Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

QM/MM and Molecular Dynamics Investigation of the Mechanism of Covalent Inhibition of TAK1 Kinase

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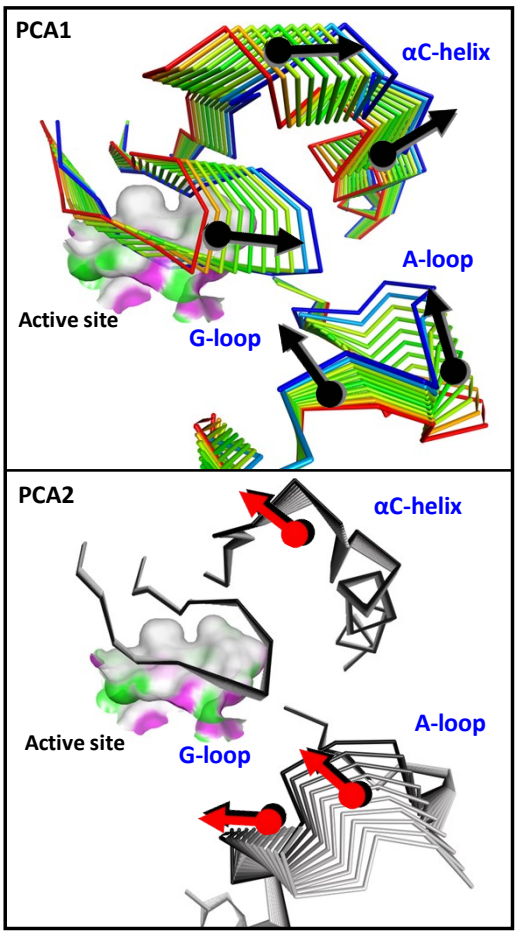

Figure S1 Illustration of the protein movements associated with PC1 and PC2 (80 ns).

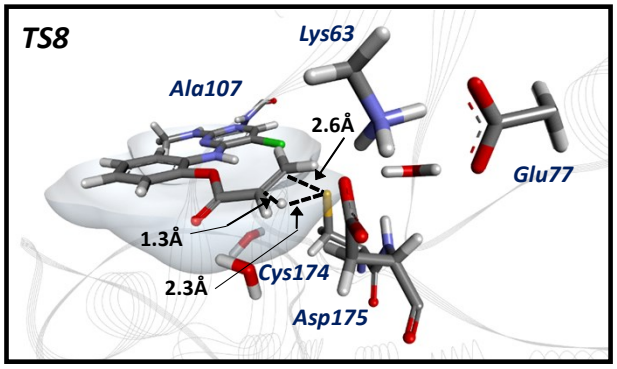

Figure S2 Illustration of the 3D structure obtained for TS8 of cluster 1. This corresponds to a direct addition process and is found to be energetically highly undesirable.

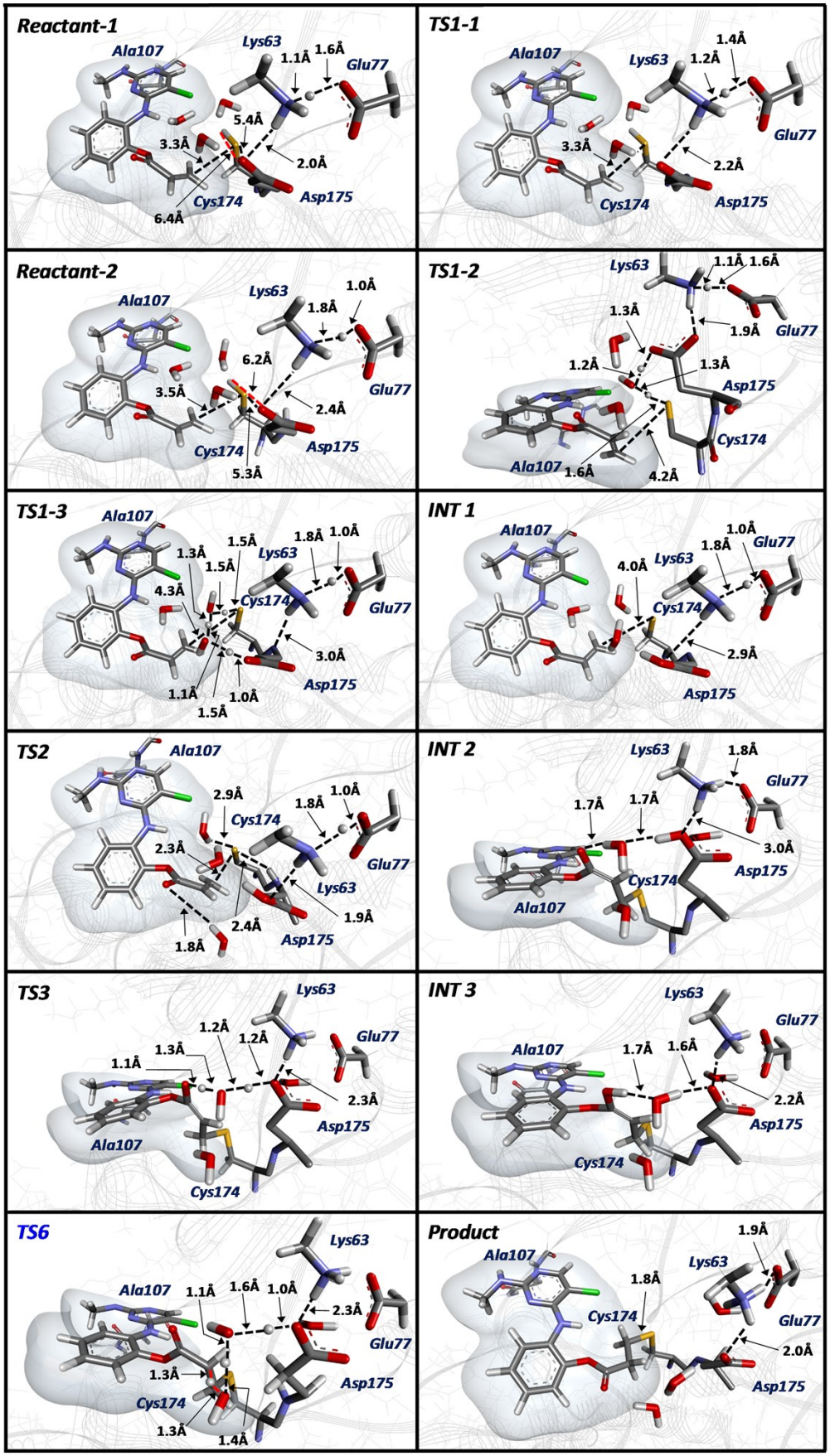

Figure S3 Illustration of the 3D structure obtained for cluster 2.

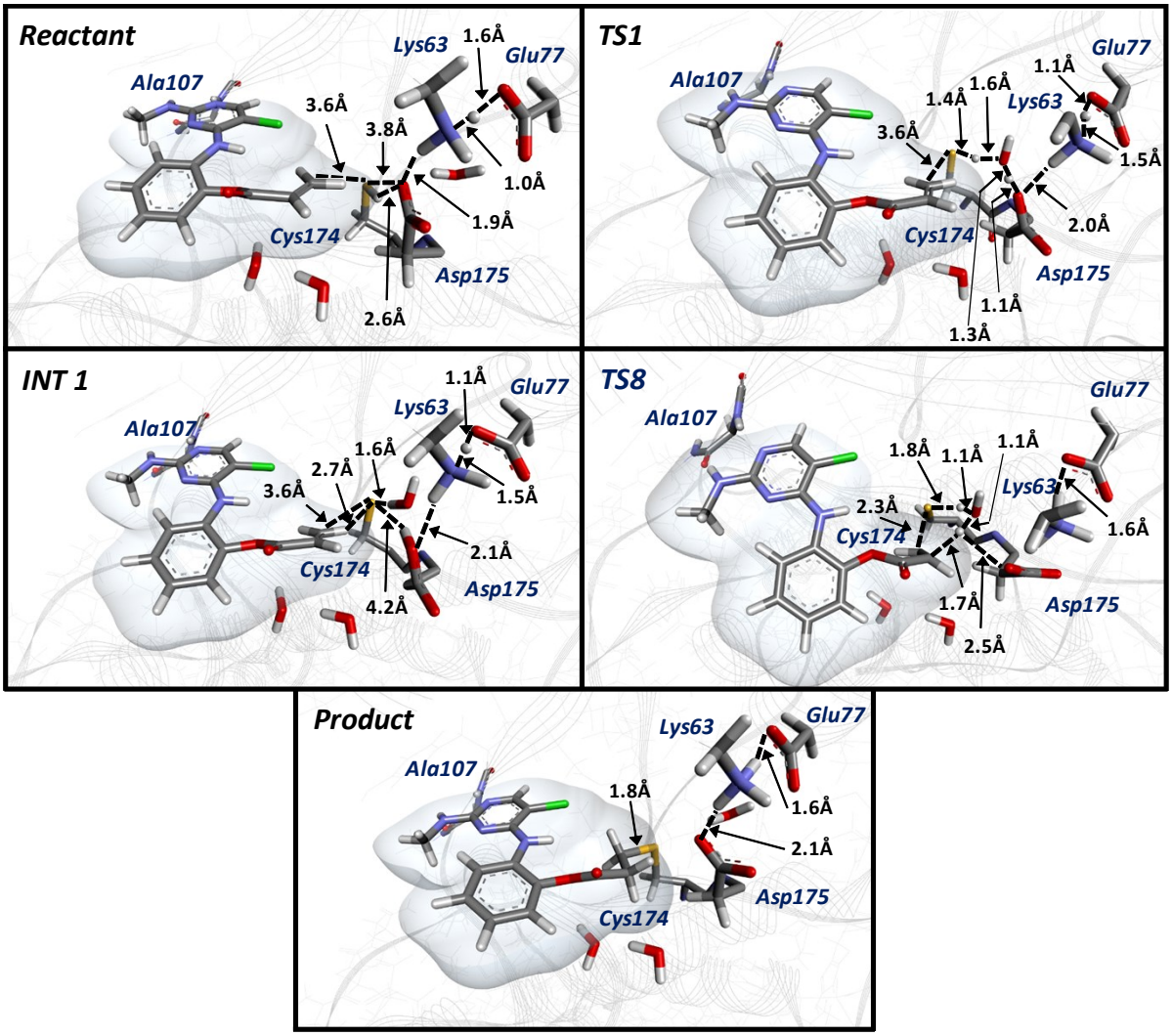

Figure S4 Illustration of the 3D structure obtained for cluster 3.

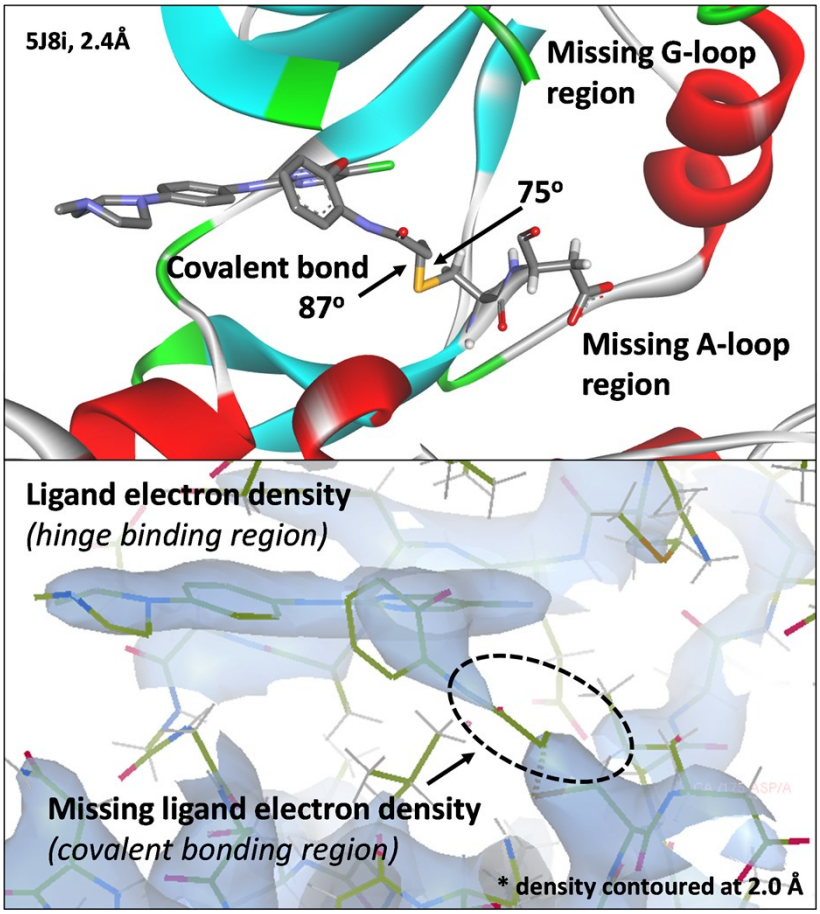

Figure S5 Electron density in TAK1 styructure 5J8I. The covalent complex formed with diamino pyrimidine inhibitor indicates high protein flexibility consistent with the MD simulations: (a) missing G-loop atoms, (b) missing A-loop atoms and (c) limited electron density associated with covalent bond resulting in a distorted bonds C-S bond.

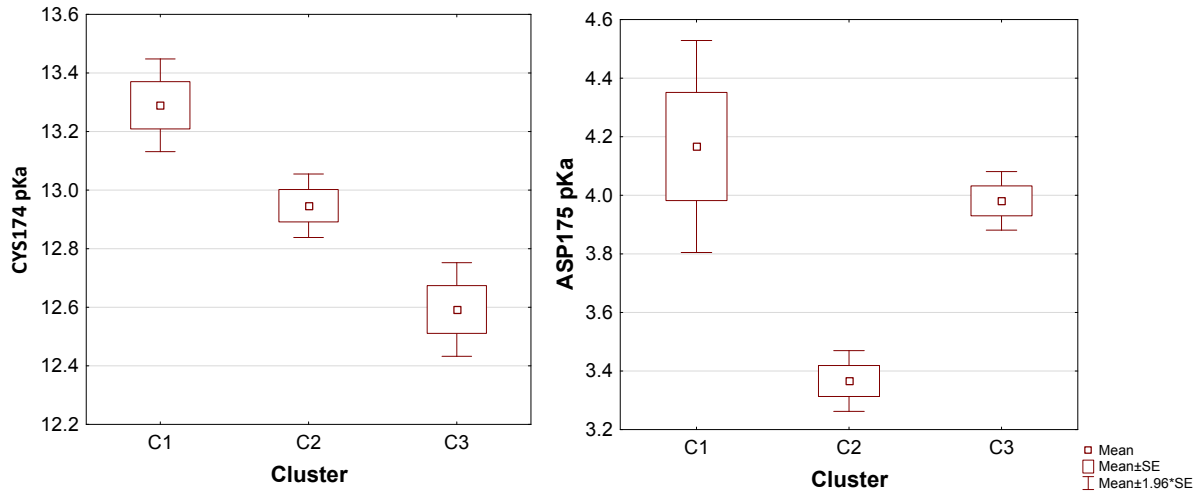

Figure S6 Distribution of predicted pKas (Propka 3) for residues Cys174 and Asp175 over the course of the 80ns simulation.

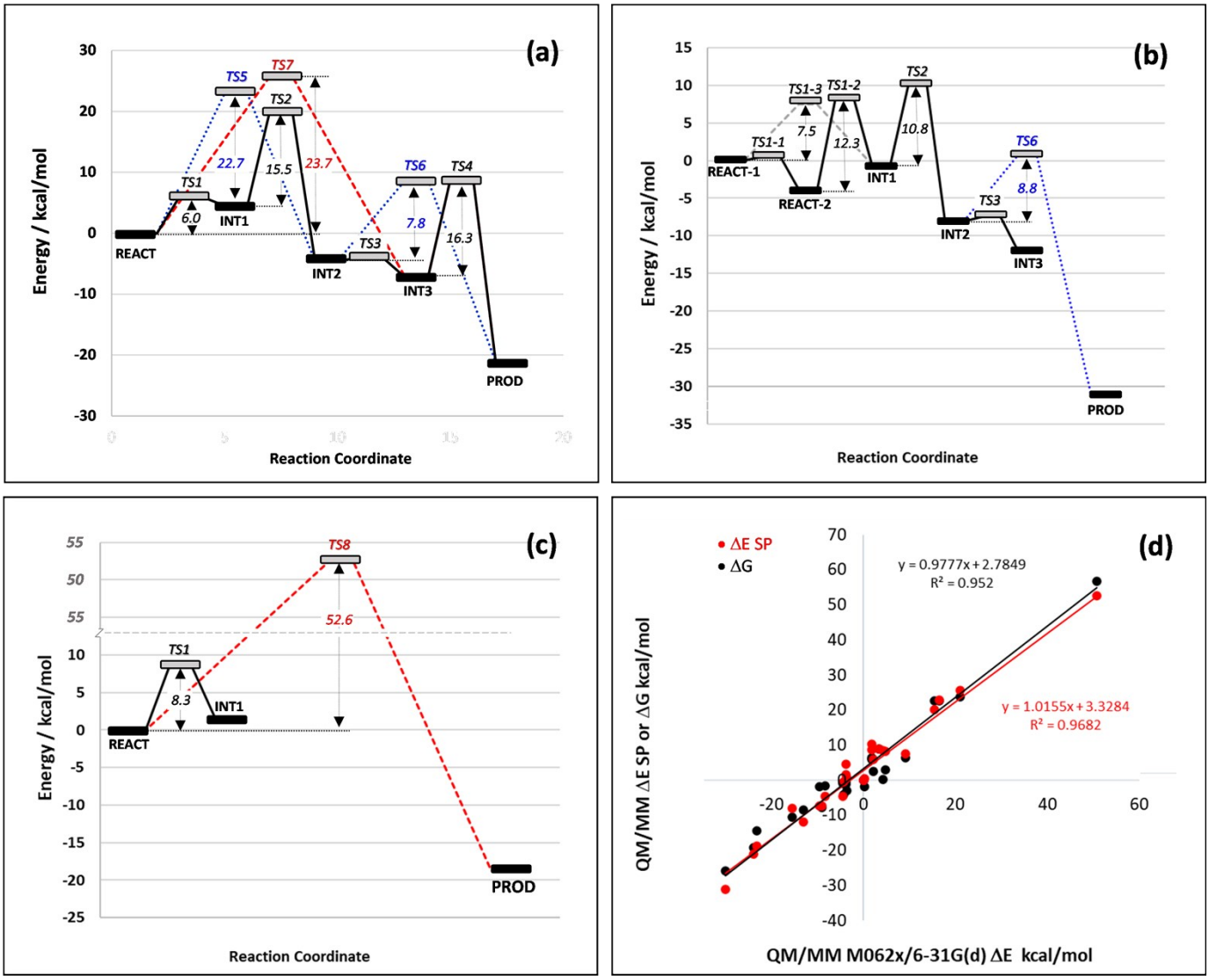

Figure S7 Energy profiles (ΔE_{sp}) (M06-2X/6-31G*//AMBER) associated for covalent adduct formation for structures representative of (a) cluster 1, (b) cluster 2 and (c) cluster 3 and (d) relationship betwene M062X/6-31G* ΔE, M06-2X/6-311++G(d,p)// M06-2X/6-31G* ΔE_{SP} and M06-2X/6-31G*ΔG

Table S1 Relative energies of stationary points for Clusters 1, 2 and 3 in kcal/mol.

ID	ΔE	ΔE_{SP}	ΔG	Cluster
REACT	0.00	0.00	0.00	One
TS1	2.23	5.96	2.46	One
INT1	-3.79	4.49	-0.56	One
TS2	15.45	20.04	22.53	One
TS5	16.43	22.93	22.72	One
TS7	21.02	25.72	23.71	One
INT2	-8.28	-4.56	-1.52	One
TS3	-4.58	-4.50	-0.92	One
TS6	1.76	8.74	6.33	One
INT3	-9.60	-7.30	-1.94	One
TS4	3.43	9.00	8.82	One
PROD	-23.85	-21.08	-19.17	One
TS8	58.47	65.52	59.06	One

ID	ΔE / A.U.	ΔE / SP	E / ΔG	Cluster
REACT1	0.00	0.00	0.00	Two
REACT2	-6.67	-3.87	-5.29	Two
TS1-1	0.28	0.55	-1.81	Two
TS1-3	4.32	8.44	0.23	Two
TS1-2	9.14	7.50	6.40	Two
INT1	-4.24	-0.50	-4.20	Two
TS2	1.85	10.31	5.84	Two
INT2	-15.58	-8.12	-10.52	Two
TS3	-9.09	-7.41	-7.85	Two
TS6	-3.67	0.72	-3.04	Two
INT3	-13.00	-12.00	-8.47	Two
PROD	-30.00	-31.18	-25.86	Two

ID	ΔE / A.U.	ΔE / SP	E / ΔG	Cluster
REACT	0.00	0.00	0.00	Three
TS1	4.86	8.34	2.85	Three
INT1	-3.85	1.69	-1.20	Three
PROD	-23.16	-18.72	-14.36	Three
TS8	50.77	52.61	56.81	Three