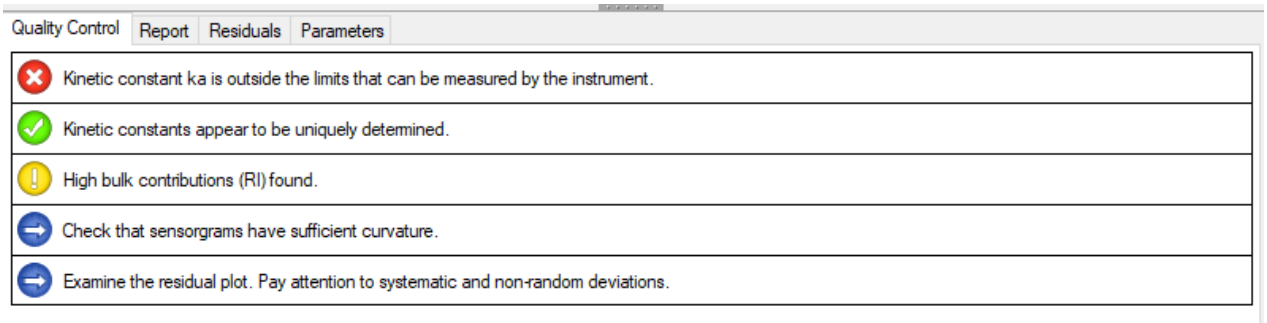


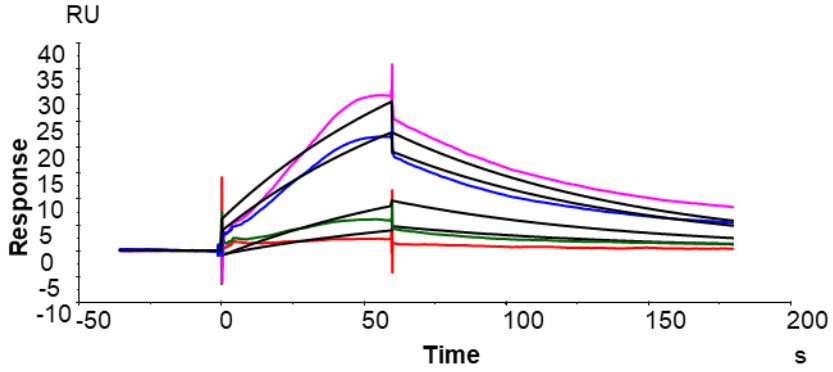
Figure S43. The SPR sensorgrams, fitting parameters and quality control table of DMA-3q (5 replicates)

- DMA-3r



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	53.94	0.01487	2.756E-4	328.9	
Cycle: 16 3.125 µM					3.125E-6
Cycle: 17 6.25 µM					6.250E-6
Cycle: 19 15 µM					1.500E-5
Cycle: 21 12.5 µM					1.250E-5

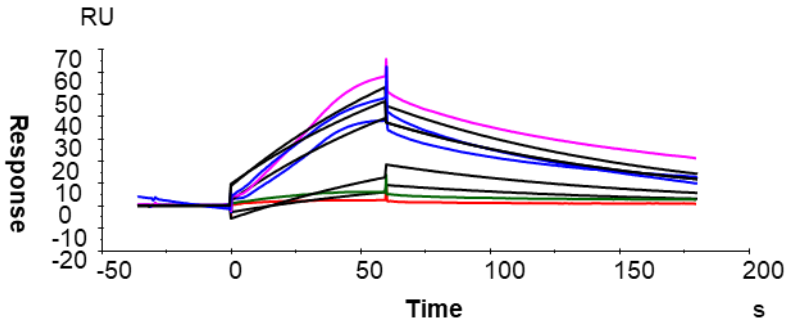




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	12.06	0.01149	9.528E-4	2925	
Cycle: 16 3.125 µM					3.125E-6
Cycle: 17 6.25 µM					6.250E-6
Cycle: 19 15 µM					1.500E-5
Cycle: 21 12.5 µM					1.250E-5

Quality Control | Report | Residuals | Parameters

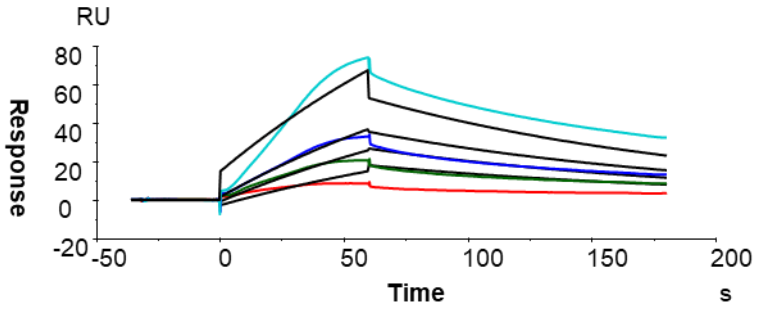
- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants were difficult to determine.
  Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	14.86	0.009526	6.412E-4	4393	
Cycle: 16 3.125 µM					3.125E-6
Cycle: 17 6.25 µM					6.250E-6
Cycle: 18 12.5 µM					1.250E-5
Cycle: 19 15 µM					1.500E-5
Cycle: 21 12.5 µM					1.250E-5

Quality Control | Report | Residuals | Parameters

- Kinetic constant ka is outside the limits that can be measured by the instrument.
- Kinetic constants were difficult to determine.
  Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	11.97	0.006908	5.771E-4	6088	
Cycle: 16 5 µM					5.000E-6
Cycle: 17 7.5 µM					7.500E-6
Cycle: 18 10 µM					1.000E-5
Cycle: 20 15 µM					1.500E-5

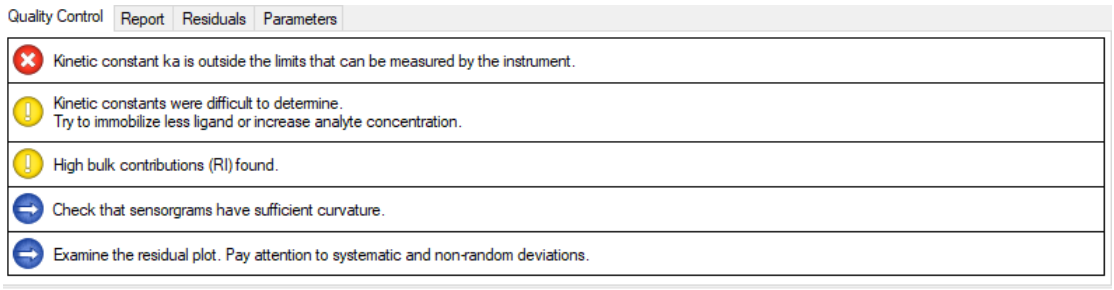
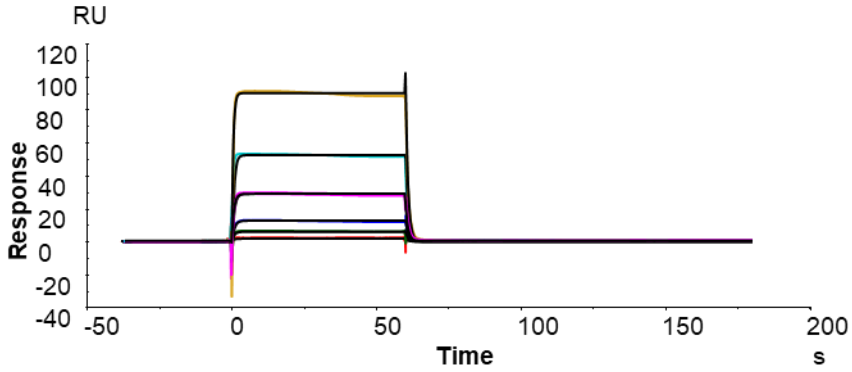
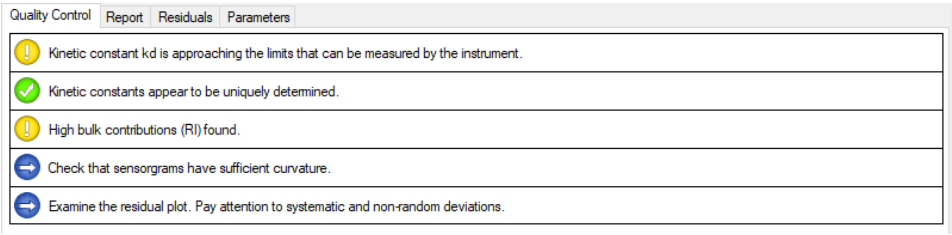


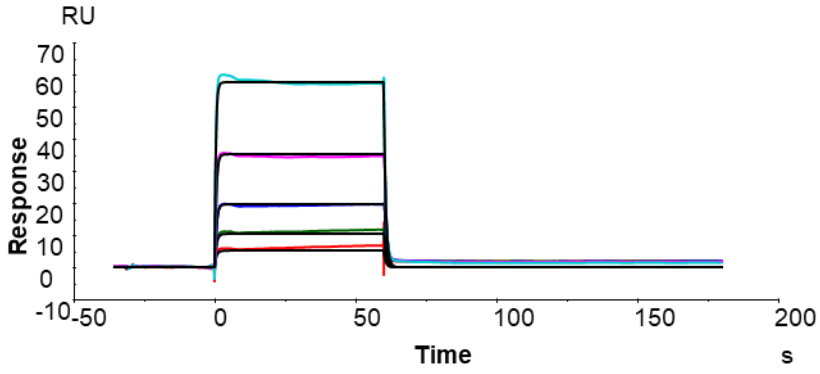
Figure S44. The SPR sensorgrams, fitting parameters and quality control table of DMA-3r (4 replicates)

- Thiazole orange

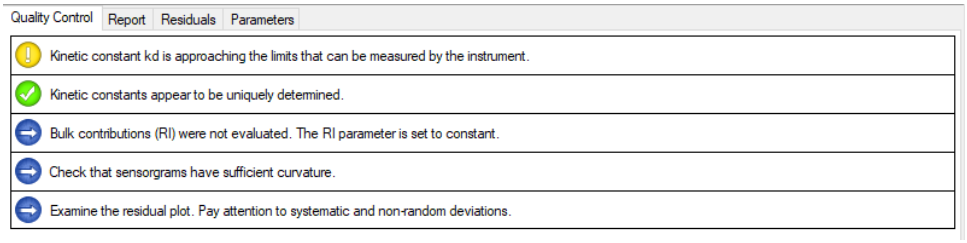


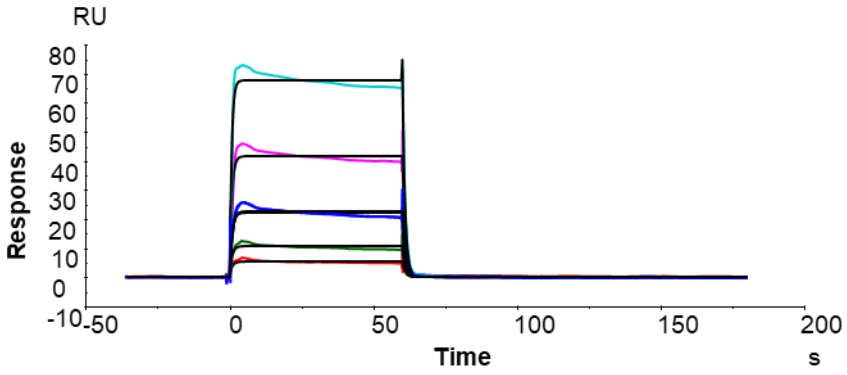
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.542E+5	1.208	7.832E-6	261.7	
Cycle: 2 0.05 µM					5.000E-8
Cycle: 3 0.2 µM					2.000E-7
Cycle: 4 0.5 µM					5.000E-7
Cycle: 5 1 µM					1.000E-6
Cycle: 6 2.5 µM					2.500E-6
Cycle: 7 5 µM					5.000E-6
Cycle: 8 1 µM					1.000E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2.046E+5	1.450	7.088E-6	160.1	
Cycle: 16 0.25 µM					2.500E-7
Cycle: 17 0.5 µM					5.000E-7
Cycle: 18 1 µM					1.000E-6
Cycle: 19 2 µM					2.000E-6
Cycle: 20 4 µM					4.000E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.047E+5	1.153	1.101E-5	280.4	
Cycle: 9 0.25 µM					2.500E-7
Cycle: 10 0.5 µM					5.000E-7
Cycle: 11 1 µM					1.000E-6
Cycle: 12 2 µM					2.000E-6
Cycle: 13 4 µM					4.000E-6
Cycle: 14 1 µM					1.000E-6

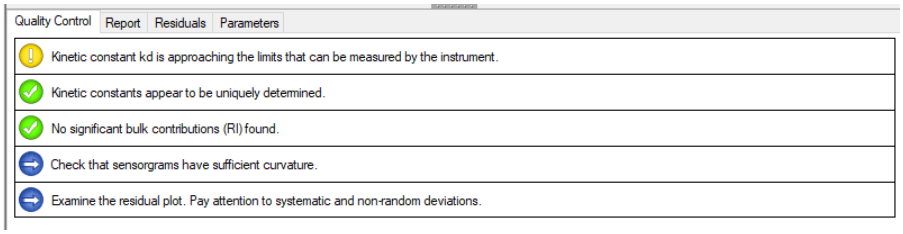
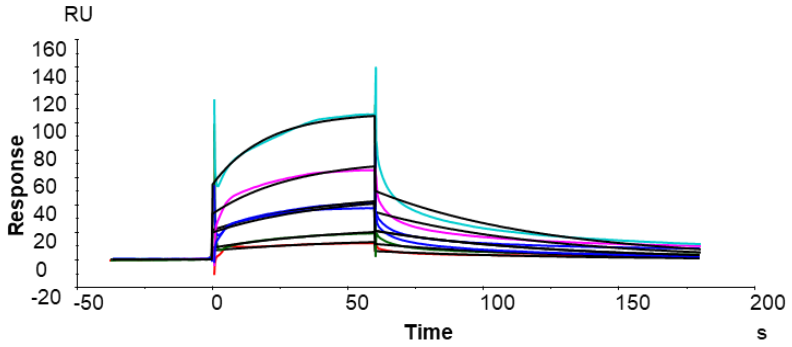
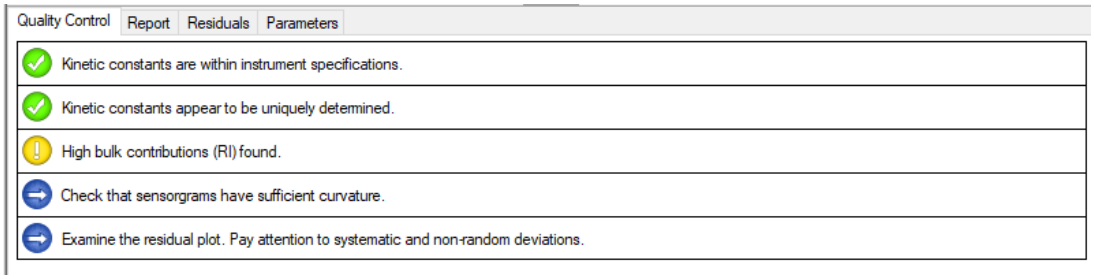


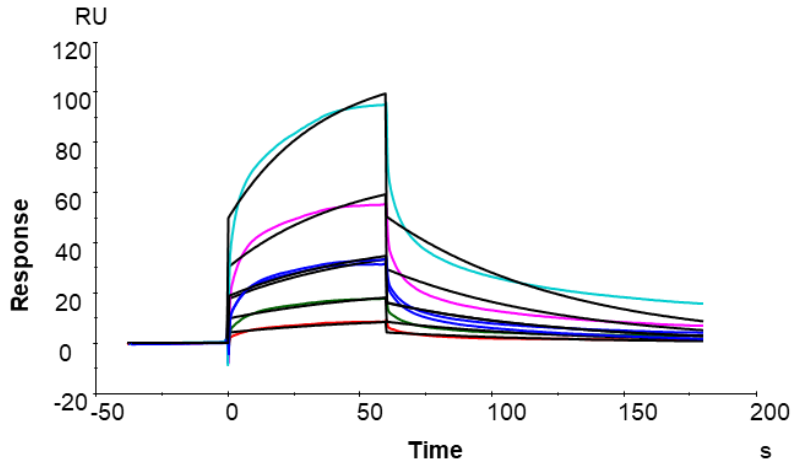
Figure S45. The SPR sensorgrams, fitting parameters and quality control table of thiazole orange (3 replicates)

- DPF m3



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	7141	0.01603	2.244E-6	75.63	
Cycle: 2 0.3125 µM					3.125E-7
Cycle: 3 0.625 µM					6.250E-7
Cycle: 4 1.25 µM					1.250E-6
Cycle: 5 2.5 µM					2.500E-6
Cycle: 6 5 µM					5.000E-6
Cycle: 7 1.25 µM					1.250E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	2743	0.01471	5.362E-6	128.2	
Cycle: 2 0.3125 µM					3.125E-7
Cycle: 3 0.625 µM					6.250E-7
Cycle: 4 1.25 µM					1.250E-6
Cycle: 5 2.5 µM					2.500E-6
Cycle: 6 5 µM					5.000E-6
Cycle: 7 1.25 µM					1.250E-6

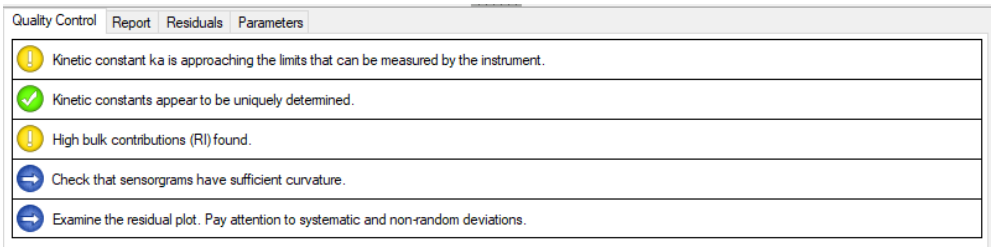
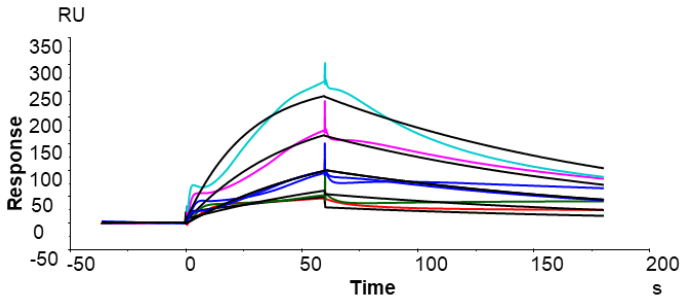


Figure S46. The SPR sensorgrams, fitting parameters and quality control table of DPF m3 (2 replicates)

- DPF m9

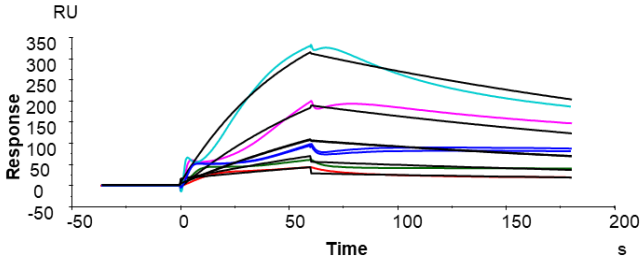


Quality Control | Report | Residuals | Parameters

Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	6492	0.007215	1.111E-6	323.5	
Cycle: 9 0.3125 µM					3.125E-7
Cycle: 10 0.625 µM					6.250E-7
Cycle: 11 1.25 µM					1.250E-6
Cycle: 12 2.5 µM					2.500E-6
Cycle: 13 5 µM					5.000E-6
Cycle: 14 1.25 µM					1.250E-6

Quality Control | Report | Residuals | Parameters

- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	3007	0.003591	1.194E-6	577.1	
Cycle: 9 0.3125 µM					3.125E-7
Cycle: 10 0.625 µM					6.250E-7
Cycle: 11 1.25 µM					1.250E-6
Cycle: 12 2.5 µM					2.500E-6
Cycle: 13 5 µM					5.000E-6
Cycle: 14 1.25 µM					1.250E-6

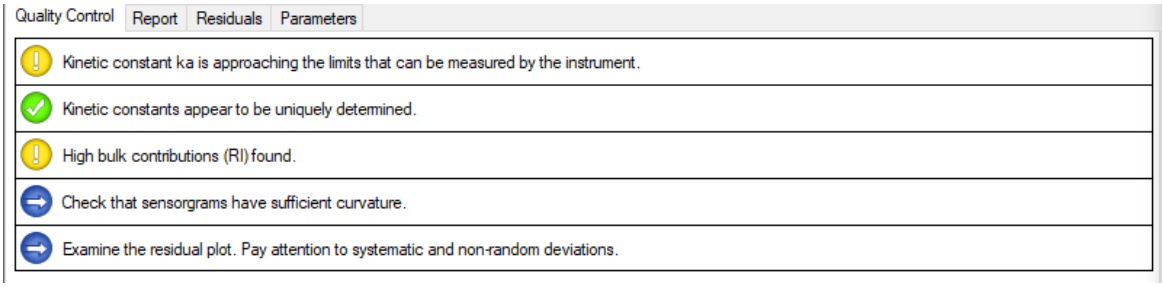
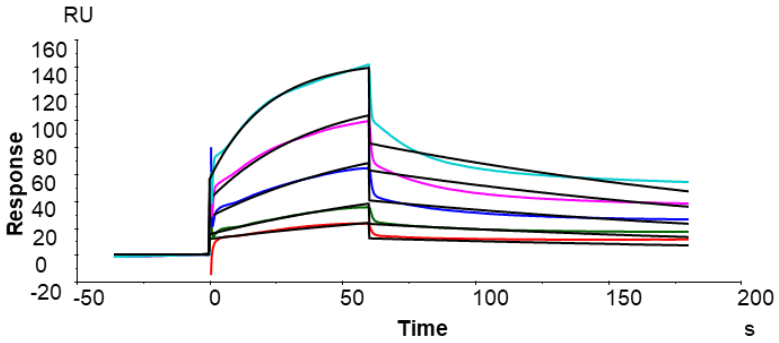


Figure S47. The SPR sensorgrams, fitting parameters and quality control table of DPF m9 (2 replicates)

- DPF m10



Quality Control | Report | Residuals | Parameters

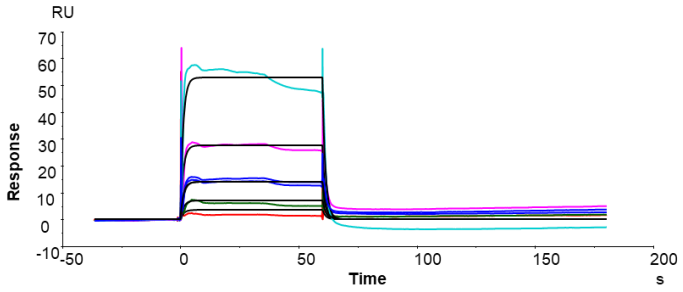
Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	8288	0.004715	5.689E-7	98.55	
Cycle: 16 0.3125 µM					3.125E-7
Cycle: 17 0.625 µM					6.250E-7
Cycle: 18 1.25 µM					1.250E-6
Cycle: 19 2.5 µM					2.500E-6
Cycle: 20 5 µM					5.000E-6

Quality Control | Report | Residuals | Parameters

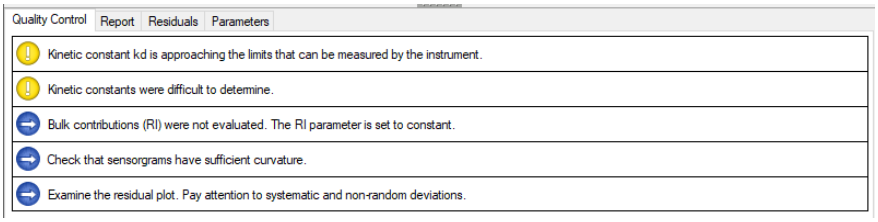
- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

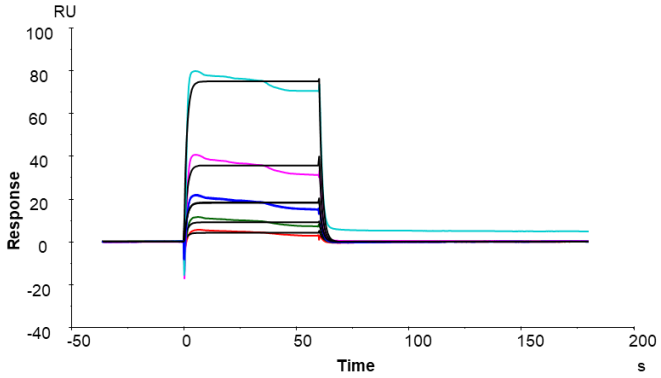
Figure S48. The SPR sensorgrams, fitting parameters and quality control table of DPF m10 (1 replicate)

- DPF p6



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.276E+4	0.7802	6.114E-5	701.3	
Cycle: 23 0.3125 µM					3.125E-7
Cycle: 24 0.625 µM					6.250E-7
Cycle: 25 1.25 µM					1.250E-6
Cycle: 26 2.5 µM					2.500E-6
Cycle: 27 5 µM					5.000E-6
Cycle: 28 1.25 µM					1.250E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.442E+4	0.7729	5.362E-5	1103	
Cycle: 23 0.3125 µM					3.125E-7
Cycle: 24 0.625 µM					6.250E-7
Cycle: 25 1.25 µM					1.250E-6
Cycle: 26 2.5 µM					2.500E-6
Cycle: 27 5 µM					5.000E-6
Cycle: 28 1.25 µM					1.250E-6

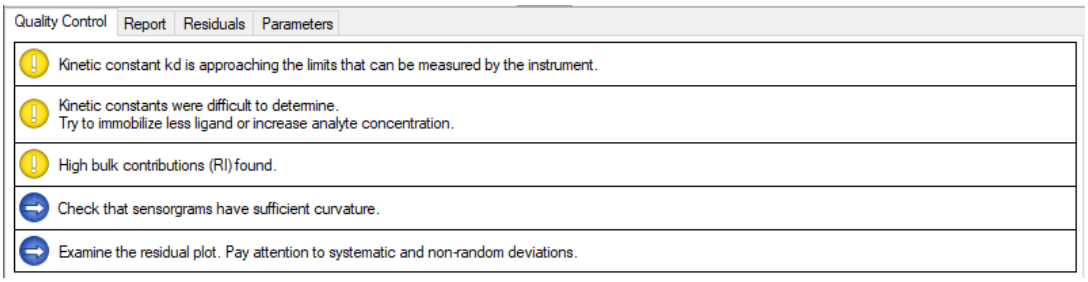
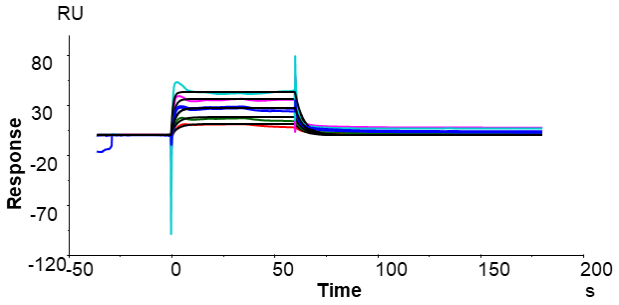
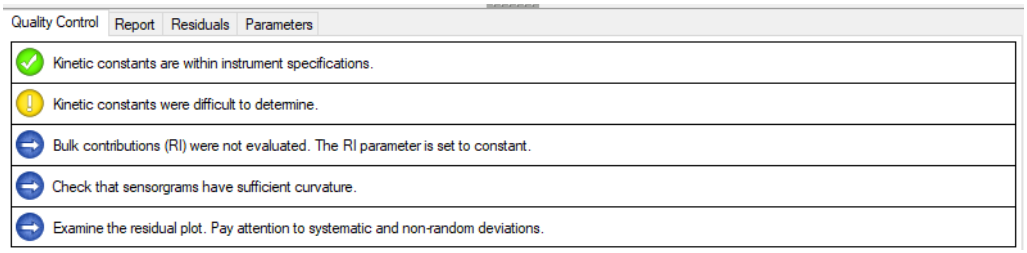


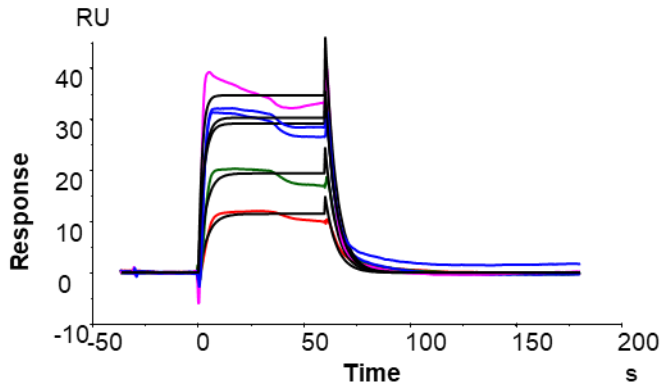
Figure S49. The SPR sensorgrams, fitting parameters and quality control table of DPF p6 (2 replicates)

- DPF p15



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.850E+5	0.2387	1.291E-6	53.53	
Cycle: 30 0.3125 µM					3.125E-7
Cycle: 31 0.625 µM					6.250E-7
Cycle: 32 1.25 µM					1.250E-6
Cycle: 33 2.5 µM					2.500E-6
Cycle: 34 5 µM					5.000E-6
Cycle: 35 1.25 µM					1.250E-6

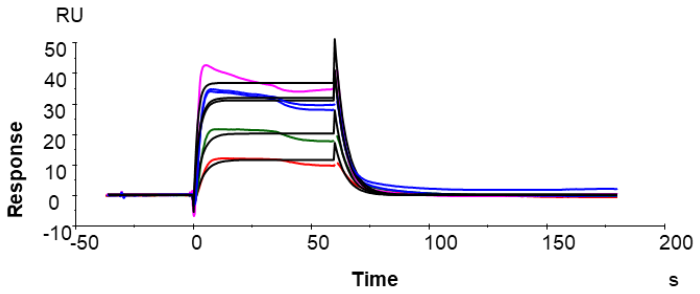




Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.832E+5	0.1956	1.068E-6	65.58	
Cycle: 9 0.3125 µM					3.125E-7
Cycle: 10 0.625 µM					6.250E-7
Cycle: 11 1.25 µM					1.250E-6
Cycle: 12 2.5 µM					2.500E-6
Cycle: 14 1.25 µM					1.250E-6

Quality Control | Report | Residuals | Parameters

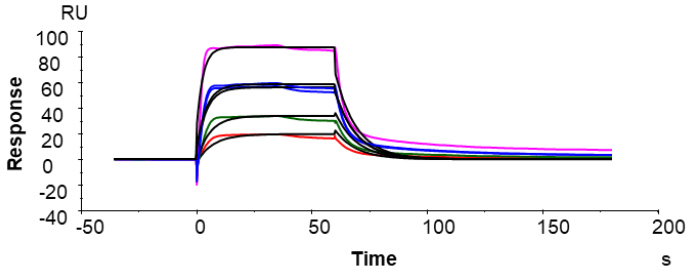
- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.971E+5	0.2122	1.077E-6	75.76	
Cycle: 37 0.3125 µM					3.125E-7
Cycle: 38 0.625 µM					6.250E-7
Cycle: 39 1.25 µM					1.250E-6
Cycle: 40 2.5 µM					2.500E-6
Cycle: 42 1.25 µM					1.250E-6

Quality Control | Report | Residuals | Parameters

- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.074E+5	0.1080	1.006E-6	97.84	
Cycle: 30 0.3125 µM					3.125E-7
Cycle: 31 0.625 µM					6.250E-7
Cycle: 32 1.25 µM					1.250E-6
Cycle: 33 2.5 µM					2.500E-6
Cycle: 35 1.25 µM					1.250E-6

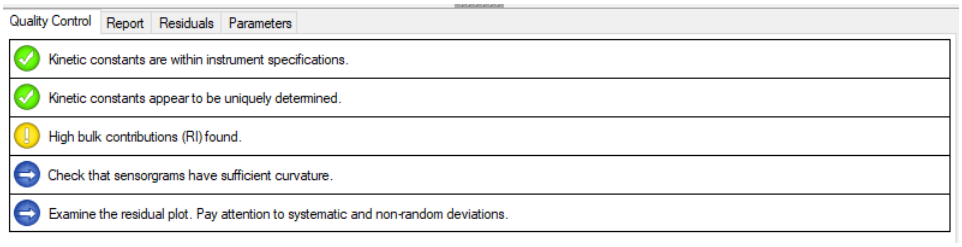
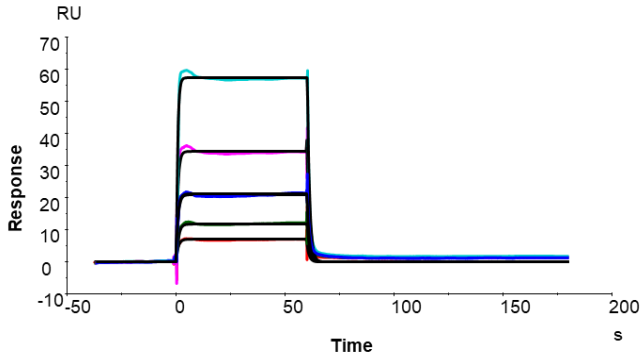
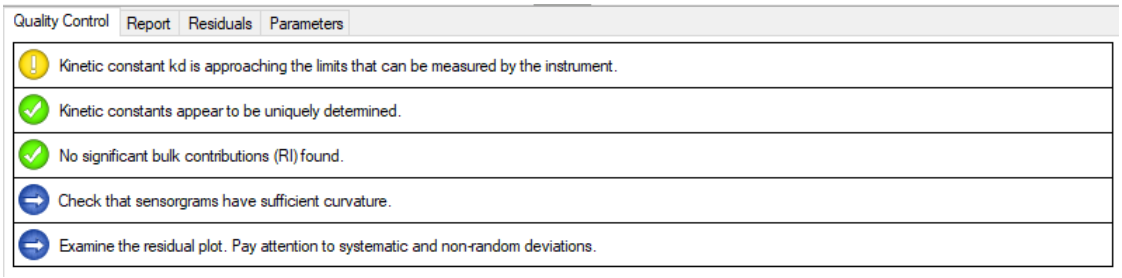


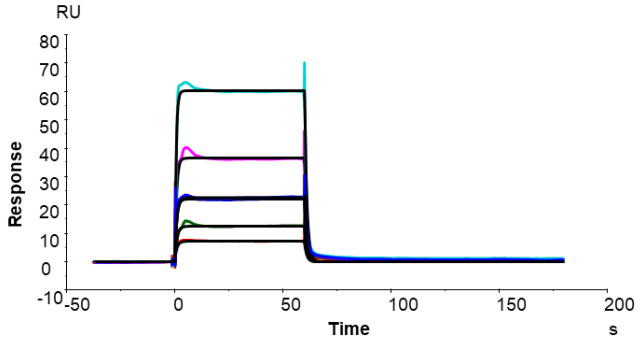
Figure S50. The SPR sensorgrams, fitting parameters and quality control table of DPF p15 (4 replicates)

- Acridine orange



Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.730E+5	0.9745	5.632E-6	144.6	
Cycle: 2 0.25 µM					2.500E-7
Cycle: 3 0.5 µM					5.000E-7
Cycle: 4 1 µM					1.000E-6
Cycle: 5 2 µM					2.000E-6
Cycle: 6 4 µM					4.000E-6
Cycle: 7 1 µM					1.000E-6





Curve	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)
	1.722E+5	0.9827	5.709E-6	154.9	
Cycle: 2 0.25 µM					2.500E-7
Cycle: 3 0.5 µM					5.000E-7
Cycle: 4 1 µM					1.000E-6
Cycle: 5 2 µM					2.000E-6
Cycle: 6 4 µM					4.000E-6
Cycle: 7 1 µM					1.000E-6

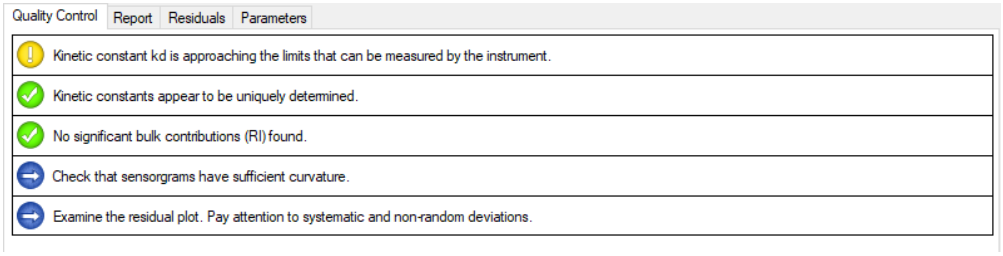
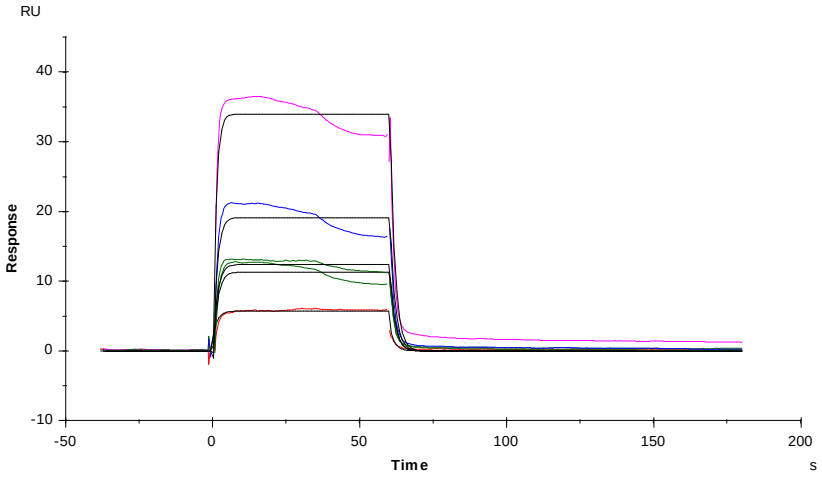
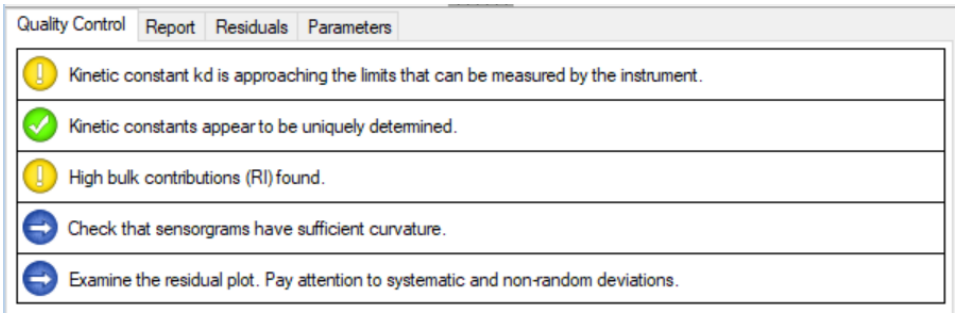


Figure S51. The SPR sensorgrams, fitting parameters and quality control table of acridine orange (2 replicates)

- **DPF m2**

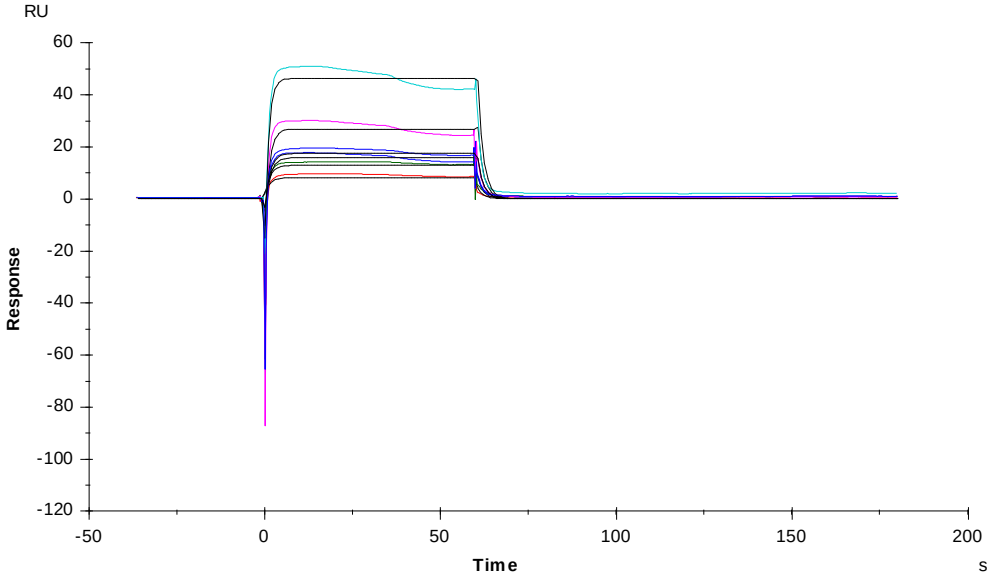




1:1 Binding	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)	tc	Flow (ul/min)	kt (RU/Ms)	RI (RU)	Chi² (RU²)	U-value
Curve	1.63E+05	0.6213	3.80E-06	120.6		4.70E+12				0.862	7
Cycle: 5 0.125 µM					1.25E-07		50	1.73E+13	1.85		
Cycle: 7 0.5 µM					5.00E-07		50	1.73E+13	-2.734		
Cycle: 8 1 µM					1.00E-06		50	1.73E+13	-6.023		
Cycle: 9 2 µM					2.00E-06		50	1.73E+13	-7.642		
Cycle: 10 0.5 µM					5.00E-07		50	1.73E+13	-1.641		

Figure S52. The SPR sensorgrams, fitting parameters and quality control table of DPF m2 (1 replicate)

- **DPF p2**



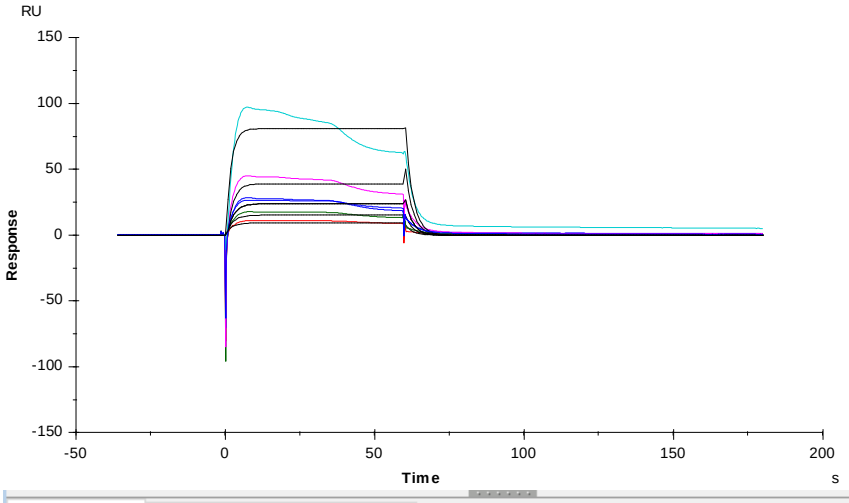
Quality Control | Report | Residuals | Parameters

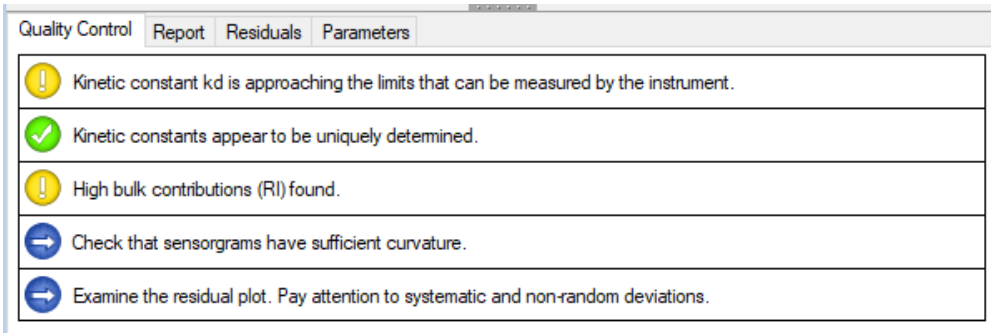
- Kinetic constant kd is approaching the limits that can be measured by the instrument.
- Kinetic constants were difficult to determine.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

1:1 Binding	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)	tc	Flow (ul/min)	kt (RU/Ms)	RI (RU)	Chi² (RU²)	U-value
Curve	1.65E+05	0.6309	3.83E-06	178.6		2.31E+11				9.66	20
Cycle: 12 0.125 µM					1.25E-07		50	8.50E+11	2.435		
Cycle: 13 0.25 µM					2.50E-07		50	8.50E+11	1.848		
Cycle: 14 0.5 µM					5.00E-07		50	8.50E+11	-4.89		
Cycle: 15 1 µM					1.00E-06		50	8.50E+11	-10.26		
Cycle: 16 2 µM					2.00E-06		50	8.50E+11	-15.13		
Cycle: 17 0.5 µM					5.00E-07		50	8.50E+11	-3.255		

Figure S53. The SPR sensorgrams, fitting parameters and quality control table of DPF p2 (1 replicate)

- **DPF p5**

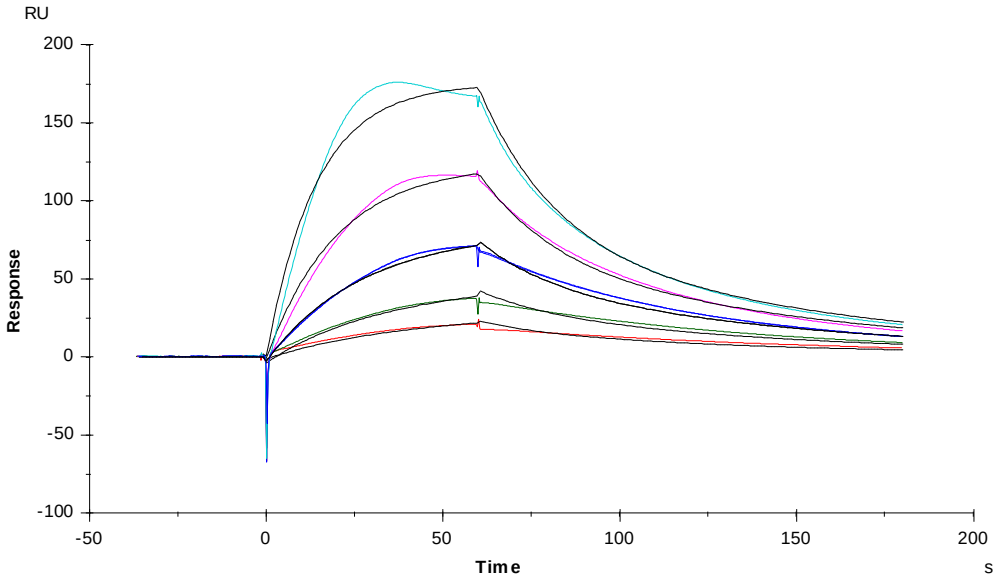




1:1 Binding	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)	tc	Flow (ul/min)	kt (RU/Ms)	RI (RU)	Chi² (RU²)	U-value
Curve	9.55E+04	0.4119	4.32E-06	299.5		1.70E+15				20.8	12
Cycle: 19 0.125 µM					1.25E-07		50	6.28E+15	0.9526		
Cycle: 20 0.25 µM					2.50E-07		50	6.28E+15	-1.114		
Cycle: 21 0.5 µM					5.00E-07		50	6.28E+15	-7.203		
Cycle: 22 1 µM					1.00E-06		50	6.28E+15	-17.29		
Cycle: 23 2 µM					2.00E-06		50	6.28E+15	-13.9		
Cycle: 24 0.5 µM					5.00E-07		50	6.28E+15	-7.218		

Figure S54. The SPR sensorgrams, fitting parameters and quality control table of DPF p5 (1 replicate)

- **DPF p8**



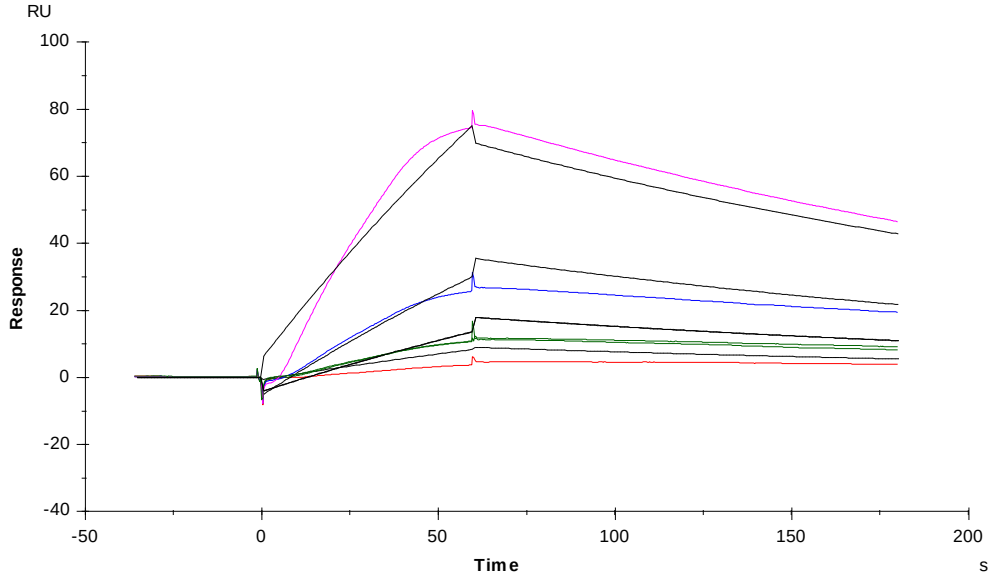
(Heterogeneous Ligand binding mode)

- Poor 1:1 fit (high Chi^2)
- Kinetics at limit of detection
- High U-value
- Fast on and off rate constants from Heterogeneous Ligand probably more representative
- Binding parameters were the average of the two binding processes

Heterogeneous Ligand	ka1 (1/Ms)	kd1 (1/s)	KD1 (M)	ka2 (1/Ms)	kd2 (1/s)	KD2 (M)	Rmax1 (RU)	Rmax2 (RU)	Conc (M)	tc	Flow (ul/min)	kt (RU/Ms)	RI (RU)	Chi² (RU²)	U-value
Curve	1.80E+05	0.01035	5.75E-08	4.04E+04	0.04786	1.18E-06	87.71	387.3		1.61E+09				15.4	N/A
Cycle: 26 0.025 µM									2.50E-08		50	5.93E+09	-1.277		
Cycle: 27 0.05 µM									5.00E-08		50	5.93E+09	-3.837		
Cycle: 28 0.1 µM									1.00E-07		50	5.93E+09	-2.784		
Cycle: 29 0.2 µM									2.00E-07		50	5.93E+09	-0.432		
Cycle: 30 0.4 µM									4.00E-07		50	5.93E+09	0.8599		
Cycle: 31 0.1 µM									1.00E-07		50	5.93E+09	-2.601		

Figure S55. The SPR sensorgrams, fitting parameters and quality control table of DPF p8 (1 replicate)

- **DPF p13**



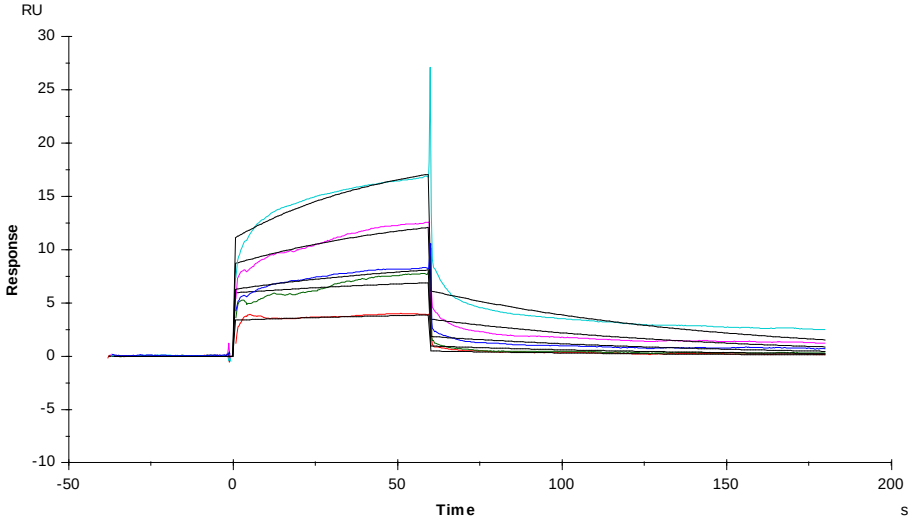
(Heterogeneous Ligand binding mode)

- Removed 0.0125 µM curve from analysis due to noise
- Poor 1:1 fit (high Chi^2)
- Heterogeneous Ligand probably more representative
- Binding parameters were the average of the two binding processes

Heterogeneous Ligand	ka1 (1/Ms)	kd1 (1/s)	KD1 (M)	ka2 (1/Ms)	kd2 (1/s)	KD2 (M)	Rmax1 (RU)	Rmax2 (RU)	Conc (M)	tc	Flow (ul/min)	kt (RU/Ms)	RI (RU)	Chi² (RU²)	U-value
Curve	5623	0.004204	7.48E-07	6920	0.004216	6.09E-07	559.2	557.9		6.35E+07				14.5	N/A
Cycle: 34 0.025 µM									2.50E-08		50	2.34E+08	-0.6447		
Cycle: 35 0.05 µM									5.00E-08		50	2.34E+08	-4.26		
Cycle: 36 0.1 µM									1.00E-07		50	2.34E+08	-5.36		
Cycle: 37 0.2 µM									2.00E-07		50	2.34E+08	5.596		
Cycle: 38 0.05 µM									5.00E-08		50	2.34E+08	-4.18		

Figure S56. The SPR sensorgrams, fitting parameters and quality control table of DPF p13 (1 replicate)

- **DMZ m3**



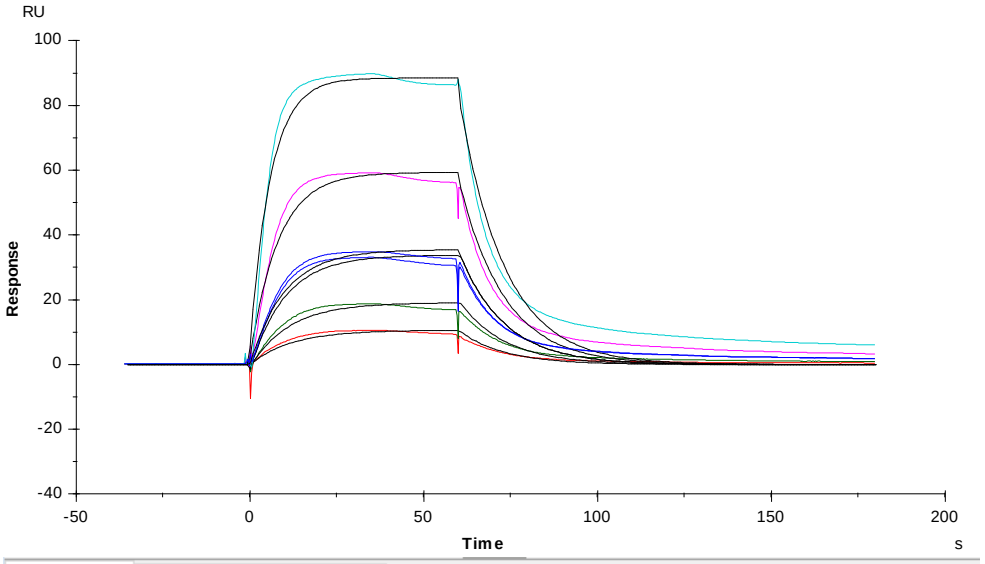
Quality Control | Report | Residuals | Parameters

- Kinetic constants are within instrument specifications.
- Kinetic constants cannot be uniquely determined. Try to immobilize less ligand or increase analyte concentration.
- High bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

1:1 Binding	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)	tc	Flow (ul/min)	kt (RU/Ms)	RI (RU)	Chi² (RU²)	U-value
Curve	5.24E+03	0.01152	2.20E-06	1.76E+01		3.19E+08				0.262	26
Cycle: 5 0.125 µM					1.25E-07		50	1.17E+09	3.379		
Cycle: 6 0.25 µM					2.50E-07		50	1.17E+09	5.937		
Cycle: 8 1 µM					1.00E-06		50	1.17E+09	8.635		
Cycle: 9 2 µM					2.00E-06		50	1.17E+09	1.10E+01		
Cycle: 10 0.5 µM					5.00E-07		50	1.17E+09	6.26E+00		

Figure S57. The SPR sensorgrams, fitting parameters and quality control table of DMZ m3 (1 replicate)

- **DMZ p8**



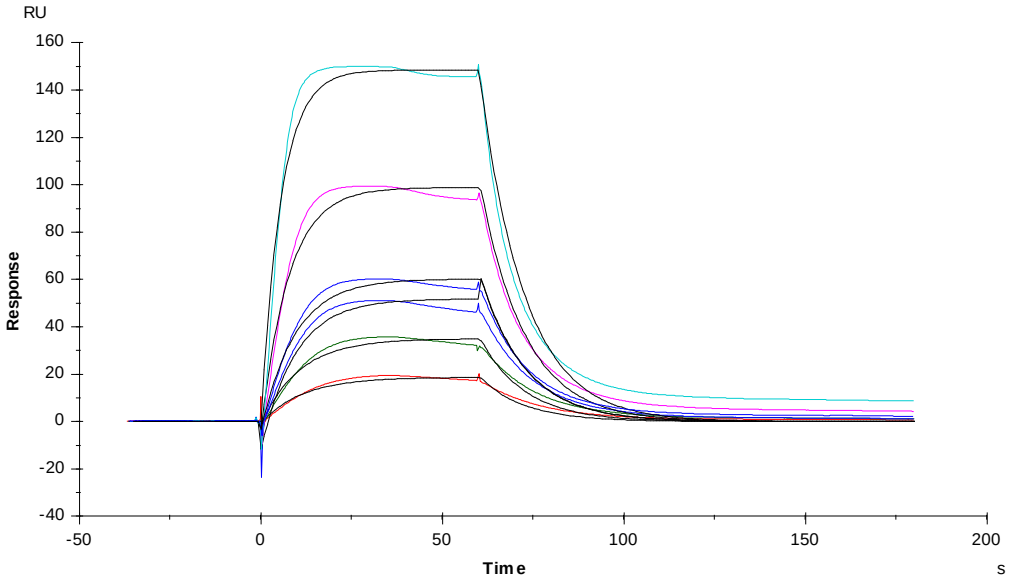
Quality Control | Report | Residuals | Parameters

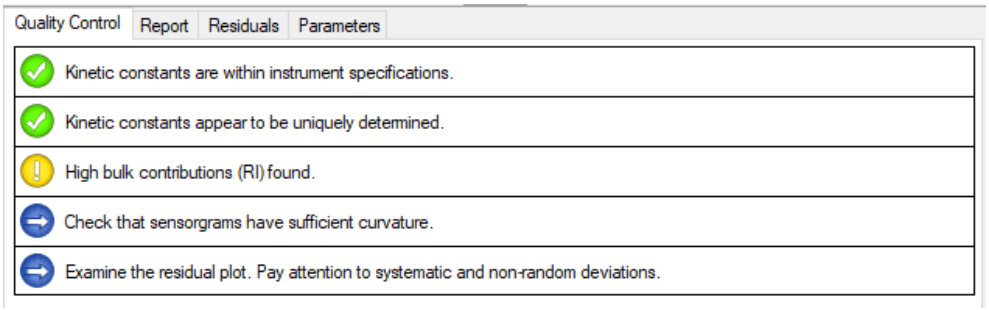
- Kinetic constants are within instrument specifications.
- Kinetic constants appear to be uniquely determined.
- No significant bulk contributions (RI) found.
- Check that sensorgrams have sufficient curvature.
- Examine the residual plot. Pay attention to systematic and non-random deviations.

1:1 Binding	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)	tc	Flow (ul/min)	kt (RU/Ms)	RI (RU)	Chi² (RU²)	U-value
Curve	9.31E+04	0.07675	8.25E-07	1.51E+02		1.55E+15				7.85	3
Cycle: 19 0.0625 µM					6.25E-08		50	5.71E+15	-0.00937		
Cycle: 20 0.125 µM					1.25E-07		50	5.71E+15	-0.7882		
Cycle: 21 0.25 µM					2.50E-07		50	5.71E+15	-1.375		
Cycle: 22 0.5 µM					5.00E-07		50	5.71E+15	2.25E+00		
Cycle: 23 1 µM					1.00E-06		50	5.71E+15	5.57E+00		
Cycle: 24 0.25 µM					2.50E-07		50	5.71E+15	3.26E-01		

Figure S58. The SPR sensorgrams, fitting parameters and quality control table of DMZ p8 (1 replicate)

- **DMZ p13**





1:1 Binding	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	Conc (M)	tc	Flow (ul/min)	kt (RU/Ms)	RI (RU)	Chi² (RU²)	U-value
Curve	1.01E+05	0.0814	8.03E-07	2.68E+02		2.75E+13				13.7	2
Cycle: 26 0.0625 µM					6.25E-08		50	1.01E+14	-0.6185		
Cycle: 27 0.125 µM					1.25E-07		50	1.01E+14	-1.053		
Cycle: 28 0.25 µM					2.50E-07		50	1.01E+14	-11.73		
Cycle: 29 0.5 µM					5.00E-07		50	1.01E+14	-3.85E+00		
Cycle: 30 1 µM					1.00E-06		50	1.01E+14	2.92E-03		
Cycle: 31 0.25 µM					2.50E-07		50	1.01E+14	-3.30E+00		

Figure S59. The SPR sensorgrams, fitting parameters and quality control table of DMZ p13 (1 replicate)

Section D. QSAR modeling

1. Descriptor calculation

$$\frac{N_1}{N_0} = e^{-\Delta E/RT}$$ **Equation S1**

Equation S1 was used to calculate the ratio of two different molecular conformations, where N_1/N_0 is the ratio of the number of molecules in the relative energy states, ΔE is the energy difference between N_0 and N_1 (3 kcal/mol), R is the ideal gas constant (0.00198588 kcal/K mol), and T is the temperature (295 K).

$$\mathrm{A} = \frac{\sum_i A_i e^{-\frac{E_i}{k_B T}}}{\sum_i e^{-\frac{E_i}{k_B T}}}$$ **Equation S2**

For a specific descriptor (A), Equation S2 was used as Boltzmann average method to account for multiple conformations of a molecule and give the final descriptor value, where A_i is the descriptor value of conformation i, E_i is the energy of conformation i, k_B is the Boltzmann constant, and T is the temperature.

2. Methods and scripts

Descriptor refinement (performed on MATLAB (R2020a), use KD data as an example)

```
load('KDdata.mat'); % this matrix contains the 1st row as the index of the variables names, 0 for response variable, here is lnKD
% find features with constant entry>=80%, delete such features resulting new
% dataset called:data_nonconst
data=KDdata;
for i=2:size(data,2)
   Y(i)=max(sum(data(:,i)==data(:,i)'));
end

idx_const=find(Y(:)>=0.8*(size(data,1)-1));
data_nonconst=data;
data_nonconst(:,idx_const)=[];

% find multicolinerity (abs(rho)>0.95) between features, delete ones with more than 1
% multicolinerity, based on the max number of multicolinerity, saved the
% refined data in the data_refine.

data_refine=data_nonconst;

cor=corrcoef(data_refine(2:size(data_refine,1),2:size(data_refine,2)));
cor=abs(cor);
[a,b]=find(cor>0.95);
A=[b,a];
id=find(b>=a);
A(id,:) = [];
uni=unique(A(:,1));
num=zeros(size(uni,1),1);

for i=1:size(uni,1)
    idx=find(uni(i)==A(:,1));
    num(i)=size(idx,1);
end

n=0;
while max(num)>1         % repeat until only one more feature is correlated

id_max=find(num==max(num));
if size(id_max,1)>1
    id_max = id_max(1,1);
else
    id_max=id_max;
end
del_col=find(A(:,1)==uni(id_max));
id_del=A(del_col,2);
```

```
data_refine(:,id_del+1)=[];

cor=corrcoef(data_refine(2:size(data_refine,1),2:size(data_refine,2)));
cor=abs(cor);
[a,b]=find(cor>0.95);
A=[b,a];
id=find(b>=a);
A(id,:) = [];
uni=unique(A(:,1));
num=zeros(size(uni,1),1);
for i=1:size(uni,1)
    idx=find(uni(i)==A(:,1));
    num(i)=size(idx,1);
end
n=n+1; % record how many steps take to complete this task
end

% in a pair of multicorrelation, delete the one with lower correlation to the
y variable
m=0;
while size(A,1)>0
    cor1=abs(corrcoef(data_refine(:,1),data_refine(:,A(1,1)+1)));
    cor1=cor1(1,end);
    cor2=abs(corrcoef(data_refine(:,1),data_refine(:,A(1,2)+1)));
    cor2=cor2(1,end);

    if cor1>=cor2
        id_del=A(1,2);
        data_refine(:,id_del+1)=[];
    else
        id_del=A(1,1);
        data_refine(:,id_del+1)=[];
    end
    cor=corrcoef(data_refine(2:size(data_refine,1),2:size(data_refine,2)));
    cor=abs(cor);
    [a,b]=find(cor>0.95);
    A=[b,a];
    id=find(b>=a);
    A(id,:) = [];
    m=m+1; % record how many steps take to complete this task
end


save('KD_data_refine.mat','data_refine');
```

Representative data splitting by Kennard-Stone algorithm and PCA (performed on RStudio v1.4.1717)

```
# load data
data <- read.csv('KD_refine.csv')

# create trainingset and testset id using kenStone on euclidian distance
library(prospectr)
xspace <- data[,-1]
ks <- kenStone(as.matrix(xspace), k=12, metric = "mahal",pc=0.99, .center =
TRUE, .scale = FALSE)
ks$test
trainid <- ks$test

# assign testset and trainingset
trainingset <- data[trainid,]
testset <- data[-trainid,]

x_train <- as.matrix(trainingset[-1])
y_train <- data.matrix(trainingset[1])
x <- x_train
y <- y_train
x_test <- as.matrix(testset[-1])
y_test <- as.matrix(testset[1])

data_pca <- data

data_pca$lnKD[trainid]=0
data_pca$lnKD[-trainid]=1

pc <- prcomp(data_pca[,-1],scale. = TRUE)
summary(pc)
plot(pc, type="lines")

library(rgl)
library(ggplot2)
library(ggfortify)
library(magrittr)

# design figure frame and axis tick
tick_frame <-
  data.frame(ticks = seq(-20, 20, length.out = 5),
             zero=0) %>%
  subset(ticks != 0)

lab_frame <- data.frame(lab = seq(-20, 20),
                        zero = 0) %>%
  subset(lab != 0)

tick_sz <- (tail(lab_frame$lab, 1) -  lab_frame$lab[1]) / 128

pc_plot <- cbind(data_pca[,1],pc$x)

# PLOT ----
ggplot(pc_plot, aes(x=pc_plot[,2],y=pc_plot[,3])) +labs(x = 'PC1 (29.93%)', y
= 'PC2 (20.81%)')+
```

```
  # y axis line
  geom_segment(x = 0, xend = 0,
               y = lab_frame$lab[1], yend = tail(lab_frame$lab, 1),
               size = 1.5) +
  # x axis line
  geom_segment(y = 0, yend = 0,
               x = lab_frame$lab[1], xend = tail(lab_frame$lab, 1),
               size = 1.5) +
  # x ticks
  geom_segment(data = tick_frame,
               aes(x = ticks, xend = ticks,
                   y = zero, yend = zero + tick_sz),size =1.5) +
  # y ticks
  geom_segment(data = tick_frame,
               aes(x = zero, xend = zero + tick_sz,
                   y = ticks, yend = ticks),size =1.5) +

  # labels
  geom_text(data=tick_frame, aes(x=ticks, y=zero, label=ticks),
            vjust=1.5,size = 6) +
  geom_text(data=tick_frame, aes(x=zero, y=ticks, label=ticks),
             hjust=1.5,size = 6) +
  # legends
  scale_color_discrete(name  ="dataset",
                       labels=c("Trainingset", "Testset"))+
  # THE DATA POINT
    geom_point(aes(color = factor(V1)),size = 4,alpha =.6) +
  scale_color_manual(labels = c("Training set", "Test set"), values =
c("dodgerblue", "red2"))+
  # title
  ggtitle("Test set molecules in 2D chemical space")+

  theme_bw()+
  theme(panel.border = element_blank(), panel.grid.major = element_blank(),
                     panel.grid.minor = element_blank())+
theme(axis.ticks.x = element_blank(),
      axis.text.x = element_blank(),
      axis.ticks.y = element_blank(),
      axis.text.y = element_blank())+
  theme(axis.title = element_text(size = 22, face = "bold"))+
  theme(plot.title = element_text(hjust = 0.5)) +theme(plot.title =
element_text(size = 30, face = "bold"))+
  theme(legend.title = element_blank(),
        legend.text = element_text(color = "black",size = 20,face =
"bold"))+theme(legend.position="none")


ggsave("datasplit.tiff", units="in", width=6, height=6, dpi=600)
```

Descriptor selection by lasso and model selection (performed on RStudio v1.4.1717)

```
# load data
data <- read.csv('KD_refine.csv')

# Creat the evaluation function: eval_results, which contains RMSE and
Rsquare
eval_results <- function(true, predicted, df) {
  SSE <- sum((predicted - true)^2)
  SST <- sum((true - mean(true))^2)
  R_square <- 1 - SSE / SST
  RMSE = sqrt(SSE/nrow(df))
  # Model performance metrics
  data.frame(
    RMSE = RMSE,
    Rsquare = R_square)
}

# create trainingset and testset id using kenStone on Mahalanobis distance
library(prospectr)
xspace <- data[,-1]
ks <- kenStone(as.matrix(xspace), k=12, metric = "mahal",pc=0.99, .center =
TRUE, .scale = FALSE)
ks$test
trainid <- ks$test


# assign testset and trainingset
trainingset <- data[trainid,]
testset <- data[-trainid,]

x_train <- as.matrix(trainingset[-1])
y_train <- data.matrix(trainingset[1])
x <- x_train
y <- y_train
x_test <- as.matrix(testset[-1])
y_test <- as.matrix(testset[1])


# lasso regression
library(glmnet)
set.seed(1)
lambdas <- 10^seq(2, -6, length = 100)

# use sv.glmnet to find the best lambda for lasso from 5-fold cv
lasso_reg <- cv.glmnet(x_train, y_train, alpha = 1, lambda = lambdas,
standardize = TRUE, nfolds = 5)
plot(lasso_reg)

# plot the shrinkage graph with multiple lambda values
lasso_model <- glmnet(x_train, y_train, alpha = 1, nlambda =100,standardize =
TRUE)
print(lasso_model)
p1 <- plot(lasso_model,xvar="lambda",label = T, lwd=4,cex.lab=
2,cex.axis=2,xlim = c(-4.5,0.5), ylim=c(-20,20))
```

```
p1.lty=2
box(lwd=4)

# chose the lambda with lowest mean-squrared error from cv
lambda_best_lasso <- lasso_reg$lambda.min
lambda_best_lasso

# build the lasso regression model using selected descriptors
lasso_model <- glmnet(x_train, y_train, alpha = 1, lambda
=lambda_best_lasso,standardize = TRUE)
summary(lasso_model)

# find the non-zero coefficients and their names
lasso.coef  <-  predict(lasso_model,type="coefficients")
lasso.coef
lasso.coef[lasso.coef!=0]
lasso_nonzerocoef <- predict(lasso_model,type="nonzero")
lasso_nonzerocoef
colnames(data[,lasso_nonzerocoef$s0+1])

# model evaluation on lasso model using all non-zero descriptors
lasso_fittings <- predict(lasso_model, s = lambda_best_lasso, newx = x)
lasso_predictions <- predict(lasso_model, s = lambda_best_lasso, newx =
x_test)
eval_results(y_test, lasso_predictions, testset)
eval_results(y_train, lasso_fittings, trainingset)

# exhaustively search for all combinations
# m = number of features in the model, data_step contains all non-zero
descriptor candidates, "results" summarizes all results
data_step <- trainingset[,append(lasso_nonzerocoef$s0+1,1,0)]
m <- 3
idx <- combn(rep(1:(length(data_step)-1)),m)
results <- NULL
for (i in 1:ncol(idx)) {

  data_exhau <- data_step[,append(idx[,i]+1,1,0)]
  mdl_exhau <- lm(lnKD~.,data=data_exhau)

  predict <- predict(mdl_exhau,newdata = testset)
  fitted <- mdl_exhau$fitted.values
  a <- eval_results(testset$lnKD,predict,testset)
  b <- eval_results(trainingset$lnKD,fitted,trainingset)

  result <- data.frame(test=a,
                       train=b
                       )
  results<- rbind(results,result)
}

# idrows find all candidates with top performance, and print out the model
summary for statistical significance check
idrows <- which(results$test.Rsquare>=0.7&results$train.Rsquare>=.7)

for (val in idrows) {
  data_exhau <- data_step[,append(idx[,val]+1,1,0)]
  mdl_exhau <- lm(lnKD~.,data=data_exhau)
```

```
  s <- summary(mdl_exhau)
  print(s)
  print(val)
  cat("R2_test:", results[val,2])
 }

# plot the curve for the top model
library(ggplot2)
# load the model
mdl <- lm(formula = "lnKD~1+PEOE_VSA_POS+vsurf_DW12+vsa_other+vsurf_ID3",
          data = trainingset)
summary(mdl)
predict <- predict(mdl,newdata = data)
id  <-  numeric(48)
id[-trainid] <- 1
data_plot <- cbind(predict,data$lnKD,id)
colnames(data_plot) <- c("predict", "obs","id")

ggplot(as.data.frame(data_plot), aes(x=obs,y=predict))+
  ggtitle(expression("Baseline model of lnK"[D]*"")) +
  xlab(expression("Observed lnK"[D]*"")) + ylab(expression("Predicted
lnK"[D]*""))+
  # THE DATA POINT
  geom_point(aes(color = factor(id)),size = 5,alpha =1) +
  xlim(min(data$lnKD)-2,max(data$lnKD)+2)+
  ylim(min(data$lnKD)-2,max(data$lnKD)+2)+
  scale_color_manual(labels = c("Training set", "Test set"), values =
c("dodgerblue", "red2"))+

  # title
  theme_bw()+
  theme(axis.ticks.length=unit(.4,"lines"))+
  theme(panel.grid.major = element_blank(),
        panel.grid.minor = element_blank())+
  theme(axis.text.y = element_text(size = 20),
        axis.text.x = element_text(size=20),
        axis.title = element_text(size = 25,face = 'bold'),title
=element_text(size = 25,face = 'bold') )+
# legend
  theme(legend.title = element_blank())+
  theme(legend.text = element_text(colour="black", size=20, face="bold"))+
  theme(legend.position = c(0.80, 0.1))+
# rec
  theme(panel.background = element_rect(colour = "black", size = 3.5))+
# ref line
  geom_abline(intercept = 0, slope = 1, color="black",
              linetype="dashed", size=1.5)

ggsave("KDmdl.tiff", units="in", width=8, height=8, dpi=600)
```

Ensemble learning-based models (performed on RStudio v1.4.1717)

```
# load data
data <- read.csv('KD_refine.csv')

# Creat the evaluation function: eval_results, which contained RMSE and
Rsquare
eval_results <- function(true, predicted, df) {
  SSE <- sum((predicted - true)^2)
  SST <- sum((true - mean(true))^2)
  R_square <- 1 - SSE / SST
  RMSE = sqrt(SSE/nrow(df))
  # Model performance metrics
  data.frame(
    RMSE = RMSE,
    Rsquare = R_square)
}

# create trainingset and testset id using kenStone on Mahalanobis distance
library(prospectr)
xspace <- data[,-1]
ks <- kenStone(as.matrix(xspace), k=12, metric = "mahal",pc=0.99, .center =
TRUE, .scale = FALSE)
ks$test
trainid <- ks$test

# assign testset and trainingset
trainingset <- data[trainid,]
testset <- data[-trainid,]

x_train <- as.matrix(trainingset[-1])
y_train <- data.matrix(trainingset[1])
x <- x_train
y <- y_train
x_test <- as.matrix(testset[-1])
y_test <- as.matrix(testset[1])

# build a tree
library(tree)
tree.KD <- tree(lnKD~.,data,subset = trainid)
plot(tree.KD)
text(tree.KD)

# evaluate the prediction and fitting
pred_KD <-predict(tree.KD,newdata = testset)
fitted <- predict(tree.KD,,newdata = trainingset)
eval_results(testset$lnKD,pred_KD,testset)
eval_results(trainingset$lnKD,fitted,trainingset)

# use CV to select best size
set.seed(1)
tree.KD_cv <- cv.tree(tree.KD)
plot(tree.KD_cv$size,tree.KD_cv$dev,type = 'b')
prune_KD <- prune.tree(tree.KD,best =6)
pred_KD <-predict(prune_KD,newdata = testset)
plot(prune_KD)
```

```
text(prune_KD)
fitted <- predict(prune_KD,,newdata = trainingset)
eval_results(testset$lnKD,pred_KD,testset)
eval_results(trainingset$lnKD,fitted,trainingset)

# bagging: set mtry = 193 in randomForest method
library(randomForest)
set.seed(1)
rf_KD <- randomForest(lnKD~.,data = trainingset,importance = TRUE,ntree =
200,sampsize=24, mtry = 193)
summary(rf_KD)
print(rf_KD)

# plot
plot(rf_KD,main ="Averaged OOB error", cex.lab=2,cex.axis=2,cex.main=2,
lwd=4, col = "red")
pred_KD <-predict(rf_KD,newdata = testset)
fitted <- predict(rf_KD,,newdata = trainingset)
eval_results(testset$lnKD,pred_KD,testset)
eval_results(trainingset$lnKD,fitted,trainingset)
varImpPlot(rf_KD,main = "Variable importance plot")


# random forest
library(randomForest)
set.seed(1)
rf_KD <- randomForest(lnKD~.,data = trainingset,importance = TRUE,sampsize =
34,ntree = 100,mty=40)
summary(rf_KD)
print(rf_KD)
plot(rf_KD,main ="Averaged OOB error", cex.lab=2,cex.axis=2,cex.main=2,
lwd=4, col = "red")
pred_KD <-predict(rf_KD,newdata = testset)
fitted <- predict(rf_KD,,newdata = trainingset)
eval_results(testset$lnKD,pred_KD,testset)
eval_results(trainingset$lnKD,fitted,trainingset)
varImpPlot(rf_KD,main = "Variable importance plot")

# plot
predict <- predict(rf_KD,newdata = data)
id  <-  numeric(48)
id[-trainid] <- 1
data_plot <- cbind(predict,data$lnKD,id)
colnames(data_plot) <- c("predict", "obs","id")

ggplot(as.data.frame(data_plot), aes(x=obs,y=predict))+
  ggtitle(expression("Baseline model of lnK"[D]*"")) +
  xlab(expression("Observed lnK"[D]*"")) + ylab(expression("Predicted
lnK"[D]*""))+
  # THE DATA POINT
  geom_point(aes(color = factor(id)),size = 5,alpha =1) +
  xlim(min(data$lnKD)-2,max(data$lnKD)+2)+
  ylim(min(data$lnKD)-2,max(data$lnKD)+2)+
  scale_color_manual(labels = c("Training set", "Test set"), values =
c("dodgerblue", "red2"))+

  # title
```

```
  theme_bw()+
  theme(axis.ticks.length=unit(.4,"lines"))+
  theme(panel.grid.major = element_blank(),
        panel.grid.minor = element_blank())+
  theme(axis.text.y = element_text(size = 20),
        axis.text.x = element_text(size=20),
        axis.title = element_text(size = 25,face = 'bold'),title
=element_text(size = 25,face = 'bold') )+
  # legend
  theme(legend.title = element_blank())+
  theme(legend.text = element_text(colour="black", size=20, face="bold"))+
  theme(legend.position = c(0.80, 0.1))+
  # rec
  theme(panel.background = element_rect(colour = "black", size = 3.5))+
  # ref line
  geom_abline(intercept = 0, slope = 1, color="black",
              linetype="dashed", size=1.5)

ggsave("rfmdl.tiff", units="in", width=8, height=8, dpi=600)

# boosting using GBM in r
library(gbm)
set.seed(1)
boost_KD <- gbm(lnKD~.,data=trainingset,distribution =
'gaussian',n.trees=2000,interaction.depth=1,
                shrinkage = 0.01,cv.folds = 5,verbose =
TRUE,n.minobsinnode=4,bag.fraction = 0.5 )
summary(boost_KD)
print(boost_KD)
sqrt(min(boost_KD$cv.error))
gbm.perf(boost_KD, method = "cv")
legend(1200, .5, c("OOB(Out Of Bag estimator method)", "CV(Cross Valdation
method)"), cex=0.8, col=c("black", "green"),  lty=1)
pred_KD <-predict(boost_KD,newdata = testset,n.trees = 990)
fitted <- predict(boost_KD,newdata = trainingset,n.trees =990)
eval_results(testset$lnKD,pred_KD,testset)
eval_results(trainingset$lnKD,fitted,trainingset)

# plot
predict <- predict(boost_KD,newdata = data,ntrees =500)
id  <-  numeric(48)
id[-trainid] <- 1
data_plot <- cbind(predict,data$lnKD,id)
colnames(data_plot) <- c("predict", "obs","id")

ggplot(as.data.frame(data_plot), aes(x=obs,y=predict))+
  ggtitle(expression("Baseline model of lnK"[D]*"")) +
  xlab(expression("Observed lnK"[D]*"")) + ylab(expression("Predicted
lnK"[D]*""))+
  # THE DATA POINT
  geom_point(aes(color = factor(id)),size = 5,alpha =1) +
  xlim(min(data$lnKD)-2,max(data$lnKD)+2)+
  ylim(min(data$lnKD)-2,max(data$lnKD)+2)+
  scale_color_manual(labels = c("Training set", "Test set"), values =
c("dodgerblue", "red2"))+

  # title
```

```
  theme_bw()+
  theme(axis.ticks.length=unit(.4,"lines"))+
  theme(panel.grid.major = element_blank(),
        panel.grid.minor = element_blank())+
  theme(axis.text.y = element_text(size = 20),
        axis.text.x = element_text(size=20),
        axis.title = element_text(size = 25,face = 'bold'),title
=element_text(size = 25,face = 'bold') )+
  # legend
  theme(legend.title = element_blank())+
  theme(legend.text = element_text(colour="black", size=20, face="bold"))+
  theme(legend.position = c(0.80, 0.1))+
  # rec
  theme(panel.background = element_rect(colour = "black", size = 3.5))+
  # ref line
  geom_abline(intercept = 0, slope = 1, color="black",
              linetype="dashed", size=1.5)

ggsave("gbmmdl.tiff", units="in", width=8, height=8, dpi=600)
```

Model assessment: Q-Q plot and Williams plot (performed on RStudio v1.4.1717)

```
# load data
data <- read.csv('KD_refine.csv')

# create trainingset and testset id using kenStone on Mahalanobis distance
library(prospectr)
xspace <- data[,-1]
ks <- kenStone(as.matrix(xspace), k=12, metric = "mahal",pc=0.99, .center =
TRUE, .scale = FALSE)
ks$test
trainid <- ks$test

# assign testset and trainingset
trainingset <- data[trainid,]
testset <- data[-trainid,]

x_train <- as.matrix(trainingset[-1])
y_train <- data.matrix(trainingset[1])
x <- x_train
y <- y_train
x_test <- as.matrix(testset[-1])
y_test <- as.matrix(testset[1])

# model gonna be assessed
mdl <- lm(formula = "lnKD~1+PEOE_VSA_POS+vsurf_DW12+vsa_other+vsurf_ID3",
          data = trainingset)
summary(mdl)

# plot q-q plot

qqnorm(mdl$residuals, pch = 19,cex = 2.5,col="blue")
qqline(mdl$residuals, col = "black", lwd = 3,lty = 2)

# Williams plot for lnKD model
library(matlib)
library(ggplot2)
wp_x <-
cbind(data$PEOE_VSA_POS,data$vsurf_DW12,data$vsa_other,data$vsurf_ID3)

h <- diag(wp_x%*%inv((t(wp_x)%*%wp_x))%*%t(wp_x))

stdres_train <- (mdl$residuals-mean(mdl$residuals))/sd(mdl$residuals)
res_test <- predict(mdl,newdata=testset)-testset$lnKD
stdres_test <- (res_test-mean(mdl$residuals))/sd(mdl$residuals)

wp_mt <- matrix(0,48,3)
wp_mt[testid,1] <-1
wp_mt[,2] <- h
wp_mt[trainid,3] <- stdres_train
wp_mt[testid,3] <- stdres_test

colnames(wp_mt)=c("id","hatvalue","stdres")

ggplot(as.data.frame(wp_mt), aes(x=hatvalue,y=stdres))+
  ggtitle(expression("Williams plot: lnK"[D]*"")) +
```

```
  xlab(expression("Leverage")) + ylab(expression("Standardized residuals"))+
  # THE DATA POINT
  geom_point(aes(color = factor(id)),size = 5,alpha =1) +
  xlim(0,0.8)+
  ylim(-4,4)+
  scale_color_manual(labels = c("Training set", "Test set"), values =
c("dodgerblue", "red2"))+

  # title
  theme_bw()+
  theme(axis.ticks.length=unit(.4,"lines"))+
  theme(panel.grid.major = element_blank(),
        panel.grid.minor = element_blank())+
  theme(axis.text.y = element_text(size = 20),
        axis.text.x = element_text(size=20),
        axis.title = element_text(size = 25,face = 'bold'),title
=element_text(size = 25,face = 'bold') )+
  # legend
  theme(legend.title = element_blank())+
  theme(legend.text = element_text(colour="black", size=20, face="bold"))+
  theme(legend.position = c(0.80, 0.1))+
  # rec
  theme(panel.background = element_rect(colour = "black", size = 3.5))+
  # ref line
  geom_abline(intercept = 3, slope = 0, color="black",
              linetype="dashed", size=1.5)+
  geom_abline(intercept = -3, slope = 0, color="black",
              linetype="dashed", size=1.5)+
  geom_vline(xintercept = 3*5/36, color="black",
              linetype="dashed", size=1.5)


  plot(diag(h),stdred,col=c("blue4"),pch =19,cex = 2,cex.lab=2,cex.axis =
2,xlim=c(0,0.5),ylim=c(-4,4))
```

Predictor stability test (performed on RStudio v1.4.1717)

```
# load data
data <- read.csv('KD_refine.csv')

# Creat the evaluation function: eval_results, which contains RMSE and
Rsquare
eval_results <- function(true, predicted, df) {
  SSE <- sum((predicted - true)^2)
  SST <- sum((true - mean(true))^2)
  R_square <- 1 - SSE / SST
  RMSE = sqrt(SSE/nrow(df))
  # Model performance metrics
  data.frame(
    RMSE = RMSE,
    Rsquare = R_square)
}



# randomize the data splitting 100 times (36:12)
results <- NULL
for (i in 1:100){
  set.seed(i)
  testid <- sample(seq_len(nrow(data)),size=12)

  # assign testset and trainingset
  trainingset <- data[-testid,]
  testset <- data[testid,]
  x_train <- as.matrix(trainingset[-1])
  y_train <- data.matrix(trainingset[1])
  x <- x_train
  y <- y_train
  x_test <- as.matrix(testset[-1])
  y_test <- as.matrix(testset[1])
    mdl <- lm(formula = "lnKD~1+PEOE_VSA_POS+vsa_other+vsurf_DW12+vsurf_ID3",
            data = trainingset) # using the same descriptors to build the
model

  predict <- predict(mdl,newdata = testset)
  fitted <- mdl$fitted.values
  a <- eval_results(testset$lnKD,predict,testset)
  b <- eval_results(trainingset$lnKD,fitted,trainingset)
  result <- data.frame(test=a,
                       train=b
  )
  results<- rbind(results,result)
}

# plot
barplot(results$test.Rsquare,xlim = c(0,i*1.2),ylim=c(-.5,1.5),lwd=3)
abline(h=mean(results$test.Rsquare), col ="Red",lwd = 5,xlim=c(0,i))
text(x = c(0.1*i,0.3*i,0.4*i,0.5*i),
     y = c(1.2,1.2,1.2,1.2),cex = 1.5,
     labels = c("R2_test = ", round(mean(results$test.Rsquare),2), "+/-",
round(sd(results$test.Rsquare),2)))
```

```
barplot(results$train.Rsquare,xlim = c(0,i*1.2),ylim=c(0,1),lwd=3)
abline(h=mean(results$train.Rsquare), col ="Red",lwd = 5,xlim=c(0,i))
text(x = c(0.1*i,0.3*i,0.4*i,0.5*i),
     y = c(0.9,0.9,0.9,0.9),cex = 1.5,
     labels = c("R2_train = ", round(mean(results$train.Rsquare),2), "+/-",
round(sd(results$train.Rsquare),2)))
```

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3. Umuhire Juru, A.; Cai, Z.; Jan, A.; Hargrove, A. E., Template-guided selection of RNA ligands using imine-based dynamic combinatorial chemistry. *Chemical Communications* **2020,** *56* (24), 3555-3558.
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