

Table S1. QM/MM Calculated Energies (kcalmol⁻¹) of the Michaelis Complex (ES) and the Relative Energies of Transition State (TS), and Product Complex (P) Observed on Reaction Pathway Described in Figure 3 at Various Levels of Theory and 6-31G** basis set with diffuse functions (6-31+G**) on O1', O5', O_{Ser21}, and N_{His498} atoms from the Jaguar library³⁴ and the MM subsystem was characterized with an OPLS_2005 all-atom force field³³

Method	Geometry	ES	TS	P
B3LYP	B3LYP	-5 595.537621	-5 595.512723	-5 595.540396
PWB6K		-5 598.255598	-5 598.221445	-5 598.255125
MPW1K		-5 594.182284	-5 594.146535	-5 594.185307
M06-2X		-5 593.571955	-5 593.546226	-5 593.573197
M05-2X		-5 595.011695	-5 594.986801	-5 595.012881
MPW1K	MPW1K	-5 594.203989	-5 594.172753	-5 594.213212
B3LYP		-5 595.517133	-5 595.492955	-5 595.517340
PWB6K		-5 598.284227	-5 598.258076	-5 598.292394
M06-2X		-5 593.563979	-5 593.543486	-5 593.570839
M05-2X		-5 595.009214	-5 594.986246	-5 595.015244
M06-2X	M06-2X	-5 593.579056	-5 593.554370	-5 593.554370
B3LYP		-5 595.531759	-5 595.509708	-5 595.509708
PWB6K		-5 598.271366	-5 598.239065	-5 598.239065
MPW1K		-5 594.193360	-5 594.160589	-5 594.160589
M05-2X		-5 595.016930	-5 594.993889	-5 594.993889