

**Table 1: Description and summary of calibration simulations.**

No.	Anchor	Sampling	Template	Scoring function <sup>1</sup>	Kolmogorv – Smirnov p-value by scoring scheme		
					Peptide score	Interface score	Reweighted score
1	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 6 (default) 2. 200 decoys per peptide.	2v5w	Default	0.2	0.03	0.69
2	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 15 2. 200 decoys per peptide	2v5w	hack_elec = 0.5	0.2	0.03	0.69
3	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 15 2. 200 decoys per peptide 3. low resolution step (centroid mode)	2v5w	Default	0.2	0.2	0.697
4	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 20 2. 200 decoys per peptide	2v5w	Default	0.2	0.03	0.2
5	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 30 2. 200 decoys per peptide	2v5w	Default	0.2	0.2	0.2
6	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 30 2. 500 decoys per peptide	2v5w	Default	0.2	0.03	0.69

<sup>1</sup> The default scoring function is described in the methods section. In a simulation where a modified version of this scoring function was used, we included a description of what was modified.

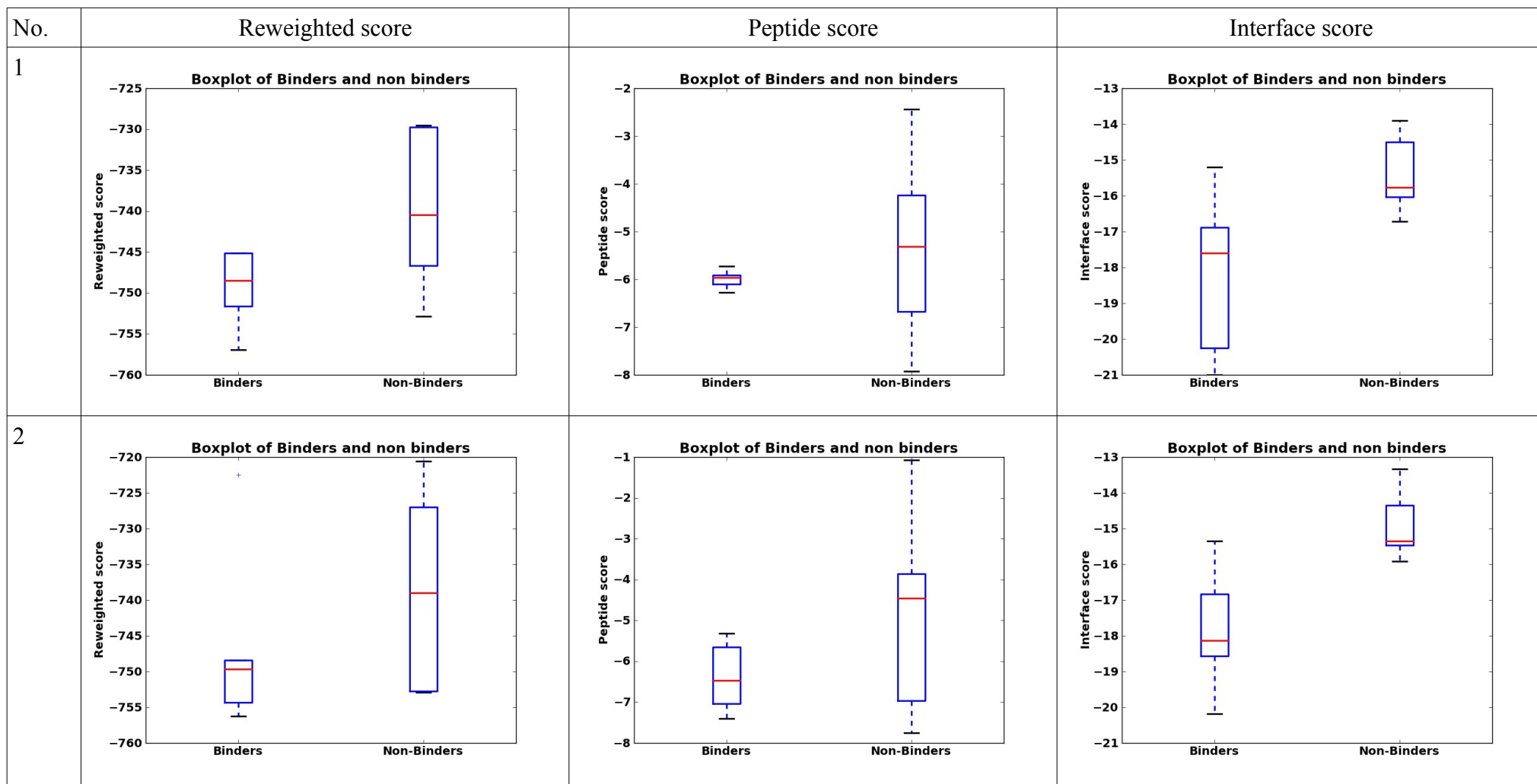
No.	Anchor	Sampling	Template	Scoring function	Kolmogorv – Smirnov p-value by scoring scheme		
7	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 60 2. 500 decoys per peptide	2v5w	Default	0.2	0.03	0.69
8	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 90 2. 900 decoys per peptide	2v5w	Default	0.69	0.69	0.03
9	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 15 2. 200 decoys per peptide	3f07	Default	0.997	0.2	0.69
10	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 15 2. 200 decoys per peptide	1t67	Default	0.69	0.69	0.69
11	acetyl-K3	1. Perturbation size = 15	2v5w	hack_elec = 0.25	0.2	0.2	0.69
12	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 15 2. 200 decoys per peptide	2v5w	Score 12 (Rosetta's default scoring function)	0.2	0.03	0.2
13	<b>Peptide:</b> X4 – (variable position – CA atom. Chosen by default.) <b>Receptor:</b> (default: center of mass)	1. Perturbation size = 20 2. 200 decoys per peptide	2v5w	Default	0.2	0.2	0.2
14	<b>Peptide:</b> acetyl-K3 (anchor was CH atom, instead of CA) <b>Receptor:</b> anchor was residue G289	1. Perturbation size = 15 2. 200 decoys per peptide	2v5w	Default	0.2	0.03	0.2
15	<b>Peptide:</b> acetyl-K3 , <b>Receptor:</b> anchor	1. Perturbation size = 15 2. 200 decoys per	2v5w	Default	0.2	0.2	0.009

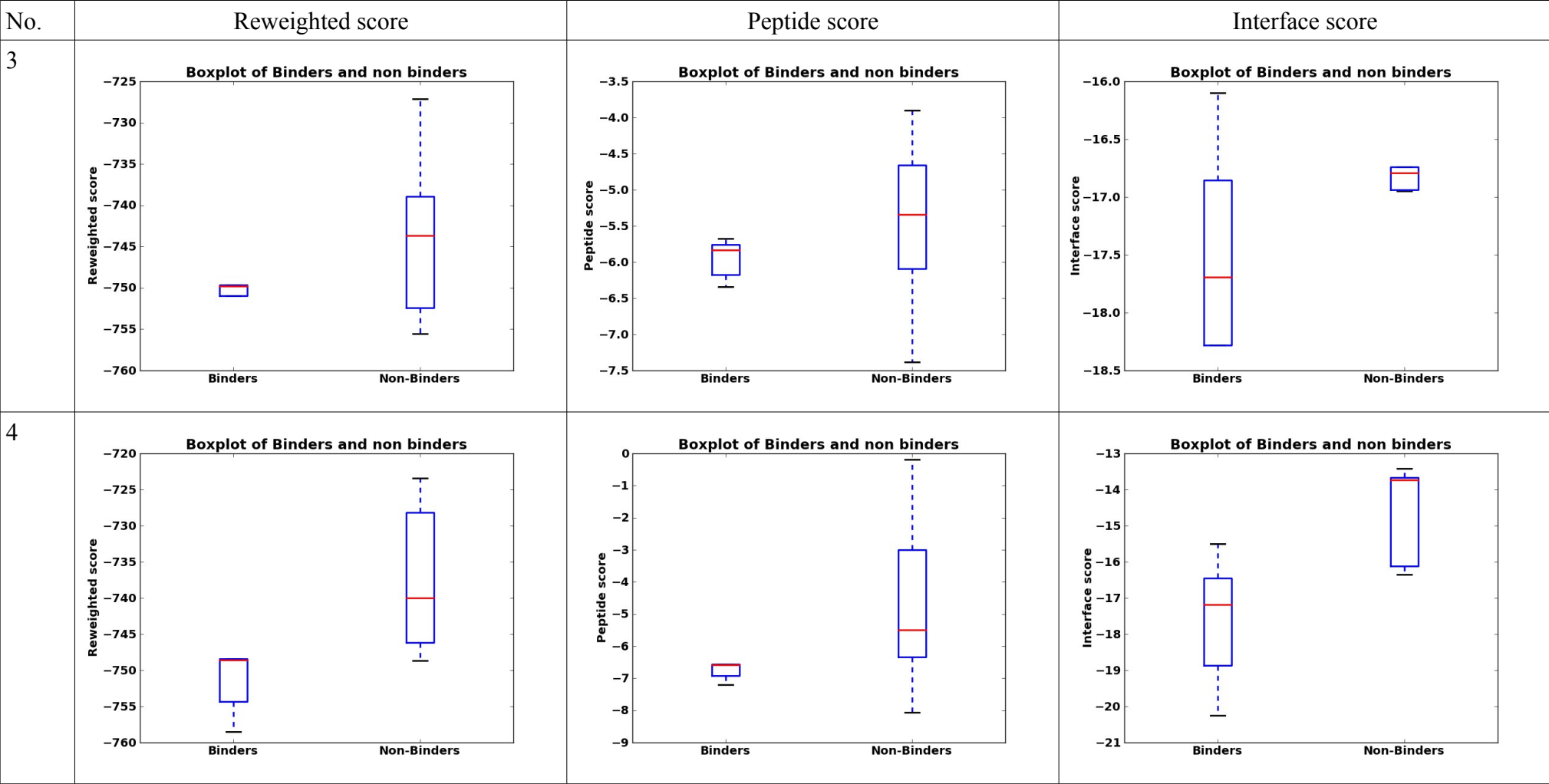
No.	Anchor was G289 <sup>2</sup>	Sampling peptide	Template	Scoring function	Kolmogorv – Smirnov p-value by scoring scheme		
16	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 15 2. 200 decoys per peptide	2v5w	SD of constraints was 0.15 Å	0.2	0.2	0.005
17	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 15 2. 200 decoys per peptide	2v5w	SD of constraints is 0.25 Å	0.2	0.03	0.2
18	<b>Peptide:</b> Acetyl-K3 <b>Receptor:</b> F194	1. Perturbation size = 8 2. 200 decoys per peptide	2v5w (threaded) <sup>3</sup>	Default	0.2	0.003	0.69

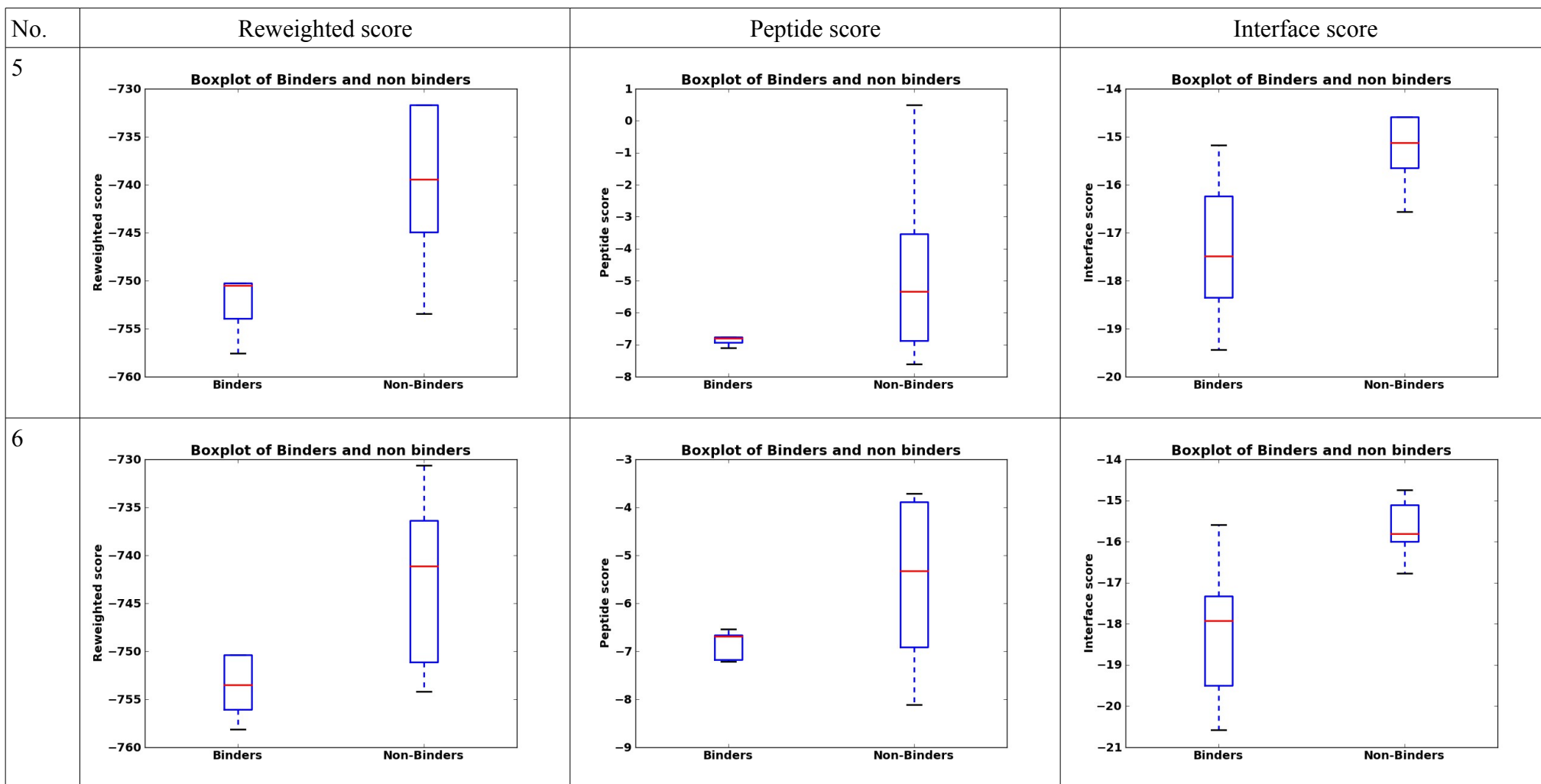
<sup>2</sup> The sequence was threaded on the peptidic substrate backbone in the 2v5w crystal. Since this peptidic substrate was only 4 amino acid long (the train/test sequences were 6 residues long), the backbone of the 2 extra residues was modeled in an extended conformation.

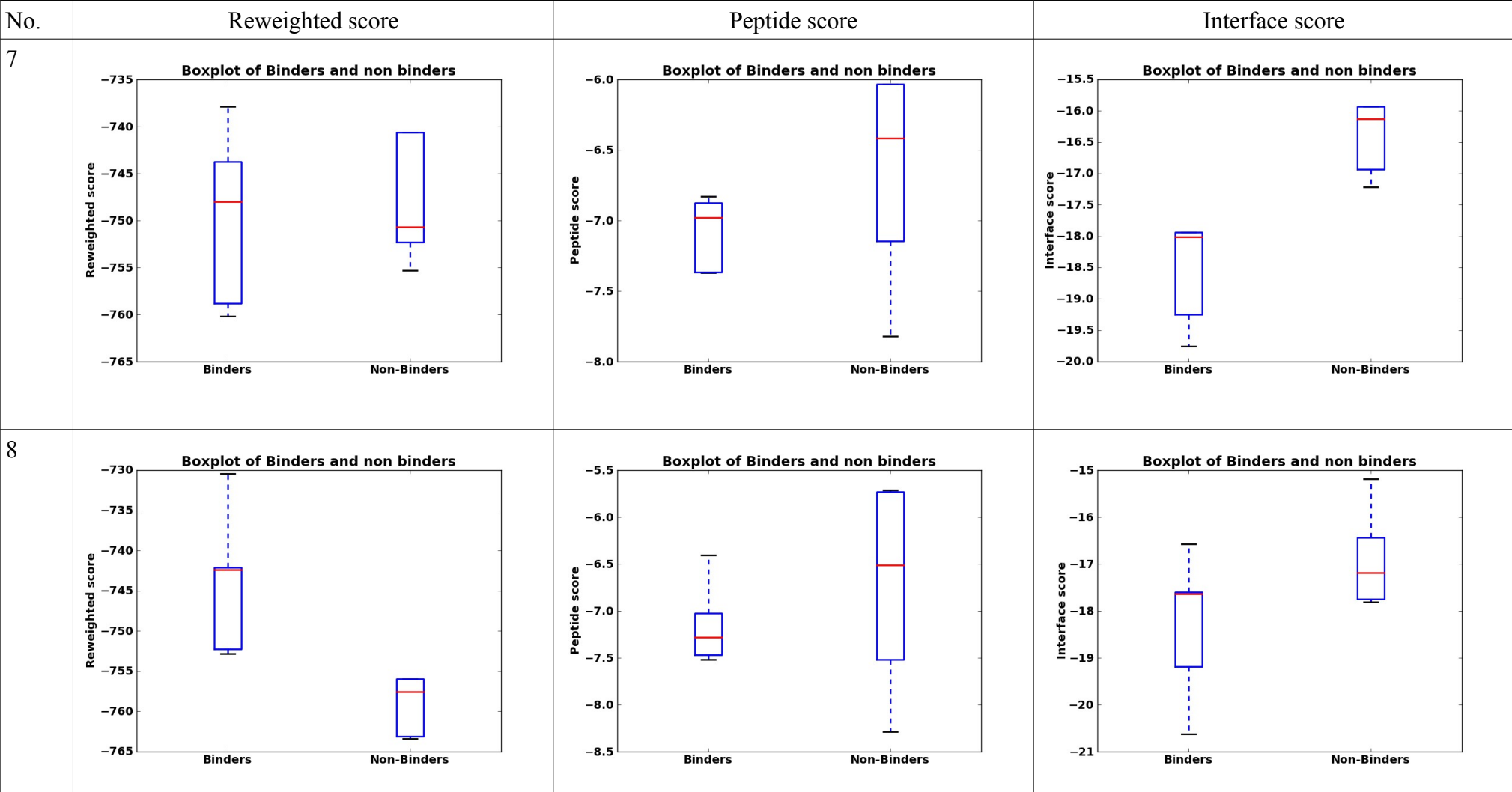
<sup>3</sup> Setting the receptor anchor to be the 289 residue, creating an axis that aligns with the Lysine residue side-chain. This axis is directed inside the pocket, and allowed the peptide to rotate while the Lysine residue stays fixed (see Figure 9)

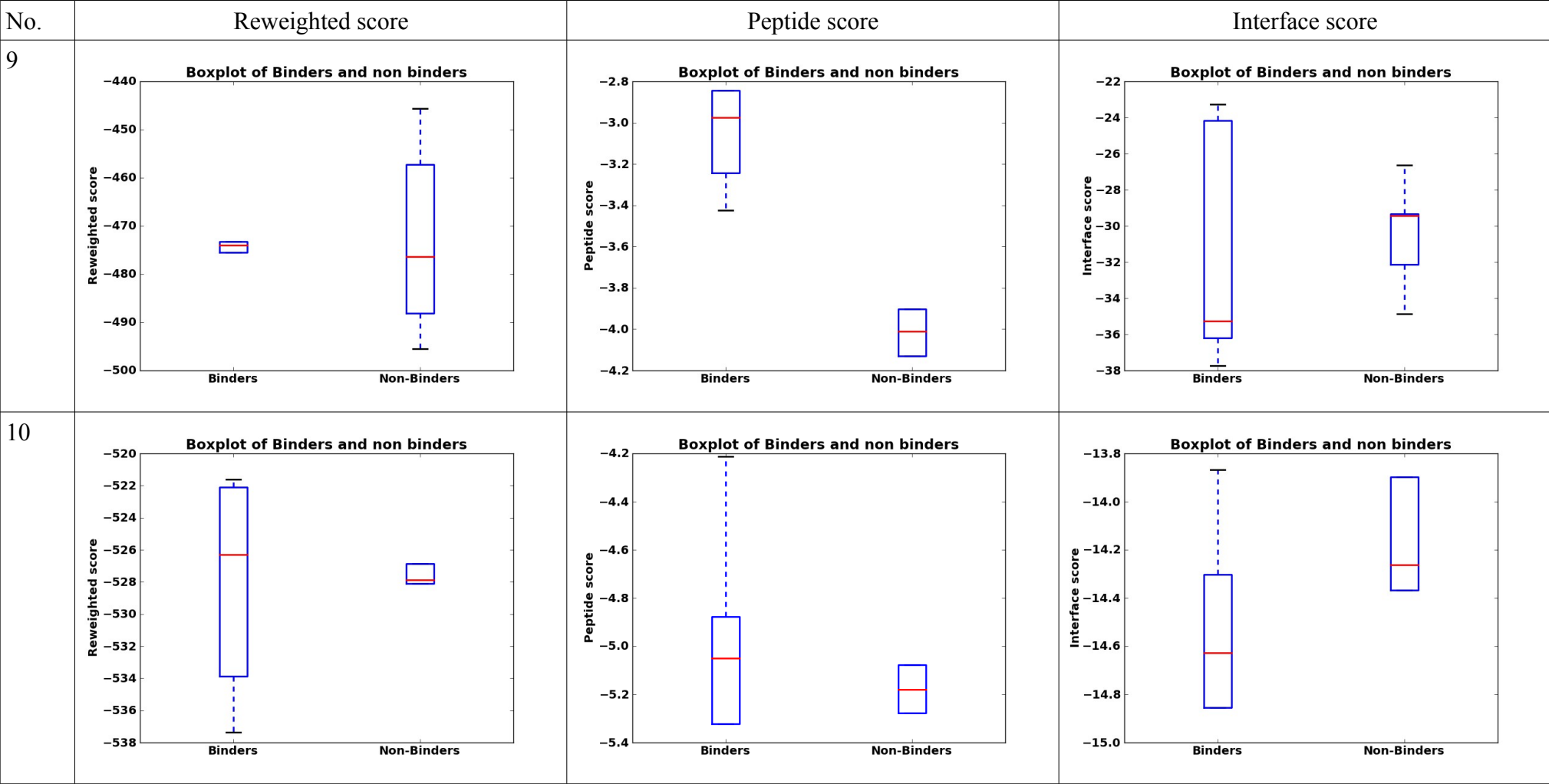
*Table 2: Training set - score vs. activity box plots for the short calibration phase*



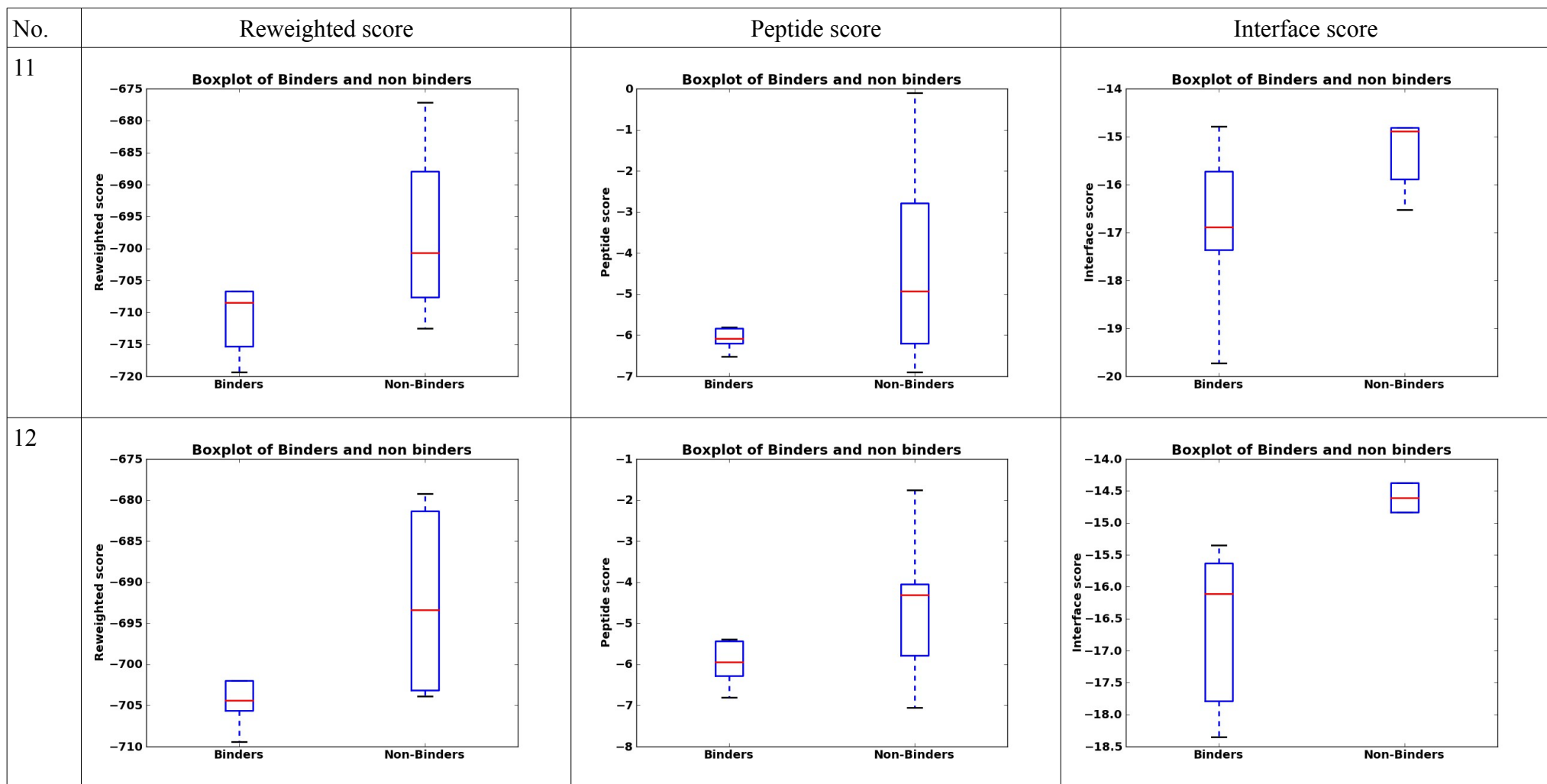


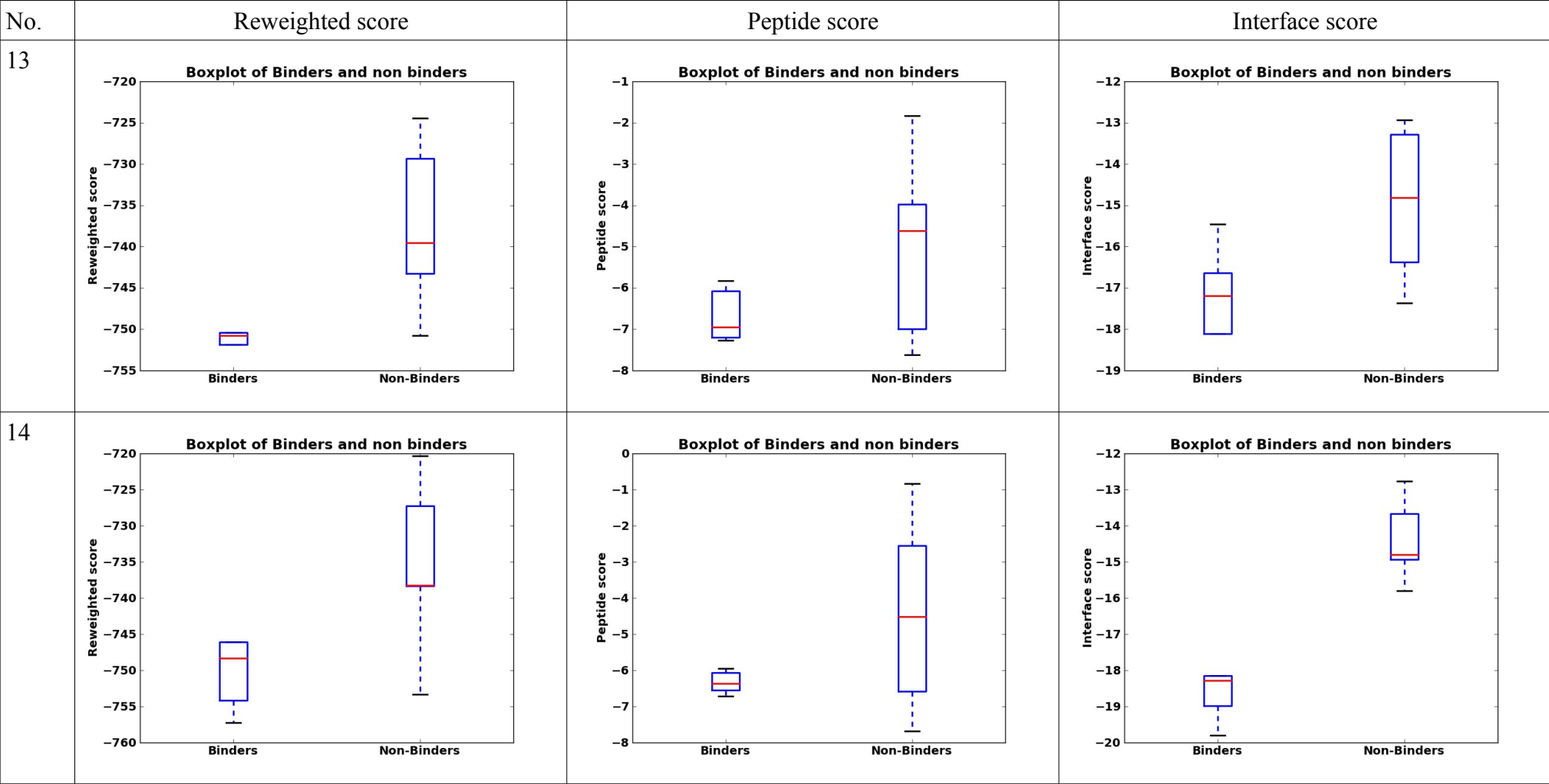


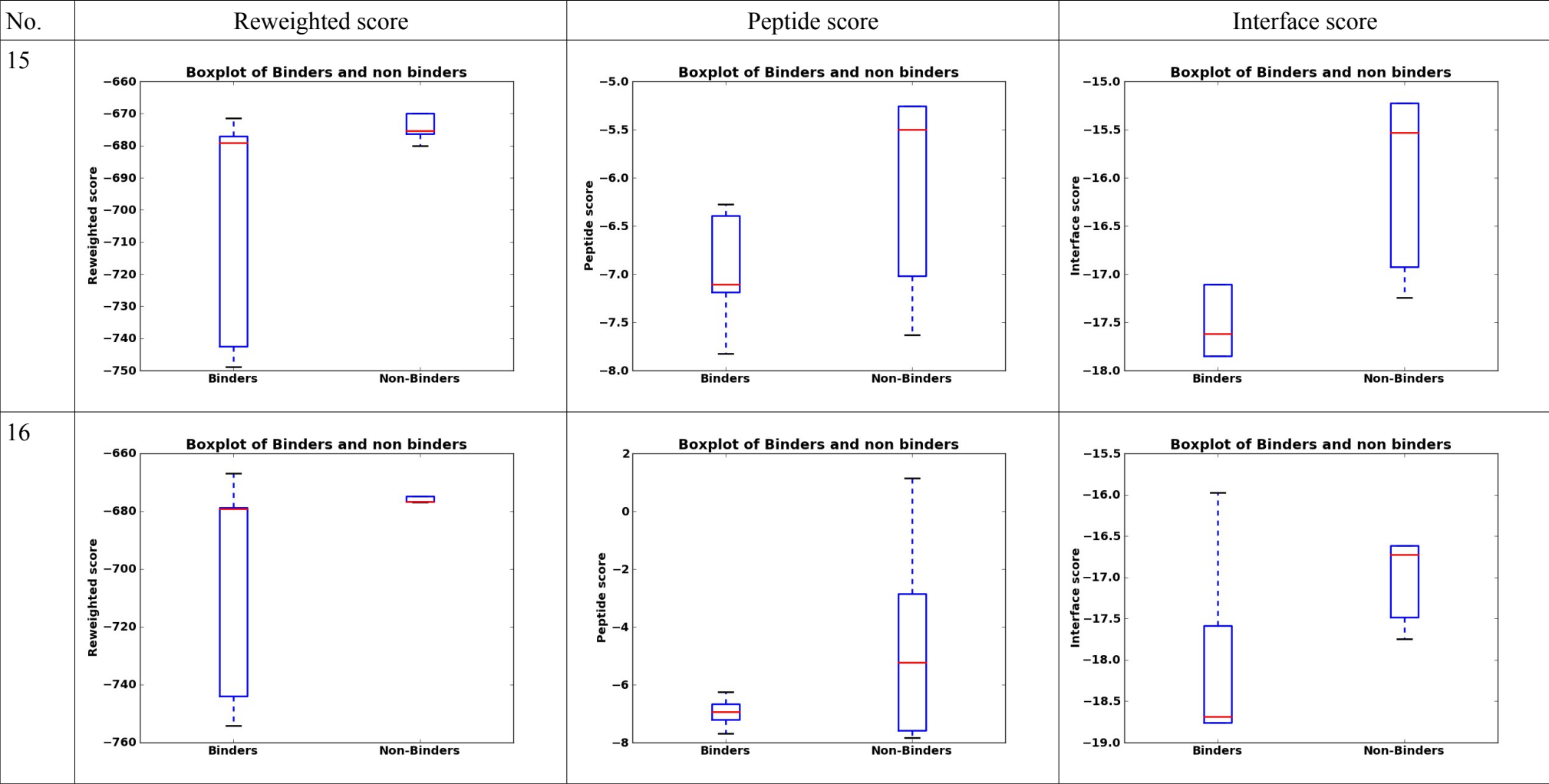


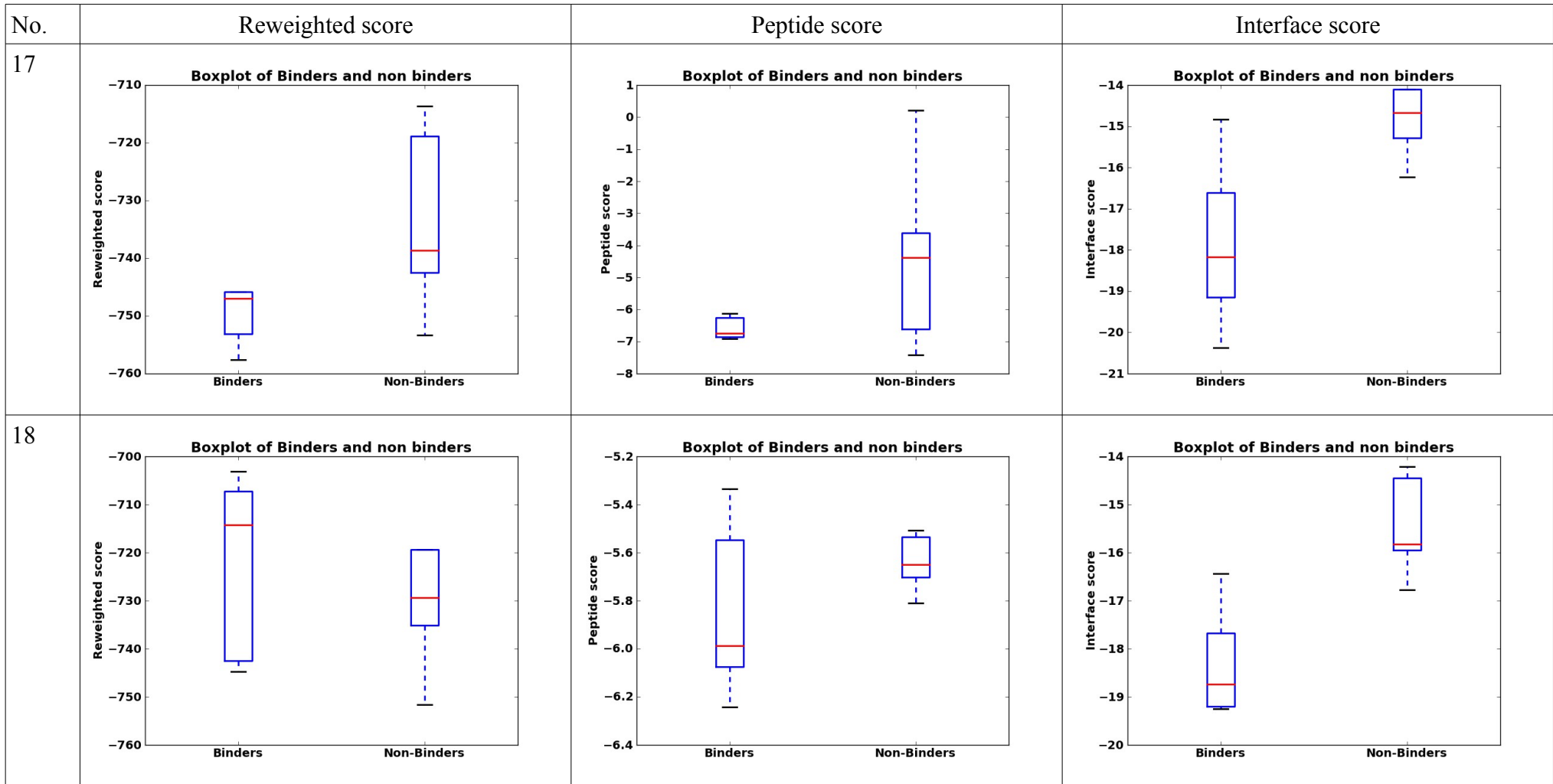




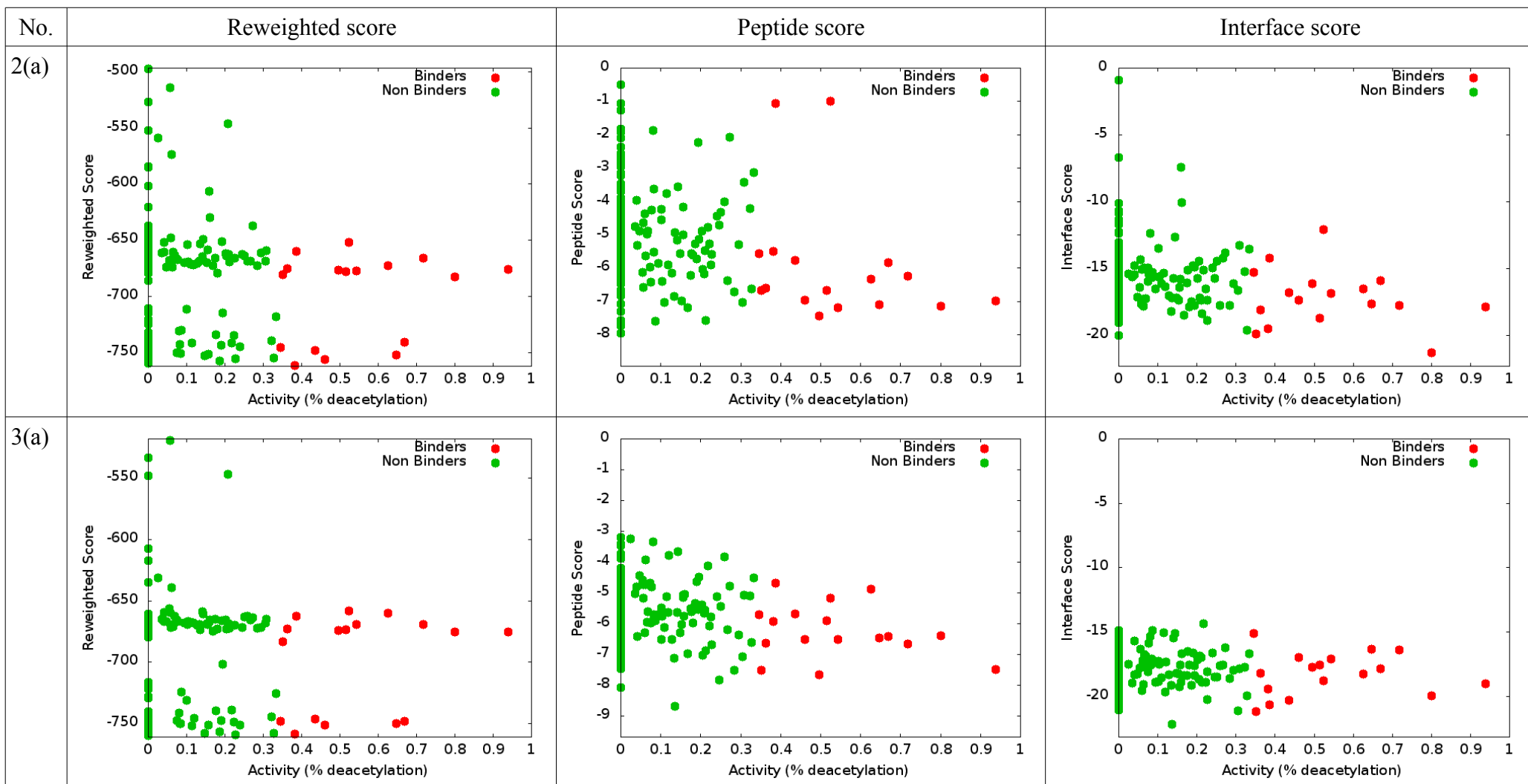




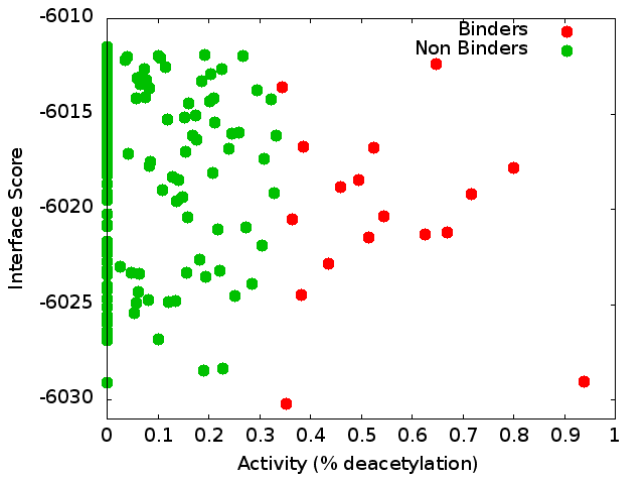
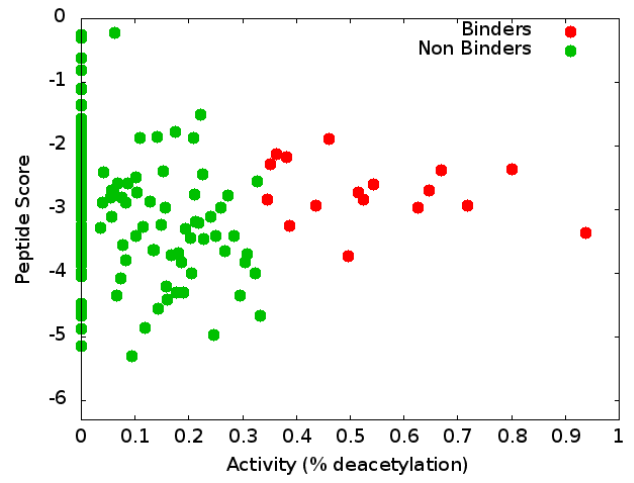
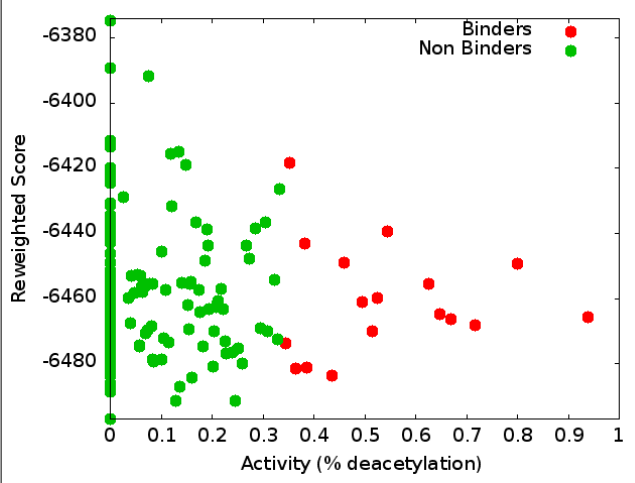




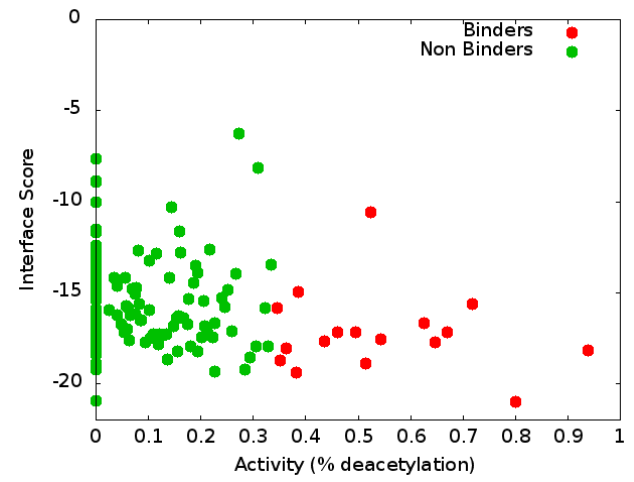
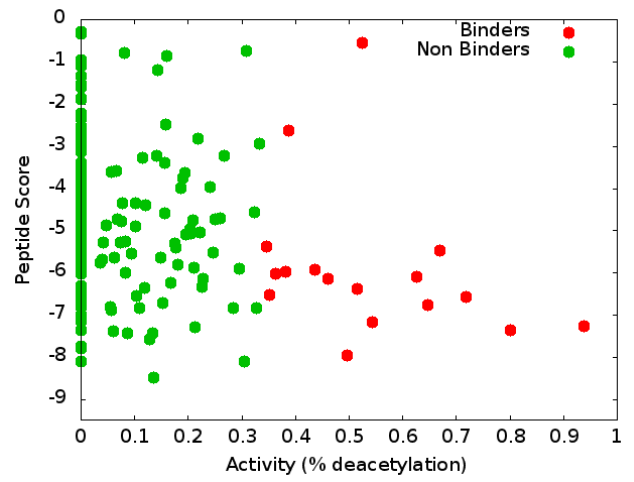
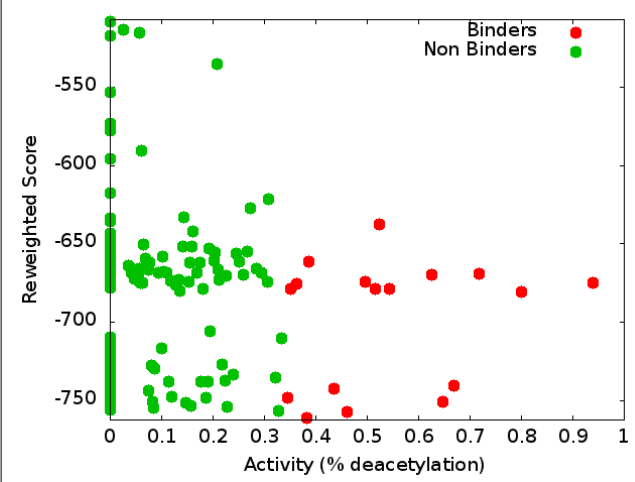
*Table 3: Training set - score vs. activity plots*



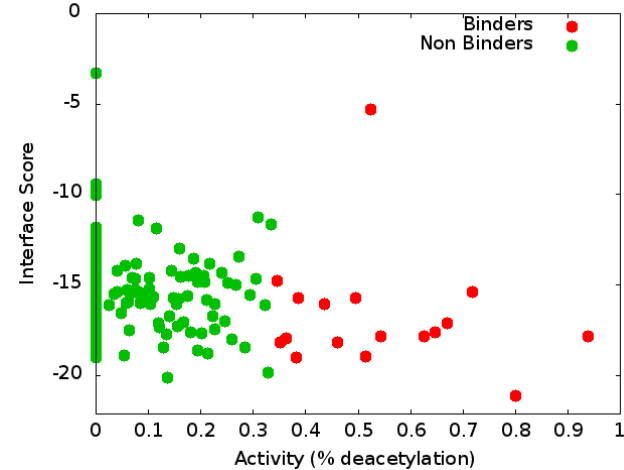
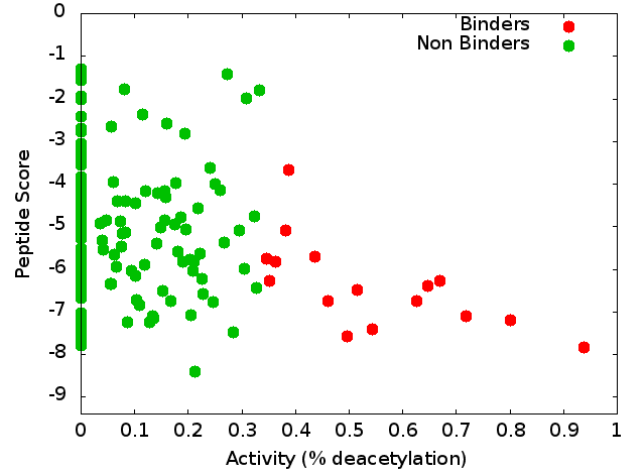
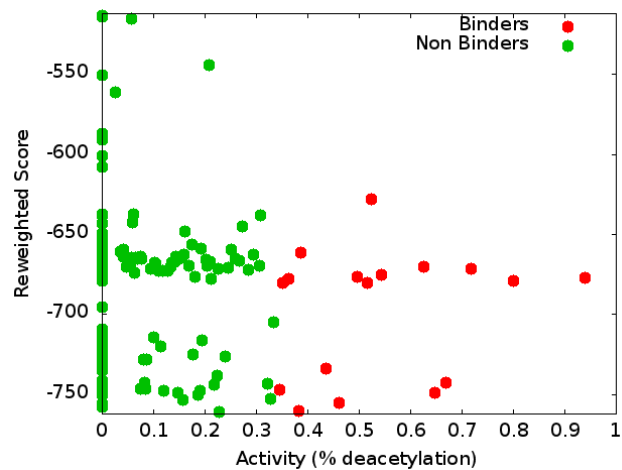
9(a)



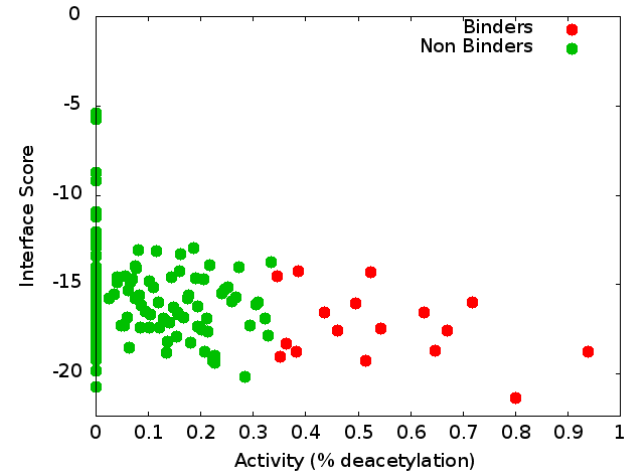
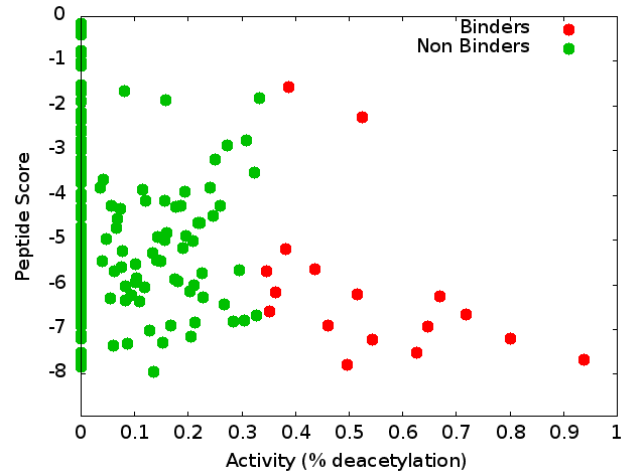
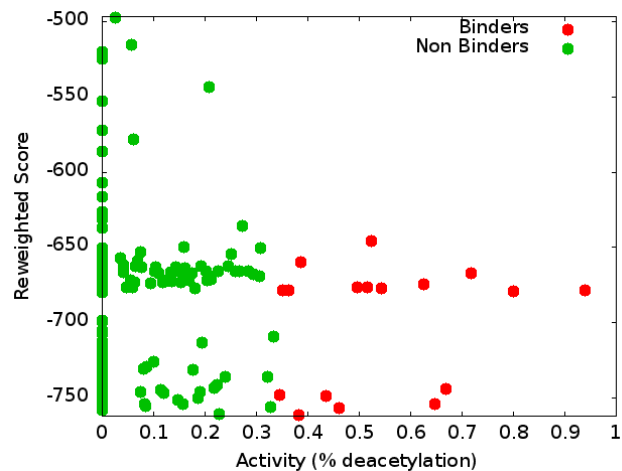
14(a)



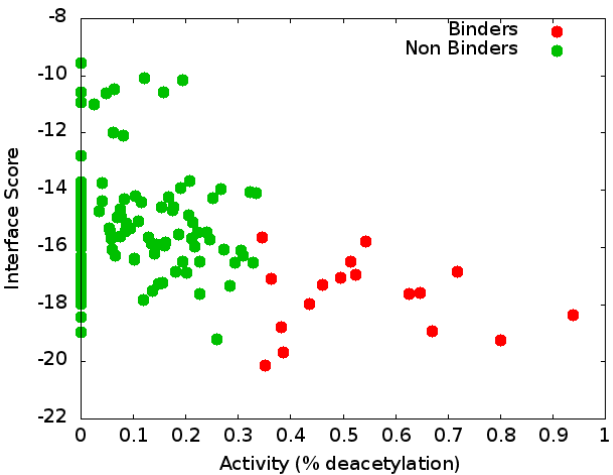
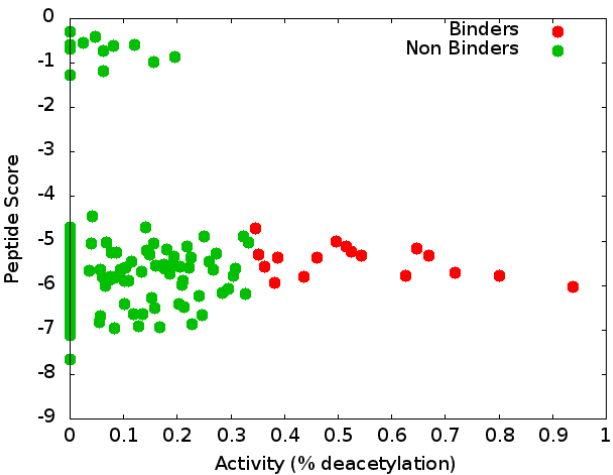
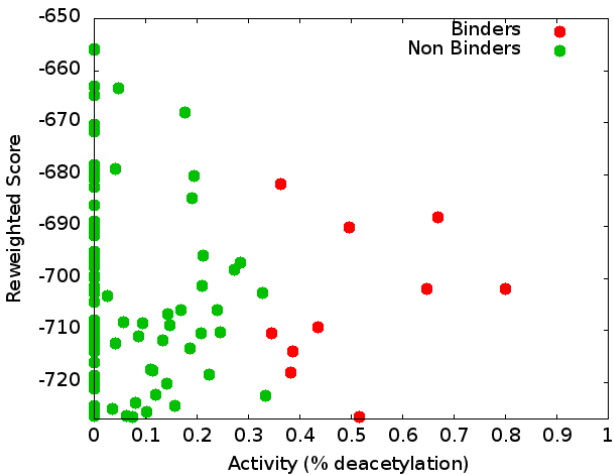
16(a)



17(a)

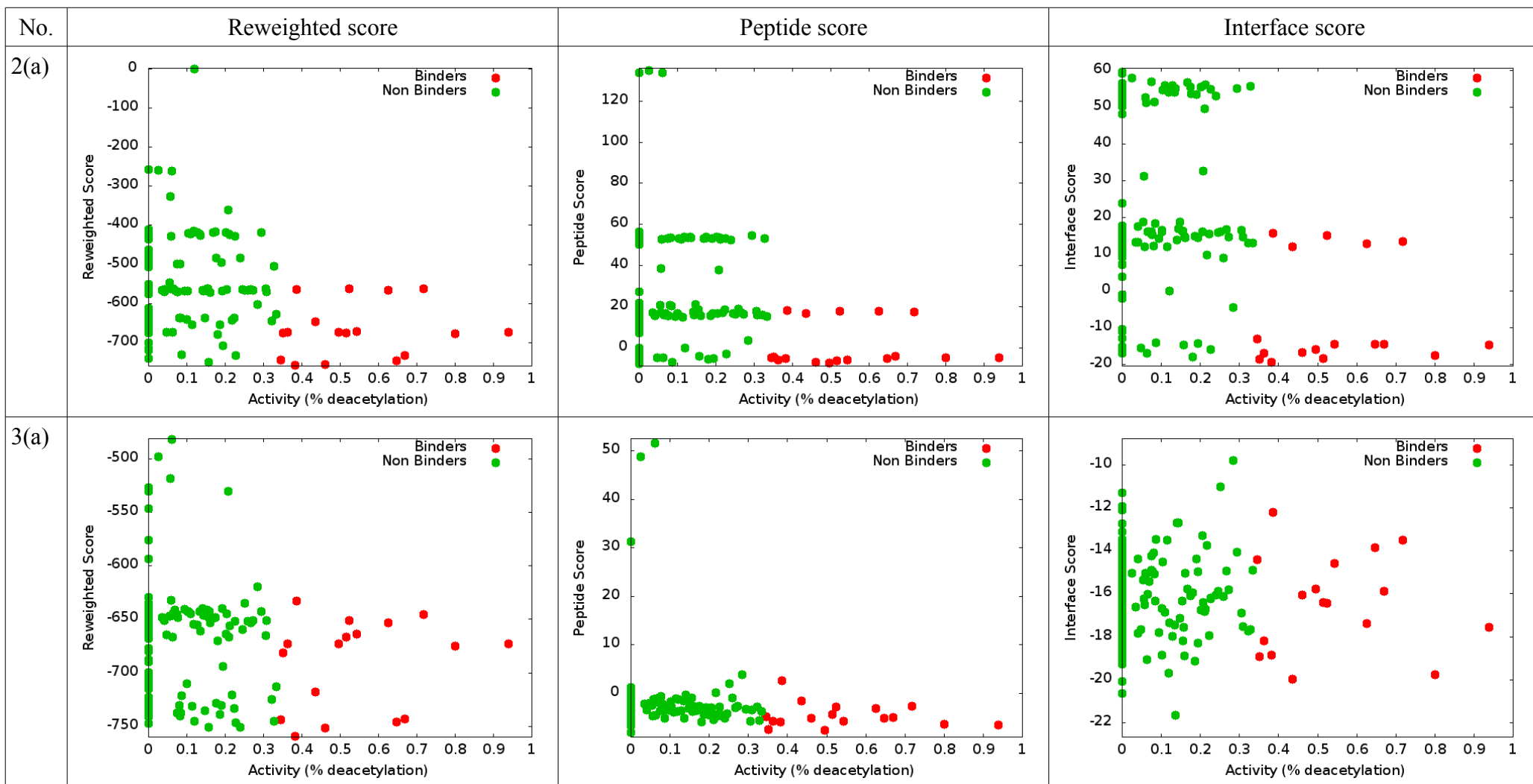


18(a)

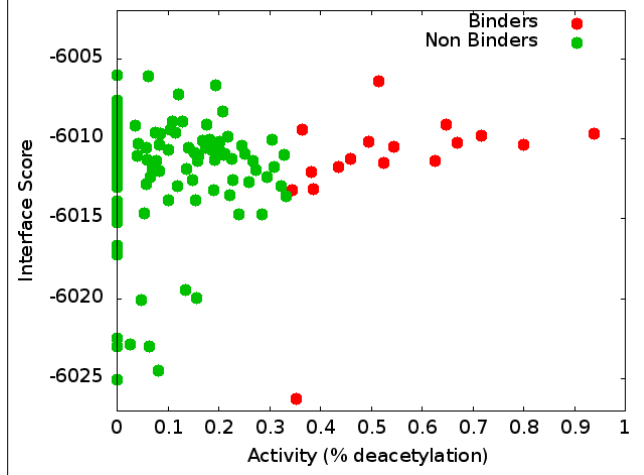
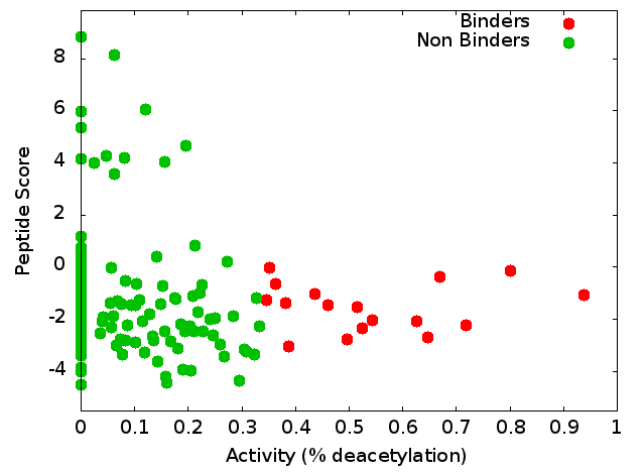
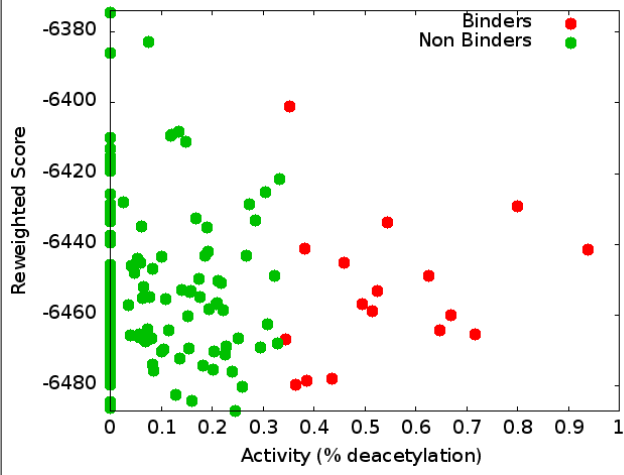




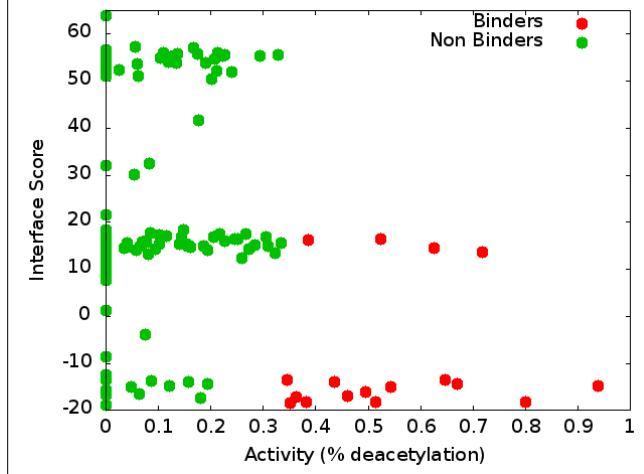
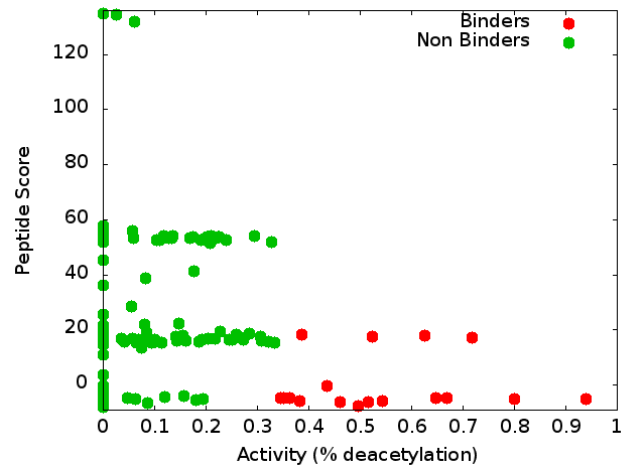
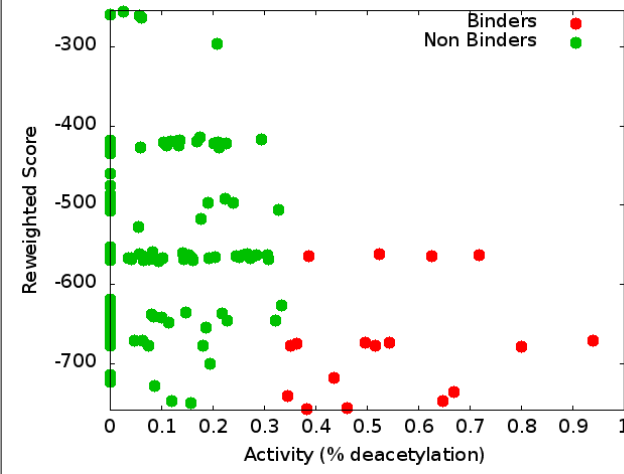
*Table 4: Training set - score vs. activity plots after clustering*



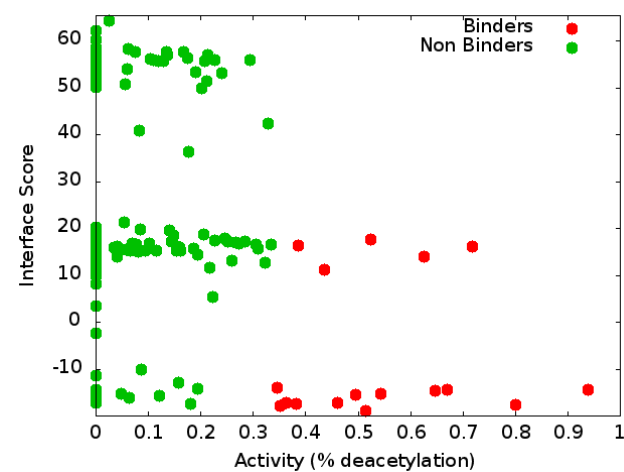
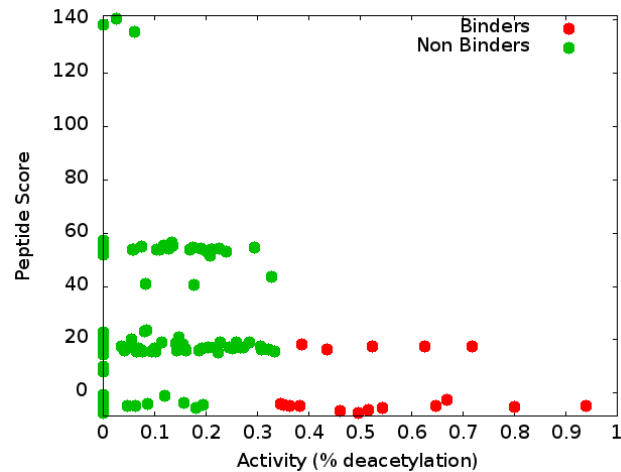
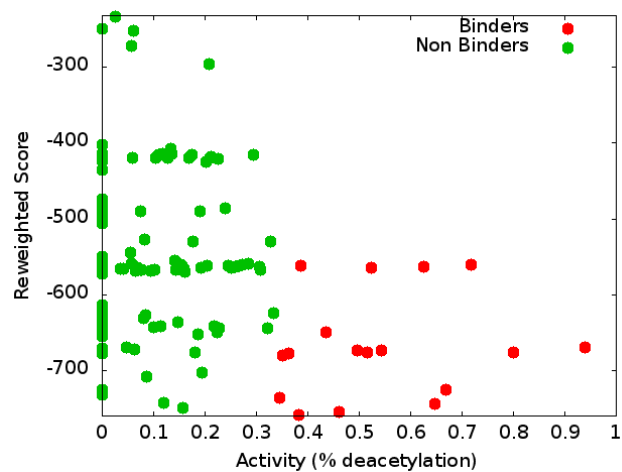
9(a)



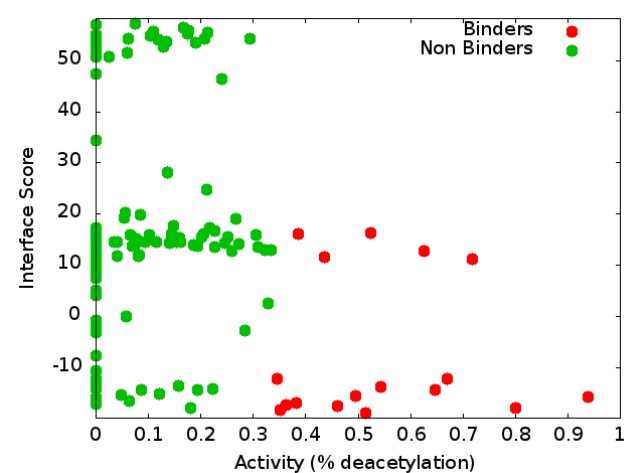
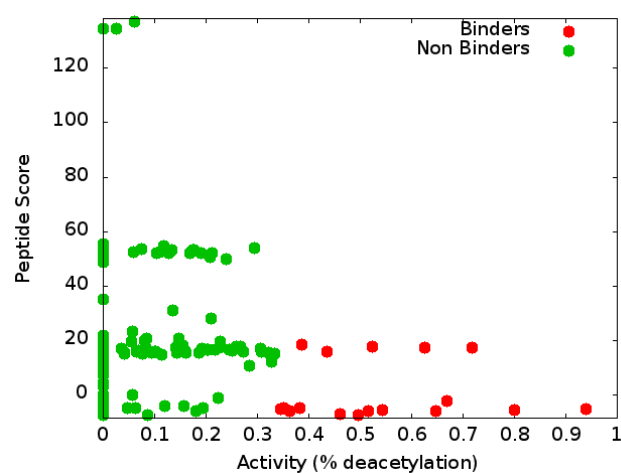
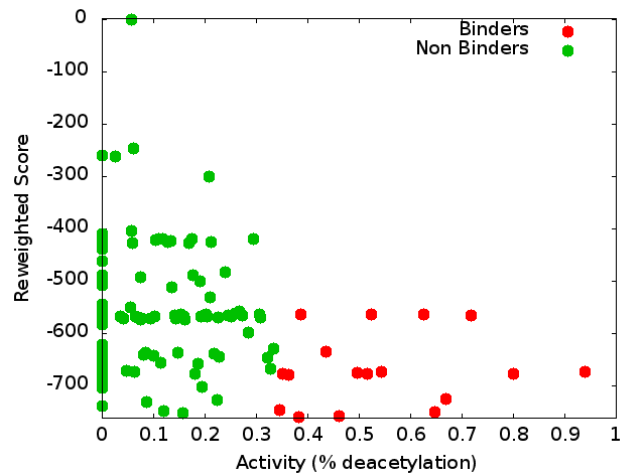
14(a)



16(a)



17(a)



18(a)

