The binding of 2-(triazolylthio)acetamides to metallo-β-lactamase CcrA determined with NMR

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1 CcrA

1.1 Primary structure

There is a four amino acid residue difference between the sequence used in the NMR experiments, as compared to the sequence used in the docking studies (PDB ID: 1A8T) (Table S1).[2] Thus, there is a 98% sequence and 100% length similarity between the sequences. Amino acid residues 171 and 208 are located in the active site at loop 10 and loop 12, respectively. Here, this region is denominated the L10-L12 binding site. The difference in hydrogen bonding properties between the side chains of Ala and Thr at position 171 has been taken into consideration. No hydrogen bonding interactions were observed between the top scoring poses and the side chain of Thr171. For the most important residues, the BBL numbering is given in Table S4–Table **S7**.[3]

Table S1. The amino acid sequence expressed and used in the NMR experiments, as compare to the sequence used in the molecular docking.

	Amino acid residue	
Residue number	NMR experiments	Crystal structure
81	**D**	N
88	**L**	I
171	**A**	T
208	**D**	N

Amino acid sequence
A[1]QKSVKISDD[10]ISITQLSDKV[20]YTYVSLAEIE[30] GWGMVPSNGM[40]IVINNHQAAL[50]LDTPINDAQ T[60]EMLVNWVTDS[70]LHAKVTTFIP[80]**D**[81]HWHGD C**L**[88]GG[90]LGYLQRKGVQ[100]SYANQMTIDL[110]AK EKGLPVPE[120]HGFTDSLTVS[130]LDGMPLQCYY[140] LGGGHATDNI[150]VVWLPTENIL[160]FGGCMLKDN Q[170]**A**[171]TSIGNISDA[180]DVTAWPKTLD[190]KVKAK FPSAR[200]YVVPGHG**D**[208]YG[210]GTELIEHTKQ[220]IV NQYIESTS[230]KP[232]

2 NMR spectroscopy

2.1 CcrA NMR resonance assignment

Table S2. $^{13}C^{\alpha}$ and $13C^{\beta}$ chemical shift resonance assignments of CcrA.

CcrA residue	δ (ppm)		CcrA residue	δ (ppm)		CcrA residue	δ (ppm)		CcrA residue	δ (ppm)		CcrA residue	δ (ppm)	
	$^{13}C^{\alpha}$	$^{13}C^{\beta}$		$^{13}C^{\alpha}$	$^{13}C^{\beta}$		$^{13}C^{\alpha}$	$^{13}C^{\beta}$		$^{13}C^{\alpha}$	$^{13}C^{\beta}$		$^{13}C^{\alpha}$	$^{13}C^{\beta}$
Ala1			Leu51	54.56	39.45	Ser101	67.60	67.60	Val151	60.26	34.92	Tyr201	56.07	42.58
Gln2	55.91		Asp52	58.52	40.66	Tyr102	55.94	42.29	Val152	61.73	42.53	Val202	61.30	33.25
Lys3	56.91	33.50	Thr53	59.70	68.88	Ala103	50.65	24.18	Trp153	53.93	35.43	Val203	58.75	34.16
Ser4	57.68	65.17	Pro54	62.41	39.82	Asn104	52.18	36.57	Leu154	50.98	40.72	Pro204	61.73	33.39
Val5	61.08	35.03	Ile55	61.71	34.88	Gln105	58.36	28.11	Pro155		32.54	Gly205	47.95	
Lys6	56.34	32.50	Asn56	50.86	41.46	Met106	58.49	35.21	Thr156	64.26	67.98	His206	55.75	31.34
Ile7	62.58	38.37	Asp57	57.81	41.32	Thr107	65.86	67.78	Glu157	54.00	32.00	Gly207	43.85	
Ser8	56.75	65.04	Ala58	55.80	18.03	Ile108	66.79	37.96	Asn158	55.19	37.56	Asp208	55.56	41.37
Asp9	57.58	40.51	Gln59	59.06	30.16	Asp109	57.79	39.80	Ile159	60.88	42.76	Tyr209	56.27	39.91
Asp10	53.65	42.51	Thr60	68.49	66.97	Leu110	58.10	41.83	Leu160	52.83	47.25	Gly210	46.46	
Ile11	61.17	41.22	Glu61	59.57	28.76	Ala111	55.94	17.53	Phe161	55.55	38.45	Gly211	44.85	
Ser12	56.79	66.54	Met62	59.00	32.52	Lys112	59.53	32.76	Gly162	44.73		Thr212	65.27	68.78
Ile13	60.13	41.83	Leu63	58.25	43.21	Glu113	59.02	29.90	Gly163	46.27		Glu213	59.49	26.82
Thr14	62.19	71.68	Val64	67.55	31.14	Lys114	56.04	33.90	Cys164	62.59	27.66	Leu214	59.10	42.30
Gln15	56.94	29.45	Asn65	55.92	37.37	Gly115	46.65		Met165	57.88	33.18	Ile215	66.30	37.80
Leu16	55.53	43.37	Trp66	62.78	28.41	Leu116	52.91	41.25	Leu166	52.79	43.73	Glu216	59.12	29.41
Ser17	56.61	65.97	Val67	67.13	31.55	Pro117			Lys167	55.59	33.73	His217	59.69	30.32
Asp18	57.99	40.74	Thr68	66.10	69.47	Val118			Asp168	52.88	42.34	Thr218	68.38	63.72
Lys19	56.29	35.61	Asp69	56.97	41.42	Pro119			Asn169	55.50	39.00	Lys219	60.73	32.06
Val20	61.94	34.27	Ser70	60.35	63.19	Glu120	59.52		Gln170	55.64	29.40	Gln220	59.32	27.75
Tyr21	55.80	41.69	Leu71	53.91	40.42	His121	55.19	32.26	Ala171	53.47	20.17	Ile221	64.50	37.78
Thr22	59.22	71.23	His72	55.70	26.36	Gly122	44.47		Thr172	61.05		Val222	66.65	31.35
Tyr23	55.23	43.10	Ala73	49.78	22.49	Phe123	55.86	43.11	Ser173	56.36	65.75	Asn223	56.09	37.67
Val24	60.87	34.69	Lys74	54.22	34.74	Thr124	61.77	70.20	Ile174	63.61	40.15	Gln224	59.17	28.15
Ser25	55.69	66.18	Val75	63.05	30.91	Asp125	57.92		Gly175	45.50		Tyr225	62.10	38.41
Leu26	54.60	44.24	Thr76	61.55	71.19	Ser126	57.18	66.45	Asn176	54.13		Ile226	65.88	38.54
Ala27	51.75	22.88	Thr77	63.58	73.43	Leu127	55.07	46.04	Ile177	60.44	38.51	Glu227	59.31	29.63
Glu28	56.26	30.38	Phe78	56.43	43.60	Thr128	62.15	69.37	Ser178	62.60	63.17	Ser228	60.71	63.69
Ile29	60.25	39.44	Ile79	57.81	44.73	Val129	60.87	33.42	Asp179	53.79	43.68	Thr229	62.50	70.08
Glu30	59.04	29.40	Pro80			Ser130	56.00	64.14	Ala180	52.12	21.55	Ser230	58.89	64.03
Gly31	45.39		Asp81	58.61		Leu131	52.48	42.38	Asp181	51.85	41.20	Lys231	54.13	32.67
Trp32	57.40	31.64	His82	56.73	27.38	Asp132	54.99	41.27	Val182	67.50	31.86	Pro232		
Gly33	44.89		Trp83	58.76	28.73	Gly133	44.88		Thr183	65.28	68.70			
Met34	54.90	31.28	His84	54.56	33.20	Met134	52.53	33.87	Ala184	53.68	19.88			
Val35	59.41	35.67	Gly85	48.17		Pro135	63.15	32.79	Trp185	60.75	28.59			
Pro36	62.01	31.83	Asp86	53.94	37.15	Leu136	55.05	41.94	Pro186	67.21				
Ser37	59.37	65.66	Cys87	59.33	31.82	Gln137	55.74	30.50	Lys187	58.93	31.67			
Asn38	51.19	41.14	Leu88	61.41	42.09	Cys138	57.02	30.33	Thr188	66.46	68.25			
Gly39	45.51		Gly89	48.02		Tyr139	58.03	42.91	Leu189	58.40	39.79			
Met40	53.88	36.69	Gly90	44.07		Tyr140	58.03	39.05	Asp190	57.75	39.97			
Ile41	60.52	42.08	Leu91	57.30	41.97	Leu141	53.65	43.18	Lys191	59.95	33.01			
Val42	60.46	34.65	Gly92	47.29		Gly142	43.60		Val192	66.75	31.91			
Ile43	59.19	40.92	Tyr93	61.84	38.07	Gly143	45.15		Lys193	58.85	32.95			
Asn44	53.79	42.50	Leu94	57.31	40.48	Gly144	46.81		Ala194	53.69	18.82			
Asn45	54.21	36.62	Gln95	59.50	27.62	His145	58.27	28.18	Lys195	57.43	32.38			
His46	58.47	27.29	Arg96	59.09	29.87	Ala146	49.26	23.25	Phe196	53.41	38.17			
Gln47	55.13	31.95	Lys97	54.38	31.56	Thr147	65.74	68.31	Pro197	64.94				
Ala48	49.28	23.56	Gly98	46.06		Asp148	53.24	40.98	Ser198	57.96	64.08			
Ala49	48.93	22.45	Val99	63.16	32.50	Asn149	54.17	41.07	Ala199	53.96	19.06			
Leu50	53.50	45.64	Gln100	55.92	30.67	Ile150	60.20	42.54	Arg200	57.43	31.39			

2.2 $^{1}H,^{15}N$ HSQC titration experiments

For the titrations, separate CcrA batches were prepared and the ligands were dissolved in the same buffer as the protein (10 mM PBS, 1.0 mM $ZnSO_4$, pH 7.0). Correlation ^{1}H, ^{15}N HSQC spectra were recorded on free ^{15}N-labeled CcrA, and upon addition of **4**, **5** and **6** as reported in Table S3. To minimize sample dilution, the volumes of the standard ligand solutions that were added in each titration step were ensured to be kept in the low microliter range. Averaged protein concentrations were used in the calculations, and the actual ligand concentrations were adjusted for the small dilution in each step. The samples were vortexed to mix the ligand and protein properly. Care was taken to avoid any foaming.

For the $^{1}H,^{15}N$ HSQC experiments, normal sampling of 4 scans and 150 phase sensitive steps in the indirect dimension, and with a total acquisition time of about 30 min, were used. In some cases, 8 scans were required to increase the s/n ratio. The experiments were performed on either a 800 MHz spectrometer with a 3 mm TCI cryogenic probe or a 900 MHz spectrometer equipped with a 5 mm TCI cryogenic probe. A constant temperature of 35 °C was maintained throughout the experiments. High precision 3 mm NMR tubes were used at all times.

The NMR data was processed using the NMRPipe software. The CCPN software (V2) containing the CcpNmr Analysis plugin was used in the data analysis, which involve both automatic analysis and manual inspection of the trajectories of the shifting peaks.

Table S3. Concentrations of the CcrA, and **4**, **5** and **6**, respectively, which were used in the titration experiments.

	Compound	**4**	**5**	**6**
	CcrA	C (mM)		
		0.25	0.15	0.20
Titration step	0	0	0	0
	1	0.031	0.029	0.050
	2	0.062	0.059	0.099
	3	0.124	0.088	0.148
	4	0.247	0.117	0.196
	5	0.495	0.145	
	6		0.213	
Final ratio CcrA:compound		1:2	1:1.4	1:1

The weighted average chemical shift perturbations (CSP) for the backbone amides were calculated from the observed chemical shift differences in the proton and nitrogen dimensions from equation 1, where the chemical shift scaling factor R_{scale} is 6.5.[4-5] The data is presented in Table S4–Table S6 and as histograms in Figure 3. If CSP data is missing there was no difference observed, or the analysis of the residue was prevented (i.e. it was overlapped, missing, or as in the case of prolyl residues, it was lacking a backbone amide proton). A CSP larger than the population mean (μ) plus one standard deviation (1σ) is considered as a significant chemical shift perturbation (SCSP).[5] Assigned $^{1}H,^{15}N$ HSQC spectra are shown in Figure S2–Figure **S11**.

Eqn. 1: $CSP = \Delta\delta(^{1}H, ^{15}N) = \sqrt{(\Delta\delta(^{1}H)^2 + ((1/R_{scale} \times \Delta\delta(^{15}N))^2)}$

Dissociation constants (K_d) and $\Delta\delta_{max}$ were obtained by least square fitting of the observed chemical shift differences ($\Delta\delta_{obs}$) and related total ligand concentrations ($[L]_t$) to equation 2, where $[P]_t$ corresponds to the total concentration of CcrA.[5] Fast exchange was observed for **4** and **5**, and slow exchange for **6** (described in 2.2.1). Thus, K_d values were only calculated for **4** and **5** using this method. In these calculation, the dissociation constants of the significantly shifted active site residues identified via the CSP and the direction of CSP analyses (described in 2.2.2) were included.

Eqn. 2: $\Delta\delta_{obs} = \Delta\delta_{max}(([P]_t + [L]_t + K_d) - (([P]_t + [L]_t + K_d)^2 - 4[P]_t[L]_t)^{1/2})/2[P]_t$

2.2.1 $^{1}H,^{15}N$ HSQC titration experiments of 6

The step-wise chemical shift changes observed in the titration series of **4** and **5** is characteristic for fast exchange processes (Figure S3, Figure **S4**, and Figure **S6**−Figure **S9**).[5-6] From the starting point, corresponding to the free form of CcrA, the ^{1}H and ^{15}N chemical shifts of the majority of the amino acid residues were changing gradually upon addition of the ligands. The chemical shifts at each titration point represent the average of the free and bound forms of CcrA. For **6**, on the other hand, the peaks of the free form were still observed in the first titration point, together with a new set of peaks representing the bound form (Figure S5, Figure **S10** and Figure **S11**). This type of transitions between a decreasing free form and an increasing bound form, appearing as two separate peaks in the NMR spectra, is characteristic for slow exchange processes. The resonances of the bound form were assigned using the qualitative 'minimum chemical shift approach', in which the unassigned peak closest to the peak of the free form is identified and assigned to corresponding bound form.[5, 7-8] Also the disappearance of the peaks of the free form and the appearance of the peaks of the bound form in the spectra were inspected.

In Figure S1, a section of the full spectra is zoomed to show the free form, the individual titration steps, as well as the transition of the peaks during the titration series. In the first titration step there was a small peak of the free form left, but the main peak was already that belonging to the bound form (cf. Figure S1 a, b and f). In the following titration steps (c.f. Figure S1 c–e and g–i) the peaks of the bound form barely changed and approached a maxima. Due to the fast transition to the complexed state the data only represented the end-points, which prevented the extraction of dissociation constants using equation 2 (vide supra) and the peak integrals as the NMR observable.[5-6, 9] It is the curved region of the titration curve between the end-points that contain the required information on the equilibrium condition. As an alternative, an approximate K_d was derived from equation 3.[9] Based on the NMR data, saturation was assumed to be reached in the last titration step, and the bound fraction of CcrA ($f_{P(bound)}$) was determined from the peak intensity ratio between the first and the last titration steps.[6] The average K_d sample mean and standard deviation calculated using the data for the residues in the L3-L5-L7 binding site showing a significant CSP and a positive K_d value (i.e. Trp32, His82, Cys87, Gly89, His145 and Gly175) was 2.3 ± 0.3 μM.

Eqn. 3: $K_d = [P] \times [L]/[PL] = (1 - f_{P(bound)})/f_{P(bound)} \times ([L]_t - f_{P(bound)}[P]_t)$

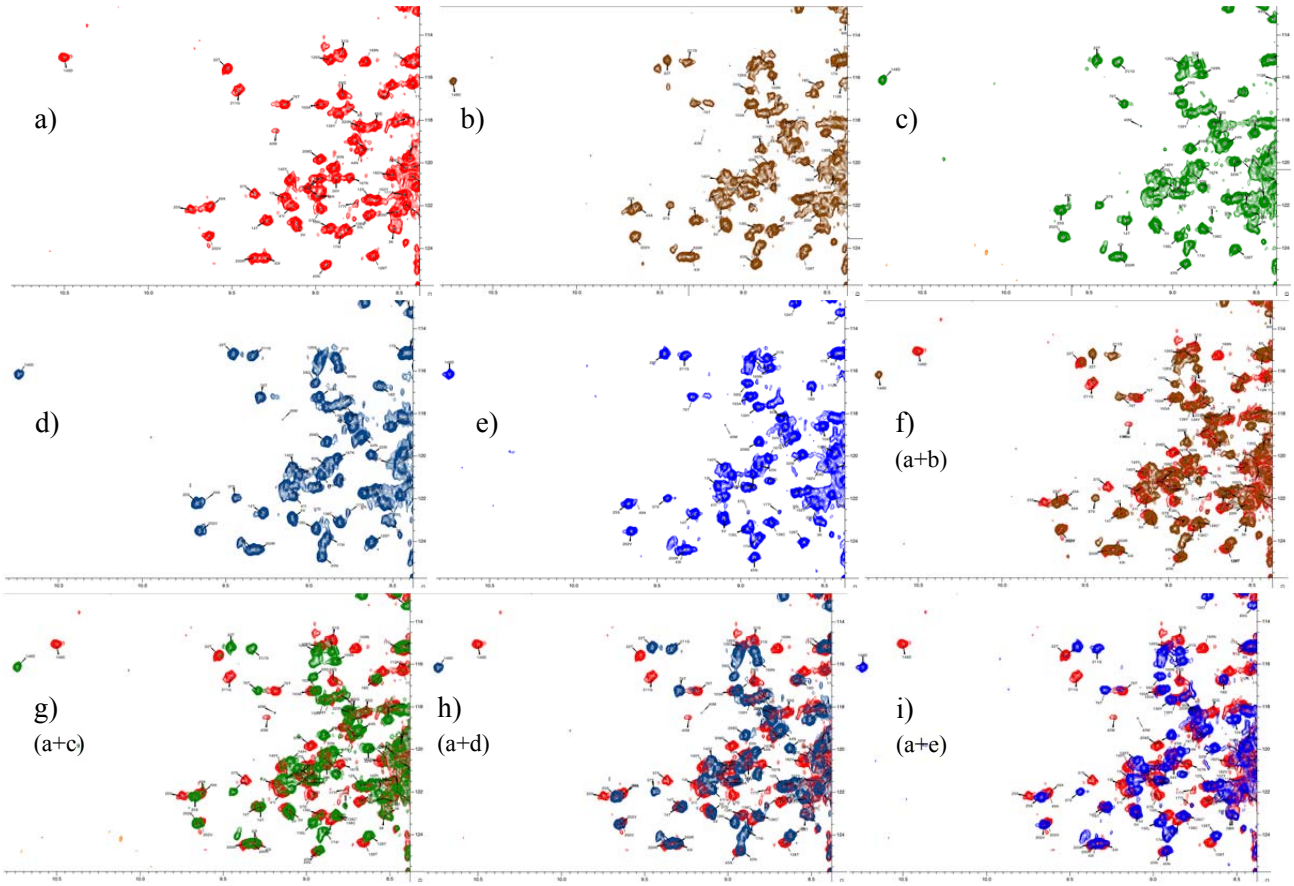


Figure S1. A zoomed region of the $^{1}H,^{15}N$ HSQC spectrum of a) free CcrA and b–e) CcrA bound to 6 in titration steps 1–4, respectively. f–i) Superpositions of a and b–e, respectively.

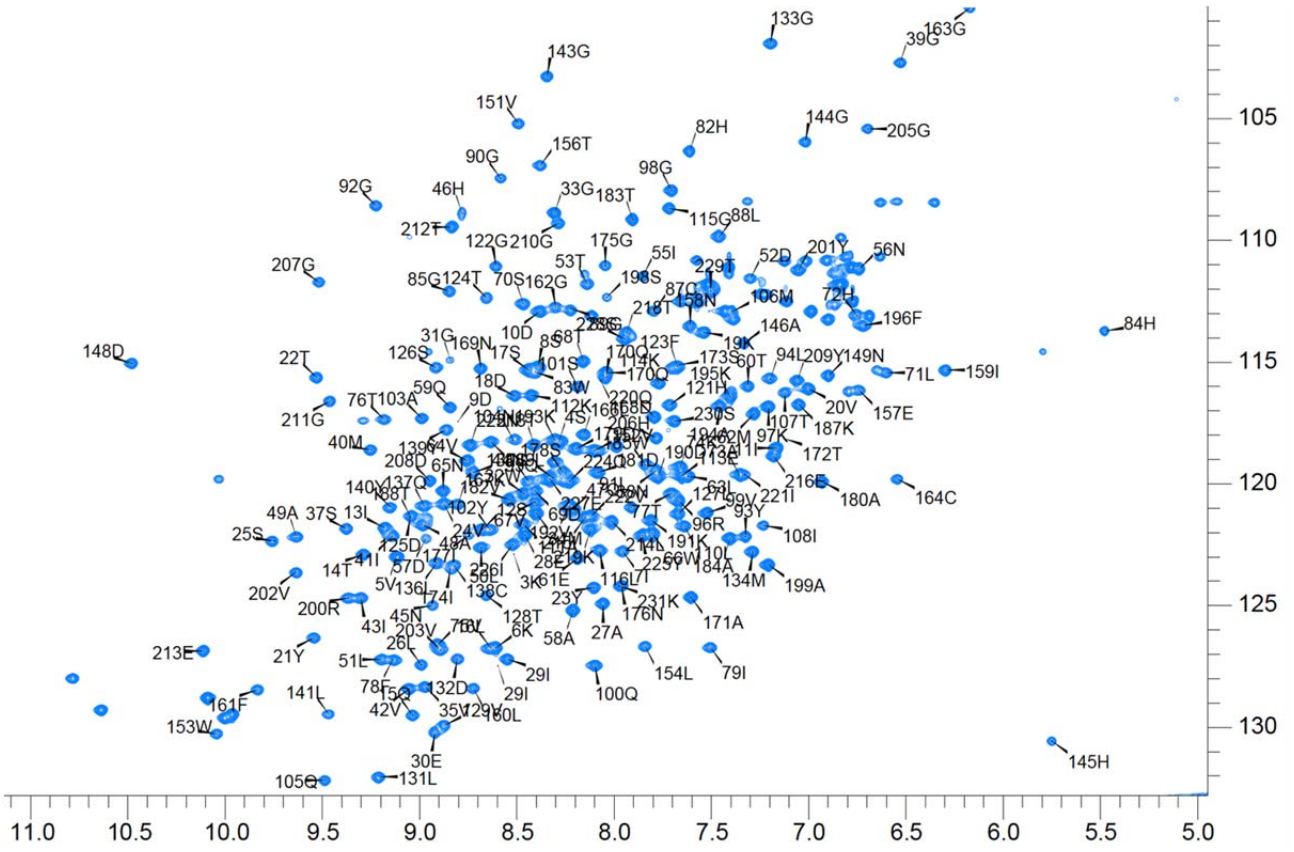


Figure S2. Assigned 800 MHz $^{1}H,^{15}N$ HSQC spectrum of CcrA.

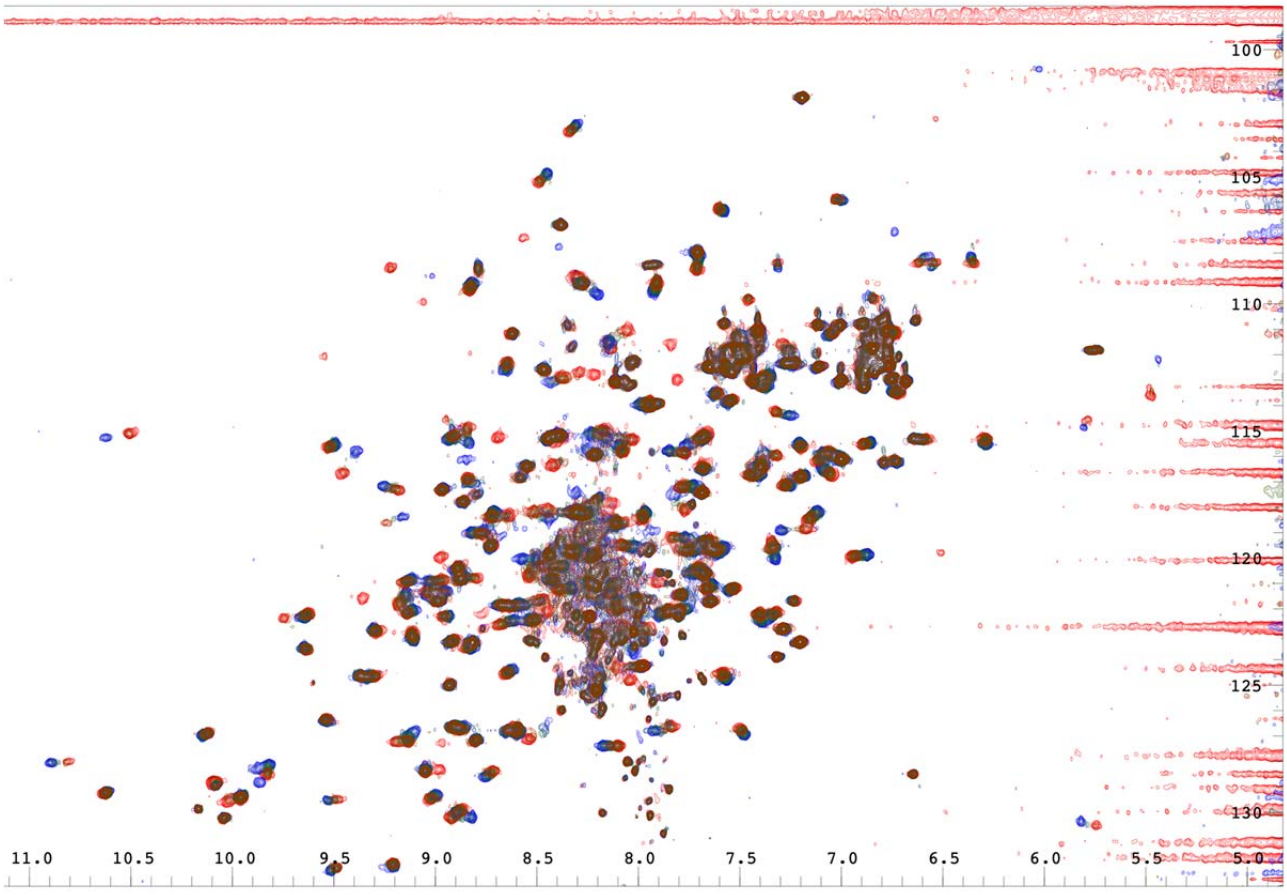


Figure S3. Superposition of the full $^{1}H,^{15}N$ HSQC spectrum of free CcrA (titration step 0 in red), and CcrA bound to **4** (titration steps 1–5, step 5 in blue).

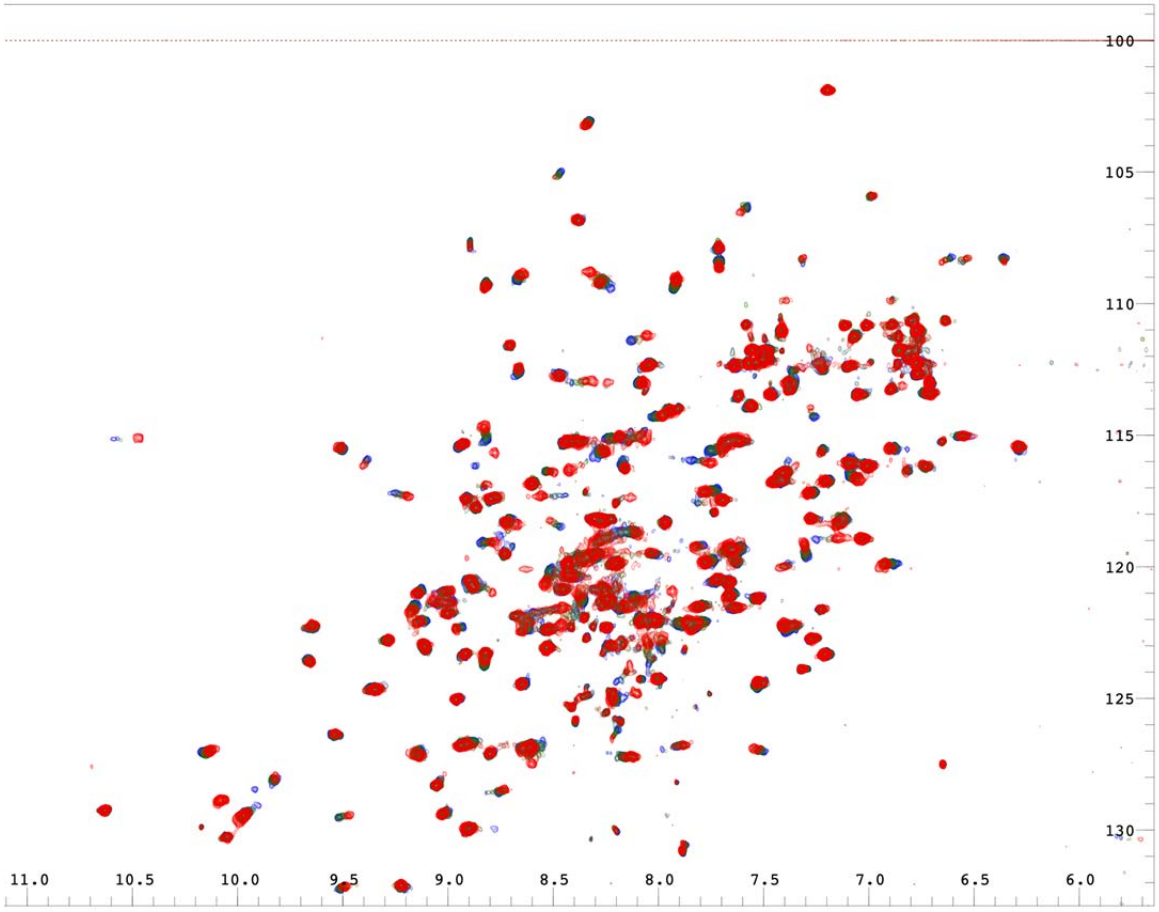


Figure S4. Superposition of the full $^{1}H,^{15}N$ HSQC spectrum of free CcrA (titration step 0 in red), and CcrA bound to **5** (titration steps 1–6, step 6 in blue).

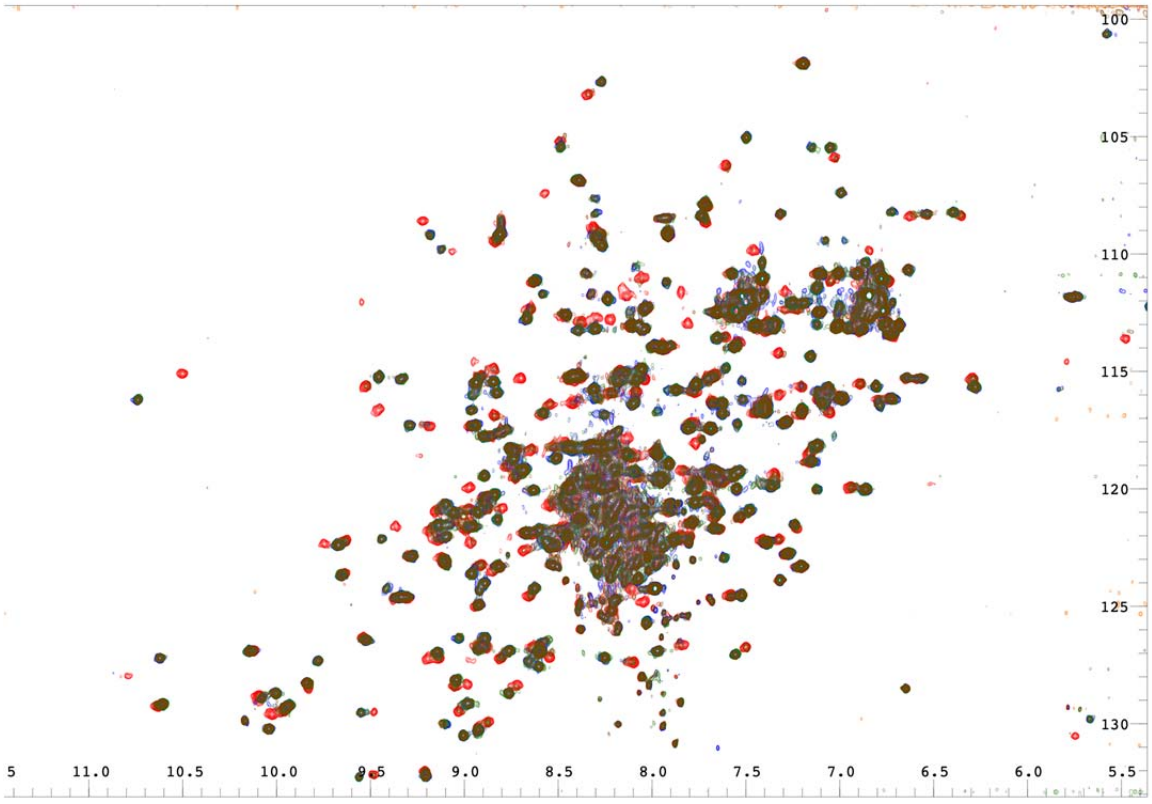


Figure S5. Superposition of the full $^{1}H,^{15}N$ HSQC spectrum of free CcrA (titration step 0 in red), and CcrA bound to **6** (titration steps 1–4, step 4 in blue).

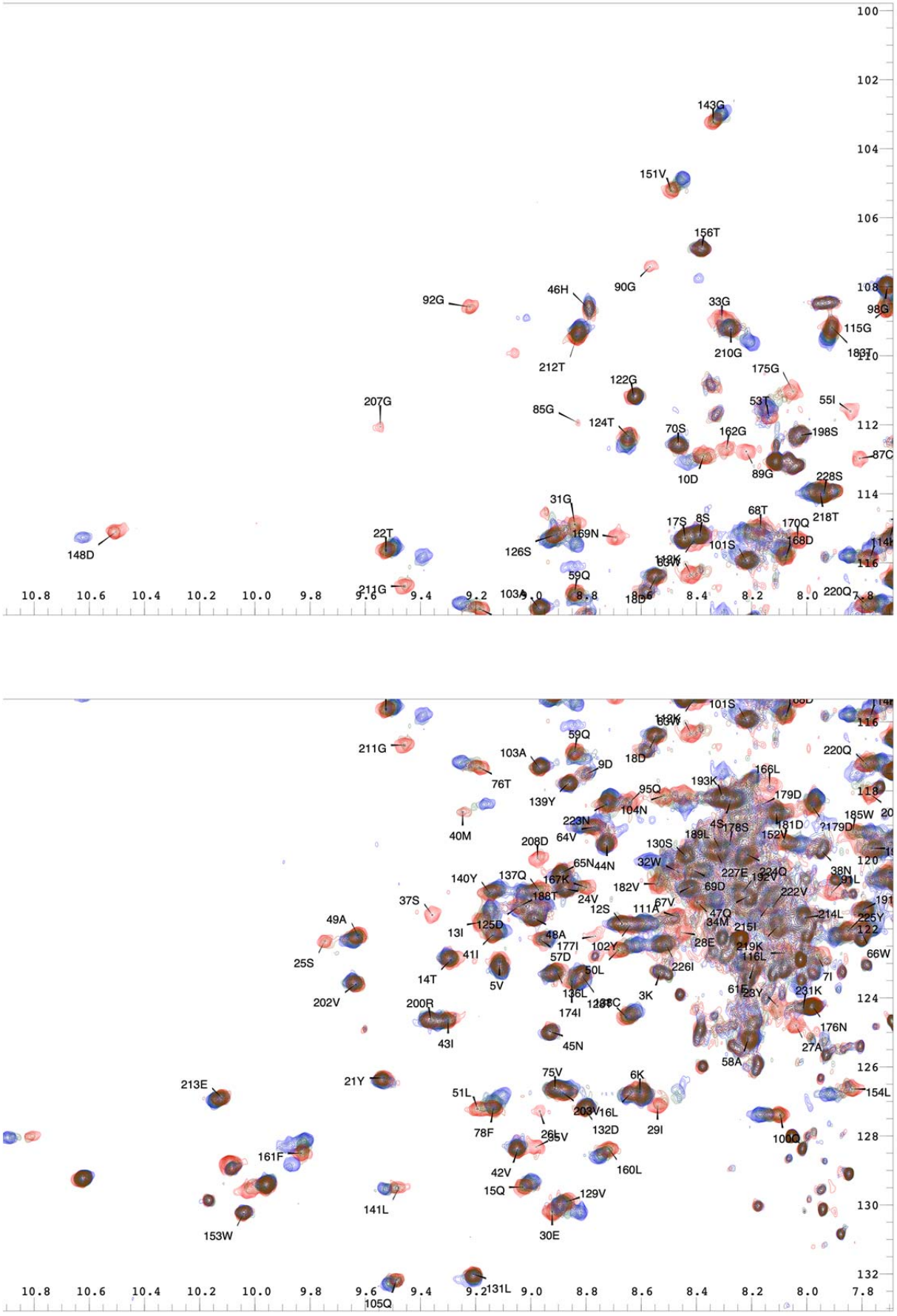


Figure S6. Superposition of zoomed regions of the $^{1}H,^{15}N$ HSQC spectrum (^{1}H 10.7−8.1 ppm vs. ^{15}N 118−100 ppm and ^{15}N 133−115 ppm) of free CcrA (in red), and CcrA bound to **4** (steps 1–5, step 5 in blue).

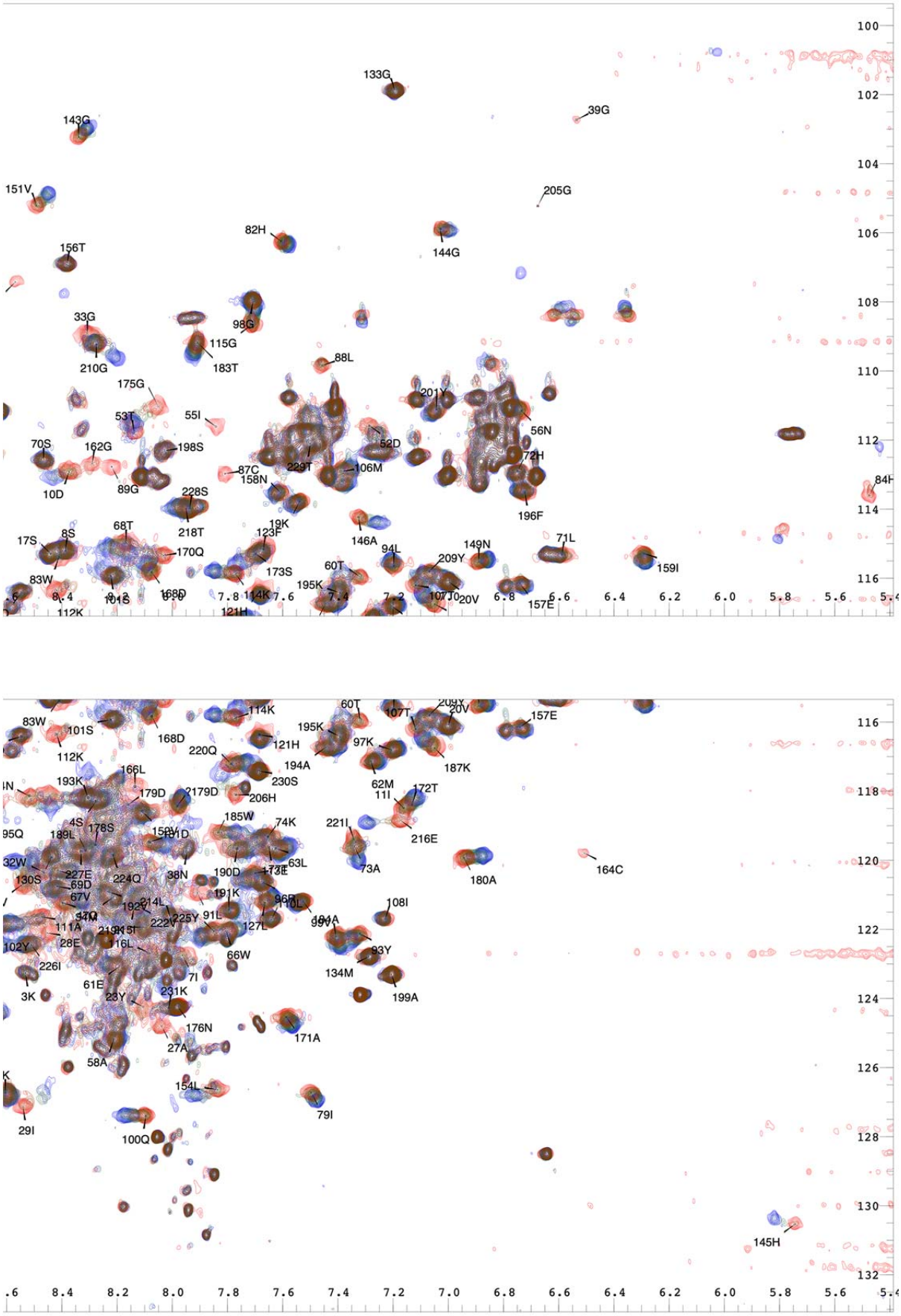


Figure S7. Superposition of zoomed regions of the ^{1}H,^{15}N HSQC spectrum (^{1}H 8.3−5.6 ppm vs. ^{15}N 118−100 ppm and ^{15}N 133−115 ppm) of free CcrA (in red), and CcrA bound to **4** (steps 1–5, step 5 in blue).

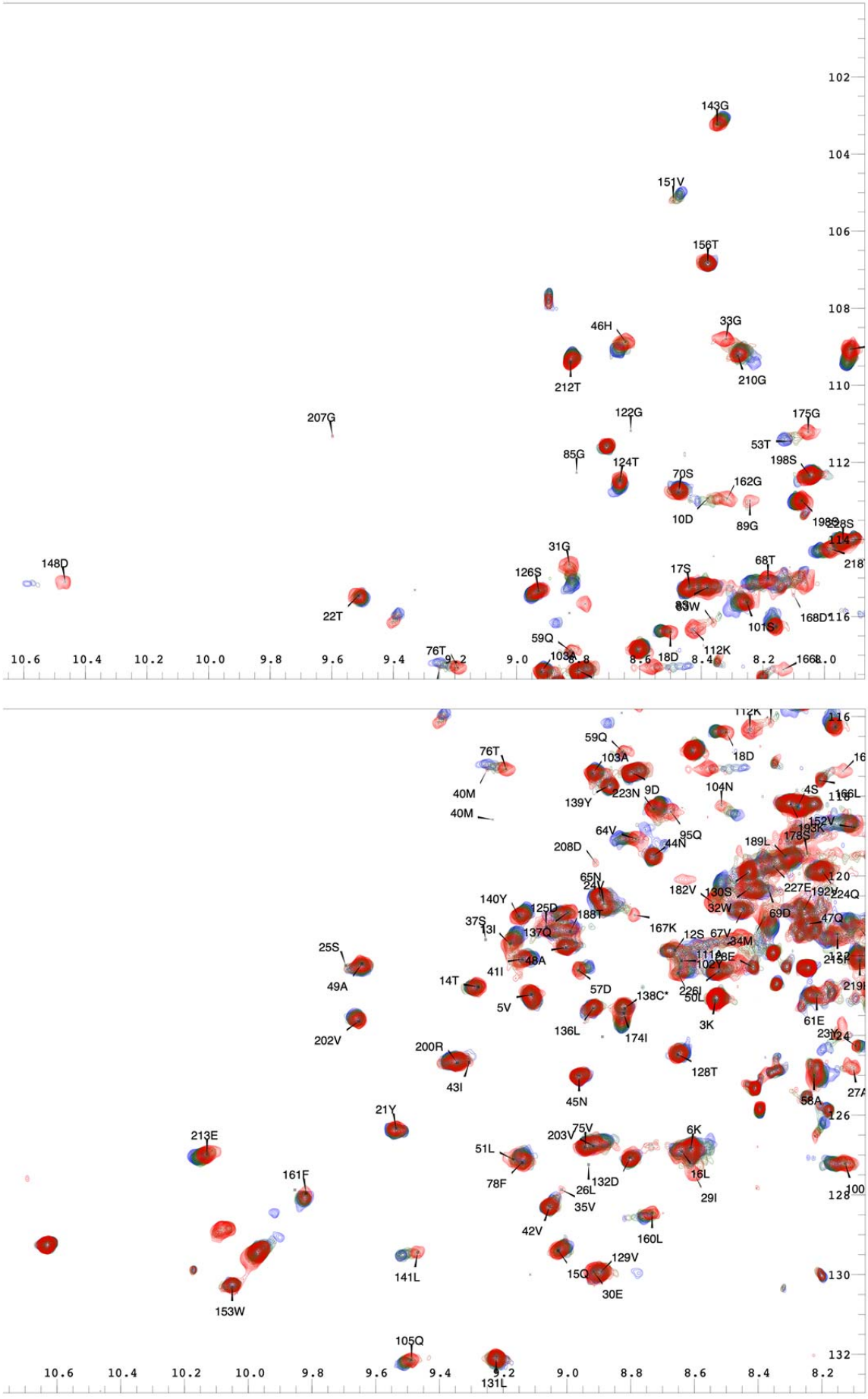


Figure S8. Superposition of zoomed regions of the ^{1}H,^{15}N HSQC spectrum (^{1}H 10.9−7.7 ppm vs. ^{15}N 118−100 ppm and ^{15}N 133−115 ppm) of free CcrA (in red) and CcrA bound to **5** (titration steps 1–6, step 6 in blue).

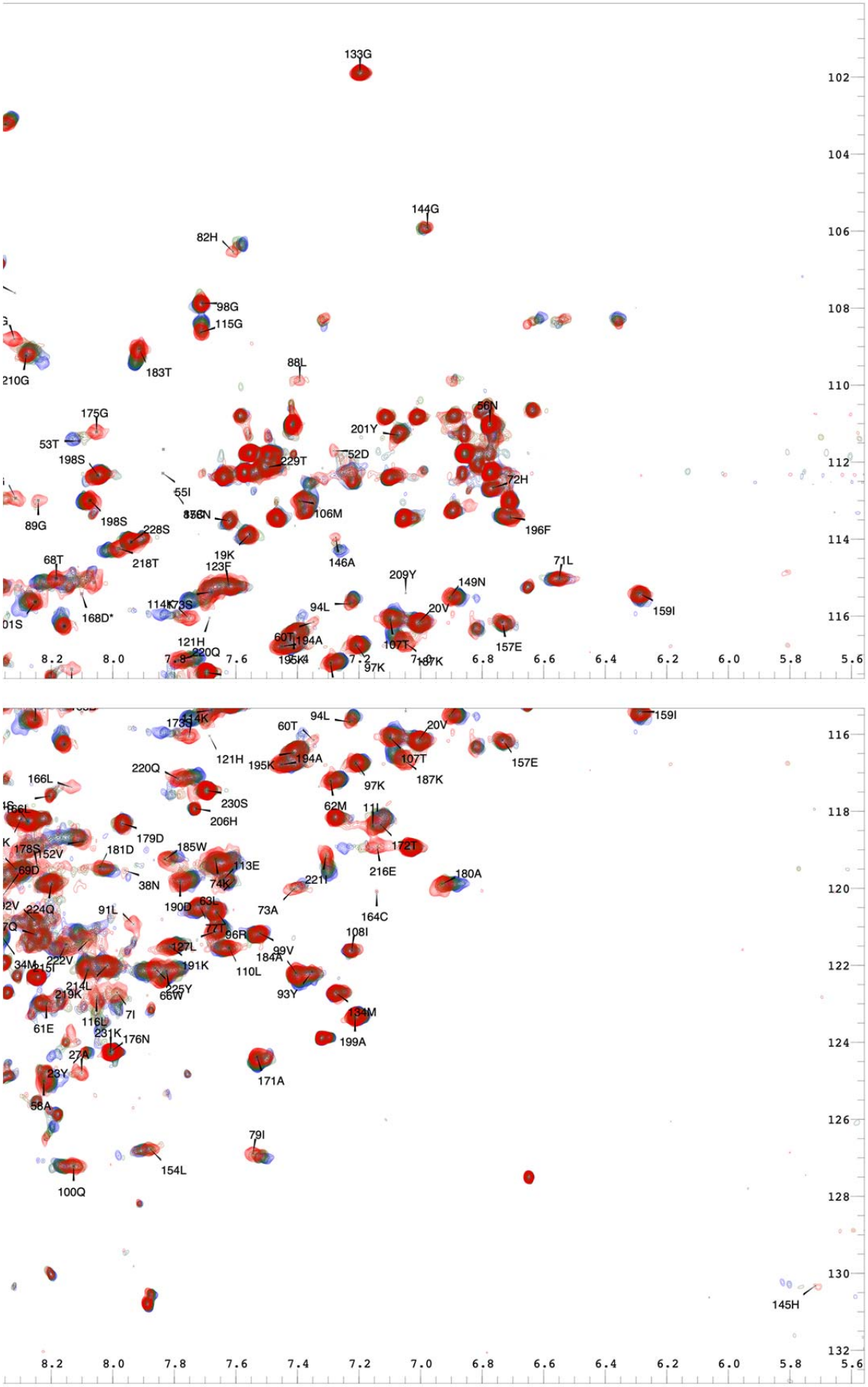
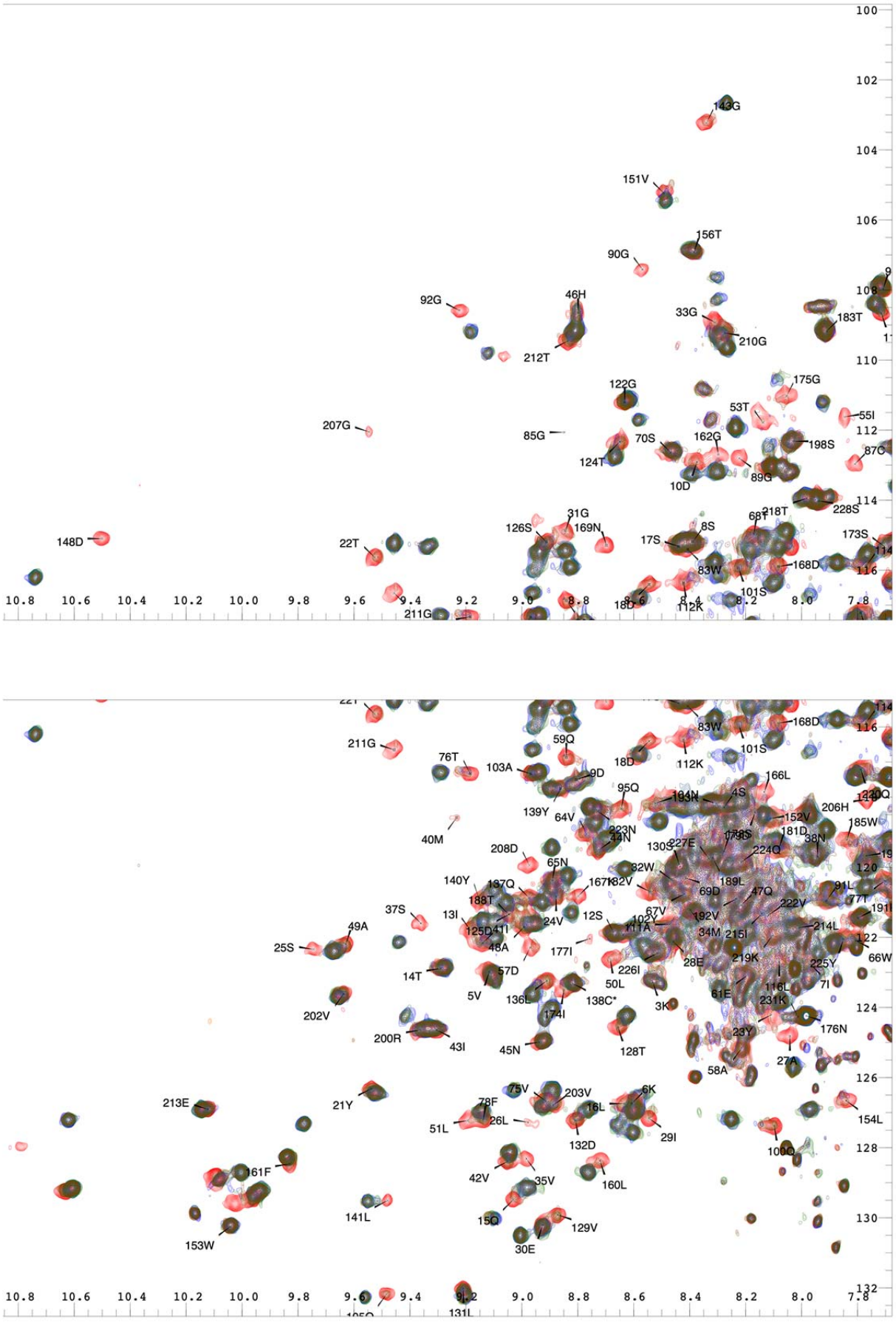
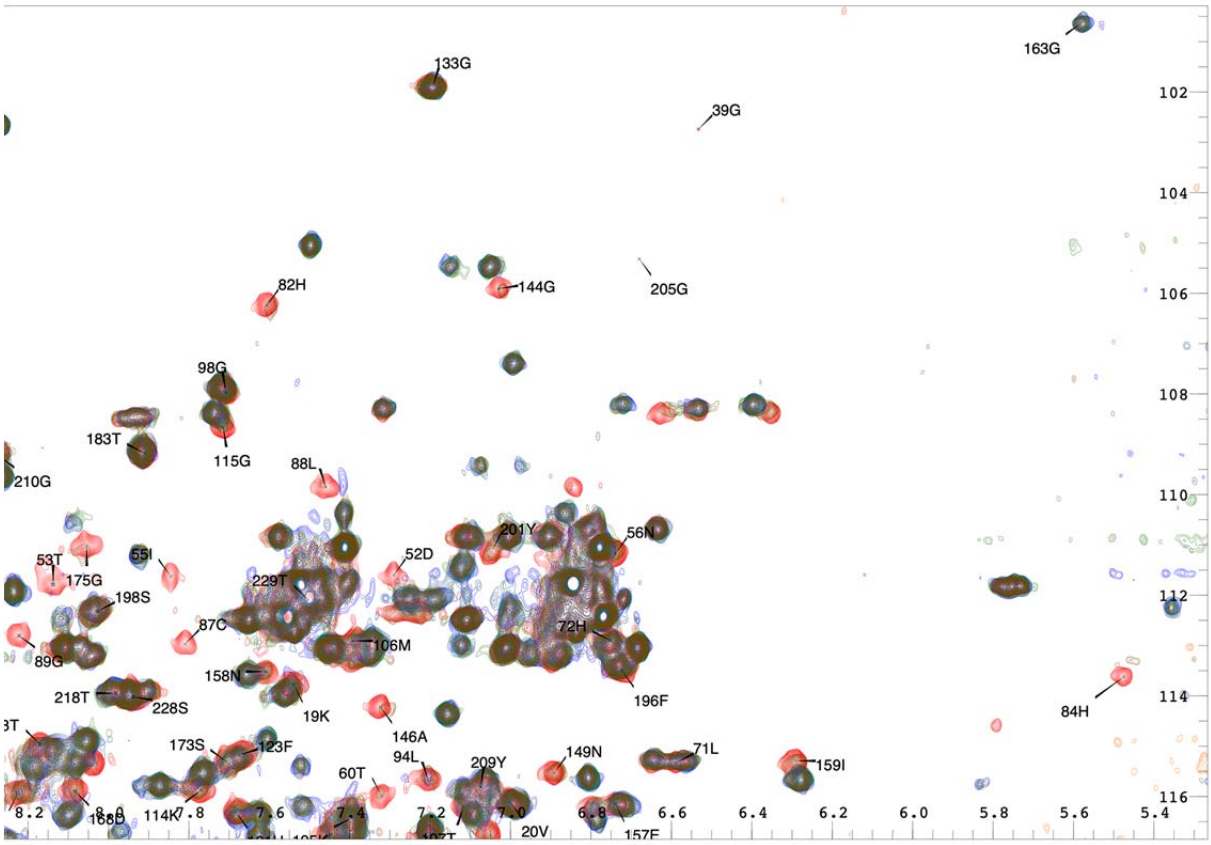


Figure S9. Superposition of zoomed regions of the ^{1}H,^{15}N HSQC spectrum (^{1}H 8.6−5.4 ppm vs. ^{15}N 118−100 ppm and ^{15}N 133−115 ppm) of free CcrA (in red) and CcrA bound to **5** (titration steps 1–6, step 6 in blue).


143G
151V
156T
90G
92G
46H
33G
183T
210G
212T
122G
175G
53T
55I
207G
85G
70S
162G
198S
87G
124T
89G
10D
31G
218T
228S
126S
169N
8S
17S
173S
148D
22T
83W
168D
101S
211G
10.8
10.6
10.4
10.2
10.0
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8

211G
76T
103A
59Q
18D
83W
168D
101S
112K
9D
95Q
166L
139Y
64V
4S
206H
152V
40M
208D
65N
130S
227E
224Q
38N
185W
140Y
167Q
82V
189L
69D
47Q
222V
37S
13I
188T
24V
12S
67V
192V
49A
25S
125D
41I
48A
177I
34M
215I
214L
28E
219K
225Y
66W
14T
57D
226I
50L
7I
5V
136L
138C*
174I
61E
231K
3K
202V
200R
43I
45N
128T
23Y
176N
58A
27A
213E
21Y
75V
203V
6K
78F
16L
154L
51L
26L
132D
29I
100Q
61F
42V
35V
160L
141L
15Q
129V
153W
30E
10.8
10.6
10.4
10.2
10.0
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8

Figure S10. Superposition of zoomed regions of the $^{1}H,^{15}N$ HSQC spectrum (^{1}H 10.8−7.7 ppm vs. ^{15}N 118−100 ppm and ^{15}N 133−115 ppm) of free CcrA (in red) and CcrA bound to **6** (titration steps 1–4, step 4 in blue).



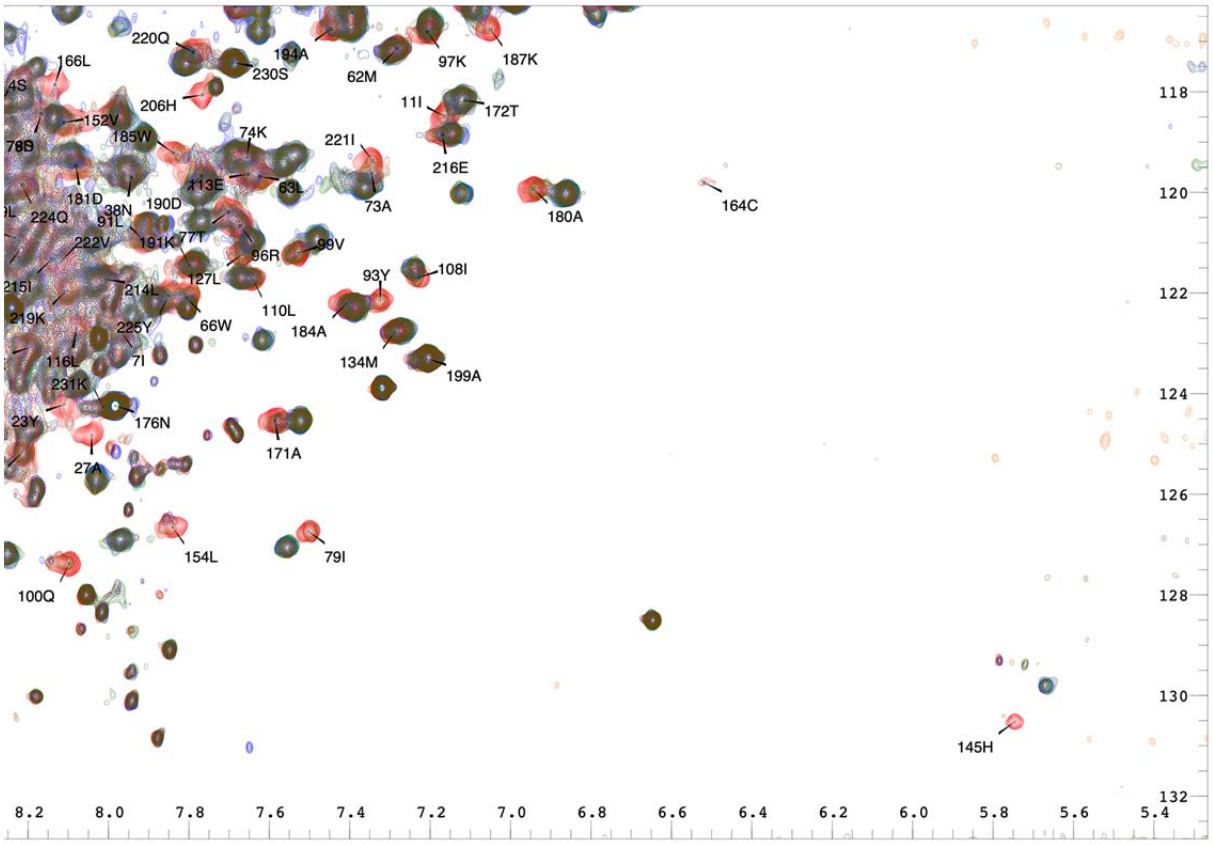


Figure S11. Superposition of zoomed regions of the $^{1}H,^{15}N$ HSQC spectrum (^{1}H 8.3−5.3 ppm vs. ^{15}N 118−100 ppm and ^{15}N 133−115 ppm) of free CcrA (in red) and CcrA bound to **6** (titration steps 1–4, step 4 in blue).

Table S4. Experimental $^{1}H,^{15}N$ HSQC titration data, and related calculated and fitted data for **4**. Residues displaying a significant chemical shift perturbation (i.e. CSP > 0.0938, where μ and 1σ were calculated to 0.0481 and 0.0456, respectively) are presented at the first page, and all other residues are presented thereafter. Active site residues are colored in orange, and those that are more likely to be involved in indirect than in direct interactions are colored in pale orange. The K_d sample mean and standard deviation calculated using the data for the residues showing a significant CSP and representing the L3-L5-L7 binding poses, as well as the whole active site were $K_{d\ L3\text{-}L5\text{-}L7\ site}$ = 11 ± 11 μM and $K_{d\ active\ site}$ = 21 ± 40 μM, respectively.

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)												$\Delta\delta_{final\text{-}initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^{1}H_{initial}$	$^{1}H_{Step1}$	$^{1}H_{Step2}$	$^{1}H_{Step3}$	$^{1}H_{Step4}$	$^{1}H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{final}$	$\Delta^{1}H$	$\Delta^{15}N$	$\Delta^{1}H,^{15}N$	μ + 1σ		
			Leu26	8.9675		8.9648	9.0129	9.0017	8.9780	127.2824		127.2128	126.9906	126.7499	126.5860	0.0105	-0.6964	0.1077	0.0938		
L3		61	Ile29	8.5409					8.4482	127.1389					126.4855	-0.0927	-0.6534	0.1367	0.0938	2.81E-05	0.1632
L3		62	Glu30	8.9226	8.9184	8.9054	8.8308	8.8254	8.8190	130.1999	130.2179	130.1517	130.1517	130.2073	130.1941	-0.1036	-0.0059	0.1036	0.0938	6.36E-06	0.1305
L3		64	Trp32	8.4662	8.4703	8.4977	8.5161	8.5669	8.5755	120.3493	120.2996	120.3142	120.2402	120.0601	120.0270	0.1093	-0.3223	0.1200	0.0938	1.84E-06	0.1244
L3		65	Gly33	8.3075	8.2945	8.2874	8.2453	8.2110	8.2002	108.9241	109.0331	109.1688	109.3688	109.5679	109.6367	-0.1073	0.7126	0.1534	0.0938	4.76E-06	0.1630
L3		67	Val35	8.9808	8.9821	9.0051	9.0116	9.0586	9.0512	128.3195	128.5854	128.9517	129.1945	129.4135	129.4583	0.0705	1.1388	0.1888	0.0938	3.90E-06	0.2296
L3		69	Ser37	9.3571					9.3489	121.5997					122.8785	-0.0082	1.2788	0.1969	0.0938	2.95E-06	0.2176
			Leu51	9.1932	9.1757	9.1662	9.1312	9.1228	9.0982	127.2246	127.1931	127.1472	127.0757	126.9808	126.7906	-0.0950	-0.4340	0.1161	0.0938	5.32E-05	0.1434
L7		117	Trp83	8.4108			8.2670	8.2634	8.2480	115.3771			115.6097	115.7989	115.7125	-0.1628	0.3354	0.1708	0.0938	6.48E-06	0.2165
L7	Z1	118	His84	5.4751	5.4716			5.4359	5.4390	113.6037	113.4762			112.4046	112.2004	-0.0361	-1.4033	0.2189	0.0938	8.97E-06	0.2215
>L7		123	Gly89	8.2196	8.2309	8.2713	8.3144	8.3609	8.4077	112.7715	112.7162	112.8186	112.9398	112.9883	113.0422	0.1881	0.2707	0.1926	0.0938	3.07E-05	0.2222
			Gly90	8.5686	8.5577	8.5532	8.5556	8.4630	8.3914	107.4260	107.5317	107.4887	107.3818	107.6971	107.7602	-0.1773	0.3341	0.1846	0.0938	1.43E-03	0.9570
			Asn104	8.5178	8.5103	8.4968	8.4732	8.4479	8.4381	118.1388	118.1803	118.2658	118.3421	118.4065	118.4869	-0.0798	0.3481	0.0961	0.0938	1.16E-05	0.1036
			Asp148	10.5039	10.5150	10.5258	10.5552	10.6123	10.6234	115.1060	115.1046	115.1479	115.0956	115.2661	115.2644	0.1196	0.1583	0.1220	0.0938	1.07E-06	0.1246
			Gly162	8.2903	8.2981	8.3919	8.4054	8.4333	8.4330	112.6811	112.8069	112.9802	112.9587	113.0233	113.1257	0.1427	0.4446	0.1582	0.0938	7.08E-06	0.2044
L10		226	Asn169	8.6923	8.6950	8.7001	8.8058	8.8396	8.8514	115.2621	115.3302	115.3318	116.0870	116.0699	116.1256	0.1591	0.8636	0.2073	0.0938	1.27E-05	0.2533
L10		227	Gln170	8.0331	8.0420	8.0690	8.1453	8.1480	8.1624	115.3436	115.3237	115.3414	115.1138	115.2825	115.2634	0.1293	-0.0802	0.1299	0.0938	4.74E-06	0.1730
L10		229	Thr172	7.1318	7.1161	7.1018	7.0930	7.0697	7.0264	118.3882	118.2629	118.1760	118.0877	118.0104	117.7592	-0.1054	-0.6290	0.1431	0.0938	1.62E-04	0.2107
L10		232	Gly175	8.0502	8.0643	8.0797	8.1016	8.1393	8.1474	111.0383	111.1136	111.2535	111.3502	111.4617	111.5335	0.0972	0.4952	0.1235	0.0938	6.48E-06	0.1329
L10		235	Ser178	8.2788	8.2596	8.2516	8.2131	8.1937	8.1697	119.5540	119.6505	119.6240	119.4570	119.3914	119.3720	-0.1091	-0.1820	0.1126	0.0938	1.57E-05	0.1368
L10		239	Val182	8.5416	8.5354	8.5280	8.5158	8.5053	8.5012	120.6946	120.6345	120.5145	120.2628	120.0946	120.0339	-0.0404	-0.6607	0.1094	0.0938	4.76E-06	0.1144
L12	Z2	263	His206	7.7695	7.7757	7.7832	7.8102	7.8095	7.8151	118.1046	118.0683	117.9923	117.8306	117.5736	117.4771	0.0457	-0.6275	0.1068	0.0938	6.99E-06	0.1145
L12		265	Asp208	8.9759	8.9599	8.8438	8.8100	8.7921	8.7656	119.9623	119.8942	119.6435	119.7140	119.5854	119.4957	-0.2104	-0.4666	0.2223	0.0938	1.31E-05	0.2752
			Gly211	9.4583	9.4550	9.4436	9.4391	9.3958	9.3911	116.6772	116.6249	116.5040	116.1239	115.9121	115.7977	-0.0672	-0.8796	0.1511	0.0938	4.11E-06	0.1606
			Ile221	7.3429	7.3404	7.3356	7.3331	7.3254	7.3245	119.3942	119.5204	119.5888	119.7243	119.9672	120.0420	-0.0184	0.6478	0.1013	0.0938	6.77E-06	0.1042

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)												$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
			Lys3	8.5319	8.5256	8.5293	8.5280	8.5269	8.5264	123.2673	123.2593	123.2715	123.2798	123.2695	123.2608	-0.0055	-0.0065	0.0056	0.0938	7.14E-07	0.0186
			Ser4	8.2759	8.2718	8.2668	8.2611	8.2544	8.2504	118.2903	118.2823	118.2721	118.2618	118.2284	118.2226	-0.0255	-0.0678	0.0276	0.0938	1.11E-05	0.0300
			Val5	9.1140	9.1150	9.1136	9.1142	9.1139	9.1138	122.9661	122.9960	123.0205	123.0731	123.1153	123.1225	-0.0003	0.1563	0.0240	0.0938	1.27E-05	0.0284
			Lys6	8.6048	8.6020	8.5985	8.5947	8.5909	8.5892	126.7234	126.7422	126.7546	126.7837	126.8142	126.8241	-0.0156	0.1008	0.0220	0.0938	6.20E-06	0.0237
			Ile7	7.9629	7.9628	7.9667	7.9764	7.9728	7.9744	122.7498	122.8141	122.9041	123.0026	123.2427	123.2607	0.0115	0.5109	0.0794	0.0938	2.04E-06	0.0823
			Ser8	8.3879	8.3890	8.3899	8.3921	8.3965	8.3979	115.1988	115.1940	115.1828	115.1724	115.1678	115.1594	0.0100	-0.0394	0.0117	0.0938	1.12E-05	0.0128
			Asp9	8.7982	8.8059	8.8013	8.7901	8.7985	8.7784	117.5173	117.5011	117.5103	117.4954	117.4674	117.4502	-0.0198	-0.0671	0.0223	0.0938	1.44E-04	0.0774
			Asp10	8.3741	8.3784	8.3740	8.3545	8.3370	8.3309	112.9080	112.9265	112.9290	112.9398	112.8617	112.9668	-0.0432	0.0588	0.0441	0.0938	7.89E-05	0.0845
			Ile11	7.1617	7.1561	7.1503	7.1367	7.1217	7.1182	118.4876	118.4484	118.3978	118.3179	118.2195	118.1875	-0.0435	-0.3001	0.0635	0.0938	4.40E-06	0.0656
			Ser12	8.6698	8.6717	8.6735	8.6808	8.6792	8.6855	121.8510	121.8657	121.8448	121.8360	121.8549	121.8575	0.0157	0.0065	0.0158	0.0938	3.14E-05	0.0266
			Ile13	9.1836	9.1749	9.1687	9.1591	9.1464	9.1433	121.8131	121.7670	121.7145	121.5533	121.4584	121.4022	-0.0403	-0.4109	0.0750	0.0938	6.95E-06	0.0803
			Thr14	9.2902	9.2906	9.2899	9.2966	9.3015	9.3028	122.9015	122.8848	122.8665	122.8612	122.8246	122.8118	0.0125	-0.0897	0.0186	0.0938	4.76E-06	0.0225
			Gln15	9.0306	9.0250	9.0184	9.0108	9.0002	8.9980	129.4852	129.4643	129.4414	129.3713	129.3428	129.3161	-0.0326	-0.1691	0.0417	0.0938	6.43E-06	0.0461
			Leu16	8.6347	8.6347	8.6347	8.6490	8.6508	8.6539	126.7466	126.7466	126.7466	126.8114	126.8300	126.8558	0.0193	0.1092	0.0256	0.0938	1.02E-05	0.0263
			Ser17	8.4401	8.4409	8.4408	8.4441	8.4476	8.4489	115.2956	115.2946	115.2994	115.3148	115.3235	115.3331	0.0089	0.0375	0.0106	0.0938	1.29E-05	0.0117
			Asp18	8.5467					8.5514	116.4129					116.3749	0.0047	-0.0381	0.0075	0.0938	1.42E-05	0.0161
			Lys19	7.5389	7.5428	7.5426	7.5491	7.5554	7.5554	113.7791	113.7811	113.7971	113.8210	113.8428	113.8428	0.0164	0.0637	0.0191	0.0938	7.95E-06	0.0242
			Val20	7.0003	7.0002	6.9993	7.0007	7.0023	7.0028	116.0928	116.1001	116.1027	116.1068	116.1154	116.1108	0.0025	0.0180	0.0037	0.0938	8.68E-06	0.0070
			Tyr21	9.5351	9.5351	9.5379	9.5379	9.5432	9.5420	126.3223	126.3223	126.3466	126.3466	126.4000	126.4112	0.0069	0.0888	0.0153	0.0938	5.13E-06	0.0156
			Thr22	9.5254	9.5204	9.5146	9.5042	9.4963	9.4936	115.6375	115.6287	115.6231	115.5782	115.5352	115.5263	-0.0318	-0.1112	0.0361	0.0938	4.33E-06	0.0391
			Tyr23	8.1055	8.1129	8.1129	8.1129	8.1129	8.1129	124.2430	124.2905	124.2905	124.2905	124.2905	124.2905	0.0075	0.0475	0.0104	0.0938	2.03E-05	0.0155
			Val24	8.8762	8.8761	8.8742	8.8734	8.8695	8.8726	120.8474	120.8536	120.8458	120.8273	120.7894	120.7674	-0.0036	-0.0800	0.0128	0.0938	1.78E-04	0.0270
			Ser25	9.7466					9.6863	122.3473					122.7511	-0.0602	0.4037	0.0865	0.0938	5.37E-06	0.1145
L3		59	Ala27	8.0387					8.0517	124.7999					124.8400	0.0130	0.0401	0.0144	0.0938	5.88E-06	0.1018
L3		60	Glu28	8.4534	8.4455	8.4803	8.4928	8.4967	8.5045	122.1025	122.0289	122.3413	122.4148	122.3993	122.4083	0.0511	0.3058	0.0695	0.0938	9.73E-06	0.1239
L3		63	Gly31	8.8412	8.8434	8.8436	8.8394	8.8371	8.8346	114.8804	114.9473	115.0319	115.1977	115.3974	115.4793	-0.0065	0.5989	0.0924	0.0938	8.31E-06	0.0945
L3		66	Met34	8.3966	8.3895	8.3807	8.3481	8.3302	8.3214	121.2299	121.2318	121.2170	121.1917	121.1839	121.1579	-0.0752	-0.0719	0.0760	0.0938	6.32E-06	0.0806
L3		68	Pro36																		
			Asn38	7.9468					7.9476	119.7430					119.7422	0.0007	-0.0008	0.0007	0.0938	9.72E-06	0.0124
			Gly39	6.5356						102.7295											
			Met40	9.2471	9.2429	9.2327	9.2060	9.1706	9.1626	118.6171	118.6016	118.5634	118.4612	118.3957	118.3646	-0.0845	-0.2525	0.0930	0.0938	2.48E-06	0.0925
			Ile41	9.1390	9.1377	9.1346	9.1211	9.1141	9.1103	122.1769	122.1661	122.1383	122.0997	122.0523	122.0310	-0.0287	-0.1459	0.0364	0.0938	6.49E-06	0.0382
			Val42	9.0482	9.0483	9.0482	9.0499	9.0499	9.0518	128.4050	128.4032	128.3912	128.3576	128.3291	128.3179	0.0036	-0.0872	0.0139	0.0938	1.26E-05	0.0146
			Ile43	9.2997	9.3050	9.3076	9.3183	9.3314	9.3343	124.6423	124.6500	124.6586	124.6699	124.6811	124.6971	0.0346	0.0548	0.0356	0.0938	4.58E-06	0.0370
			Asn44	8.7244	8.7248	8.7251	8.7275	8.7306	8.7319	119.5010	119.5120	119.5239	119.5468	119.5432	119.5560	0.0076	0.0549	0.0113	0.0938	1.34E-05	0.0142
			Asn45	8.9302	8.9333	8.9306	8.9320	8.9303	8.9316	124.9789	124.9948	124.9910	125.0085	125.0318	125.0229	0.0013	0.0439	0.0069	0.0938	9.17E-06	0.0171
			His46	8.7917					8.7876	108.6323					108.5524	-0.0041	-0.0799	0.0130	0.0938	2.73E-06	0.0305
			Gln47	8.2125	8.2110	8.2087	8.2075	8.2071	8.2059	121.0582	121.0708	121.0812	121.1009	121.1047	121.0982	-0.0067	0.0400	0.0091	0.0938	1.38E-05	0.0125
			Ala48	8.9885	8.9874	8.9876	8.9841	8.9837	8.9845	121.6942	121.6799	121.6830	121.6710	121.6721	121.6685	-0.0040	-0.0257	0.0056	0.0938	1.05E-05	0.0096

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)												$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
			Ala49	9.6268	9.6296	9.6322	9.6372	9.6454	9.6471	122.1850	122.2041	122.2274	122.2717	122.3003	122.3174	0.0203	0.1324	0.0288	0.0938	5.63E-06	0.0305
			Leu50	8.6824	8.6767	8.6698	8.6953	8.6838	8.6717	122.6182	122.6030	122.5785	122.5702	122.5157	122.5409	-0.0107	-0.0774	0.0160	0.0938	1.47E-05	0.0709
			Asp52	7.2866	7.2751	7.2751	7.2751	7.2751	7.2751	111.5786	111.7014	111.7014	111.7014	111.7014	111.7014	-0.0115	0.1229	0.0221	0.0938	2.03E-05	0.0326
			Thr53	8.1374	8.1608	8.1584	8.1640	8.1589	8.1533	111.8000	111.6202	111.6160	111.7267	111.8333	111.9276	0.0158	0.1276	0.0252	0.0938	1.85E-05	0.1018
			Pro54																		
L5		87	Ile55	7.8420	7.8420	7.8420	7.8420	7.8420	7.8420	111.6100	111.6100	111.6100	111.6100	111.6100	111.6100	0.0000	0.0000	0.0000			
			Asn56	6.7350	6.7408	6.7483	6.7638	6.7745	6.7808	111.1513	111.1241	111.1026	111.0720	111.0697	111.0773	0.0458	-0.0740	0.0472	0.0938	8.25E-06	0.0525
			Asp57	8.9681	8.9590	8.9513	8.9450	8.9328	8.9294	122.2934	122.2709	122.2967	122.3209	122.2872	122.2537	-0.0387	-0.0397	0.0392	0.0938	1.06E-05	0.0491
			Ala58	8.2124	8.2088	8.2063	8.2063	8.1963	8.1957	125.1857	125.1865	125.1793	125.1793	125.1642	125.1591	-0.0167	-0.0266	0.0172	0.0938	1.27E-07	0.0171
			Gln59	8.8411	8.8414	8.8420	8.8446	8.8472	8.8414	116.8580	116.8974	116.9089	116.9768	117.0406	117.0302	0.0003	0.1722	0.0265	0.0938	1.49E-05	0.0365
			Thr60	7.3191	7.3225	7.3274	7.3415	7.3588	7.3722	115.9676	115.9510	115.9643	115.9214	115.9228	115.8705	0.0531	-0.0971	0.0552	0.0938	9.21E-05	0.0751
			Glu61	8.1917	8.1944	8.1990	8.2172	8.2328	8.2392	123.0746	123.0682	123.0630	123.0267	122.9831	122.9755	0.0475	-0.0991	0.0499	0.0938	5.39E-06	0.0503
			Met62	7.2804	7.2762	7.2710	7.2646	7.2546	7.2522	117.1325	117.1324	117.1353	117.1323	117.1361	117.1379	-0.0282	0.0053	0.0282	0.0938	4.42E-06	0.0298
			Leu63	7.6254	7.6213	7.6180	7.6000	7.5844	7.5775	119.6572	119.6818	119.6806	119.6561	119.5546	119.5961	-0.0479	-0.0611	0.0488	0.0938	1.06E-05	0.0593
			Val64	8.7679	8.7728	8.7812	8.7994	8.8179	8.8246	119.0455	119.0500	119.0407	119.0263	119.0080	119.0024	0.0566	-0.0430	0.0570	0.0938	5.50E-06	0.0589
			Asn65	8.8878	8.8885	8.8885	8.8909	8.8924	8.8927	120.3736	120.3777	120.3921	120.4101	120.4289	120.4355	0.0048	0.0619	0.0107	0.0938	4.48E-06	0.0115
			Trp66	7.8034	7.7991	7.7871	7.7794	7.7567	7.7559	122.0783	122.0689	122.0502	122.0166	121.9850	121.9830	-0.0475	-0.0953	0.0497	0.0938	1.91E-05	0.0593
			Val67	8.4167	8.4163	8.4155	8.4218	8.4249	8.4249	120.7598	120.7684	120.7837	120.8124	120.8265	120.8265	0.0082	0.0667	0.0131	0.0938	2.67E-06	0.0173
			Thr68	8.1672	8.1730	8.1823	8.2119	8.2259	8.2339	114.9753	115.0012	115.0249	115.0744	115.1012	115.1164	0.0667	0.1411	0.0701	0.0938	6.46E-06	0.0751
			Asp69	8.4131	8.4065	8.3977	8.3892	8.3892	8.3892	120.2917	120.3030	120.2986	120.3097	120.3097	120.3097	-0.0239	0.0181	0.0241	0.0938	2.17E-05	0.0345
			Ser70	8.4661	8.4652	8.4652	8.4643	8.4649	8.4655	112.6084	112.6031	112.5861	112.5695	112.5673	112.5502	-0.0006	-0.0582	0.0090	0.0938	2.83E-05	0.0111
			Leu71	6.5884	6.5916	6.5942	6.6018	6.6097	6.6139	115.3195	115.3371	115.3421	115.3453	115.3428	115.3277	0.0255	0.0082	0.0255	0.0938	1.49E-05	0.0290
			His72	6.7498	6.7507	6.7493	6.7521	6.7535	6.7531	112.9035	112.9412	112.9525	112.9638	112.9977	112.9940	0.0033	0.0905	0.0143	0.0938	1.39E-05	0.0209
			Ala73	7.3406					7.3225	119.6001					119.5579	-0.0182	-0.0421	0.0193	0.0938	5.90E-05	0.0494
			Lys74	7.6534	7.6565	7.6597	7.6695	7.6802	7.6822	119.3172	119.3317	119.3445	119.3622	119.4002	119.4142	0.0288	0.0969	0.0325	0.0938	3.05E-06	0.0333
			Val75	8.9123	8.9097	8.9093	8.9081	8.9064	8.9066	126.6542	126.6430	126.6493	126.6255	126.6128	126.6102	-0.0056	-0.0440	0.0088	0.0938	1.01E-05	0.0130
			Thr76	9.1848	9.1920	9.1987	9.2140	9.2501	9.2561	117.3328	117.2979	117.2651	117.2424	117.1896	117.1664	0.0713	-0.1664	0.0757	0.0938	1.67E-06	0.0750
			Thr77	7.6992	7.6990	7.7055	7.7167	7.7268	7.7304	120.3696	120.4195	120.4439	120.5098	120.5723	120.5901	0.0312	0.2205	0.0461	0.0938	5.15E-06	0.0514
			Phe78	9.1366	9.1353	9.1341	9.1328	9.1309	9.1273	127.2256	127.1991	127.1631	127.1021	127.0555	126.9944	-0.0093	-0.2312	0.0368	0.0938	4.27E-05	0.0417
			Ile79	7.4964	7.4929	7.4889	7.4831	7.4772	7.4746	126.7232	126.7583	126.8005	126.8422	126.9299	126.9627	-0.0218	0.2395	0.0428	0.0938	8.88E-06	0.0448
			Pro80																		
			Asp81																		
L7	Z1	116	His82	7.6048	7.6008	7.5960	7.5889	7.5803	7.5762	106.2470	106.2574	106.2754	106.3024	106.3317	106.3421	-0.0286	0.0951	0.0322	0.0938	9.13E-06	0.0341
>L7		119	Gly85	8.8291					8.7864	111.9389					111.9444	-0.0427	0.0055	0.0427			
>L7	Z2	120	Asp86																		
>L7		121	Cys87	7.8085	7.8241	7.8550				112.9734	112.9861	113.0855									
>L7		122	Leu88	7.4570					7.4471	109.8384					109.6507	-0.0099	-0.1877	0.0305	0.0938	9.31E-04	0.1450

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)												$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
			Leu91	7.9096	7.9172	7.9039	7.9008	7.8995	7.8906	120.9449	120.9616	121.0274	121.1184	121.2297	121.1032	-0.0189	0.1583	0.0308	0.0938	4.45E-05	0.0889
			Gly92	9.2203	9.2205	9.2205	9.2155			108.5832	108.6418	108.6418	108.5319						0.0938	2.52E-06	0.0504
			Tyr93	7.3215	7.3235	7.3281	7.3369	7.3469	7.3502	122.1288	122.1577	122.1919	122.2311	122.2965	122.3035	0.0287	0.1748	0.0393	0.0938	3.87E-06	0.0413
			Leu94	7.1971	7.1969	7.2007	7.2044	7.2070	7.1969	115.6404	115.7021	115.5968	115.5483	115.4903	115.7021	-0.0002	0.0617	0.0095	0.0938	1.75E-04	0.1138
			Gln95	8.6404	8.6490	8.6576	8.6491	8.6445	8.6576	118.3276	118.3698	118.3798	118.3426	118.3383	118.3574	0.0172	0.0298	0.0178	0.0938	3.03E-05	0.0549
			Arg96	7.6709	7.6720	7.6732	7.6768	7.6809	7.6820	120.6424	120.6411	120.6349	120.6167	120.5937	120.5893	0.0111	-0.0530	0.0138	0.0938	2.29E-06	0.0138
			Lys97	7.2054	7.2020	7.1990	7.1931	7.1876	7.1832	116.8032	116.7991	116.7950	116.7862	116.7758	116.7737	-0.0223	-0.0295	0.0227	0.0938	1.86E-05	0.0248
			Gly98	7.7075	7.7079	7.7091	7.7111	7.7140	7.7156	107.9620	107.9654	107.9706	107.9828	107.9844	107.9913	0.0081	0.0293	0.0092	0.0938	1.94E-05	0.0102
			Val99	7.5250	7.5274	7.5309	7.5378	7.5449	7.5481	121.1969	121.2016	121.2106	121.2197	121.2336	121.2413	0.0230	0.0445	0.0240	0.0938	8.29E-06	0.0251
			Gln100	8.0953	8.1008	8.1068	8.1343	8.1603	8.1685	127.3867	127.3934	127.3784	127.4015	127.3819	127.3842	0.0732	-0.0025	0.0732	0.0938	3.64E-06	0.0744
			Ser101	8.2223	8.2172	8.2146	8.2141	8.2146	8.2140	115.9369	115.9390	115.9310	115.9206	115.9115	115.9071	-0.0083	-0.0298	0.0095	0.0938	8.79E-06	0.0148
			Tyr102	8.6408	8.6331	8.6123	8.6048	8.5897	8.5968	121.8988	121.8859	121.8487	121.8484	121.8307	121.8425	-0.0439	-0.0563	0.0448	0.0938	9.19E-06	0.0660
			Ala103	8.9716	8.9703	8.9681	8.9659	8.9610	8.9611	117.3203	117.3077	117.3064	117.2859	117.2651	117.2588	-0.0105	-0.0614	0.0141	0.0938	1.36E-06	0.0155
			Gln105	9.4875	9.4860	9.4922	9.5032	9.5150	9.5165	132.1719	132.2000	132.2174	132.2351	132.2754	132.2934	0.0290	0.1215	0.0345	0.0938	3.31E-06	0.0405
			Met106	7.3888	7.3855	7.3762	7.3666	7.3561	7.3510	112.9099	112.8943	112.8772	112.8374	112.8089	112.8103	-0.0379	-0.0996	0.0409	0.0938	7.46E-06	0.0443
			Thr107	7.1186	7.1125	7.1125	7.1011	7.0922	7.0881	116.2042	116.1456	116.1456	115.9958	115.9073	115.8770	-0.0305	-0.3272	0.0589	0.0938	5.08E-06	0.0608
			Ile108	7.2285	7.2291	7.2298	7.2352	7.2353	7.2390	121.6949	121.6843	121.6831	121.7069	121.6811	121.6799	0.0105	-0.0150	0.0107	0.0938	2.52E-05	0.0178
			Asp109																		
			Leu110	7.6409	7.6412	7.6406	7.6409	7.6404	7.6391	121.7131	121.7174	121.7170	121.7009	121.6929	121.6810	-0.0018	-0.0321	0.0053	0.0938	6.25E-05	0.0089
			Ala111	8.4721	8.4812	8.4933	8.4832	8.4921	8.4890	121.6429	121.6884	121.7100	121.6984	121.7068	121.7267	0.0170	0.0838	0.0213	0.0938	8.49E-06	0.0548
			Lys112	8.4190	8.4104	8.3966	8.3817	8.3836	8.3824	116.3514	116.3187	116.2235	116.1440	116.1529	116.2166	-0.0366	-0.1348	0.0420	0.0938	1.41E-05	0.0713
			Glu113	7.6496	7.6419	7.6369	7.6311	7.6138	7.6075	119.6267	119.6289	119.6100	119.6745	119.7529	119.7806	-0.0421	0.1539	0.0483	0.0938	9.85E-06	0.0551
			Lys114	7.7705	7.7763	7.7825	7.8161	7.8427	7.8509	115.8760	115.8672	115.8566	115.8219	115.7915	115.7915	0.0804	-0.0845	0.0814	0.0938	3.06E-06	0.0823
			Gly115	7.7123	7.7106	7.7060	7.7032	7.6971	7.7004	108.6671	108.6198	108.5514	108.3922	108.2536	108.1266	-0.0119	-0.5406	0.0840	0.0938	3.08E-05	0.0929
L8		168	Leu116	8.0819	8.0753	8.0787	8.0793	8.0812	8.0799	122.7001	122.8099	123.1497	123.1497	123.1420	123.1394	-0.0020	0.4393	0.0676	0.0938	2.07E-05	0.1033
			Pro117																		
			Val118																		
			Pro119																		
			Glu120																		
			His121	7.6839	7.6835	7.6832	7.6846	7.6822	7.6812	116.3682	116.4221	116.4593	116.4889	116.5070	116.5365	-0.0027	0.1683	0.0260	0.0938	1.93E-05	0.0315
			Gly122	8.6280	8.6233	8.6208	8.6209	8.6209	8.6197	111.1825	111.1728	111.1711	111.1762	111.1867	111.1827	-0.0083	0.0003	0.0083	0.0938	1.58E-05	0.0136
			Phe123	7.6702	7.6777	7.6800	7.6828	7.6813	7.6813	115.1616	115.2071	115.2416	115.2607	115.2622	115.2622	0.0111	0.1006	0.0191	0.0938	2.33E-05	0.0309
			Thr124	8.6471	8.6474	8.6479	8.6487	8.6518	8.6506	112.3170	112.3731	112.4141	112.4906	112.5601	112.5857	0.0034	0.2686	0.0415	0.0938	6.48E-06	0.0446
			Asp125	9.0455					8.9546	121.3541					121.3040	-0.0908	-0.0501	0.0912	0.0938	4.64E-06	0.0930
			Ser126	8.9090	8.9114	8.9129	8.9191	8.9268	8.9290	115.1825	115.2105	115.2293	115.2740	115.3129	115.3342	0.0200	0.1517	0.0308	0.0938	7.37E-06	0.0323
			Leu127	7.6647	7.6606	7.6549	7.6463	7.6382	7.6350	121.2251	121.1900	121.1647	121.1095	121.0586	121.0308	-0.0296	-0.1944	0.0421	0.0938	7.93E-06	0.0449
			Thr128	8.6539	8.6529	8.6529	8.6399	8.6318	8.6283	124.5567	124.5395	124.5395	124.4961	124.4354	124.4232	-0.0256	-0.1336	0.0328	0.0938	3.29E-06	0.0329
			Val129	8.8690	8.8722	8.8755	8.8822	8.8912	8.8952	129.8992	129.9251	129.9364	129.9569	129.9794	129.9948	0.0262	0.0955	0.0300	0.0938	1.17E-05	0.0323
			Ser130	8.4369	8.4366	8.4343	8.4325	8.4311	8.4292	119.9128	119.9041	119.8939	119.8863	119.8825	119.8796	-0.0077	-0.0331	0.0093	0.0938	1.67E-05	0.0109
			Leu131	9.2085	9.2080	9.2072	9.2074	9.2100	9.2118	132.0083	132.0275	132.0445	132.0738	132.0984	132.1149	0.0033	0.1066	0.0167	0.0938	1.47E-05	0.0191

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)												$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
			Asp132	8.8062	8.8049	8.8022	8.7993	8.7956	8.7963	127.2099	127.2029	127.1915	127.1759	127.1477	127.1412	-0.0099	-0.0687	0.0145	0.0938	1.85E-06	0.0160
			Gly133	7.1930	7.1922	7.1917	7.1933	7.1934	7.1939	101.8917	101.8905	101.8917	101.8914	101.8992	101.8963	0.0009	0.0046	0.0011	0.0938	8.50E-06	0.0049
			Met134	7.2870	7.2868	7.2851	7.2842	7.2839	7.2839	122.7841	122.7882	122.7926	122.7832	122.7906	122.7852	-0.0031	0.0011	0.0031	0.0938	9.76E-06	0.0068
			Pro135																		
			Leu136	8.9079	8.9106	8.9110	8.9188	8.9239	8.9261	123.2251	123.2362	123.2562	123.2712	123.2968	123.3062	0.0182	0.0811	0.0220	0.0938	6.14E-06	0.0246
			Gln137	8.9729	8.9788	8.9794	9.0053	9.0250	9.0298	120.8661	120.8789	120.8892	120.9015	120.9207	120.9259	0.0569	0.0598	0.0576	0.0938	2.07E-06	0.0591
			Cys138	8.8177	8.8160	8.8171	8.8159	8.8186	8.8178	123.3267	123.3166	123.3213	123.3157	123.3291	123.3078	0.0001	-0.0189	0.0029	0.0938	6.38E-05	0.0144
			Tyr139	8.8601	8.8590	8.8614	8.8626	8.8636	8.8652	117.7461	117.7676	117.7657	117.7866	117.8042	117.8139	0.0051	0.0678	0.0116	0.0938	1.49E-05	0.0160
			Tyr140	9.1491	9.1436	9.1396	9.1326	9.1226	9.1180	120.9621	120.9413	120.9184	120.8900	120.8405	120.8220	-0.0311	-0.1401	0.0379	0.0938	1.06E-05	0.0400
			Leu141	9.4779	9.4919	9.4977	9.4977	9.5257	9.5305	129.4984	129.4949	129.5160	129.5160	129.5355	129.5462	0.0527	0.0479	0.0532	0.0938	5.78E-06	0.0555
			Gly142																		
			Gly143	8.3393	8.3341	8.3257	8.3206	8.3076	8.3044	103.2283	103.1938	103.1384	103.0738	102.9949	102.9608	-0.0349	-0.2675	0.0539	0.0938	6.89E-06	0.0571
			Gly144	7.0293	7.0233	7.0203	7.0063	7.0032	6.9974	105.8883	105.9096	105.9102	105.9167	105.9285	105.9500	-0.0319	0.0618	0.0333	0.0938	1.68E-05	0.0382
L9	Z1	196	His145	5.7441	5.7558	5.7669	5.7839	5.8149	5.8193	130.5358	130.5407	130.4638	130.4818	130.3848	130.3541	0.0752	-0.1817	0.0802	0.0938	3.07E-06	0.0885
			Ala146	7.3251	7.3167	7.3122	7.2883	7.2644	7.2538	114.2376	114.2575	114.2859	114.3422	114.3746	114.3929	-0.0713	0.1553	0.0752	0.0938	8.33E-06	0.0783
			Thr147																		
			Asn149	6.8893	6.8833	6.8790	6.8684	6.8569	6.8546	115.5170	115.5000	115.5023	115.4839	115.4603	115.4567	-0.0347	-0.0603	0.0359	0.0938	3.17E-06	0.0382
			Ile150																		
			Val151	8.4921	8.4844	8.4778	8.4646	8.4530	8.4486	105.2112	105.1817	105.1077	105.0063	104.9071	104.8623	-0.0435	-0.3489	0.0691	0.0938	6.90E-06	0.0735
			Val152	8.1091	8.1091	8.1072	8.1121	8.1119	8.1147	118.5850	118.5850	118.6267	118.6748	118.6895	118.6834	0.0056	0.0983	0.0161	0.0938	7.92E-06	0.0222
			Trp153	10.0418	10.0408	10.0411	10.0385	10.0400	10.0401	130.2555	130.2446	130.2384	130.2216	130.2083	130.2079	-0.0017	-0.0476	0.0075	0.0938	7.27E-06	0.0107
			Leu154	7.8353	7.8428	7.8501	7.8889	7.9101	7.9221	126.6426	126.6510	126.6322	126.7560	126.7922	126.8224	0.0868	0.1798	0.0911	0.0938	6.80E-06	0.0969
			Pro155																		
			Thr156	8.3814	8.3806	8.3784	8.3813	8.3812	8.3791	106.9213	106.9129	106.9060	106.9057	106.8898	106.8807	-0.0023	-0.0406	0.0066	0.0938	2.16E-05	0.0129
			Glu157	6.7402	6.7344	6.7327	6.7281	6.7268	6.7246	116.1464	116.1422	116.1727	116.1988	116.2321	116.2387	-0.0156	0.0923	0.0211	0.0938	8.64E-06	0.0275
			Asn158	7.6075	7.6088	7.6124	7.6190	7.6263	7.6263	113.5216	113.5154	113.5239	113.5396	113.5390	113.5390	0.0189	0.0174	0.0190	0.0938	9.73E-06	0.0229
			Ile159	6.2905	6.2899	6.2876	6.2856	6.2849	6.2829	115.2868	115.3218	115.3519	115.4144	115.4908	115.5215	-0.0076	0.2347	0.0369	0.0938	8.94E-06	0.0385
			Leu160	8.7176	8.7225	8.7236	8.7366	8.7493	8.7526	128.3687	128.4019	128.4363	128.5059	128.5735	128.6096	0.0350	0.2409	0.0510	0.0938	6.59E-06	0.0537
			Phe161	9.8322	9.8281	9.8240	9.8239	9.8213	9.8184	128.5041	128.4682	128.3944	128.2784	128.1529	128.1132	-0.0138	-0.3909	0.0617	0.0938	5.67E-06	0.0649
			Gly163		6.1704	6.1704	6.1704	6.0481	6.0258		100.4578	100.4578	100.4578	100.7321	100.7664						
L10	Z2	221	Cys164	6.5072						119.7912											
L10		222	Met165																		
L10		223	Leu166	8.1350	8.2083	8.2024	8.2004	8.1905	8.1879	117.8707	117.7227	117.6910	117.6488	117.6065	117.5959	0.0528	-0.2748	0.0677	0.0938	1.06E-05	0.1391
L10		224	Lys167	8.7984	8.8118	8.8130	8.8366	8.8420	8.8625	120.7995	120.7826	120.7621	120.7524	120.6980	120.7341	0.0641	-0.0654	0.0649	0.0938	4.40E-05	0.0834
L10		225	Asp168	8.0747	8.0757	8.0780	8.0811	8.0909	8.0925	115.8272	115.7658	115.7324	115.6515	115.5930	115.5636	0.0178	-0.2636	0.0443	0.0938	6.47E-06	0.0485
L10		228	Ala171	7.5872					7.5638	124.5391					124.7870	-0.0235	0.2478	0.0448	0.0938	5.91E-06	0.0475
L10		230	Ser173	7.6994	7.7075	7.7280	7.7535	7.7517	7.7644	115.2841	115.3306	115.2864	115.4294	115.5224	115.5805	0.0650	0.2964	0.0794	0.0938	1.36E-05	0.1065
L10		231	Ile174	8.8516	8.8432	8.8357	8.8315	8.8253	8.8241	123.5167	123.5216	123.4698	123.4981	123.5152	123.5165	-0.0275	-0.0002	0.0275	0.0938	6.71E-06	0.0402
L10		233	Asn176	7.9802					7.9834	124.2352					124.2594	0.0032	0.0242	0.0049	0.0938	7.26E-06	0.0059
L10		234	Ile177	8.7659	8.7626	8.7832	8.7687	8.7668	8.7640	122.2116	122.3789	122.5631	122.8007	122.8103	122.7600	-0.0019	0.5484	0.0844	0.0938	2.02E-05	0.0000

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)												$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
L10		236	Asp179	8.1600					8.2005	118.3940					118.7737	0.0405	0.3797	0.0711	0.0938	7.33E-01	172.5928
L10		237	Ala180	6.9431	6.9360	6.9287	6.9021	6.8797	6.8726	119.9303	119.9166	119.9074	119.8988	119.8746	119.8717	-0.0705	-0.0586	0.0711	0.0938	3.96E-06	0.0734
L10		238	Asp181	8.0826	8.0770	8.0673	8.0494	8.0300	8.0225	119.4721	119.4824	119.4970	119.5235	119.5593	119.5534	-0.0601	0.0813	0.0614	0.0938	6.33E-06	0.0641
L10		240	Thr183	7.9090	7.9100	7.9126	7.9172	7.9220	7.9220	109.1739	109.2236	109.2691	109.3706	109.4496	109.4496	0.0130	0.2757	0.0444	0.0938	4.97E-06	0.0508
L10		241	Ala184	7.4068	7.4028	7.3995	7.3957	7.3913	7.3896	122.2047	122.2396	122.2807	122.3562	122.4387	122.4722	-0.0172	0.2674	0.0446	0.0938	7.30E-06	0.0467
			Trp185	7.8336	7.8239	7.8174	7.7980	7.7722	7.7657	119.1851	119.1904	119.1807	119.1931	119.1977	119.1843	-0.0678	-0.0009	0.0678	0.0938	4.01E-06	0.0700
			Pro186																		
			Lys187	7.0496	7.0560	7.0582	7.0747	7.0873	7.0929	116.7515	116.7115	116.6801	116.5660	116.4978	116.4557	0.0432	-0.2958	0.0628	0.0938	7.59E-06	0.0657
			Thr188	9.0385	9.0297	9.0424	9.0439	9.0511	9.0521	121.3354	121.3596	121.3822	121.3553	121.4831	121.4726	0.0136	0.1371	0.0251	0.0938	2.55E-06	0.0528
			Leu189	8.3141	8.3141	8.3189	8.3138	8.3049	8.3013	119.7139	119.7139	119.7419	119.7494	119.7493	119.7493	-0.0127	0.0354	0.0139	0.0938	8.77E-06	0.0186
			Asp190	7.7654	7.7567	7.7505	7.7375	7.7261	7.7195	119.6661	119.6610	119.6670	119.6735	119.6482	119.6716	-0.0458	0.0055	0.0458	0.0938	1.18E-05	0.0514
			Lys191	7.7948	7.7910	7.7863	7.7812	7.7764	7.7753	121.4367	121.4423	121.4527	121.4490	121.4506	121.4665	-0.0195	0.0299	0.0200	0.0938	9.20E-06	0.0237
			Val192	8.2298	8.2298	8.2333	8.2409	8.2460	8.2482	120.9193	120.9193	120.9256	120.9372	120.9605	120.9780	0.0183	0.0587	0.0204	0.0938	9.21E-06	0.0214
			Lys193	8.3059	8.3058	8.3035	8.3033	8.3047	8.3040	118.1869	118.1921	118.1911	118.1961	118.1934	118.1992	-0.0019	0.0124	0.0027	0.0938	1.46E-05	0.0071
			Ala194	7.4440	7.4398	7.4331	7.4234	7.4131	7.4095	116.7294	116.7454	116.7430	116.7455	116.7406	116.7384	-0.0346	0.0090	0.0346	0.0938	6.07E-06	0.0376
			Lys195	7.3920	7.3929	7.3943	7.3975	7.3996	7.4014	116.4226	116.4191	116.4085	116.4183	116.4129	116.4134	0.0094	-0.0092	0.0095	0.0938	1.14E-05	0.0116
			Phe196	6.7224	6.7255	6.7279	6.7340	6.7401	6.7432	113.5110	113.4961	113.4843	113.4514	113.4294	113.4183	0.0208	-0.0928	0.0252	0.0938	8.87E-06	0.0267
			Pro197																		
			Ser198	8.0292	8.0259	8.0295	8.0267	8.0307	8.0280	112.3120	112.3041	112.3016	112.2769	112.3079	112.2752	-0.0012	-0.0368	0.0058	0.0938	3.33E-05	0.0266
			Ala199	7.2055	7.2040	7.2031	7.2029	7.2030	7.2030	123.3036	123.3022	123.3041	123.3028	123.3051	123.3069	-0.0025	0.0033	0.0025	0.0938	9.77E-06	0.0043
			Arg200	9.3625	9.3671	9.3662	9.3662	9.3724	9.3681	124.6480	124.6402	124.6343	124.6343	124.6160	124.6028	0.0056	-0.0452	0.0089	0.0938	8.56E-05	0.0227
			Tyr201	7.0427	7.0445	7.0459	7.0528	7.0557	7.0588	111.1193	111.1404	111.1598	111.1825	111.2109	111.2270	0.0161	0.1076	0.0231	0.0938	1.20E-05	0.0256
			Val202	9.6339	9.6343	9.6357	9.6409	9.6441	9.6466	123.6092	123.5993	123.5866	123.5508	123.5301	123.5191	0.0126	-0.0901	0.0188	0.0938	9.51E-06	0.0198
			Val203	8.8841	8.8810	8.8757	8.8770	8.8762		126.7521	126.7399	126.7213	126.6968	126.6469					0.0938	3.20E-05	0.0312
			Pro204																		
			Gly205	6.6758						105.2242											
L12		264	Gly207	9.5457	9.5457	9.5457	9.5457	9.5457	9.5457	112.0580	112.0580	112.0580	112.0580	112.0580	112.0580	0.0000	0.0000	0.0000			
			Tyr209	7.0691	7.0662	7.0631	7.0642	7.0631	7.0675	115.8012	115.8320	115.8285	115.8678	115.9147	115.9147	-0.0016	0.1135	0.0175	0.0938	1.44E-05	0.0286
			Gly210	8.2752	8.2750	8.2757	8.2774	8.2829	8.2869	109.2293	109.2118	109.2075	109.2074	109.2016	109.1921	0.0117	-0.0373	0.0131	0.0938	1.35E-04	0.0217
			Thr212	8.8334	8.8324	8.8306	8.8280	8.8253	8.8247	109.4416	109.4106	109.3806	109.3188	109.2514	109.2200	-0.0087	-0.2216	0.0352	0.0938	8.82E-06	0.0364
			Glu213	10.1202	10.1235	10.1269	10.1345	10.1432	10.1469	126.8948	126.9014	126.9208	126.9510	126.9653	126.9765	0.0268	0.0817	0.0296	0.0938	8.38E-06	0.0314
			Leu214	8.0057	8.0069	8.0081	8.0118	8.0157	8.0173	121.6792	121.6469	121.6469	121.6369	121.6097	121.6125	0.0115	-0.0667	0.0154	0.0938	6.04E-06	0.0189
			Ile215	8.1385	8.1421	8.1455	8.1697	8.1868	8.1908	121.3343	121.3569	121.3560	121.5306	121.6074	121.6370	0.0523	0.3026	0.0700	0.0938	2.32E-06	0.0719
			Glu216	7.1724	7.1800	7.1971	7.2088	7.2143	7.2354	118.8475	118.8673	118.8521	118.8695	118.8932	118.8725	0.0630	0.0249	0.0631	0.0938	5.05E-05	0.0781
			His217																		
			Thr218	7.9501	7.9600	7.9741	7.9937	8.0215	8.0266	113.9942	113.9689	113.9824	113.9706	113.9790	113.9790	0.0764	-0.0152	0.0765			

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)												$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
			Lys219	8.1058	8.1061	8.1058	8.1079	8.1089	8.1098	121.9376	121.8950	121.8545	121.7980	121.7246	121.6968	0.0040	-0.2408	0.0373	0.0938	7.47E-06	0.0391
			Gln220	7.7866	7.7786	7.7688	7.7501	7.7337	7.7289	117.2077	117.2132	117.1970	117.1777	117.1685	117.1589	-0.0577	-0.0488	0.0582	0.0938	4.64E-06	0.0625
			Val222	8.1218	8.1313	8.1278	8.1327	8.1379	8.1394	121.3511	121.3360	121.2489	121.1627	121.0812	121.0424	0.0176	-0.3087	0.0507	0.0938	7.51E-06	0.0623
			Asn223	8.7261	8.7230	8.7203	8.7175	8.7124	8.7115	118.3947	118.3604	118.3339	118.2704	118.1941	118.1745	-0.0146	-0.2202	0.0369	0.0938	4.08E-06	0.0381
			Gln224	8.2147	8.2189	8.2220	8.2260	8.2333	8.2358	119.8499	119.8565	119.8602	119.8753	119.8845	119.8869	0.0211	0.0370	0.0218	0.0938	7.23E-06	0.0234
			Tyr225	7.8496	7.8538	7.8587	7.8758	7.8916	7.8963	122.0547	122.0703	122.1115	122.1511	122.1906	122.2091	0.0467	0.1543	0.0524	0.0938	4.41E-06	0.0550
			Ile226	8.5103	8.5139	8.5167	8.5271	8.5327	8.5356	122.4524	122.4548	122.4356	122.4404	122.4450	122.4346	0.0253	-0.0178	0.0255	0.0938	6.72E-06	0.0290
			Glu227	8.3306	8.3301	8.3294	8.3549	8.3693	8.3720	119.7383	119.7408	119.7377	119.7168	119.6954	119.7054	0.0414	-0.0329	0.0417	0.0938	1.74E-06	0.0445
			Ser228	7.9372	7.9399	7.9431	7.9490	7.9550	7.9573	113.9874	113.9985	114.0054	114.0056	114.0038	114.0033	0.0201	0.0159	0.0203	0.0938	6.65E-06	0.0221
			Thr229	7.4996	7.5036	7.5036	7.5036	7.5036	7.5036	112.0972	112.0925	112.0925	112.0925	112.0925	112.0925	0.0040	-0.0047	0.0041	0.0938	2.03E-05	0.0061
			Ser230	7.6869	7.6863	7.6856	7.6864	7.6872	7.6872	117.4185	117.4239	117.4278	117.4306	117.4427	117.4427	0.0003	0.0242	0.0037	0.0938	1.13E-05	0.0058
			Lys231	8.0127	8.0325	8.0549	8.0665	8.0693	8.0723	124.2836	124.2545	124.2836	124.3321	124.2901	124.4340	0.0596	0.1504	0.0639	0.0938	2.35E-05	0.0988
			Pro232																		

Table S5. Experimental $^{1}H,^{15}N$ HSQC titration data, and related calculated and fitted data for **5**. Residues displaying a significant chemical shift perturbation (i.e. CSP > 0.0726, where μ and 1σ were calculated to 0.374 and 0.353, respectively) are presented at the first page, and all other residues are presented thereafter. Active site residues are colored in orange, and those that are more likely to be involved in indirect than in direct interactions are colored in pale orange. The K_d sample mean and standard deviation calculated using the data for the residues showing a significant CSP and representing the L3-L5-L7 binding poses, as well as the whole active site were $K_{d\ L3\text{-}L5\text{-}L7\ site}$ = 34 ± 43 μM and $K_{d\ active\ site}$ = 41 ± 59 μM, respectively.

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)														$\Delta\delta_{final\text{-}initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^{1}H_{initial}$	$^{1}H_{Step1}$	$^{1}H_{Step2}$	$^{1}H_{Step3}$	$^{1}H_{Step4}$	$^{1}H_{Step5}$	$^{1}H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{Step5}$	$^{15}N_{final}$	$\Delta^{1}H$	$\Delta^{15}N$	$\Delta^{1}H,^{15}N$	μ + 1σ		
			Asp10	8.3788	8.3705	8.3444	8.3654	8.3303	8.3234	8.3008	112.9321	112.9210	112.9546	113.0093	113.0889	113.2442	113.2692	-0.0780	0.3371	0.0937	0.0726	9.07E-06	0.1419
L3		61	Ile29	8.6002						8.5489	127.4735						126.6198	-0.0513	-0.8537	0.1410	0.0726	3.23E-06	0.1569
L3		62	Glu30	8.9160	8.8867	8.8485	8.8245	8.8197	8.7797	8.7783	129.9276	129.9371	129.9580	129.8578	129.8633	129.9235	129.9481	-0.1377	0.0205	0.1377	0.0726	2.68E-06	0.1538
L3		63	Gly31	8.8282	8.8274	8.8227	8.8217	8.8186	8.8183	8.8163	114.6596	114.7640	114.9354	115.0009	115.0662	115.0890	115.1677	-0.0119	0.5082	0.0791	0.0726	1.39E-05	0.0943
L3		64	Trp32	8.4281	8.4477	8.4668	8.4946	8.5048	8.5181	8.5412	120.3194	120.3234	120.2680	120.2588	120.1632	120.1761	120.1266	0.1131	-0.1928	0.1169	0.0726	1.04E-04	0.2231
L3		65	Gly33	8.3199	8.3085	8.2779	8.2712	8.2603	8.2392	8.2292	108.7997	108.9324	109.1432	109.1428	109.1740	109.2548	109.4138	-0.0906	0.6140	0.1309	0.0726	6.58E-05	0.2101
L3		67	Val35	9.0169	9.0055	9.0013	8.9751	8.9809	8.9928	8.9724	127.8714	128.1542	128.5613	128.6662	128.8682	129.0979	129.1904	-0.0445	1.3190	0.2077	0.0726	4.14E-07	0.1659
L3		69	Ser37	9.2551						9.1842	121.5999						122.3115	-0.0709	0.7116	0.1304	0.0726	5.75E-06	0.1750
L5		87	Ile55	7.8372	7.8203	7.8006	7.7762	7.7725	7.7694	7.7647	112.2883	112.3755	112.3279	112.3319	112.2405	112.2647	112.2144	-0.0725	-0.0739	0.0734	0.0726	5.04E-06	0.0776
L7	Z1	118	His84	5.4652	5.4614	5.4612		5.4407		5.4472	113.7651	113.2616	112.9834		113.0743		112.7926	-0.0180	-0.9725	0.1507	0.0726	1.32E-05	0.2326
>L7		123	Gly89	8.2421	8.2705	8.2807	8.3221	8.3542	8.3878	8.3709	112.9895	113.1038	113.0334	112.9728	112.9660	112.9181	112.7976	0.1288	-0.1919	0.1322	0.0726	3.17E-06	0.1754
			Ala111	8.4546	8.4841	8.5125	8.5144	8.5451	8.5908	8.5955	121.5383	121.5822	121.6412	121.6567	121.7374	121.7033	121.7250	0.1409	0.1867	0.1438	0.0726	4.65E-08	0.1403
			Lys114	7.7522	7.7664	7.7907	7.7937	7.8090	7.8321	7.8440	116.0651	116.0242	116.0019	115.9541	115.9873	115.9605	115.9739	0.0918	-0.0912	0.0929	0.0726	1.54E-04	0.2116
			His121	7.6855	7.6866	7.6914	7.7146	7.7659	7.7822	7.7910	116.0412	116.0054	116.0022	115.8358	115.9519	115.9689	115.9395	0.1054	-0.1017	0.1066	0.0726	1.96E-06	0.1185
			Asp125	9.0652						8.9783	121.2783						121.2932	-0.0869	0.0149	0.0869	0.0726	1.65E-06	0.0924
L9	Z1	196	His145	5.7174	5.7424	5.7602	5.7796	5.7908	5.8024	5.8243	130.3228	130.3244	130.3393	130.2440	130.2083	130.2867	130.2351	0.1068	-0.0877	0.1077	0.0726	8.58E-05	0.2005
			Asp148	10.4656	10.5006	10.5261	10.5382	10.5538	10.5691	10.5881	115.1030	115.0754	115.0981	115.2188	115.1846	115.1344	115.1487	0.1225	0.0456	0.1227	0.0726	1.86E-05	0.1662
			Gly162	8.3155	8.3444	8.3663	8.3971	8.3890	8.4123	8.4120	112.9381	112.9416	112.9582	112.9874	113.0495	113.0041	113.0137	0.0965	0.0755	0.0972	0.0726	9.79E-06	0.1444
L10		224	Lys167	8.7875	8.8061	8.8226	8.8141	8.8306	8.8389	8.8642	120.9822	120.8655	120.8086	120.8391	120.7711	120.7530	120.7186	0.0767	-0.2636	0.0868	0.0726	1.02E-04	0.1906
L10		226	Asn169		8.7961	8.8413	8.8351	8.8707		8.8727		115.7743	115.8363	115.9298	116.1048		116.1712	0.0766	0.3969	0.0979	0.0726	1.05E-05	0.1813
L10		227	Gln170		8.0848	8.1002	8.1156	8.1395		8.1690		115.1100	115.1046	115.1049	115.2110		115.1216	0.0843	0.0116	0.0843	0.0726	2.14E-04	0.2904
L10		229	Thr172	7.1288	7.1232	7.1051	7.0991	7.0726	7.0420	7.0268	118.3531	118.2497	118.1619	118.0913	118.0007	117.7498	118.2233	-0.1020	-0.1298	0.1039	0.0726	2.64E-01	262.9586
L10		230	Ser173	7.6791	7.6905	7.7033	7.7207	7.7350	7.7479	7.7533	115.3682	115.4236	115.4499	115.5014	115.5856	115.5856	115.6028	0.0742	0.2346	0.0826	0.0726	1.35E-05	0.0989
L10		232	Gly175	8.0526	8.0628	8.0909	8.1028	8.1133	8.1205	8.1320	111.2157	111.2442	111.3227	111.2891	111.3675	111.4031	111.4136	0.0795	0.1978	0.0851	0.0726	4.79E-06	0.0965
L10		239	Val182	8.5418	8.5360	8.5258	8.5265	8.5172	8.5194	8.5151	120.6663	120.5745	120.4798	120.3857	120.2395	120.2252	120.1479	-0.0267	-0.5184	0.0841	0.0726	2.29E-06	0.0864
L12		265	Asp208	8.9104	8.9119	8.8857	8.8706	8.8487	8.8564	8.8492	119.6690	119.5016	119.0911	119.1048	119.1732	119.0488	119.0450	-0.0612	-0.6240	0.1138	0.0726	1.12E-05	0.1966
			Glu216	7.1408	7.1621	7.1805	7.2035	7.2159	7.2315	7.2490	118.9129	118.9455	118.9372	118.9315	118.8973	118.9035	118.9799	0.1082	0.0670	0.1087	0.0726	8.21E-05	0.1884
			Ser228	7.9397	7.9867	7.9967	8.0030	8.0124	8.0181	8.0204	114.0750	114.2544	114.2822	114.2980	114.3111	114.2938	114.2975	0.0808	0.2225	0.0877	0.0726	1.49E-05	0.1262

For cells colored in grey, the first titration points were used for estimating the ^{1}H and $^{1}H,^{15}N$ Δδ since the initial data points were missing. The absolute values were not used in any further calculations, but the sign of the ^{1}H Δδ were used in the DSCP analysis.

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)														Δδ$_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	Δδ$_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{Step5}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{Step5}$	$^{15}N_{final}$	Δ^{1}H	Δ^{15}N	Δ^{1}H,^{15}N	μ + 1σ		
			Lys3	8.5338	8.5321	8.5314	8.5307	8.5313	8.5311	8.5290	123.0993	123.0841	123.0743	123.0667	123.0685	123.0606	123.0491	-0.0048	-0.0501	0.0091	0.0726	7.38E-05	0.0163
			Ser4	8.2760	8.2722	8.2697	8.2670	8.2670	8.2643	8.2616	118.2640	118.2591	118.2511	118.2508	118.2508	118.2390	118.2333	-0.0144	-0.0307	0.0152	0.0726	5.08E-05	0.0223
			Val5	9.1116	9.1109	9.1136	9.1148	9.1125	9.1153	9.1162	122.9812	123.0050	123.0195	123.0356	123.0516	123.0607	123.0684	0.0046	0.0872	0.0142	0.0726	1.04E-06	0.0175
			Lys6	8.6114	8.6112	8.6089	8.6064	8.6064	8.6068	8.6032	126.8296	126.8425	126.8686	126.8629	126.8629	126.8994	126.8922	-0.0082	0.0626	0.0127	0.0726	8.81E-04	0.1066
			Ile7	7.9859	7.9907	7.9810	7.9794	7.9893	7.9910	7.9864	122.7050	122.8039	122.8455	122.9157	122.9208	123.0206	123.0894	0.0004	0.3843	0.0591	0.0726	1.38E-04	0.1494
			Ser8	8.3800	8.3854	8.3882	8.3917	8.3917	8.3944	8.3977	115.2463	115.2300	115.2161	115.2084	115.2084	115.2013	115.1939	0.0176	-0.0524	0.0194	0.0726	2.39E-05	0.0247
			Asp9	8.7975	8.7980	8.7980	8.7992	8.7980	8.7978	8.7978	117.4041	117.4156	117.4156	117.4327	117.4204	117.4240	117.4481	0.0003	0.0439	0.0068	0.0726	4.74E-03	0.2750
			Ile11	7.1549	7.1459	7.1446	7.1368	7.1350	7.1279	7.1255	118.3911	118.3616	118.3048	118.2896	118.2704	118.1826	118.1790	-0.0294	-0.2121	0.0439	0.0726	5.98E-06	0.0502
			Ser12	8.6610	8.6728	8.6725	8.6800	8.6785	8.6847	8.6811	121.8702	121.8443	121.8553	121.8716	121.8713	121.8659	121.8936	0.0200	0.0234	0.0203	0.0726	3.12E-05	0.0467
			Ile13	9.1783	9.1758	9.1694	9.1664	9.1635	9.1653	9.1526	121.7068	121.6642	121.6092	121.5416	121.4992	121.4854	121.4752	-0.0257	-0.2317	0.0440	0.0726	1.50E-04	0.1035
			Thr14	9.2777	9.2833	9.2869	9.2936	9.2908	9.2948	9.2985	122.7821	122.7940	122.8046	122.8079	122.8006	122.8040	122.8014	0.0208	0.0193	0.0211	0.0726	8.72E-06	0.0300
			Gln15	9.0276	9.0235	9.0208	9.0160	9.0160	9.0136	9.0101	129.4002	129.3895	129.3531	129.3542	129.3542	129.3423	129.3188	-0.0175	-0.0814	0.0216	0.0726	3.18E-05	0.0305
			Leu16	8.6400	8.6451	8.6373	8.6466	8.6466	8.6466	8.6536	126.9035	126.8788	126.9001	126.8896	126.8896	126.8896	126.8598	0.0136	-0.0437	0.0152	0.0726	1.23E-05	0.0372
			Ser17	8.4372	8.4416	8.4433	8.4464	8.4464	8.4490	8.4487	115.2328	115.2576	115.2702	115.2806	115.2806	115.2993	115.2905	0.0115	0.0577	0.0146	0.0726	2.06E-05	0.0221
			Asp18	8.5004						8.5346	116.3935						116.3677	0.0342	-0.0258	0.0345	0.0726	1.12E-05	0.0483
			Lys19	7.5556	7.5595	7.5595	7.5630	7.5630	7.5691	7.5677	113.8744	113.8773	113.8773	113.8725	113.8725	113.8968	113.8701	0.0121	-0.0043	0.0121	0.0726	1.71E-02	1.6916
			Val20	7.0068	7.0064	7.0083	7.0085	7.0095	7.0089	7.0107	116.1653	116.1594	116.1639	116.1652	116.1634	116.1649	116.1611	0.0039	-0.0042	0.0039	0.0726	2.03E-04	0.0154
			Tyr21	9.5364	9.5376	9.5402	9.5402	9.5414	9.5445	9.5462	126.3321	126.3521	126.3655	126.3747	126.4097	126.3926	126.4018	0.0098	0.0698	0.0145	0.0726	4.55E-05	0.0271
			Thr22	9.5130	9.5110	9.5110	9.5037	9.5019	9.5046	9.4997	115.4566	115.4731	115.4731	115.5185	115.4965	115.5311	115.5418	-0.0133	0.0852	0.0186	0.0726	1.67E-03	0.2855
			Tyr23	8.0942	8.0903	8.0876	8.0833	8.0815	8.0776	8.0737	124.2653	124.2577	124.2501	124.2803	124.2339	124.2500	124.2704	-0.0205	0.0051	0.0205	0.0726	2.35E-06	0.0280
			Val24	8.8839	8.8802	8.8810	8.8788	8.8806	8.8793	8.8778	120.7050	120.7345	120.7685	120.8027	120.7895	120.7899	120.7827	-0.0061	0.0776	0.0134	0.0726	1.20E-05	0.0279
			Ser25	9.6944						9.6854	122.2449						122.3889	-0.0090	0.1441	0.0239	0.0726	2.65E-04	0.2290
			Leu26		8.9319	8.9319	8.9319	8.9319	8.9319			127.2400	127.2400	127.2400	127.2400	127.2400							
L3		59	Ala27	8.1010						8.1625	124.8079						124.9552	0.0615	0.1473	0.0655	0.0726	1.30E-04	0.1503
L3		60	Glu28	8.4148	8.4154	8.4129	8.4160	8.4153	8.4158	8.4155	122.2919	122.2730	122.2772	122.2969	122.2731	122.2895	122.3169	0.0007	0.0250	0.0039	0.0726	4.23E-04	0.0720
L3		66	Met34	8.3811	8.3786	8.3728	8.3684	8.3622	8.3600	8.3554	121.0310	121.1108	121.1748	121.2371	121.2814	121.2771	121.2809	-0.0257	0.2499	0.0462	0.0726	1.29E-05	0.0619
L3		68	Pro36																				
			Asn38	7.9604						7.9500	119.5388						119.7188	-0.0104	0.1800	0.0296	0.0726	6.84E-05	0.1362
			Gly39																				
			Met40	9.2505	9.2593	9.2741	9.2625	9.2799	9.2793	9.2793	117.3368	117.2450	117.2079	117.2344	117.3063	117.1911	117.2071	0.0288	-0.1297	0.0350	0.0726	7.92E-06	0.0708
			Ile41	9.1389	9.1365	9.1274	9.1239	9.1215	9.1149	9.1140	122.0848	122.0848	122.0781	122.0452	122.0289	122.0687	122.0539	-0.0249	-0.0310	0.0253	0.0726	4.27E-06	0.0327
			Val42	9.0551	9.0569	9.0559	9.0547	9.0547	9.0562	9.0556	128.2949	128.3157	128.3229	128.3127	128.3127	128.3195	128.3226	0.0005	0.0278	0.0043	0.0726	9.74E-06	0.0117
			Ile43	9.3064	9.3119	9.3128	9.3364	9.3528	9.3512	9.3550	124.6791	124.6156	124.6438	124.6456	124.6491	124.6438	124.6579	0.0486	-0.0212	0.0487	0.0726	3.87E-06	0.0659
			Asn44	8.7295	8.7274	8.7318	8.7311	8.7311	8.7337	8.7325	119.4979	119.5065	119.5204	119.5306	119.5306	119.5290	119.5389	0.0030	0.0409	0.0070	0.0726	2.66E-05	0.0178
			Asn45	8.9617	8.9617	8.9617	8.9617	8.9617	8.9617	8.9620	125.0260	125.0252	125.0259	125.0262	125.0259	125.0262	125.0271	0.0003	0.0011	0.0004	0.0726	4.59E-02	0.1786
			His46	8.6459						8.6734	108.8709						109.1132	0.0275	0.2423	0.0463	0.0726	5.03E-05	0.0739
			Gln47	8.2478	8.2459	8.2425	8.2403	8.2419	8.2415	8.2405	121.2131	121.2119	121.2081	121.2168	121.2318	121.2183	121.2204	-0.0073	0.0072	0.0074	0.0726	3.22E-07	0.0135
			Ala48	9.0025	9.0031	9.0033	9.0070	9.0043	9.0021	9.0025	121.7967	121.7835	121.7742	121.7906	121.7822	121.7830	121.7572	0.0000	-0.0396	0.0061	0.0726	1.21E-03	0.1292

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)														$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{Step5}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{Step5}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
			Ala49	9.6432	9.6456	9.6449	9.6427	9.6422	9.6452	9.6449	122.2040	122.2368	122.2533	122.3026	122.2714	122.3047	122.3394	0.0017	0.1354	0.0209	0.0726	3.81E-04	0.1071
			Leu50	8.6513	8.6434	8.6522	8.6344	8.6258	8.6228	8.6190	122.4424	122.4329	122.4370	122.3809	122.3686	122.3657	122.4098	-0.0323	-0.0326	0.0327	0.0726	1.29E-05	0.0654
			Leu51	9.1689	9.1943	9.2136	9.2389	9.2239	9.2285	9.2116	127.1083	127.1083	127.1810	127.2052	127.4026	127.0877	126.9963	0.0427	-0.1120	0.0461	0.0726	8.48E-04	1.0337
			Asp52	7.2832	7.2783	7.2724	7.2606	7.2675	7.2712	7.2693	111.7069	111.7697	111.8043	111.6211	111.9133	112.0743	112.0024	-0.0139	0.2955	0.0475	0.0726	3.33E-07	0.1197
			Thr53		8.0441	8.0420	8.0427	8.0416	8.0415	8.0418		112.3324	112.3239	112.3162	112.3114	112.3145	112.2989				0.0726	3.82E-06	0.0136
			Pro54																				
			Asn56	6.7746	6.7758	6.7758	6.7773	6.7773	6.7779	6.7784	111.0164	111.0190	111.0190	111.0256	111.0256	111.0299	111.0367	0.0038	0.0203	0.0049	0.0726	2.31E-04	0.0128
			Asp57	8.9644	8.9603	8.9532	8.9493	8.9383	8.9350	8.9280	122.3640	122.3357	122.3042	122.3379	122.3117	122.2910	122.2820	-0.0364	-0.0820	0.0385	0.0726	1.93E-06	0.0418
			Ala58	8.2246	8.2179	8.2112	8.2078	8.2040	8.2023	8.1990	124.9990	125.0228	125.0012	125.0308	124.9981	125.0167	125.0413	-0.0256	0.0423	0.0264	0.0726	9.38E-06	0.0392
			Gln59	8.8256	8.8236	8.8289	8.8381	8.8348	8.8211	8.8346	116.8841	116.8456	116.8956	116.9417	116.9487	116.9679	117.0131	0.0091	0.1291	0.0218	0.0726	3.71E-03	1.1830
			Thr60	7.3484	7.3394	7.3503	7.3575	7.3439	7.3892	7.3795	116.1529	116.0574	116.2255	116.0214	116.0486	116.0411	115.9490	0.0312	-0.2039	0.0442	0.0726	3.93E-04	0.5366
			Glu61	8.2159	8.2241	8.2307	8.2353	8.2376	8.2408	8.2411	122.9919	122.9897	122.9907	123.0083	122.9783	122.9796	122.9921	0.0251	0.0002	0.0251	0.0726	1.42E-05	0.0381
			Met62	7.2924	7.2864	7.2773	7.2721	7.2672	7.2641	7.2614	117.2134	117.1889	117.1899	117.1673	117.1729	117.1684	117.1672	-0.0310	-0.0462	0.0318	0.0726	1.41E-05	0.0415
			Leu63	7.6051	7.5979	7.6007	7.5986	7.6103	7.6233	7.6204	119.7820	119.4040	119.2452	119.3328	119.2288	119.3109	119.3791	0.0153	-0.4029	0.0639	0.0726	1.68E-05	0.1858
			Val64	8.7833	8.7939	8.8025	8.8120	8.8196	8.8284	8.8357	119.0705	119.0740	119.0477	119.0650	119.0614	119.0752	119.0465	0.0524	-0.0240	0.0525	0.0726	6.67E-05	0.0863
			Asn65	8.8954	8.8989	8.8999	8.9009	8.9028	8.9030	8.9010	120.4957	120.4936	120.5012	120.5014	120.5168	120.5192	120.5443	0.0056	0.0486	0.0094	0.0726	2.49E-04	0.0349
			Trp66	7.8255	7.8110	7.8039	7.7967	7.7883	7.7841	7.7783	122.1410	122.1286	122.1208	122.1275	122.1172	122.0776	122.0809	-0.0472	-0.0601	0.0481	0.0726	1.47E-05	0.0602
			Val67	8.4469	8.4470	8.4494	8.4545	8.4545	8.4561	8.4551	120.8381	120.8517	120.8292	120.8569	120.8569	120.8792	120.8784	0.0082	0.0403	0.0103	0.0726	1.03E-05	0.0204
			Thr68	8.1834	8.1915	8.2039	8.2200	8.2358	8.2335	8.2408	115.0197	115.0471	115.1035	115.0869	115.1213	115.1200	115.1140	0.0574	0.0943	0.0592	0.0726	8.80E-06	0.0760
			Asp69	8.3679	8.4227	8.4145	8.4092	8.4068	8.4051	8.3981	120.3103	120.3211	120.3342	120.3376	120.3398	120.3456	120.3813	0.0302	0.0710	0.0321	0.0726	3.50E-06	0.1033
			Ser70	8.4738	8.4728	8.4737	8.4710	8.4728	8.4725	8.4695	112.7698	112.7516	112.7350	112.7249	112.6998	112.6877	112.6810	-0.0043	-0.0888	0.0143	0.0726	5.87E-05	0.0266
			Leu71	6.5496	6.5577	6.5602	6.5590	6.5624	6.5639	6.5682	115.0250	115.0190	115.0295	115.0380	115.0163	115.0167	115.0396	0.0186	0.0145	0.0188	0.0726	3.84E-05	0.0335
			His72	6.7638	6.7687	6.7715	6.7711	6.7708	6.7725	6.7718	112.6674	112.6786	112.6926	112.7038	112.6702	112.6702	112.7094	0.0081	0.0421	0.0103	0.0726	2.15E-04	0.0556
			Ala73	7.4115						7.3838	120.0234						119.8315	-0.0277	-0.1918	0.0405	0.0726	6.04E-06	0.0705
			Lys74	7.6663	7.6541	7.6482	7.6450	7.6450	7.6565	7.6593	119.2391	119.3225	119.3478	119.3586	119.3586	119.3755	119.4092	-0.0070	0.1701	0.0271	0.0726	4.73E-05	0.0682
			Val75	8.9420	8.9411	8.9411	8.9376	8.9391	8.9397	8.9373	126.7949	126.7826	126.7826	126.7685	126.7781	126.7636	126.7679	-0.0048	-0.0270	0.0063	0.0726	1.15E-03	0.0965
			Thr76	9.1903	9.1983	9.2119	9.2309	9.2483	9.2567	9.2522	117.3266	117.2742	117.2609	117.2504	117.2445	117.2030	117.1825	0.0619	-0.1441	0.0658	0.0726	9.97E-06	0.0879
			Thr77	7.7205	7.7201	7.7234	7.7224	7.7224	7.7286	7.7285	120.4335	120.4611	120.4862	120.5020	120.5020	120.5252	120.5596	0.0080	0.1262	0.0210	0.0726	5.27E-04	0.0959
			Phe78	9.1400	9.1387	9.1362	9.1386	9.1342	9.1357	9.1329	127.1871	127.1512	127.1094	127.1034	127.0699	127.0544	127.0281	-0.0071	-0.1590	0.0255	0.0726	2.82E-05	0.0372
			Ile79	7.5441	7.5317	7.5234	7.5163	7.5131	7.5163	7.5030	126.8853	126.9379	126.9527	126.9640	126.9867	126.9640	127.0146	-0.0411	0.1294	0.0457	0.0726	8.46E-05	0.0906
			Pro80																				
			Asp81																				
L7	Z1	116	His82	7.6096	7.5980	7.5880	7.5929	7.5834	7.5808	7.5782	106.5315	106.4560	106.3637	106.3488	106.3552	106.3548	106.3517	-0.0314	-0.1798	0.0419	0.0726	1.14E-05	0.0691
L7		117	Trp83	8.3596	8.3703	8.3407	8.3411	8.3421	8.3127	8.3112	116.1489	116.1100	116.1466	115.9900	115.9145	115.8463	115.8314	-0.0484	-0.3176	0.0688	0.0726	1.21E-05	0.1100
>L7		119	Gly85	8.8050						8.8050	112.2664						112.2665	0.0000	0.0001	0.0000	0.0726		
>L7	Z2	120	Asp86																				
>L7		121	Cys87	7.7984	7.7984	7.7984	7.7982	7.7984	7.7984	7.7984	112.7700	112.7700	112.7700	112.7700	112.7700	112.7700	112.7700	0.0000	0.0000	0.0000	0.0726	2.51E-05	0.0005
>L7		122	Leu88	7.3924						7.4036	109.8895						109.6741	0.0112	-0.2155	0.0350	0.0726	4.16E-02	22.7523

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)														$\Delta\delta_{final-initial}$ (ppm)		CSP		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{Step5}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{Step5}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
			Gly90																				
			Leu91	7.9329	7.9571	7.9709	7.9325	7.9567	7.9283	7.9443	120.9340	120.7842	120.7980	120.9411	120.9051	121.0161	120.8322	0.0113	-0.1019	0.0193	0.0726	3.92E-04	0.6190
			Gly92		8.8969	8.8978	8.8925	8.8925	8.8976	8.8905		107.8031	107.7212	107.6605	107.6605	107.7059	107.6636				0.0726	1.28E-04	0.0883
			Tyr93	7.3534	7.3565	7.3530	7.3557	7.3557	7.3627	7.3634	122.1688	122.2192	122.2151	122.2550	122.2550	122.2694	122.2904	0.0100	0.1215	0.0212	0.0726	3.02E-05	0.0381
			Leu94	7.2308	7.2255	7.2227	7.2191	7.2176	7.2161	7.2201	115.6810	115.6110	115.6047	115.5691	115.5433	115.5176	115.4939	-0.0107	-0.1872	0.0307	0.0726	2.71E-05	0.0455
			Gln95	8.6730	8.6833	8.7129	8.7388	8.7381	8.7498	8.7392	118.3906	118.3685	118.2599	118.2735	118.2560	118.2718	118.2456	0.0663	-0.1450	0.0699	0.0726	5.39E-06	0.1062
			Arg96	7.6614	7.6653	7.6677	7.6704	7.6704	7.6729	7.6768	120.6245	120.6276	120.6197	120.5984	120.5984	120.5966	120.6010	0.0154	-0.0236	0.0158	0.0726	6.85E-05	0.0269
			Lys97	7.2101	7.2057	7.2028	7.1972	7.1960	7.1952	7.1923	116.7500	116.7486	116.7454	116.7422	116.7503	116.7327	116.7165	-0.0178	-0.0335	0.0185	0.0726	3.30E-05	0.0278
			Gly98	7.7088	7.7116	7.7126	7.7143	7.7145	7.7155	7.7164	107.8746	107.8892	107.9000	107.9096	107.9007	107.9162	107.9213	0.0075	0.0467	0.0104	0.0726	1.25E-05	0.0148
			Val99	7.5208	7.5265	7.5304	7.5341	7.5341	7.5413	7.5430	121.1749	121.1835	121.1985	121.2025	121.2025	121.2066	121.2105	0.0222	0.0356	0.0228	0.0726	3.06E-05	0.0307
			Gln100	8.1271	8.1271	8.1510	8.1532	8.1591	8.1667	8.1704	127.2151	127.2176	127.2263	127.2096	127.2248	127.1994	127.2186	0.0433	0.0036	0.0433	0.0726	3.32E-06	0.0486
			Ser101	8.2512	8.2577	8.2658	8.2701	8.2679	8.2712	8.2806	115.6279	115.6321	115.6111	115.6262	115.5987	115.6129	115.6350	0.0294	0.0071	0.0294	0.0726	1.68E-04	0.0825
			Tyr102	8.6416	8.6417	8.6305	8.6178	8.6230	8.6190	8.6107	122.1301	122.1105	122.1244	122.0030	122.0515	122.0200	122.0446	-0.0309	-0.0855	0.0336	0.0726	8.83E-07	0.0571
			Ala103	8.9190	8.9178	8.9178	8.9147	8.9136	8.9139	8.9128	117.4302	117.4090	117.4090	117.3884	117.4032	117.3709	117.3625	-0.0062	-0.0677	0.0121	0.0726	4.01E-04	0.0609
			Asn104	8.5151	8.5063	8.4890	8.4897	8.4767	8.4730	8.4679	118.2350	118.2841	118.3124	118.3635	118.4447	118.4447	118.4715	-0.0472	0.2365	0.0596	0.0726	1.44E-05	0.0792
			Gln105	9.4873	9.4945	9.5039	9.5083	9.5104	9.5149	9.5154	132.1319	132.1563	132.1642	132.2015	132.2062	132.2298	132.2348	0.0280	0.1029	0.0322	0.0726	1.17E-05	0.0420
			Met106	7.3943	7.3863	7.3813	7.3791	7.3754	7.3706	7.3647	113.0083	112.9783	112.9614	112.9540	112.9488	112.9349	112.8954	-0.0296	-0.1128	0.0343	0.0726	1.28E-04	0.0659
			Thr107	7.0983	7.0954	7.0929	7.0897	7.0879	7.0875	7.0829	116.0946	116.0622	116.0586	116.0245	116.0418	116.0401	116.0299	-0.0154	-0.0647	0.0183	0.0726	1.88E-05	0.0274
			Ile108	7.2239	7.2253	7.2266	7.2284	7.2284	7.2304	7.2318	121.6114	121.6280	121.6291	121.6290	121.6290	121.6364	121.6195	0.0079	0.0081	0.0080	0.0726	2.28E-04	0.0270
			Asp109																				
			Leu110	7.6217	7.6261	7.6345	7.6348	7.6389	7.6391	7.6427	121.5489	121.5584	121.5547	121.5601	121.5490	121.5658	121.5874	0.0210	0.0386	0.0218	0.0726	3.48E-05	0.0344
			Lys112	8.4260	8.4275	8.4084	8.4089	8.4227	8.4246	8.4109	116.3380	116.2980	116.3082	116.3528	116.3643	116.3923	116.3872	-0.0150	0.0492	0.0168	0.0726	1.29E-04	0.1257
			Glu113	7.6426	7.6371	7.6269	7.6274	7.6261	7.6261	7.6253	119.7808	119.7691	119.7596	119.7883	119.8061	119.8203	119.8179	-0.0173	0.0371	0.0182	0.0726	7.12E-06	0.0325
			Gly115	7.7134	7.7111	7.7106	7.7101	7.7109	7.7093	7.7095	108.6278	108.5731	108.5138	108.4603	108.4321	108.3914	108.3556	-0.0039	-0.2722	0.0421	0.0726	1.23E-05	0.0476
L8		168	Leu116	8.0530	8.0511	8.0474	8.0436	8.0408	8.0363	8.0350	122.8137	122.9405	123.0177	122.9362	122.8937	122.9444	122.9575	-0.0179	0.1439	0.0285	0.0726	1.37E-05	0.0795
			Pro117																				
			Val118																				
			Pro119																				
			Glu120																				
			Gly122		8.7059	8.7069	8.7061	8.7096	8.7095	8.7063		111.5791	111.5828	111.5763	111.6063	111.6096	111.5911				0.0726	4.70E-03	0.3815
			Phe123	7.6235	7.6193	7.6146	7.6148	7.6144	7.6144	7.6151	115.1832	115.2135	115.2181	115.2432	115.2238	115.2417	115.2643	-0.0083	0.0810	0.0150	0.0726	1.85E-05	0.0292
			Thr124	8.6640	8.6633	8.6649	8.6629	8.6647	8.6640	8.6670	112.4719	112.5047	112.5389	112.5767	112.6053	112.6042	112.6560	0.0031	0.1841	0.0285	0.0726	1.53E-04	0.0621
			Ser126	8.9285	8.9340	8.9340	8.9406	8.9440	8.9457	8.9482	115.3300	115.3408	115.3408	115.3836	115.3927	115.3964	115.4292	0.0196	0.0992	0.0249	0.0726	8.52E-05	0.0434
			Leu127	7.6677	7.6640	7.6597	7.6549	7.6508	7.6475	7.6471	121.1332	121.1068	121.0875	121.0680	121.0455	121.0384	121.0145	-0.0205	-0.1187	0.0275	0.0726	3.36E-06	0.0291
			Thr128	8.6515	8.6499	8.6499	8.6437	8.6437	8.6437	8.6387	124.4808	124.4845	124.4845	124.4571	124.4571	124.4469	124.4583	-0.0128	-0.0226	0.0133	0.0726	3.75E-03	0.3197
			Val129	8.8932	8.8949	8.8943	8.8953	8.8971	8.8969	8.9020	129.9317	129.9393	129.9368	129.9402	129.9550	129.9546	129.9898	0.0088	0.0582	0.0125	0.0726	1.82E-02	1.5052
			Ser130	8.4312	8.4296	8.4300	8.4271	8.4289	8.4278	8.4257	119.9143	119.8999	119.9017	119.8891	119.8948	119.8950	119.8962	-0.0056	-0.0181	0.0062	0.0726	1.06E-05	0.0129
			Leu131	9.2219	9.2219	9.2215	9.2211	9.2214	9.2241	9.2193	132.0784	132.0784	132.1062	132.1136	132.1231	132.1320	132.1416	-0.0025	0.0632	0.0100	0.0726	5.24E-02	4.0974

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)														$\Delta\delta_{final-initial}$ (ppm)		CSP		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{Step5}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{Step5}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
			Asp132	8.8016	8.8012	8.8004	8.8011	8.8011	8.8021	8.7994	127.0719	127.0972	127.1073	127.1213	127.1213	127.1114	127.1185	-0.0022	0.0465	0.0075	0.0726	4.00E-05	0.0170
			Gly133	7.1966	7.1969	7.1969	7.1958	7.1959	7.1962	7.1961	101.8879	101.8942	101.8942	101.8885	101.8891	101.8963	101.8886	-0.0005	0.0007	0.0005	0.0726	1.55E-03	0.0441
			Met134	7.2748	7.2746	7.2754	7.2760	7.2760	7.2756	7.2761	122.7181	122.7317	122.7272	122.7375	122.7375	122.7275	122.7377	0.0013	0.0196	0.0033	0.0726	7.73E-05	0.0128
			Pro135																				
			Leu136	8.9171	8.9152	8.9155	8.9162	8.9160	8.9181	8.9191	123.3145	123.2974	123.2741	123.3001	123.2968	123.2932	123.3120	0.0020	-0.0025	0.0020	0.0726	2.58E-05	0.0208
			Gln137	8.9971	9.0000	9.0063	9.0116	9.0126	9.0195	9.0181	120.9166	120.9061	120.9194	120.9349	120.9354	120.9378	120.9415	0.0210	0.0250	0.0214	0.0726	3.10E-07	0.0242
			Cys138	8.8192	8.8208	8.8216	8.8217	8.8211	8.8213	8.8212	123.3209	123.2820	123.2663	123.2919	123.2788	123.2793	123.2734	0.0021	-0.0475	0.0076	0.0726	9.85E-06	0.0200
			Tyr139	8.8652	8.8629	8.8621	8.8665	8.8662	8.8672	8.8696	117.7277	117.7369	117.7574	117.7671	117.7634	117.7706	117.7664	0.0044	0.0388	0.0074	0.0726	1.02E-05	0.0170
			Tyr140	9.1519	9.1459	9.1411	9.1371	9.1347	9.1324	9.1264	121.0114	120.9859	120.9714	120.9239	120.9285	120.9057	120.8781	-0.0254	-0.1333	0.0327	0.0726	6.71E-05	0.0535
			Leu141	9.4687	9.4755	9.4907	9.5003	9.5003	9.5143	9.5182	129.4414	129.4667	129.4621	129.4843	129.4843	129.5025	129.5156	0.0495	0.0743	0.0508	0.0726	1.26E-05	0.0596
			Gly142																				
			Gly143	8.3485	8.3432	8.3382	8.3321	8.3321	8.3305	8.3247	103.2277	103.1913	103.1446	103.1195	103.1195	103.0815	103.0652	-0.0238	-0.1624	0.0345	0.0726	2.88E-05	0.04628
			Gly144	6.9776	6.9898	6.9881	6.9949	6.9865	6.9883	6.9928	105.9083	105.8958	105.9230	105.9298	105.9242	105.9712	105.9769	0.0151	0.0686	0.0185	0.0726	8.49E-06	0.04818
			Ala146	7.2753	7.2757	7.2796	7.2695	7.2663	7.2631	7.2588	113.9539	114.0894	114.1105	114.2454	114.2436	114.2839	114.3299	-0.0165	0.3760	0.0602	0.0726	9.08E-06	0.07652
			Thr147																				
			Asn149	6.9055	6.8938	6.8890	6.8829	6.8829	6.8769	6.8722	115.5271	115.5027	115.5086	115.5005	115.5005	115.4888	115.4863	-0.0333	-0.0408	0.0339	0.0726	1.69E-05	0.0421
			Ile150																				
			Val151	8.4910	8.4929	8.4784	8.4733	8.4733	8.4704	8.4635	105.2092	105.1869	105.1681	105.0804	105.0804	105.0297	105.0039	-0.0275	-0.2054	0.0419	0.0726	1.11E-05	0.0540
			Val152	8.0980	8.1087	8.1137	8.1157	8.1198	8.1202	8.1244	118.7815	118.7040	118.7069	118.7059	118.7000	118.6966	118.6883	0.0263	-0.0931	0.0300	0.0726	1.54E-05	0.0419
			Trp153	10.0502	10.0492	10.0499	10.0480	10.0480	10.0506	10.0465	130.2890	130.2627	130.2580	130.2538	130.2538	130.2507	130.2212	-0.0038	-0.0678	0.0111	0.0726	1.87E-03	0.1578
			Leu154	7.8773	7.8842	7.8787	7.9015	7.9027	7.9072	7.9122	126.7846	126.7477	126.8117	126.7747	126.8038	126.7762	126.8290	0.0349	0.0445	0.0355	0.0726	3.77E-06	0.0654
			Pro155																				
			Thr156	8.3786	8.3788	8.3780	8.3790	8.3790	8.3773	8.3798	106.8328	106.8393	106.8326	106.8583	106.8583	106.8505	106.8448	0.0012	0.0120	0.0022	0.0726	1.00E-03	0.0708
			Glu157	6.7330	6.7342	6.7309	6.7318	6.7318	6.7307	6.7293	116.1559	116.1588	116.1863	116.2100	116.1936	116.2127	116.2279	-0.0037	0.0719	0.0117	0.0726	3.30E-06	0.0179
			Asn158	7.6209	7.6209	7.6209	7.6225	7.6225	7.6232	7.6240	113.5229	113.5229	113.5229	113.5294	113.5461	113.5322	113.5208	0.0031	-0.0022	0.0031	0.0726	1.10E-02	0.5047
			Ile159	6.2880	6.2891	6.2888	6.2865	6.2867	6.2850	6.2855	115.4161	115.4145	115.4354	115.4392	115.4720	115.4692	115.4941	-0.0025	0.0779	0.0123	0.0726	1.35E-03	0.1436
			Leu160	8.7326	8.7390	8.7462	8.7399	8.7538	8.7577	8.7613	128.4595	128.4929	128.5193	128.5294	128.5489	128.5646	128.5826	0.0287	0.1231	0.0343	0.0726	3.71E-07	0.0442
			Phe161	9.8180	9.8247	9.8232	9.8218	9.8272	9.8287	9.8220	127.9649	128.0692	128.0794	128.1165	128.0854	128.0897	128.1106	0.0039	0.1458	0.0228	0.0726	4.47E-02	5.6167
			Gly163																				
L10	Z2	221	Cys164																				
L10		222	Met165																				
L10		223	Leu166	8.1337	8.1491	8.1509	8.1550	8.1702	8.1805	8.1478	117.3756	117.2584	117.2706	117.3440	117.3822	117.3510	117.3822	0.0141	0.0066	0.0141	0.0726		
L10		225	Asp168		8.1618	8.1654	8.1663	8.1685	8.1725	8.1719		116.2462	116.2314	116.2182	116.1637	116.1781	116.1225	0.0101	-0.1237	0.0215	0.0726	2.48E-03	0.4547
L10		228	Ala171	7.5314						7.5301	124.3721						124.5774	-0.0013	0.2053	0.0316	0.0726	3.22E-05	0.0415
L10		231	Ile174	8.8215	8.8291	8.8283	8.8281	8.8278	8.8272	8.8253	123.4484	123.5892	123.6458	123.6758	123.7112	123.7317	123.7377	0.0038	0.2894	0.0447	0.0726	1.61E-05	0.0638
L10		233	Asn176	8.0066						7.9994	124.2414						124.2530	-0.0072	0.0115	0.0075	0.0726	3.52E-04	0.0281
L10		234	Ile177																				
L10		235	Ser178	8.2455	8.2452	8.2461	8.2464				119.4541	119.4005	119.5020	119.4580							0.0726	5.57E-06	0.0548

For cells colored in grey, the first titration points were used for estimating the ^1H and $^1H,^{15}N$ Δδ since the initial data points were missing. The absolute values were not used in any further calculations, but the sign of the ^1H Δδ were used in the DSCP analysis.

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)														$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{Step5}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{Step5}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
L10		236	Asp179	7.9680						7.9652	118.3175						118.2763	-0.0028	-0.0412	0.0069	0.0726	1.46E-04	0.0290
L10		237	Ala180	6.9305	6.9241	6.9149	6.9067	6.9067	6.8959	6.8875	119.8914	119.8838	119.8682	119.8689	119.8689	119.8734	119.8752	-0.0430	-0.0162	0.0431	0.0726	2.34E-04	0.1095
L10		238	Asp181	8.0412	8.0338	8.0334	8.0301	8.0191	8.0186	8.0146	119.4405	119.4736	119.5045	119.5036	119.5288	119.5167	119.5487	-0.0266	0.1082	0.0314	0.0726	3.27E-05	0.0480
L10		240	Thr183	7.9145	7.9169	7.9202	7.9230	7.9239	7.9260	7.9281	109.0618	109.1301	109.2063	109.3063	109.3411	109.3832	109.4339	0.0136	0.3720	0.0588	0.0726	7.02E-06	0.0627
L10		241	Ala184	7.4044	7.4025	7.3991	7.3979	7.3979	7.3947	7.3956	122.1997	122.2493	122.2796	122.3241	122.3241	122.3666	122.3982	-0.0088	0.1984	0.0318	0.0726	3.98E-05	0.0443
			Trp185	7.8303	7.8226	7.8165	7.8060	7.8006	7.7992	7.7934	119.2511	119.2226	119.1863	119.2139	119.2038	119.1965	119.1775	-0.0370	-0.0736	0.0387	0.0726	6.75E-06	0.0466
			Pro186																		0.0726		
			Lys187	7.0529	7.0614	7.0666	7.0721	7.0792	7.0861	7.0907	116.6805	116.6636	116.5968	116.5871	116.5352	116.5232	116.4871	0.0379	-0.1934	0.0481	0.0726	1.54E-05	0.0582
			Thr188	8.9899	8.9982	8.9985	9.0438	9.0424	9.0509	9.0529	121.3942	121.4022	121.3574	121.3903	121.3917	121.3781	121.4293	0.0631	0.0351	0.0633	0.0726	3.61E-06	0.0839
			Leu189	8.3148	8.3111	8.3079	8.3039	8.3021	8.3018	8.2992	119.4968	119.5377	119.5495	119.5668	119.5329	119.5493	119.5959	-0.0155	0.0991	0.0217	0.0726	1.50E-04	0.0632
			Asp190	7.7812	7.7726	7.7601	7.7528	7.7485	7.7451	7.7381	119.8310	119.7999	119.7896	119.7668	119.7698	119.7570	119.7483	-0.0430	-0.0827	0.0449	0.0726	1.66E-05	0.0562
			Lys191	7.8143	7.8078	7.8039	7.7979	7.7970	7.7948	7.7926	121.5104	121.5016	121.4999	121.4831	121.4749	121.4722	121.4832	-0.0217	-0.0272	0.0221	0.0726	8.81E-06	0.0275
			Val192	8.2549	8.2548	8.2554	8.2551	8.2543	8.2546	8.2564	120.8258	120.8605	120.8607	120.8772	120.8930	120.9021	120.9147	0.0015	0.0889	0.0138	0.0726	3.43E-05	0.0201
			Lys193	8.2973	8.3006	8.3017	8.3035	8.3035	8.3046	8.3042	118.2002	118.1911	118.1834	118.1849	118.1849	118.1812	118.1794	0.0068	-0.0208	0.0075	0.0726	1.31E-05	0.0112
			Ala194	7.4521	7.4456	7.4385	7.4337	7.4316	7.4273	7.4231	116.7882	116.7794	116.7781	116.7776	116.7760	116.7651	116.7700	-0.0290	-0.0182	0.0291	0.0726	2.16E-05	0.0369
			Lys195	7.4117	7.4090	7.4080	7.4080	7.4074	7.4079	7.4086	116.4771	116.4548	116.4425	116.4335	116.4324	116.4300	116.4350	-0.0030	-0.0421	0.0072	0.0726	1.33E-05	0.0130
			Phe196	6.7081	6.7149	6.7212	6.7248	6.7291	6.7305	6.7323	113.4335	113.4265	113.4160	113.4068	113.4136	113.3949	113.3870	0.0242	-0.0464	0.0252	0.0726	5.67E-06	0.0302
			Pro197																		0.0726		
			Ser198	8.0734	8.0815	8.0854	8.0901	8.0880	8.0895	8.0963	112.9940	113.0051	113.0063	113.0139	112.9989	113.0095	113.0158	0.0229	0.0218	0.0231	0.0726	1.84E-02	2.0003
			Ala199	7.2128	7.2106	7.2075	7.2058	7.2058	7.2051	7.2046	123.3347	123.3278	123.3215	123.3170	123.3170	123.3074	123.3062	-0.0083	-0.0284	0.0093	0.0726	1.11E-05	0.0121
			Arg200	9.3448	9.3452	9.3476	9.3487	9.3539	9.3539	9.3620	124.6809	124.6609	124.6556	124.6451	124.6509	124.6423	124.6509	0.0172	-0.0300	0.0178	0.0726	1.40E-02	1.6127
			Tyr201	7.0744	7.0712	7.0668	7.0636	7.0693	7.0687	7.0644	111.2985	111.2770	111.2565	111.2116	111.2505	111.2403	111.2266	-0.0101	-0.0720	0.0150	0.0726	1.48E-06	0.0310
			Val202	9.6530	9.6567	9.6547	9.6608	9.6596	9.6616	9.6659	123.6452	123.5992	123.6049	123.5788	123.5666	123.5468	123.5483	0.0129	-0.0968	0.0197	0.0726	2.28E-05	0.0341
			Val203	8.9168	8.9147	8.9024	8.8930	8.8865	8.8899	8.8835	126.7731	126.7268	126.7183	126.6944	126.6577	126.6527	126.6493	-0.0333	-0.1238	0.0384	0.0726	3.72E-06	0.0503
			Pro204																				
			Gly205																				
L12	Z2	263	His206	7.7302	7.7327	7.7326	7.7325	7.7353	7.7378	7.7386	117.9304	117.9357	117.9465	117.9341	117.9431	117.9478	117.9364	0.0084	0.0060	0.0084	0.0726	2.66E-04	0.0383
L12		264	Gly207	9.5977							111.3142												
			Tyr209	7.0483	7.0638	7.0416	7.0366	7.0638	7.0495	7.0560	115.4016	115.5348	115.5003	115.3339	115.4085	115.2535	115.5176	0.0077	0.1159	0.0194	0.0726	1.22E-03	1.2673
			Gly210	8.2811	8.2794	8.2763	8.2718	8.2718	8.2694	8.2713	109.2273	109.1840	109.1562	109.1324	109.1324	109.1342	109.1238	-0.0098	-0.1036	0.0187	0.0726	1.26E-05	0.0280
			Gly211		9.4004	9.3963	9.3942	9.3912	9.3864	9.3852		116.1218	116.0777	116.0508	115.9907	115.9426	115.9266				0.0726	2.13E-06	0.0382
			Thr212	8.8243	8.8242	8.8226	8.8226	8.8226	8.8226	8.8224	109.4000	109.3613	109.3317	109.3135	109.3135	109.2779	109.2421	-0.0019	-0.1579	0.0244	0.0726	1.15E-04	0.0438
			Glu213	10.1292	10.1382	10.1405	10.1473	10.1531	10.1555	10.1606	126.9857	127.0159	127.0244	127.0483	127.0435	127.0538	127.0573	0.0314	0.0716	0.0333	0.0726	1.28E-05	0.0396
			Leu214	8.0177	8.0188	8.0161	8.0179	8.0167	8.0153	8.0142	122.0073	122.0014	122.0163	121.9936	122.0112	122.0284	122.0347	-0.0035	0.0274	0.0055	0.0726	2.36E-06	0.0163
			Ile215	8.1511	8.1553	8.1583	8.1680	8.1790	8.1779	8.1823	121.4559	121.4771	121.4993	121.5105	121.5192	121.5744	121.5835	0.0312	0.1276	0.0369	0.0726	4.49E-06	0.0396
			His217																				
			Thr218		7.9430	7.9460	7.9478	7.9488	7.9506	7.9526		114.0613	114.0469	114.0367	114.0398	114.0294	114.0135				0.0726	2.79E-05	0.0956
			Lys219	8.0810	8.0836	8.0876	8.0876	8.0920	8.0920	8.0922	122.1207	122.0950	122.0572	122.0572	122.0125	122.0125	121.9671	0.0111	-0.1536	0.0261	0.0726	1.18E-04	0.0492

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)														$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)		K_d (M)	$\Delta\delta_{max}$ (ppm)
				$^1H_{initial}$	$^1H_{Step1}$	$^1H_{Step2}$	$^1H_{Step3}$	$^1H_{Step4}$	$^1H_{Step5}$	$^1H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{Step4}$	$^{15}N_{Step5}$	$^{15}N_{final}$	Δ^1H	$\Delta^{15}N$	$\Delta^1H,^{15}N$	$\mu + 1\sigma$		
			Gln220	7.7876	7.7723	7.7576	7.7481	7.7416	7.7316	7.7238	117.1533	117.1466	117.1260	117.1168	117.0976	117.0813	117.0689	-0.0638	-0.0844	0.0651	0.0726	1.63E-05	0.0789
			Ile221	7.3074	7.3038	7.3017	7.3004	7.3006	7.2995	7.2989	119.1318	119.2305	119.3885	119.4150	119.5091	119.5271	119.6005	-0.0085	0.4687	0.0726	0.0726	1.54E-05	0.0874
			Val222	8.0774	8.0929	8.1008	8.1100	8.1125	8.1181	8.1218	121.3395	121.3130	121.2782	121.2302	121.2009	121.1610	121.1318	0.0444	-0.2077	0.0547	0.0726	1.11E-05	0.0661
			Asn223	8.7284	8.7205	8.7171	8.7127	8.7095	8.7080	8.7061	118.3258	118.2847	118.2580	118.2376	118.2087	118.1872	118.1775	-0.0223	-0.1483	0.0319	0.0726	5.68E-06	0.0362
			Gln224	8.1992	8.2011	8.2027	8.2051	8.2052	8.2067	8.2085	119.8788	119.8794	119.8709	119.8751	119.8681	119.8731	119.8694	0.0094	-0.0094	0.0095	0.0726	4.76E-05	0.0158
			Tyr225	7.8625	7.8673	7.8771	7.8870	7.8942	7.8984	7.9028	122.0813	122.1076	122.1289	122.1275	122.1386	122.1554	122.1621	0.0403	0.0808	0.0422	0.0726	1.75E-06	0.0437
			Ile226	8.5245	8.5267	8.5282	8.5309	8.5333	8.5334	8.5368	122.4016	122.3947	122.3919	122.3934	122.3876	122.3920	122.4113	0.0123	0.0097	0.0124	0.0726	7.27E-04	0.0715
			Glu227	8.3508	8.3579	8.3624	8.3659	8.3738	8.3751	8.3802	119.7673	119.7278	119.7223	119.7085	119.7030	119.7003	119.6971	0.0295	-0.0702	0.0314	0.0726	1.44E-05	0.0382
			Thr229	7.5014	7.5033	7.5042	7.5048	7.5029	7.5048	7.5048	112.1329	112.1270	112.1195	112.1151	112.1121	112.1061	112.1002	0.0033	-0.0328	0.0061	0.0726	6.35E-05	0.0145
			Ser230	7.6947	7.6946	7.6945	7.6946	7.6950	7.6956	7.6944	117.4603	117.4597	117.4608	117.4594	117.4685	117.4661	117.4643	-0.0004	0.0040	0.0007	0.0726	2.36E-02	0.5163
			Lys231	8.0066	8.0043	8.0036	8.0026	8.0034	8.0029	7.9995	124.2415	124.2443	124.2498	124.2493	124.2526	124.2528	124.2527	-0.0071	0.0112	0.0073	0.0726	3.27E-04	0.0265
			Pro232																				

Table S6. Experimental $^{1}H,^{15}N$ HSQC titration data, and related calculated and fitted data for **6**. Residues displaying a significant chemical shift perturbation (i.e. CSP > 0.1306, where μ and 1σ were calculated to 0.658 and 0.648, respectively) are presented at the first page, and all other residues are presented thereafter. Active site residues are colored in orange, and those that are more likely to be involved in indirect than in direct interactions are colored in pale orange.

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)										$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)	
				$^{1}H_{initial}$	$^{1}H_{Step1}$	$^{1}H_{Step2}$	$^{1}H_{Step3}$	$^{1}H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{final}$	$\Delta^{1}H$	$\Delta^{15}N$	$\Delta^{1}H,^{15}N$	μ + 1σ
			Leu26	8.9784	9.0242	9.0255	9.0304	9.0329	127.2751	126.3012	126.3244	126.3769	126.3793	0.0545	-0.8958	0.1482	0.1306
L3		64	Trp32	8.4647	8.6318	8.6293	8.6305	8.6311	120.3570	120.0617	120.0523	120.0569	120.0592	0.1664	-0.2978	0.1726	0.1306
L3		67	Val35	8.9837	9.1152	9.1070	9.0984	9.0956	128.3151	130.0007	129.9672	130.0074	130.0131	0.1118	1.6981	0.2842	0.1306
			Met40	9.2330		9.1910	9.1585	9.0930	118.5854		118.3708	118.3805	118.6400	-0.1400	0.0546	0.1403	0.1306
L7	Z1	116	His82	7.6064	7.4996	7.4970	7.4965	7.4967	106.2443	105.0671	105.0582	105.0400	105.0369	-0.1097	-1.2074	0.2157	0.1306
L7	Z1	118	His84	5.4744	5.4471	5.3553	5.3569	5.3557	113.6192	113.2985	112.2517	112.2278	112.2409	-0.1187	-1.3782	0.2430	0.1306
>L7		121	Cys87	7.8090	7.6071	7.6039	7.6049	7.6044	112.9643	114.8644	114.8592	114.8516	114.8604	-0.2047	1.8961	0.3563	0.1306
>L7		123	Gly89	8.2227	8.3923	8.3946	8.3970	8.3941	112.8046	113.3026	113.2738	113.2475	113.2667	0.1714	0.4621	0.1855	0.1306
			Gly90	8.5690	8.3184	8.3134	8.3071	8.2994	107.4157	107.6050	107.6451	107.6351	107.6600	-0.2696	0.2443	0.2722	0.1306
			Tyr93	7.3240	7.3263	7.6160	7.6157	7.6182	122.1432	122.1703	122.9412	122.9269	122.9239	0.2941	0.7807	0.3177	0.1306
			Gln100	8.0973	8.2510	8.2503	8.2515	8.2517	127.3836	127.1946	127.1752	127.2131	127.1918	0.1544	-0.1919	0.1572	0.1306
			Asp125	9.0442				8.8258	121.3444				121.3101	-0.2184	-0.0344	0.2184	0.1306
L9	Z1	196	His145	5.7465	5.6702	5.6666	5.6676	5.6701	130.5256	129.7834	129.8003	129.8086	129.8090	-0.0764	-0.7167	0.1341	0.1306
			Ala146	7.3241	7.1571	7.1559	7.1559	7.1567	114.2178	114.3569	114.3568	114.3720	114.3631	-0.1673	0.1454	0.1688	0.1306
			Asp148	10.5003	10.7376	10.7361	10.7420	10.7403	115.0988	116.2152	116.1966	116.2249	116.2059	0.2400	1.1072	0.2943	0.1306
			Leu154	7.8410	7.8541	7.9687	7.9712	7.9700	126.6575	126.6312	126.8982	126.8971	126.9000	0.1290	0.2425	0.1343	0.1306
			Gly162	8.2977	8.5871	8.5792	8.5827	8.5819	112.6972	111.7240	111.7287	111.7035	111.6966	0.2841	-1.0007	0.3232	0.1306
L10		226	Asn169	8.6978	8.8282	8.8270	8.8251	8.8223	115.2862	115.9084	115.9117	115.8987	115.8936	0.1245	0.6074	0.1557	0.1306
L10		230	Ser173	7.7068	7.8720	7.8739	7.8734	7.8720	115.3047	115.7933	115.7781	115.7704	115.7819	0.1651	0.4772	0.1807	0.1306
L10		232	Gly175	8.0540	8.2352	8.2349	8.2352	8.2355	111.0300	111.9134	111.9289	111.9330	111.9360	0.1815	0.9060	0.2289	0.1306
			Lys187	7.0498	7.0607	7.1129	7.1134	7.1127	116.7613	116.6562	115.9057	115.8931	115.8750	0.0630	-0.8863	0.1502	0.1306
			Gly211	9.4564	9.3300	9.3358	9.3363	9.3367	116.6530	115.3092	115.3370	115.3313	115.3311	-0.1197	-1.3220	0.2360	0.1306

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)										$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)	
				$^{1}H_{initial}$	$^{1}H_{Step1}$	$^{1}H_{Step2}$	$^{1}H_{Step3}$	$^{1}H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{final}$	$\Delta^{1}H$	$\Delta^{15}N$	$\Delta^{1}H,^{15}N$	$\mu + 1\sigma$
			Lys3	8.5318	8.5307	8.5270	8.5277	8.5275	123.2710	123.2547	123.2416	123.2565	123.2576	-0.0043	-0.0134	0.0048	0.1306
			Ser4	8.2775	8.2594	8.2540	8.2539	8.2538	118.2911	118.2216	118.2082	118.2007	118.1984	-0.0236	-0.0927	0.0276	0.1306
			Val5	9.1165	9.1057	9.0997	9.1013	9.1003	122.9815	123.0647	123.0783	123.0828	123.0828	-0.0163	0.1013	0.0225	0.1306
			Lys6	8.6068	8.6019	8.5995	8.5990	8.5991	126.7389	126.8992	126.9292	126.9308	126.9301	-0.0077	0.1912	0.0304	0.1306
			Ile7	7.9697	7.9736	7.9739	7.9733	7.9739	122.7620	122.9145	123.0135	123.1419	123.1339	0.0042	0.3719	0.0574	0.1306
			Ser8	8.3892	8.3951	8.3975	8.3997	8.3992	115.1889	115.1875	115.1946	115.1864	115.1869	0.0100	-0.0020	0.0100	0.1306
			Asp9	8.8056	8.7970	8.7876	8.8127	8.8249	117.5024	117.5731	117.5575	117.6110	117.6485	0.0193	0.1462	0.0296	0.1306
			Asp10	8.3743	8.2992	8.2992	8.3034	8.3048	112.9090	113.1979	113.2058	113.1824	113.1870	-0.0695	0.2780	0.0816	0.1306
			Ile11	7.1642	7.1204	7.1198	7.1199	7.1211	118.4852	118.1453	118.1458	118.1547	118.1612	-0.0431	-0.3241	0.0659	0.1306
			Ser12	8.6722	8.6697	8.6682	8.6685	8.6694	121.8596	121.8677	121.8720	121.8760	121.8783	-0.0028	0.0187	0.0040	0.1306
			Ile13	9.1842	9.1385	9.1346	9.1373	9.1361	121.7920	121.5632	121.5429	121.5429	121.5433	-0.0481	-0.2487	0.0615	0.1306
			Thr14	9.2894	9.2847	9.2751	9.2760	9.2744	122.8880	122.8623	122.8807	122.8734	122.8890	-0.0150	0.0010	0.0150	0.1306
			Gln15	9.0304	8.9825	8.9815	8.9830	8.9834	129.4815	129.1286	129.1335	129.1299	129.1314	-0.0471	-0.3500	0.0715	0.1306
			Leu16	8.6347	8.7610	8.7608	8.7603	8.7616	126.7446	126.8980	126.9084	126.9050	126.8973	0.1269	0.1527	0.1291	0.1306
			Ser17	8.4400	8.4345	8.4280	8.4286	8.4274	115.3195	115.2520	115.2214	115.2252	115.2210	-0.0126	-0.0985	0.0197	0.1306
			Asp18	8.5453				8.5789	116.4061				116.7610	0.0336	0.3549	0.0641	0.1306
			Lys19	7.5396	7.5588	7.5585	7.5603	7.5595	113.7767	113.9217	113.9433	113.9539	113.9566	0.0199	0.1799	0.0341	0.1306
			Val20	7.0012	6.9924	6.9878	6.9874	6.9873	116.1046	116.1515	116.1717	116.1658	116.1709	-0.0139	0.0663	0.0172	0.1306
			Tyr21	9.5381	9.5274	9.5237	9.5238	9.5250	126.3165	126.4059	126.4412	126.4511	126.4497	-0.0131	0.1332	0.0243	0.1306
			Thr22	9.5266	9.4557	9.4548	9.4533	9.4545	115.6314	115.2164	115.2073	115.2340	115.2304	-0.0721	-0.4009	0.0949	0.1306
			Tyr23	8.1091	8.0733	8.0727	8.0718	8.0731	124.2151	123.8230	123.8257	123.8364	123.8348	-0.0359	-0.3803	0.0687	0.1306
			Val24	8.8775	8.9306	8.9254	8.9272	8.9274	120.8391	120.9861	120.9850	120.9934	120.9883	0.0499	0.1492	0.0550	0.1306
			Ser25	9.7447				9.6713	122.3444				122.4001	-0.0734	0.0557	0.0739	0.1306
			Ala27	8.0419				8.0303	124.8189				125.6587	-0.0116	0.8398	0.1297	0.1306
L3		60	Glu28	8.4583	8.4500	8.4510	8.4578	8.4576	122.1250	121.9765	121.9760	121.9691	121.9624	-0.0007	-0.1627	0.0250	0.1306
L3		61	Ile29	8.5449				8.5155	127.1663				126.5559	-0.0294	-0.6104	0.0984	0.1306
L3		62	Glu30	8.9258	9.0044	9.0034	9.0055	9.0061	130.2056	130.5055	130.5045	130.4982	130.4979	0.0803	0.2923	0.0921	0.1306
L3		63	Gly31	8.8436	8.8435	8.8445	8.8439	8.8432	114.8769	115.4402	115.4502	115.4477	115.4569	-0.0005	0.5800	0.0892	0.1306
L3		65	Gly33	8.3092	8.2688	8.2657	8.2670	8.2662	108.9241	109.6468	109.6445	109.6373	109.6459	-0.0430	0.7218	0.1191	0.1306
L3		66	Met34	8.3977	8.3787	8.3754	8.3780	8.3790	121.2224	121.2547	121.2859	121.3026	121.3007	-0.0187	0.0784	0.0223	0.1306
L3		68	Pro36														0.1306
L3		69	Ser37	9.3608				9.4378	121.6023				122.1341	0.0770	0.5318	0.1124	0.1306
			Asn38	7.9430				7.9540	119.6954				119.5504	0.0111	-0.1450	0.0249	0.1306
			Gly39	6.5328					102.7400								0.1306
			Ile41	9.1409	9.1299	9.0895	9.0936	9.0948	122.1751	122.1048	122.0185	122.0371	122.0376	-0.0461	-0.1375	0.0507	0.1306
			Val42	9.0511	9.0440	9.0417	9.0431	9.0419	128.3958	128.1481	128.1291	128.1513	128.1410	-0.0092	-0.2547	0.0402	0.1306
			Ile43	9.3040	9.3124	9.3108	9.3350	9.3390	124.6463	124.6194	124.5863	124.6017	124.5954	0.0351	-0.0509	0.0359	0.1306
			Asn44	8.7257	8.6856	8.6854	8.6834	8.6811	119.5177	119.1967	119.2008	119.1992	119.1826	-0.0447	-0.3351	0.0682	0.1306
			Asn45	8.9372	8.9279	8.9212	8.9199	8.9186	124.9894	124.9654	124.9562	124.9432	124.9463	-0.0186	-0.0431	0.0198	0.1306
			His46	8.7988				8.8040	108.6530				108.5321	0.0051	-0.1208	0.0193	0.1306
			Gln47	8.2160	8.2186	8.2180	8.2178	8.2177	121.0867	121.1306	121.1595	121.1464	121.1504	0.0017	0.0637	0.0100	0.1306
			Ala48	8.9912	8.9835	8.9535	8.9560	8.9534	121.7027	121.6435	121.6104	121.6181	121.6223	-0.0378	-0.0803	0.0397	0.1306

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)										$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)	
				$^{1}H_{initial}$	$^{1}H_{Step1}$	$^{1}H_{Step2}$	$^{1}H_{Step3}$	$^{1}H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{final}$	$\Delta^{1}H$	$\Delta^{15}N$	$\Delta^{1}H,^{15}N$	$\mu + 1\sigma$
			Ala49	9.6288	9.6336	9.6248	9.6248	9.6248	122.1911	122.2169	122.2269	122.2269	122.2269	-0.0040	0.0358	0.0068	0.1306
			Leu50	8.6836	8.6836	8.6823	8.6833	8.6823	122.6188	122.6188	122.6188	122.6273	122.6230	-0.0013	0.0042	0.0015	0.1306
			Leu51	9.1926	9.1795	9.1837	9.1857	9.1866	127.2274	127.2141	127.0914	127.0682	126.9522	-0.0060	-0.2751	0.0428	0.1306
			Asp52	7.2900	7.2771	7.2782	7.2808	7.2792	111.5975	111.6144	111.7074	111.6525	111.6187	-0.0108	0.0211	0.0113	0.1306
			Thr53	8.1375	8.1276	8.1401	8.1166		111.7885	111.8023	111.7508	111.7361					0.1306
			Pro54														0.1306
L5		87	Ile55	7.8453	7.9201	7.9181	7.9282	7.9298	111.6209	111.1777	111.1893	111.2203	111.2215	0.0845	-0.3994	0.1045	0.1306
			Asn56	6.7395	6.7422	6.7465	6.7619	6.7764	111.1737	111.0967	111.0728	111.0387	111.0523	0.0368	-0.1214	0.0413	0.1306
			Asp57	8.9699	8.9545	8.9532	8.9634	8.9569	122.2955	122.2362	122.2700	122.7396	122.8260	-0.0130	0.5305	0.0827	0.1306
			Ala58	8.2144	8.2114	8.2138	8.2097	8.2138	125.1639	125.1747	125.2014	125.2065	125.2014	-0.0006	0.0375	0.0058	0.1306
			Gln59	8.8409	8.9624	8.9608	8.9632	8.9620	116.8716	116.6684	116.6708	116.6434	116.6579	0.1211	-0.2137	0.1255	0.1306
			Thr60	7.3214	7.3246	7.2967	7.2992	7.3046	115.9851	115.9343	116.0205	115.9973	115.9741	-0.0169	-0.0110	0.0170	0.1306
			Glu61	8.1920	8.1952	8.1902	8.1927	8.1933	123.0741	123.0808	123.1010	123.0960	123.1516	0.0014	0.0776	0.0120	0.1306
			Met62	7.2826	7.2845	7.2951	7.2972	7.2973	117.1445	117.1662	117.1936	117.1952	117.1975	0.0147	0.0530	0.0168	0.1306
			Leu63	7.6247	7.5516	7.5501	7.5483	7.5479	119.6844	120.0081	119.9927	119.9959	120.0047	-0.0768	0.3203	0.0913	0.1306
			Val64	8.7682	8.7410	8.7377	8.7344	8.7338	119.0547	118.7298	118.7364	118.7232	118.7251	-0.0344	-0.3295	0.0613	0.1306
			Asn65	8.8906	8.8901	8.8912	8.8935	8.8930	120.3815	120.4576	120.5920	120.5993	120.5993	0.0025	0.2178	0.0336	0.1306
			Trp66	7.8060	7.8025	7.8008	7.8017	7.8008	122.0978	122.2813	122.3087	122.3087	122.3033	-0.0052	0.2055	0.0320	0.1306
			Val67	8.4193	8.4470	8.4466	8.4407	8.4414	120.7662	120.7249	120.7057	120.7331	120.7064	0.0221	-0.0599	0.0239	0.1306
			Thr68	8.1706	8.1886	8.1855	8.1804	8.1786	114.9653	115.3851	115.3966	115.4012	115.4284	0.0080	0.4631	0.0717	0.1306
			Asp69	8.4143	8.4721	8.4686	8.4705	8.4699	120.3078	120.4707	120.4723	120.4799	120.4752	0.0557	0.1674	0.0613	0.1306
			Ser70	8.4682	8.4635	8.4571	8.4597	8.4609	112.6374	112.5946	112.5899	112.5774	112.5854	-0.0073	-0.0519	0.0108	0.1306
			Leu71	6.5889	6.5684	6.5633	6.5645	6.5626	115.3292	115.2749	115.2884	115.3059	115.3111	-0.0264	-0.0181	0.0265	0.1306
			His72	6.7521	6.7508	6.7535	6.7521	6.7532	112.8975	112.9659	113.0100	113.0387	113.0387	0.0011	0.1412	0.0217	0.1306
			Ala73	7.3454				7.3517	119.6117				119.6420	0.0063	0.0303	0.0078	0.1306
			Lys74	7.6558	7.6580	7.6813	7.6846	7.6834	119.2987	119.2968	119.2456	119.2390	119.2523	0.0276	-0.0464	0.0285	0.1306
			Val75	8.9146	8.9127	8.9185	8.9221	8.9209	126.6710	126.6851	126.8148	126.8294	126.8211	0.0064	0.1501	0.0240	0.1306
			Thr76	9.1846	9.2891	9.2884	9.2901	9.2874	117.3351	117.2851	117.3077	117.2928	117.3060	0.1028	-0.0291	0.1029	0.1306
			Thr77	7.7021	7.7698	7.7692	7.7686	7.7672	120.3873	120.5600	120.5746	120.5762	120.5673	0.0651	0.1800	0.0708	0.1306
			Phe78	9.1377	9.1439	9.1417	9.1423	9.1449	127.2176	126.9968	126.9400	126.9477	126.9305	0.0072	-0.2871	0.0448	0.1306
			Ile79	7.5021	7.4952	7.5536	7.5562	7.5538	126.7415	126.7685	127.0489	127.0483	127.0440	0.0517	0.3025	0.0695	0.1306
			Pro80														0.1306
			Asp81														0.1306
L7		117	Trp83	8.4067	8.3106	8.3101	8.3088	8.3091	115.4090	115.7605	115.7515	115.7490	115.7471	-0.0976	0.3382	0.1106	0.1306
>L7		119	Gly85	8.8484				8.8467	112.0618				112.0928	-0.0017	0.0310	0.0051	0.1306
>L7	Z2	120	Asp86														0.1306
>L7		122	Leu88	7.4591				7.4146	109.8561				110.3930	-0.0445	0.5369	0.0938	0.1306

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)										$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)	
				$^{1}H_{initial}$	$^{1}H_{Step1}$	$^{1}H_{Step2}$	$^{1}H_{Step3}$	$^{1}H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{final}$	$\Delta^{1}H$	$\Delta^{15}N$	$\Delta^{1}H,^{15}N$	$\mu + 1\sigma$
			Leu91	7.9117	7.9170	7.9104	7.9010	7.8997	120.9584	120.8788	120.8819	120.8697	120.8735	-0.0120	-0.0849	0.0178	0.1306
			Gly92	9.2237	9.1875	9.1871	9.1777	9.1812	108.5815	109.2282	109.2109	109.1997	109.1655	-0.0425	0.5840	0.0994	0.1306
			Leu94	7.2045	7.2032	7.1898	7.1967	7.2044	115.6817	115.5872	115.7070	115.6453	115.6178	-0.0001	-0.0639	0.0098	0.1306
			Gln95	8.6436	8.7254	8.7228	8.7249	8.7276	118.3321	118.3268	118.2845	118.3056	118.3225	0.0840	-0.0096	0.0840	0.1306
			Arg96	7.6723	7.6730	7.6898	7.6895	7.6894	120.6601	120.6204	120.5306	120.5199	120.5195	0.0171	-0.1406	0.0276	0.1306
			Lys97	7.2072	7.2012	7.2009	7.2015	7.2018	116.8044	116.7184	116.6346	116.6491	116.6400	-0.0054	-0.1645	0.0259	0.1306
			Gly98	7.7082	7.7154	7.7183	7.7177	7.7187	107.9680	107.9062	107.8837	107.8776	107.8813	0.0104	-0.0867	0.0169	0.1306
			Val99	7.5266	7.5287	7.4811	7.4821	7.4819	121.2033	121.1995	120.9139	120.9252	120.9213	-0.0447	-0.2821	0.0623	0.1306
			Ser101	8.2250	8.2156	8.2859	8.2982	8.3058	115.9294	115.9007	116.1128	116.1351	116.1718	0.0808	0.2424	0.0890	0.1306
			Tyr102	8.6382	8.5629	8.5660	8.5650	8.5705	121.9260	122.2004	122.2247	122.2085	122.2234	-0.0677	0.2974	0.0817	0.1306
			Ala103	8.9678	8.9584	8.9353	8.9385	8.9405	117.3377	117.3171	117.2972	117.2957	117.2785	-0.0273	-0.0592	0.0288	0.1306
			Asn104	8.5230	8.5104	8.5081	8.5098	8.5097	118.1783	118.6897	118.7038	118.6930	118.6919	-0.0133	0.5137	0.0801	0.1306
			Gln105	9.4835	9.4835	9.5608	9.5601	9.5617	132.1770	132.1770	132.2677	132.2761	132.2726	0.0782	0.0956	0.0796	0.1306
			Met106	7.3917	7.3783	7.3790	7.3448	7.3442	112.9073	112.8967	112.9112	113.0180	112.9495	-0.0476	0.0422	0.0480	0.1306
			Thr107	7.1170	7.0946	7.0919	7.0919	7.0922	116.1972	116.3082	116.3292	116.3082	116.3151	-0.0248	0.1179	0.0307	0.1306
			Ile108	7.2278	7.2365	7.2377	7.2387	7.2375	121.6911	121.5589	121.5211	121.5301	121.5222	0.0097	-0.1690	0.0278	0.1306
			Asp109														0.1306
			Leu110	7.6412	7.6670	7.6673	7.6683	7.6691	121.7263	121.6785	121.6852	121.6787	121.6903	0.0279	-0.0360	0.0285	0.1306
			Ala111	8.4715	8.6000	8.5976	8.5986	8.5995	121.6340	121.7804	121.7669	121.7561	121.7610	0.1280	0.1269	0.1295	0.1306
			Lys112	8.4218	8.4141	8.3841	8.3799	8.3953	116.3597	116.3379	116.1657	116.3675	116.1747	-0.0264	-0.1850	0.0388	0.1306
			Glu113	7.6510	7.6324	7.5646	7.5639	7.5639	119.6356	119.6335	119.4183	119.4181	119.4178	-0.0871	-0.2178	0.0933	0.1306
			Lys114	7.7694	7.7651	7.7650	7.7650	7.7635	115.8771	115.5424	115.5255	115.5287	115.5253	-0.0058	-0.3518	0.0544	0.1306
			Gly115	7.7145	7.7368	7.7351	7.7343	7.7367	108.6677	108.3974	108.3865	108.3840	108.3797	0.0221	-0.2880	0.0495	0.1306
L8		168	Leu116	8.0801	8.0791	8.0762	8.0791	8.0785	122.7023	123.1176	123.0920	123.1153	123.1059	-0.0015	0.4036	0.0621	0.1306
			Pro117														0.1306
			Val118														0.1306
			Pro119														0.1306
			Glu120														0.1306
			His121	7.6836	7.6777	7.6235	7.6277	7.6282	116.3066	116.3148	116.3354	116.4096	116.4261	-0.0554	0.1195	0.0584	0.1306
			Gly122	8.6322	8.6291	8.6245	8.6223	8.6192	111.2094	111.1816	111.1586	111.1260	111.1221	-0.0131	-0.0873	0.0187	0.1306
			Phe123	7.6749	7.6805	7.6787	7.6771	7.6775	115.1775	115.2414	115.2502	115.2513	115.2438	0.0027	0.0663	0.0105	0.1306
			Thr124	8.6498	8.6501	8.6673	8.6683	8.6693	112.3355	112.3874	112.7490	112.7624	112.7666	0.0195	0.4311	0.0691	0.1306
			Ser126	8.9119	8.9374	8.9363	8.9347	8.9352	115.1962	115.4602	115.4568	115.4702	115.4630	0.0233	0.2668	0.0472	0.1306
			Leu127	7.6659	7.6483	7.6458	7.6476	7.6457	121.2219	121.0016	120.9680	120.9683	120.9583	-0.0202	-0.2636	0.0453	0.1306
			Thr128	8.6560	8.6453	8.6245	8.6266	8.6230	124.5670	124.5749	124.2269	124.2301	124.2326	-0.0330	-0.3343	0.0611	0.1306
			Val129	8.8725	8.8779	8.9269	8.9272	8.9276	129.9158	129.9623	130.2847	130.2898	130.2773	0.0550	0.3615	0.0782	0.1306
			Ser130	8.4379	8.4330	8.4326	8.4331	8.4340	119.9105	119.9453	119.9742	119.9858	119.9790	-0.0040	0.0685	0.0113	0.1306
			Leu131	9.2088	9.2069	9.2051	9.2035	9.2045	132.0113	132.1652	132.2077	132.2118	132.2083	-0.0043	0.1970	0.0306	0.1306

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)										$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)	
				$^{1}H_{initial}$	$^{1}H_{Step1}$	$^{1}H_{Step2}$	$^{1}H_{Step3}$	$^{1}H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{final}$	$\Delta^{1}H$	$\Delta^{15}N$	$\Delta^{1}H,^{15}N$	$\mu + 1\sigma$
			Asp132	8.8074	8.7991	8.7991	8.7991	8.7991	127.2251	127.1665	127.1665	127.1665	127.1665	-0.0083	-0.0586	0.0123	0.1306
			Gly133	7.1939	7.1946	7.1936	7.1936	7.1943	101.9010	101.9055	101.9084	101.9014	101.9082	0.0004	0.0072	0.0012	0.1306
			Met134	7.2883	7.2799	7.2733	7.2729	7.2718	122.7818	122.7575	122.7419	122.7490	122.7404	-0.0165	-0.0413	0.0177	0.1306
			Pro135														0.1306
			Leu136	8.9102	8.9153	8.9605	8.9607	8.9620	123.2380	123.2486	123.6302	123.5981	123.6095	0.0518	0.3715	0.0771	0.1306
			Gln137	8.9740	8.9900	8.9900	8.9971	8.9981	120.8740	120.9044	120.9882	121.0339	121.0225	0.0240	0.1485	0.0332	0.1306
			Cys138	8.8177	8.8163	8.8165	8.8180	8.8186	123.3206	123.2953	123.2899	123.2939	123.2930	0.0009	-0.0276	0.0043	0.1306
			Tyr139	8.8621	8.8621	8.8955	8.8984	8.8952	117.7577	117.7577	117.7896	117.7662	117.7700	0.0331	0.0123	0.0331	0.1306
			Tyr140	9.1514	9.1373	9.0949	9.0961	9.0956	120.9559	120.9124	120.6531	120.6493	120.6531	-0.0558	-0.3028	0.0727	0.1306
			Leu141	9.4798	9.4798	9.5463	9.5493	9.5501	129.5080	129.5080	129.5257	129.5265	129.5383	0.0704	0.0303	0.0705	0.1306
			Gly142														0.1306
			Gly143	8.3402	8.3302	8.2675	8.2677	8.2666	103.2255	103.1787	102.6638	102.6660	102.6597	-0.0736	-0.5657	0.1140	0.1306
			Gly144	7.0296	7.0491	7.0510	7.0513	7.0515	105.9098	105.4748	105.4786	105.4729	105.4847	0.0219	-0.4252	0.0690	0.1306
			Thr147														0.1306
			Asn149	6.8914	6.8084	6.8067	6.8056	6.8063	115.5307	115.6106	115.6241	115.6307	115.6258	-0.0851	0.0950	0.0864	0.1306
			Ile150														0.1306
			Val151	8.4931	8.4892	8.4881	8.4845	8.4854	105.2321	105.4355	105.4696	105.4332	105.4242	-0.0078	0.1922	0.0306	0.1306
			Val152	8.1107	8.1107	8.1111	8.1057	8.1082	118.6095	118.6095	118.5203	118.5636	118.5163	-0.0026	-0.0932	0.0146	0.1306
			Trp153	10.0410	10.0412	10.0385	10.0377	10.0403	130.2486	130.2135	130.2146	130.2155	130.2091	-0.0008	-0.0395	0.0061	0.1306
			Pro155														0.1306
			Thr156	8.3842	8.3896	8.3892	8.3870	8.3890	106.9182	106.8685	106.8543	106.8516	106.8492	0.0047	-0.0690	0.0116	0.1306
			Glu157	6.7398	6.7241	6.7205	6.7217	6.7210	116.1469	116.1666	116.1670	116.1611	116.1624	-0.0188	0.0156	0.0190	0.1306
			Asn158	7.6090	7.6090	7.6573	7.6548	7.6564	113.5178	113.5178	113.5665	113.5844	113.5699	0.0474	0.0520	0.0481	0.1306
			Ile159	6.2903	6.2874	6.2772	6.2774	6.2776	115.2921	115.3460	115.6699	115.6674	115.6708	-0.0128	0.3788	0.0597	0.1306
			Leu160	8.7206	8.7632	8.7641	8.7647	8.7635	128.3726	128.7139	128.7179	128.7249	128.7125	0.0429	0.3399	0.0676	0.1306
			Phe161	9.8301	9.8379	9.8371	9.8383	9.8385	128.4630	128.2759	128.2657	128.2664	128.2685	0.0084	-0.1945	0.0311	0.1306
			Gly163		5.5819	5.5796	5.5775	5.5757		100.6371	100.6476	100.5988	100.6509				0.1306
L10	Z2	221	Cys164	6.5187					119.8041								0.1306
L10		222	Met165														0.1306
L10		223	Leu166	8.1331	8.1816	8.1809	8.1777	8.1767	117.8598	117.5157	117.5110	117.5300	117.4912	0.0436	-0.3686	0.0715	0.1306
L10		224	Lys167	8.7982	8.8382	8.8381	8.8376	8.8360	120.8235	120.2534	120.2497	120.2572	120.2426	0.0377	-0.5809	0.0970	0.1306
L10		225	Asp168	8.0834	8.0899	8.0835	8.0802	8.0770	115.8952	115.8003	115.3465	115.3135	115.2930	-0.0064	-0.6022	0.0929	0.1306
L10		227	Gln170		8.0396	8.1425		8.1392		115.3214	115.0984		115.1017	0.0996	-0.2197	0.1052	0.1306
L10		228	Ala171	7.5853				7.5230	124.5345				124.5580	-0.0623	0.0234	0.0624	0.1306
L10		229	Thr172	7.1141	7.0293	7.0323	7.0282	7.0210	118.1707	117.6962	117.7238	117.7557	117.7073	-0.0930	-0.4634	0.1172	0.1306
L10		231	Ile174	8.8496		8.8898	8.8897	8.8888	123.4975		124.0342	124.0088	124.0140	0.0391	0.5165	0.0886	0.1306
L10		233	Asn176	7.9827				7.9832	124.2414				124.2492	0.0005	0.0078	0.0013	0.1306
L10		234	Ile177	8.7570	8.8887	8.7656	8.7684	8.7690	122.0402	124.0319	122.8273	122.8283	122.8050	0.0120	0.7648	0.1183	0.1306

For cells colored in grey, the first titration points were used for estimating the ^{1}H and $^{1}H,^{15}N$ $\Delta\delta$ since the initial data points were missing. The absolute values were not used in any further calculations, but the sign of the ^{1}H $\Delta\delta$ were used in the DSCP analysis.

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)										$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)	
				$^{1}H_{initial}$	$^{1}H_{Step1}$	$^{1}H_{Step2}$	$^{1}H_{Step3}$	$^{1}H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{final}$	$\Delta^{1}H$	$\Delta^{15}N$	$\Delta^{1}H,^{15}N$	$\mu + 1\sigma$
L10		235	Ser178	8.2774	8.1984	8.1976	8.2015	8.2027	119.5550	119.1778	119.1964	119.1915	119.1952	-0.0747	-0.3598	0.0930	0.1306
L10		236	Asp179	8.1671				8.1344	118.4370				118.5083	-0.0328	0.0713	0.0345	0.1306
L10		237	Ala180	6.9431	6.8630	6.8609	6.8617	6.8615	119.9289	120.0243	120.0248	120.0198	120.0395	-0.0816	0.1106	0.0833	0.1306
L10		238	Asp181	8.0809	8.0914	8.0922	8.0864	8.0859	119.4655	119.2379	119.2307	119.2600	119.2726	0.0050	-0.1929	0.0301	0.1306
L10		239	Val182	8.5420	8.5257	8.5253	8.5082	8.5260	120.7008	120.5113	120.5114	120.4746	120.6217	-0.0160	-0.0791	0.0201	0.1306
L10		240	Thr183	7.9103	7.9177	7.9190	7.9190	7.9191	109.1765	109.1689	109.1458	109.1458	109.1442	0.0089	-0.0323	0.0102	0.1306
L10		241	Ala184	7.4079	7.3906	7.3863	7.3874	7.3862	122.2079	122.2731	122.2795	122.2825	122.2852	-0.0217	0.0773	0.0247	0.1306
			Trp185	7.8385	7.9131	7.9115	7.9111	7.9105	119.2191	118.9302	118.9267	118.9287	118.9259	0.0720	-0.2932	0.0849	0.1306
			Pro186														0.1306
			Thr188	9.0471	9.0570	9.0571	9.0585	9.0567	121.3444	121.0136	121.0251	121.0223	121.0062	0.0096	-0.3383	0.0529	0.1306
			Leu189	8.3170	8.3142	8.3090	8.3090	8.3095	119.7394	119.7128	119.7057	119.7087	119.7116	-0.0076	-0.0279	0.0087	0.1306
			Asp190	7.7686	7.7571	7.7548	7.7572	7.7546	119.6735	119.8182	119.8608	119.8748	119.8553	-0.0140	0.1818	0.0313	0.1306
			Lys191	7.7985	7.7879	7.7831	7.7839	7.7842	121.4505	121.4252	121.4112	121.4220	121.4123	-0.0143	-0.0382	0.0155	0.1306
			Val192	8.2327	8.3090	8.3064	8.3085	8.3069	120.9042	120.9277	120.9361	120.9373	120.9322	0.0743	0.0281	0.0744	0.1306
			Lys193	8.3058	8.3120	8.3267	8.3277	8.3275	118.1856	118.1864	118.2023	118.2029	118.2034	0.0216	0.0179	0.0218	0.1306
			Ala194	7.4468	7.4359	7.3955	7.3948	7.3961	116.7496	116.7364	116.6936	116.6830	116.7043	-0.0507	-0.0453	0.0512	0.1306
			Lys195	7.3950	7.3974	7.3967	7.3975	7.3982	116.4282	116.4812	116.5182	116.5067	116.4960	0.0032	0.0678	0.0109	0.1306
			Phe196	6.7229	6.7287	6.7300	6.7300	6.7300	113.5020	113.4134	113.3819	113.3819	113.3819	0.0071	-0.1201	0.0198	0.1306
			Pro197														0.1306
			Ser198	8.0278	8.0359	8.0371	8.0363	8.0347	112.3189	112.3137	112.3233	112.3139	112.3092	0.0069	-0.0097	0.0071	0.1306
			Ala199	7.2071	7.2046	7.2038	7.2043	7.2045	123.3054	123.2944	123.2909	123.2998	123.2912	-0.0026	-0.0143	0.0034	0.1306
			Arg200	9.3624	9.3464	9.3341	9.3167	9.3244	124.6472	124.5996	124.5919	124.5989	124.6013	-0.0380	-0.0459	0.0387	0.1306
			Tyr201	7.0474	7.0454	7.1225	7.1220	7.1232	111.1412	111.1307	111.4497	111.4457	111.4802	0.0758	0.3390	0.0920	0.1306
			Val202	9.6367	9.6576	9.6561	9.6545	9.6539	123.6114	123.6875	123.7007	123.7092	123.7110	0.0172	0.0996	0.0230	0.1306
			Val203	8.8874	8.8833	8.8882	8.8875	8.8883	126.7850	126.7286	126.3474	126.3566	126.3294	0.0009	-0.4556	0.0701	0.1306
			Pro204														0.1306
			Gly205	6.6797					105.3189								0.1306
L12	Z2	263	His206	7.7665	7.7337	7.7330	7.7317	7.7312	118.0620	117.9003	117.8945	117.8995	117.9067	-0.0353	-0.1552	0.0426	0.1306
L12		264	Gly207	9.5466					112.0497								0.1306
L12		265	Asp208	8.9730	8.8954	8.8951	8.8927	8.8920	119.9430	119.4490	119.4554	119.4535	119.4490	-0.0810	-0.4941	0.1111	0.1306
			Tyr209	7.0744	7.0654	7.0601	7.0622	7.0611	115.8107	115.7488	115.6703	115.7022	115.6635	-0.0133	-0.1472	0.0262	0.1306
			Gly210	8.2742	8.2825	8.2896	8.2929	8.2964	109.2279	109.2489	109.3103	109.3099	109.3350	0.0222	0.1071	0.0276	0.1306
			Thr212	8.8354	8.8102	8.8084	8.8082	8.8087	109.4553	109.1819	109.1577	109.1528	109.1582	-0.0267	-0.2971	0.0529	0.1306
			Glu213	10.1220	10.1435	10.1444	10.1432	10.1434	126.9096	126.9183	126.9104	126.8999	126.9022	0.0214	-0.0075	0.0214	0.1306
			Leu214	8.0079	8.0263	8.0278	8.0318	8.0304	121.7269	121.7831	121.7958	121.7869	121.7684	0.0225	0.0414	0.0234	0.1306
			Ile215	8.1414	8.1881	8.1870	8.1877	8.1889	121.3222	121.8023	121.8011	121.8086	121.8120	0.0475	0.4898	0.0891	0.1306
			Glu216	7.1693	7.1449	7.1449	7.1454	7.1461	118.8475	118.8354	118.8509	118.8404	118.8410	-0.0233	-0.0065	0.0233	0.1306
			His217														0.1306
			Thr218	7.9809	7.9933	7.9927	7.9886	7.9874	113.9474	113.9347	113.9324	113.9101	113.8901	0.0065	-0.0573	0.0109	0.1306

Loop	Zinc lig.	BBL no.	CcrA residue	δ (ppm)										$\Delta\delta_{final-initial}$ (ppm)		CSP (ppm)	
				$^{1}H_{initial}$	$^{1}H_{Step1}$	$^{1}H_{Step2}$	$^{1}H_{Step3}$	$^{1}H_{final}$	$^{15}N_{initial}$	$^{15}N_{Step1}$	$^{15}N_{Step2}$	$^{15}N_{Step3}$	$^{15}N_{final}$	$\Delta^{1}H$	$\Delta^{15}N$	$\Delta^{1}H,^{15}N$	$\mu + 1\sigma$
			Lys219	8.1045	8.1031	8.0861	8.0908	8.0771	121.9507	121.8895	121.8546	121.8685	121.8219	-0.0275	-0.1288	0.0339	0.1306
			Gln220	7.7886	7.7889	7.8053	7.8075	7.8081	117.2130	117.2156	117.4315	117.4352	117.4359	0.0195	0.2229	0.0394	0.1306
			Ile221	7.3437	7.3608	7.3600	7.3643	7.3645	119.3728	119.8750	119.8885	119.9175	119.9145	0.0208	0.5417	0.0859	0.1306
			Val222	8.1190	8.0434	8.0413	8.0420	8.0418	121.3753	120.9296	120.9432	120.9401	120.9265	-0.0772	-0.4488	0.1036	0.1306
			Asn223	8.7295	8.7554	8.7535	8.7564	8.7573	118.3961	118.2697	118.2790	118.2624	118.2779	0.0278	-0.1182	0.0332	0.1306
			Gln224	8.2152	8.2201	8.2182	8.2364	8.2273	119.8558	119.8593	119.8958	119.9297	119.9010	0.0121	0.0452	0.0139	0.1306
			Tyr225	7.8503	7.8839	7.8854	7.8846	7.8854	122.0587	122.1642	122.1769	122.1722	122.1811	0.0351	0.1224	0.0398	0.1306
			Ile226	8.5147	8.5419	8.5425	8.5431	8.5433	122.4502	122.4523	122.4533	122.4463	122.4643	0.0286	0.0141	0.0287	0.1306
			Glu227	8.3322	8.3847	8.3808	8.3832	8.3821	119.7497	119.7284	119.7301	119.7346	119.7346	0.0499	-0.0151	0.0500	0.1306
			Ser228	7.9386	7.9483	7.9493	7.9500	7.9505	114.0218	113.9896	113.9898	113.9922	113.9921	0.0119	-0.0297	0.0127	0.1306
			Thr229	7.5036	7.5006	7.4994	7.4987	7.4991	112.0905	112.0667	112.0572	112.0591	112.0533	-0.0045	-0.0372	0.0073	0.1306
			Ser230	7.6892	7.6875	7.6859	7.6863	7.6862	117.4253	117.4356	117.4419	117.4411	117.4381	-0.0030	0.0128	0.0036	0.1306
			Lys231	8.0129	8.0278	8.0371	8.0577	8.0601	124.2667	124.2796	124.2816	124.2832	124.2531	0.0472	-0.0136	0.0472	0.1306
			Pro232														

2.2.2 Direction of chemical shift perturbation (DCSP) analysis

Table S7. DCSP analysis data for compounds **4**–**6**. The DCSP is different if the signs of (Δ^1H,Δ^{15}N) are not all = (+,+), (+,−), (−,+) or (−,−); and the DSCP is the same if the signs of (Δ^1H,Δ^{15}N) are all = (+,+), (+,−), (−,+) or (−,−). The residues are ordered based on their position in the active site (i.e. on cross sections of the active site). For cells colored in grey, the first titration points were used in the calculations of the ^{1}H and ^{15}N Δδ since the initial data points were missing. In 1A8T, residues 88, 171 and 208 correspond to Ile, Ala and Asn (Table S1).

				Compound:	4		5		6		4	5	6	4, 5 & 6	4 & 5	5 & 6	4 & 6	
	Loop	Zinc lig.	BBL no.	CcrA residue	$\Delta\delta_{final-initial}$ (ppm)						Significant CSP			Direction of CSP				Max. no. of *1*
					Δ^1H	Δ^{15}N	Δ^1H	Δ^{15}N	Δ^1H	Δ^{15}N	$\Delta\delta(^1H,^{15}N) > \mu + 1\sigma$			*1* = different; *0* = same				
L3-L5-L7 binding site	L3		60	Glu28	0.0511	0.3058	0.0007	0.0250	-0.0007	-0.1627				*1*	*0*	*1*	*1*	*1*
	L5		87	Ile55	0.0000	0.0000	-0.0725	-0.0739	0.0845	-0.3994		SCSP		*1*	*1*	*1*	*1*	*1*
	>L7		122	Leu88	-0.0099	-0.1877	0.0112	-0.2155	-0.0445	0.5369				*1*	*1*	*1*	*1*	*1*
	>L7		123	Gly89	0.1881	0.2707	0.1288	-0.1919	0.1714	0.4621	SCSP	SCSP	SCSP	*1*	*1*	*1*	*0*	*1*
	L3		61	Ile29	-0.0927	-0.6534	-0.0513	-0.8537	-0.0294	-0.6104	SCSP	SCSP		*0*	*0*	*0*	*0*	*1*
	L3		62	Glu30	-0.1036	-0.0059	-0.1377	0.0205	0.0803	0.2923	SCSP	SCSP		*1*	*1*	*1*	*1*	*1*
	L7		117	Trp83	-0.1628	0.3354	-0.0484	-0.3176	-0.0976	0.3382	SCSP			*1*	*1*	*1*	*0*	*1*
	>L7		119	Gly85	-0.0427	0.0055	-0.0000	0.0001	-0.0017	0.0310				*0*	*0*	*0*	*0*	*1*
Catalytic site	L7	Z1	116	His82	-0.0286	0.0951	-0.0314	-0.1798	-0.1097	-1.2074			SCSP	*1*	*1*	*0*	*1*	*1*
	L7	Z1	118	His84	-0.0361	-1.4033	-0.0180	-0.9725	-0.1187	-1.3782	SCSP	SCSP	SCSP	*0*	*0*	*0*	*0*	*1*
	>L7	Z2	120	Asp86														
	L9	Z1	196	His145	0.0752	-0.1817	0.1068	-0.0877	-0.0764	-0.7167		SCSP		*1*	*0*	*1*	*1*	*1*
	L10	Z2	221	Cys164														
	L12	Z2	263	His206	0.0457	-0.6275	0.0084	0.0060	-0.0353	-0.1552	SCSP			*1*	*1*	*1*	*1*	*1*
	L10		232	Gly175	0.0972	0.4952	0.0795	0.1978	0.1815	0.9060	SCSP	SCSP	SCSP	*0*	*0*	*0*	*0*	*1*
	L10		233	Asn176	0.0032	0.0242	-0.0072	0.0115	0.0005	0.0078				*1*	*1*	*1*	*0*	*1*
L3-L10 b. site	L10		235	Ser178	-0.1091	-0.1820			-0.0747	-0.3598	SCSP						*0*	*1*
	L3		63	Gly31	-0.0065	0.5989	-0.0119	0.5082	-0.0005	0.5800		SCSP		*0*	*0*	*0*	*0*	*1*
	L3		64	Trp32	0.1093	-0.3223	0.1131	-0.1928	0.1664	-0.2978	SCSP	SCSP	SCSP	*0*	*0*	*0*	*0*	*1*
	L3		65	Gly33	-0.1073	0.7126	-0.0906	0.6140	-0.0430	0.7218	SCSP	SCSP		*0*	*0*	*0*	*0*	*1*
	L3		66	Met34	-0.0752	-0.0719	-0.0257	0.2499	-0.0187	0.0784				*1*	*1*	*0*	*1*	*1*
	L3		67	Val35	0.0705	1.1388	-0.0445	1.3190	0.1118	1.6981	SCSP	SCSP	SCSP	*1*	*1*	*1*	*0*	*1*
L10-L12 binding site	L10		224	Lys167	0.0641	-0.0654	0.0767	-0.2636	0.0377	-0.5809		SCSP		*0*	*0*	*0*	*0*	*1*
	L10		228	Ala171	-0.0235	0.2478	-0.0013	0.2053	-0.0623	0.0234				*0*	*0*	*0*	*0*	*1*
	L10		230	Ser173	0.0650	0.2964	0.0742	0.2346	0.1651	0.4772		SCSP	SCSP	*0*	*0*	*0*	*0*	*1*
	L10		225	Asp168	0.0178	-0.2636	0.0101	-0.1237	-0.0064	-0.6022				*1*	*0*	*1*	*1*	*1*
	L12		264	Gly207	0.0000	0.0000												*1*
	L10		227	Gln170	0.1293	-0.0802	0.0843	0.0116	0.0996	-0.2197	SCSP	SCSP		*1*	*1*	*1*	*0*	*1*
	L12		265	Asp208	-0.2104	-0.4666	-0.0612	-0.6240	-0.0810	-0.4941	SCSP	SCSP		*0*	*0*	*0*	*0*	*1*
											Σ*1* active site residues =			14	11	12	9	27
											Σ*1* **L3-L5-L7 binding site residues** =			5	5	5	3	7
											Σ*1* **L3-L10 binding site residues** =			0	0	0	0	3
											Σ*1* **L10-L12 binding site residues** =			2	1	2	1	7

2.2.2.1 Per residue plots of CSP data

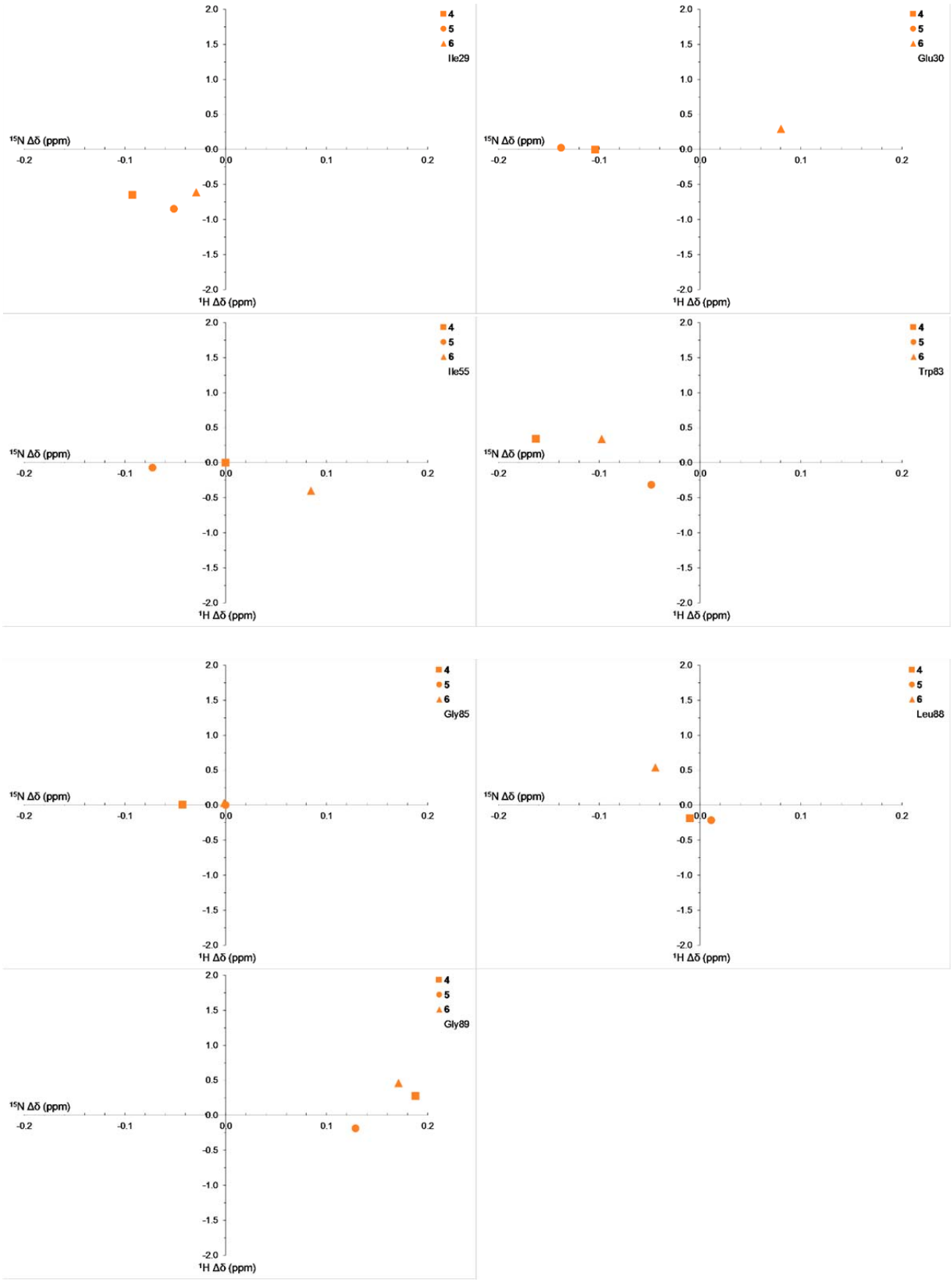


Figure S12. Per residue plots of the ^{15}N and ^{1}H Δδ for residues 29, 30, 55, 83, 85, 88 and 89 in the L3-L5-L7 binding site.

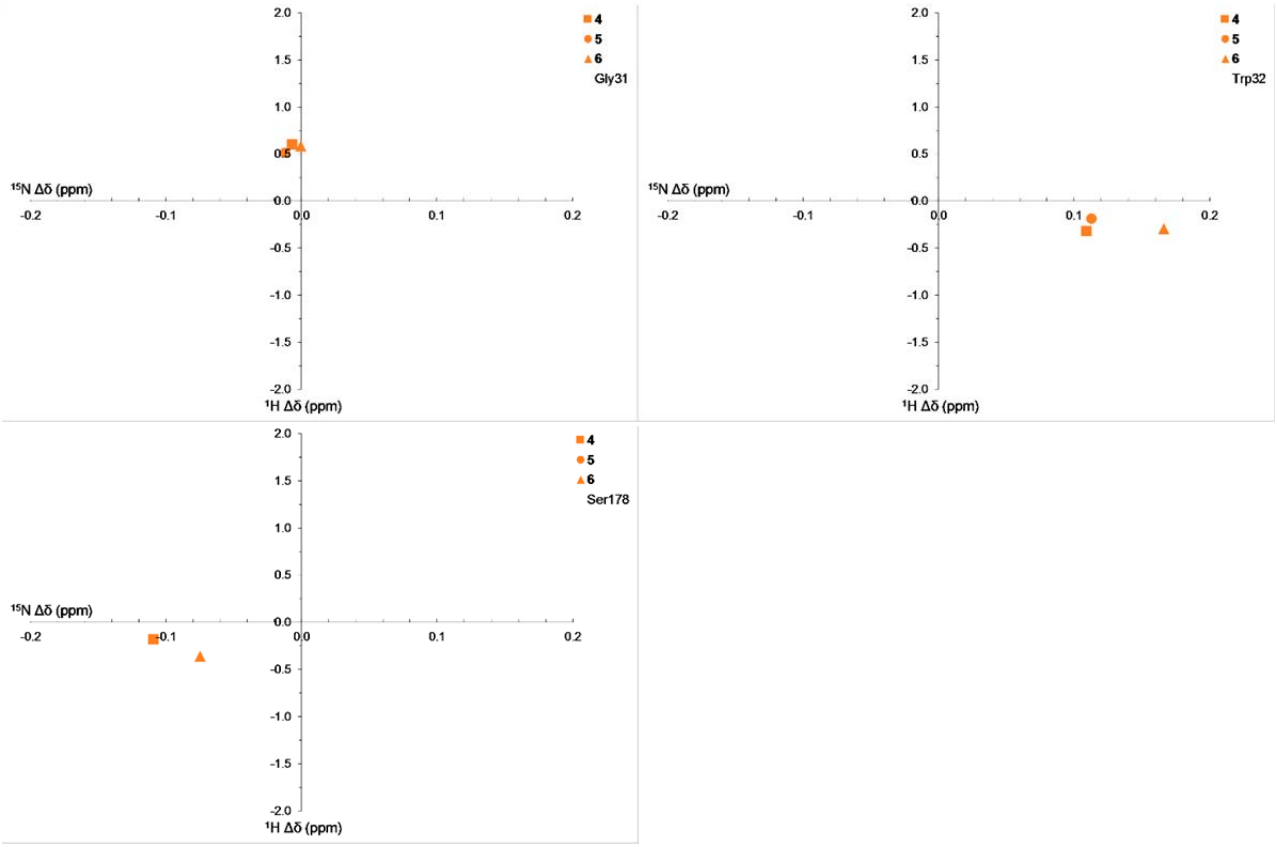


Figure S13. Per residue plots of the ^{15}N and ^{1}H Δδ for residues 31, 32 and 178 in the L3-L10 binding site.

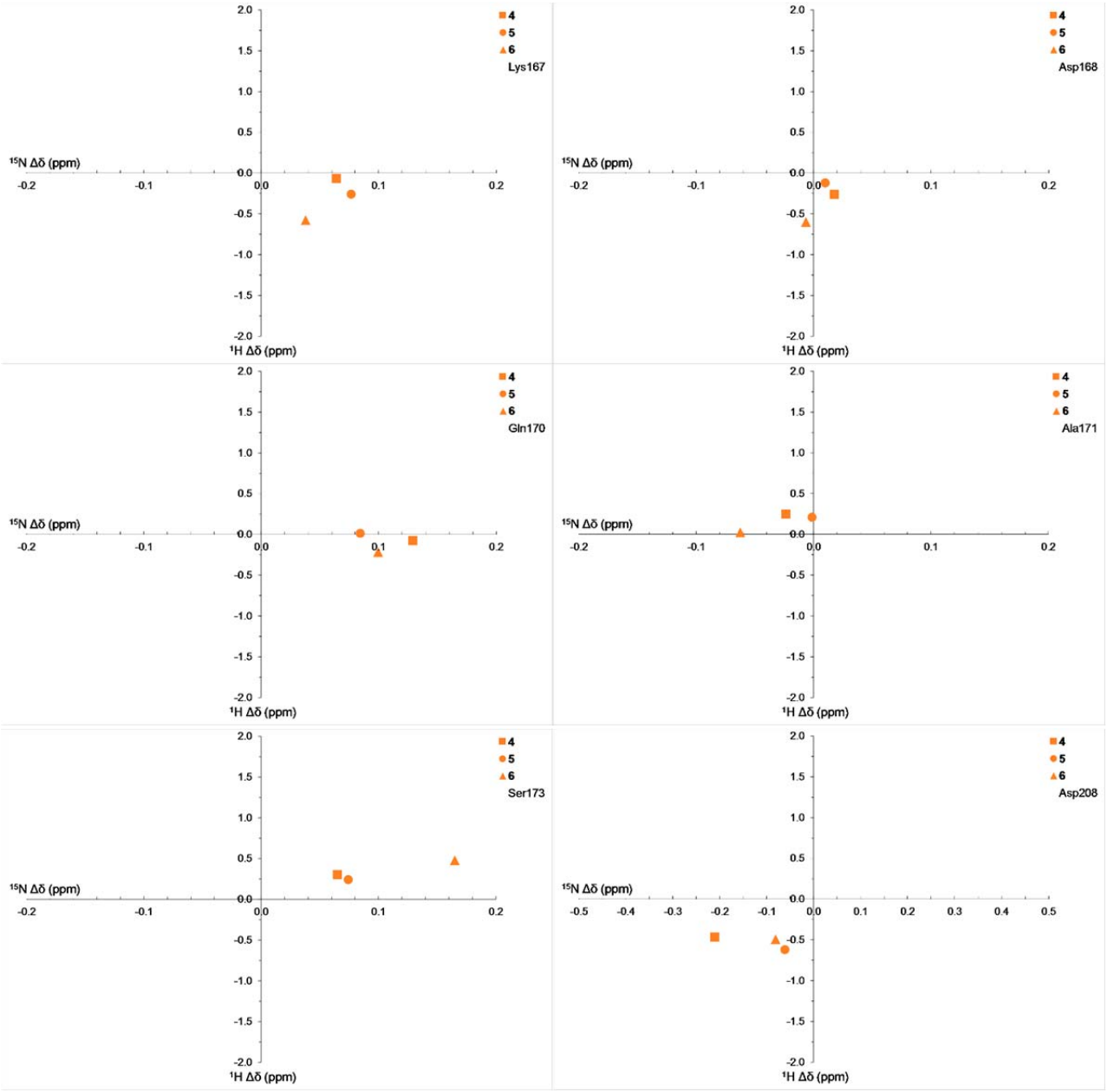


Figure S14. Per residue plots of the ^{15}N and ^{1}H Δδ for residues 167, 168, 170, 171, 173 and 208 in the L10-L12 binding site.

3 Molecular docking

3.1 General information

Schrödinger software (Schrödinger, LLC, New York, NY, 2019) was used for all the steps in the molecular docking. Unless otherwise stated, default settings were used in the computations. The crystal structure of CcrA (PDB ID 1A8T, chain A) was prepared using the Protein Preparation Wizard; involving Prime to fill in missing side chains and loops, Epik to generate heteroatom states (pH 7.0 ± 2.0), PropKa (pH 7) to optimize the hydrogen bond network (sampling of water orientations when appropriate), and the OPLS3e force field in the restrained minimization (hydrogens only). The Receptor Grid Generation module in Glide was used to define the active site by creating a rectangular box centered on the native ligand (i.e. biphenyltetrazole type inhibitor L-159.061) and extending in all directions to encompass ligands of similar size (i.e. 16.5 Å) or ligands < 22 Å (see 3.2.1 for details). Grids with 8, 1 and 0 water molecules in the active site were generated and validated, resulting in the selection of grid G1-b (i.e. a grid with 1 water molecule kept in the active site, and extending in all directions to encompass ligands < 22 Å) for all the docking studies. The ligands were converted to 3D all atom structures using LigPrep. Epik was used to generate possible ionization states at target pH 7 ± 2, including metal binding states. Tautomers were selected to be generated. The molecular docking was performed using Glide. Default settings were used for the ligand parameters. All compounds were docked using the flexible docking mode, with sampling of nitrogen inversions and ring conformations (only for L-159.061), and with extra precision (XP) rescoring. Biased sampling of torsions was selected for amides by penalizing non-planar conformations. Epik state penalties was selected to be added to the docking score. A maximum of 100 poses were selected to be generated for each ligand. Post-docking minimization was used, and per-residue interaction scores were written for residues within 10 Å from the grid center. Prime MM-GBSA rescoring of docking poses (VSGB 2.0 solvation model and OPLS3e force field) were performed providing poses ranked based on free energy of binding (ΔG_{bind} in kcal mol^{-1}).[10] For these calculations, flexibility was allowed for residues within 10 Å from the ligands, and minimization was selected as sampling method. Structural interaction fingerprints (SIFts) in Canvas was used for representation and analysis of the docking poses.[11] Side chain, zinc ion, and hydrogen bonding interactions were used to generate the SIFts. The similarity between the SIFts were evaluated using the Tanimoto similarity metric, and clustering was performed using the Flexible Beta linkage method. Epik (Schrödinger, LLC, New York, NY, 2020) was used for empirical predictions of aqueous p*K*a values (Section 3.4).

3.2 Verification of the docking method

Among the variety of CcrA inhibitors reported previously,[2, 12-29] there are crystal structures reported for four CcrA-ligand complexes.[12-13, 20] The complex with the ligand most similar in size and structure to the 2TTA type CcrA inhibitors was selected to be used in the study, i.e. PDB ID 1A8T (2.5 Å resolution) with ligand L-159.061 (Figure S15).[13]

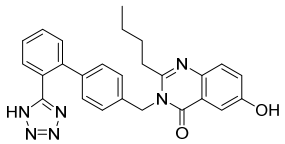


Figure S15. The structure of the native biphenyltetrazole ligand L-159.061.

3.2.1 Redocking of the native ligand

After the protein preparation and grid generation steps the native biphenyltetrazole ligand L-159.061 (Figure S15) was re-docked into the active site of CcrA (PDB ID 1A8T) for validation of the docking method. Three grids denominated G8, G1 and G0 were generated with 8, 1 and 0 water molecules, respectively, kept in the active site, and with the active site defined as a rectangular box centered on the native ligand L-159.061 and extending in all directions to encompass ligands of similar size. In the X-ray structure there are two water molecules involved in hydrogen bonding with the ligand. Water molecule number 315 is interacting with the

carbonyl oxygen, and water molecule number 289 is interacting with the ethereal oxygen, of the 4*H*-3,1-benzoxazin-4-one moiety. In grid G8, the water molecules with a distance shorter than 5 Å to a heteroatom were kept, including number 315 and 289, whereas in grid G1 only 315 was kept. Water 315 is hydrogen bonding with the neutral Lys167 residue (p*K*a 6.64 predicted by Epik), and was considered to be the most important water to keep for the docking of the native ligand. It was also considered to be relevant for the docking of the 2TTA compounds. Since the 2TTA compounds are slightly larger than the native ligand, a second G1 grid, labeled G1-b, extending in all directions to encompass ligands < 22 Å was generated. In addition, Ser37, Ser173 and Thr171 were defined as rotatable groups. The results from scoring-in-place Glide calculations of L-159.061 employing the different grids are presented in Table S8, and the poses from the XP dockings are shown in Figure S16.

Table S8. Validation of docking method by re-docking of the native biphenyltetrazole ligand L-159.061 into the active site of CcrA (PDB ID 1A8T).

Settings				Results	
Precision[a]	Ligand sampling	Post-docking minimization	Grid[b]	RMSD[c] (Å)	Glide score (kcal mol^{-1})
SP	Score in place	No	G8	0	-4.506
SP	Score in place	No	G1	0	-3.593
SP	Score in place	No	G1-b	0	-3.727
SP	Score in place	No	G0	0	-3.157
XP	Score in place	No	G8	0	-4.294
XP	Score in place	No	G1	0	-2.465
XP	Score in place	No	G1-b	0	-2.522
XP	Score in place	No	G0	0	-1.883
SP	Rigid	No	G8	0.444	-5.806
		Yes		0.858	-6.576
SP	Rigid	No	G1	0.383	-4.857
		Yes		1.505	-4.990
SP	Rigid	No	G1-b	0.495	-4.795
		Yes		1.256	-5.141
SP	Rigid	No	G0	0.658	-4.535
		Yes		1.503	-5.036
XP	Rigid	No	G8	0.582	-4.720
		Yes		1.039	-5.127
XP	Rigid	No	G1	0.344	-3.844
		Yes		1.279	-3.878
XP	Rigid	No	G1-b	0.585	-3.690
		Yes		1.250	-4.017
XP	Rigid	No	G0	0.431	-3.515
		Yes		1.187	-3.772
SP	Flexible	No	G8	1.465	-4.173
		Yes		1.148	-4.864
SP	Flexible	No	G1	1.442	-4.589
		Yes		1.281	-4.592
SP	Flexible	No	G1-b	1.091	-4.655
		Yes		1.251	-3.952
SP	Flexible	No	G0	1.402	-4.355
		Yes		1.427	-4.291
XP	Flexible	No	G8	0.950	-4.896
		Yes		1.039	-5.301
XP	Flexible	No	G1	1.278	-4.036
		Yes		1.592	-4.299
XP	Flexible	No	G1-b	1.091	-3.537
		Yes		1.270	-3.454
XP	Flexible	No	G0	1.701	-5.088
		Yes		1.780	-4.608

[a]SP = standard precision, XP = extra precision; [b]The name is related to the number of water molecules kept in the active site; [c]RMSD to the input ligand geometry using the maximum common substructure.

In the X-ray structure, the phenyl hydrogen atom (H17) that is pointing towards the tetrazole ring lies slightly out of the plane of the aromatic ring (Figure S16). Thus, if post-docking minimization is performed, the ring will never adopt the native conformation in the docking. Accordingly, larger RMSD's to the input ligand geometry were expected and observed when post-docking minimization was used in the rigid dockings. Smaller differences were observed between the RMSD's for the non-minimized and minimized ligands in the flexible dockings.

As can be seen in Table S8, both standard precision (SP) and extra precision (XP) docking with rigid and flexible ligand sampling were producing poses with a RMSD below the accepted 2 Å limit, and docking scores comparable to those obtained by the scoring-in-place calculations. Glide grid G1-b, and extra precision (XP) docking with flexible ligand sampling was selected to be used for the ligands in this study.

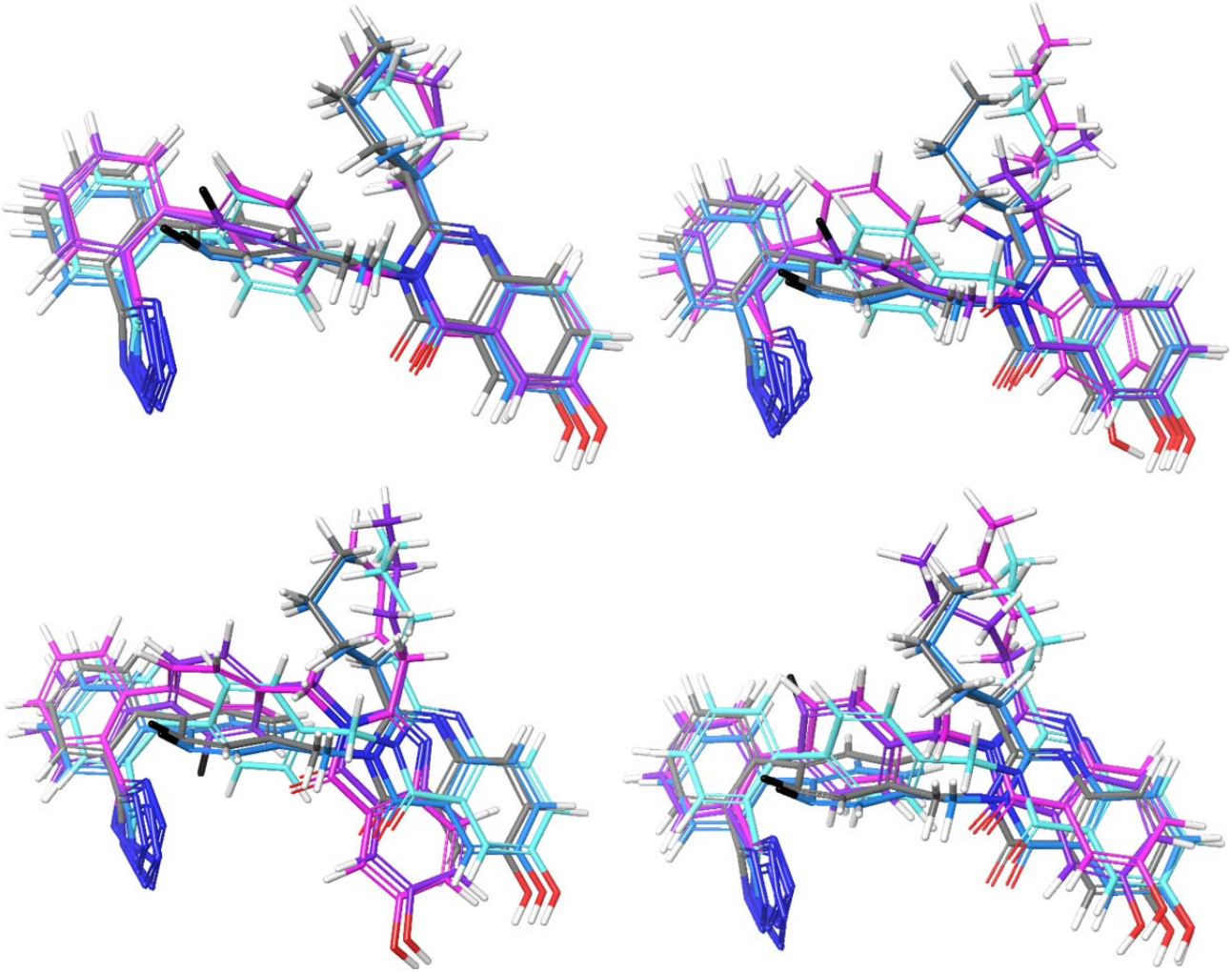


Figure S16. The original pose (grey) and re-docked poses (XP rigid with no post-docking minimization in blue; XP rigid with post-docking minimization in cyan; XP flexible with no post-docking minimization in violet; XP flexible with post-docking minimization in magenta), respectively, of the native ligand using the G8 (top left), G1 (top right), G0 (bottom left) and G1-b (bottom right) glide grids. Hydrogen H17 (PDB atom name) colored in black is out of plane of the phenyl ring in the X-ray structure (grey), and in the docked poses generated without post-docking minimization (blue and violet).

3.3 Molecular docking, MM-GBSA rescoring and SIFt based clustering of 4–6

Compounds **4**–**6** were investigated by molecular docking as described in the general information. The ionization state and tautomer variants generated by LigPrep are shown in Table S9. In line with previous data, both of the two *1H*-1,2,4-tautomers, as well as its deprotonated forms, were predicted by LigPrep, but not the less stable *4H*-1,2,4-tautomer or its deprotonated form.[30] The poses with a docking score smaller than -3 are presented in Table S10.

Table S9. Ionization state and tautomer variants of **4**–**6** generated by LigPrep and submitted to docking into CcrA.

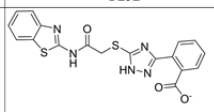
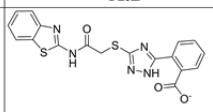
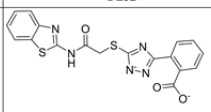
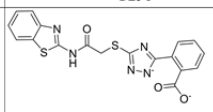
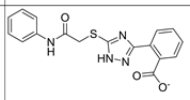
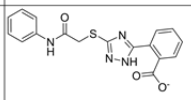
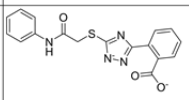
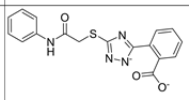
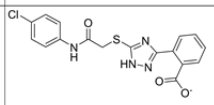
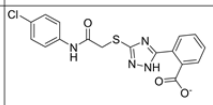
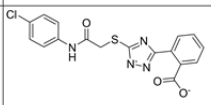
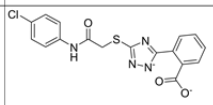
	Variant			
Cmpd (X)	**X.1**	**X.2**	**X.3**	**X.4**
4				
5				
6				

Table S10. A summary of the results from the molecular docking, MM-GBSA rescoring and SIFt based clustering of **4**–**6** divided into three sub tables labeled accordingly. The top ranked pose (MM-GBSA) among each of the three main clusters of poses are marked with bold squares.

4		XP docking		SIFt based clustering				MM-GBSA		SIFt based clustering			
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Entry ID dendrogram	Cluster index	Cluster size	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Entry ID dendrogram	Cluster index	Cluster size	Binding pose
4.2	0.427	-9.563	1	9012	1	16	L3-L5-L7	-107.26	1	9605	6	5	L3-L5-L7
4.2	0.427	-9.077	2	9022	2	13	L3-L5-L7	-105.97	2	9608	9	6	L3-L5-L7
4.3	0.573	-9.037	3	9030	2	13	L3-L5-L7	-69.08	15	9647	5	4	L3-L5-L7
4.2	0.427	-9.028	4	9023	3	7	L3-L10	-93.19	7	9623	4	5	L3-L10
4.1	0.573	-8.947	5	9020	1	16	L3-L5-L7	-95.46	6	9620	6	5	L3-L5-L7
4.2	0.427	-8.942	6	9026	2	13	L3-L5-L7	-99.33	5	9617	9	6	L3-L5-L7
4.3	0.573	-8.847	7	9034	2	13	L3-L5-L7	-56.22	20				
4.3	0.573	-8.817	8	9036	2	13	L3-L5-L7	-57.13	19				
4.3	0.573	-8.530	9	9041	2	13	L3-L5-L7	-64.56	17				
4.1	0.573	-8.487	10	9029	1	16	L3-L5-L7	-68.02	16				
4.3	0.573	-8.268	11	9043	1	16	L3-L5-L7	-70.46	14	9644	5	4	L3-L5-L7
4.1	0.573	-8.034	12	9038	1	16	L3-L5-L7	-90.67	8	9626	5	4	L3-L5-L7
4.1	0.573	-7.919	13	9039	5	8	L10-L12	-81.81	11	9635	12	4	L10-L12
4.1	0.573	-7.896	14	9040	5	8	L10-L12	-103.68	3	9611	11	6	L10-L12
4.2	0.427	-7.759	15	9042	1	16	L3-L5-L7	-101.70	4	9614	6	5	L3-L5-L7
4.3	0.573	-7.451	16					-71.81	13	9641	9	6	L3-L5-L7
4.1	0.573	-6.942	17					-84.28	10	9632	11	6	L10-L12
4.2	0.427	-5.990	18					-90.21	9	9629	6	5	L3-L5-L7
4.3	0.573	-5.712	19					-59.15	18				
4.3	0.573	-5.656	20					-71.91	12	9638	11	6	L10-L12
4.4	0.427	-4.588	21					-53.15	21				
4.4	0.427	-4.252	22					-50.32	22				
4.4	0.427	-4.069	23					-45.11	23				

5

		XP docking		SIFt based clustering				MM-GBSA		SIFt based clustering			
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Entry ID dendrogram	Cluster index	Cluster size	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Entry ID dendrogram	Cluster index	Cluster size	Binding pose
5.2	0.427	-10.095	1	9004	1	16	L3-L5-L7	-103.56	7	9668	7	6	L3-L5-L7
5.2	0.427	-10.056	2	9005	1	16	L3-L5-L7	-84.99	20				
5.2	0.427	-9.920	3	9006	3	7	L3-L10	-96.87	9	9674	4	5	L3-L10
5.2	0.427	-9.814	4	9007	1	16	L3-L5-L7	-88.29	17				
5.2	0.427	-9.544	5	9009	3	7	L3-L10	-114.55	1	9650	3	4	L3-L10
5.2	0.427	-9.489	6	9010	3	7	L3-L10	-109.70	4	9659	3	4	L3-L10
5.2	0.427	-9.468	7	9011	1	16	L3-L5-L7	-104.31	6	9665	6	5	L3-L5-L7
5.2	0.427	-9.412	8	9014	1	16	L3-L5-L7	-109.81	3	9656	4*	5	L3-L5-L7
5.2	0.427	-9.394	9	9015	3	7	L3-L10	-110.59	2	9653	3	4	L3-L10
5.2	0.427	-9.247	10	9017	1	16	L3-L5-L7	-94.86	14	9689	4*	5	L3-L5-L7
5.1	0.573	-9.058	11	9018	4	1	L3-L10	-96.55	10	9677	2	2	L3-L10
5.3	0.573	-9.032	12	9031	5	8	L10-L12	-76.75	26				
5.2	0.427	-8.976	13	9021	2	13	L3-L5-L7	-105.52	5	9662	9	6	L3-L5-L7
5.3	0.573	-8.903	14	9033	5	8	L10-L12	-76.80	25				
5.2	0.427	-8.891	15	9024	2	13	L3-L5-L7	-82.69	22				
5.1	0.573	-8.762	16					-95.52	12	9683	7	6	L3-L5-L7
5.4	0.427	-8.754	17					-76.83	24				
5.1	0.573	-8.740	18					-74.80	28				
5.4	0.427	-8.737	19					-67.77	31				
5.1	0.573	-8.691	20					-101.38	8	9671	11	6	L10-L12
5.1	0.573	-8.675	21					-95.28	13	9686	2	2	L3-L10
5.1	0.573	-8.649	22					-84.95	21				
5.1	0.573	-8.531	23					-87.25	18				
5.1	0.573	-8.483	24					-89.60	16				
5.1	0.573	-8.346	25					-95.86	11	9680	1	1	—
5.4	0.427	-8.207	26					-49.11	37				
5.3	0.573	-8.127	27					-50.12	36				
5.4	0.427	-8.070	28					-52.10	34				
5.1	0.573	-8.061	29					-77.86	23				
5.3	0.573	-7.908	30					-92.64	15	9692	11	6	L10-L12
5.1	0.573	-7.864	31					-71.35	30				
5.1	0.573	-7.606	32					-71.99	29				
5.1	0.573	-7.275	33					-85.25	19				
5.1	0.573	-7.197	34					-75.33	27				
5.4	0.427	-5.843	35					-45.90	38				
5.3	0.573	-4.842	36					-65.94	33				
5.3	0.573	-4.255	37					-67.29	32				
5.4	0.427	-4.213	38					-51.99	35				

6

		XP docking		SIFt based clustering				MM-GBSA		SIFt based clustering			
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Entry ID dendrogram	Cluster index	Cluster size	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Entry ID dendrogram	Cluster index	Cluster size	Binding pose
6.2	0.427	-10.523	1	9002	1	16	L3-L5-L7	-108.57	3	9701	7	6	L3-L5-L7
6.2	0.427	-10.226	2	9003	1	16	L3-L5-L7	-82.18	12	9728	7	6	L3-L5-L7
6.1	0.573	-9.542	3	9008	1	16	L3-L5-L7	-102.31	4	9704	7	6	L3-L5-L7
6.2	0.427	-9.412	4	9013	3	7	L3-L10	-115.16	2	9698	4	5	L3-L10
6.2	0.427	-9.308	5	9016	3	7	L3-L10	-116.52	1	9695	3	4	L3-L10
6.3	0.573	-9.304	6	9028	2	13	L3-L5-L7	-55.12	20				
6.3	0.573	-8.973	7	9032	2	13	L3-L5-L7	-74.05	17				
6.1	0.573	-8.887	8	9019	2	13	L3-L5-L7	-74.32	16				
6.3	0.573	-8.852	9	9035	5	8	L10-L12	-81.67	13	9731	11	6	L10-L12
6.1	0.573	-8.704	10	9025	2	13	L3-L5-L7	-74.77	15	9737	5	4	L3-L5-L7
6.1	0.573	-8.458	11	9027	2	13	L3-L5-L7	-96.21	6	9710	9	6	L3-L5-L7
6.2	0.427	-8.154	12	9037	1	16	L3-L5-L7	-86.27	11	9725	7	6	L3-L5-L7
6.3	0.573	-7.989	13	9044	5	8	L10-L12	-92.66	9	9719	12	4	L10-L12
6.3	0.573	-7.934	14	9045	5	8	L10-L12	-75.46	14	9734	10	1	L10-L12
6.3	0.573	-7.727	15	9046	5	8	L10-L12	-64.34	18				
6.3	0.573	-7.711	16					-93.88	7	9713	12	4	L10-L12
6.2	0.427	-7.638	17					-98.33	5	9707	9	6	L3-L5-L7
6.1	0.573	-7.240	18					-93.88	8	9716	8	1	L3-L5-L7
6.3	0.573	-5.610	19					-91.77	10	9722	12	4	L10-L12
6.4	0.427	-5.528	20					-55.43	19				
6.4	0.427	-4.212	21					-50.74	22				
6.4	0.427	-4.182	22					-46.21	23				
6.4	0.427	-4.139	23					-51.17	21				

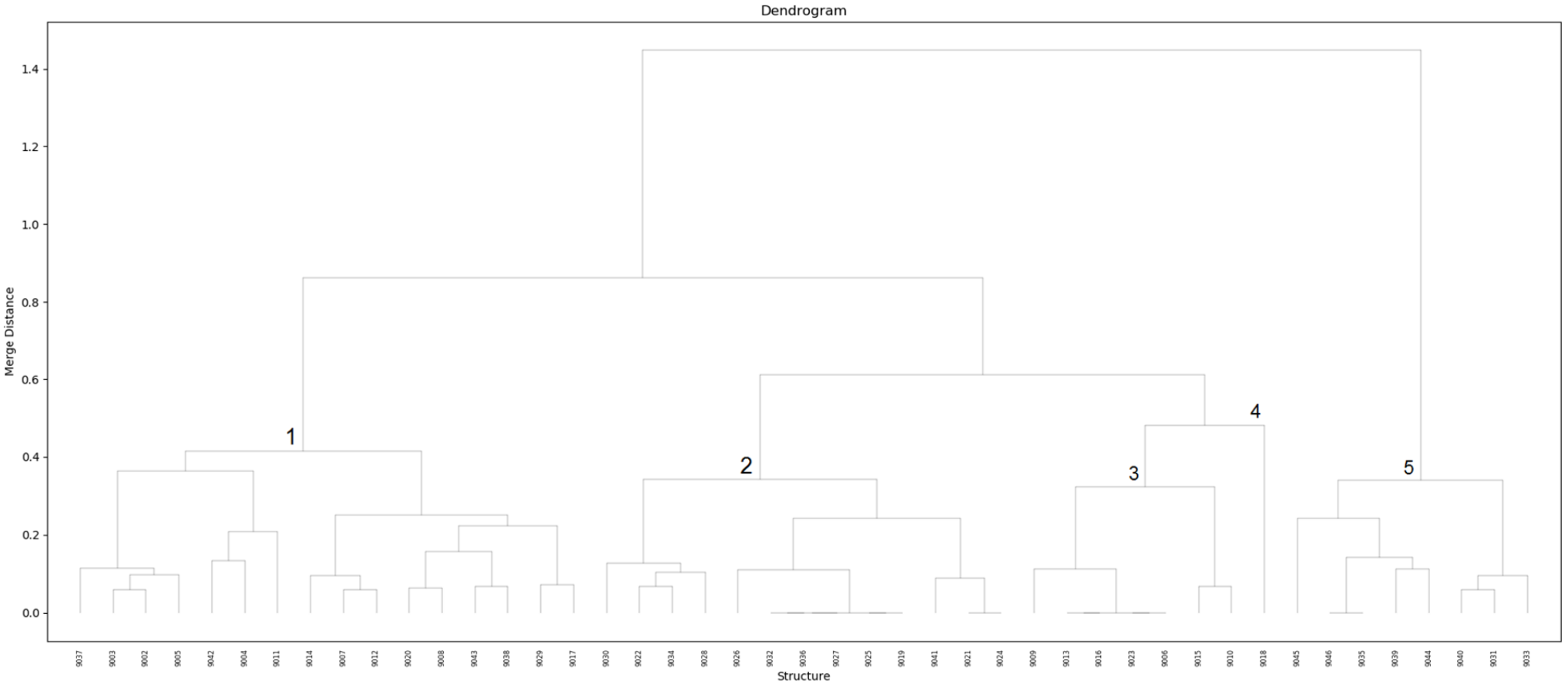


Figure S17. Hierarchical clustering of SIFts generated for the top fifteen ranked docking poses, based on the XP gscore, of **4**–**6**. Clusters 1 and 2 correspond to L3-L5-L7 poses (65%), clusters 3 and 4 correspond to L3-L10 poses (18%), and cluster 5 corresponds to L10-L12 poses (18%).

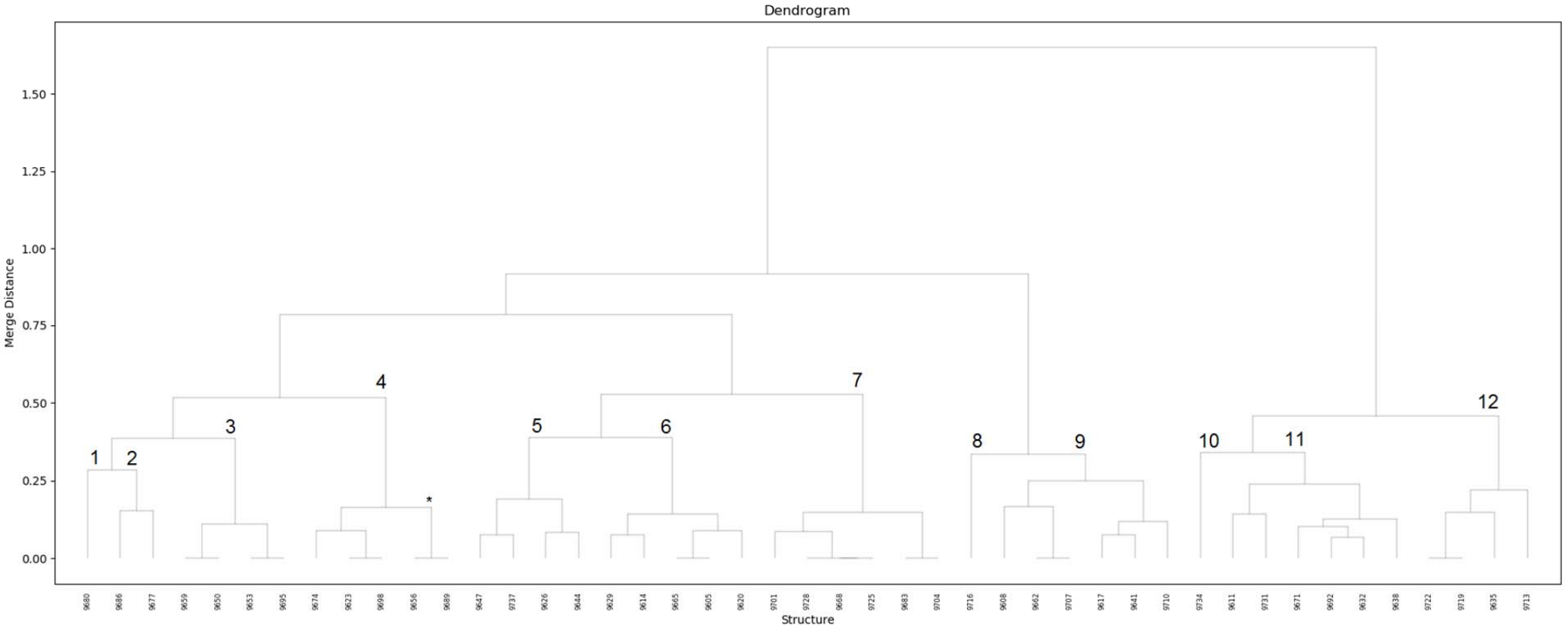


Figure S18. Hierarchical clustering of SIFts generated for the top fifteen ranked docking poses, based on the MM-GBSA binding free energies, of **4**–**6**. Cluster 1 corresponds to a minor pose(2%), clusters 2–4 correspond to L3-L10 poses (20%), clusters 4* and 5–9 correspond to L3-L5-L7 poses (53%), and clusters 10–12 correspond to L10-L12 poses (24%).

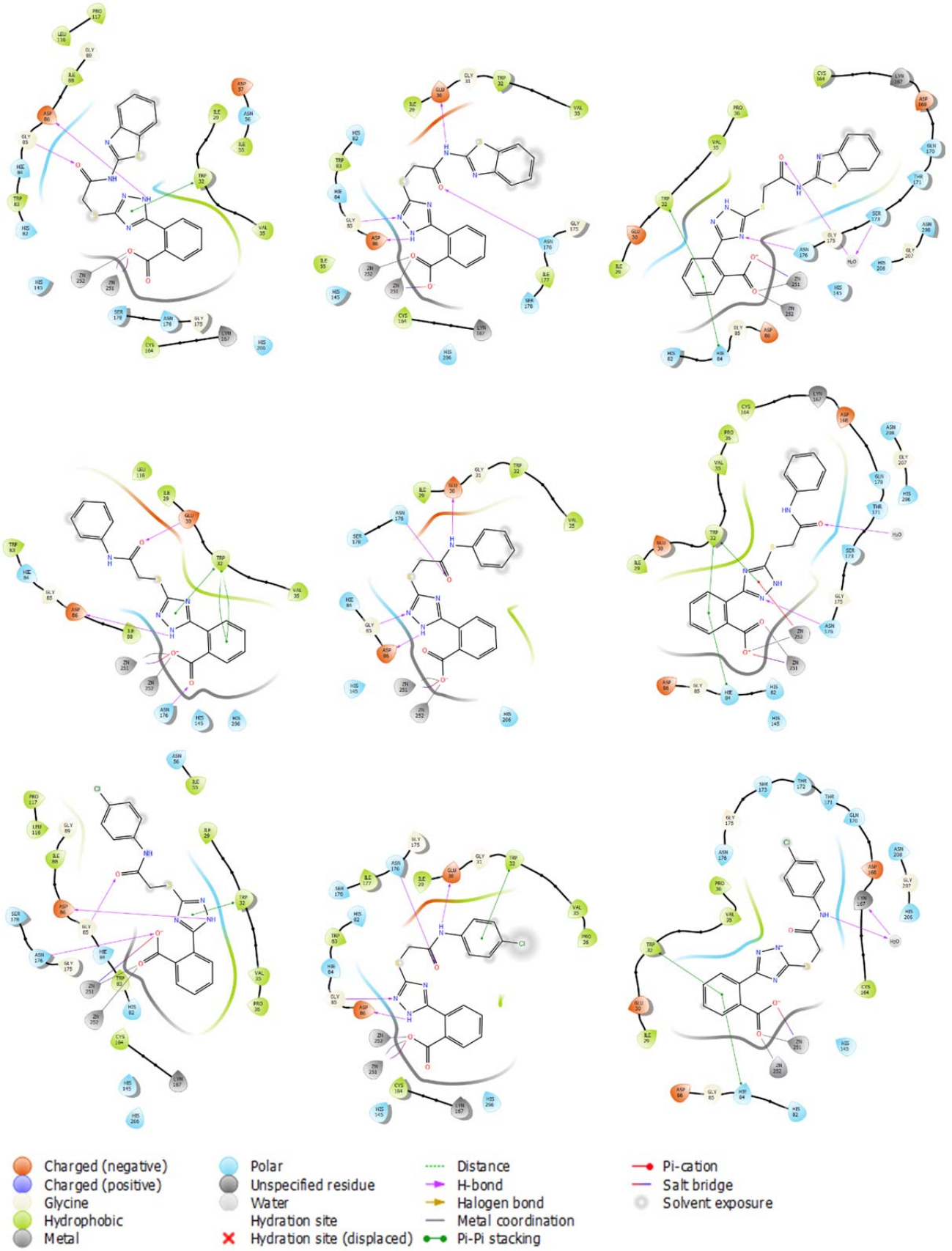


Figure S19. Ligand interaction diagrams for the top scoring pose (MM-GBSA, PDB 1A8T[2]) of **4** (top), **5** (middle) and **6** (bottom) in L3-L5-L7 (left), L3-L10 (middle) and L10 L12 (right) binding poses, respectively.

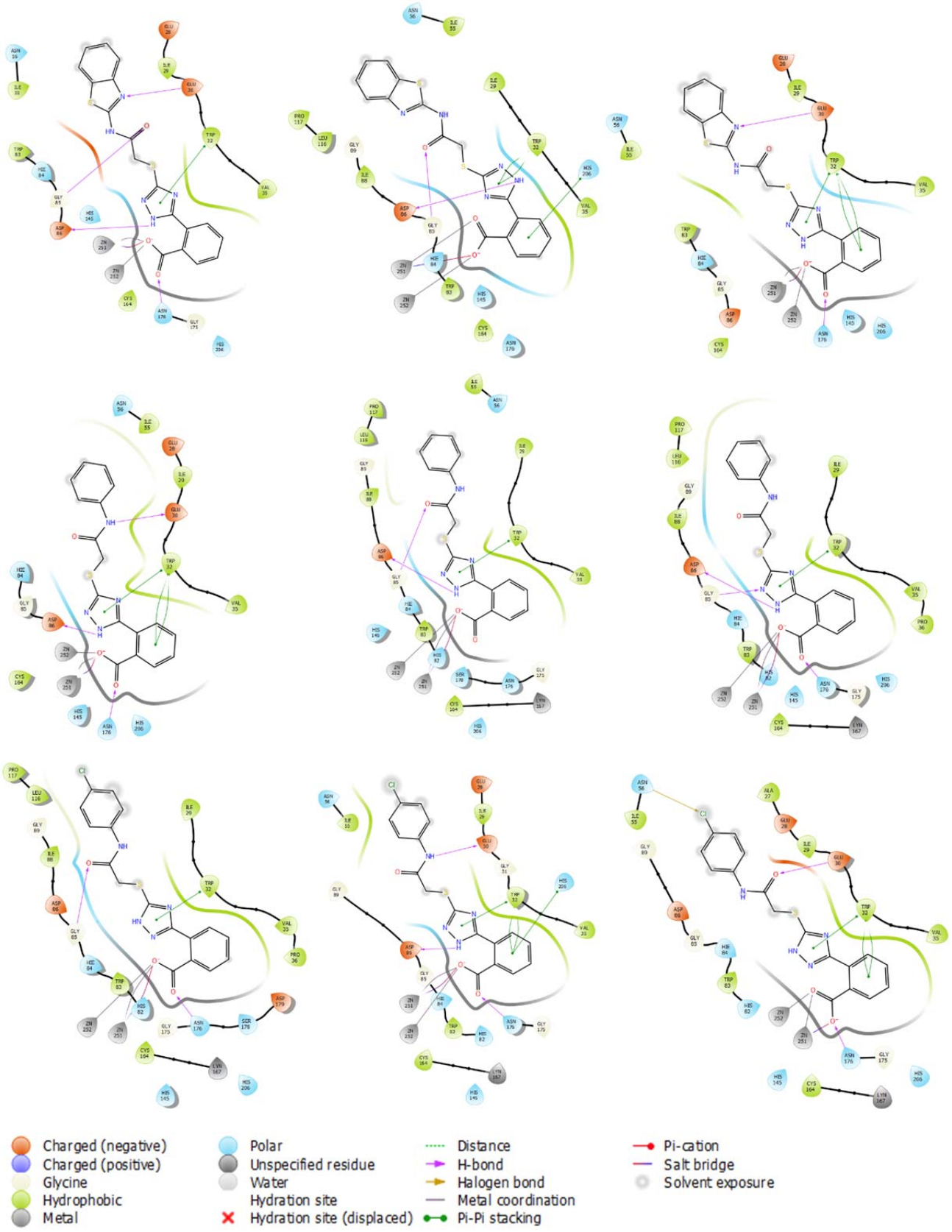


Figure S20. Ligand interaction diagrams for the L3-L5-L7 poses ranked as second (left), third (middle) and fourth (right) best (MM-GBSA, PDB 1A8T[2]), of **4** (top), **5** (middle) and **6** (bottom), respectively.

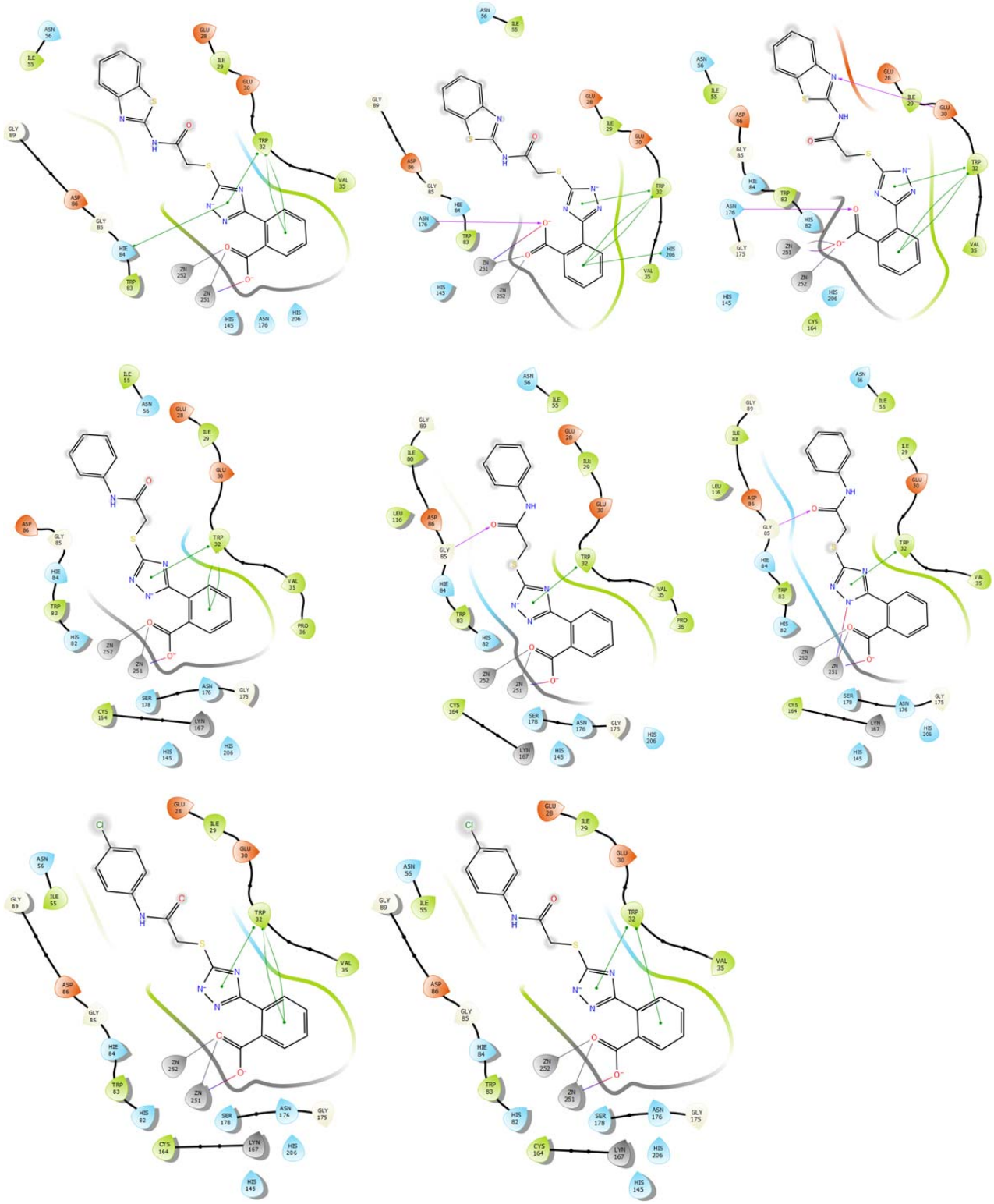
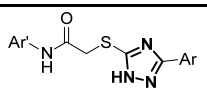
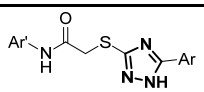
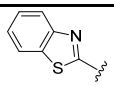
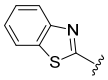
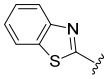
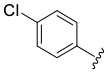
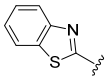
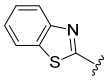


Figure S21. Ligand interaction diagrams for the top scoring L3-L5-L7 poses (MM-GBSA, PDB 1A8T[2]), of **4** (top), **5** (middle) and **6** (bottom), where the triazole moiety of the compounds are deprotonated. For **4**, the poses ranked as number 13 (left), 15 (middle) and 19 (right) are shown. For **5**, the poses ranked as number 24 (left) 36 (middle) and 37 (right) are shown. For **6**, the poses ranked as number 17 (left) and 20 (right) are shown.

3.4 Prediction of aqueous p*K*a values for 1–10

Epik (Schrödinger, LLC, New York, NY, 2020) was used for empirical predictions of aqueous p*K*a values. As shown in Table S15, *1H*-1,2,4-triazole tautomer **B** (or the corresponding deprotonated form) was the main tautomeric form among the top ranked L3-L5-L7 binding poses for **1**, **2**, **7**, **8** and **10** (Table S11), whereas for **9** it was *1H*-1,2,4-triazole tautomer **A**. The predicted p*K*a values for the triazole, and the substituents on the aryl moieties (Ar) in **1**, **2** and **7**–**10** are higher with the 1,2,4-triazole in tautomeric form **B** than in tautomeric form **A**.

Table S11. Aqueous p*K*a values at pH 7 predicted for *1*H-1,2,4-triazole tautomer **A** and **B** of **1**−**10**.

			 **A**			 **B**		
			pK_a					
Cmpd	Ar'	Ar	Triazole NH	Ar OH	Ar COOH	Triazole NH	Ar OH	Ar COOH
1			7.5 ± 2.2	8.9 ± 0.7		10.5 ± 2.2	9.4 ± 0.7	
2								
3			7.0 ± 2.2			10.1 ± 2.2		
4			7.6 ± 2.2		3.7 ± 0.6	10.5 ± 2.2		3.9 ± 0.7
5								
6								
7			6.9 ± 2.2	0.2 ± 2.0		8.8 ± 2.2	0.8 ± 2.0	
8								
9			6.9 ± 2.2	0.1 ± 2.0		8.8 ± 2.2	0.6 ± 2.0	
10								

3.5 Molecular docking, MM-GBSA rescoring and SIFt based clustering of 1–3 and 7–10

Compounds **1**–**3** and **7**–**10** were investigated by molecular docking as described in the general information. The ionization state and tautomer variants generated by LigPrep are shown in Table S12. In line with previous data, one or both of the two *1H*-1,2,4-tautomers, and often also its deprotonated forms, were predicted by LigPrep, but not the less stable *4H*-1,2,4-tautomer or its deprotonated form.[30] The docking scores (XP gscore and MM-GBSA) and the results from the SIFt based clustering are presented in Table S13.

Table S12. Ionization state and tautomer variants of CcrA inhibitors **1**–**3** and the prospective inhibitors **7**–**10** generated by LigPrep and submitted to docking into CcrA.

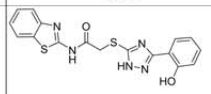
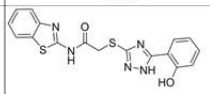
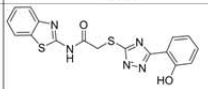
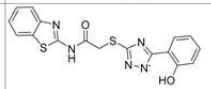
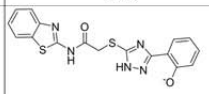
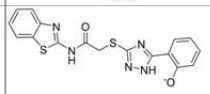
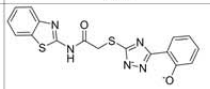
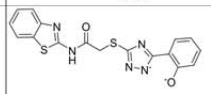
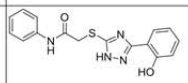
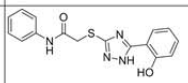
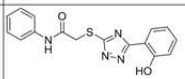
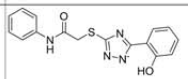
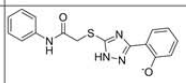
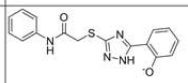
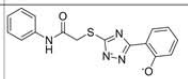
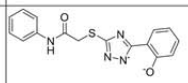
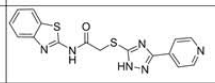
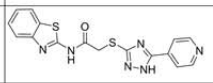
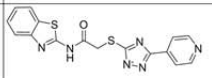
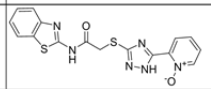
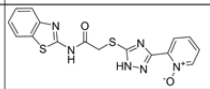
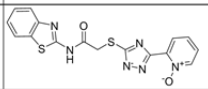
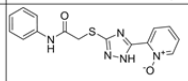
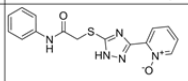
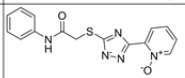
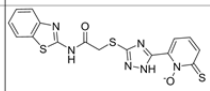
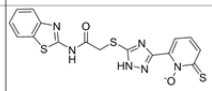
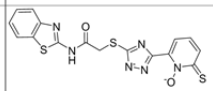
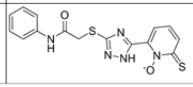
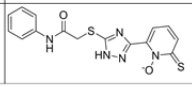
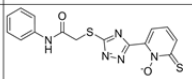
	Variant							
Cmpd (X)	**X.1**	**X.2**	**X.3**	**X.4**	**X.5**	**X.6**	**X.7**	**X.8**
1								
2								
3								
7								
8								
9								
10								

Table S13. A summary of the results from the molecular docking, MM-GBSA rescoring and SIFt based clustering of **1**–**3** and **7**–**10** divided into seven sub tables labeled accordingly. Top ranked pose (MM-GBSA) among each of the main clusters of binding poses are marked with bold squares.

1 *Phenols*		XP docking		SIFt based clustering	MM-GBSA		SIFt based clustering
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Binding pose
1.2	0.427	-4.832	1	L3-L5-L7	-74.81	2	L3-L5-L7
1.4		-4.786	2	L10-L12	-52.20	10	L10-L12
1.4		-4.688	3	L10-L12	-55.79	7	L10-L12
1.3	0.573	-4.510	4	L3-L5-L7	-47.98	16	
1.1	0.573	-4.341	5	L3-L5-L7	-68.24	5	L3-L5-L7
1.4		-4.273	6	L10-L12	-77.95	1	L10-L12
1.2	0.427	-4.177	7	L3-L5-L7	-71.33	4	L3-L5-L7
1.2	0.427	-4.131	8	L3-L5-L7	-72.51	3	L3-L5-L7
1.4		-4.064	9	L10-L12	-50.77	11	
1.2	0.427	-3.734	10		-65.04	6	L3-L10
1.1	0.573	-3.597	11		-50.41	12	
1.4		-3.487	12		-55.52	8	L10-L12
1.4		-3.480	13		-48.41	14	
1.4		-3.335	14		-48.29	15	
1.3	0.573	-3.322	15		-49.25	13	
1.3	0.573	-3.286	16		-42.06	17	
1.4		-3.154	17		-55.34	9	L10-L12

1	*Phenolate anions*	XP docking		SIFt based clustering	MM-GBSA		SIFt based clustering
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Binding pose
1.6		-9.001	1	L3-L5-L7	-53.55	18	
1.7		-8.896	2	L3-L10	-46.52	27	
1.7		-8.876	3	L3-L5-L7	-52.43	20	
1.6		-8.869	4	L3-L5-L7	-65.23	6	L3-L5-L7
1.6		-8.757	5	L3-L5-L7	-60.83	9	L3-L5-L7
1.5		-8.327	6	L10-L12	-62.09	8	L10-L12
1.5		-8.313	7	L10-L12	-58.66	11	
1.6		-8.276	8	L3-L5-L7	-56.89	13	
1.8		-8.268	9	L10-L12	-34.24	41	
1.6		-8.258	10	L3-L5-L7	-39.11	38	
1.5		-8.228	11		-73.68	4	L10-L12
1.5		-8.165	12		-57.28	12	
1.5		-8.130	13		-79.43	1	L10-L12
1.8		-8.118	14		-48.89	25	
1.8		-8.003	15		-26.97	43	
1.8		-7.997	16		-66.59	5	L10-L12
1.7		-7.881	17		-46.40	28	
1.5		-7.850	18		-49.10	24	
1.8		-7.815	19		-39.16	37	
1.7		-7.653	20		-26.58	44	
1.5		-7.610	21		-53.37	19	
1.8		-7.603	22		-9.18	46	
1.8		-7.594	23		-36.36	40	
1.5		-7.524	24		-77.11	3	L10-L12
1.7		-7.408	25		-27.69	42	
1.5		-7.365	26		-54.31	17	
1.8		-7.362	27		-64.99	7	L10-L12
1.8		-7.310	28		-41.00	34	
1.8		-7.307	29		-51.66	22	
1.8		-7.288	30		-40.37	35	
1.5		-7.286	31		-79.02	2	L10-L12
1.8		-7.253	32		-58.86	10	L10-L12
1.5		-7.249	33		-55.94	14	
1.8		-7.235	34		-37.35	39	
1.8		-7.228	35		-48.71	26	
1.5		-7.177	36		-43.69	29	
1.7		-7.175	37		-42.48	33	
1.8		-7.037	38		-52.40	21	
1.7		-7.014	39		-49.19	23	
1.8		-6.957	40		-21.73	45	
1.8		-6.713	41		-55.47	15	
1.7		-6.694	42		-42.49	32	
1.7		-6.574	43		-42.92	30	
1.7		-5.244	44		-42.91	31	
1.7		-4.729	45		-39.54	36	
1.7		-4.441	46		-55.23	16	

2 *Phenols*		XP docking		SIFt based clustering	MM-GBSA		SIFt based clustering
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Binding pose
2.4	0.427	-5.571	1	L3-L5-L7	-56.28	15	
2.3	0.573	-5.548	2	L3-L5-L7	-72.30	2	L3-L5-L7
2.3	0.573	-5.532	3	L3-L5-L7	-71.24	3	L3-L5-L7
2.3	0.573	-5.396	4	L3-L5-L7	-46.12	22	
2.3	0.573	-5.262	5	L7(Trp83)	-39.23	31	
2.1	0.573	-4.801	6	L3-L5-L7	-68.20	4	L3-L5-L7
2.3	0.573	-4.643	7	L7(Trp83)	-34.86	34	
2.2	0.427	-4.562	8	L3-L5-L7	-39.83	30	
2.1	0.573	-4.537	9	L3-L5-L7	-56.14	16	
2.4	0.427	-4.460	10	L3-L5-L7	-40.49	29	
2.3	0.573	-4.128	11		-63.76	6	L7(Trp83)
2.1	0.573	-4.119	12		-61.31	9	L3-L10
2.3	0.573	-4.089	13		-36.80	33	
2.1	0.573	-4.083	14		-59.03	12	
2.1	0.573	-3.933	15		-74.28	1	L10-L12
2.1	0.573	-3.823	16		-46.94	21	
2.1	0.573	-3.809	17		-67.54	5	L10-L12
2.1	0.573	-3.789	18		-43.14	25	
2.2	0.427	-3.773	19		-43.45	24	
2.2	0.427	-3.706	20		-60.89	10	L3-L10
2.1	0.573	-3.640	21		-59.59	11	L3-L5-L7
2.4	0.427	-3.597	22		-54.37	17	
2.1	0.573	-3.544	23		-61.49	8	
2.4	0.427	-3.520	24		-42.08	26	
2.4	0.427	-3.517	25		-50.08	19	
2.1	0.573	-3.490	26		-61.67	7	L7(Trp83)
2.4	0.427	-3.462	27		-51.39	18	
2.3	0.573	-3.459	28		-38.28	32	
2.1	0.573	-3.455	29		-44.76	23	
2.3	0.573	-3.340	30		-48.29	20	
2.4	0.427	-3.295	31		-41.91	27	
2.1	0.573	-3.283	32		-41.47	28	
2.1	0.573	-3.277	33		-58.24	13	
2.1	0.573	-3.059	34		-57.92	14	

2	*Phenolate anions*	XP docking		SIFt based clustering	MM-GBSA		SIFt based clustering
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Binding pose
2.6	0.427	-9.117	1	L3-L5-L7	-50.05	22	
2.8	0.427	-8.868	2	L3-L5-L7	-32.64	36	
2.6	0.427	-8.742	3	L3-L10	-56.23	17	
2.6	0.427	-8.693	4	L3-L5-L7	-68.62	11	
2.5	0.573	-8.634	5	L10-L12	-54.93	20	
2.6	0.427	-8.617	6	L3-L5-L7	-81.67	1	L3-L5-L7
2.7	0.573	-8.572	7	L10-L12	-45.36	28	
2.7	0.573	-8.506	8	L10-L12	-30.03	40	
2.8	0.427	-8.489	9	L10-L12	-29.54	41	
2.8	0.427	-8.422	10	L3-L5-L7	-49.81	23	
2.7	0.573	-8.413	11		-32.18	37	
2.8	0.427	-8.409	12		-31.28	39	
2.6	0.427	-8.344	13		-52.25	21	
2.6	0.427	-8.318	14		-68.80	10	L7(Trp83)
2.6	0.427	-8.308	15		-68.46	12	
2.7	0.573	-8.248	16		-48.82	24	
2.6	0.427	-8.215	17		-80.60	2	L3-L10
2.5	0.573	-8.147	18		-70.51	7	L3-L5-L7
2.5	0.573	-8.119	19		-59.88	14	
2.8	0.427	-8.101	20		-47.06	26	
2.6	0.427	-8.074	21		-62.04	13	
2.7	0.573	-8.009	22		-29.40	42	
2.5	0.573	-7.928	23		-55.32	18	
2.6	0.427	-7.786	24		-72.65	6	L3-L10
2.7	0.573	-7.772	25		-42.01	31	
2.5	0.573	-7.750	26		-74.16	5	L10-L12
2.8	0.427	-7.704	27		-34.82	35	
2.6	0.427	-7.658	28		-79.74	3	L3-L10
2.5	0.573	-7.640	29		-56.57	16	
2.7	0.573	-7.623	30		-29.28	43	
2.8	0.427	-7.603	31		-44.80	30	
2.6	0.427	-7.584	32		-47.19	25	
2.7	0.573	-7.570	33		-31.54	38	
2.7	0.573	-7.529	34		-37.14	34	
2.8	0.427	-7.496	35		-44.83	29	
2.7	0.573	-7.485	36		-41.07	32	
2.5	0.573	-7.475	37		-68.96	9	L10-L12
2.5	0.573	-7.416	38		-76.15	4	L10-L12
2.5	0.573	-7.409	39		-55.10	19	
2.5	0.573	-7.387	40		-57.33	15	
2.5	0.573	-7.379	41		-70.41	8	L10-L12
2.7	0.573	-7.368	42		-22.79	44	
2.6	0.427	-6.901	43		-37.42	33	
2.8	0.427	-3.621	44		-46.75	27	

3		XP docking		SIFt based clustering	MM-GBSA		SIFt based clustering
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Binding pose
3.2	0.427	-4.912	1	L10-L12	-68.86	4	L10-L12
3.2	0.427	-4.830	2	L10-L12	-49.34	13	
3.2	0.427	-4.576	3	L10-L12	-67.65	5	L10-L12
3.2	0.427	-4.491	4	L7(Trp83)	-72.15	2	L7(Trp83)
3.1	0.573	-4.383	5	L7(Trp83)	-49.77	12	
3.2	0.427	-4.352	6	L10-L12	-57.11	9	L10-L12
3.3	0.573	-4.296	7	L3-L5-L7*	-55.16	11	L3-L5-L7*
3.2	0.427	-4.214	8	L7(Trp83)	-77.42	1	L7(Trp83)
3.1	0.573	-4.152	9	L7(Trp83)	-57.77	8	L7(Trp83)
3.3	0.573	-3.914	10		-46.63	14	
3.2	0.427	-3.798	11		-69.84	3	L10-L12
3.1	0.573	-3.748	12		-65.51	6	L10-L12
3.2	0.427	-3.471	13		-46.13	15	
3.2	0.427	-3.325	14		-63.93	7	L7(Trp83)
3.3	0.573	-3.116	15		-24.48	16	
3.1	0.573	-3.029	16		-56.29	10	L10-L12

L3-L5-L7* = flipped Binding pose with the benzothiazole in the catalytic zinc site and the pyridine in the L3-L5-L7 binding site

7		XP docking		SIFt based clustering	MM-GBSA		SIFt based clustering
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Binding pose
7.2	0.573	-7.880	1	L3-L5-L7	-62.41	3	L3-L5-L7
7.2	0.573	-7.758	2	L3-L5-L7	-71.28	1	L3-L5-L7
7.2	0.573	-7.297	3	L3-L5-L7	-58.48	6	L3-L5-L7
7.2	0.573	-6.404	4	L3-L5-L7	-62.24	4	L3-L5-L7
7.2	0.573	-6.397	5	L3-L5-L7	-41.96	13	
7.2	0.573	-6.200	6	L7(Trp83)	-54.72	9	L7(Trp83)
7.2	0.573	-6.195	7	L3-L5-L7	-64.07	2	L3-L5-L7
7.3	1	-6.066	8	L3-L5-L7	-51.26	11	
7.2	0.573	-5.928	9	L3-L5-L7	-60.57	5	L3-L5-L7
7.3	1	-5.864	10	L3-L5-L7	-49.33	12	
7.2	0.573	-4.754	11		-56.59	7	L7(Trp83)
7.2	0.573	-4.255	12		-53.25	10	L7(Trp83)
7.2	0.573	-4.154	13		-56.42	8	L7(Trp83)

8		XP docking		SIFt based clustering	MM-GBSA		SIFt based clustering
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Binding pose
8.3	1	-7.773	1	L10-L12	-39.51	14	
8.2	0.573	-7.756	2	L10-L12	-40.03	13	
8.3	1	-7.598	3	L7(Trp83)	-38.89	15	
8.2	0.573	-7.542	4	L3-L5-L7	-47.03	7	L3-L5-L7
8.3	1	-7.409	5	L3-L5-L7	-31.63	18	
8.3	1	-6.862	6	L3-L10	-45.97	9	L3-L10
8.3	1	-5.833	7	L7(Trp83)	-36.59	17	
8.2	0.573	-5.750	8	L3-L5-L7	-53.86	5	L3-L5-L7
8.3	1	-5.708	9	L3-L5-L7	-56.40	4	L3-L5-L7
8.3	1	-4.443	10	L3-L5-L7	-44.56	10	L3-L5-L7
8.3	1	-4.195	11		-36.73	16	
8.1	0.427	-4.182	12		-41.46	12	
8.3	1	-4.179	13		-42.13	11	
8.1	0.427	-3.922	14		-47.06	6	—
8.2	0.573	-3.891	15		-46.38	8	L10-L12
8.1	0.427	-3.365	16		-61.71	3	L7(Trp83)
8.1	0.427	-3.341	17		-67.41	1	L7(Trp83)
8.2	0.427	-2.377	18		-66.65	2	L7(Trp83)

9		XP docking		SIFt based clustering	MM-GBSA		SIFt based clustering
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Binding pose
9.2	0.573	-8.415	1	L3-L5-L7	-64.89	3	L3-L5-L7
9.1	0.427	-7.541	2	L3-L5-L7	-80.36	1	L3-L5-L7
9.3	1	-7.235	3	L3-L5-L7	-21.91	9	L3-L5-L7
9.1	0.427	-6.527	4	L7(Trp83)	-65.64	2	L7(Trp83)
9.1	0.427	-6.258	5	L7(Trp83)	-56.46	4	L7(Trp83)
9.3	1	-5.748	6	L3-L5-L7	-40.03	8	L3-L5-L7
9.3	1	-5.621	7	L7(Trp83)	-44.41	6	L7(Trp83)
9.3	1	-5.345	8	L10-L12	-2.11	11	
9.2	0.573	-4.841	9	—	-44.00	7	L10(174Ile)
9.1	0.427	-4.765	10	L3-L5-L7	-54.90	5	L3-L5-L7
9.3	1	-4.060	11		-16.26	10	

10		XP docking		SIFt based clustering	MM-GBSA		SIFt based clustering
Cmpd. variant	Tautomer probability	XP gscore kcal mol^{-1}	Rank	Binding pose	ΔG_{bind} kcal mol^{-1}	Rank	Binding pose
10.2	0.573	-8.253	1	L3-L5-L7	-56.09	9	L3-L5-L7
10.2	0.573	-7.989	2	L3-L5-L7	-73.11	4	L3-L5-L7
10.1	0.427	-7.960	3	L7(Trp83)	-66.15	7	L7(Trp83)
10.2	0.573	-7.917	4	L3-L5-L7	-55.85	10	L3-L5-L7
10.1	0.427	-7.868	5	L3-L10	-76.28	3	L3-L10
10.1	0.427	-7.845	6	L3-L10	-71.78	5	L3-L10
10.1	0.427	-7.844	7	L3-L5-L7	-77.18	2	L3-L5-L7
10.1	0.427	-7.749	8	L3-L5-L7	-68.09	6	L3-L5-L7
10.1	0.427	-7.474	9	L3-L10	-80.57	1	L3-L10
10.3	1	-7.428	10	L3-L10	-47.66	13	
10.2	0.573	-7.236	11		-58.16	8	L3-L5-L7
10.3	1	-7.050	12		-35.92	19	
10.3	1	-6.920	13		-48.41	11	
10.3	1	-6.510	14		-32.99	21	
10.3	1	-6.272	15		-37.76	17	
10.3	1	-6.244	16		-47.33	14	
10.3	1	-6.064	17		-48.04	12	
10.3	1	-5.834	18		-39.61	16	
10.3	1	-5.361	19		-36.06	18	
10.3	1	-5.223	20		-33.80	20	
10.3	1	-5.040	21		-41.38	15	

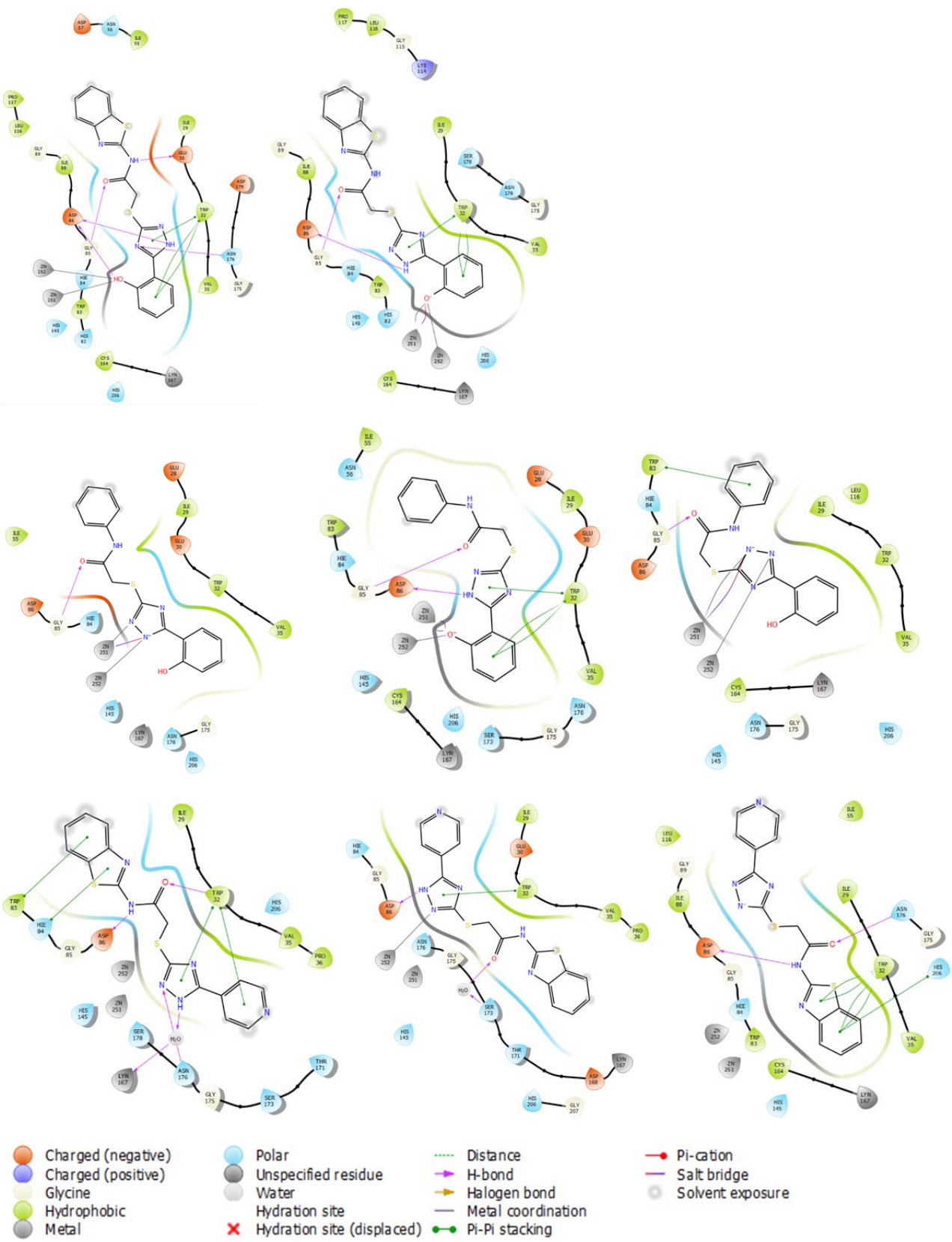


Figure S22. Ligand interaction diagrams for relevant poses (MM-GBSA, PDB 1A8T[2]) of **1** (top), **2** (middle) and **3** (bottom). For **1**, top scoring L3-L5-L7 poses of the phenol (left) and phenolate (right) forms are shown. For **2**, the top scoring L3-L5-L7 poses of the phenol (left) and phenolate (middle) forms, as well as the L7(Trp83) pose ranked as number 6 (in which the triazole coordinate the zinc ions) are shown. For **3**, the top scoring L7(Trp83) (left) and L10L12 poses (middle) are shown, as well as the minor L3-L5-L7 pose ranked as number 11 that is discussed in the paper (right).

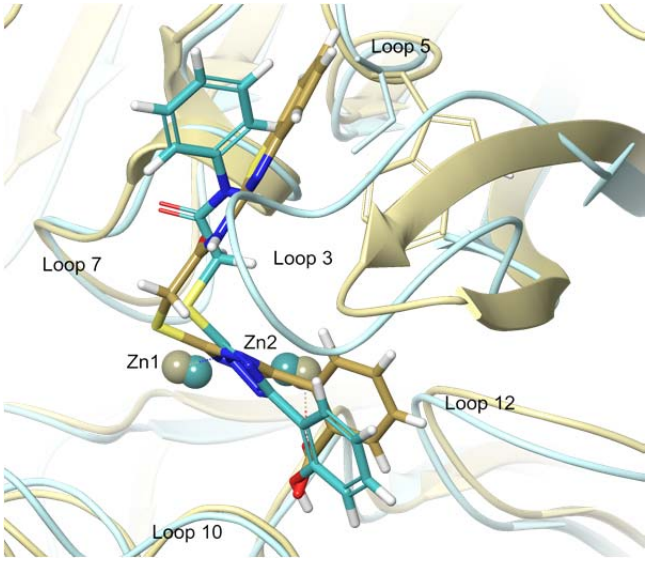


Figure S23. The top ranked pose (MM-GBSA) from the docking of **2** (turquoise) into the active site of CcrA (PDB 1A8T[2]) (for interaction diagram see Figure S22) superimposed with the crystal structure of **4** (light brown) in complex with VIM-2 (PDB 5LSC[31]). The triazole moiety is negatively charged in both **2** and **4**. The larger angles between the triazole nitrogens and the zinc ions in CcrA is a result of the shorter distance between the two zinc ions in CcrA compared to VIM-2 (2.84 Å versus 3.88 Å).

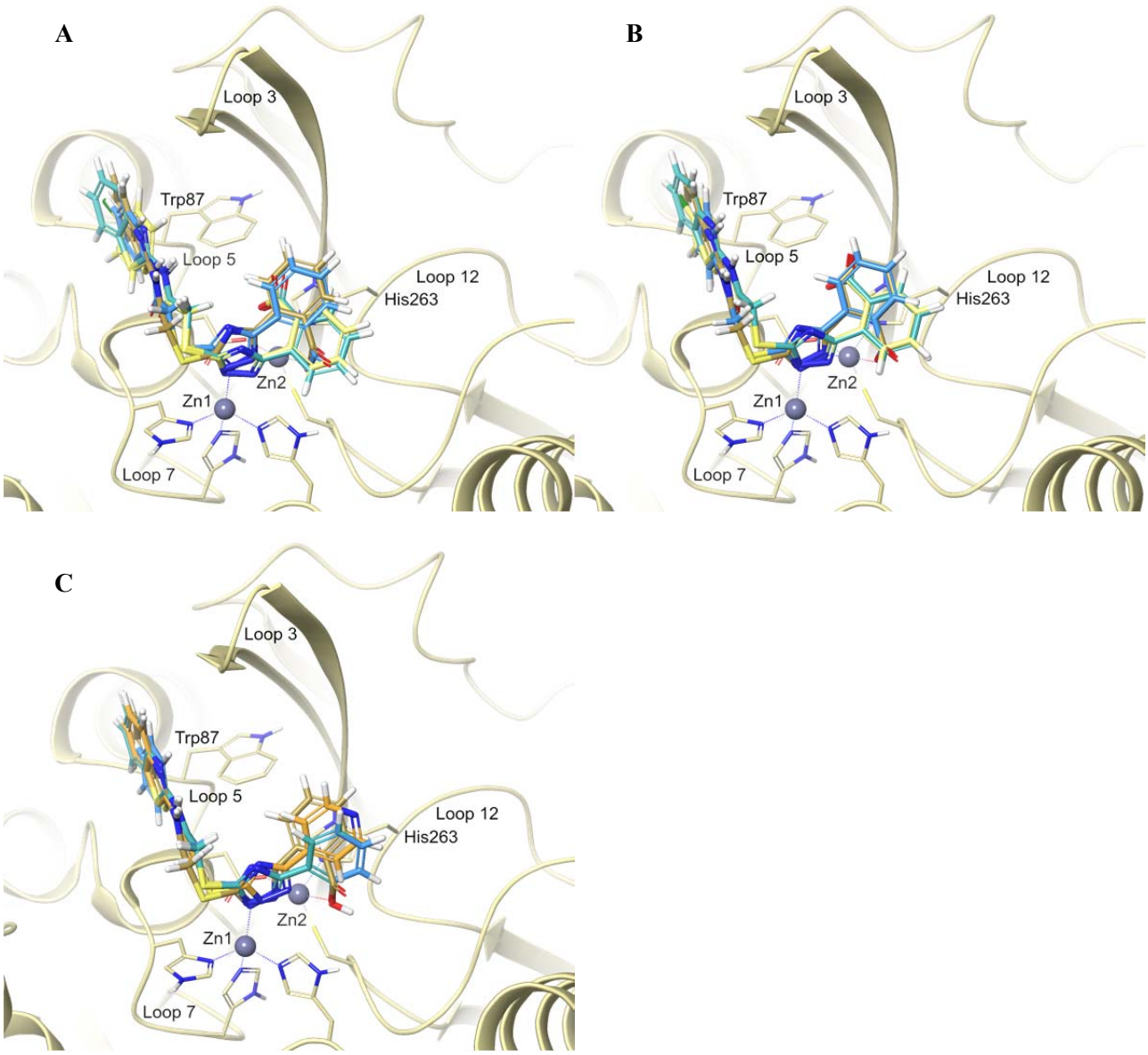


Figure S24. Poses from docking in the active site of VIM-2 (PDB 5LSC[31]). A) MM-GBSA poses for **4** (turquoise), **5** (blue) and **6** (yellow); B) glide poses for **4** (turquoise), **5** (blue) and **6** (yellow); and C) MM-GBSA poses for **1** (turquoise), **2** (blue) and **3** (orange) showing the smallest RMSD to the native ligand (**4**). Four such L3-L5-L7 type poses were received for **2** (see Figure S22 and Figure **S23**) upon docking into the active site of CcrA (PDB 1A8T[2]), but none for **1** or **3**–**6** (see Figure S21). One likely reason for these differences is the shorter distance between the zinc ions in CcrA (2.84 Å versus 3.88 Å).[32]

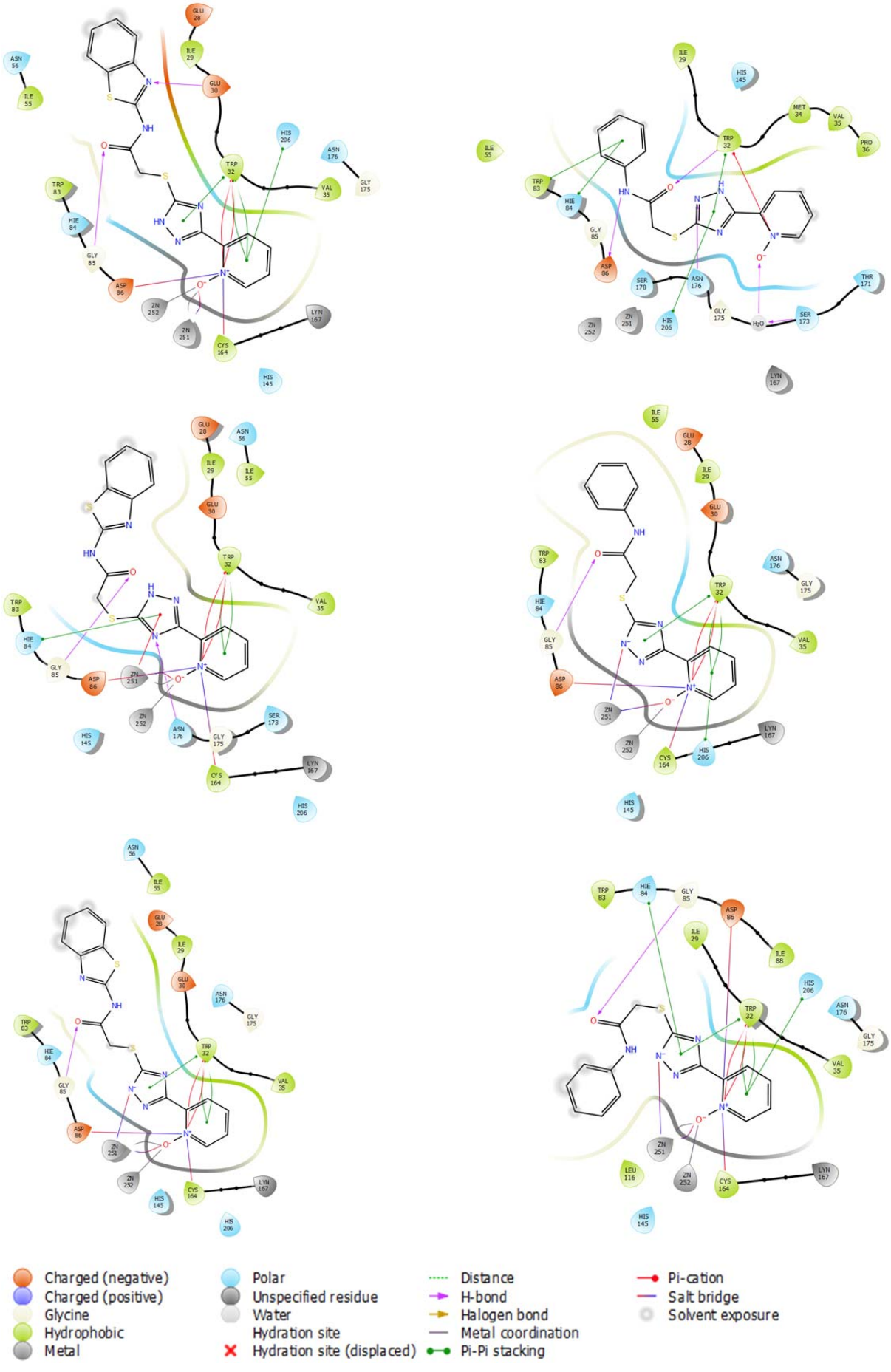


Figure S25. Ligand interaction diagrams for the L3-L5-L7 poses (MM-GBSA, PDB 1A8T[2]) of **7** (left) ranked as number 2 (top), 4 (middle) and 11 (bottom), and for the L3-L5-L7 poses of **8** (right) ranked as number 1 (top), 4 (middle) and 10 (bottom). The poses are shown in Figure S27 as well.

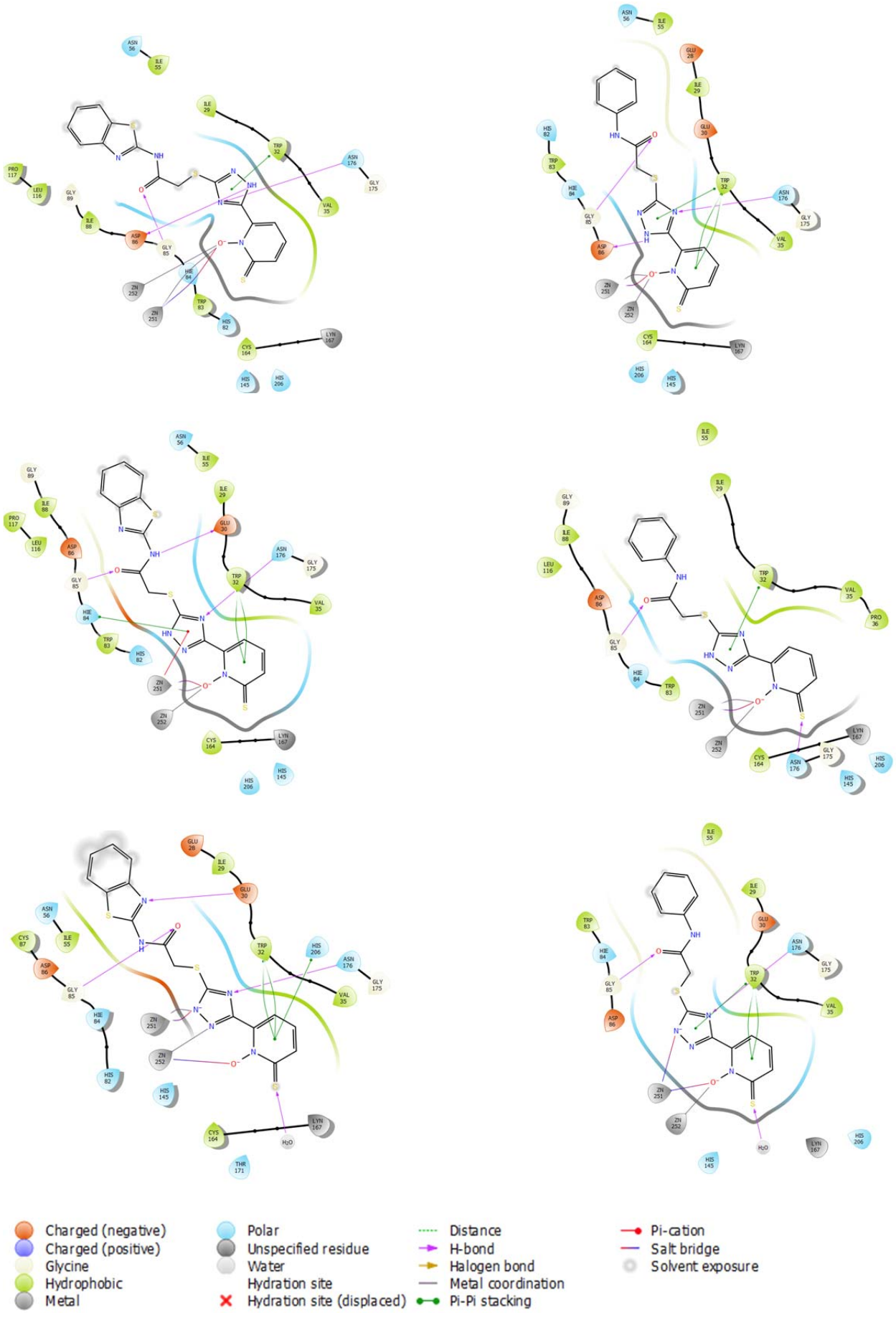


Figure S26. Ligand interaction diagrams for the L3-L5-L7 poses (MM-GBSA, PDB 1A8T[2]) of **9** (left) ranked as number 1 (top), 3 (middle) and 8 (bottom), and for the L3-L5-L7 poses of **10** (right) ranked as number 2 (top), 8 (middle) and 11 (bottom). The poses are shown in Figure S27 as well.

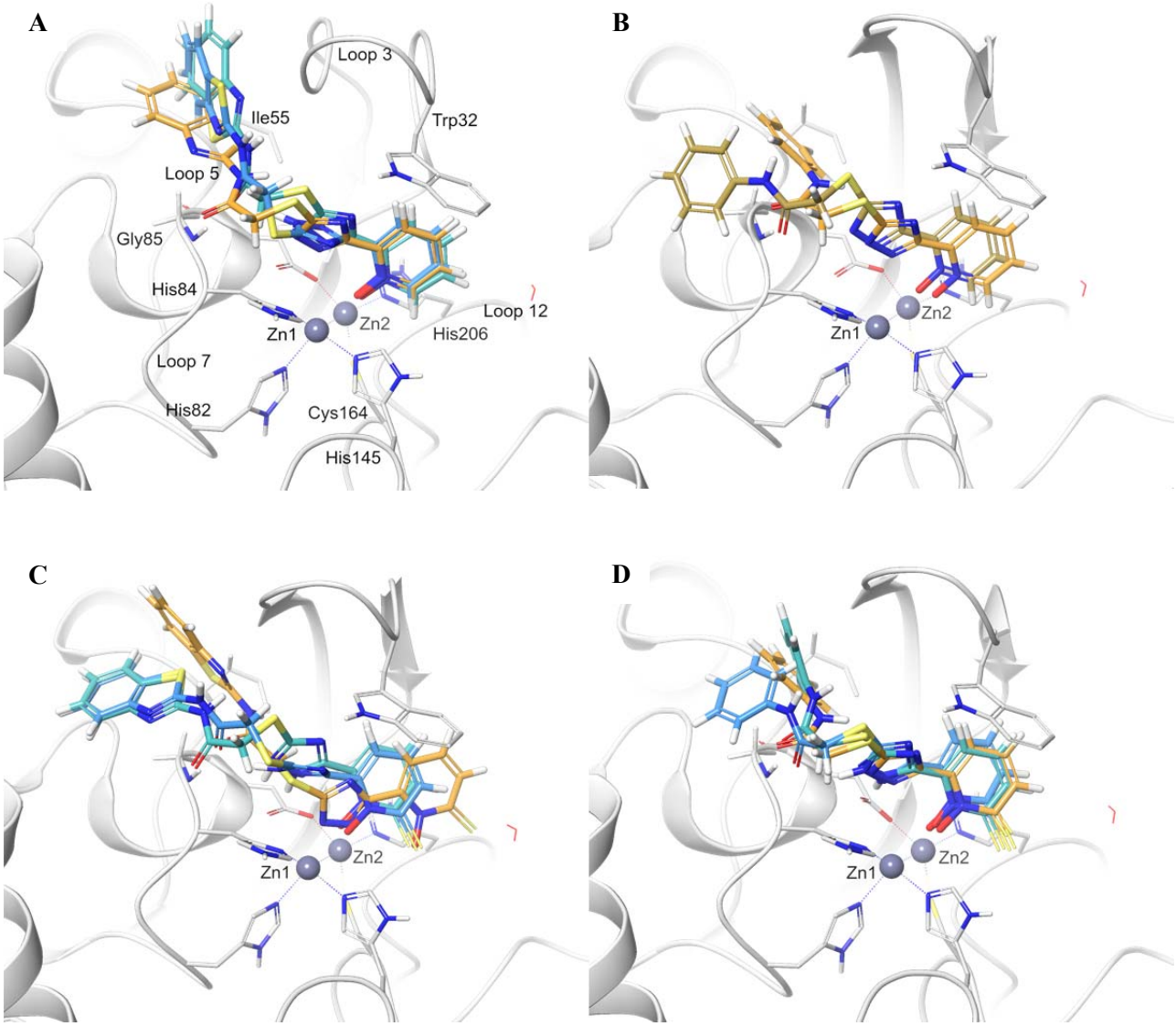
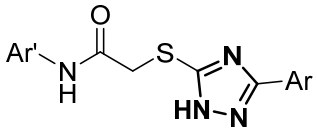


Figure S27. Relevant poses (MM-GBSA) from the docking of **7**–**10** into the active site of CcrA (PDB 1A8T[2]). A) the poses ranked as number 2 (turquoise), 4 (blue) and 11 (orange) for **7**; B) the poses ranked as number 4 (orange) and 10 (light brown) for **8**; C) the poses ranked as number 1 (turquoise), 3 (blue) and 8 (orange) for **9**; and D) the poses ranked as number 2 (turquoise), 8 (blue) and 11 (orange) for **10**. For interaction diagrams see Figure S25 and Figure **S26**.

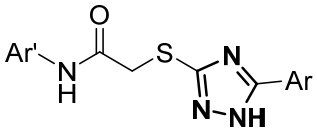
Table S14. A summary of the results from the molecular docking, MM-GBSA rescoring and SIFt based analysis and clustering of **1**–**10**. For **4**–**6**, the results of the top fifteen ranked poses were included in the clustering, while the top ten ranked poses were included for **1**–**3** and **7**–**10**.

		Binding poses (%)				
Compound	Method	L3-L5-L7	L7(Trp83)	L3-L10	L10-L12	Others
4	XP docking	80		7	13	
	MM-GBSA	67		7	27	
5	XP docking	53		33	13	
	MM-GBSA	40		40	13	7
6	XP docking	60		13	27	
	MM-GBSA	53		13	33	
$\Sigma_{4\text{-}6}$	XP docking	65		18	18	
	MM-GBSA	53		20	24	2
1 *phenols*	XP docking	56			44	
	MM-GBSA	40		10	50	
1 *phenolates*	XP docking	60		10	30	
	MM-GBSA	20			80	
2 *phenols*	XP docking	80	20			
	MM-GBSA	40	20	20	20	
2 *phenolates*	XP docking	50		10	40	
	MM-GBSA	20	10	30	40	
3	XP docking		44		44	11
	MM-GBSA		40		60	
7	XP docking	90	10			
	MM-GBSA	60	40			
8	XP docking	50	20	10	20	
	MM-GBSA	40	30	10	10	10
9	XP docking	50	30		10	10
	MM-GBSA	50	38			13
10	XP docking	50	10	40		
	MM-GBSA	60	10	30		
$\Sigma_{1\text{-}2}$	XP docking	62	5	5	29	0
	MM-GBSA	30	8	15	48	0
$\Sigma_{7,8}$	XP docking	70	15	5	10	0
	MM-GBSA	50	35	5	5	5
$\Sigma_{9,10}$	XP docking	50	20	20	5	5
	MM-GBSA	55	24	15	0	6

Table S15. A summary of the data in Table S9, Table **S10**, Table **S12** and Table **S13** showing the correlation between binding pose and main *1H*-1,2,4-triazole tautomeric form (or the corresponding deprotonated form) identified for the top scoring poses of **1**–**10**.



Tautomer **A**



Tautomer **B**

Cmpds	Binding pose/s	*1H*-1,2,4-triazole tautomer[a]
1, **2**	L3-L5-L7 L3-L10 L7(Trp83)	**B** ≥ **A**
	L10-L12	**A** ≥ **B**
3	L7(Trp83) L10-L12	**B** ≥ **A**
4–**6**	L3-L5-L7 L3-L10	**B** ≥ **A**
	L10-L12	**A** ≥ **B**
7	L3-L5-L7 L7(Trp83)	**B**
9	L3-L5-L7 L7(Trp83)	**A** > **B**
8, **10**	L3-L5-L7	**B** ≥ **A**
	L3-L10 L7(Trp83)	**A** > **B**

[a]Or the corresponding deprotonated form.

4 References

(1) Yang, S.-K.; Kang, J. S.; Oelschlaeger, P.; Yang, K.-W., Azolylthioacetamide: A Highly Promising Scaffold for the Development of Metallo-β-lactamase Inhibitors. *ACS Med. Chem. Lett.* **2015**, *6* (4), 455–460.
(2) Toney, J. H.; Cleary, K. A.; Hammond, G. G.; Yuan, X.; May, W. J.; Hutchins, S. M.; Ashton, W. T.; Vanderwall, D. E., Structure-activity relationships of biphenyl tetrazoles as metallo-β-lactamase inhibitors. *Bioorg. Med. Chem. Lett.* **1999**, *9* (18), 2741–2746.
(3) Galleni, M.; Lamotte-Brasseur, J.; Rossolini, G. M.; Spencer, J.; Dideberg, O.; Frère, J.-M., Standard Numbering Scheme for Class B β-Lactamases. *Antimicrob. Agents Chemother.* **2001**, *45* (3), 660–663.
(4) Mulder, F. A. A.; Schipper, D.; Bott, R.; Boelens, R., Altered flexibility in the substrate-binding site of related native and engineered high-alkaline Bacillus subtilisins. *J. Mol. Biol.* **1999**, *292* (1), 111–123.
(5) Williamson, M. P., Using chemical shift perturbation to characterise ligand binding. *Prog. Nucl. Magn. Reson. Spectrosc.* **2013**, *73*, 1–16.
(6) Teilum, K.; Kunze, M. B. A.; Erlendsson, S.; Kragelund, B. B., (S)Pinning down protein interactions by NMR. *Protein Science* **2017**, *26* (3), 436-451.
(7) Farmer, B. T.; Constantine, K. L.; Goldfarb, V.; Friedrichs, M. S.; Wittekind, M.; Yanchunas, J.; Robertson, J. G.; Mueller, L., Localizing the NADP+ binding site on the MurB enzyme by NMR. *Nat. Struct. Biol.* **1996**, *3* (12), 995-997.
(8) Lüttgen, H.; Robelek, R.; Mühlberger, R.; Diercks, T.; Schuster, S. C.; Köhler, P.; Kessler, H.; Bacher, A.; Richter, G., Transcriptional Regulation by Antitermination. Interaction of RNA with NusB Protein and NusB/NusE Protein Complex of Escherichia coli. *J. Mol. Biol.* **2002**, *316* (4), 875-885.
(9) Fielding, L., NMR Methods for the Determination of Protein- Ligand Dissociation Constants. *Current Topics in Medicinal Chemistry* **2003**, *3* (1), 39-53.
(10) Guimarães, C. R. W.; Cardozo, M., MM-GB/SA Rescoring of Docking Poses in Structure-Based Lead Optimization. *J. Chem. Inf. Model.* **2008**, *48* (5), 958–970.
(11) Deng, Z.; Chuaqui, C.; Singh, J., Structural Interaction Fingerprint (SIFt): A Novel Method for Analyzing Three-Dimensional Protein−Ligand Binding Interactions. *J. Med. Chem.* **2004**, *47* (2), 337–344.
(12) Fitzgerald, P. M. D.; Wu, J. K.; Toney, J. H., Unanticipated Inhibition of the Metallo-β-lactamase from Bacteroides fragilis by 4-Morpholineethanesulfonic Acid (MES): A Crystallographic Study at 1.85-Å Resolution. *Biochemistry* **1998**, *37* (19), 6791–6800.
(13) Toney, J. H.; Fitzgerald, P. M. D.; Grover-Sharma, N.; Olson, S. H.; May, W. J.; Sundelof, J. G.; Vanderwall, D. E.; Cleary, K. A.; Grant, S. K.; Wu, J. K.; Kozarich, J. W.; Pompliano, D. L.; Hammond, G. G., Antibiotic sensitization using biphenyl tetrazoles as potent inhibitors of Bacteroides fragilis metallo-β-lactamase. *Chem. Biol.* **1998**, *5* (4), 185–196.
(14) Greenlee, M. L.; Laub, J. B.; Balkovec, J. M.; Hammond, M. L.; Hammond, G. G.; Pompliano, D. L.; Epstein-Toney, J. H., Synthesis and SAR of thioester and thiol inhibitors of IMP-1 Metallo-β-Lactamase. *Bioorg. Med. Chem. Lett.* **1999**, *9* (17), 2549–2554.
(15) Nagano, R.; Adachi, Y.; Imamura, H.; Yamada, K.; Hashizume, T.; Morishima, H., Carbapenem Derivatives as Potential Inhibitors of Various β-Lactamases, Including Class B Metallo-β-Lactamases. *Antimicrob. Agents Chemother.* **1999**, *43* (10), 2497–2503.
(16) Scrofani, S. D. B.; Chung, J.; Huntley, J. J. A.; Benkovic, S. J.; Wright, P. E.; Dyson, H. J., NMR Characterization of the Metallo-β-lactamase from Bacteroides fragilis and Its Interaction with a Tight-Binding Inhibitor: Role of an Active-Site Loop. *Biochemistry* **1999**, *38* (44), 14507–14514.
(17) Green, B. G.; Toney, J. H.; Kozarich, J. W.; Grant, S. K., Inhibition of Bacterial Peptide Deformylase by Biaryl Acid Analogs. *Arch. Biochem. Biophys.* **2000**, *375* (2), 355–358.
(18) Payne, D. J.; Du, W.; Bateson, J. H., β-Lactamase epidemiology and the utility of established and novel beta-lactamase inhibitors. *Expert Opin. Investig. Drugs* **2000**, *9* (2), 247–261.
(19) Sandanayaka, V. P.; Feigelson, G. B.; Prashad, A. S.; Yang, Y.; Petersen, P. J., Allyl and propargyl substituted penam sulfones as versatile intermediates toward the syntheses of new β-lactamase inhibitors. *Bioorg. Med. Chem. Lett.* **2001**, *11* (8), 997–1000.
(20) Payne, D. J.; Hueso-Rodríguez, J. A.; Boyd, H.; Concha, N. O.; Janson, C. A.; Gilpin, M.; Bateson, J. H.; Cheever, C.; Niconovich, N. L.; Pearson, S.; Rittenhouse, S.; Tew, D.; Díez, E.; Pérez, P.; de la Fuente, J.; Rees, M.; Rivera-Sagredo, A., Identification of a Series of Tricyclic Natural Products as Potent Broad-Spectrum Inhibitors of Metallo-β-Lactamases. *Antimicrob. Agents Chemother.* **2002**, *46* (6), 1880–1886.
(21) Boerzel, H.; Koeckert, M.; Bu, W.; Spingler, B.; Lippard, S. J., Zinc-Bound Thiolate−Disulfide Exchange: A Strategy for Inhibiting Metallo-β-lactamases. *Inorg. Chem.* **2003**, *42* (5), 1604–1615.
(22) Siemann, S.; Clarke, A. J.; Viswanatha, T.; Dmitrienko, G. I., Thiols as Classical and Slow-Binding Inhibitors of IMP-1 and Other Binuclear Metallo-β-lactamases. *Biochemistry* **2003**, *42* (6), 1673–1683.

(23) Tabei, K.; Feng, X.; Venkatesan, A. M.; Abe, T.; Hideki, U.; Mansour, T. S.; Siegel, M. M., Mechanism of Inactivation of β-Lactamases by Novel 6-Methylidene Penems Elucidated Using Electrospray Ionization Mass Spectrometry. *J. Med. Chem.* **2004**, *47* (14), 3674–3688.
(24) Venkatesan, A. M.; Agarwal, A.; Abe, T.; Ushirogochi, H.; Yamamura, I.; Kumagai, T.; Petersen, P. J.; Weiss, W. J.; Lenoy, E.; Yang, Y.; Shlaes, D. M.; Ryan, J. L.; Mansour, T. S., Novel imidazole substituted 6-methylidene-penems as broad-spectrum β-lactamase inhibitors. *Bioorg. Med. Chem.* **2004**, *12* (22), 5807–5817.
(25) Venkatesan, A. M.; Gu, Y.; Santos, O. D.; Abe, T.; Agarwal, A.; Yang, Y.; Petersen, P. J.; Weiss, W. J.; Mansour, T. S.; Nukaga, M.; Hujer, A. M.; Bonomo, R. A.; Knox, J. R., Structure−Activity Relationship of 6-Methylidene Penems Bearing Tricyclic Heterocycles as Broad-Spectrum β-Lactamase Inhibitors: Crystallographic Structures Show Unexpected Binding of 1,4-Thiazepine Intermediates. *J. Med. Chem.* **2004**, *47* (26), 6556–6568.
(26) Irwin, J. J.; Raushel, F. M.; Shoichet, B. K., Virtual Screening against Metalloenzymes for Inhibitors and Substrates. *Biochemistry* **2005**, *44* (37), 12316–12328.
(27) Venkatesan, A. M.; Agarwal, A.; Abe, T.; Ushirogochi, H.; Yamamura, I.; Ado, M.; Tsuyoshi, T.; Dos Santos, O.; Gu, Y.; Sum, F.-W.; Li, Z.; Francisco, G.; Lin, Y.-I.; Petersen, P. J.; Yang, Y.; Kumagai, T.; Weiss, W. J.; Shlaes, D. M.; Knox, J. R.; Mansour, T. S., Structure-Activity Relationship of 6-Methylidene Penems Bearing 6,5 Bicyclic Heterocycles as Broad-Spectrum β-Lactamase Inhibitors: Evidence for 1,4-Thiazepine Intermediates with C7 R Stereochemistry by Computational Methods. *J. Med. Chem.* **2006**, *49* (15), 4623–4637.
(28) Roll, D. M.; Yang, Y.; Wildey, M. J.; Bush, K.; Lee, M. D., Inhibition of metallo-β-lactamases by pyridine monothiocarboxylic acid analogs. *J. Antibiot.* **2010**, *63*, 255–257
(29) Shi, P.; Zhang, Y.; Li, Y.; Bian, L., Probing the interaction of L-captopril with metallo-β-lactamase CcrA by fluorescence spectra and molecular dynamic simulation. *Luminescence* **2018**, *33* (5), 954–961.
(30) Minkin, V. I.; Garnovskii, A. D.; Elguero, J.; Katritzky, A. R.; Denisko, O. V., The Tautomerism of Heterocycles: Five-membered Rings with Two or More Heteroatoms. In *Advances in Heterocyclic Chemistry*, Katritzky, A. R., Ed. Academic Press: 2000; Vol. 76, pp 157–323.
(31) Christopeit, T.; Yang, K.-W.; Yang, S.-K.; Leiros, H.-K. S., The structure of the metallo-b-lactamase VIM-2 in complex with a triazolylthioacetamide inhibitor. *Acta Crystallogr. F* **2016**, *72* (11), 813–819.
(32) Rivière, G.; Oueslati, S.; Gayral, M.; Créchet, J.-B.; Nhiri, N.; Jacquet, E.; Cintrat, J.-C.; Giraud, F.; van Heijenoort, C.; Lescop, E.; Pethe, S.; Iorga, B. I.; Naas, T.; Guittet, E.; Morellet, N., NMR Characterization of the Influence of Zinc(II) Ions on the Structural and Dynamic Behavior of the New Delhi Metallo-β-Lactamase-1 and on the Binding with Flavonols as Inhibitors. *ACS Omega* **2020**, *5* (18), 10466-10480.