Electronic Supplementary Information for manuscript

Impact of the Halogen PB Radii in the Estimation of Protein-Ligand Binding Energies Using MM-PBSA Calculations

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Supporting Figures and Tables

Supporting Figures

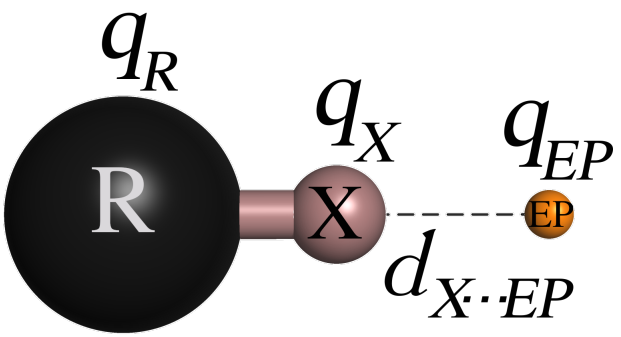

Figure S1: Scheme for extra points (EPs) added to a covalently-bound halogen atom. The model parameters are the X$\cdots$EP distance ($d_{X\ldots EP}$) and the atomic charges of the EP, halogen, and the remaining particles (q_{EP}, q_X, and q_R, respectively).

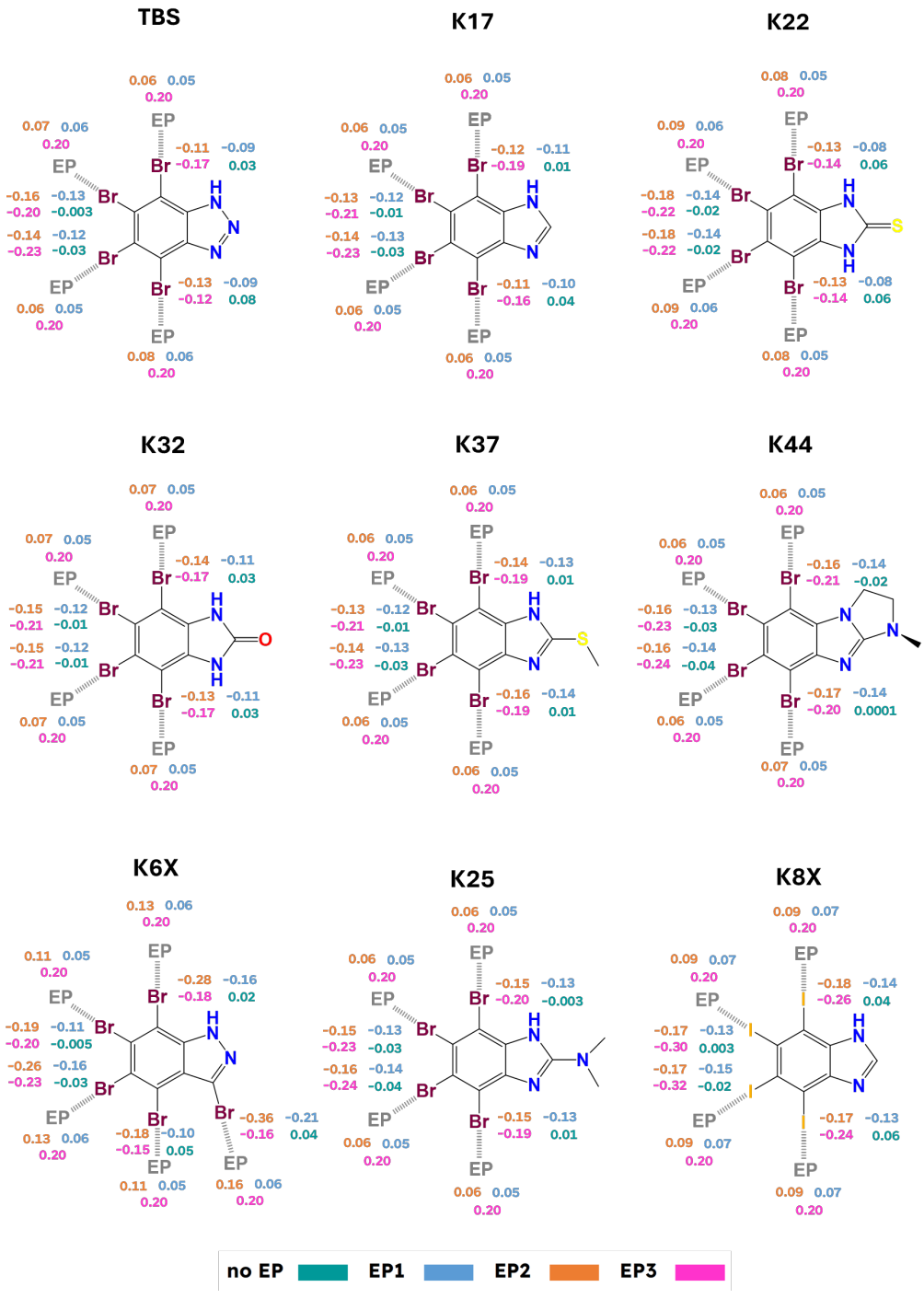

Figure S2: Charges obtained for the EP and halogen for **set A** using **no EP**, **EP1**, **EP2**, and **EP3** charge models.

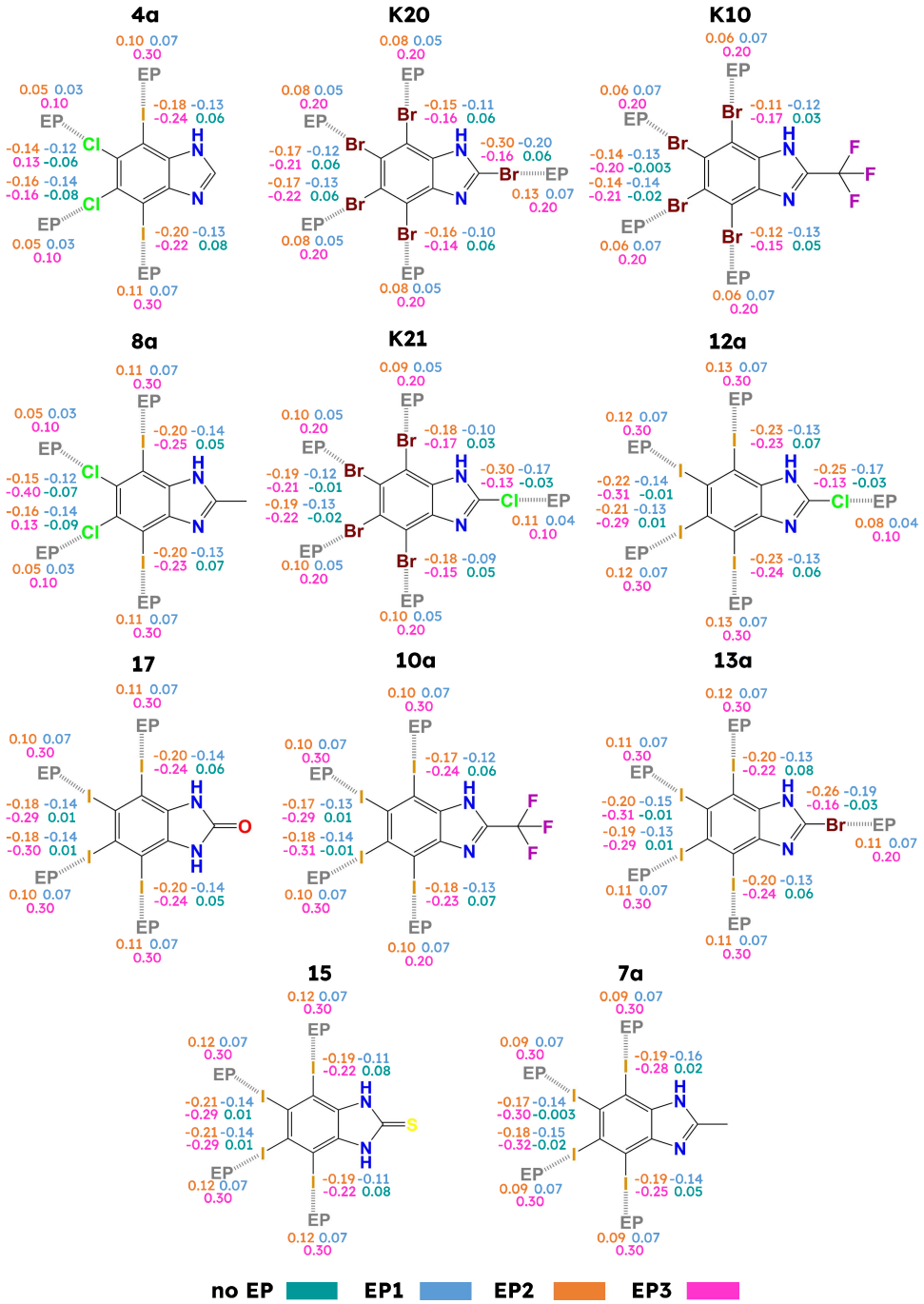

Figure S3: Charges obtained for the EP and halogen for **set B** using **no EP**, **EP1**, **EP2**, and **EP3** charge models.

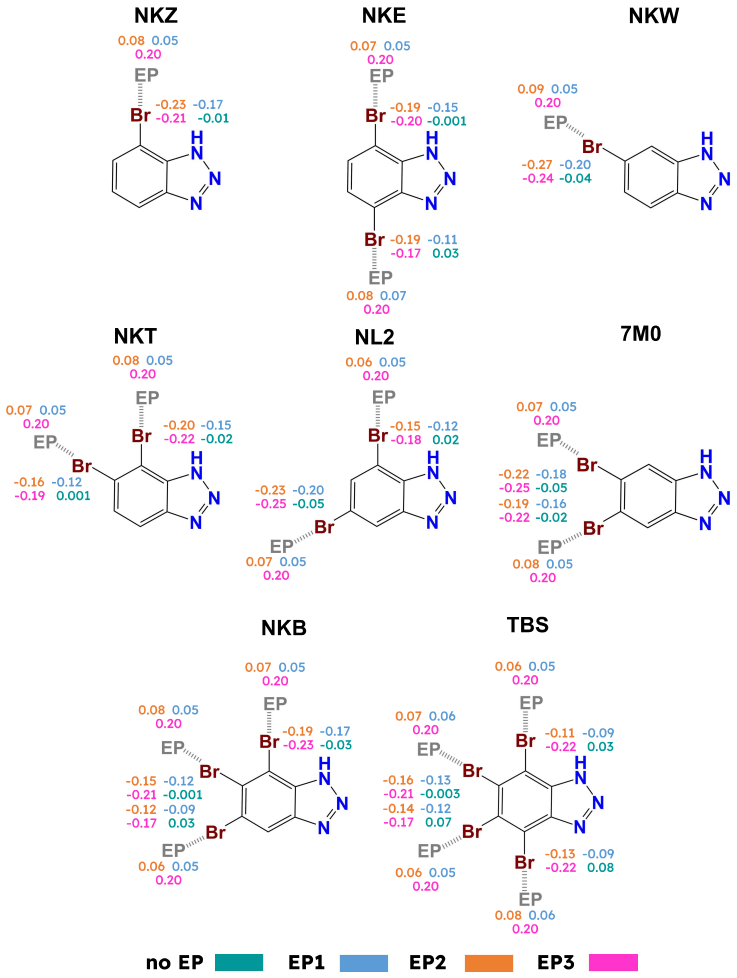

Figure S4: Charges obtained for the EP and halogen for **set C** using **no EP**, **EP1**, **EP2**, and **EP3** charge models.

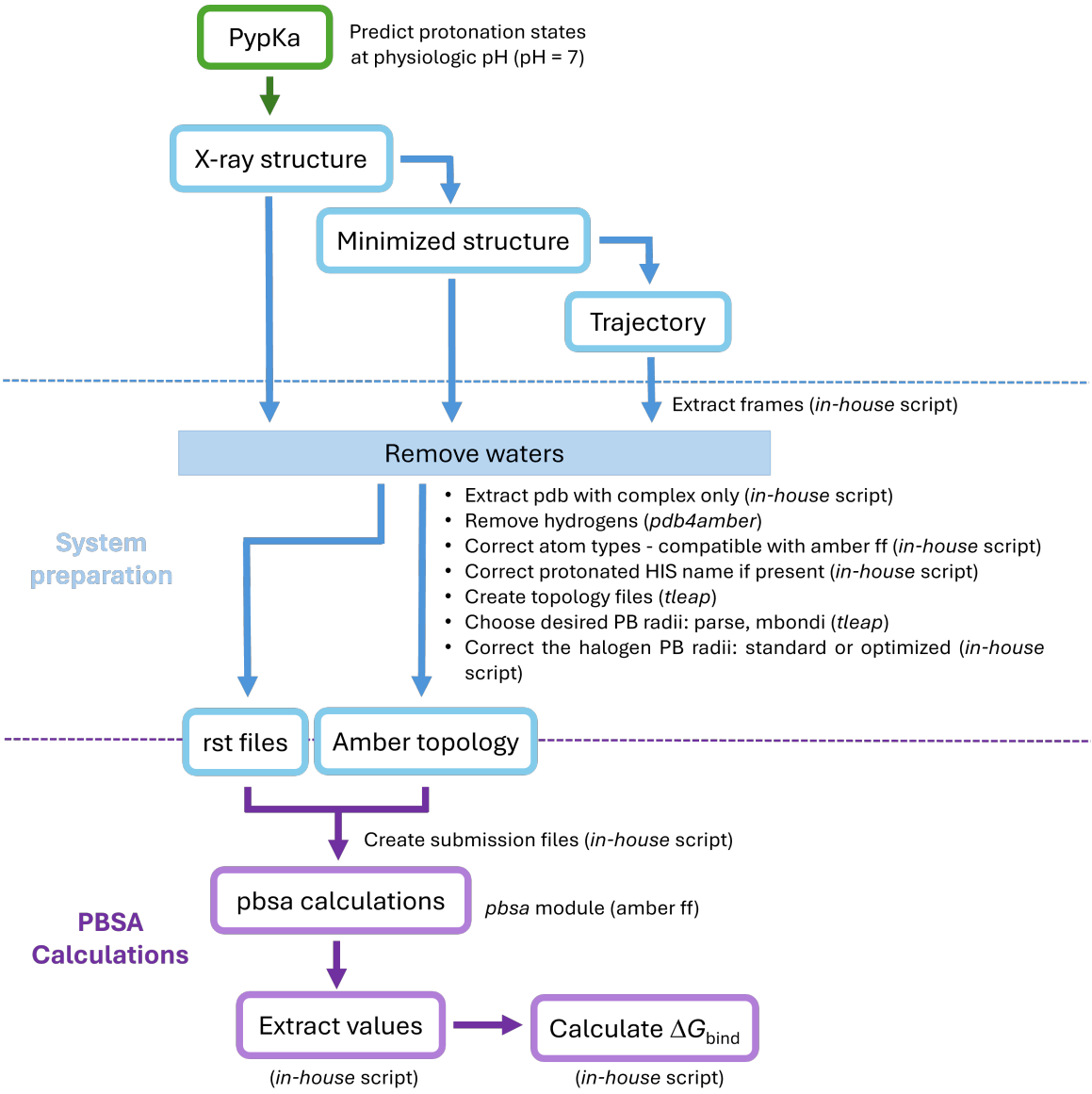

Figure S5: MM-PBSA workflow employed in this work.

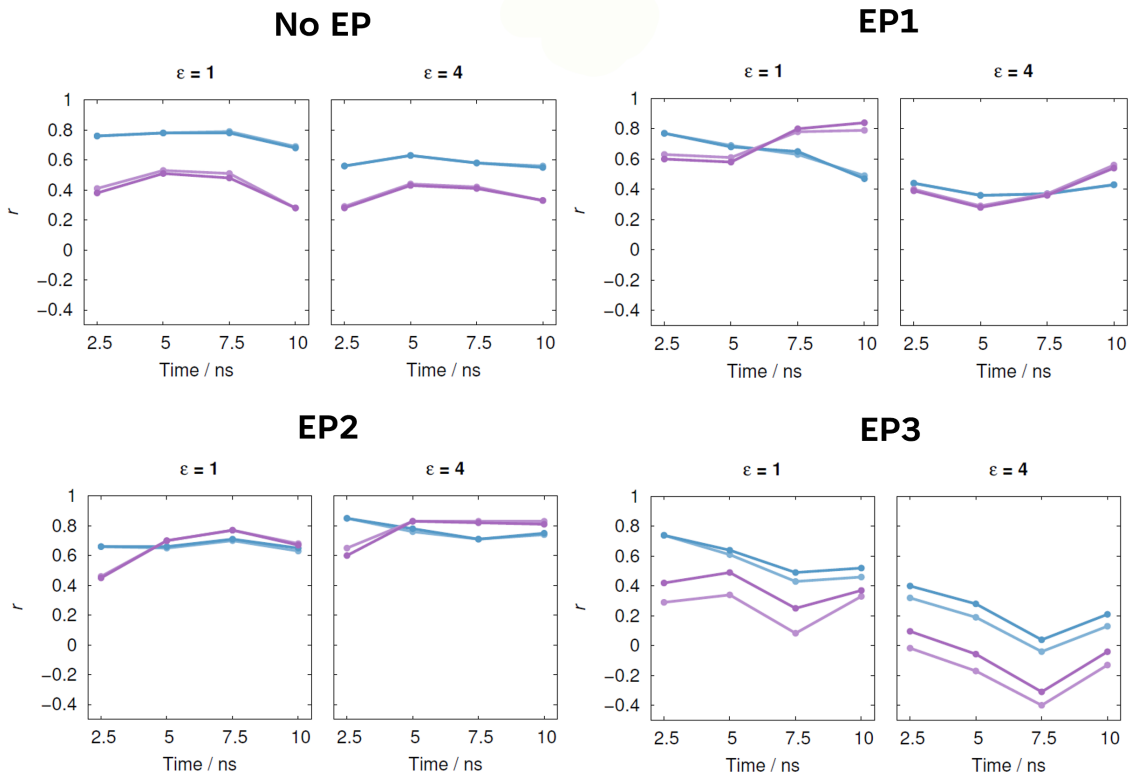

Figure S6: Variation of the Pearson coefficients (r) obtained for **Set A** using different segments of 2.5 ns (0-2.5 ns, 2.5-5 ns, 5-7.5 ns, and 7.5-10 ns). Color code: **pb2** (blue) and **pb3** (purple); r_{std} (lighter) and r_{opt} (darker).

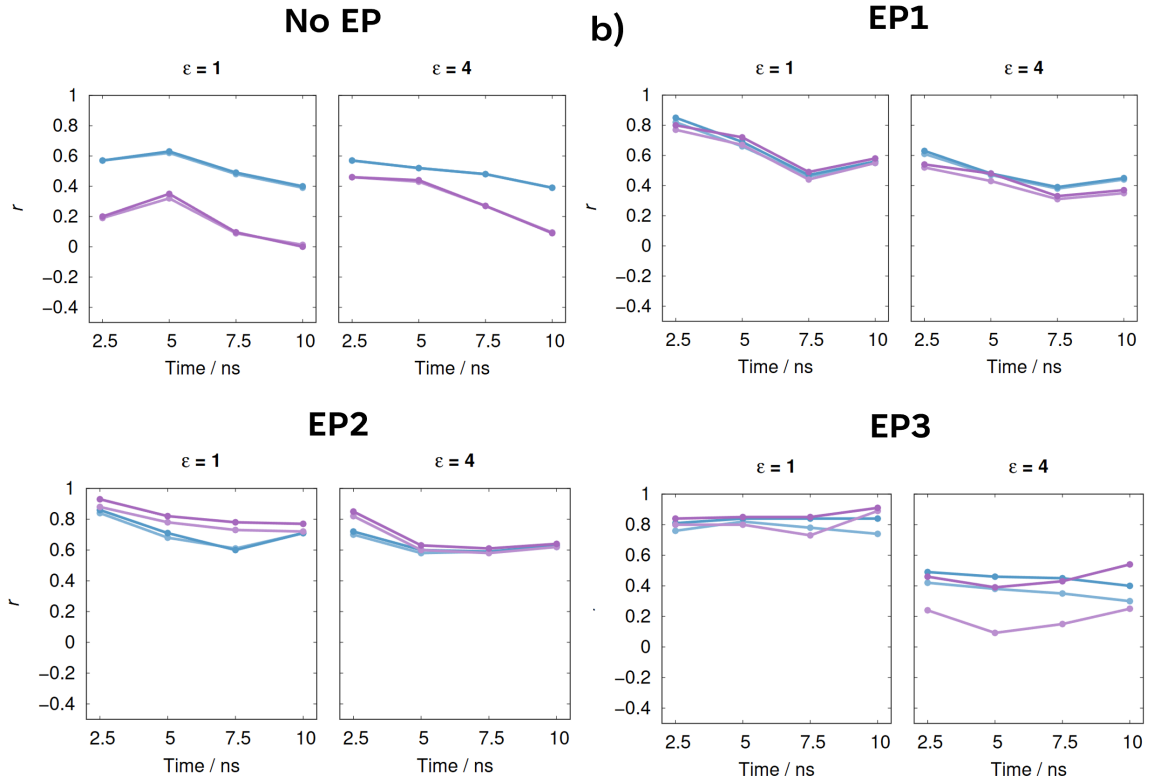

Figure S7: Variation of the Pearson coefficients (r) obtained for **Set B** using different segments of 2.5 ns (0-2.5 ns, 2.5-5 ns, 5-7.5 ns, and 7.5-10 ns). Color code: **pb2** (blue) and **pb3** (purple); r_{std} (lighter) and r_{opt} (darker).

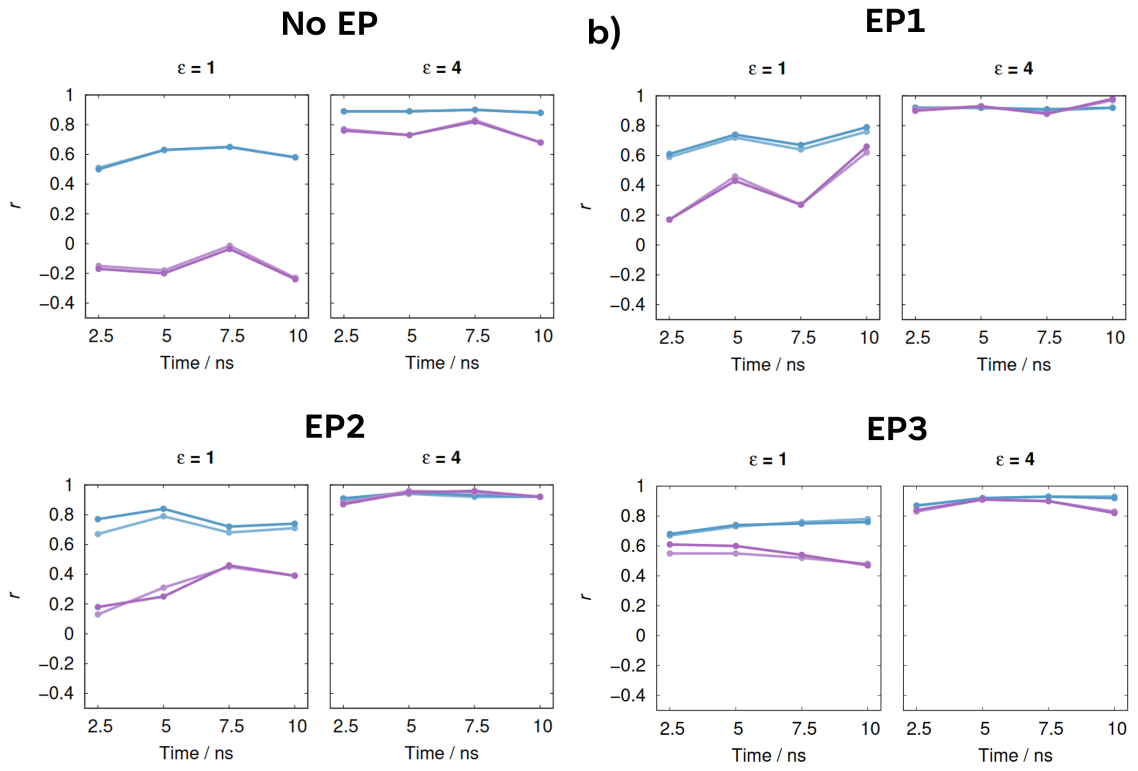

Figure S8: Variation of the Pearson coefficients (r) obtained for **Set C** using different segments of 2.5 ns (0-2.5 ns, 2.5-5 ns, 5-7.5 ns, and 7.5-10 ns). Color code: **pb2** (blue) and **pb3** (purple); r_{std} (lighter) and r_{opt} (darker).

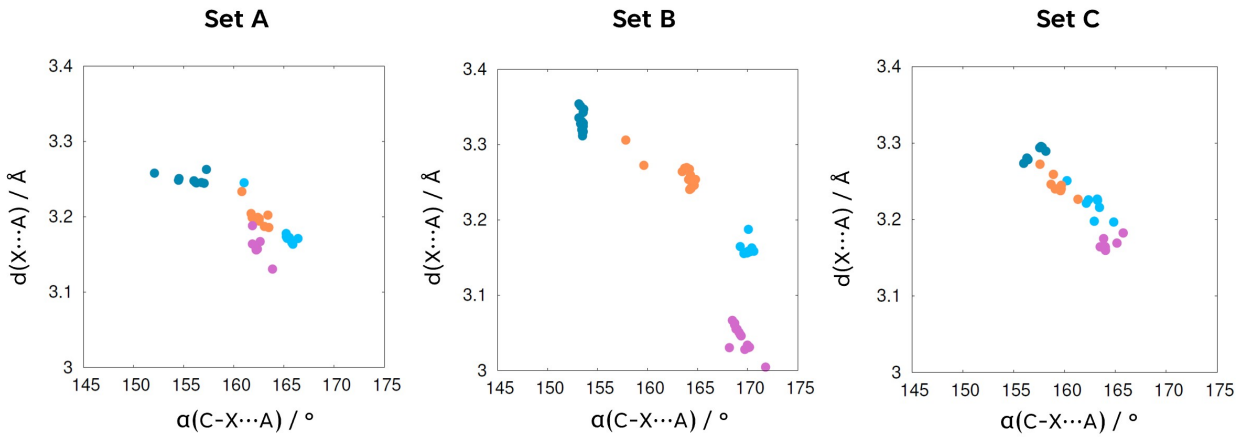

Figure S9: Average distances and angles between the halogens and halogen bond (XB) acceptors (X$\cdots$A and αC-X$\cdots$A) for the XBs obtained for each set and each charge method. **no EP** (green), **EP1** (light blue), **EP2** (orange), and **EP3** (pink).

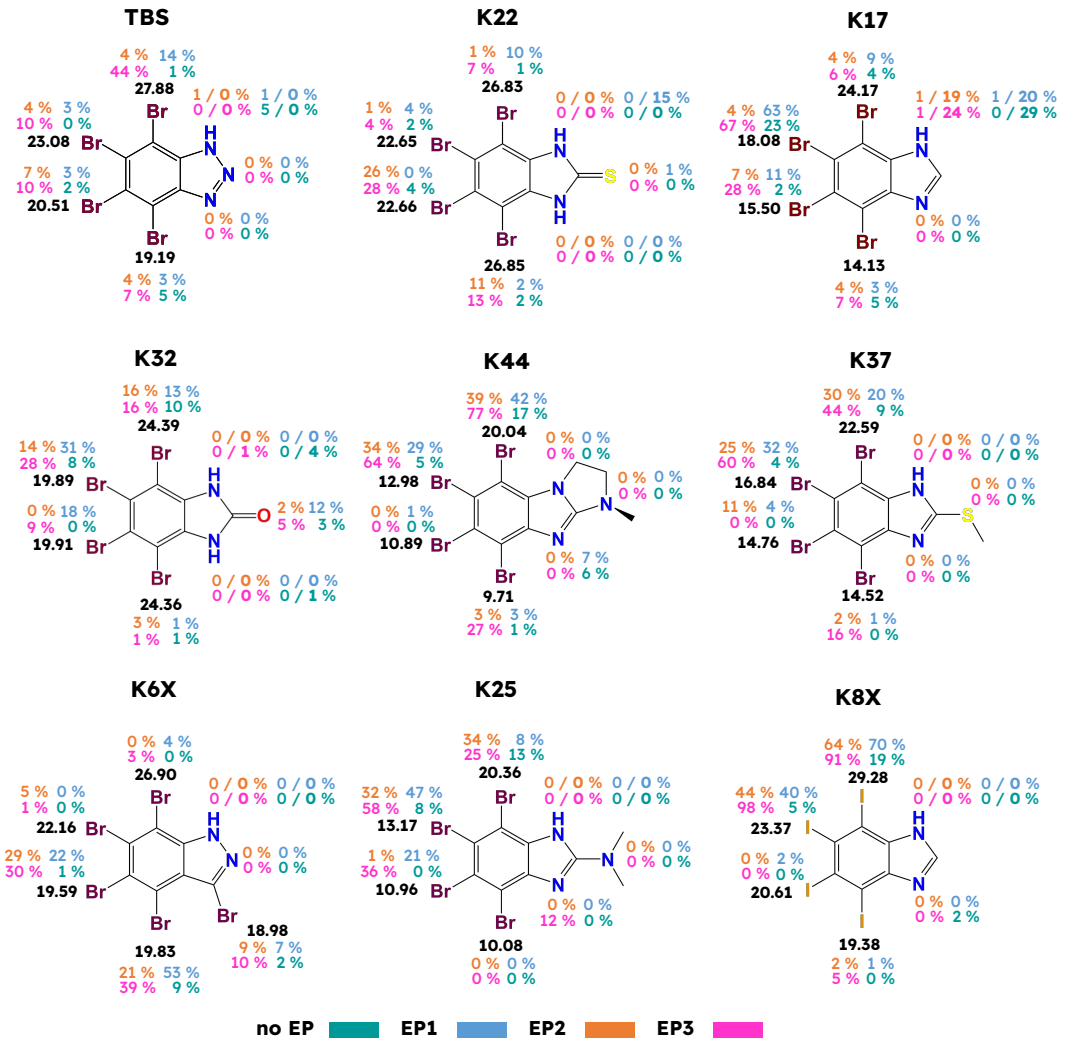

Figure S10: Maximum of the electrostatic potential on the halogen ($V_{S,max}$ in kcal mol^{-}1, black) along with the percentage of contribution of XBs and HBs obtained for each XB donor and HB donor (bold) and acceptor, for **Set A** using RESP charges (**no EP**), **EP1**, **EP2**, and **EP3**.

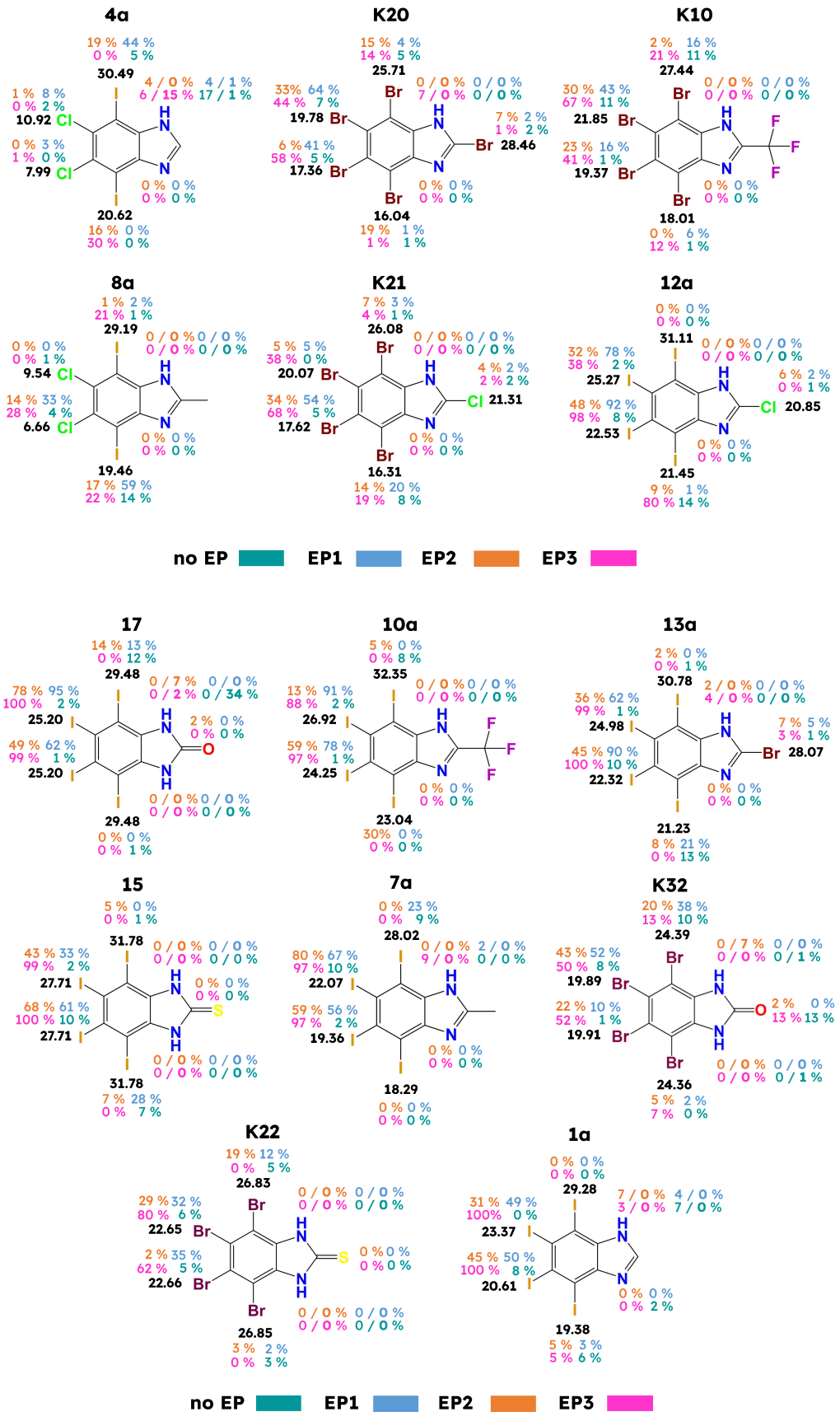

Figure S11: Maximum of the electrostatic potential on the halogen ($V_{S,max}$ in kcal mol^{-}1, black) along with the percentage of contribution of XBs and HBs obtained for each XB donor and HB donor (bold) and acceptor, for some compounds of **Set B** using RESP charges (**no EP**), **EP1**, **EP2**, and **EP3**.

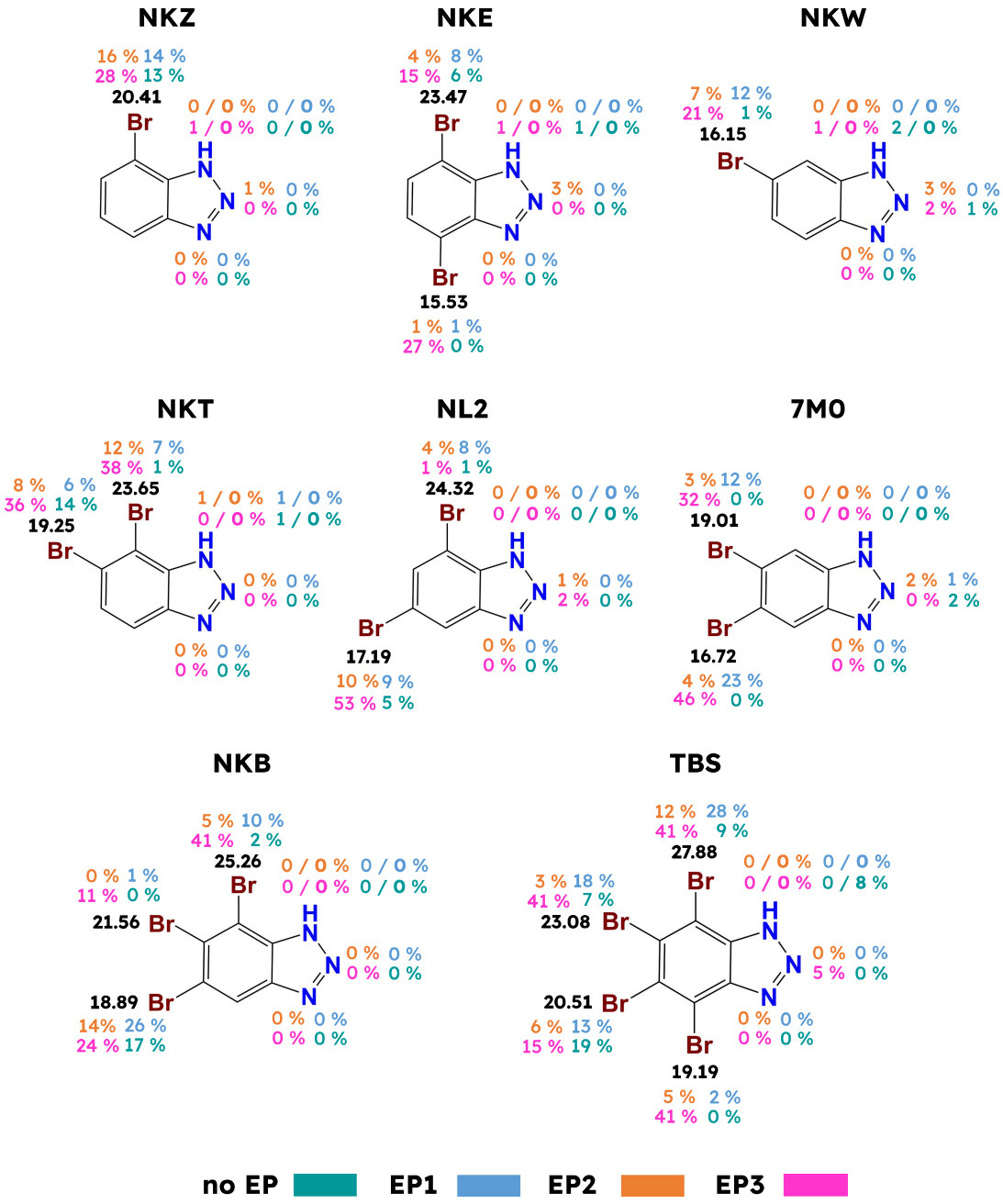

Figure S12: Maximum of the electrostatic potential on the halogen ($V_{S,max}$ in kcal mol[1], black) along with the percentage of contribution of XBs and HBs obtained for each XB donor and HB donor (bold) and acceptor, for **Set C** using RESP charges (**no EP**), **EP1**, **EP2**, and **EP3**.

Supporting Tables

Table S1: Summary of the parameters ($d_{X\cdots EP}$ in Å; q_{EP}, q_X, and q_R) used for models ***EP1***, ***EP2***, and ***EP3***.

Model	***EP1***			***EP2***			***EP3***		
Halogen	Cl	Br	I	Cl	Br	I	Cl	Br	I
$d_{X\cdots EP}$	1.948	2.020	2.150	minimizes RESP error			1.000	1.300	1.600
q_{EP}	RESP fitted			RESP fitted			0.1	0.2	0.3
q_X	RESP fitted			RESP fitted			RESP fitted without EP charge of the EP subtracted		
q_R	RESP fitted			RESP fitted			RESP fitted without EP		

Table S2: Values (kcal mol^{-1}) obtained using gmx_MMPBSA *vs* our workflow using `pbsa` (italics) for each energy term for the ligand (**TBS**, PDB: 1J91), receptor, and complex. These results were obtained for 5 frames of an MD trajectory (50 ps) along with standard radii without an EP (r_{std}) with the **pb2** setup.

	Ligand					**Receptor**					**Complex**				
Frames	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
$\mathbf{E}_{vdw}$	-1.72	-1.76	-1.68	-1.73	-1.79	-2809.3	-2742.6	-2764.2	-2745.1	-2739.9	-2849.3	-2780.7	-2800.9	-2785.4	-2781.9
	-1.72	*-1.76*	*-1.68*	*-1.73*	*-1.79*	*-2809.3*	*-2742.6*	*-2764.2*	*-2745.2*	*-2739.9*	*-2849.3*	*-2780.8*	*-2800.9*	*-2785.5*	*-2781.9*
$\mathbf{E}_{ele}$	-16.24	-16.58	-16.47	-16.46	-16.43	-23419.1	-23265.5	-23510.8	-23527.4	-23539.6	-23451.5	-23296.6	-23541.6	-23557.4	-23567.4
	-16.24	*-16.58*	*-16.47*	*-16.47*	*-16.43*	*-23419.1*	*-23265.5*	*-23510.7*	*-23527.4*	*-23539.4*	*-23451.5*	*-23296.6*	*-23541.5*	*-23557.4*	*-23567.2*
$\Delta\mathbf{G}_{PB}$	-8.55	-8.29	-8.74	-8.50	-8.39	-4714.4	-4789.4	-4661.9	-4643.9	-4664.6	-4691.5	-4770.8	-4640.9	-4625.6	-4649.6
	-8.55	*-8.29*	*-8.74*	*-8.49*	-8.39	*-4714.4*	*-4789.4*	*-4661.9*	*-4643.9*	*-4664.7*	*-4691.6*	*-4770.9*	*-4640.9*	*-4625.6*	*-4649.7*
$\Delta\mathbf{G}_{nonpolar}$	2.50	2.46	2.53	2.45	2.49	115.1	118.5	116.0	116.5	116.2	114.1	117.6	115.1	115.6	115.4
	2.50	*2.46*	*2.53*	*2.45*	*2.49*	*115.1*	*118.5*	*116.1*	*116.5*	*116.2*	*114.1*	*117.6*	*115.1*	*115.6*	*115.4*
$\Delta\mathbf{G}_{solv}$	-6.05	-5.83	-6.21	-6.05	-5.90	-4599.3	-4670.8	-4545.8	-4527.5	-4548.4	-4577.4	-4653.2	-4525.8	-4510.0	-4534.2
	-6.05	*-5.83*	*-6.21*	*-6.05*	*-5.90*	*-4599.3*	*-4670.9*	*-4545.8*	*-4527.4*	*-4548.5*	*-4577.5*	*-4652.3*	*-4525.9*	*-4510.0*	*-4534.3*
Average															
ΔG_{bind}	-27.47 ± 2.71														
	-27.43 ± 2.69														

Table S3: Distance criterion used to assign halogen bonds[?] .

Pair	**Distance threshold (Å)**
O···Cl	3.27
O···Br	3.37
O···I	3.50
N···Cl	3.30
N···Br	3.40
N···I	3.53
S···Cl	3.55
S···Br	3.65
S···I	3.78

Table S4: Pearson coefficients (r) between experimental and calculated ΔG_{bind} values using four charge models (**no EP**, **EP1**, **EP2**, and **EP3**) and PBSA setups (**pb2** and **pb3**) with standard (r_{std}) or optimized (r_{opt}) halogen radius. Results are from MM-PBSA calculations on crystallographic (X-ray) and minimized (min) structures with $\epsilon_{\text{in}} = 1$. Values in square brackets correspond to the 95 % confidence intervals. Double asterisks (**) indicate statistical significance ($p < 0.05$), whereas values marked with a single asterisk (*) indicate a suggestive trend ($0.05 \leq p < 0.10$).†

Structure	Setup	no EP		EP1		EP2		EP3	
		r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}
Set A									
X-ray	**pb2**	0.25 [−0.33, 0.79]	0.25 [−0.33, 0.80]	0.22 [−0.45, 0.80]	0.26 [−0.46, 0.87]	0.27 [−0.38, 0.87]	0.33 [−0.37, 0.89]	0.18 [−0.43, 0.74]	0.31 [−0.37, 0.85]
	pb3	0.22 [−0.38, 0.75]	0.22 [−0.38, 0.75]	0.18 [−0.50, 0.75]	0.16 [−0.52, 0.75]	0.24 [−0.41, 0.80]	0.23 [−0.42, 0.81]	0.14 [−0.48, 0.69]	0.22 [−0.44, 0.79]
min	**pb2**	0.23 [−0.29, 0.69]	0.24 [−0.31, 0.69]	0.52 [−0.10, 0.86]	0.56 [−0.05, 0.87]	0.69 [0.13, 0.96]	0.71 [0.19, 0.95]	0.64 [−0.06, 0.93]	0.65 [−0.06, 0.94]
	pb3	−0.01 [−0.57, 0.59]	−0.01 [−0.57, 0.59]	0.28 [−0.38, 0.77]	0.30 [−0.37, 0.83]	0.31 [−0.42, 0.78]	0.39 [−0.31, 0.85]	0.28 [−0.63, 0.87]	0.24 [−0.61, 0.84]
Set B									
X-ray	**pb2**	−0.76 [−0.90, −0.61]	−0.76 [−0.90, −0.61]	−0.70 [−0.89, −0.46]	−0.70 [−0.88, −0.50]	−0.78 [−0.94, −0.57]	−0.77 [−0.93, −0.57]	−0.64 [−0.90, −0.28]	−0.58 [−0.89, −0.20]
	pb3	−0.75 [−0.90, −0.60]	−0.74 [−0.89, −0.58]	**−0.70*** [−0.88, −0.50]	**−0.67*** [−0.85, −0.47]	−0.77 [−0.92, −0.56]	−0.75 [−0.91, −0.54]	−0.67 [−0.89, −0.37]	−0.54 [−0.84, −0.17]
min	**pb2**	**0.52**** [0.11, 0.79]	**0.56**** [0.20, 0.81]	**0.41*** [0.03, 0.70]	**0.50*** [0.13, 0.77]	0.50 [0.05, 0.80]	0.57 [0.17, 0.83]	0.34 [0.14, 0.72]	0.34 [0.14, 0.77]
	pb3	0.36 [−0.04, 0.67]	0.57 [0.28, 0.81]	0.46 [0.04, 0.75]	0.53 [0.14, 0.79]	0.56 [0.06, 0.85]	0.61 [0.15, 0.87]	0.34 [0.14, 0.73]	0.34 [−0.05, 0.67]
Set C									
X-ray	**pb2**	0.40 [−0.51, 0.86]	0.40 [−0.50, 0.86]	0.47 [−0.31, 0.88]	0.49 [−0.34, 0.89]	0.40 [−0.85, 0.92]	0.43 [−0.80, 0.93]	0.72 [0.38, 0.96]	0.74 [0.42, 0.97]
	pb3	−0.05 [−0.78, 0.78]	0.06 [−0.79, 0.79]	0.02 [−0.76, 0.84]	0.08 [−0.72, 0.88]	−0.14 [−0.88, 0.98]	−0.04 [−0.83, 0.97]	0.45 [−0.21, 0.91]	0.54 [−0.04, 0.93]
min	**pb2**	0.55 [0.15, 0.89]	0.55 [0.10, 0.88]	0.68 [0.40, 0.93]	0.70 [0.40, 0.93]	0.60 [0.27, 0.90]	0.65 [0.29, 0.91]	0.82 [0.60, 0.97]	0.85 [0.62, 0.98]
	pb3	0.01 [−0.88, 0.66]	0.00 [−0.86, 0.68]	0.14 [−0.82, 0.74]	0.19 [−0.76, 0.80]	0.05 [−0.82, 0.71]	0.13 [−0.79, 0.79]	0.54 [0.03, 0.95]	0.49 [−0.08, 0.90]

† Uncertainty in the Pearson correlation coefficients was estimated using Efron's nonparametric bootstrap with 10000 resamples of paired molecular systems. The associated 95 % confidence intervals were obtained using the percentile method. Statistical significance between Pearson correlation coefficients obtained with standard (r_{std}) and optimized (r_{opt}) halogen radii was assessed using a paired permutation test. Specifically, the observed difference in correlation coefficients (Δr was compared with a null distribution generated by enumerating all possible permutations of standard and optimized predictions within each system, thereby preserving the paired structure of the data. Two-sided p-values were computed as the fraction of permutations yielding a difference in correlation coefficients with absolute value greater than or equal to that observed. Statistical significance was defined as $p < 0.05$, whereas values in the range $0.05 \leq p < 0.10$ were considered indicative of suggestive trends.

Table S5: Pearson coefficients (r) between experimental and calculated ΔG_{bind} values using four charge models (**no EP**, **EP1**, **EP2**, and **EP3**) and PBSA setups (**pb2** and **pb3**) with standard (r_{std}) or optimized (r_{opt}) halogen radius. Results are from MM-PBSA calculations on crystallographic (X-ray) and minimized (min) structures with $\epsilon_{\text{in}} = 4$. Values in square brackets correspond to the 95 % confidence intervals. Double asterisks (**) indicate statistical significance ($p < 0.05$), whereas values marked with a single asterisk (*) indicate a suggestive trend ($0.05 \leq p < 0.10$).

Structure	Setup	no EP		EP1		EP2		EP3	
		r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}
Set A									
X-ray	**pb2**	0.21 [−0.33, 0.78]	0.21 [−0.32, 0.76]	0.20 [−0.36, 0.78]	0.22 [−0.35, 0.77]	0.25 [−0.29, 0.82]	0.27 [−0.28, 0.81]	0.20 [−0.34, 0.78]	0.25 [−0.31, 0.79]
	pb3	0.14 [−0.43, 0.75]	0.13 [−0.45, 0.77]	0.12 [−0.46, 0.75]	0.12 [−0.48, 0.77]	0.17 [−0.40, 0.78]	0.17 [−0.42, 0.81]	0.12 [−0.44, 0.74]	0.14 [−0.45, 0.78]
min	**pb2**	0.53 [0.09, 0.93]	0.53 [0.06, 0.92]	0.70 [0.32, 0.96]	0.72 [0.31, 0.96]	0.73 [0.35, 0.98]	0.74 [0.33, 0.98]	0.61 [0.18, 0.97]	0.66 [0.21, 0.94]
	pb3	0.31 [−0.27, 0.80]	0.31 [−0.32, 0.79]	0.51 [0.01, 0.88]	0.50 [−0.08, 0.89]	0.52 [−0.01, 0.87]	0.53 [−0.04, 0.88]	0.38 [−0.23, 0.86]	0.35 [−0.22, 0.82]
Set B									
X-ray	**pb2**	−0.75 [−0.90, −0.58]	−0.75 [−0.89, −0.58]	−0.71 [−0.88, −0.52]	−0.71 [−0.88, −0.52]	−0.84 [−0.93, −0.72]	−0.83 [−0.93, −0.72]	−0.77 [−0.90, −0.63]	−0.77 [−0.89, −0.63]
	pb3	−0.75 [−0.88, −0.60]	−0.75 [−0.88, −0.59]	−0.70 [−0.87, −0.50]	−0.69 [−0.87, −0.50]	−0.82 [−0.93, −0.70]	−0.82 [−0.92, −0.70]	−0.77 [−0.89, −0.64]	−0.77 [−0.88, −0.63]
min	**pb2**	0.66 [0.43, 0.85]	0.67 [0.45, 0.86]	**0.62**** [0.40, 0.83]	**0.66**** [0.46, 0.86]	0.61 [0.36, 0.83]	0.63 [0.39, 0.84]	0.34 [0.08, 0.65]	0.34 [0.13, 0.69]
	pb3	0.77 [0.63, 0.90]	0.81 [0.69, 0.92]	0.66 [0.43, 0.91]	0.69 [0.50, 0.93]	0.70 [0.46, 0.88]	0.72 [0.52, 0.89]	0.34 [−0.11, 0.66]	0.34 [−0.40, 0.65]
Set C									
X-ray	**pb2**	0.85 [0.47, 1.00]	0.86 [0.47, 1.00]	0.89 [0.60, 1.00]	0.89 [0.60, 1.00]	0.87 [0.59, 1.00]	0.87 [0.59, 1.00]	0.87 [0.55, 1.00]	0.87 [0.57, 1.00]
	pb3	0.78 [0.37, 1.00]	0.77 [0.34, 0.99]	0.82 [0.53, 0.99]	0.83 [0.56, 0.99]	0.79 [0.42, 1.00]	0.81 [0.47, 1.00]	0.87 [0.68, 0.99]	0.89 [0.73, 0.99]
min	**pb2**	0.87 [0.64, 0.99]	0.87 [0.63, 0.99]	0.89 [0.68, 0.99]	0.90 [0.69, 0.99]	0.88 [0.65, 0.99]	0.89 [0.66, 0.99]	0.90 [0.71, 0.99]	0.90 [0.71, 0.99]
	pb3	0.62 [0.21, 0.94]	0.62 [0.22, 0.94]	0.69 [0.33, 0.95]	0.69 [0.35, 0.96]	0.63 [0.21, 0.94]	0.64 [0.25, 0.95]	0.68 [0.16, 0.92]	0.66 [0.13, 0.92]

Table S6: Pearson coefficients (r) obtained for the linear correlation between experimental and calculated ΔG_{bind} values in **Set A** using four charge models - **no EP**, **EP1**, **EP2** and **EP3** - and pbsa setups **pb2** and **pb3** with standard (r_{std}) or optimized (r_{opt}) halogen radius. These results were obtained by performing MM-PBSA calculations on different segments of the MD trajectories and a solute dielectric (ϵ_{in}) = 1.

segment	**setup**	**No EP**		**EP1**		**EP2**		**EP3**	
		r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}
0-10 ns	**pb2**	0.79	0.79	0.68	0.68	0.79	0.80	0.59	0.62
	pb3	0.33	0.28	0.73	0.71	0.85	0.83	0.31	0.42
0-2.5 ns	**pb2**	0.76	0.76	0.77	0.77	0.85	0.85	0.74	0.74
	pb3	0.41	0.38	0.63	0.60	0.65	0.60	0.29	0.42
2.5-5 ns	**pb2**	0.78	0.78	0.69	0.68	0.76	0.78	0.61	0.64
	pb3	0.53	0.51	0.61	0.58	0.83	0.83	0.34	0.49
0-5 ns	**pb2**	0.78	0.78	0.75	0.75	0.81	0.83	0.70	0.71
	pb3	0.49	0.46	0.63	0.60	0.80	0.77	0.32	0.46
5-7.5 ns	**pb2**	0.79	0.78	0.63	0.65	0.71	0.71	0.43	0.49
	pb3	0.51	0.48	0.78	0.80	0.83	0.82	0.08	0.25
7.5-10 ns	**pb2**	0.69	0.68	0.49	0.47	0.74	0.75	0.46	0.52
	pb3	0.28	0.28	0.79	0.84	0.83	0.81	0.33	0.37
5-10 ns	**pb2**	0.74	0.74	0.57	0.57	0.73	0.73	0.45	0.51
	pb3	0.40	0.38	0.81	0.85	0.85	0.83	0.22	0.32

Table S7: Pearson coefficients (r) obtained for the linear correlation between experimental and calculated ΔG_{bind} values in **Set A** using four charge models - **no EP**, **EP1**, **EP2** and **EP3** - and pbsa setups **pb2** and **pb3** with standard (r_{std}) or optimized (r_{opt}) halogen radius. These results were obtained by performing MM-PBSA calculations on different segments of the MD trajectories and a solute dielectric (ϵ_{in}) = 4.

Sampling time	**setup**	**No EP**		**EP1**		**EP2**		**EP3**	
		r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}
0-10 ns	**pb2**	0.60	0.60	0.40	0.40	0.67	0.68	0.15	0.24
	pb3	0.40	0.39	0.41	0.40	0.70	0.69	-0.20	-0.10
0-2.5 ns	**pb2**	0.56	0.65	0.44	0.44	0.66	0.66	0.32	0.40
	pb3	0.29	0.28	0.40	0.39	0.46	0.45	-0.02	0.09
2.5-5 ns	**pb2**	0.63	0.63	0.36	0.36	0.65	0.66	0.19	0.28
	pb3	0.44	0.43	0.29	0.28	0.70	0.70	-0.17	-0.06
0-5 ns	**pb2**	0.61	0.61	0.40	0.40	0.66	0.67	0.26	0.34
	pb3	0.37	0.38	0.34	0.35	0.60	0.59	-0.10	0.02
5-7.5 ns	**pb2**	0.58	0.58	0.37	0.37	0.70	0.71	-0.04	0.04
	pb3	0.42	0.41	0.37	0.36	0.77	0.77	-0.40	-0.31
7.5-10 ns	pb2	0.56	0.55	0.43	0.43	0.63	0.65	0.13	0.21
	pb3	0.33	0.33	0.56	0.54	0.68	0.67	-0.13	-0.04
5-10 ns	**pb2**	0.57	0.57	0.40	0.40	0.67	0.68	0.05	0.13
	pb3	0.38	0.37	0.46	0.45	0.76	0.75	-0.27	-0.18

Table S8: Pearson coefficients (r) obtained for the linear correlation between experimental and calculated ΔG_{bind} values in **Set B** using four charge models - **no EP**, **EP1**, **EP2** and **EP3** - and pbsa setups **pb2** and **pb3** with standard (r_{std}) or optimized (r_{opt}) halogen radius. These results were obtained by performing MM-PBSA calculations on different segments of the MD trajectories and a solute dielectric (ϵ_{in}) = 1.

Sampling time	**setup**	**No EP**		**EP1**		**EP2**		**EP3**	
		r_{std}	r_{opt}	r_{std}	r_{opt}	$r_{\text{std}})$	r_{opt}	$r_{\text{std}})$	r_{opt}
0-10 ns	**pb2**	0.54	0.55	0.64	0.67	0.74	0.75	0.80	0.85
	pb3	0.18	0.18	0.64	0.68	0.86	0.91	0.88	0.89
0-2.5 ns	**pb2**	0.57	0.57	0.82	0.85	0.84	0.86	0.76	0.81
	pb3	0.19	0.20	0.77	0.80	0.88	0.93	0.80	0.84
2.5-5 ns	**pb2**	0.62	0.63	0.66	0.69	0.68	0.71	0.82	0.84
	pb3	0.32	0.35	0.67	0.72	0.78	0.82	0.80	0.85
0-5 ns	**pb2**	0.62	0.63	0.76	0.80	0.78	0.81	0.79	0.83
	pb3	0.31	0.33	0.75	0.78	0.87	0.91	0.83	0.86
5-7.5 ns	**pb2**	0.48	0.49	0.46	0.47	0.61	0.60	0.78	0.84
	pb3	0.09	0.10	0.44	0.49	0.73	0.78	0.73	0.85
7.5-10 ns	**pb2**	0.39	0.40	0.55	0.56	0.71	0.71	0.74	0.84
	pb3	<0.01	<0.01	0.55	0.58	0.72	0.77	0.89	0.91
5-10 ns	**pb2**	0.44	0.45	0.51	0.52	0.67	0.66	0.77	0.85
	pb3	0.05	0.05	0.51	0.55	0.76	0.82	0.84	0.89

Table S9: Pearson coefficients (r) obtained for the linear correlation between experimental and calculated ΔG_{bind} values in **Set B** using four charge models - **no EP**, **EP1**, **EP2** and **EP3** - and pbsa setups **pb2** and **pb3** with standard (r_{std}) or optimized (r_{opt}) halogen radius. These results were obtained by performing MM-PBSA calculations on different segments of the MD trajectories and a solute dielectric (ϵ_{in}) = 4.

Sampling time	**setup**	**No EP**		**EP1**		**EP2**		**EP3**	
		r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}
0-10 ns	**pb2**	0.50	0.51	0.49	0.50	0.64	0.65	0.36	0.45
	pb3	0.35	0.35	0.43	0.46	0.72	0.76	0.19	0.47
0-2.5 ns	**pb2**	0.57	0.57	0.61	0.63	0.70	0.72	0.42	0.49
	pb3	0.46	0.46	0.52	0.54	0.82	0.85	0.24	0.46
2.5-5 ns	**pb2**	0.52	0.52	0.47	0.48	0.58	0.60	0.38	0.46
	pb3	0.43	0.44	0.43	0.48	0.60	0.63	0.09	0.39
0-5 ns	**pb2**	0.55	0.55	0.55	0.57	0.65	0.66	0.40	0.47
	pb3	0.46	0.47	0.49	0.53	0.75	0.79	0.17	0.43
5-7.5 ns	**pb2**	0.48	0.48	0.38	0.39	0.59	0.59	0.35	0.45
	pb3	0.27	0.27	0.31	0.33	0.58	0.61	0.15	0.43
7.5-10 ns	pb2	0.39	0.39	0.44	0.45	0.62	0.63	0.30	0.40
	pb3	0.10	0.09	0.35	0.37	0.62	0.64	0.25	0.54
5-10 ns	**pb2**	0.44	0.44	0.42	0.42	0.61	0.61	0.33	0.43
	pb3	0.19	0.19	0.33	0.36	0.62	0.66	0.20	0.49

Table S10: Pearson coefficients (r) obtained for the linear correlation between experimental and calculated ΔG_{bind} values in **Set C** using four charge models - **no EP**, **EP1**, **EP2** and **EP3** - and pbsa setups **pb2** and **pb3** with standard (r_{std}) or optimized (r_{opt}) halogen radius. These results were obtained by performing MM-PBSA calculations on different segments of the MD trajectories and a solute dielectric (ϵ_{in}) = 1.

Sampling time	**setup**	**No EP**		**EP1**		**EP2**		**EP3**	
		r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}
0-10 ns	**pb2**	0.60	0.60	0.70	0.73	0.73	0.78	0.74	0.74
	pb3	-0.15	-0.17	0.40	0.40	0.37	0.38	0.53	0.56
0-2.5 ns	**pb2**	0.51	0.50	0.59	0.61	0.67	0.77	0.67	0.68
	pb3	-0.15	-0.17	0.17	0.17	0.13	0.18	0.55	0.61
2.5-5 ns	**pb2**	0.63	0.63	0.72	0.74	0.79	0.84	0.73	0.74
	pb3	-0.2	-0.18	0.46	0.43	0.31	0.25	0.55	0.60
0-5 ns	**pb2**	0.58	0.57	0.68	0.70	0.75	0.82	0.70	0.72
	pb3	-0.17	-0.19	0.33	0.31	0.22	0.23	0.56	0.61
5-7.5 ns	**pb2**	0.65	0.65	0.64	0.67	0.68	0.72	0.76	0.75
	pb3	-0.01	-0.04	0.27	0.27	0.45	0.46	0.52	0.54
7.5-10 ns	**pb2**	0.58	0.58	0.76	0.79	0.71	0.74	0.78	0.76
	pb3	-0.23	-0.24	0.62	0.66	0.39	0.39	0.50	0.51
5-10 ns	**pb2**	0.62	0.62	0.71	0.74	0.70	0.73	0.77	0.76
	pb3	-0.12	-0.14	0.46	0.48	0.43	0.43	0.48	0.47

Table S11: Pearson coefficients (r) obtained for the linear correlation between experimental and calculated ΔG_{bind} values in **Set C** using four charge models - **no EP**, **EP1**, **EP2** and **EP3** - and pbsa setups **pb2** and **pb3** with standard (r_{std}) or optimized (r_{opt}) halogen radius. These results were obtained by performing MM-PBSA calculations on different segments of the MD trajectories and a solute dielectric (ϵ_{in}) = 4.

Sampling time	**setup**	**No EP**		**EP1**		**EP2**		**EP3**	
		r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}	r_{std}	r_{opt}
0-10 ns	**pb2**	0.89	0.90	0.92	0.92	0.92	0.93	0.91	0.91
	pb3	0.79	0.79	0.95	0.95	0.95	0.95	0.89	0.89
0-2.5 ns	**pb2**	0.89	0.89	0.92	0.92	0.90	0.91	0.87	0.87
	pb3	0.77	0.76	0.90	0.90	0.88	0.87	0.83	0.84
2.5-5 ns	**pb2**	0.89	0.89	0.92	0.92	0.94	0.95	0.92	0.92
	pb3	0.73	0.73	0.93	0.93	0.96	0.95	0.91	0.91
0-5 ns	**pb2**	0.89	0.89	0.92	0.92	0.93	0.93	0.90	0.90
	pb3	0.77	0.77	0.94	0.94	0.95	0.95	0.88	0.88
5-7.5 ns	**pb2**	0.90	0.90	0.90	0.91	0.92	0.93	0.93	0.93
	pb3	0.83	0.82	0.88	0.88	0.95	0.96	0.90	0.90
7.5-10 ns	**pb2**	0.68	0.68	0.92	0.92	0.92	0.92	0.93	0.92
	pb3	0.88	0.88	0.97	0.98	0.92	0.92	0.83	0.82
5-10 ns	**pb2**	0.89	0.90	0.91	0.92	0.92	0.92	0.93	0.93
	pb3	0.77	0.77	0.95	0.95	0.94	0.94	0.87	0.87

Table S12: Halogen Bonds (XBs) established in the X-ray and minimized structures obtained for each charge model - no EP, **EP1**, **EP2**, and **EP3** - for **Set A**.

systems	X-ray	Minimized structure			
		no EP	EP1	EP2	EP3
TBS	1	0	1	0	0
K25	2	0	1	1	1
K37	2	0	1	0	2
K44	2	1	1	1	1
K32	2	1	1	1	1
K22	1	0	0	1	1
K17	2	1	2	2	2
K6X	1	1	2	2	2
K8X	2	0	1	0	2

Table S13: Halogen Bonds (XBs) established in the X-ray and minimized structures obtained for each charge model - no EP, **EP1**, **EP2**, and **EP3** - for **Set B**.

systems	X-ray	Minimized structure			
		no EP	EP1	EP2	EP3
4a	1	0	0	0	0
8a	1	1	1	1	0
10a	2	1	1	1	2
12a	2	0	1	1	2
13a	2	1	1	1	2
15	2	0	1	1	2
K10	2	1	1	1	1
K22	2	0	1	1	1
7a	2	1	1	1	2
17	2	0	1	1	2
K32	2	0	0	0	1
K21	2	0	1	1	1
K20	2	0	1	1	1
1a	2	0	1	1	2

Table S14: Halogen Bonds (XBs) established in the X-ray and minimized structures obtained for each charge model - no EP, **EP1**, **EP2**, and **EP3** - for **Set C**.

systems	X-ray	Minimized structure			
		no EP	EP1	EP2	EP3
NKZ	0	0	0	0	0
NKW	0	0	0	0	0
NKT	1	0	1	1	1
NL2	0	0	0	0	0
NKE	0	0	0	0	0
7M0	0	0	0	0	0
NKB	1	1	1	1	1
TBS	1	0	0	0	0

Table S15: Percentage of frames where at least one HB is formed (HB %) and average number of HBs formed during the trajectory ($\overline{x}$ HBs) for **Sets A-C**. The number of HB acceptors (nA) and donors (nD) present on the inhibitor (nX) and the number of HBs present on the X-ray structure (X-ray) is also shown. The reported errors ($\approx$ 95% confidence) correspond to $\pm$2 SEM (SEM = standard error of the mean).

system	nA/nD	X-ray	HBs % ($\overline{x}$ HBs)			
			no EP	EP1	EP2	EP3
Set A						
TBS	3/1	0	5 ± 6.9 (1.0 ± 0.01)	1 ± 0.5 (1.0 ± 0.00)	1 ± 2.1 (1.0 ± 0.01)	0 ± 0.0 (0.0 ± 0.00)
K25	3/2	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	12 ± 16.0 (1.0 ± 0.00)
K37	2/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
K44	3/2	0	6 ± 12.3 (0.3 ± 0.67)	7 ± 12.9 (0.3 ± 0.67)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
K32	3/0	0	8 ± 10.0 (1.0 ± 0.18)	12 ± 11.4 (1.0 ± 0.00)	2 ± 4.3 (0.6 ± 0.67)	6 ± 7.8 (1.0 ± 0.00)
K22	3/1	0	0 ± 0.0 (0.0 ± 0.00)	15 ± 30.3 (0.6 ± 0.67)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
K17	2/1	0	29 ± 15 (1.0 ± 0.00)	21 ± 6.3 (1.0 ± 0.00)	20 ± 11.1 (1.0 ± 0.00)	25 ± 3.9 (1.0 ± 0.00)
K6X	3/1	0	2 ± 0.2 (0.6 ± 0.67)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
K8X	2/1	0	2 ± 4.8 (0.3 ± 0.67)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
Set B						
4a	2/1	0	18 ± 1.4 (1.0 ± 0.01)	5 ± 6.2 (0.6 ± 0.67)	5 ± 6.1 (0.6 ± 0.67)	18 ± 21.5 (0.7 ± 0.71)
8a	2/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
10a	2/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
12a	2/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
13a	2/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	2 ± 2.6 (1.0 ± 0.00)	4 ± 7.2 (0.6 ± 0.67)
15	3/2	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
K10	2/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
K22	3/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
7a	2/1	0	2 ± 4.1 (0.6 ± 0.67)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	9 ± 9.3 (1.0 ± 0.00)
17	3/1	0	34 ± 34.2 (1.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	9 ± 1.9 (1.0 ± 0.00)	2 ± 0.9 (1.0 ± 0.00)
K32	3/2	0	15 ± 16.9 (1.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	9 ± 12.9 (1.0 ± 0.00)	13 ± 5.7 (1.0 ± 0.00)
K21	2/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
K20	2/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	8 ± 9.2 (1.0 ± 0.00)
1a	2/1	0	7 ± 13.7 (1.0 ± 0.00)	4 ± 1.8 (1.0 ± 0.00)	7 ± 3.9 (1.0 ± 0.00)	3 ± 5.3 (1.0 ± 0.00)
Set C						
NKZ	3/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	1 ± 1.6 (1.0 ± 0.04)	1 ± 1.9 (0.6 ± 0.67)
NKW	3/1	1	3 ± 0.6 (1.0 ± 0.01)	0 ± 0.0 (0.0 ± 0.00)	3 ± 3.4 (1.0 ± 0.02)	3 ± 1.8 (1.0 ± 0.05)
NKT	3/1	0	1 ± 4.9 (1.0 ± 0.00)	1 ± 1.7 (0.6 ± 0.67)	1 ± 1.8 (0.6 ± 0.69)	0 ± 0.0 (0.0 ± 0.00)
NL2	3/1	1	2 ± 2.4 (1.0 ± 0.03)	0 ± 0.0 (0.0 ± 0.00)	1 ± 1.7 (1.0 ± 0.00)	2 ± 0.3 (1.0 ± 0.03)
NKE	3/1	0	1 ± 0.4 (1.0 ± 0.03)	0 ± 0.0 (0.0 ± 0.00)	3 ± 1.0 (1.0 ± 0.11)	1 ± 1.4 (1.0 ± 0.01)
7M0	3/1	1	2 ± 0.8 (1.0 ± 0.00)	1 ± 1.2 (1.0 ± 0.05)	2 ± 1.0 (1.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
NKB	3/1	0	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)
TBS	3/1	0	8 ± 16.5 (1.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	0 ± 0.0 (0.0 ± 0.00)	5 ± 4.9 (1.0 ± 0.03)