

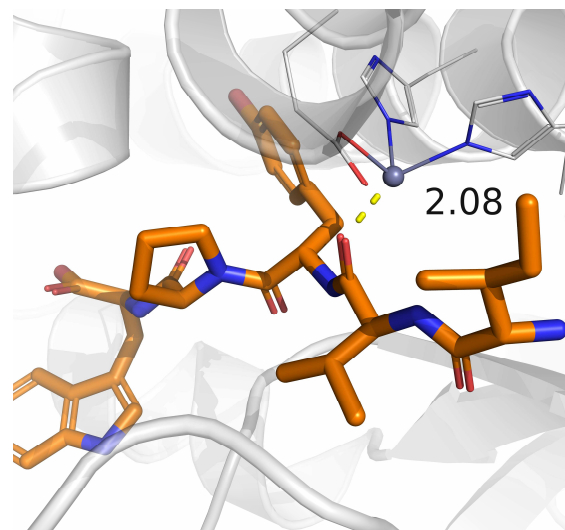
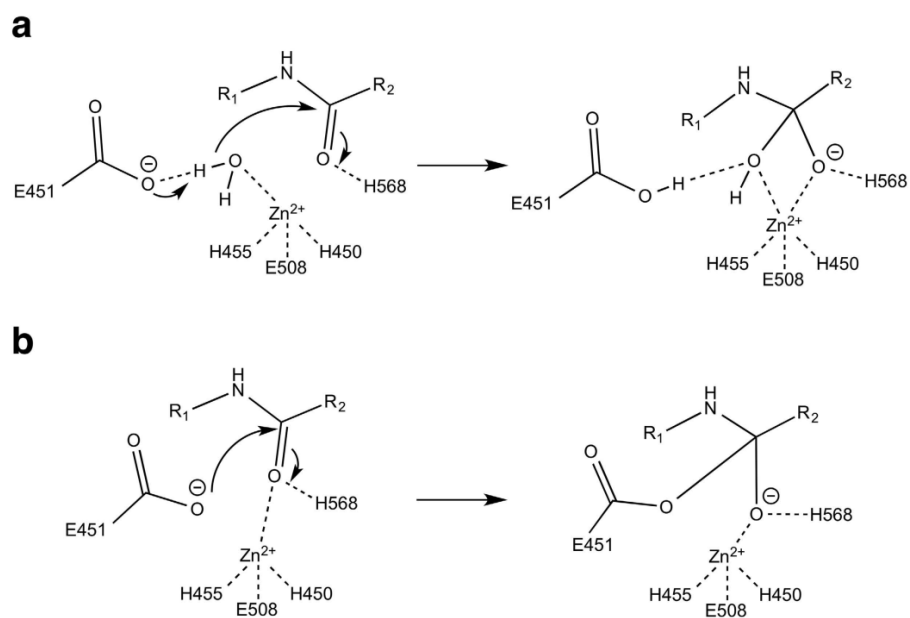
Mechanism of the human DPP III catalysed hydrolysis of neuropeptides tynorphin and Leu-enkephalin

ANTONIJA TOMIĆ

IRB 14/02/2022



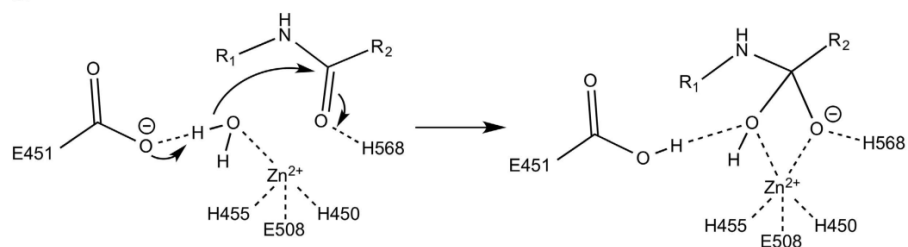
P. Kumar et al. *Sci Rep.* 6: 23787 (2016)



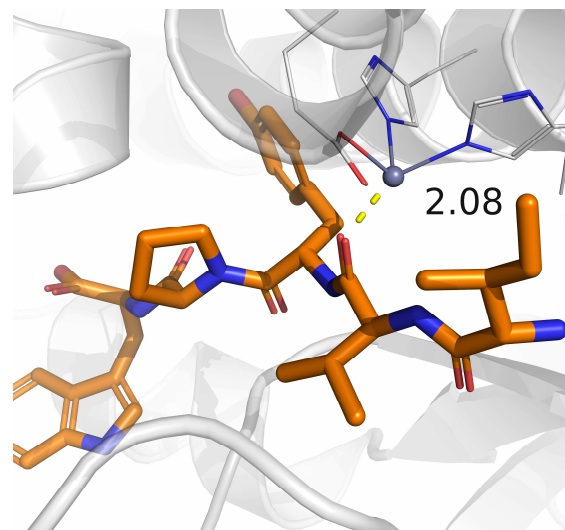
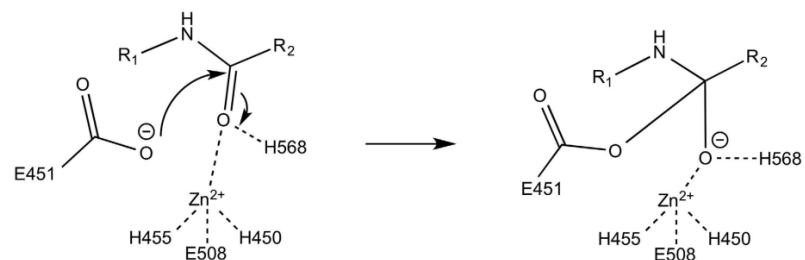
DPP III - IVYPW
(2016. pdb: 5e3c)

P. Kumar et al. *Sci Rep.* 6: 23787 (2016)

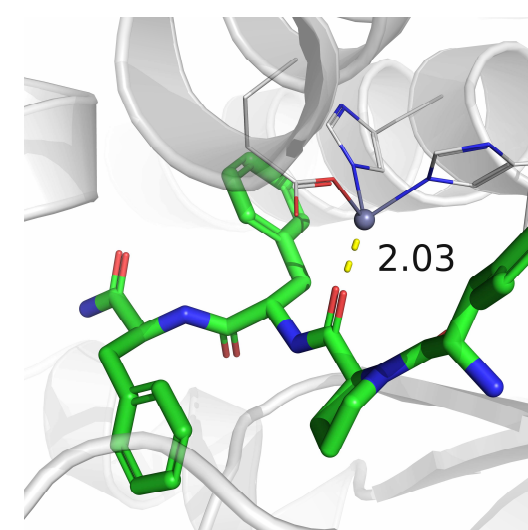
a



b



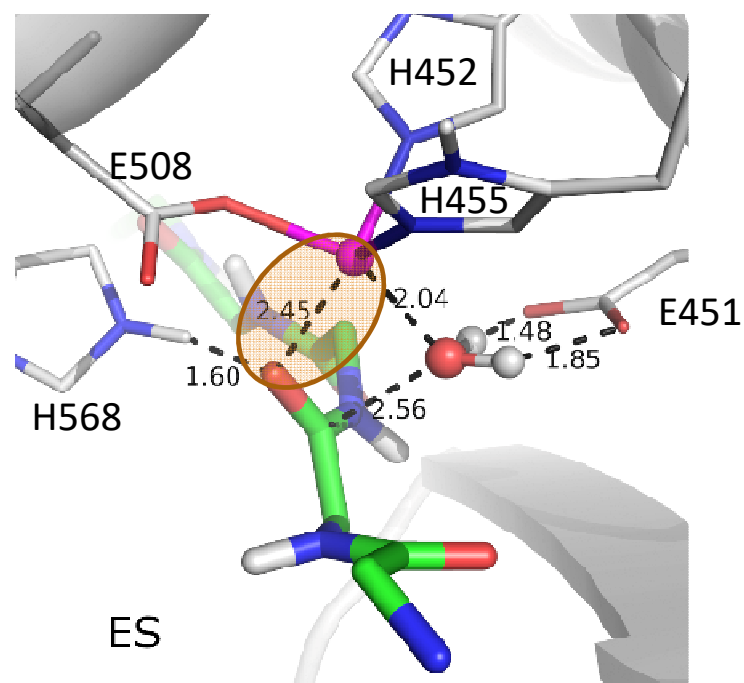
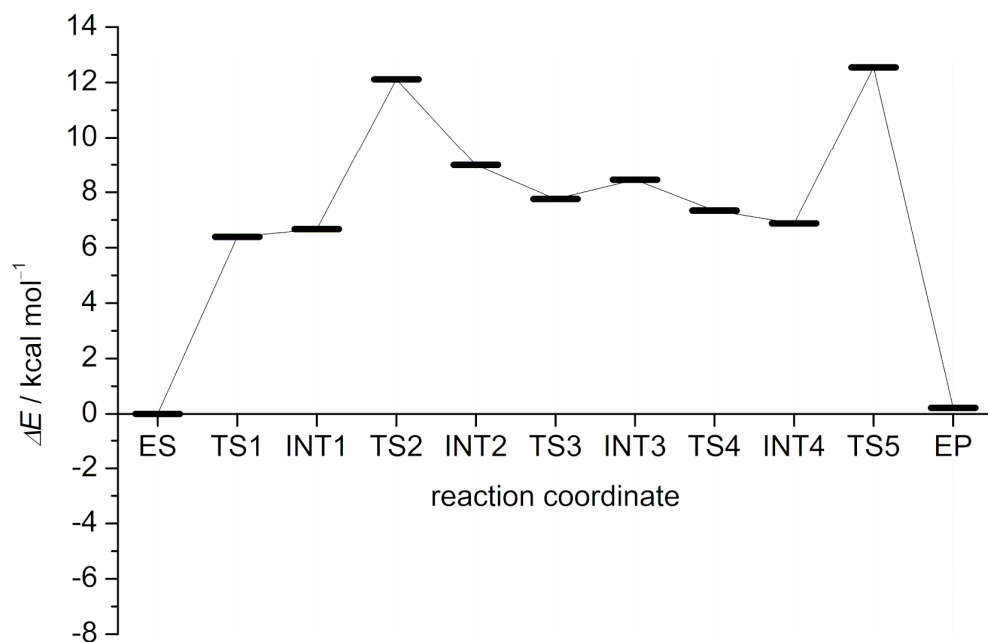
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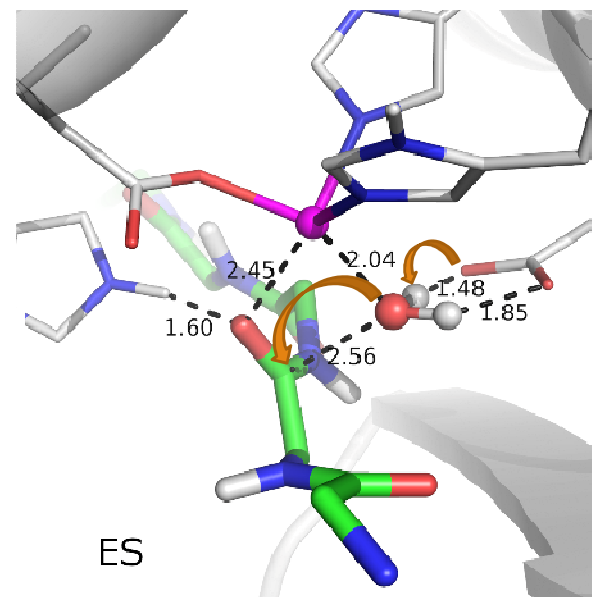
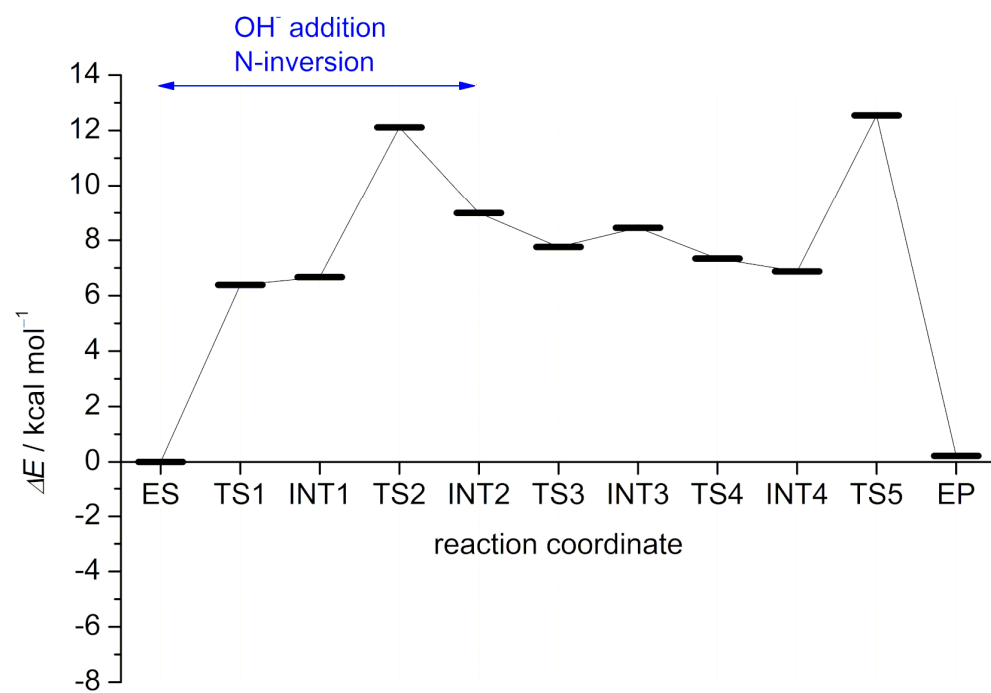


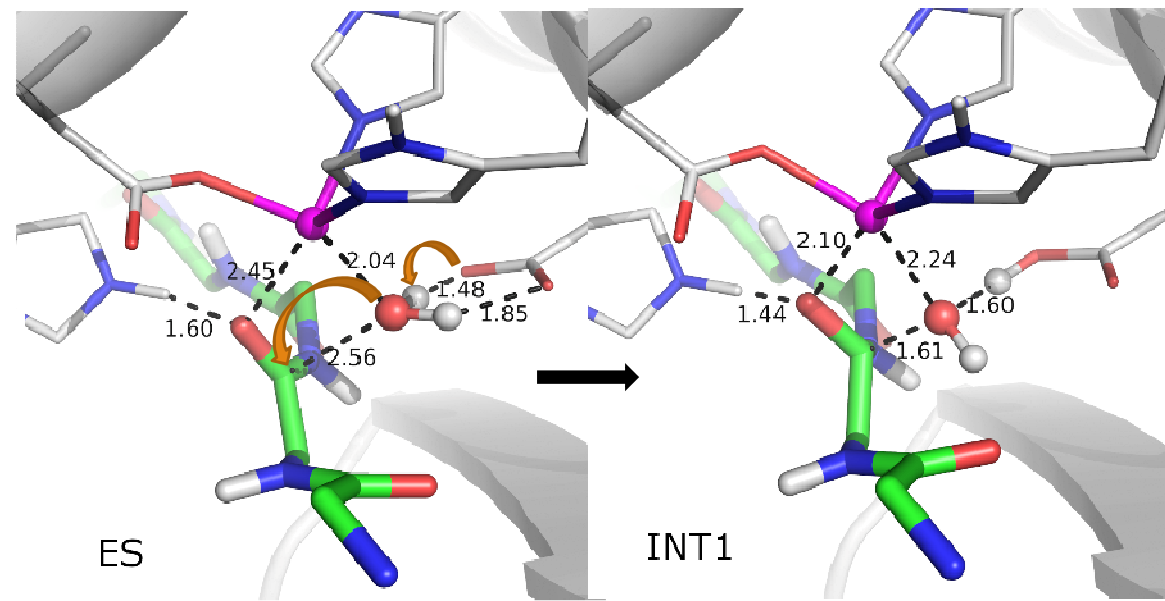
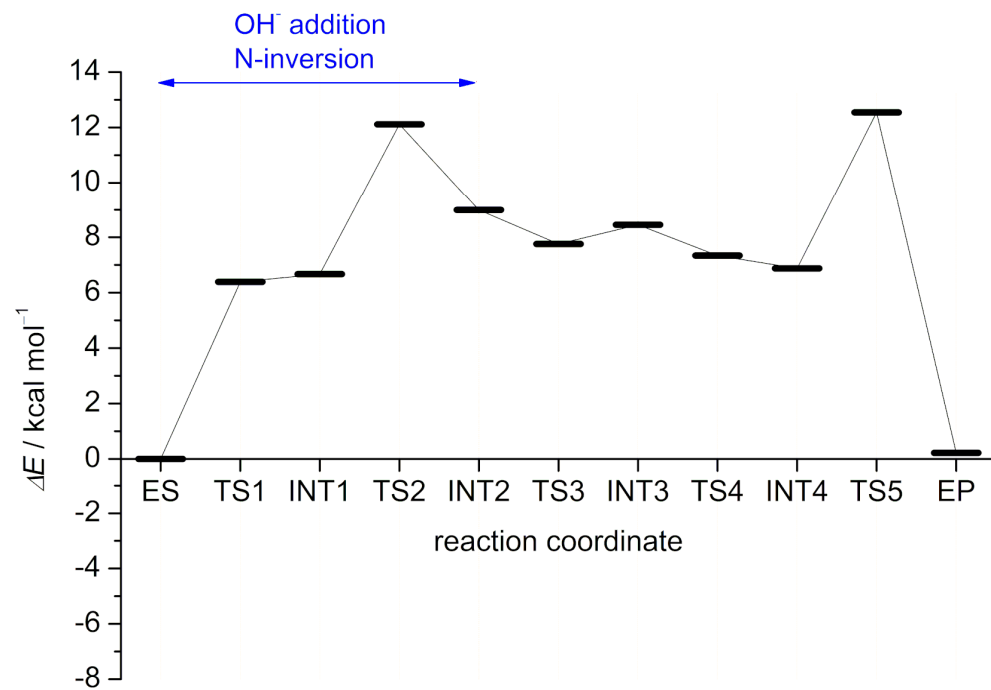
DPP III - endomorphin2
(2016. pdb: 5ehh)

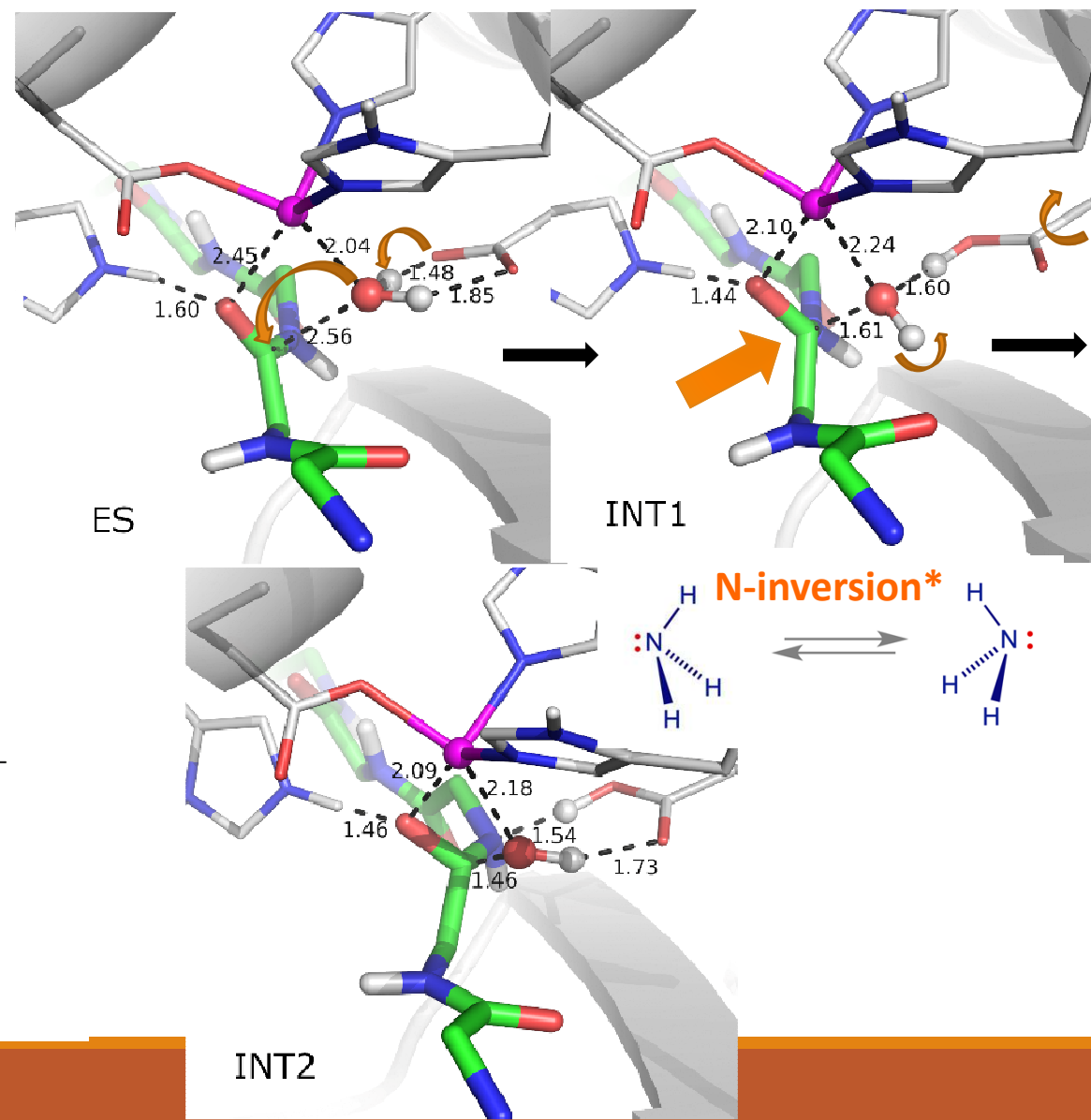
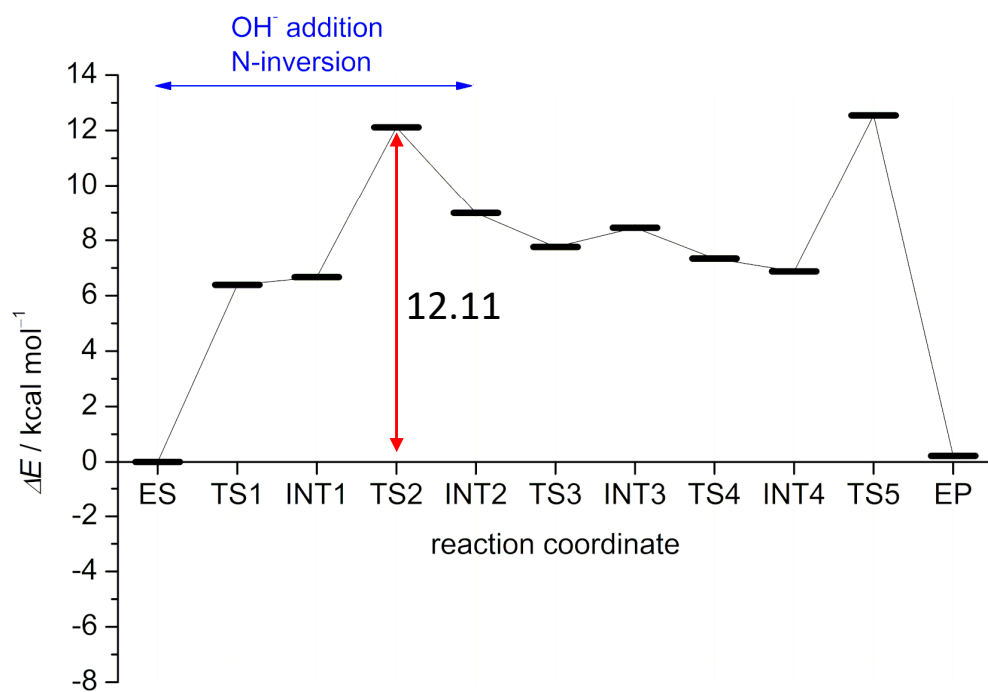
HIDROLIZA Leu-enkefalina

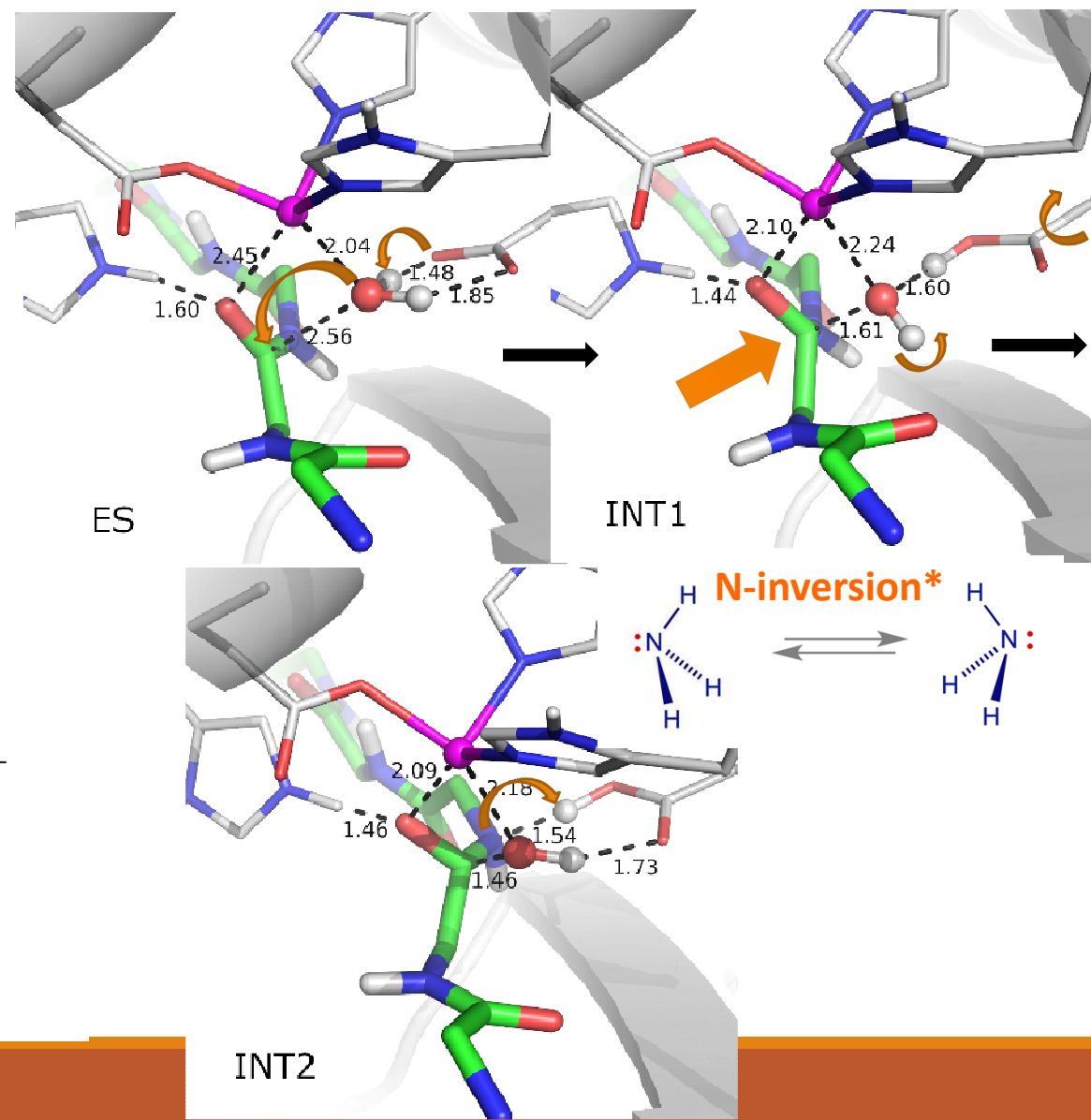
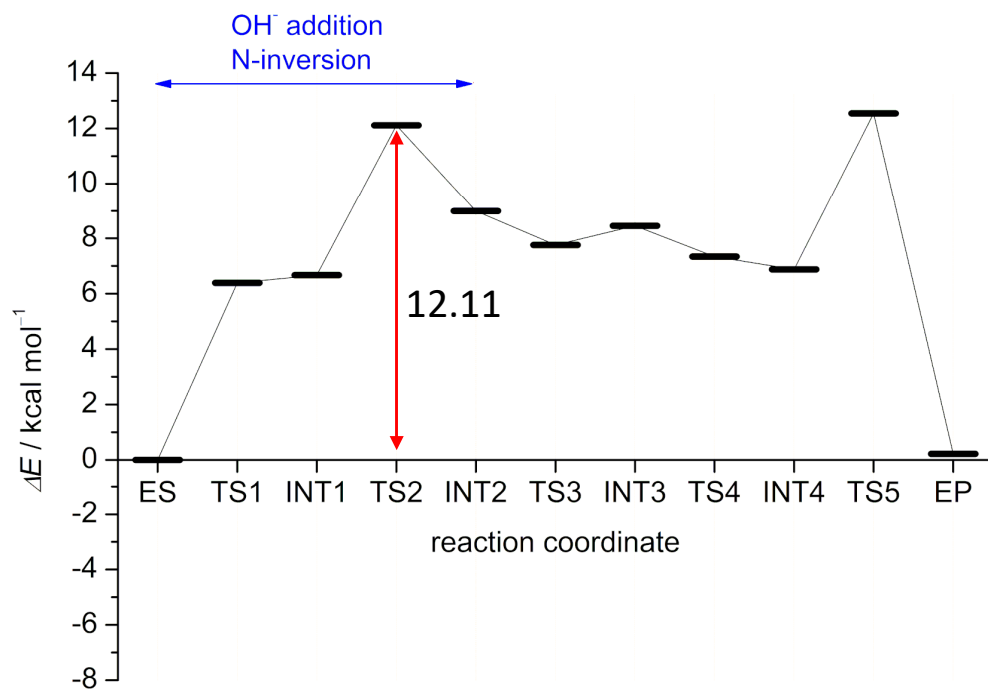
ONIOM (Gaussian 09 Rev. D01) \rightarrow B97D/[6-31G(d)+LanL2DZ-ECP] + ZPVE_{B97D/[6-31G(d)+LanL2DZ-ECP]}

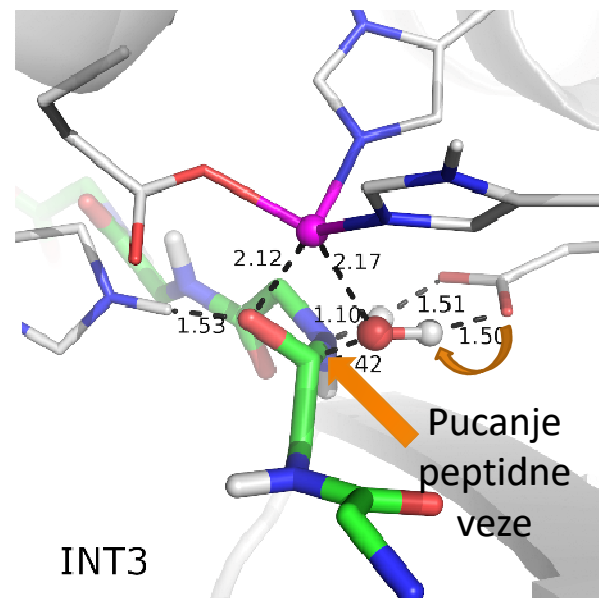
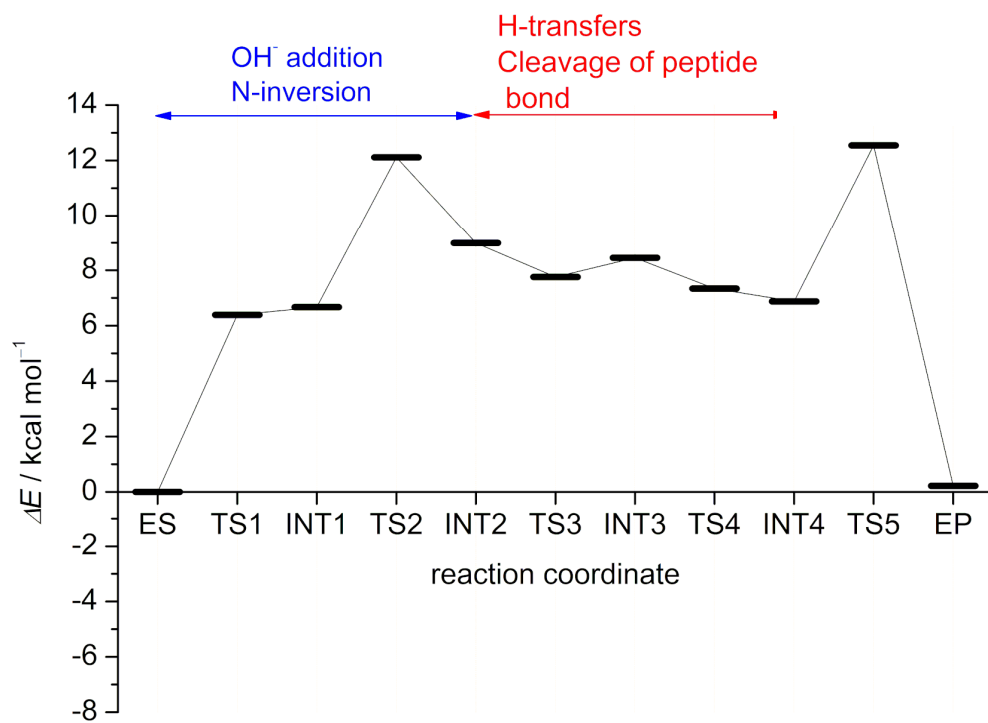


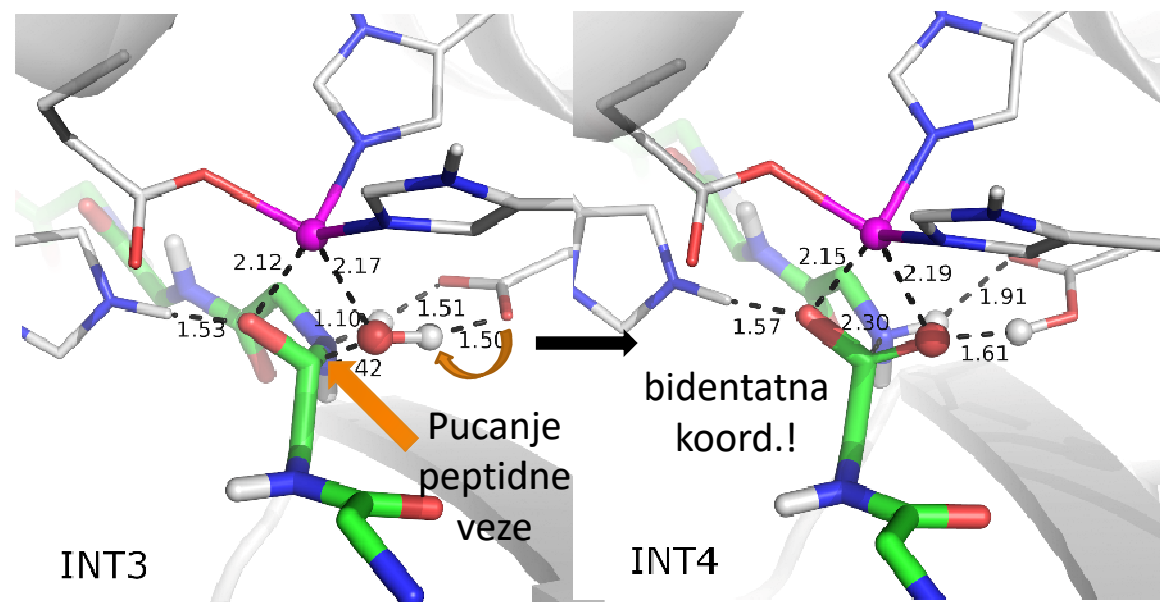
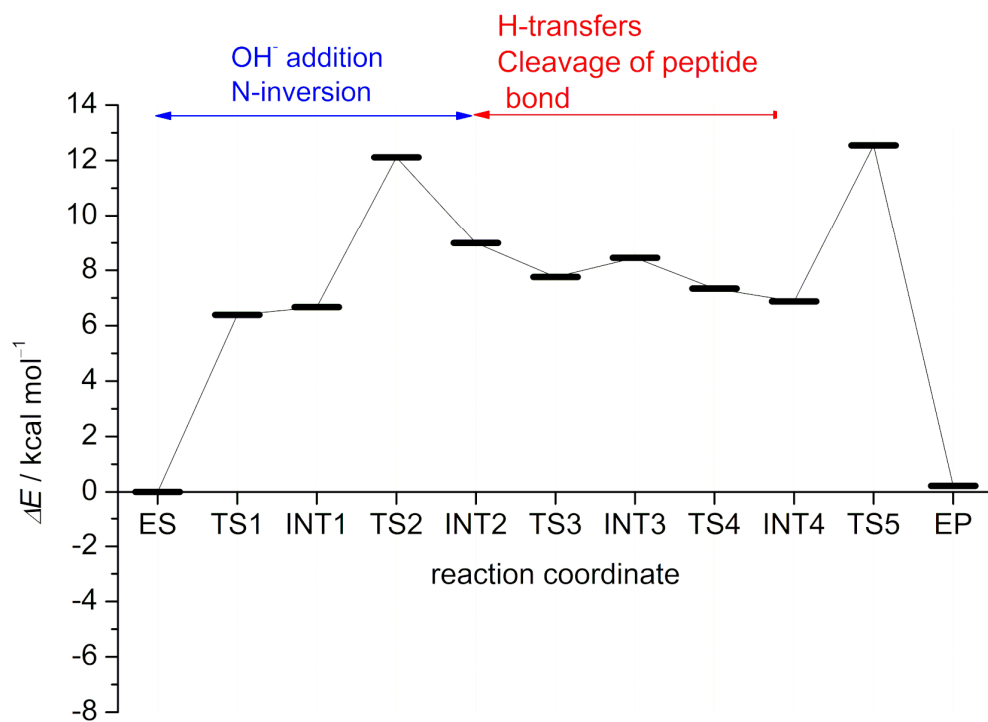


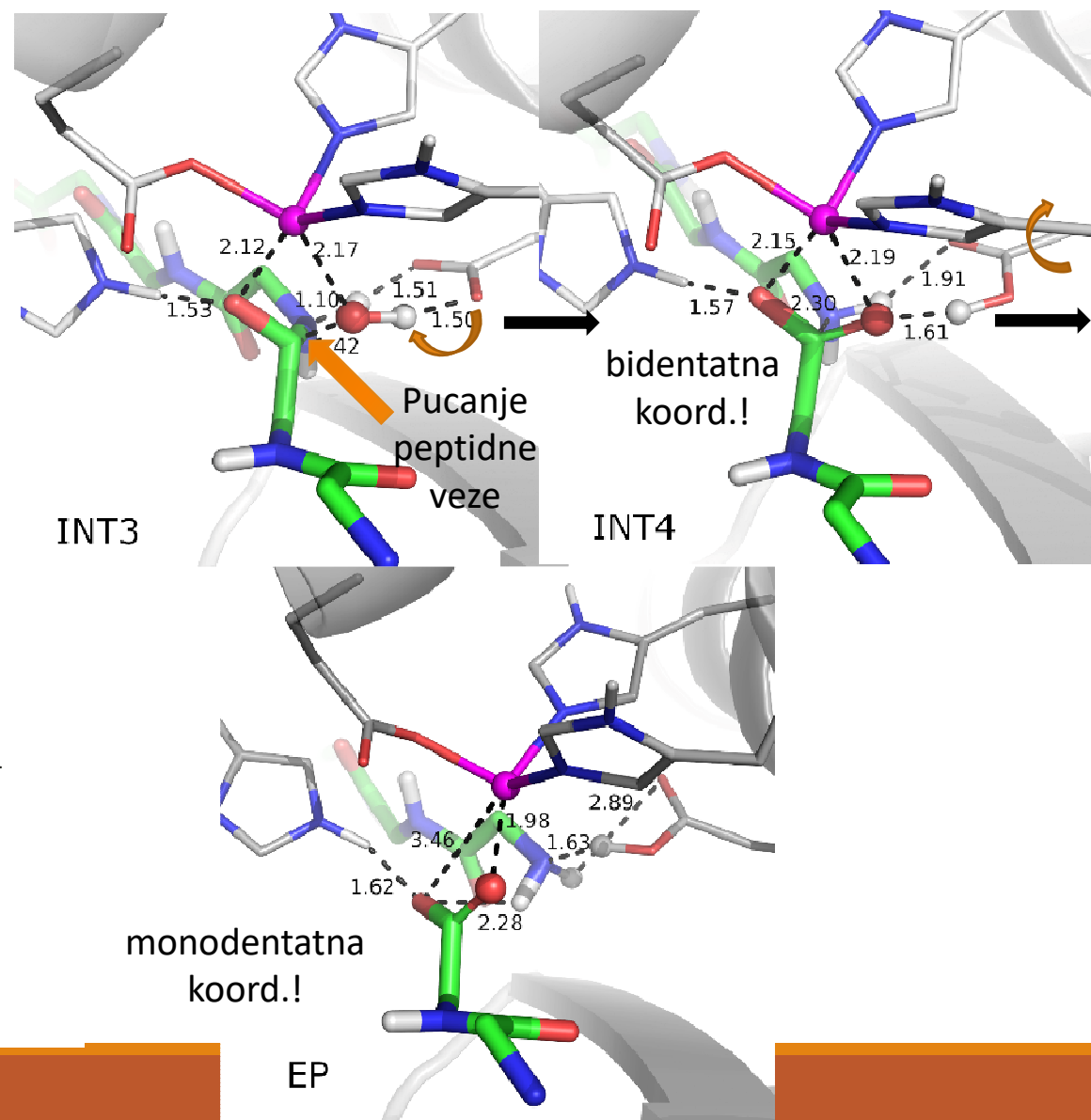
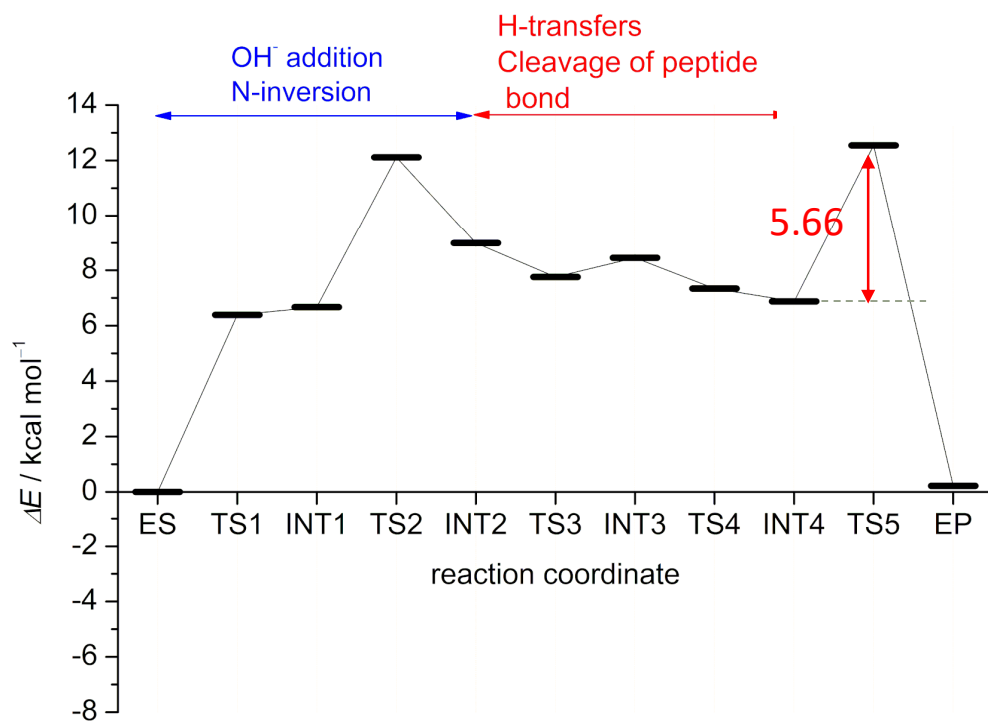






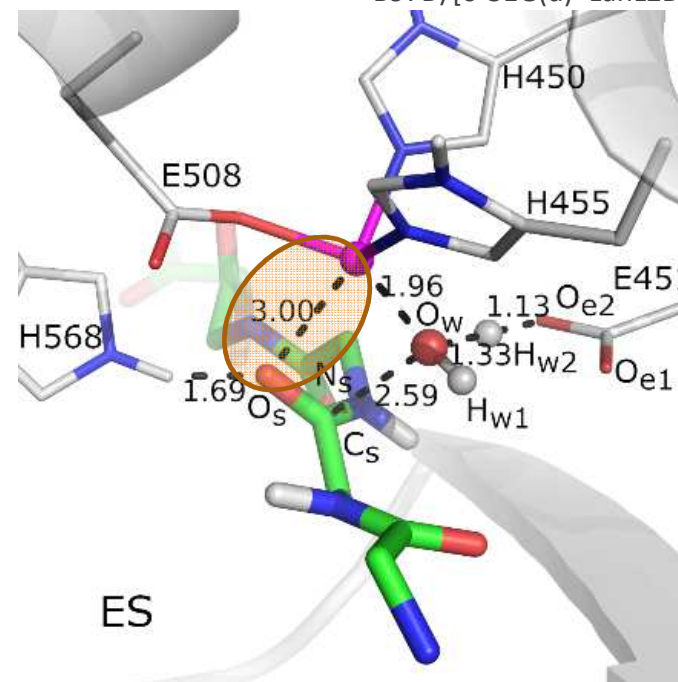
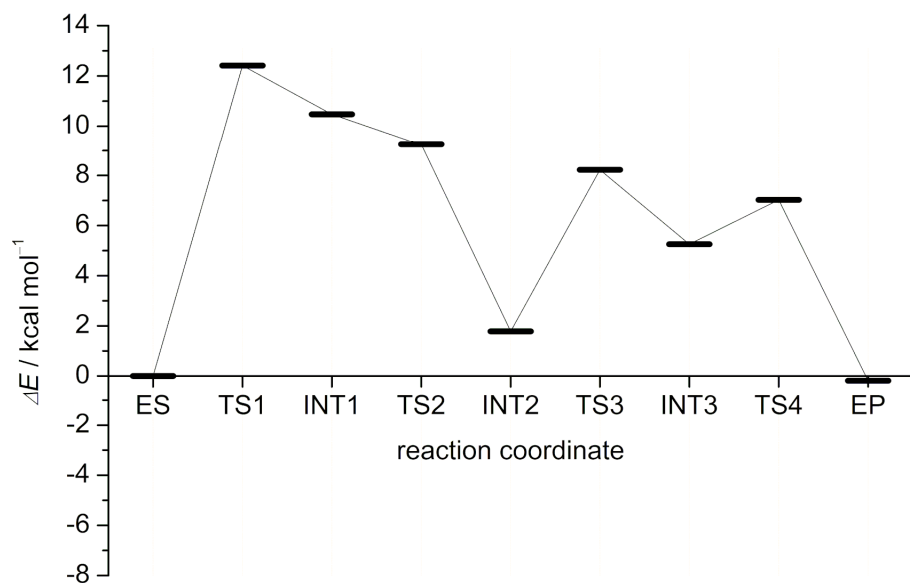


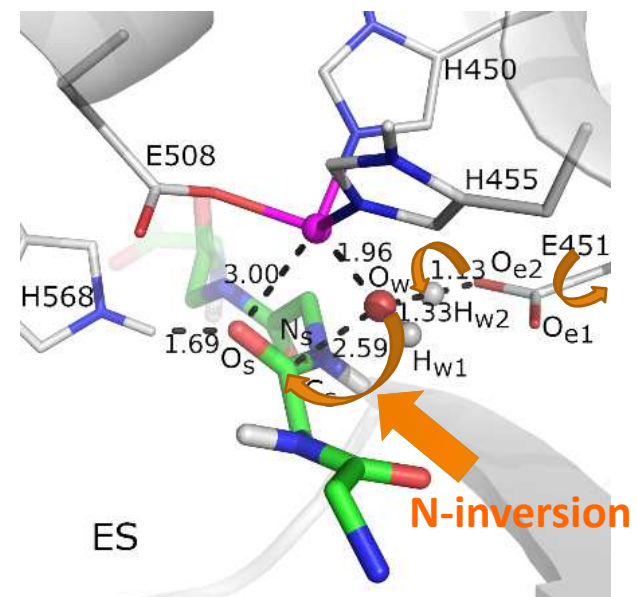
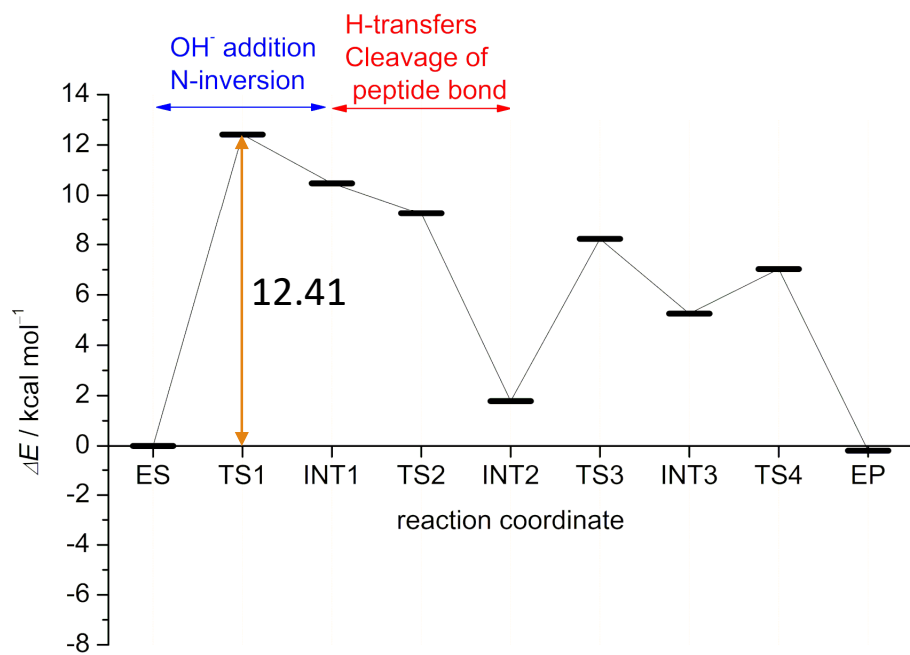


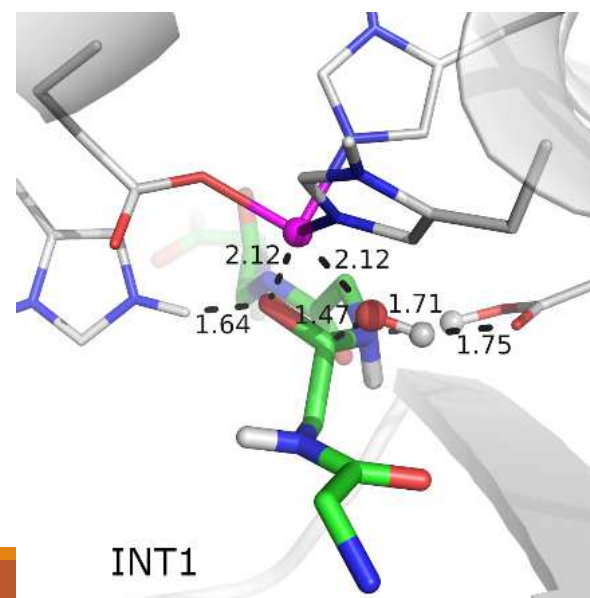
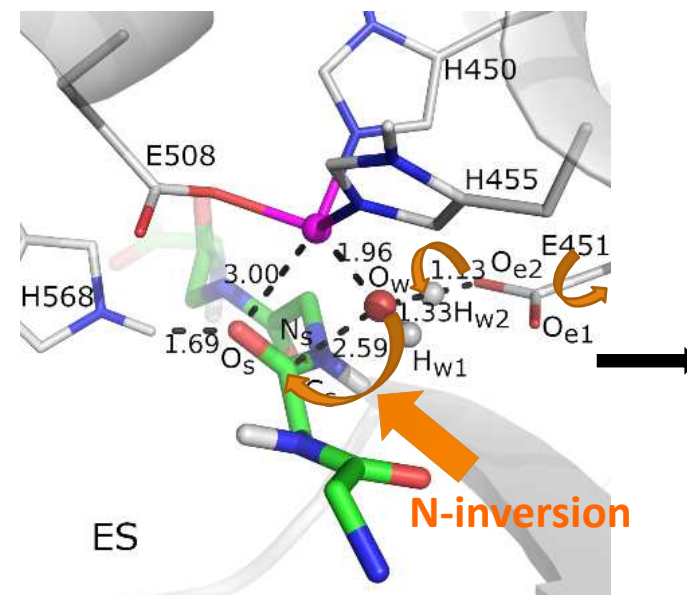
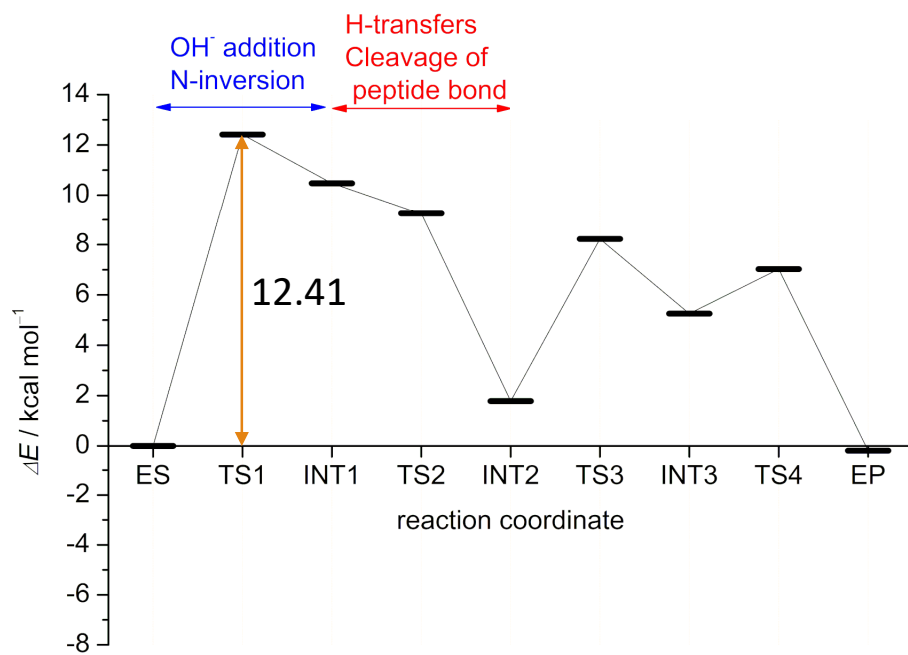


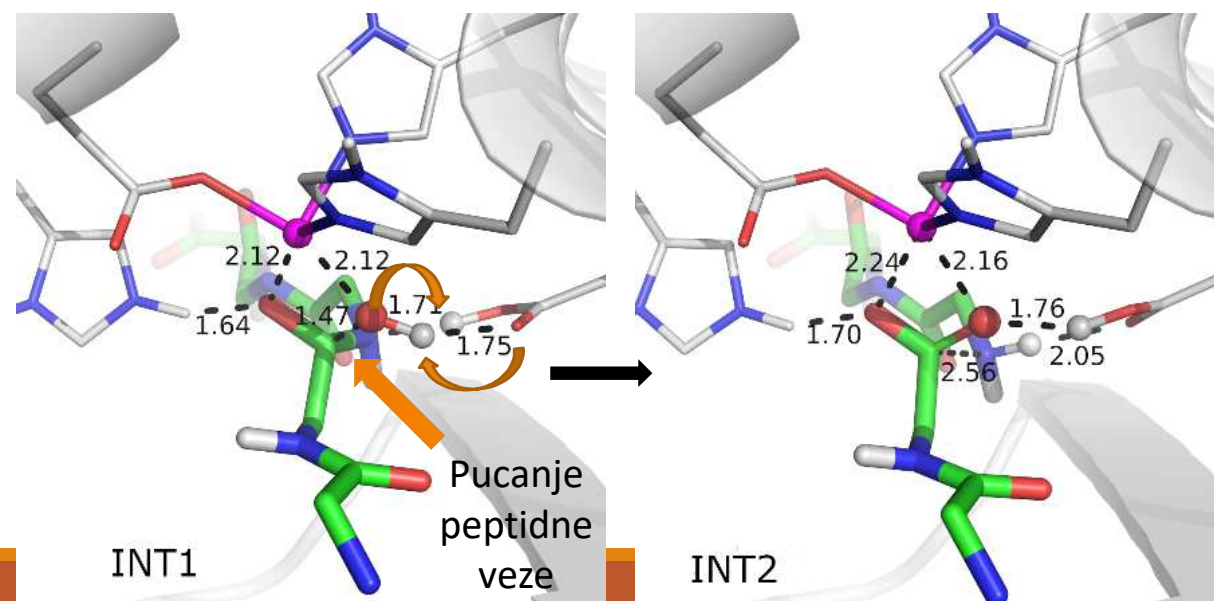
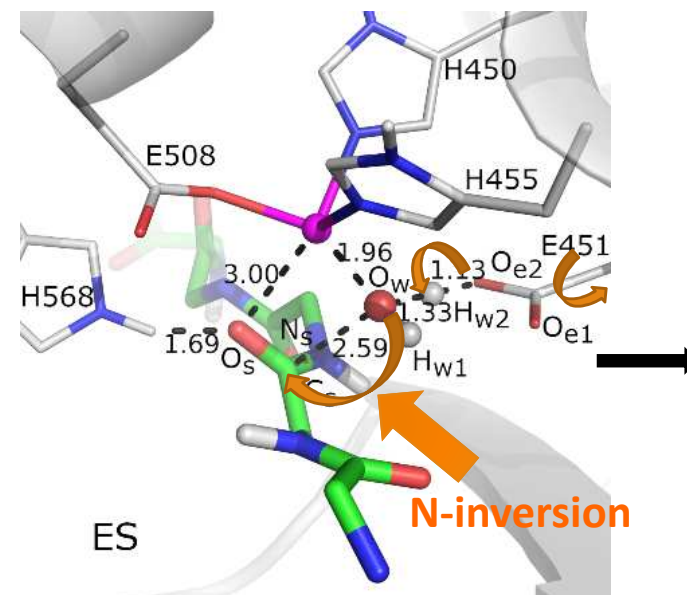
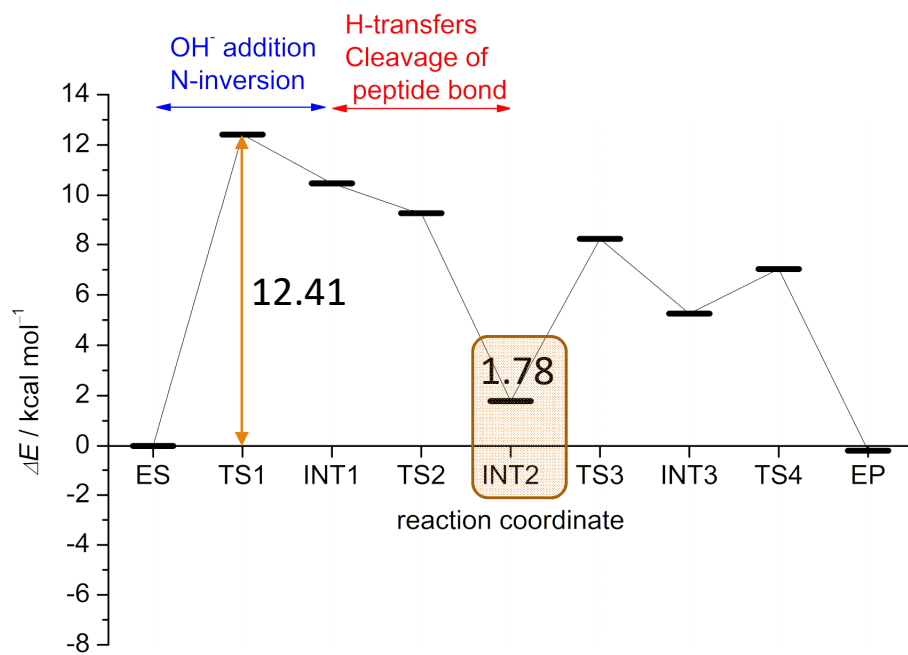
HIDROLIZA tinorfina

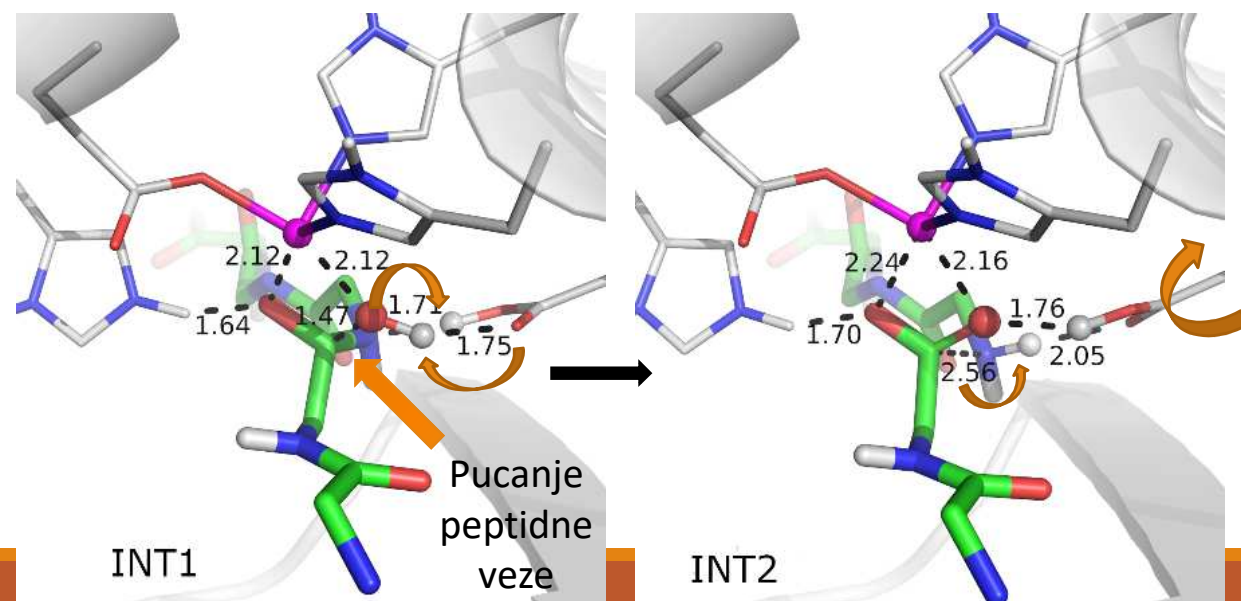
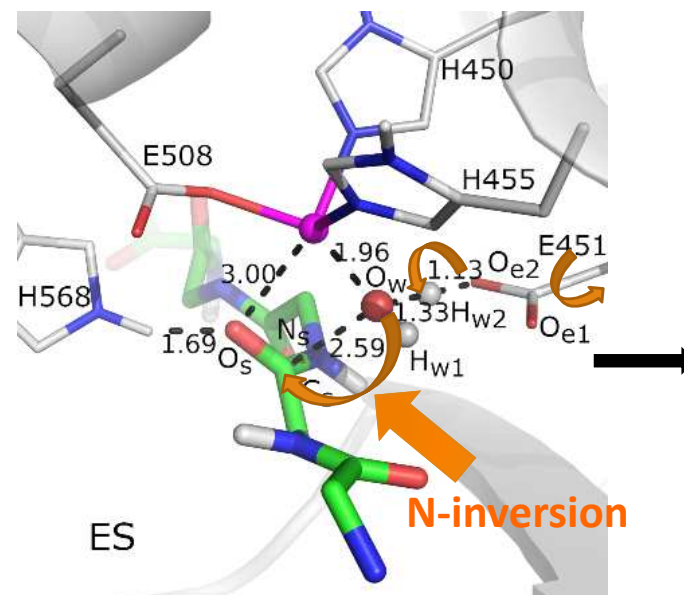
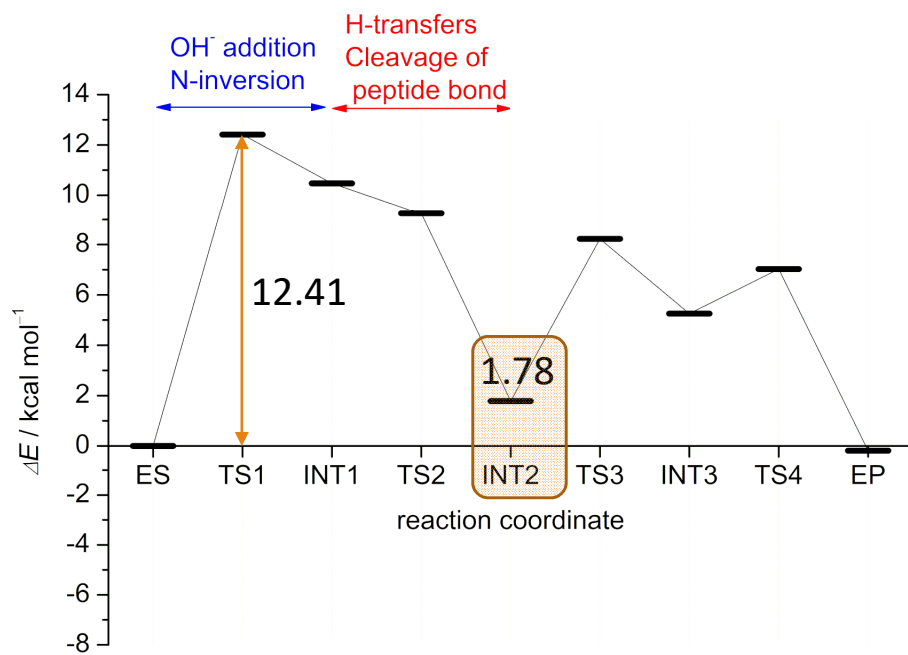
ONIOM (Guassian 09 Rev. D01) - B97D/[6-31G(d)+LanL2DZ-ECP] + ZPVE_{B97D/[6-31G(d)+LanL2DZ-ECP]}

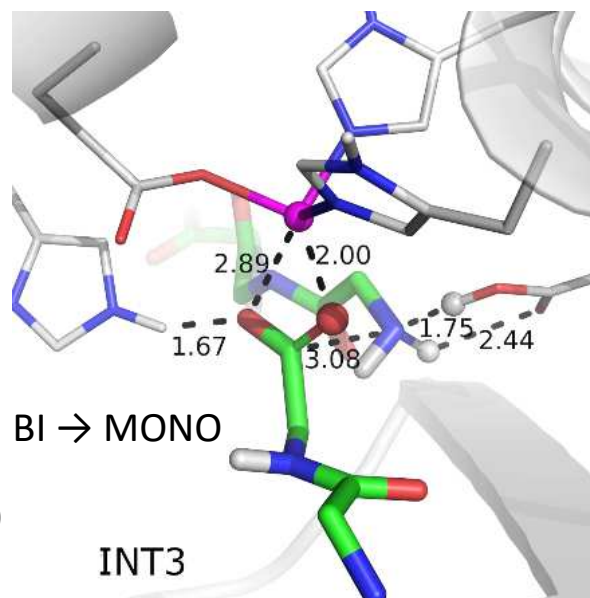
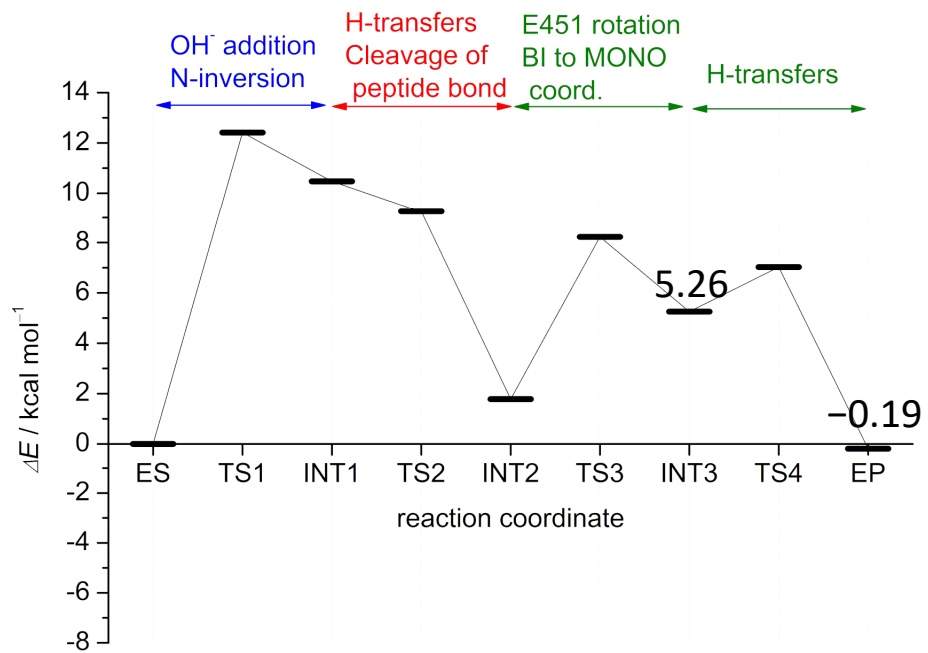


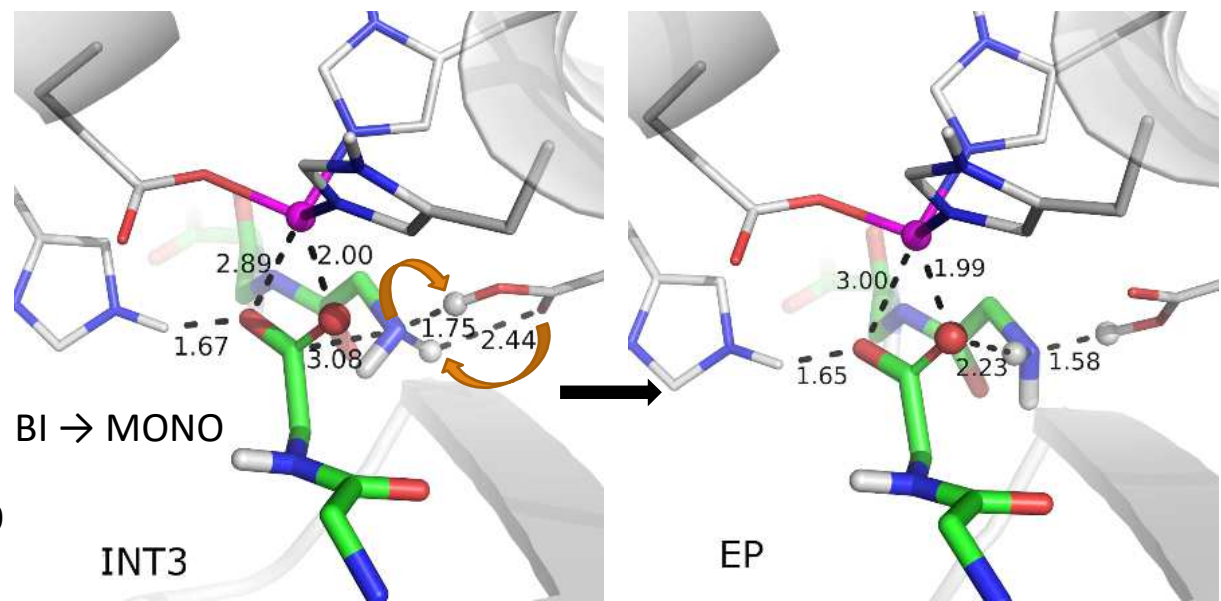
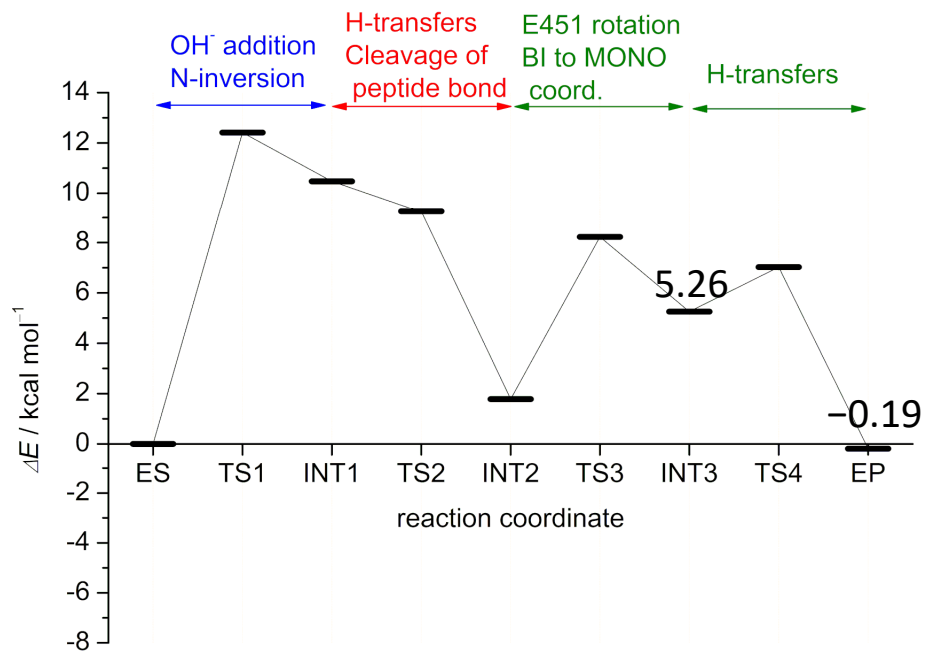




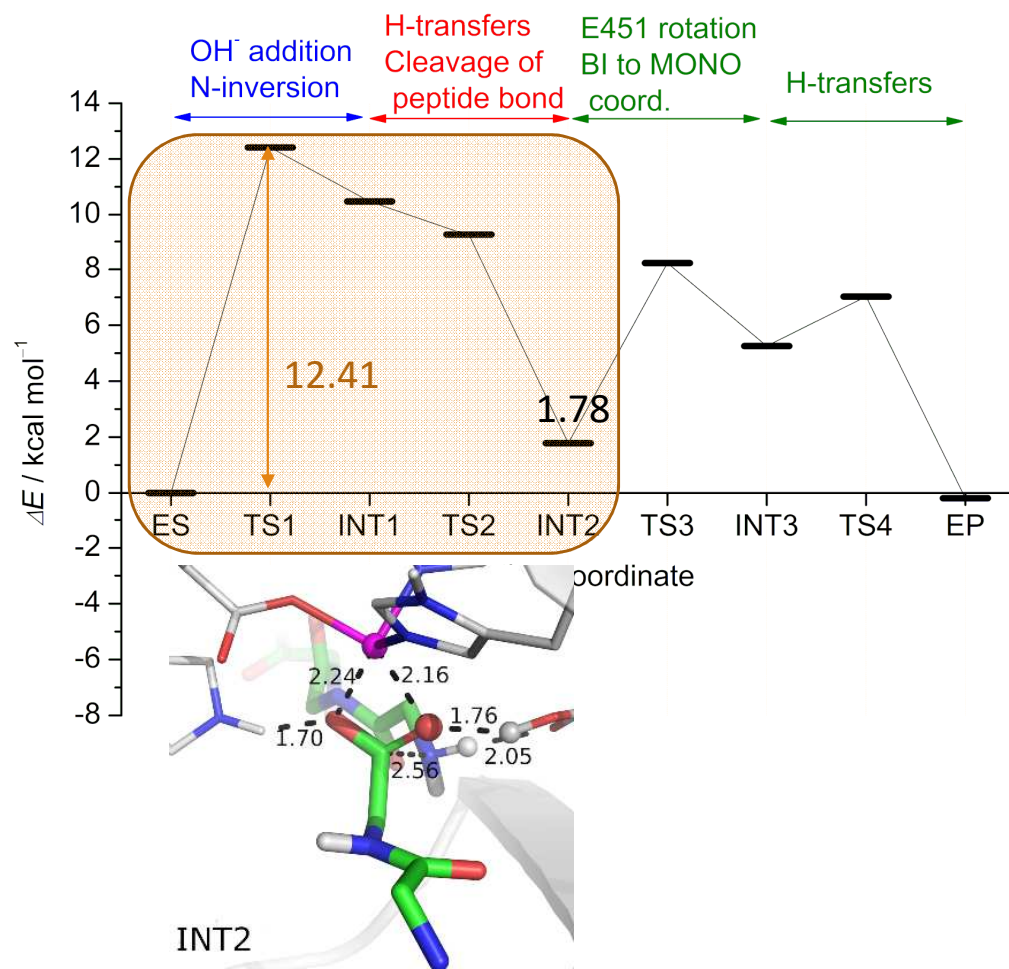




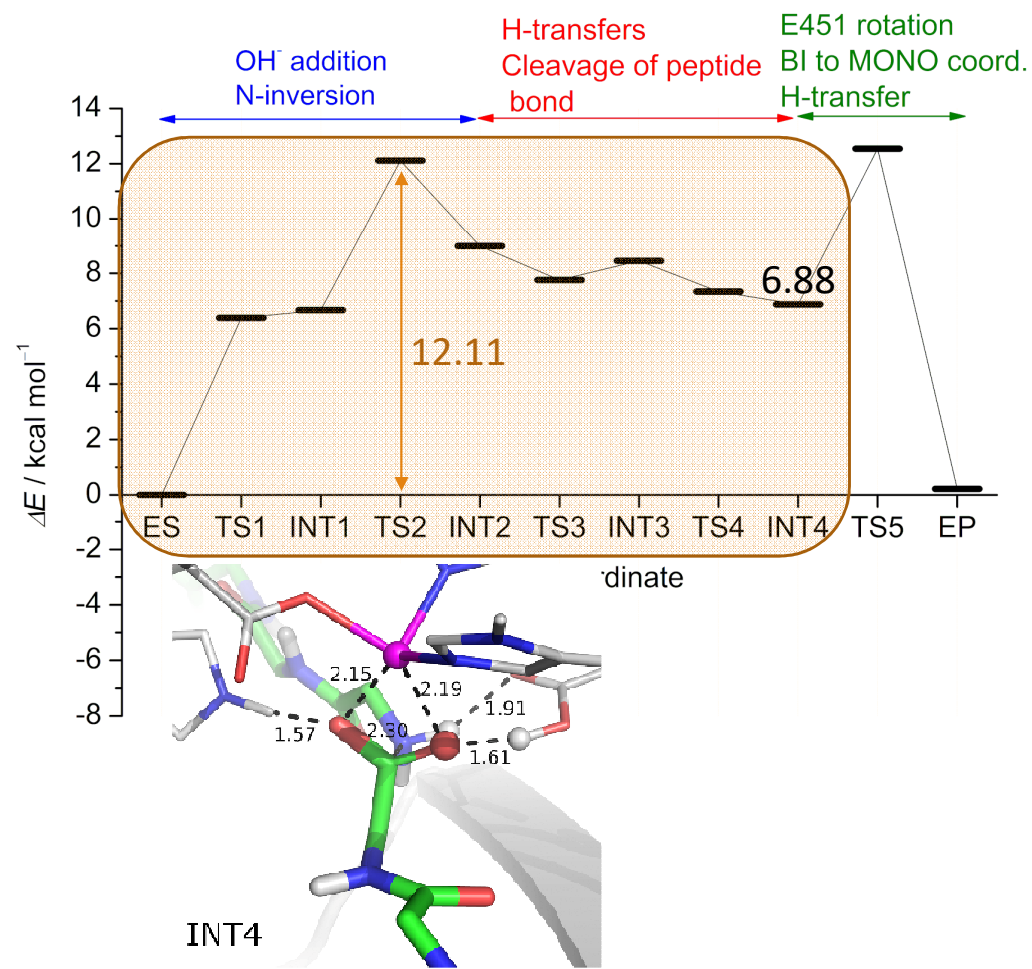




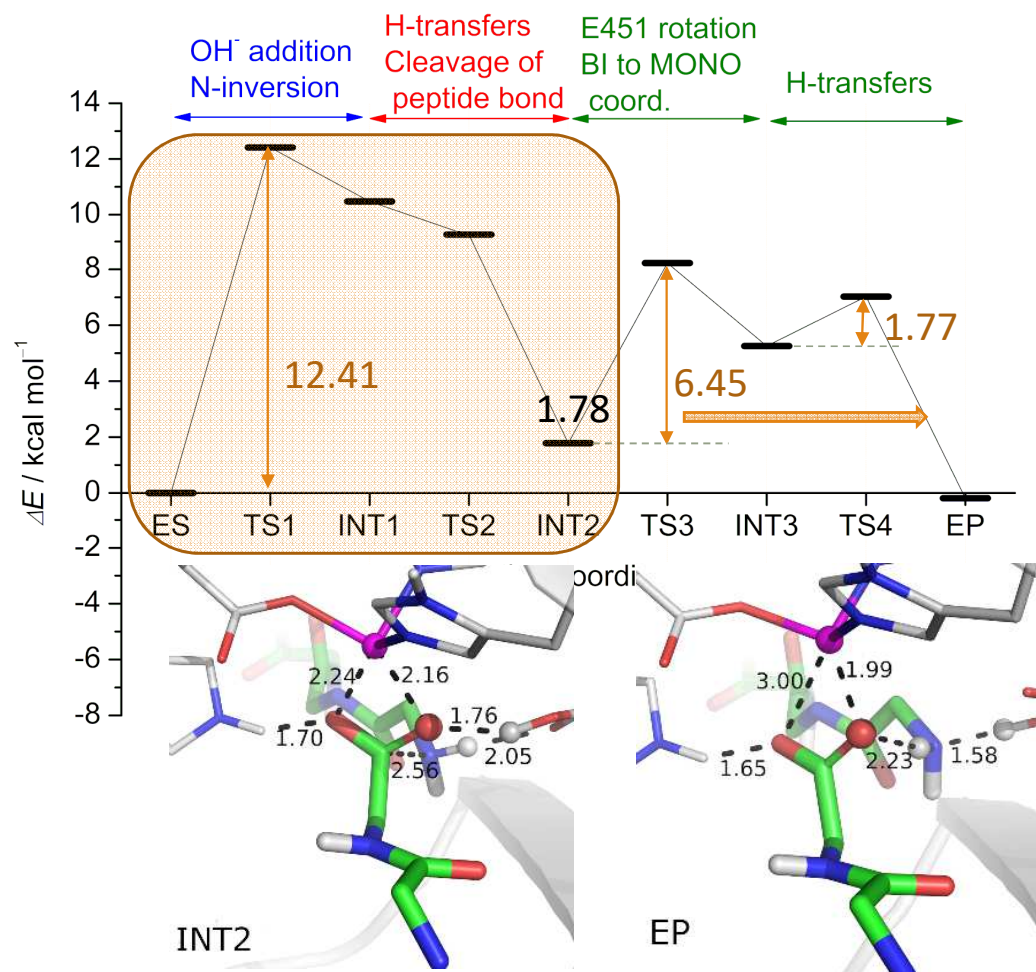
DPP III - tinorfin



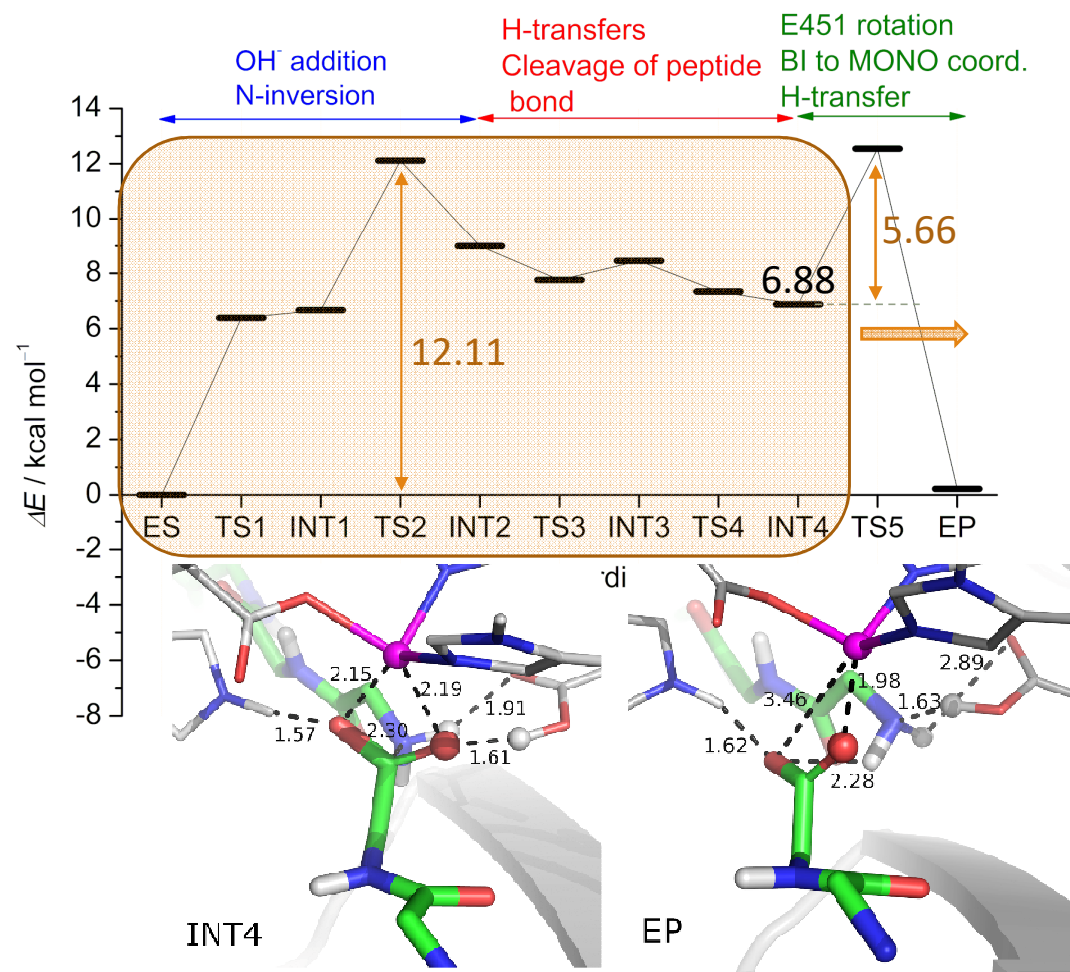
DPP III - Leu-enkefalin



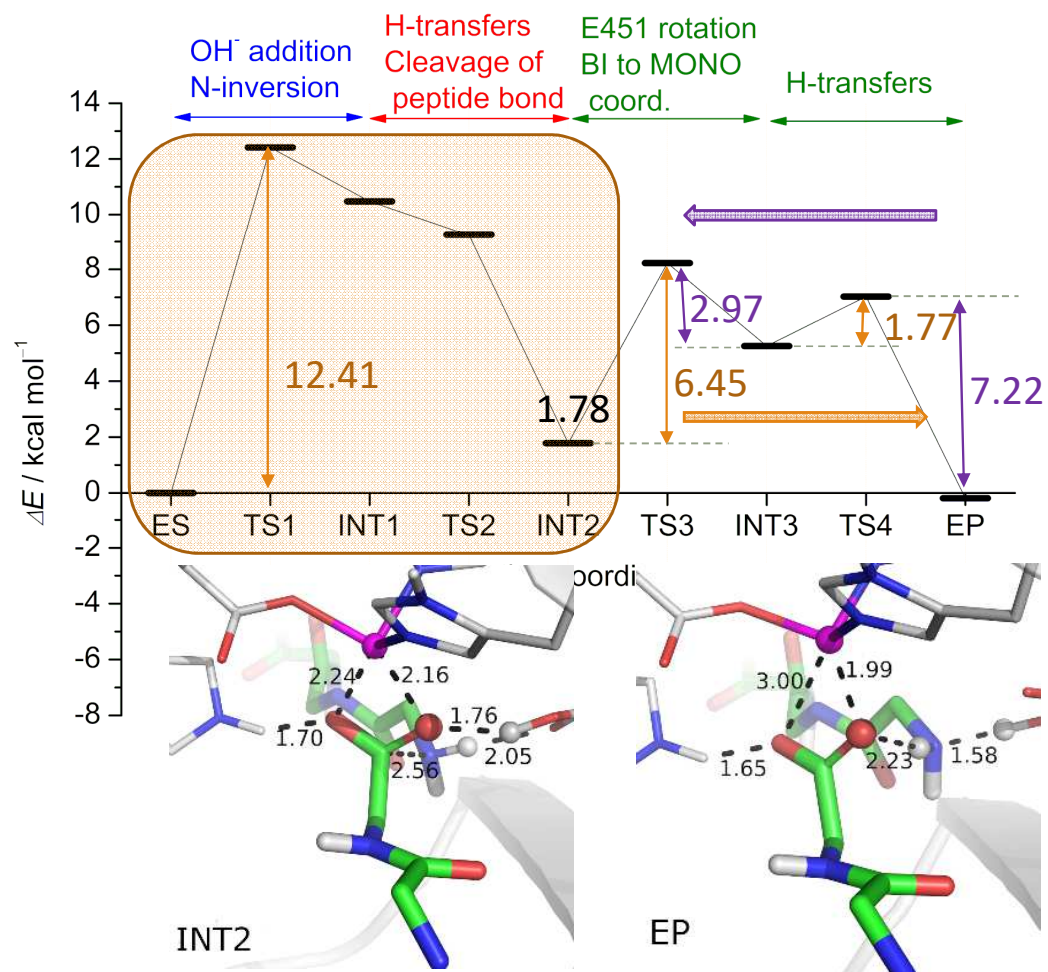
DPP III - tinorfin



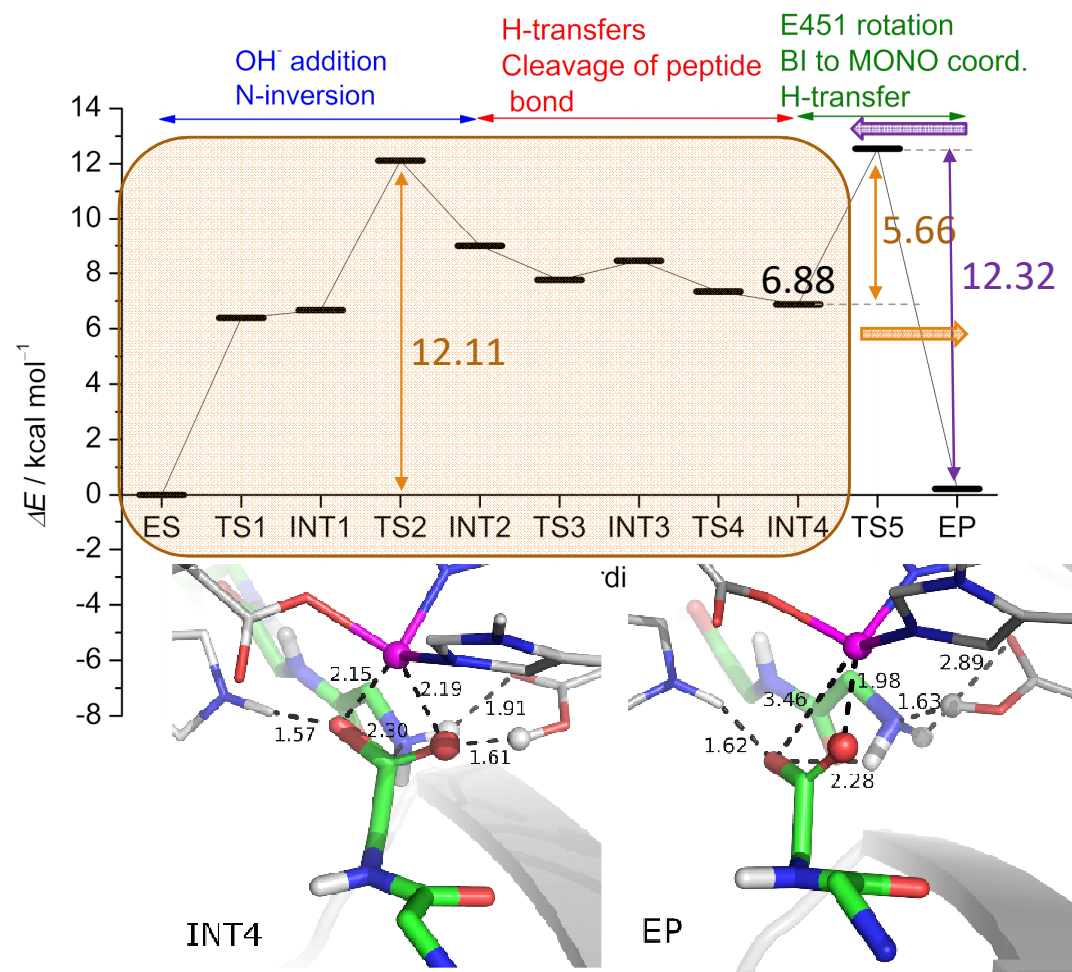
DPP III - Leu-enkefalin



DPP III - tinorfin



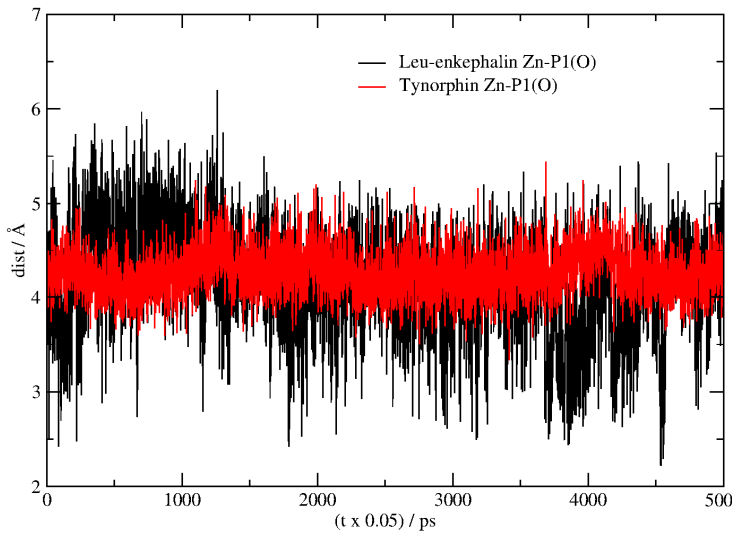
DPP III - Leu-enkefalin



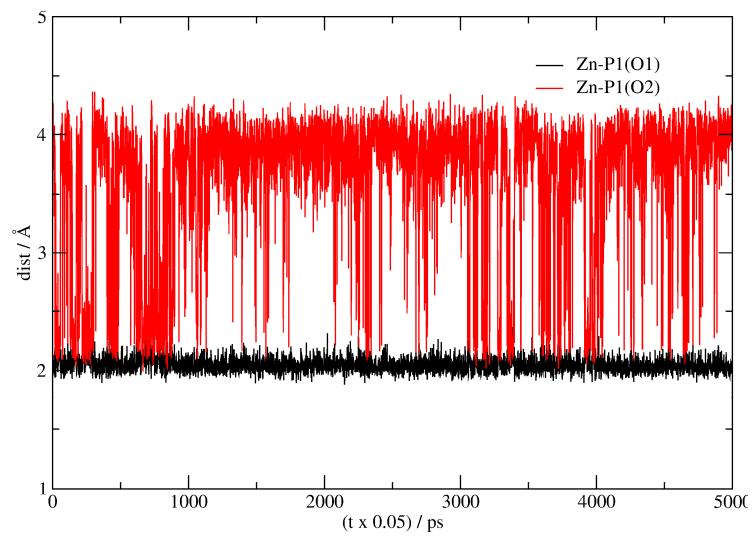
MD simulations

100 ns, NpT , 300 K, ff14SB, hybrid bonded/nonbonded parameters for Zn^{2+}

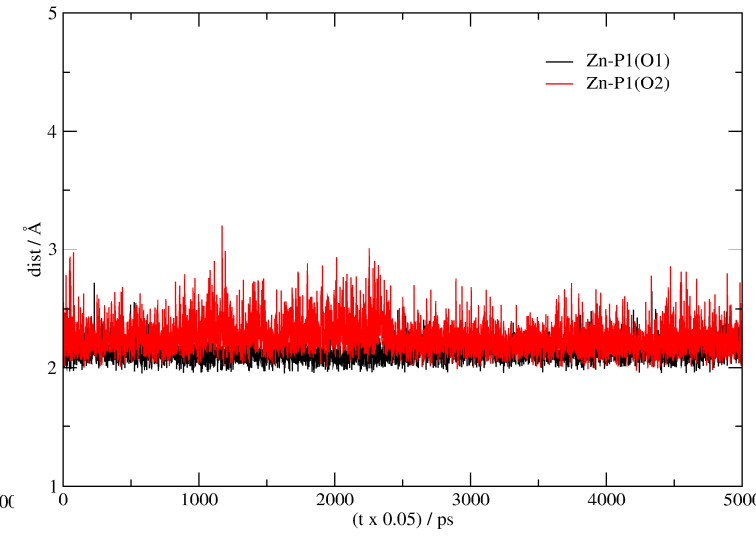
SUPSTRATE



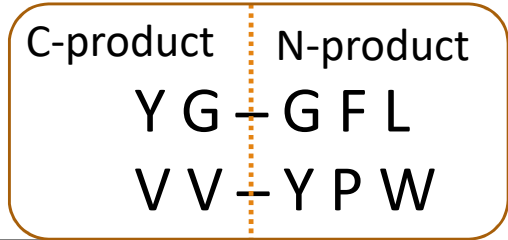
YG + GFL



VV + YPW



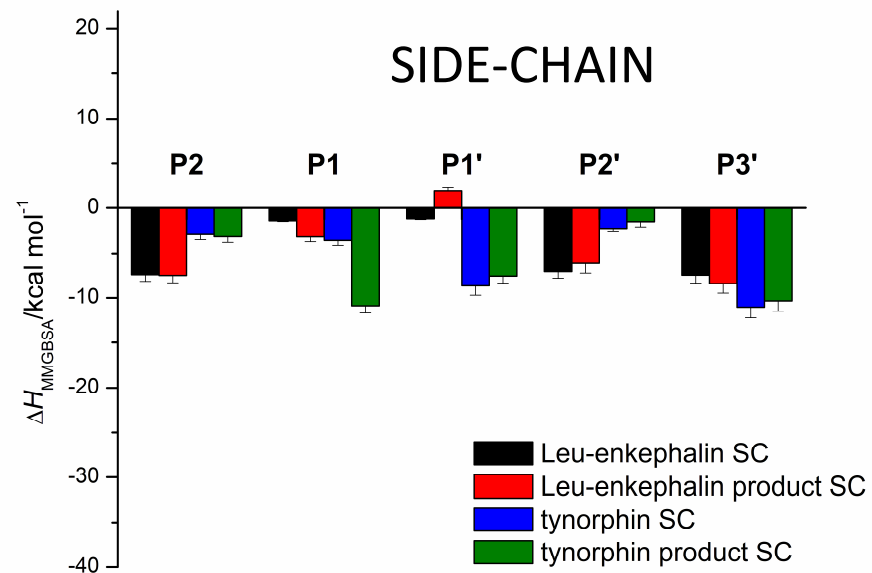
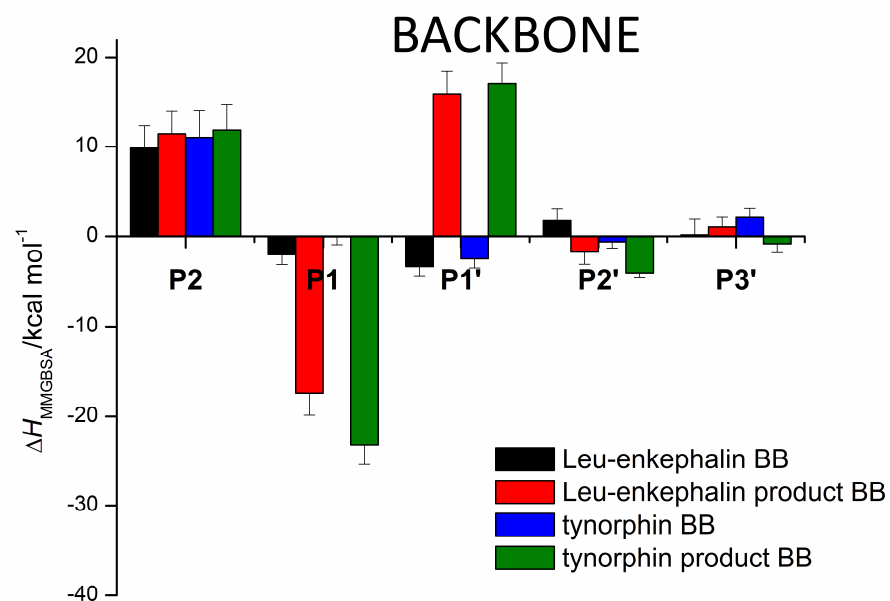
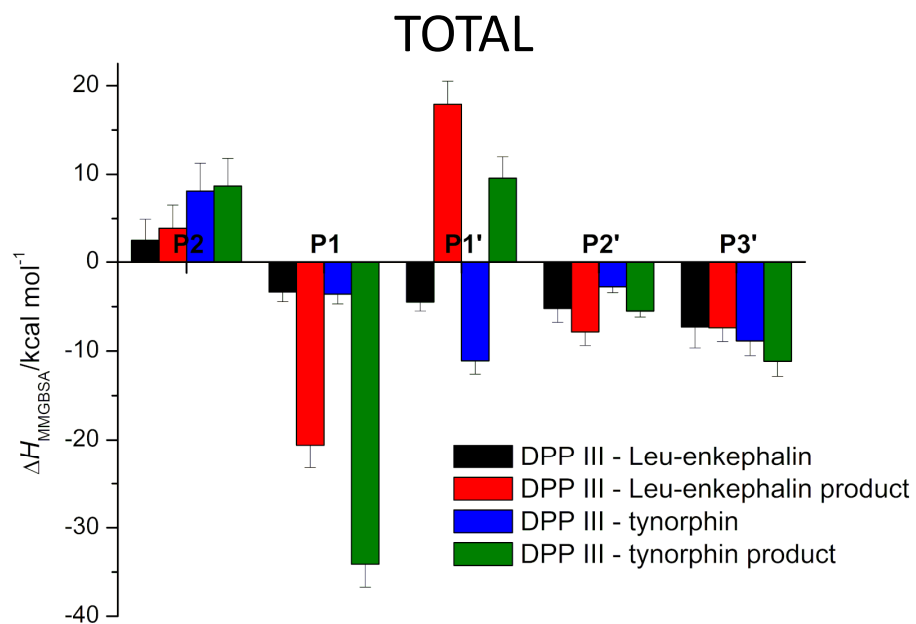
MM/PBSA binding energy



MM/PBSA	complex	receptor	ligand	$\Delta H/$ (kcal/mol)	$SD/$ (kcal/mol)
Complex with SUBSTRATE	DPP III – Leu-enkephalin	DPP III + WAT	Leu-enkephalin	-17.73	4.83
	DPP III – tynorphin	DPP III + WAT	tynorphin	-26.56	5.33
Complex with PRODUCT	DPP III – Leu-enkephalin	DPP III + C-prod	N-prod	-6.97	3.80
	DPP III – tynorphin	DPP III + C-prod	N-prod	-27.88	2.93
	DPP III – Leu-enkephalin	DPP III + N-prod	C-prod	-18.13	4.56
	DPP III – tynorphin	DPP III + N-prod	C-prod	-34.40	3.43

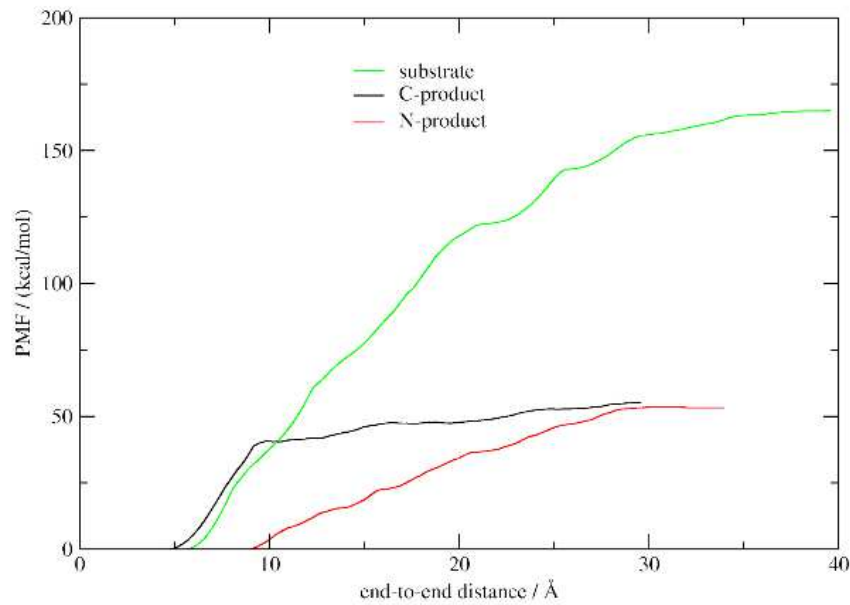
MM-GBSA per-residue binding energy

	P2	P1	P1'	P2'	P3'
Tynorphin	V	V	Y	P	W
Leu-enkephalin	Y	G	G	F	L

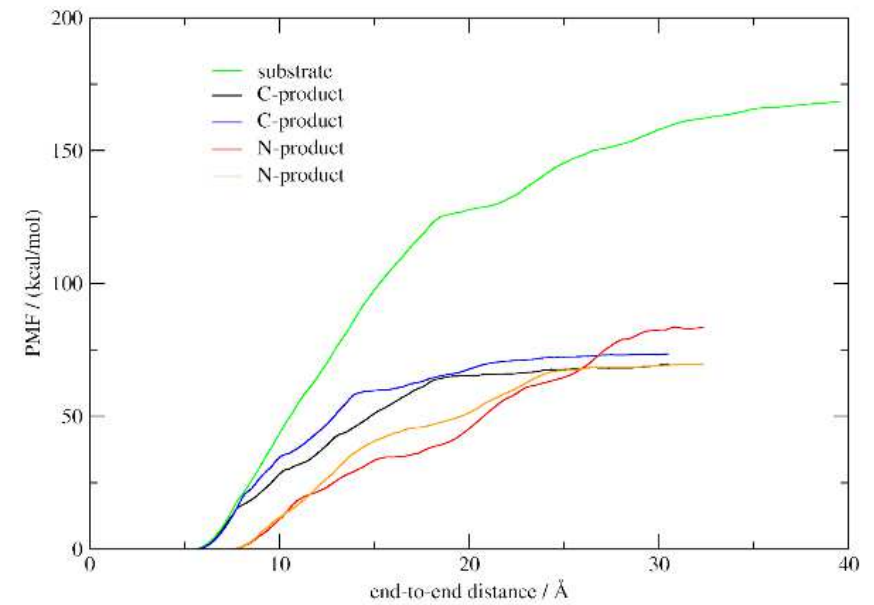


ASMD (adaptive steered MD) simulations

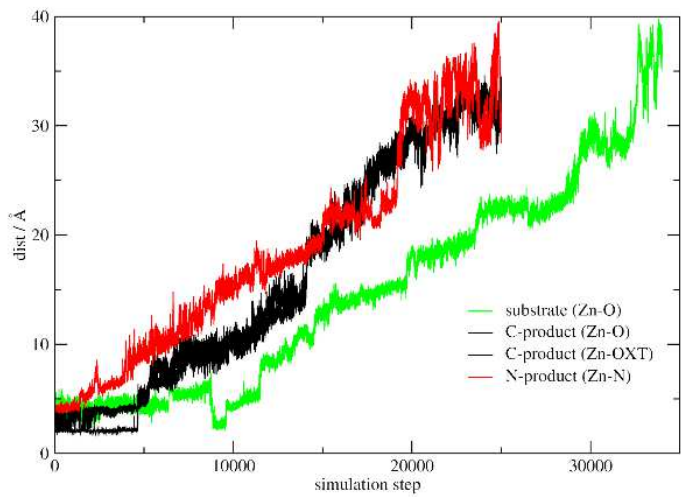
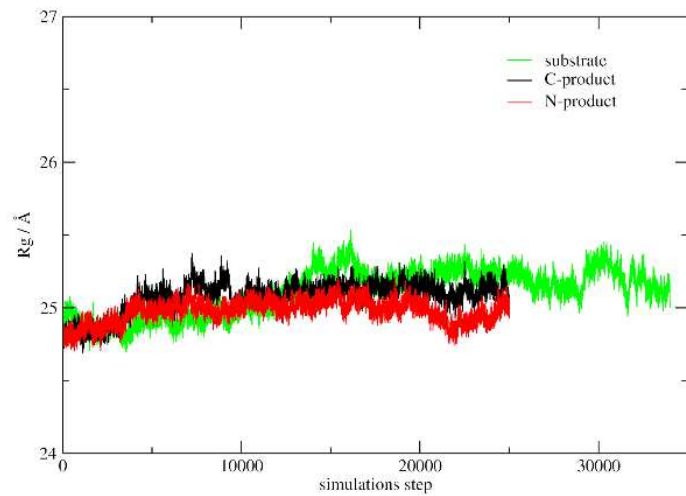
DPP III - Leu-enkephalin



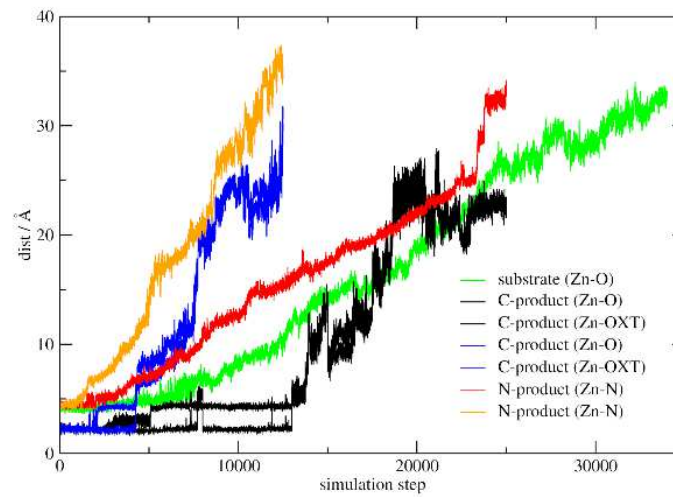
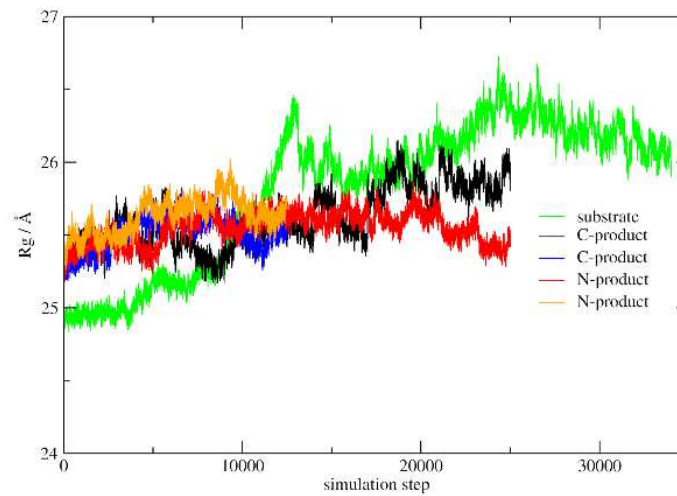
DPP III - tynorphin



DPP III – Leu-enkefalin



DPP III – tinorfin



HVALA!
