

Table S1. QM/MM calculations of the energetics for the ring-opening reactions of inhibitions in the active site of MMP2^a

inhibitor	barrier height	reaction enthalpy	
		P1 (unprotonated product)	P2 (protonated product)
(<i>R</i>)-SB-3CT (3) ^b EE ^c	19.9	-21.1	-0.7
(<i>R</i>)-SB-3CT (3) ^b ME ^c	21.2	-24.0	-9.5
oxirane analogue (4) ^b EE ^c	21.5	-13.1	-15.1
oxirane analogue (4) ^b ME ^c	22.9	-14.8	-21.9

(a) ONIOM(B3LYP/6-311+G(d,p):AMBER)//ONIOM(B3LYP/6-31G(d):AMBER) level of theory; energies in kcal/mol.

(b) See Figure 5.

(c) EE: electronic embedding; ME: mechanical embedding.

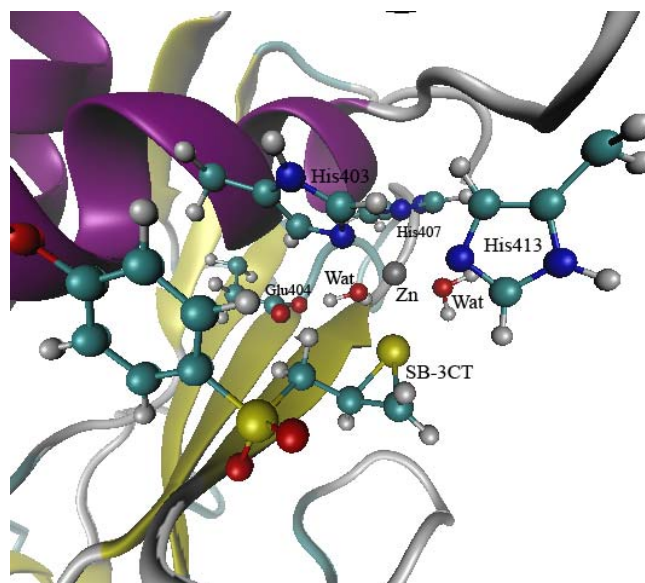


FIGURE S1. The active site of the reactant complex from an optimal conformation in molecular dynamics simulation for the MMP2 and (*S*)-SB-3CT. Residues are shown in ball-and-stick representation with atom colored according to atom types (H, C, N, O, S, Zn, shown in white, cyan, blue, red, yellow, and grey, respectively).

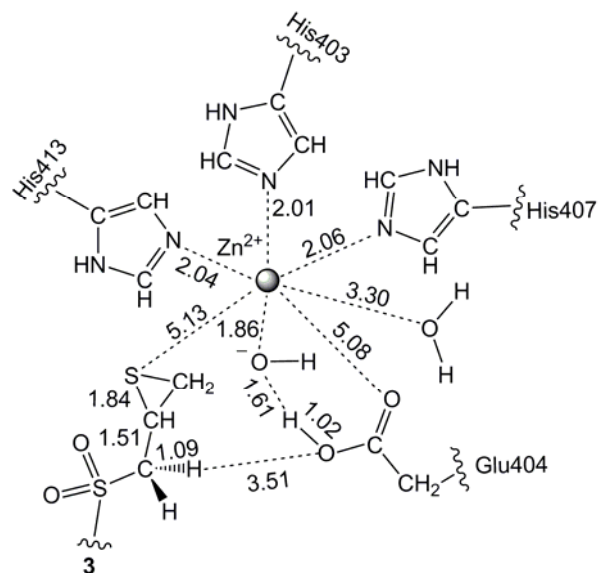
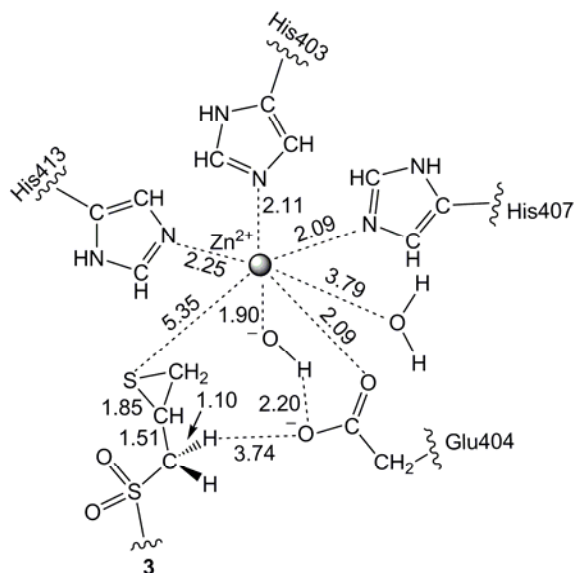
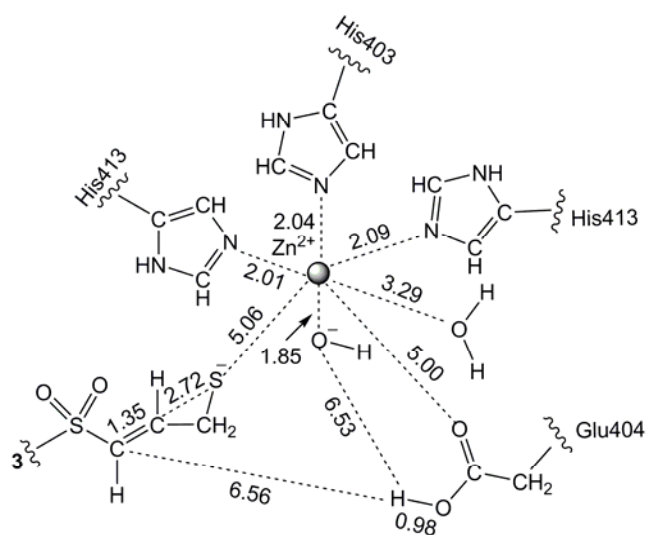


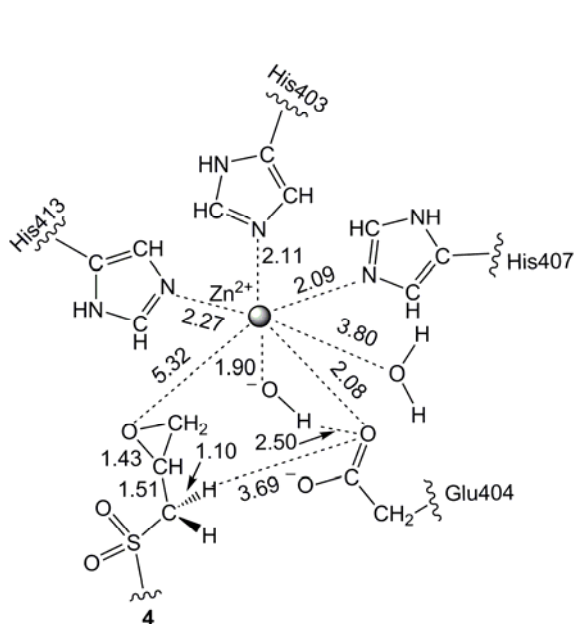
FIGURE S2. QM/MM calculations of the complex of *(R)*-SB-3CT (**3**) and MMP2 with two waters at the active site optimized at the ONIOM(B3LYP/6-31G(d):AMBER) level of theory. Key bond lengths are in Å. Ball-and-stick representation of QM region and cartoon representation of protein are shown in Figure 2.



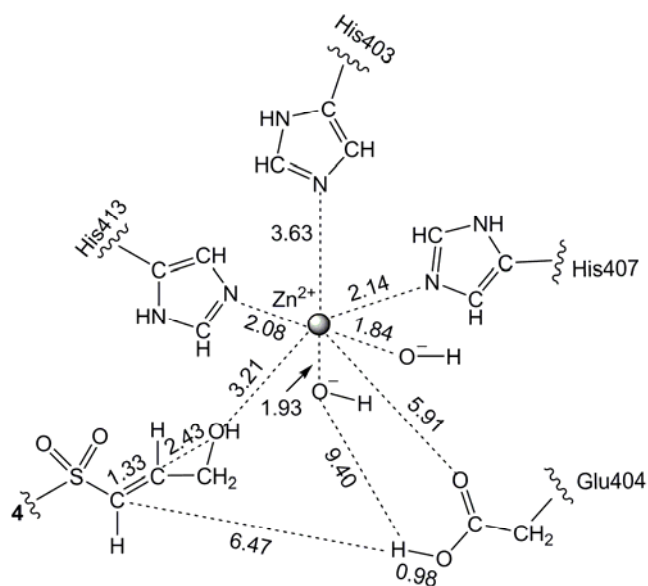
3-R 0.0



3-P 15.8



4-R 0.0



4-P 6.6

FIGURE S3. Reactants and products for (*R*)-SB-3CT (**3**) and its oxirane analogue (**4**) with hydroxide in the MMP2 active site optimized at the ONIOM(B3LYP/6-31G(d):AMBER) level of theory. Energies (in kcal/mol) were calculated at ONIOM(B3LYP/6-311+G(d,p):AMBER) using an electronic embedding scheme with the reactant complexes as reference states. Key bond lengths are in Å. Ball-and-stick representation of QM region and cartoon representation of protein are shown in Figure 3.

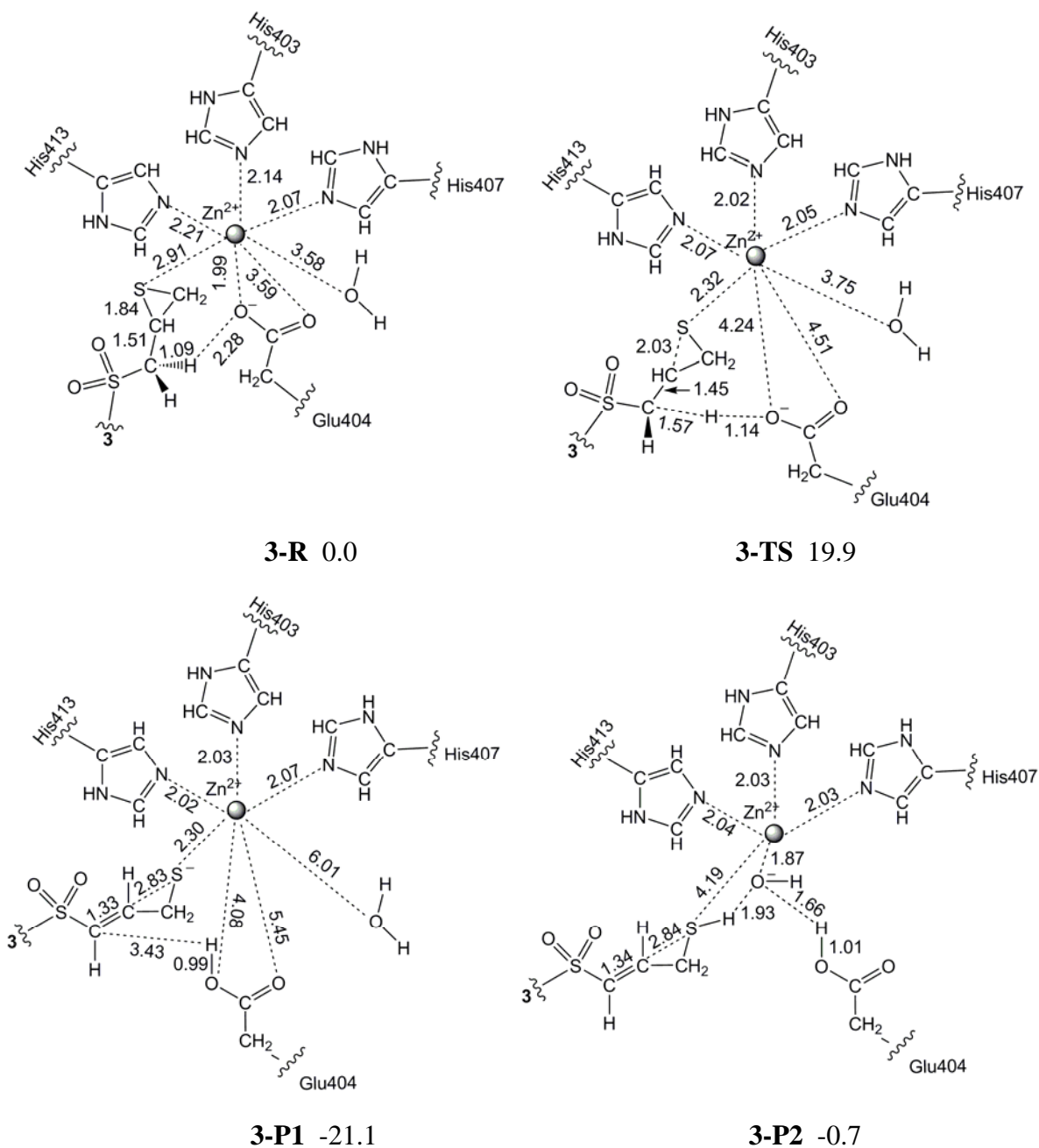
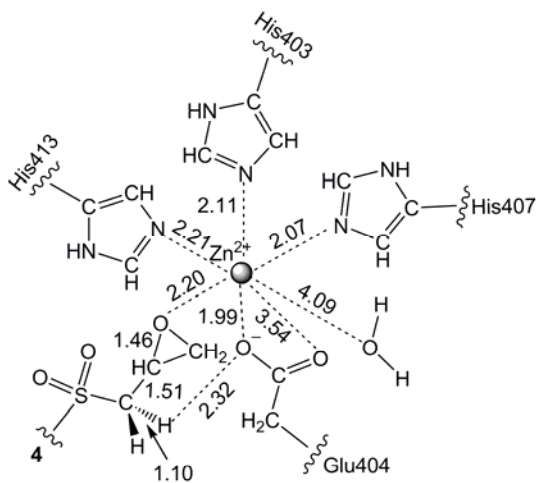
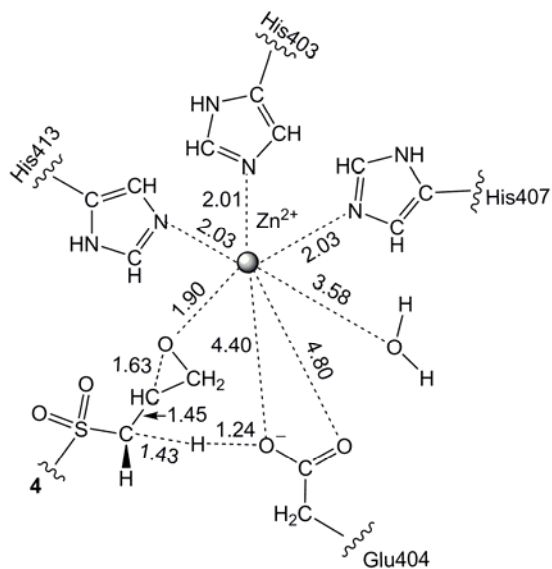


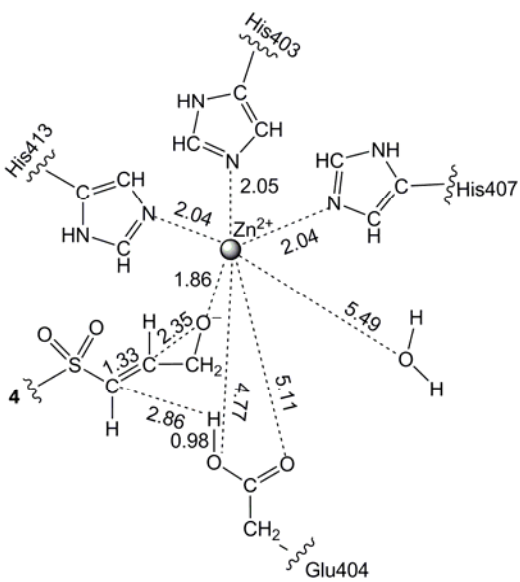
FIGURE S4. Reactants, transition states and products for (*R*)-SB-3CT (**3**) and its oxirane analogue (**4**) at MMP2 active site optimized at ONIOM(B3LYP/6-31G(d):AMBER) level of theory. Energies (in kcal/mol) were calculated at ONIOM(B3LYP/6-311+G(d,p):AMBER) using electronic embedding with the reactant complexes used as reference states. Key bond lengths are in Å. Ball-and-stick representation of QM region and cartoon representation of protein are shown in Figure 5.



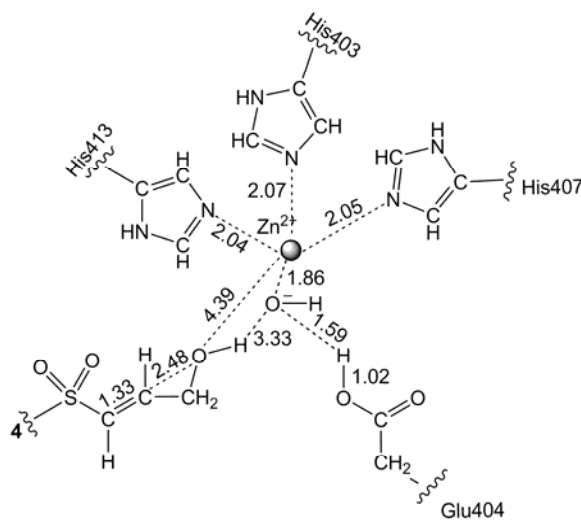
4-R 0.0



4-TS 21.5



4-P1 -13.1



4-P2 -15.1

FIGURE S4. (continued)

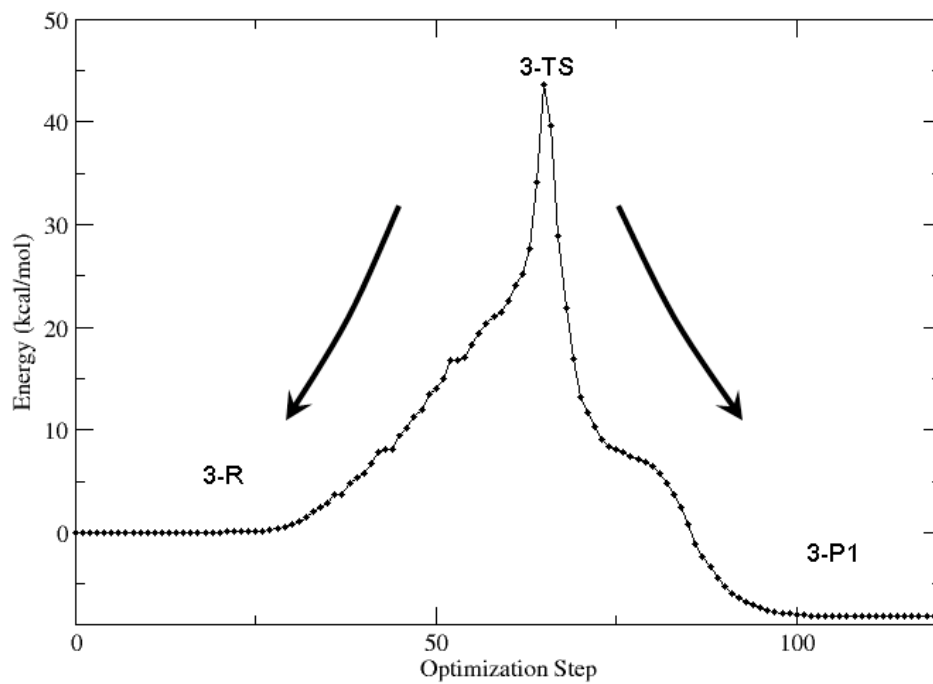


FIGURE S5. Optimization paths from transition state of (*R*)-SB-3CT (**3-TS**) to reactant and product. Optimization from **3-TS** to reactant side and product side were combined. The highest point along the path is transition state. Optimizations were carried out at ONIOM(B3LYP/6-31G(d):AMBER) level of theory using mechanical embedding. Relative energies with respect to reactant state were plotted in kcal/mol.

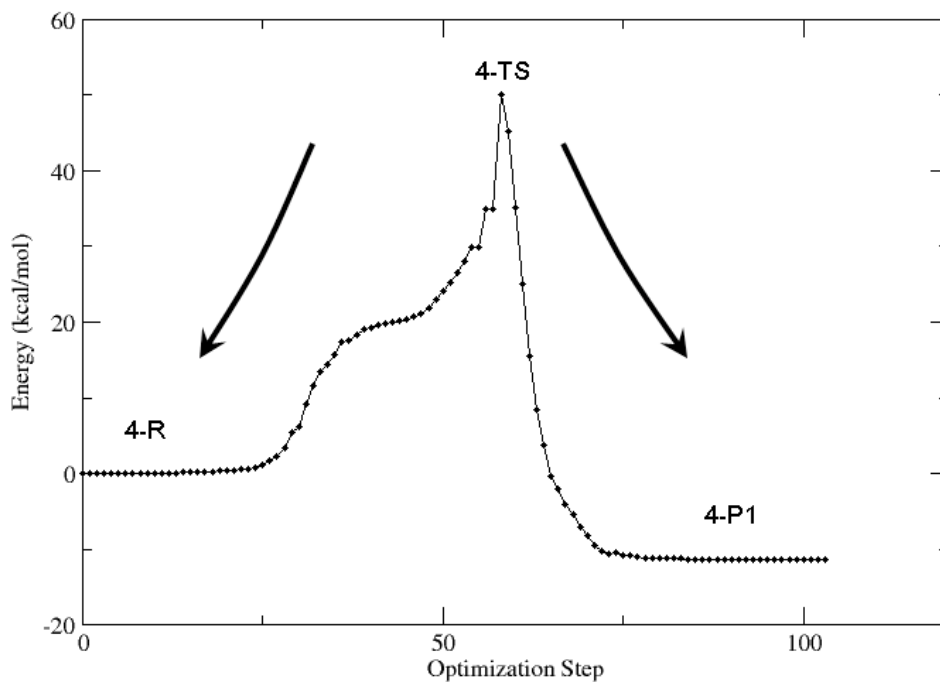


FIGURE S6. Optimization paths from transition state of (*R*)-SB-3CT oxirane analogue (**4-TS**) to reactant and product. Optimization from **4-TS** to reactant side and product side were combined. The highest point along the path is transition state. Optimizations were carried out at ONIOM(B3LYP/6-31G(d):AMBER) level of theory using mechanical embedding. Relative energies with respect to reactant state were plotted in kcal/mol.

AMBER force field parameters used for zinc ions

atomic symbol	atomic mass
Zn	65.4

Lennard-Jones 6-12 potential for zinc ions

atomic symbol	R^* (Å)	ϵ (kcal/mol)
Zn	1.10	0.0125