Supporting Information

Molecular Determinants for the Activation/Inhibition of Bak Protein by BH3 Peptides

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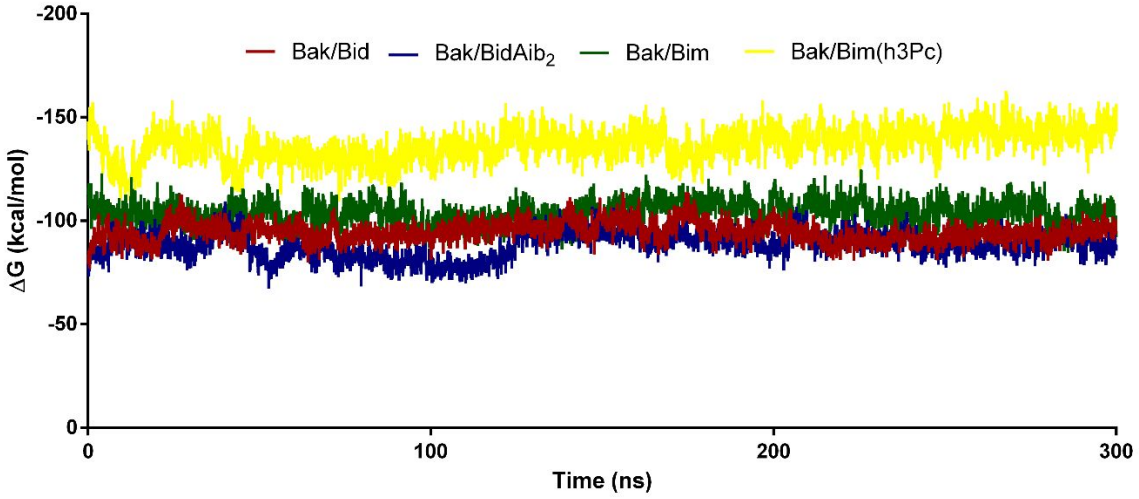

Figure S1: Total ΔG_{PB} binding free energy represented as time function of the Bak/X complexes, being X different BH3 peptides: Bid (red), $BidAib_2$ (blue), Bim (green) and Bim(h3Pc) (yellow).

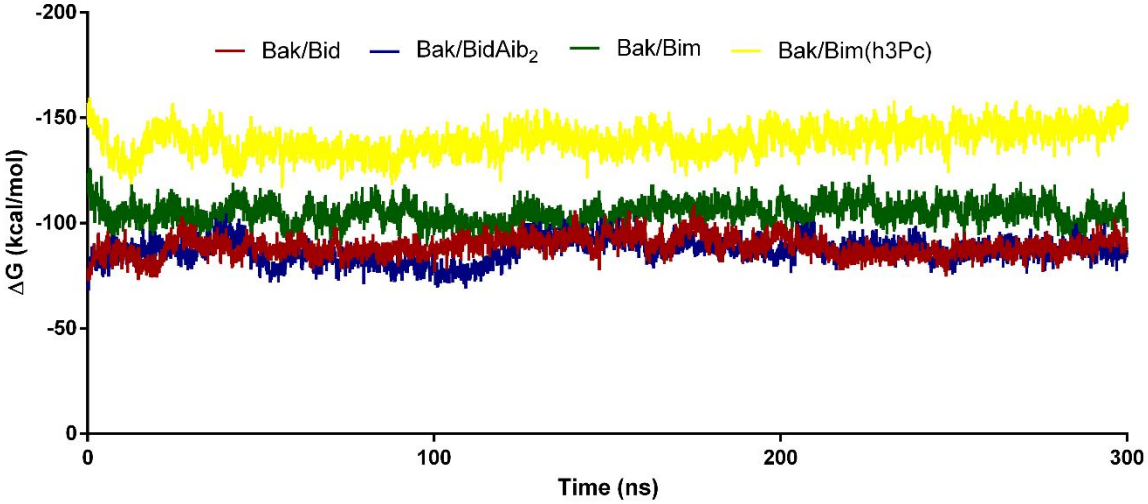

Figure S2: Total ΔG_{GB} binding free energy represented as time function of the Bak/X complexes. being X different BH3 peptides: Bid (red), $BidAib_2$ (blue), Bim (green) and Bim(h3Pc) (yellow).

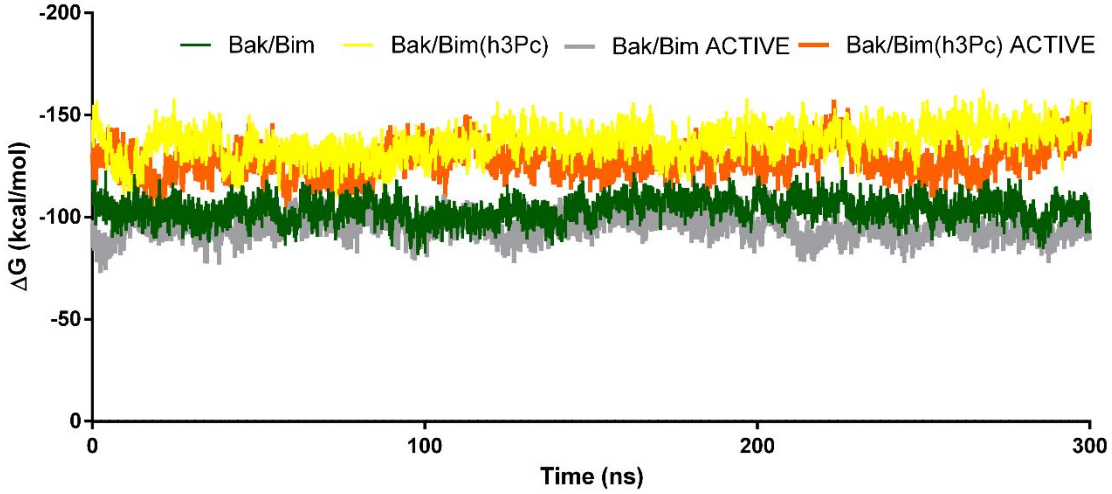

Figure S3: Total ΔG_{PB} binding free energy represented as time function of the Bak/X complexes, being X different BH3 peptides and in *inactive* and *active* conformations: the *inactive* conformations, Bim (green) and Bim(h3Pc) (yellow), and the *active* conformation, Bim (grey) and Bim(h3Pc) (orange).

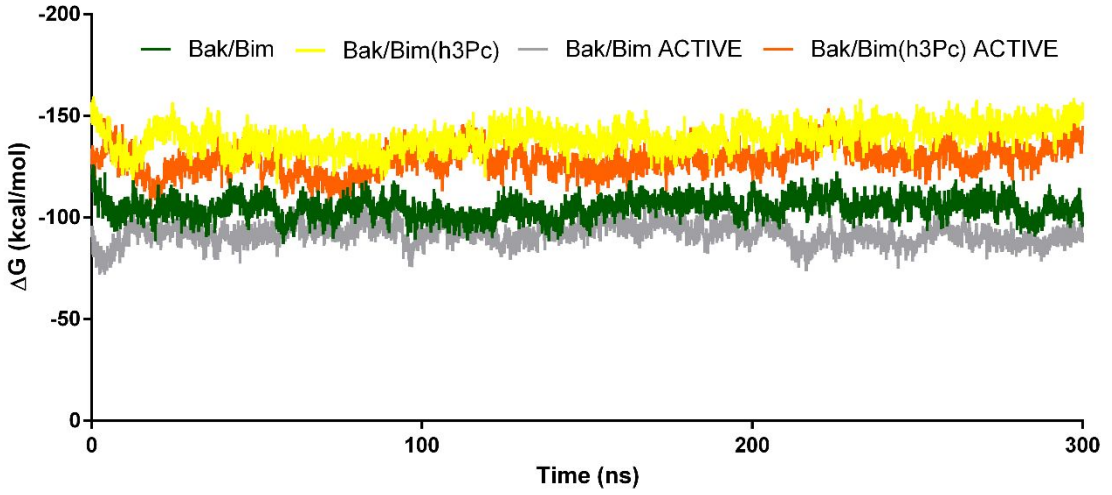

Figure S4: Total ΔG_{GB} binding free energy represented as time function of the Bak/X complexes, being X different BH3 peptides and in *inactive* and *active* conformations: the *inactive* conformations, Bim (green) and Bim(h3Pc) (yellow), and the active conformation, Bim (grey) and Bim(h3Pc) (orange).

Table S1: Average total ΔG (kcal/mol) from Bak residues of three molecular dynamics simulations in the complexes between Bak and all BH3 peptides: Bid, $BidAib_2$, Bim, Bim(h3Pc) on their *inactive* conformations and Bim and Bim(h3Pc) on their *active* conformations.

	Bak/Bid	Bak/$BidAib_2$	Bak/Bim	Bak/Bim(h3Pc)	Bak/Bim ACTIVE	Bak/Bim(h3Pc) ACTIVE
ARG 42	0.05 ± 0.01	0.14 ± 0.03	0.08 ± 0.03	-11.57 ± 0.10	0.10 ± 0.02	-11.72 ± 0.12
ILE 85	-1.75 ± 0.49	-2.82 ± 0.26	-4.59 ± 0.17	-5.20 ± 0.22	-3.49 ± 0.49	-4.73 ± 0.10
ASN 86	-0.11 ± 0.08	-0.40 ± 0.14	0.00 ± 0.06	-4.26 ± 0.01	-0.12 ± 0.07	-1.17 ± 0.10
ARG 88	-0.02 ± 0.05	0.08 ± 0.07	-2.23 ± 0.29	-4.18 ± 0.73	-0.99 ± 0.19	-4.87 ± 0.80
TYR 89	-2.35 ± 0.05	-2.38 ± 0.06	-3.28 ± 0.19	-4.72 ± 0.10	-2.85 ± 0.30	-4.89 ± 0.46
PHE 93	-1.30 ± 0.07	-2.70 ± 0.03	-1.68 ± 0.15	-2.58 ± 0.21	-1.38 ± 0.24	-2.66 ± 0.07
MET 96	-3.11 ± 0.05	-3.80 ± 0.08	-2.91 ± 0.10	-3.31 ± 0.08	-3.18 ± 0.06	-3.83 ± 0.16
LEU 100	-2.25 ± 0.06	-2.12 ± 0.03	-2.26 ± 0.15	-2.58 ± 0.03	-2.14 ± 0.06	-2.20 ± 0.11
ILE 114	-4.20 ± 0.02	-4.42 ± 0.02	-3.95 ± 0.03	-4.19 ± 0.07	-4.18 ± 0.06	-3.93 ± 0.14
LEU 118	-3.26 ± 0.07	-3.32 ± 0.03	-3.44 ± 0.06	-3.57 ± 0.03	-3.55 ± 0.02	-3.68 ± 0.07
ASN 124	-4.39 ± 0.01	-3.23 ± 0.33	-3.77 ± 0.07	-3.11 ± 0.24	-3.64 ± 0.03	-1.86 ± 0.13
GLY 126	-2.79 ± 0.07	-2.15 ± 0.10	-2.83 ± 0.02	-2.55 ± 0.04	-2.34 ± 0.12	-1.88 ± 0.03
ARG 127	-9.64 ± 0.03	-8.48 ± 0.53	-9.01 ± 0.04	-8.78 ± 0.25	-9.26 ± 0.07	-5.77 ± 0.65
ALA 130	-1.82 ± 0.01	-1.83 ± 0.11	-1.95 ± 0.01	-2.46 ± 0.01	-1.94 ± 0.06	-2.96 ± 0.02
ARG 137	-0.06 ± 0.01	-0.02 ± 0.00	0.00 ± 0.01	-8.51 ± 0.39	0.00 ± 0.01	-8.57 ± 0.56

Table S2: Average distances (in Å) between pharmacophore points, represented as the most relevant energetical residues (Ile 148, Leu 152, Ile/9R1 155, Asp 157 and Phe 159) from Bim and Bim(h3Pc) in the interaction with pro-apoptotic Bak.

		ILE148 - LEU152	LEU152 - ILE155	ILE155 - ASP157	ASP157 - PHE159	ILE148 - ILE155	ILE148 - ASP157	ILE148 - PHE159	LEU152 - ASP157	LEU152 - PHE159	ILE155 - PHE159
Bak/Bim	**AVG**	7.30	6.07	9.42	10.56	10.48	15.81	15.96	10.75	9.64	6.49
	Std. Dev	0.58	0.41	0.22	0.24	0.49	0.35	0.55	0.34	0.45	0.37
Bak/Bim (ACTIVE)	**AVG**	6.12	6.22	9.49	11.14	10.30	15.68	17.20	11.20	11.47	8.47
	Std. Dev	0.35	0.38	0.22	0.34	0.35	0.29	0.63	0.30	0.58	0.54

		ILE148 - LEU152	LEU152 - 9R1155	9R1155 - ASP157	ASP157 - PHE159	ILE148 - 9R1155	ILE148 - ASP157	ILE148 - PHE159	LEU152 - ASP157	LEU152 - PHE159	9R1155 - PHE159
Bak/Bim(h3Pc)	**AVG**	6.29	7.62	14.50	10.64	11.48	15.62	15.93	11.14	10.33	7.08
	Std. Dev	0.48	0.46	0.34	0.32	0.58	0.34	0.56	0.39	0.53	0.41
Bak/Bim(h3Pc) (ACTIVE)	**AVG**	6.13	8.17	14.46	10.61	11.99	15.80	15.70	11.21	10.09	6.61
	Std. Dev	0.37	0.41	0.32	0.30	0.44	0.44	0.43	0.49	0.40	0.49

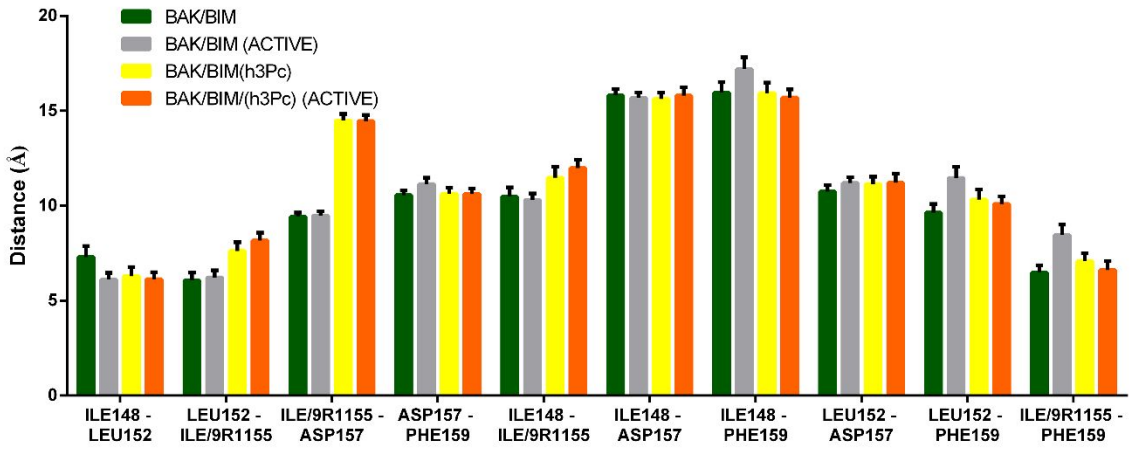

Figure S5: Average distances between pharmacophore features from Bim and Bim(h3Pc) in complex with Bak. In green and grey, average distances from Bak/Bim complex in inactive and active conformation are represented respectively. In yellow and orange, average distances from Bak/Bim(h3Pc) complex in inactive and active conformation are shown respectively

Table S3: Average angles (in °) between pharmacophore points, represented as the most relevant energetical residues (Ile 148, Leu 152, Ile/9R1 155, Asp 157 and Phe 159) from Bim and Bim(h3Pc) in the interaction with pro-apoptotic Bak.

		ILE148 - LEU152 - ILE155	ILE148 - ILE155 - ASP157	ILE148 - ILE155 - PHE159	LEU152 - ILE155 - ASP157	LEU152 - ILE155 - PHE159	ILE155 - ASP157 - PHE159
Bak/Bim	**AVG**	103.4	105.0	139.8	84.9	100.5	37.2
	Std. Dev.	5.8	3.2	6.9	3.8	6.5	2.1
Bak/Bim (ACTIVE)	**AVG**	113.4	104.9	132.6	88.5	98.3	47.7
	Std. Dev.	5.7	2.9	5.1	3.7	4.6	3.2
		ILE148 - LEU152 - 9R1155	**ILE148 - 9R1155 - ASP157**	**ILE148 - 9R1155 - PHE159**	**LEU152 - 9R1155 - ASP157**	**LEU152 - 9R1155 - PHE159**	**9R1155 - ASP157 - PHE159**
Bak/Bim(h3Pc)	**AVG**	111.7	72.9	116.3	49.3	89.4	27.5
	Std. Dev.	7.5	2.2	5.3	3.1	6.2	2.8
Bak/Bim(h3Pc) (ACTIVE)	**AVG**	113.5	72.7	111.9	50.5	85.3	25.0
	Std. Dev.	5.9	2.4	3.6	3.2	3.9	2.4

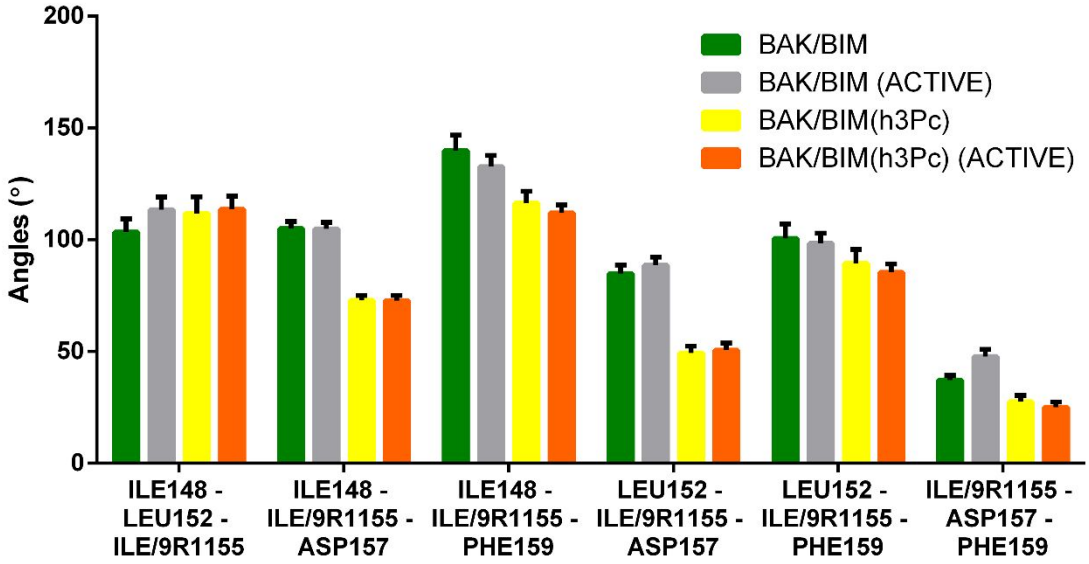

Figure S6: Average angles between pharmacophore features from Bim and Bim(h3Pc) in complex with Bak. In green and grey, average angles from Bak/Bim complex in inactive and active conformation are represented respectively. In yellow and orange, average angles from Bak/Bim(h3Pc) complex in inactive and active conformation are shown respectively