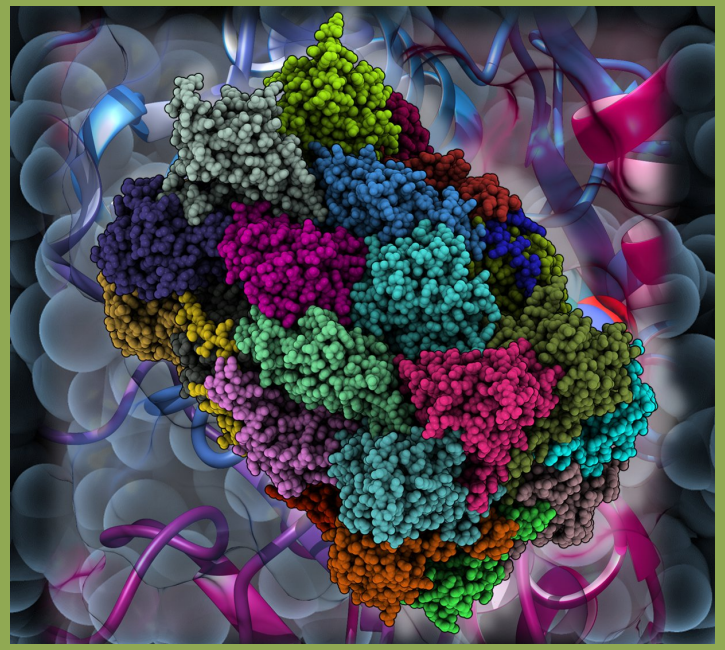
16th RES USERS CONFERENCE 14-15th September 2022

QM/MM STUDIES ON THE INHIBITION OF *HUMAN* 20S PROTEASOME

THE ROLE OF ELECTROSTATIC EFFECTS IN BIOCATALYSIS



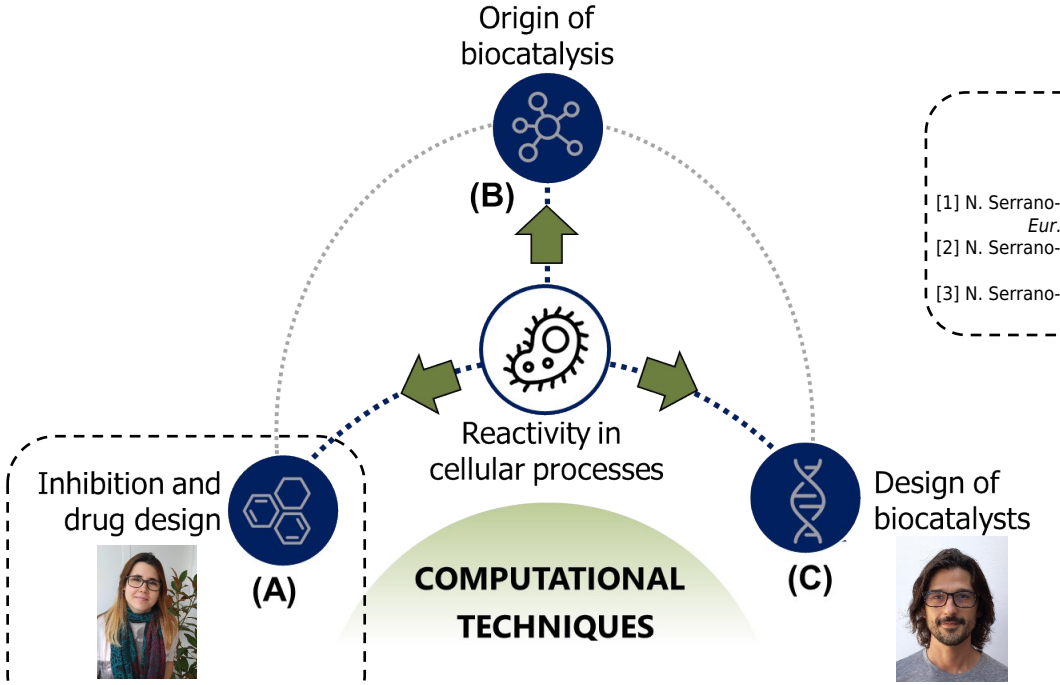
Katarzyna Świderek

Biocomp group, Universitat Jaume I, Spain

BioComp group http://www.biocomp.uji.es/

StopProt project http://www.biocomp.uji.es/swiderek/home.html

RESEARCH INTEREST

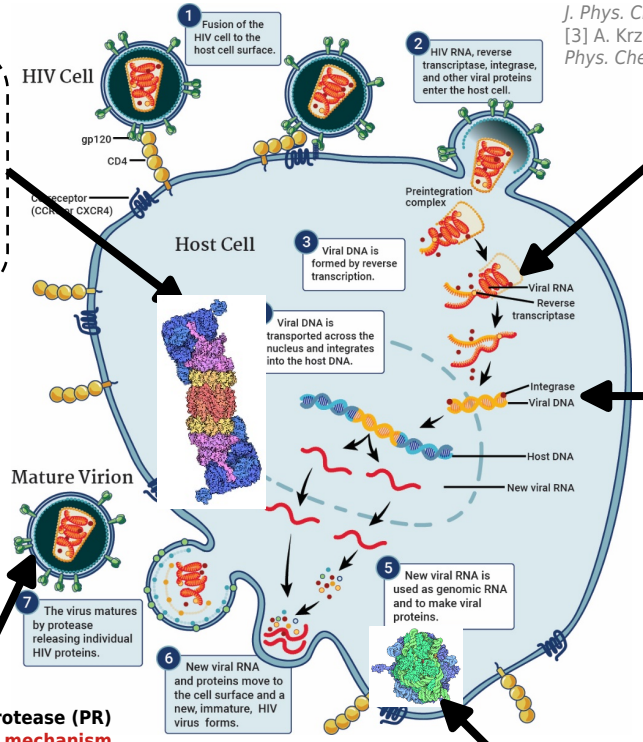


Natalia Serrano Aparicio, PhD student

Miquel Àngel Galmés, PhD student

Multiscale
QM/MM Methods

20S Proteasome
Reaction mechanism
Under studies
Inhibition
[1] N. Serrano-Aparicio, **K. Świderek***, V. Moliner*
Eur. J. Med. Chem. **2019**, 164, 399-407.
[2] N. Serrano-Aparicio, V. Moliner,* **K. Świderek***
ACS Catal. **2021** 11, 3575–3589.
[3] N. Serrano-Aparicio, V. Moliner,* **K. Świderek***
2021 submitted.



Viral protease (PR)
HIV-1 Reaction mechanism
[1] A. Krzemińska, V. Moliner,* **K. Świderek***
J. Am. Chem. Soc. **2016**, 138, 16283-98.
COVID19 Mpro reaction mechanism
[1] **K.Świderek*,** V Moliner*
Chem. Sci. **2020**,11, 10626-30.
COVID19 Mpro Inhibition
[1] K. Arafet, N. Serrano-Aparicio A. Lodola A. Mulholland, F. V. González, **K. Świderek***, V. Moliner* *Chem. Sci.* **2021** 12, 1433-1444

Reverse transciptase (RT) enzyme
HIV-1 Inhibition
[1] K. Świderek, S. Martí, V. Moliner
Phys. Chem. Chem. Phys. **2012**, 14, 12614-24.
[2] A. Krzemińska, P. Paneth, V. Moliner*, **K. Świderek***
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Phys. Chem. Chem. Phys. **2016**, 18, 310-17.

Integrase (IN) enzyme
HIV-1 Reaction mechanism
[1] A. Krzeminska, **K. Świderek***
J. Chem. Inf. Model. 2019, 59, 2995-3005.

Ribosome 70S
Reaction mechanism
[1] **K. Świderek**, I. Tuñón, S. Martí, V. Moliner, J. Bertran
Chem.Commun. **2012**, 48, 11253-55.
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[3] **K. Świderek**, S. Marti, I. Tuñón, V. Moliner, J. Bertran
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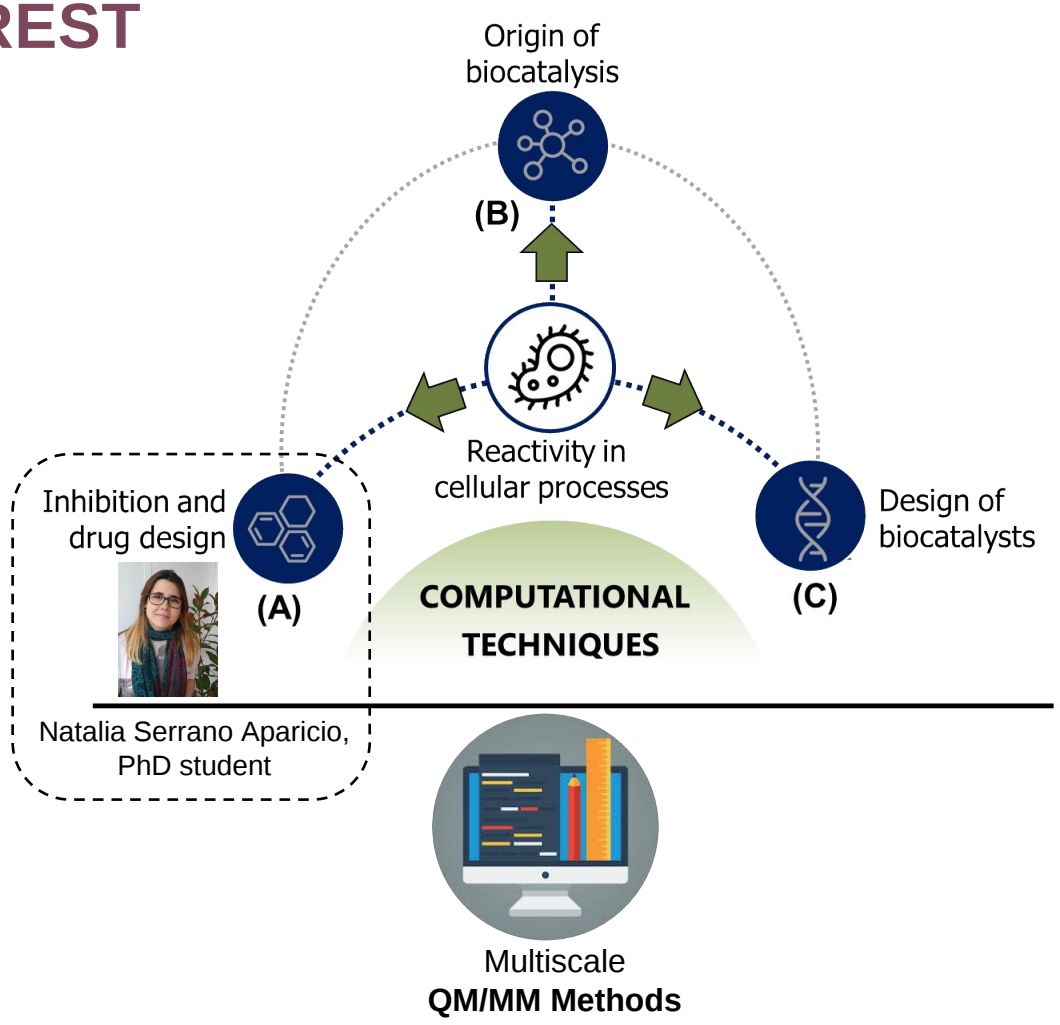

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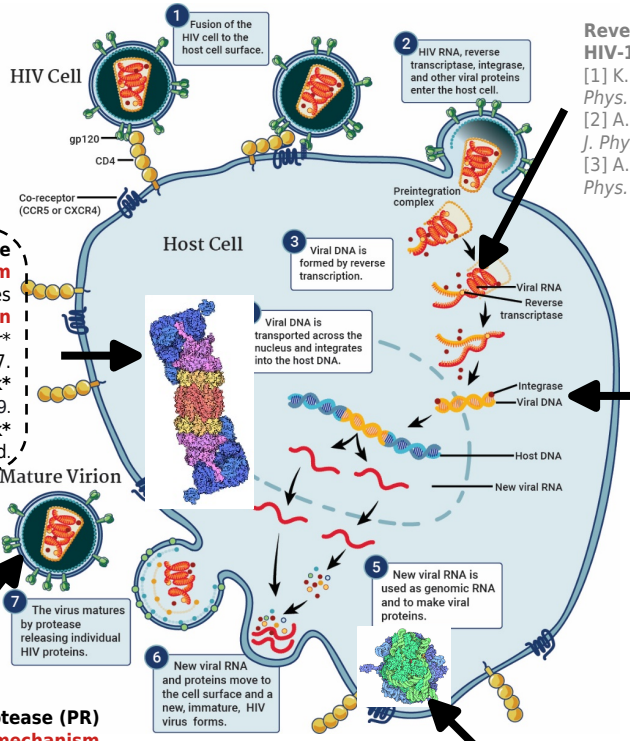

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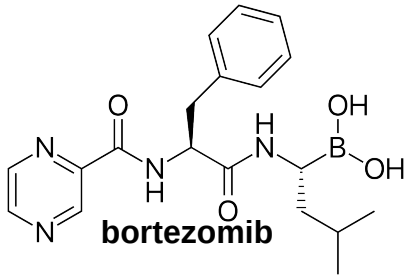
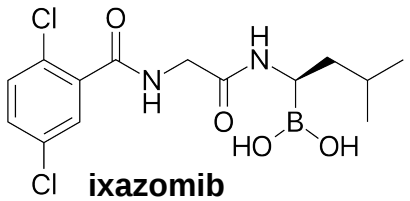
20S PROTEASOME – ROLE AND CHARACTERISTIC

Designed covalent inhibitors can be classified based on the nature of the electrophilic warhead employed to interact with Thr1. Therefore, using this rule, **eight groups** of covalent inhibitors can be distinguished such as **aldehydes**, **boronates**, **epoxyketones**, **α-ketoaldehydes**, **vinyl sulfones**, **syrbactins**, **bacteria-specific oxariazol-2-ones**, and **β-lactones**.

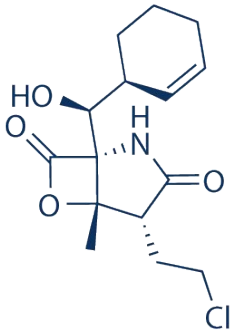
However, inhibitory studies have led to just three peptide-like compounds approved by the Food and Drug Administration (FDA) for cancer treatment: two peptide boronate inhibitors, **bortezomib** (VELCADE) and **ixazomib** (NINLARO), and the peptide epoxyketone inhibitor **carfilzomib** (KYPROLIS).



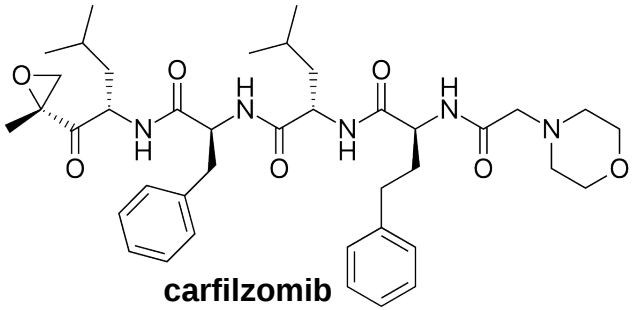
bortezomib



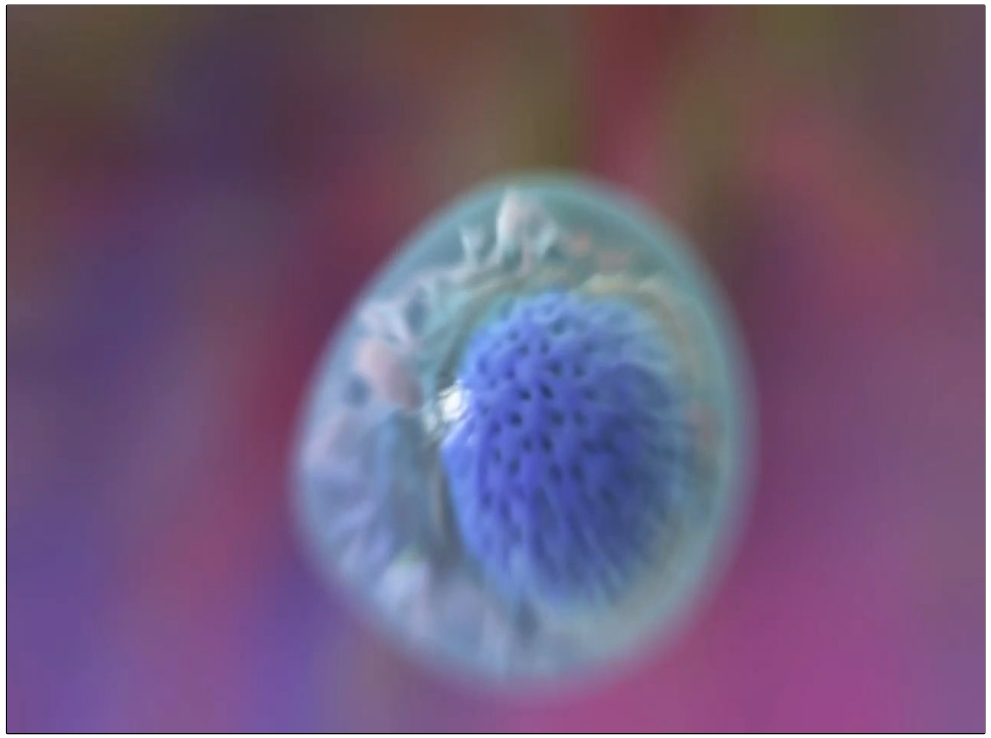
ixazomib



Salinosporamide A,
Marizomib, (NPI-0052)



carfilzomib



Medi-mation.com

The Nobel Prize in Chemistry 2004 : A. Ciechanover; A. Hershko, I. Rose "for the discovery of ubiquitin-mediated protein degradation."
Huber, E.H. et al. Cell. 2012, 148, 727-738.
Saha, A and Warshel, A. PNAS 2021 118 just accepted.

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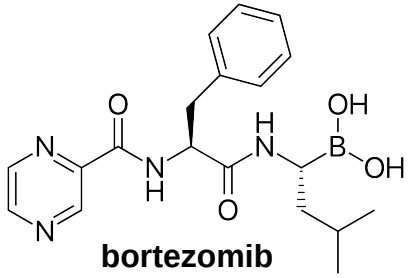
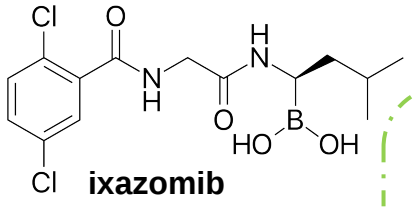
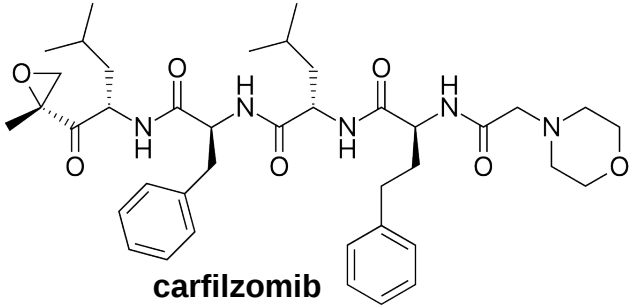


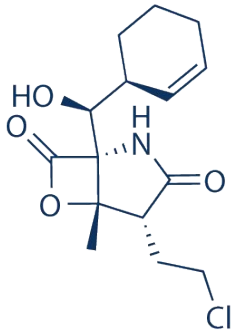
bortezomib



ixazomib

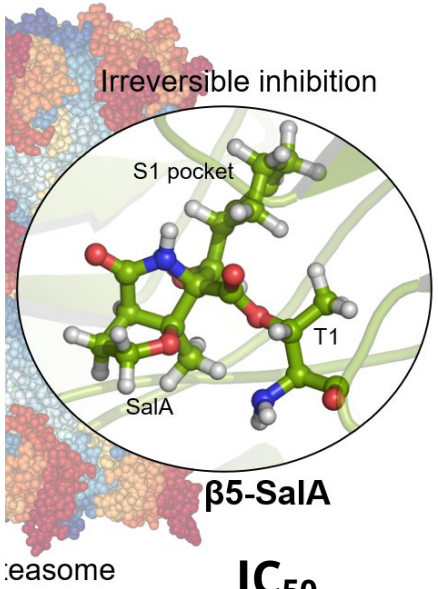


carfilzomib



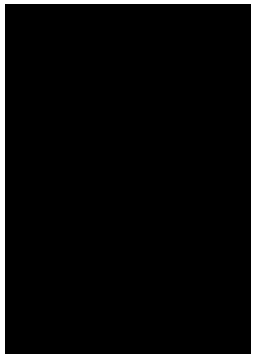
Salinosporamide A,
Marizomib, (NPI-0052)

COVALENT INHIBITION OF PROTEASOME 20S



IC_{50}
0.8 ± 0.08 nM

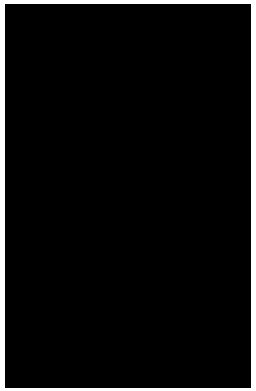
Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141.



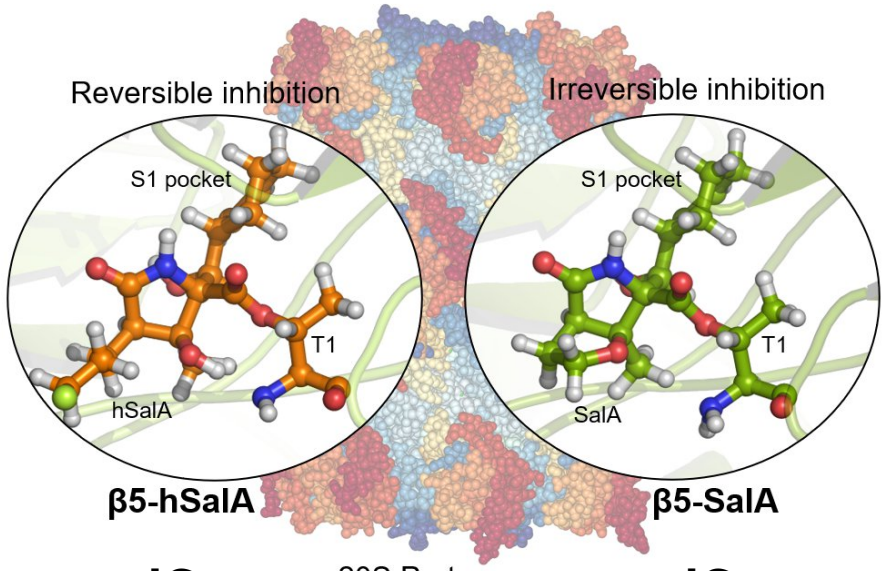
salinosporamide A (SalA)

COVALENT INHIBITION OF PROTEASOME 20S

Nguyen, H. et al. *J. Org. Chem.* **2011**, 76, 2–12.
Groll, M. et al. *Marine Drugs* **2018**, 16, 240.



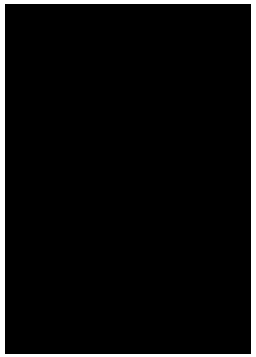
homo-salinosporamide A (hSalA)



IC_{50}
0.7 ± 0.04 nM

IC_{50}
0.8 ± 0.08 nM

Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141.



salinosporamide A (SalA)

What is the origin of different inhibition character of SalA and hSalA?

QM/MM MD METHODS

VTST **Rate constant**

[redacted]

Gibbs free energy barrier

WHAM (Wighted Histogram Analysis Method)

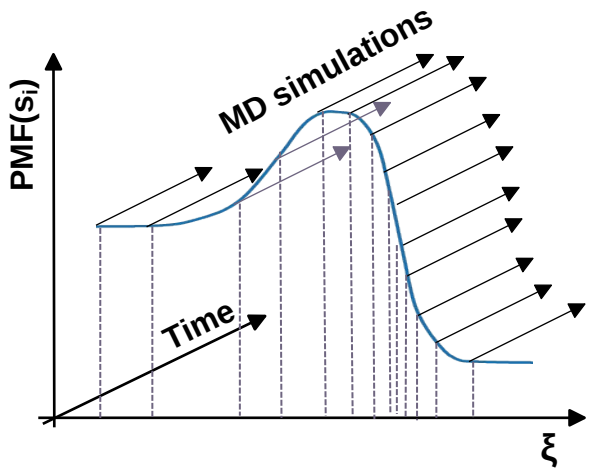
[redacted]

[redacted]

[redacted]

Umbrella Sampling (US)

To study an enzyme catalyzed reaction within the substrate-environment equilibrium approximation:
Transition State Theory (TST)



Biased QM/MM (**AM1/MM**) MD simulation along a distinguished reaction coordinate : **Potential Mean Force**

Spline correction method (M06-2X:AM1/MM)

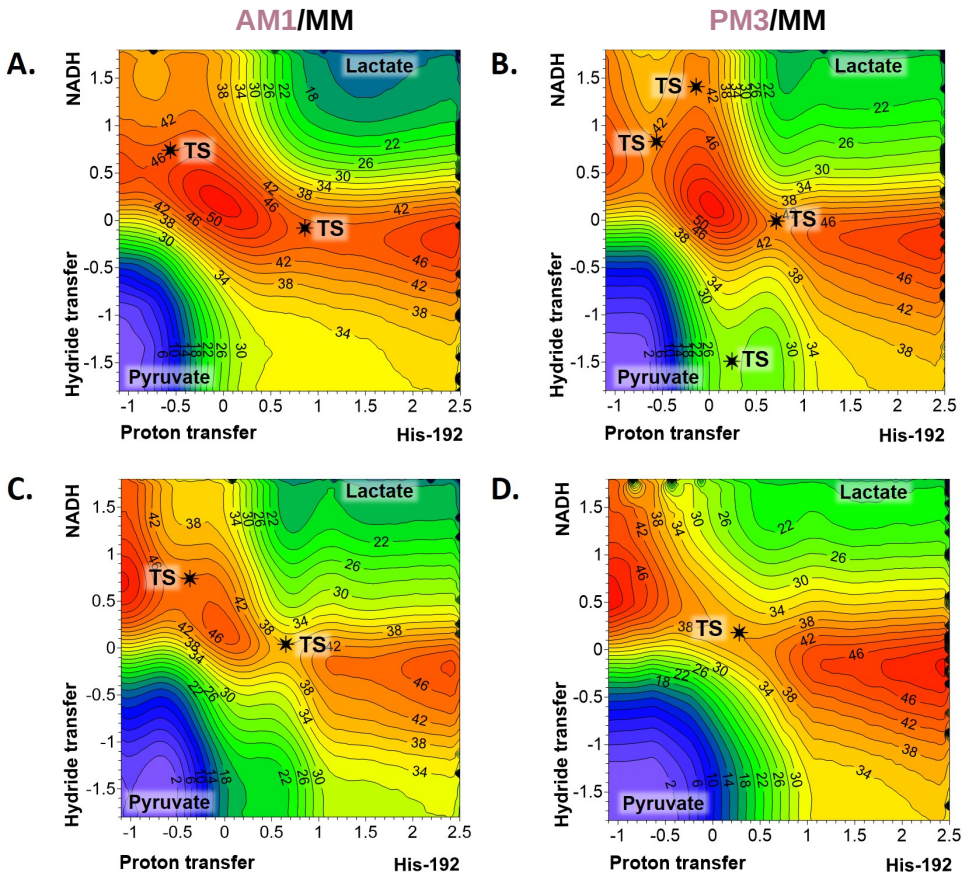
[redacted]

Kumar, S.; Rosenberg, J. M.; Bouzida, D.; Swendsen, R. H.; Kollman, P. A. *J. Comput. Chem.* **1992**, *13*, 1011–1021.

Ruiz-Pernía, J. J.; Silla, E.; Tuñón, I.; Martí, S. *J. Phys. Chem. B* **2006**, *110*, 17663–17670.
Chuang, Y.-Y.; Corchado, J. C.; Truhlar, D. G. *J. Phys. Chem. A* **1999**, *103*, 1140–1149.

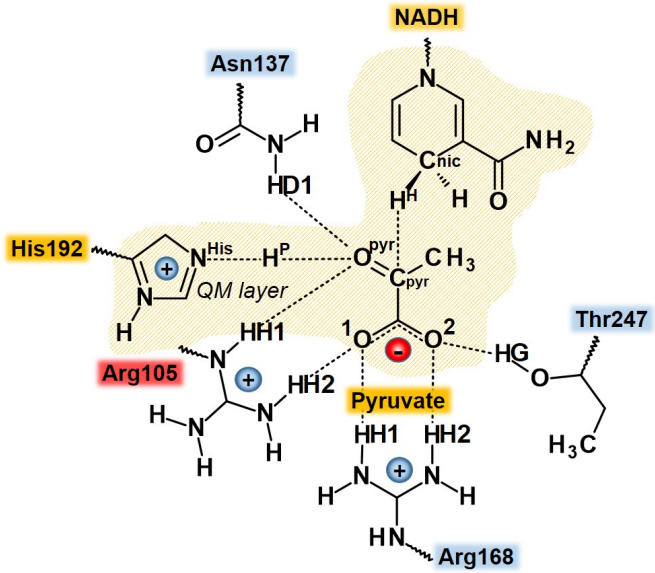
QM/MM MD METHODS

PMF computed at semiempirical level (SE/MM)



Spline correction method (M06-2X/MM)

[redacted]



K. Świderek, I. Tuñón, S. Martí, V. Moliner. ACS Catal. 2015, 5, 1172-1185.

QM/MM MD METHODS

Spline correction method (M06-2X/MM)

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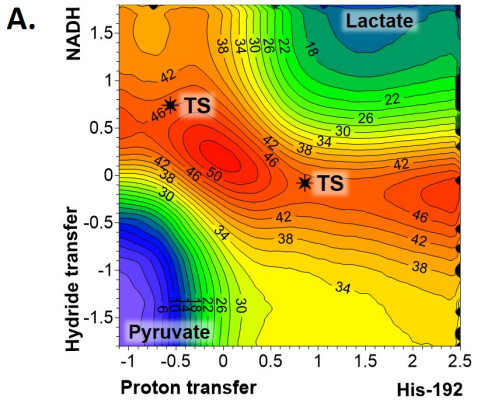
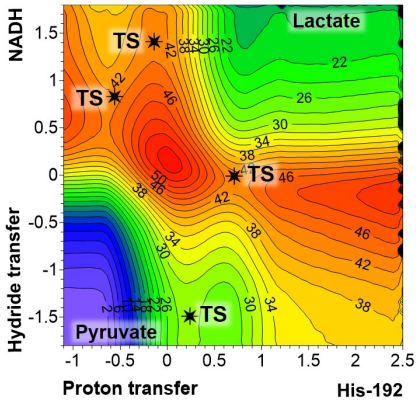
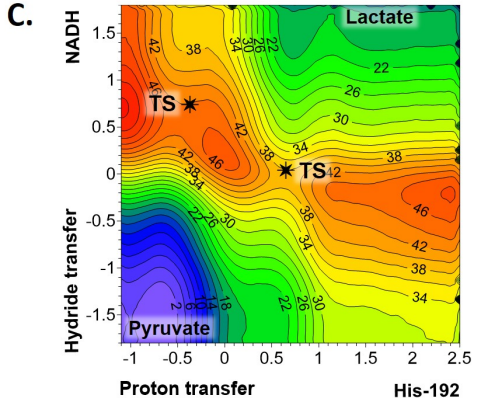
PMF computed at semiempirical level (SE/MM)

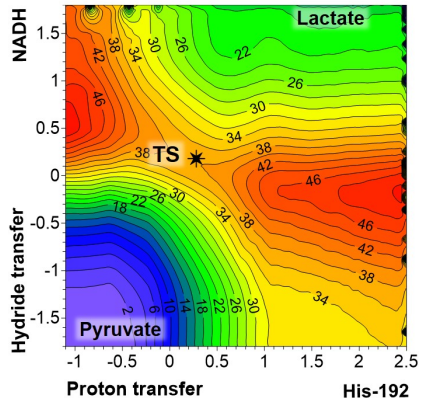
AM1/MM



PM3/MM





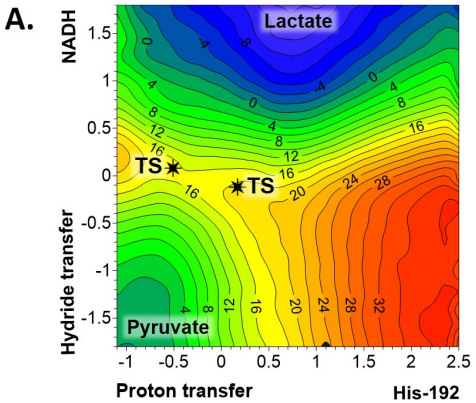


PDDG/MM

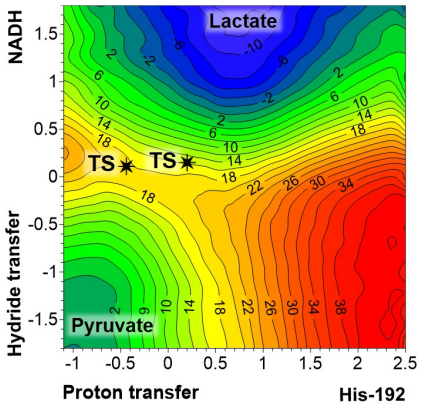
RM1/MM

Corrected PMF at M06-2X/6-31+G(d,p) level

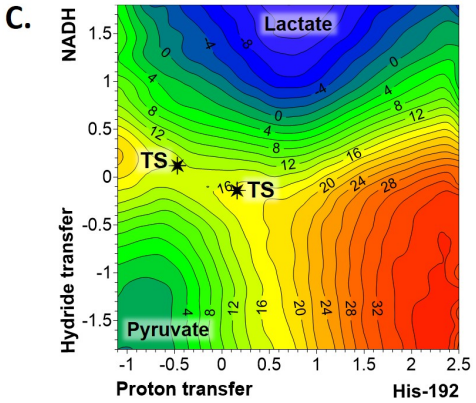
B3LYP:AM1/MM

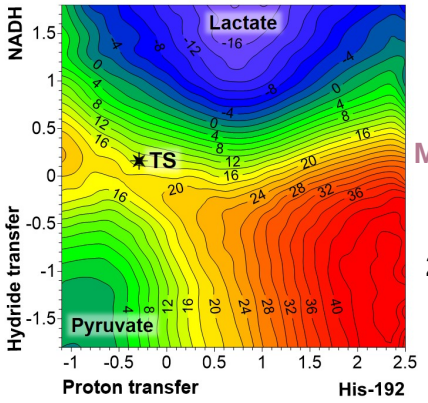


M06-2X:AM1/MM



M06-2X:AM1/MM
19.0 kcal·mol^{-1}
MP2:AM1/MM
19.0 kcal·mol^{-1}





M06-2X:RM1/MM
20.0 kcal·mol^{-1}
MP2:RM1/MM
20.0 kcal·mol^{-1}

mPW1PW91:AM1/MM

MP2:AM1/MM

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QM/MM MD METHODS

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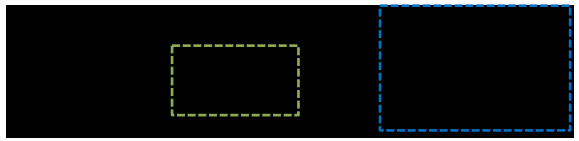


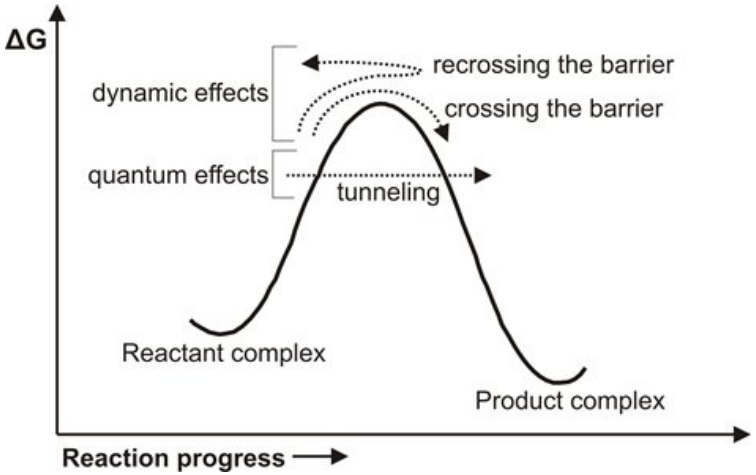
Transmission coefficient

Gibbs free energy barrier

Transmission coefficient

Tunneling

Recrossing



Equilibium and Kinetic Isotope Effects

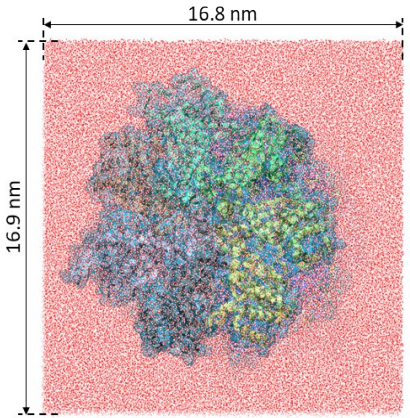
$$IE = \frac{\left(\frac{Q_a}{Q_b}\right)_L}{\left(\frac{Q_a}{Q_b}\right)_H} e^{-1/RT(\Delta ZPE_L - \Delta ZPE_H)}$$

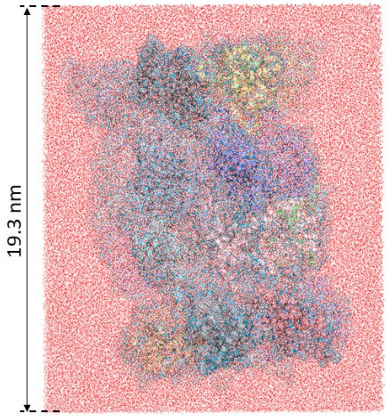
Translational, rotational and vibrational contribution

$$KIE = KIE^{QC} \times \frac{\gamma_L}{\gamma_H} \times \frac{\kappa_L}{\kappa_H} = KIE^{QC} \times KIE^{\gamma} \times KIE^{\kappa}$$

QM/MM MD METHODS

Model for MM MD simulations

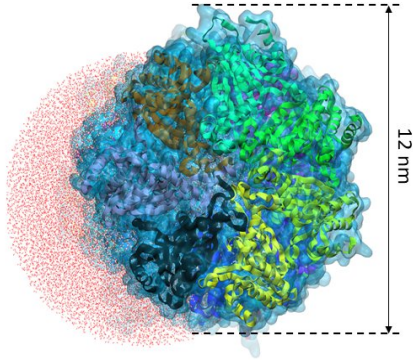


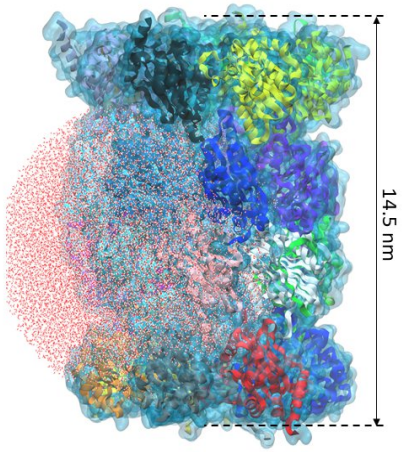


527 831 atoms in total

Model for QM/MM MD simulations

60 Å water sphere centred on Thr1





152 390 atoms

ChemComm

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Cite this: *Chem. Commun.*, 2017, 53, 284

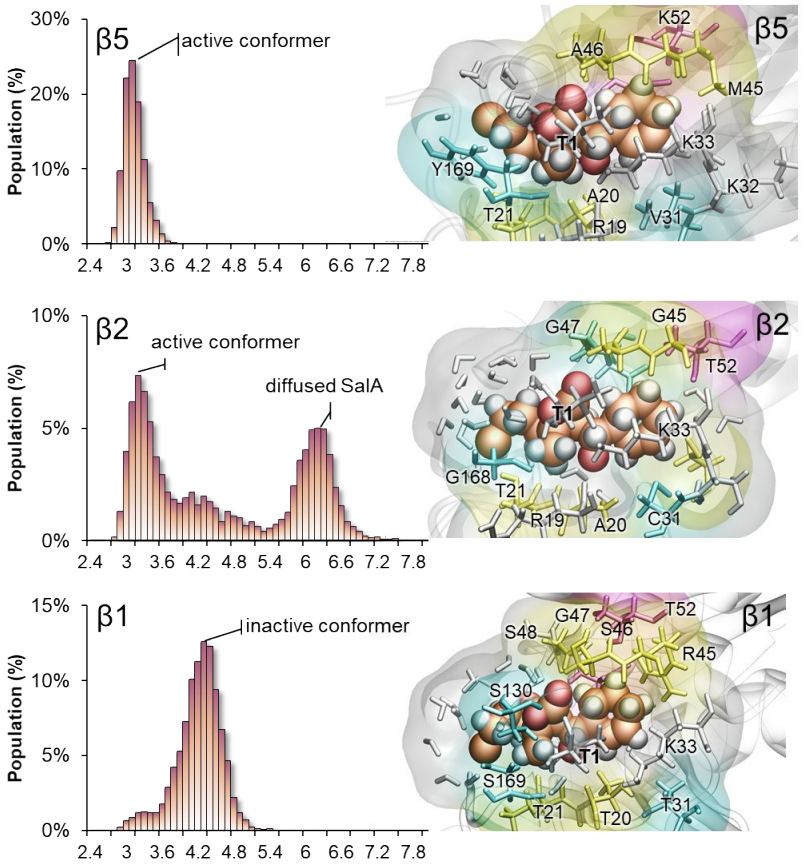
Computational tools for the evaluation of laboratory-engineered biocatalysts

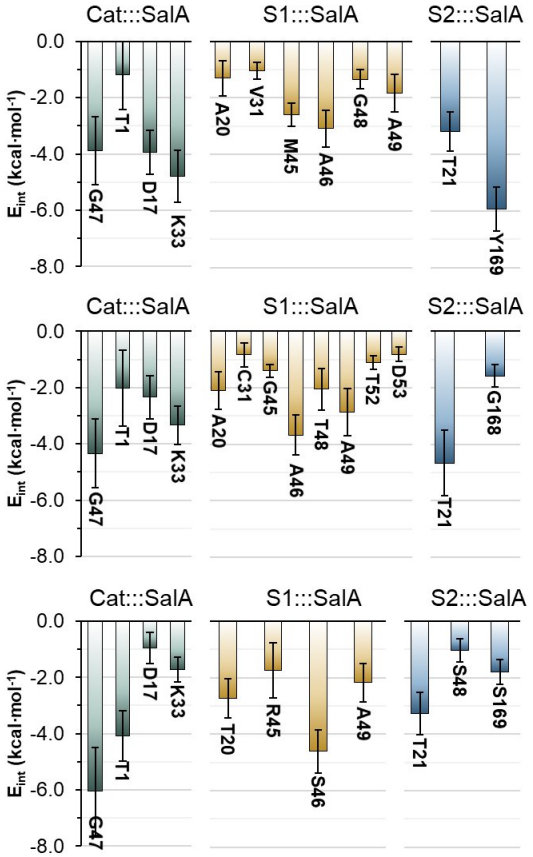
Adrian Romero-Rivera,[a] Marc Garcia-Borràs[b] and Sílvia Osuna*[a]

	Accounting for:				Useful for studying:							References:	
Computational strategy	QM	MM	Active site	Whole enzyme	Protein flexibility	Enantioselectivity/ Stereoselectivity	Substrate scope	Reaction mechanism	Conformational dynamics	Effect of distal mutations	Computational cost	Computational strategy	Key examples
Cluster model	✔	✗	✔	✗	✗	✔	✔	✔	✗	✗	+	89, 90	91-93
Theozyme	✔	✗	✔	✗	✗	✔	✔	✔	✗	✗	+	84-87	88
QM/MM	✔	✔	✔	✔	✗	✔	✔	✔	✗	✗	++	94-96	97, 98
QM/MM-MD	✔	✔	✔	✔	✔	✔	✔	✔	✗	✗	++++	99	99
EVB	✔	✔	✔	✔	✗	✔	✔	✔	✗	✗	++	100-102	103, 104
MD	✗	✔	✔	✔	✔	✔	✔	✗	✔	✔	+	105-108	109, 110
MC	✗	✔	✔	✔	✔	✔	✔	✗	✔	✔	+	111, 112	113

RECOGNITION STEP of SalA

$$E + SalA \overset{K_i}{\leftrightarrow} E\square SalA \xrightarrow{k_{inact}} E{-}PC$$

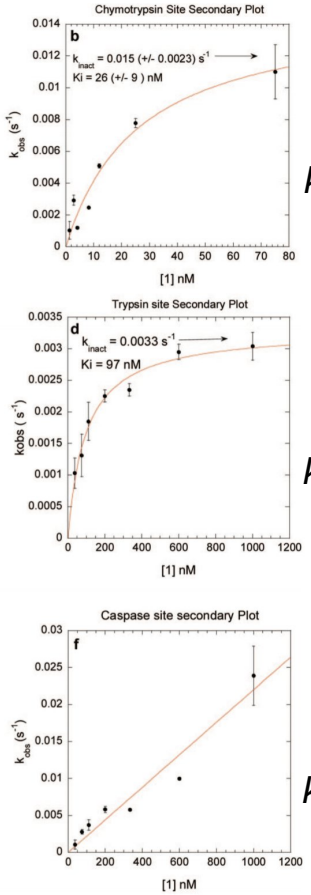




K_i = 23 ± nM[a]
IC_{50} = 2.0 ± 0.3 nM[a]
IC_{50} = 0.8 ± 0.08[b]
E_{int} = -54.1 ± 3.1 kcal·mol

K_i = 97 ± nM[a]
IC_{50} = 59 ± 1 nM[a]
IC_{50} = 39 ± 7[b]
E_{int} = -45.8 ± 3.3 kcal·mol

K_i > 1000 nM[a]
IC_{50} = 2600 ± 200 nM[a]
IC_{50} =111 ± 22[b]
E_{int} = -42.6 ± 2.8 kcal·mol



Experimental data

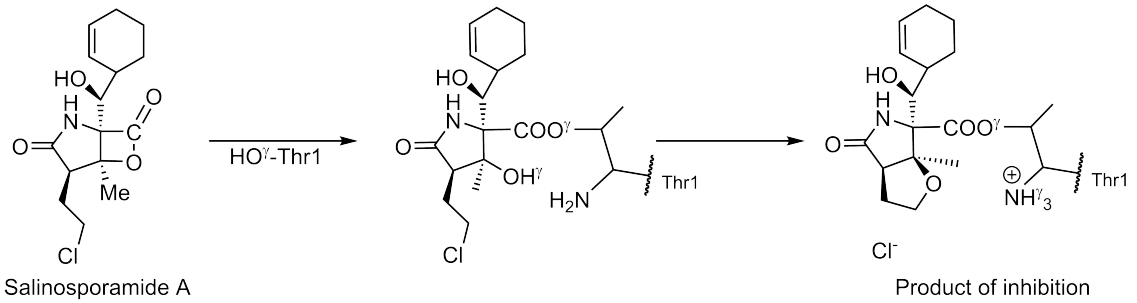
k_{inact} = 0.015 s^{-1} [b]

k_{inact} = 0.0033 s^{-1} [b]

k_{inact} >> 0.02 s^{-1} [b]

Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.
(a) Manam, R. R. et al. *J. Med. Chem.* **2008**, *51*, 6711–6724.
(b) Groll, M. et al. Mar. Drugs **2018**, 16, 240–249.

20S PROTEASOME INHIBITION WITH SalA

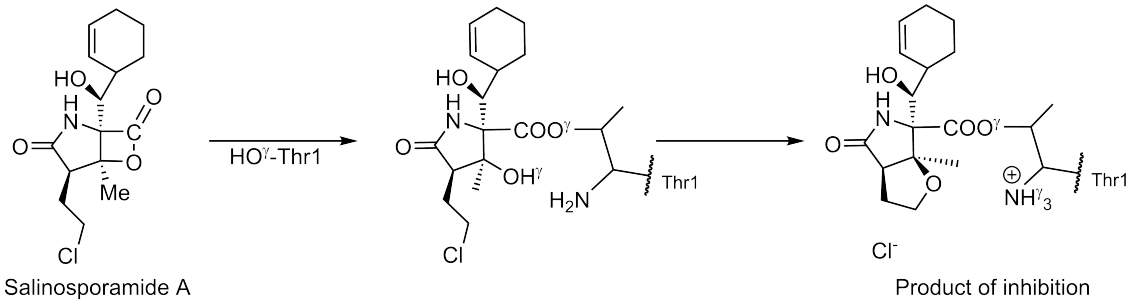


Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141
Macherla, V.R. et al. *J. Med. Chem.* **2005**, 48, 3684-3687

SalA-assisted mechanism

$$E + SalA \overset{K_i}{\leftrightarrow} E\square SalA \xrightarrow{k_{inact}} E{-}PC$$

20S PROTEASOME INHIBITION WITH SalA



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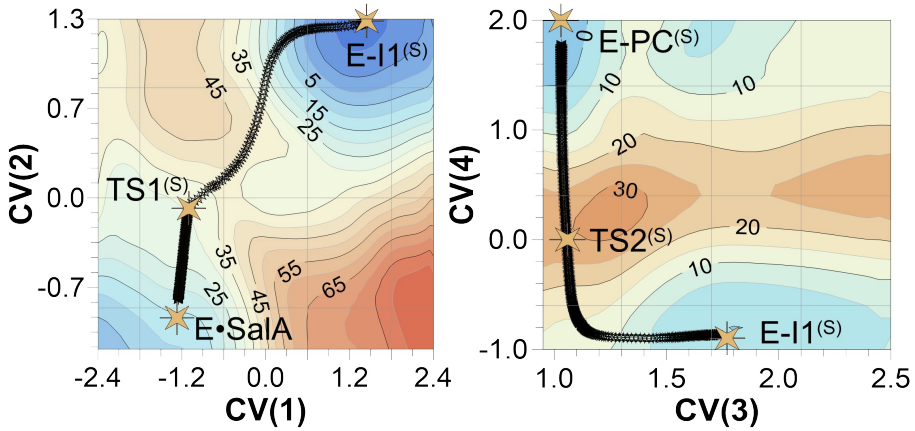
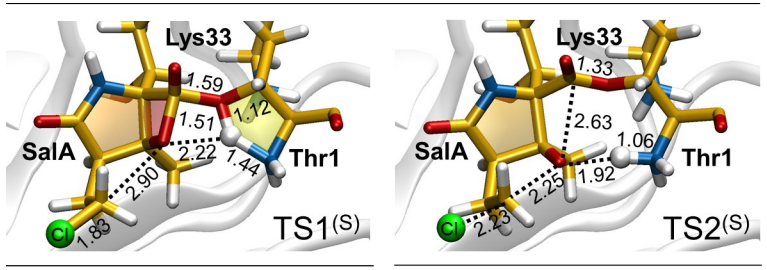
Macherla, V.R. et al. *J. Med. Chem.* **2005**, 48, 3684-3687

SalA-assisted mechanism

2D-PMF M06-2X:AM1/MM

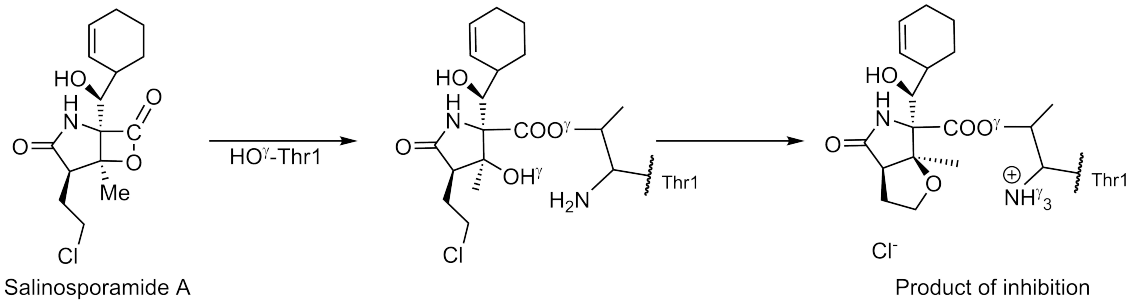


Applied collective variables are defined as follow:
CV(1) = $d(O^{\gamma Thr1}–H^{\gamma Thr1}) – d(H^{\gamma Thr1}–O2^{SalA})$, CV(2) = $d(O2^{SalA}–C1^{SalA}) – d(O^{\gamma Thr1}–C1^{SalA})$,
CV(3) = $d(H^{\gamma Thr1}–N^{Thr1})$, CV(4) = $d(O2^{SalA}–C3^{SalA}) – (C3^{SalA}–Cl)$,



TS structures at M06-2X/MM

20S PROTEASOME INHIBITION WITH SalA



Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141
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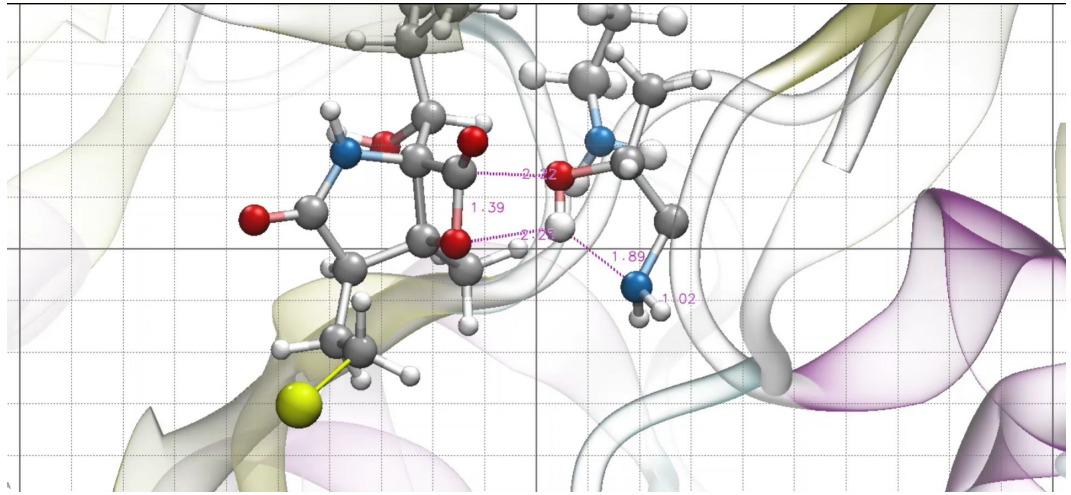
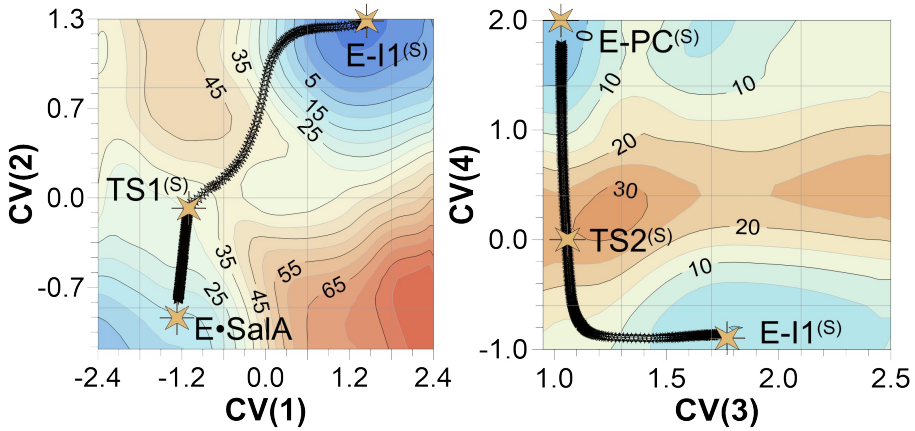
SalA-assisted mechanism



2D-PMF M06-2X:AM1/MM



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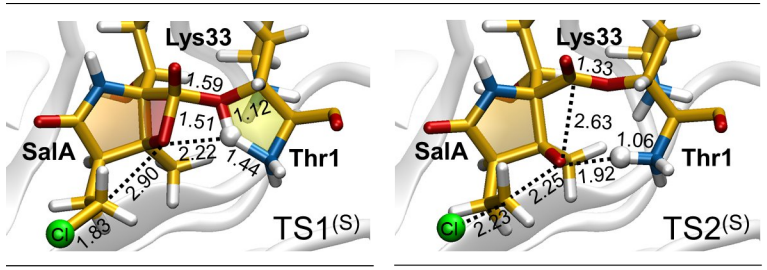
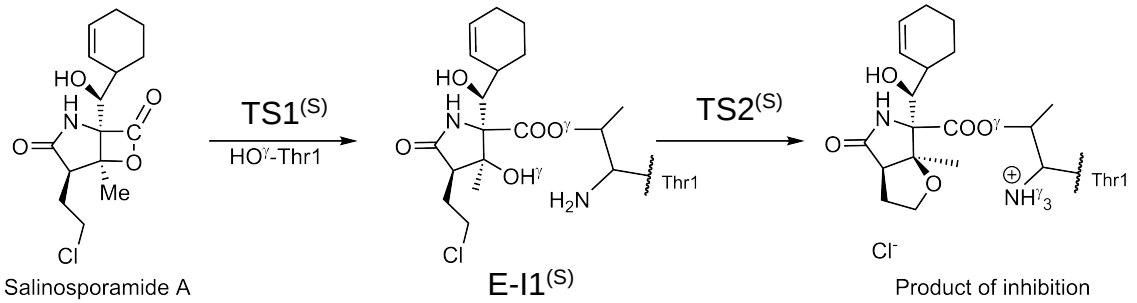


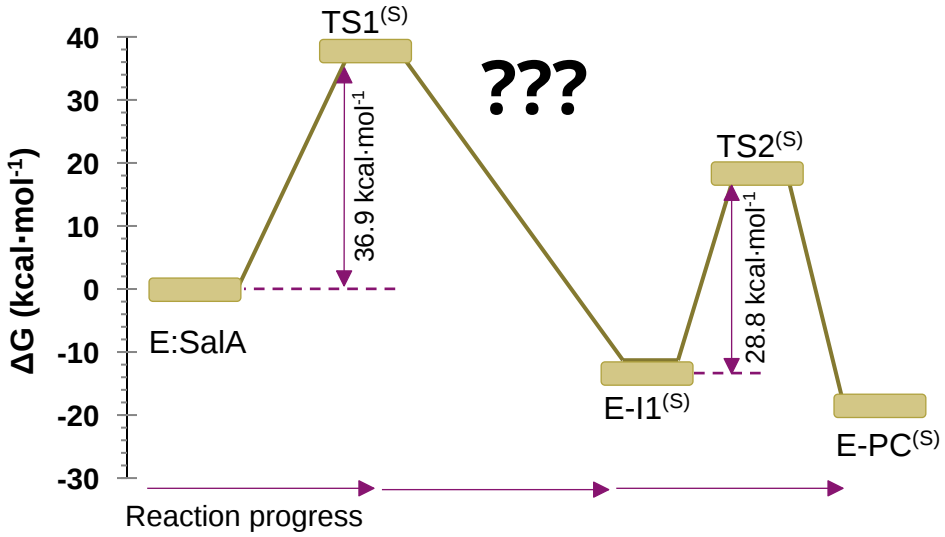
TS structures at M06-2X/MM

20S PROTEASOME INHIBITION WITH SalA

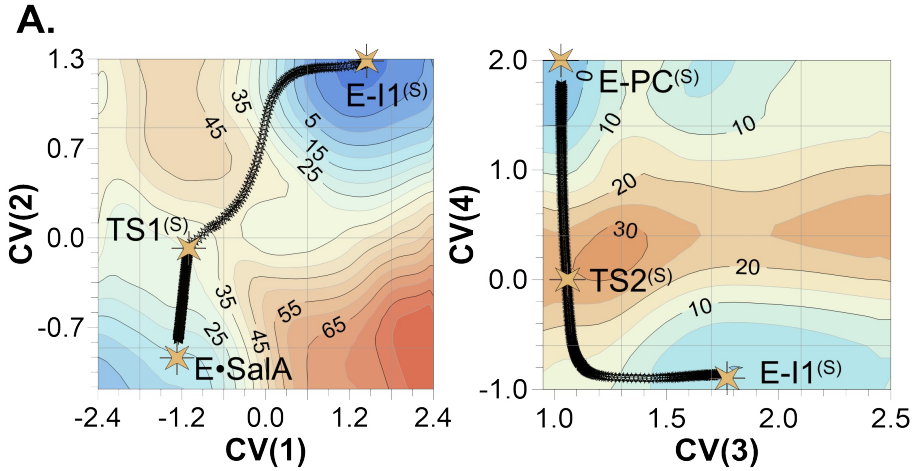


Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141
Macherla, V.R. et al. *J. Med. Chem.* **2005**, 48, 3684-3687

SalA-assisted mechanism



2D-PMF M06-2X:AM1/MM



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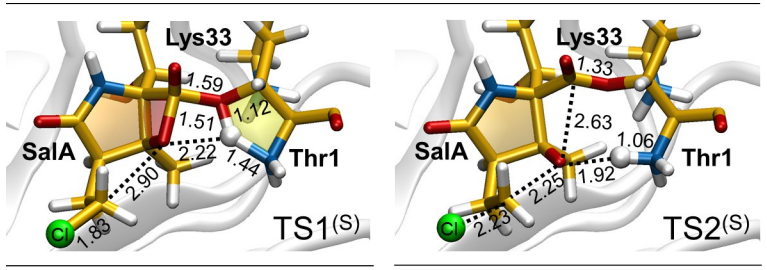
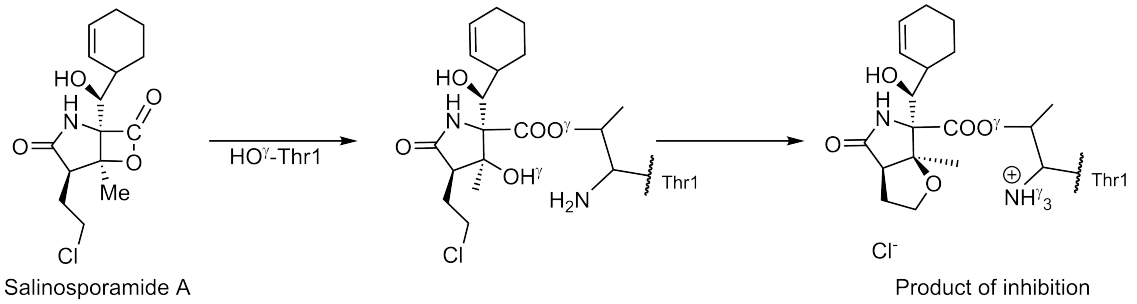


TS structures at M06-2X/MM

20S PROTEASOME INHIBITION WITH SalA



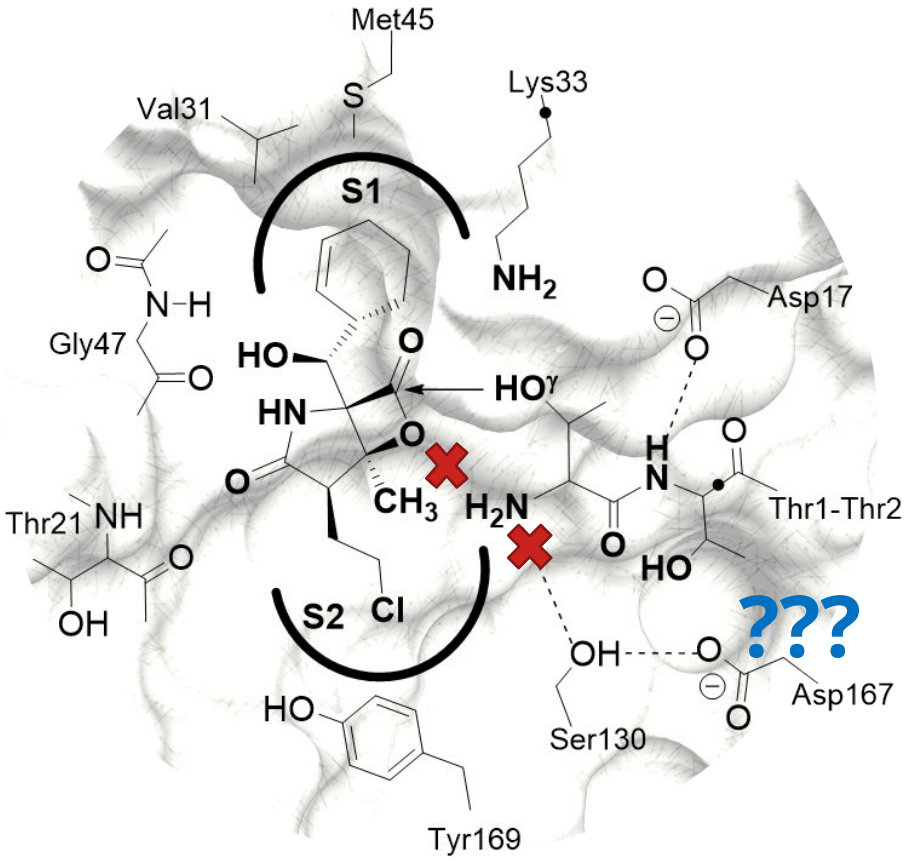
Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141
Macherla, V.R. et al. *J. Med. Chem.* **2005**, 48, 3684-3687

SalA-assisted mechanism

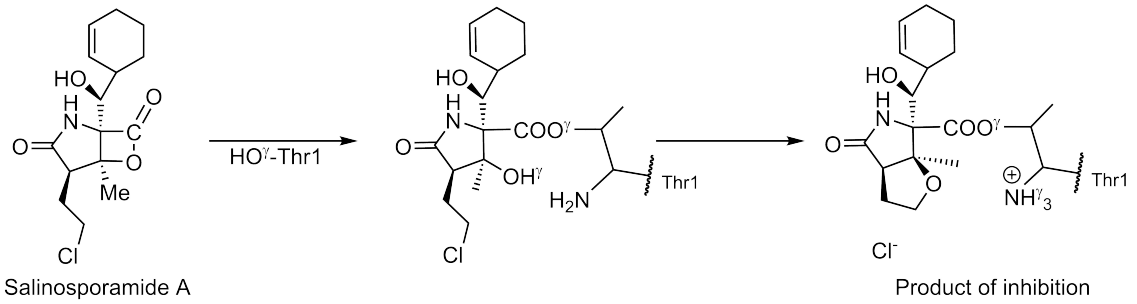
*„X-ray data on the **β5-D167N** mutant indicate that the β5 propeptide is hydrolysed, but due to reorientation of Ser129OH, the interaction with Asn166-O$^{\delta}$ is disrupted"*

Huber E.M. et al. *Nat. Commun.* **2016**, 7, 10900

Active site of the β5 subunit



20S PROTEASOME INHIBITION WITH SalA



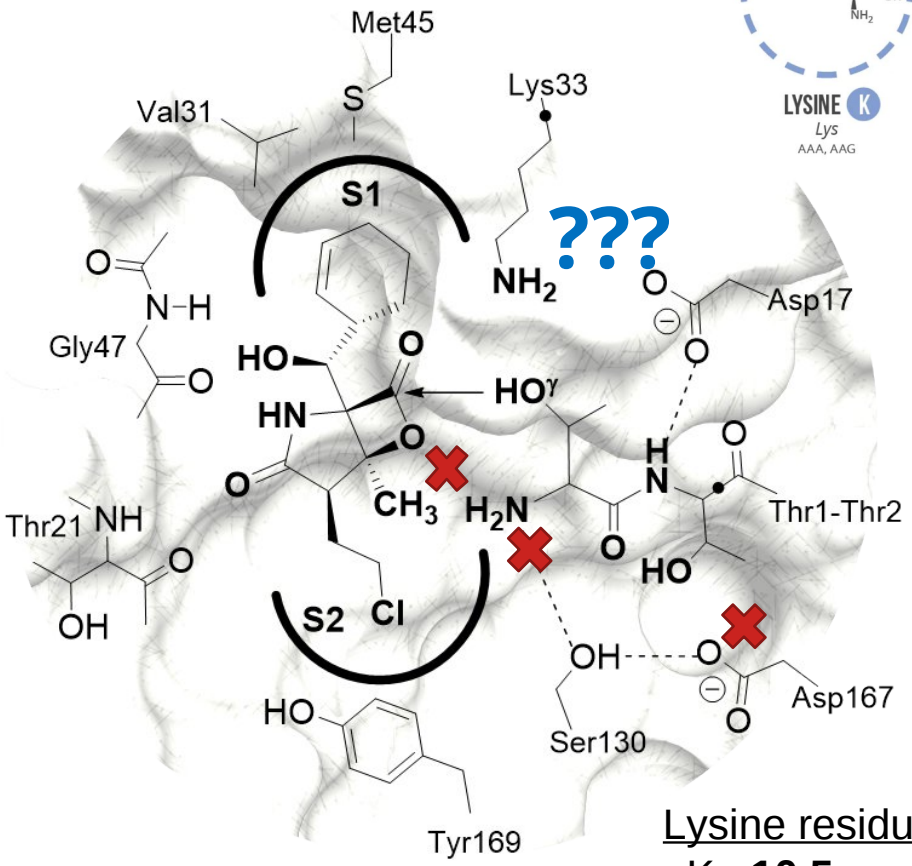
Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141
Macherla, V.R. et al. *J. Med. Chem.* **2005**, 48, 3684-3687

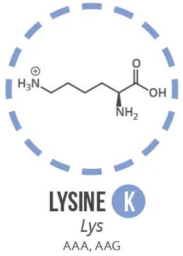
SalA-assisted mechanism

*„The proof for the key function of Lys33 was obtained from the **β5-K33A** mutant, with the propeptide expressed separately from the main subunit. The Thr1 N terminus of this mutant is not blocked by the propeptide, yet its catalytic activity is reduced by ~83%."*

Huber E.M. et al. *Nat. Commun.* **2016**, 7, 10900

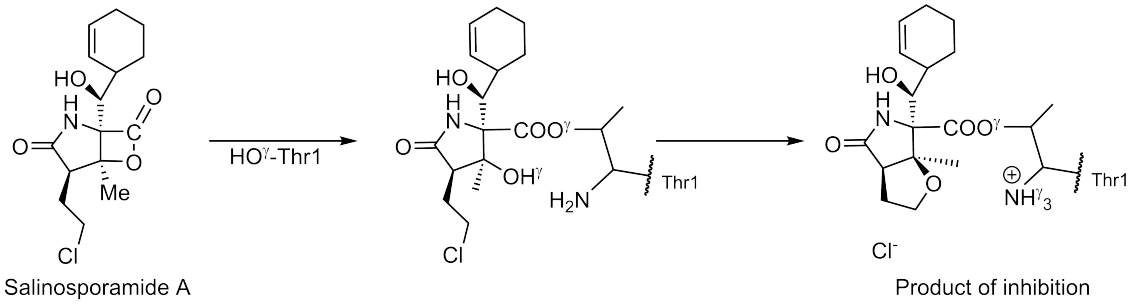
Active site of the β5 subunit





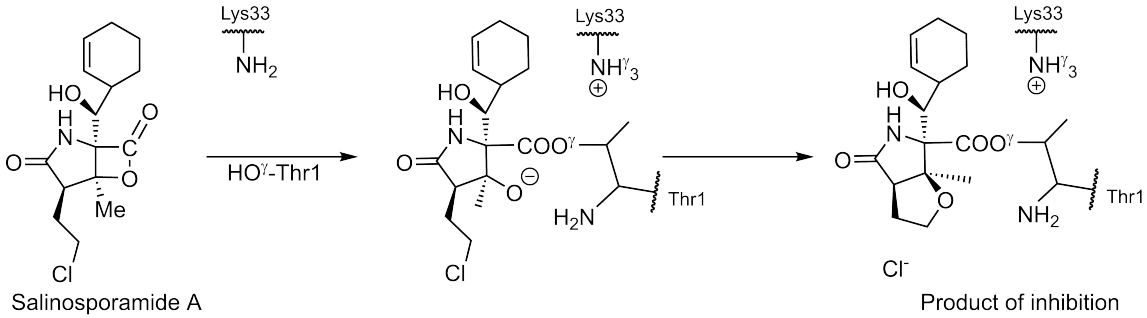
<u>Lysine residue</u>:
pKa **10.5**
pKa$^{theor.}$ **9.48**

20S PROTEASOME INHIBITION WITH SalA



Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141
Macherla, V.R. et al. *J. Med. Chem.* **2005**, 48, 3684-3687

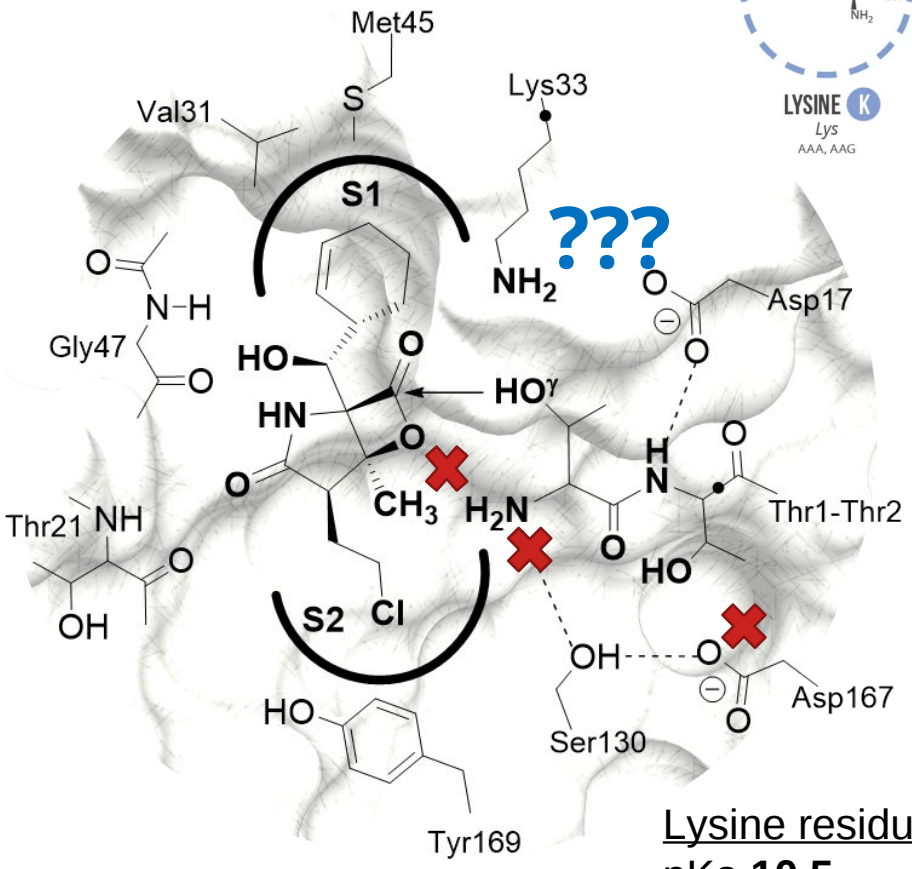
SalA-assisted mechanism

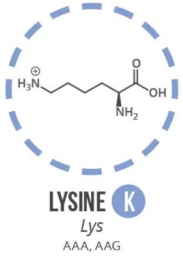


Huber E.M. et al. *Nat. Commun.* **2016**, 7, 10900
Groll, M. et al. *Marine Drugs* ***2018**, 16, 240*

Lys-assisted mechanism

Active site of the β5 subunit





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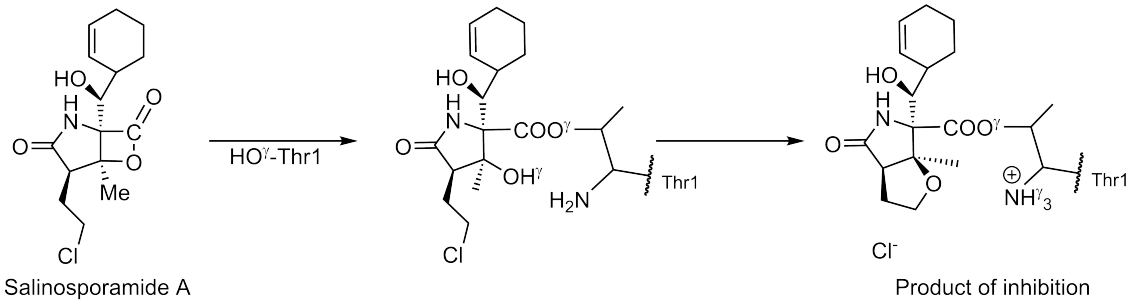
20S PROTEASOME INHIBITION WITH SalA



Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141
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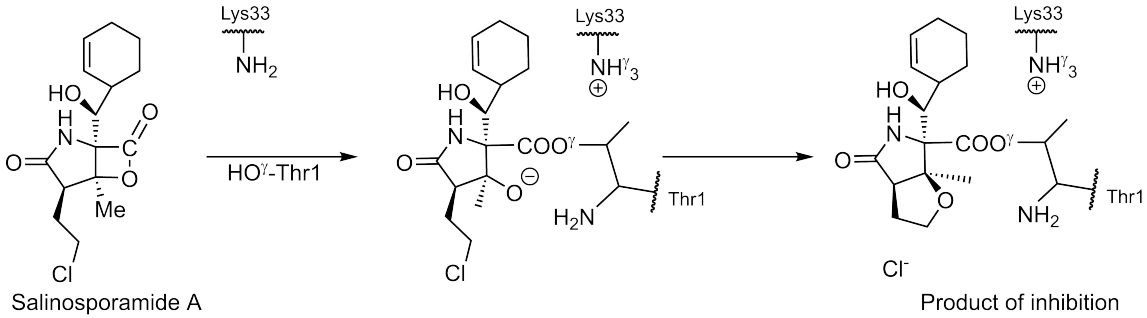
SalA-assisted mechanism



Huber E.M. et al. *Nat. Commun.* **2016**, 7, 10900
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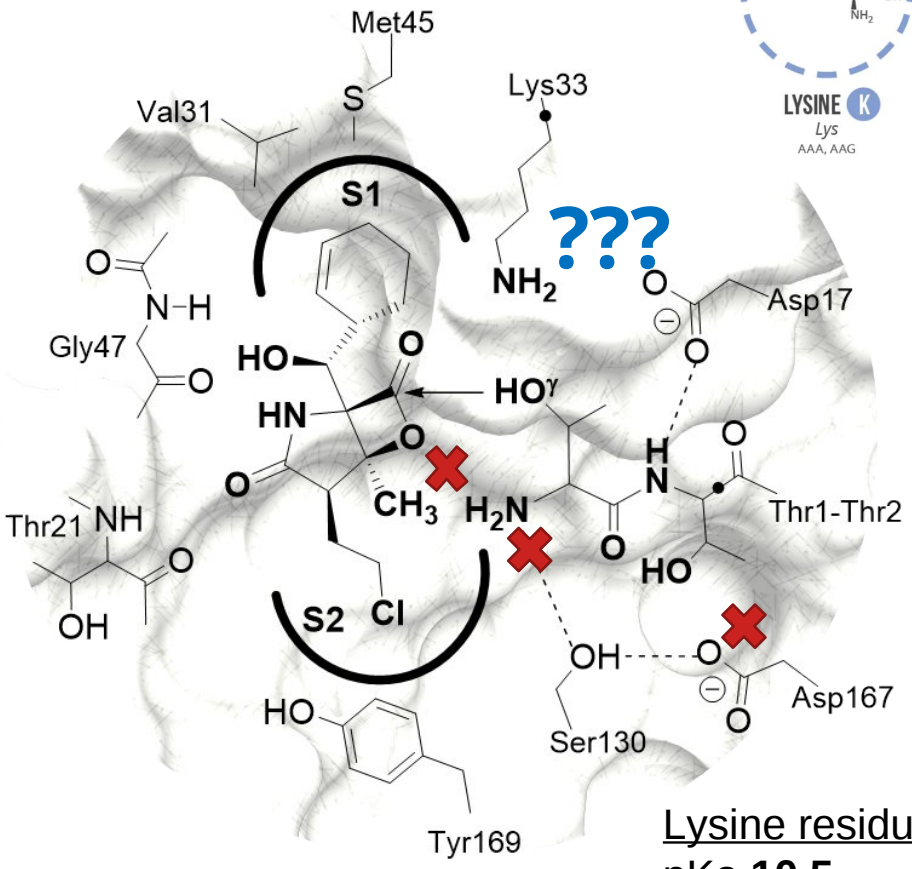
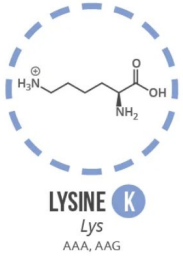
Lys-assisted mechanism

Active site of the β5 subunit





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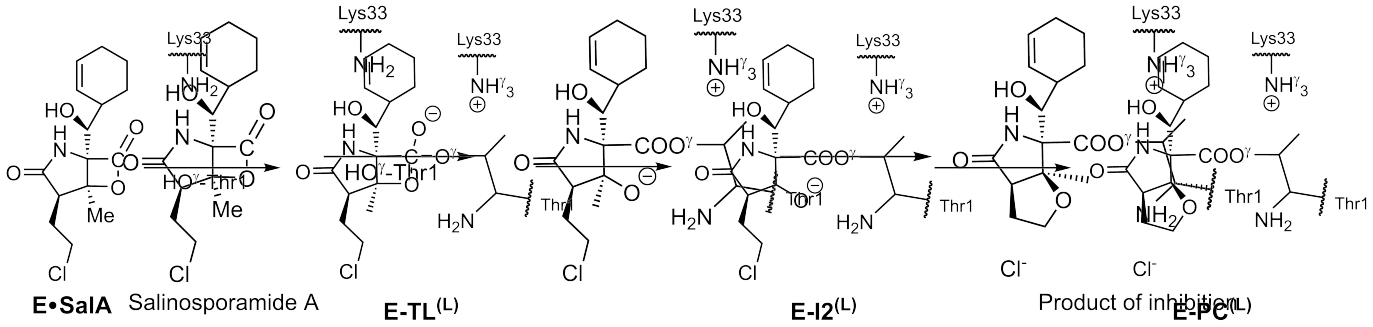
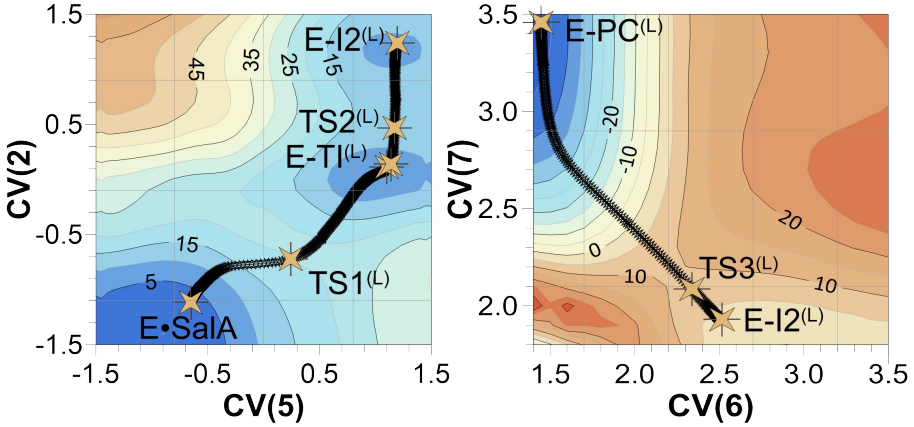
20S PROTEASOME INHIBITION WITH SalA



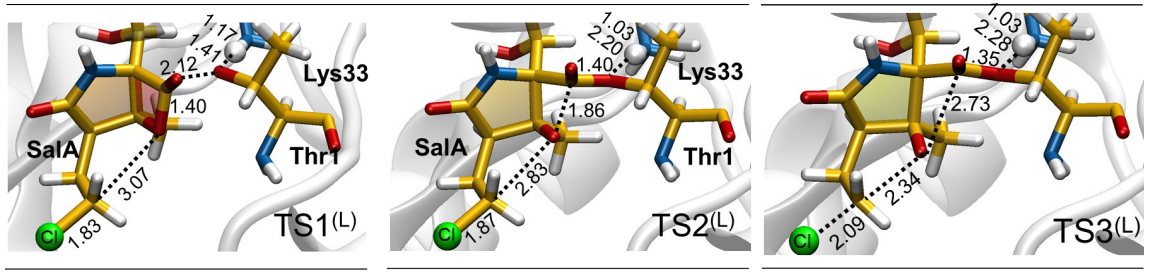
Huber E.M. et al. *Nat. Commun.* **2016**, *7*, 10908.
Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.
Groll, M. et al. *Marine Drugs* ***2018***, *16, 240*

Lys-assisted mechanism

2D-PMF M06-2X:AM1/MM

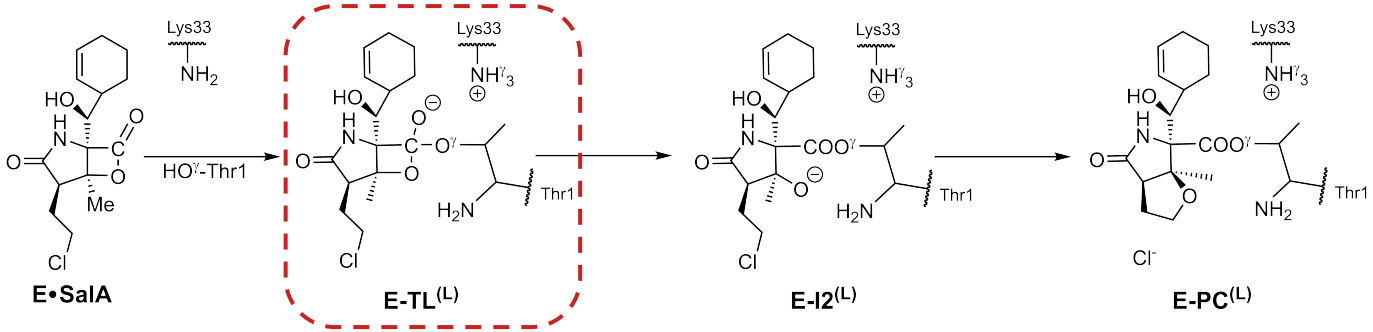


Applied collective variables are defined as follow:
CV(2) = $d(O2^{SalA}–C1^{SalA}) – d(O^{\gamma Thr1}–C1^{SalA})$, CV(5) = $d(O^{\gamma Thr1}\text{-}H^{\gamma Thr1}) – d(H^{\gamma Thr1}\text{-}N^{\zeta Lys33})$,
CV(6) = $d(O2^{SalA}\text{-}C3^{SalA})$, and CV(7) = $d(C3^{SalA}\text{-}Cl)$.



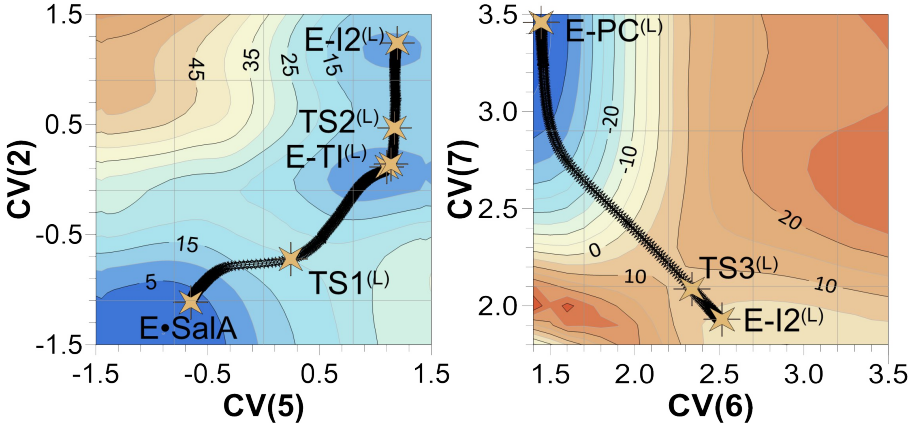
TS structures at M06-2X/MM

20S PROTEASOME INHIBITION WITH SalA



Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.

2D-PMF M06-2X:AM1/MM



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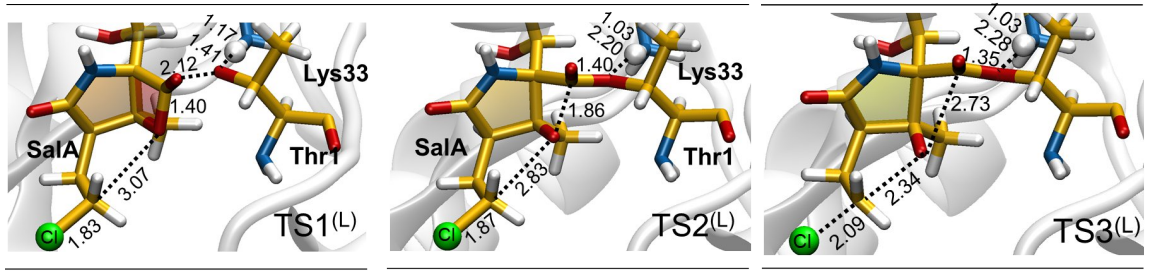
The existence of E-TI is especially interesting since the formation of a tetrahedral intermediate was previously excluded based on experimental studies on β-lactone inhibitors in **serine proteases**.

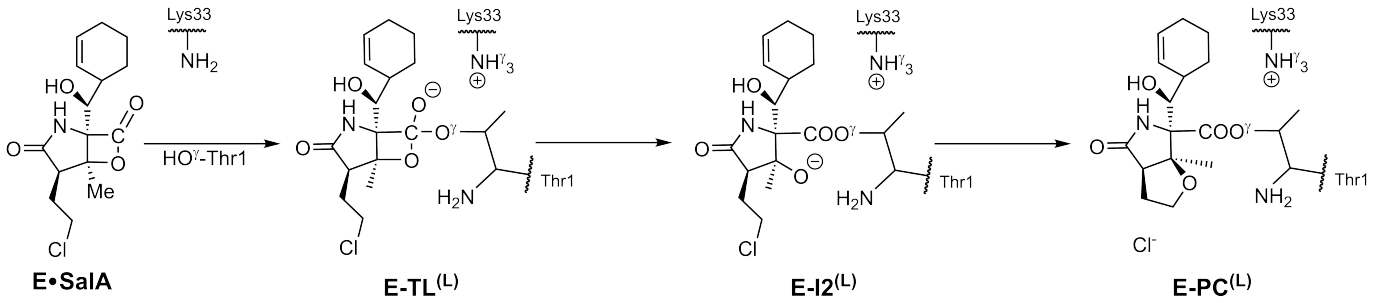
It was suggested that the tetrahedral TSs generated in the acylation reaction may **not be stabilized**, and thus the relief of high ring strain energy associated with the lactone ring cleavage may constitute the driving force for the acylation reaction.

Kim, D. H. et al. *Bioorganic Med. Chem.* **2002**, 10, 2553–2560



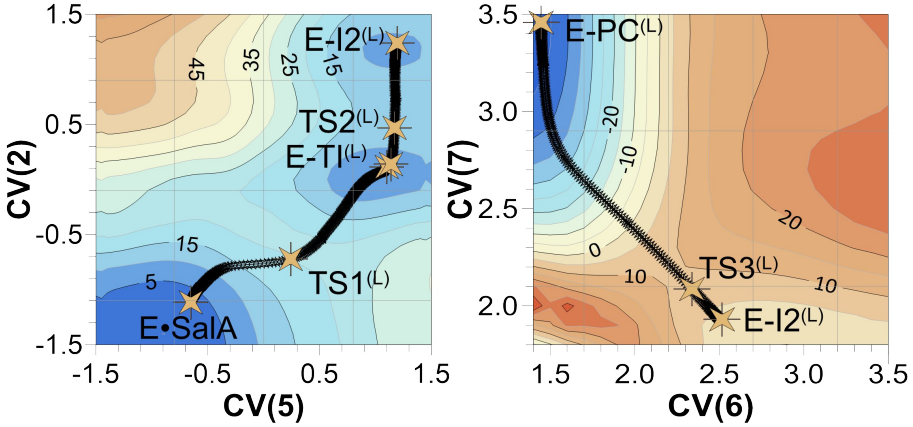
TS structures at M06-2X/MM

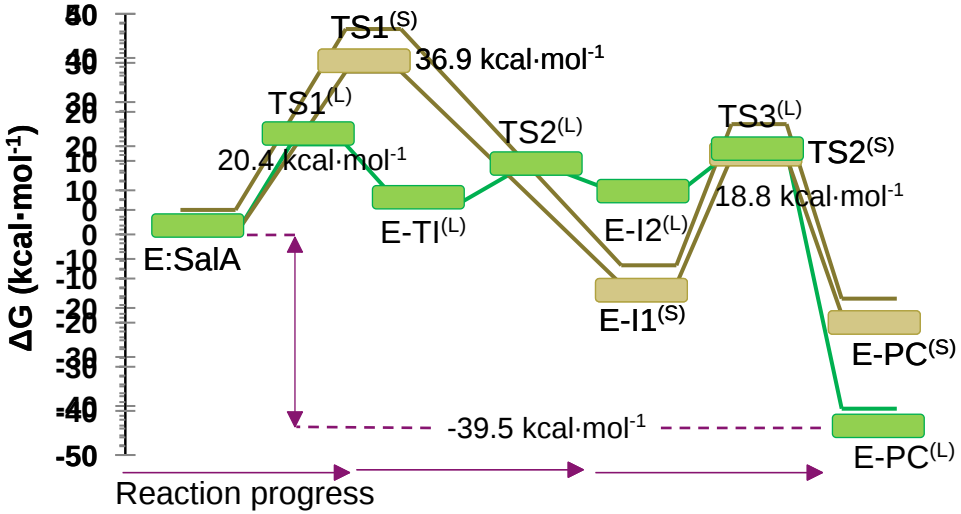
20S PROTEASOME INHIBITION WITH SalA



Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.

2D-PMF M06-2X:AM1/MM





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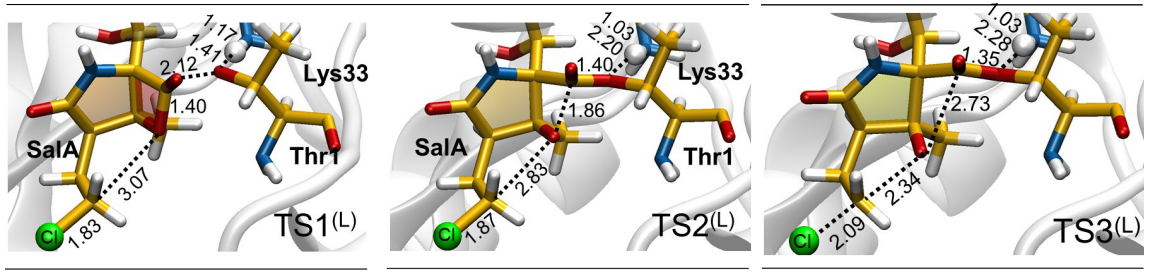
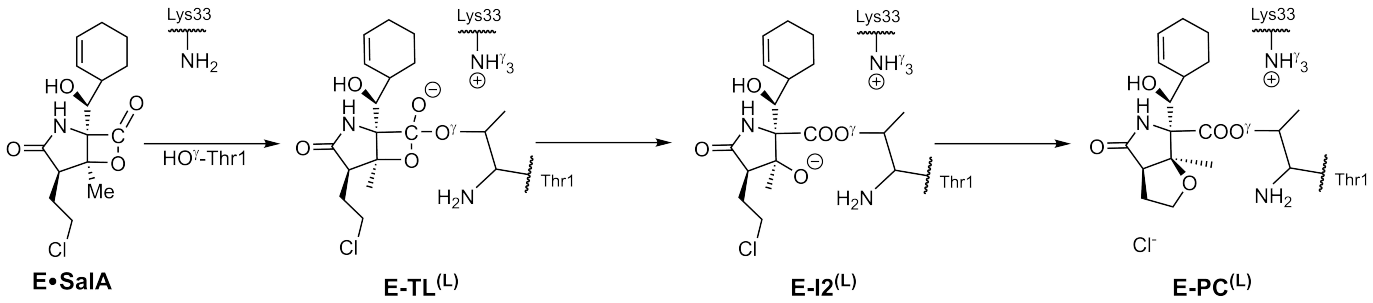


TS structures at M06-2X/MM

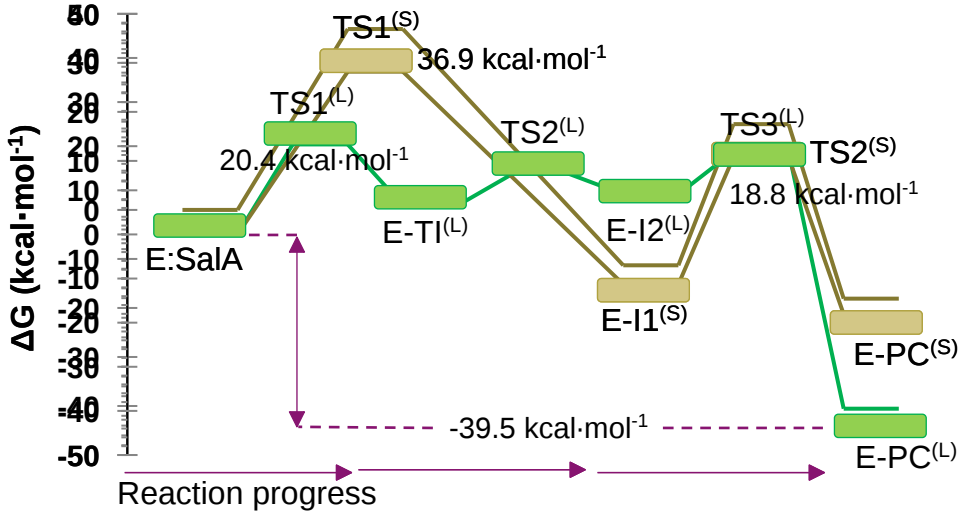
Exp. k_{inact} of 0.015 s^{-1}
(20.9 kcal·mol^{-1} at T= 37 ℃)

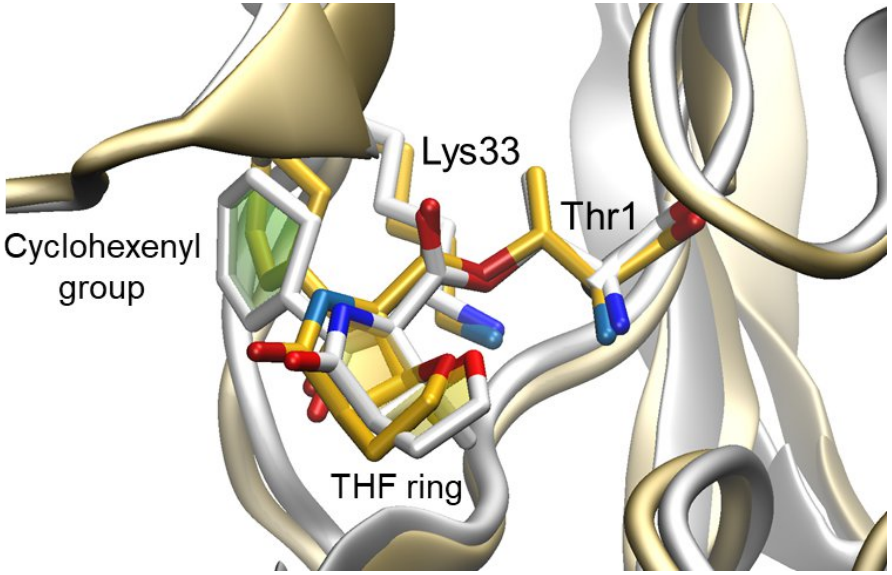
Manam, R. R et al. J. Med. Chem. **2008**, 51, 6711– 6724.

20S PROTEASOME INHIBITION WITH SalA



Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.

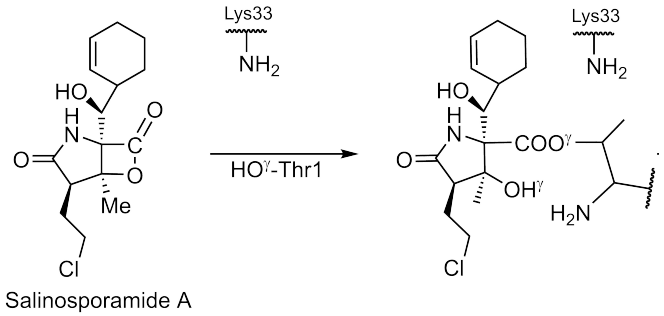




Overlay of the crystal structure of 20S proteasome in complex with SalA with PDB code 2FAK, (in grey) and the product complex obtained from our QM/MM MD studies of the Lys33-assisted reaction pathway (in orange).

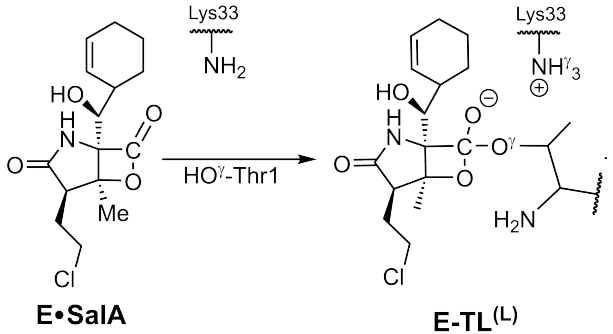
Exp. k_{inact} of 0.015 s^{-1}
(20.9 kcal·mol^{-1} at T= 37 ℃)

20S PROTEASOME INHIBITION WITH SalA



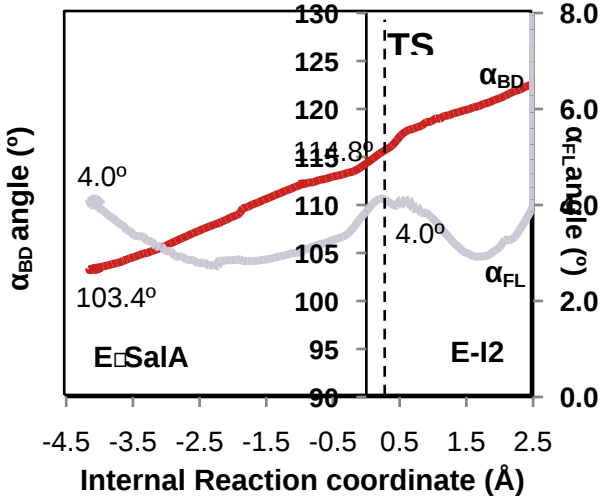
Salinosporamide A

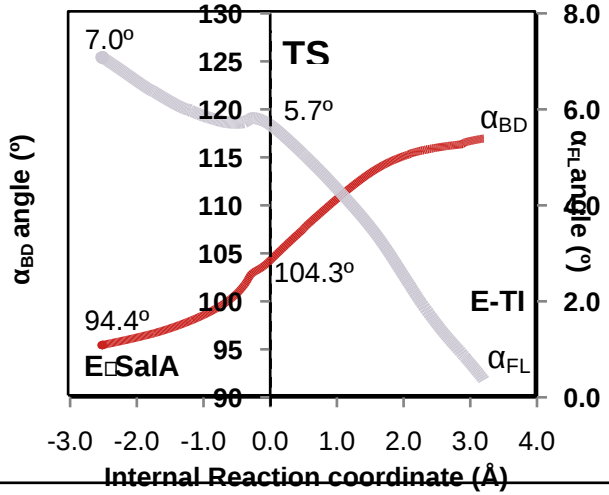
Groll, M. et al. *J. Am. Chem. Soc.* **2006**, 128, 5136-5141
Macherla, V.R. et al. *J. Med. Chem.* **2005**, 48, 3684-3687



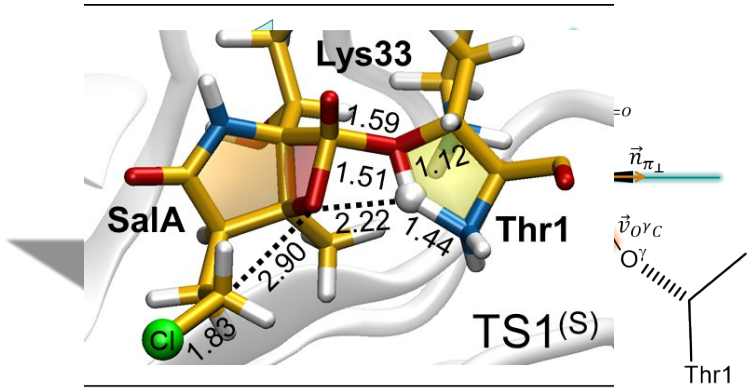
E•SalA **E-TL(L)**

Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.

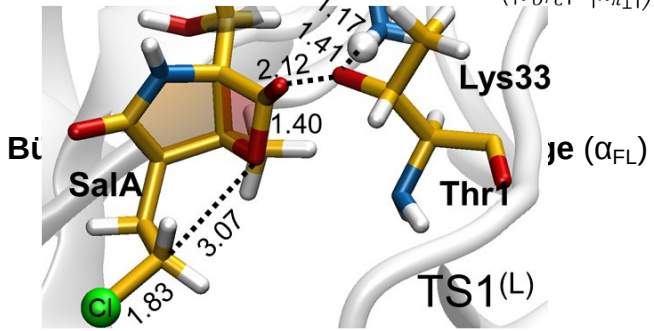




Nucleophilic attack trajectory

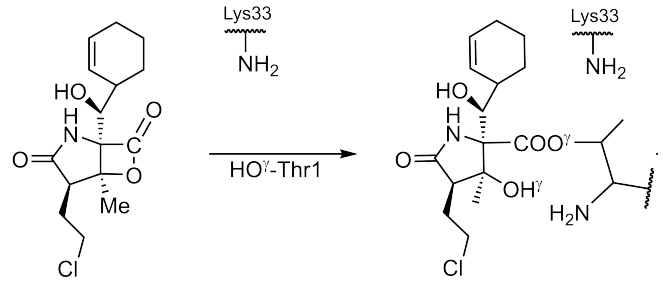


$\alpha_{BD} = \measuredangle(Nu: -C - O)$ $\alpha_{FL} = \arcsin\left(\frac{|\vec{v}_{O^{\gamma}C} \cdot \vec{n}_{\pi_\perp}|}{|\vec{v}_{O^{\gamma}C}| \cdot |\vec{n}_{\pi_\perp}|}\right)$



Bürgi, H. B.et al. *J. Am. Chem. Soc.* **1973**, *95*, 5065–5067.
Bürgi, H. B.et al. *Tetrahedron* **1974**, *30*, 1563–1572.
Heathcock, C.H. Aldrichimica Acta, **1990**, 23, 94-111.

20S PROTEASOME INHIBITION WITH SalA



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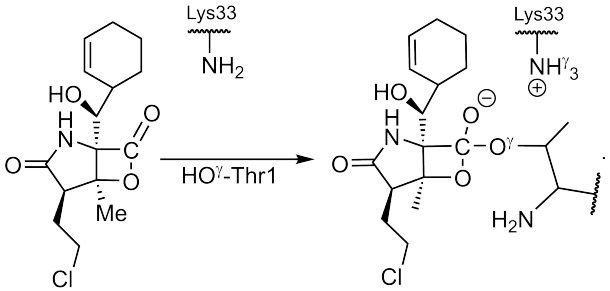
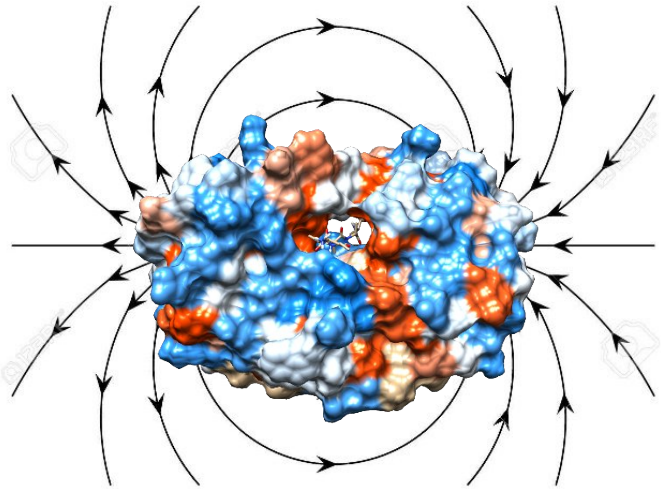
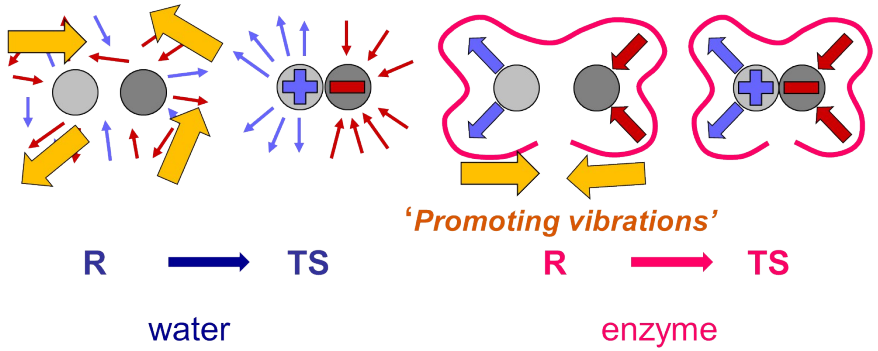


E•SalA **E-TL$^{(L)}$**

Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.

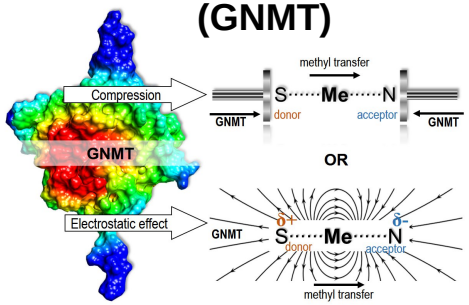
Electrostatic effects

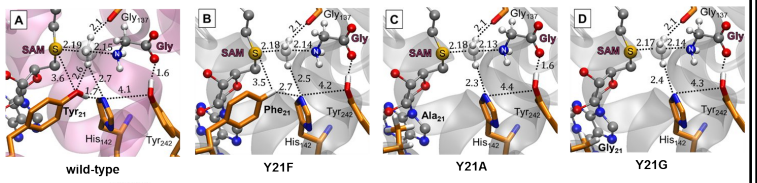


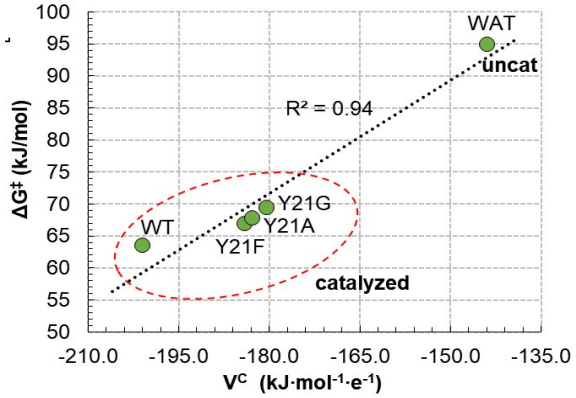


Adamczyk AJ et al. *PNAS* **2011**, 108, 14115-14120.
Moliner V. *PNAS* **2011**, 108, 15013-15014.

Glycine N-mehtyltransferase (GNMT)

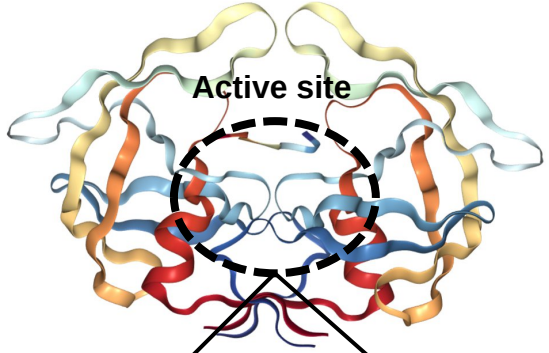


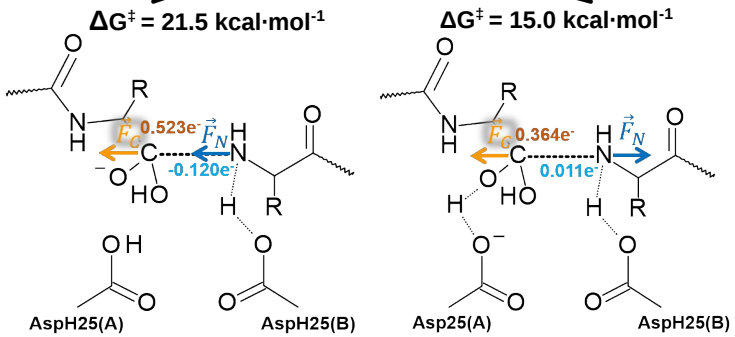




K. Świderek at al. J. Am. Chem. Soc. **2018**, 140, 4327–4334, JACS Highlights, Biofisica Highlights, F1000Prime Highlights**, GEQC-RSEQ Best Publication Award in 2018** (postdoctoral research category) for excellent contribution.

Aspartic Protease HIV-1

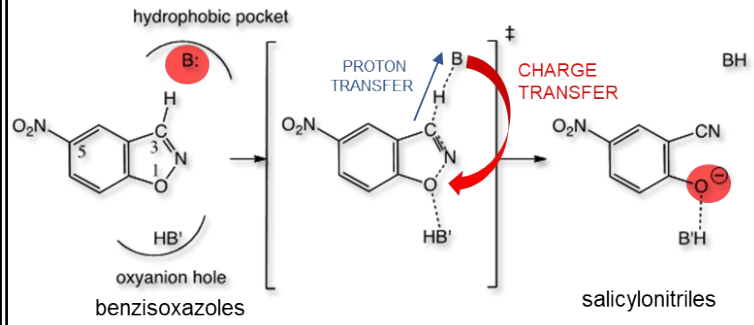


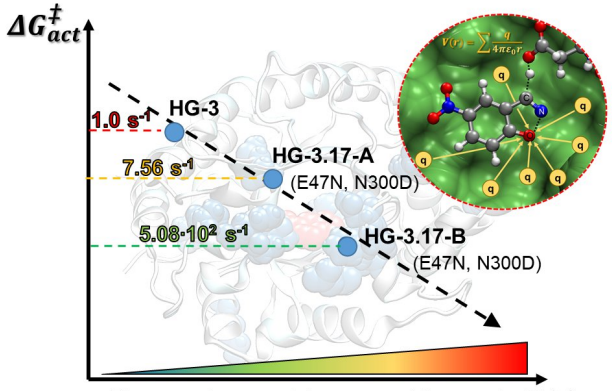


TS2(OA) TS2(GD)

Krzemińska A. et al. *J. Am. Chem. Soc.* **2016**, 138, 16283-16298.

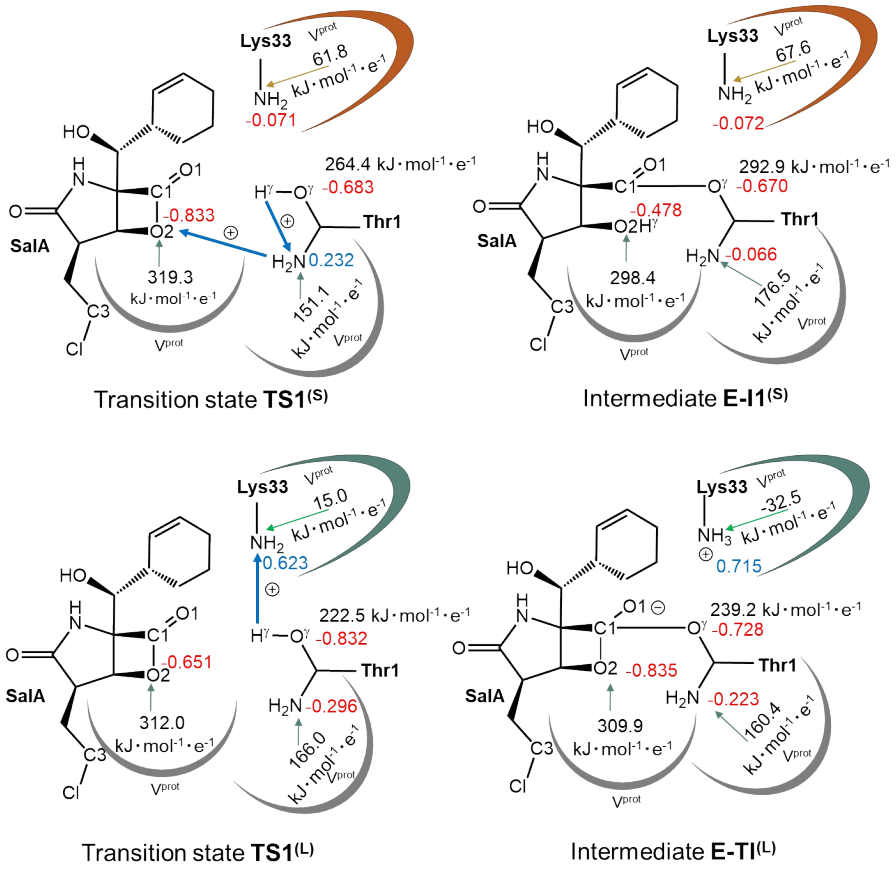
de novo design enzymes
KEMP eliminase

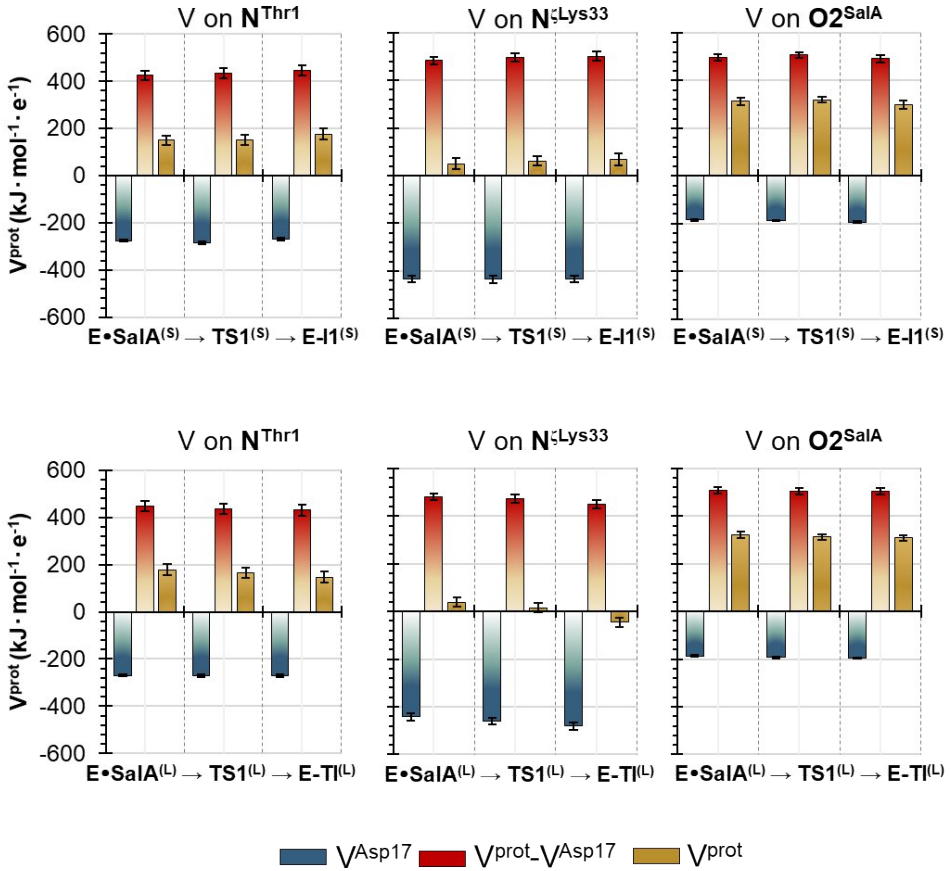




K. Świderek et al. *Arch. Biochem. Biophys.* **2015**, 582, 68–79.
K. Świderek et al. *ACS Catal.* **2015**, 5, 2587−2595.
K. Świderek et al. *Chem. Eur. J.* **2017**, 23, 7582 – 7589.

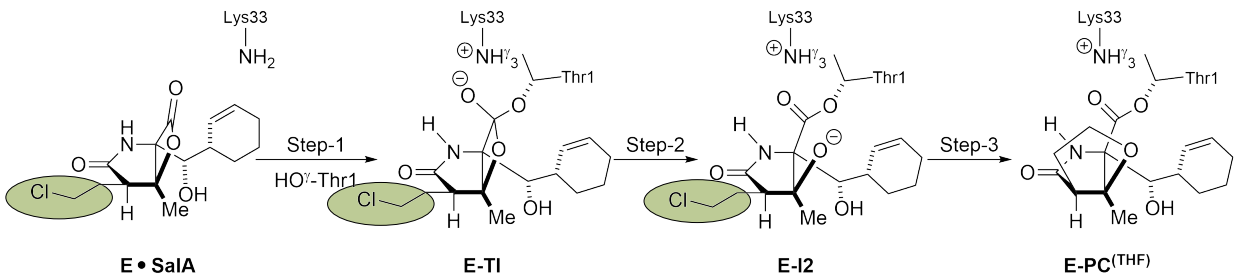
20S PROTEASOME INHIBITION WITH SalA



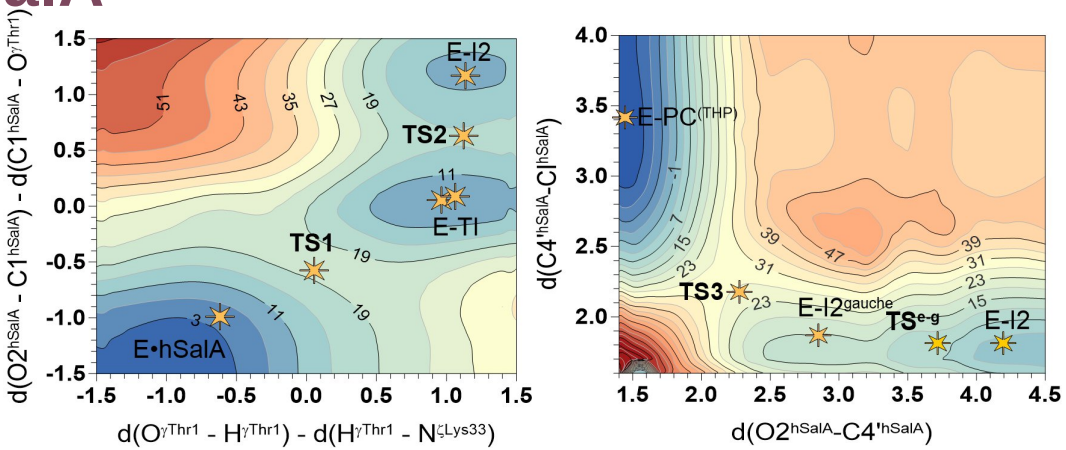


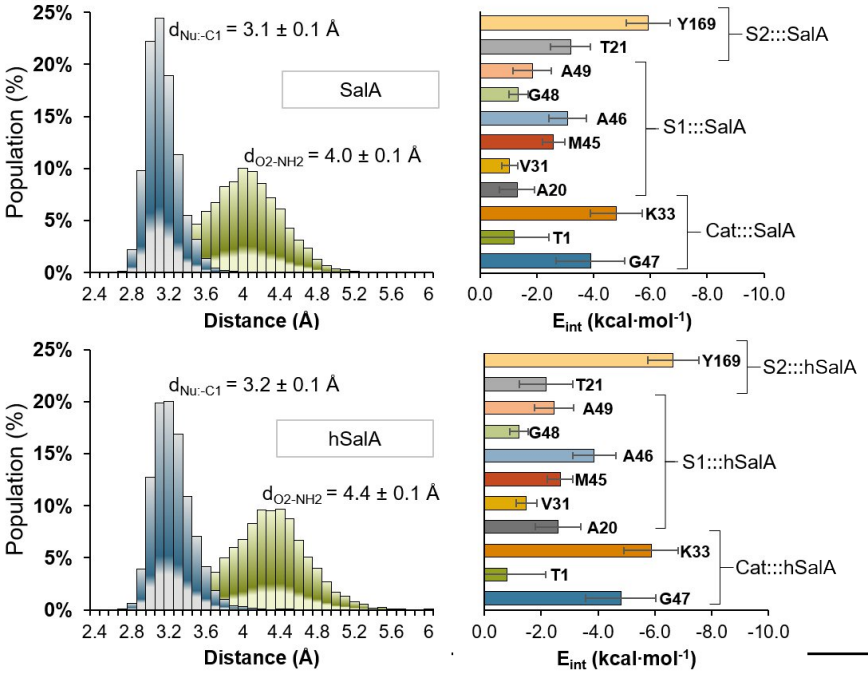
Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.

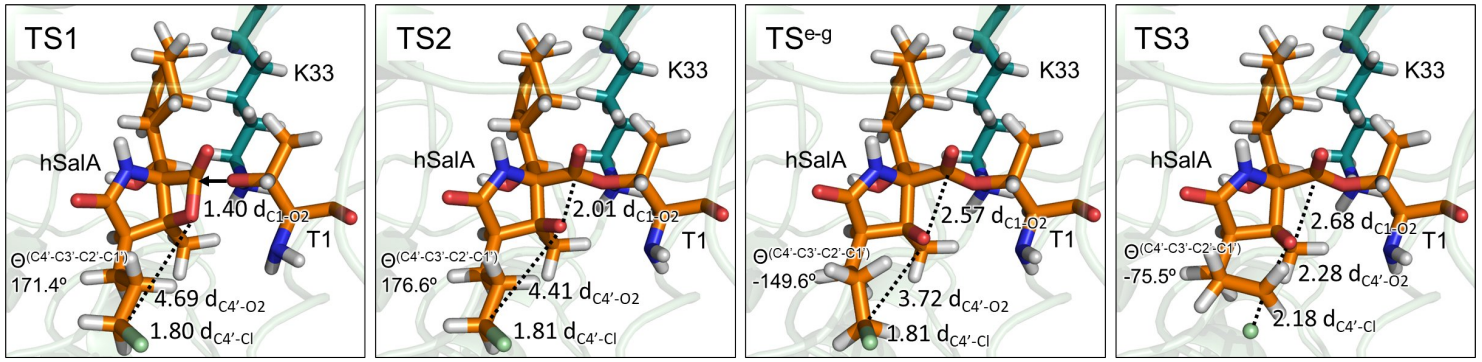
20S PROTEASOME INHIBITION WITH hSalA



2D-PMF M06-2X:AM1/MM



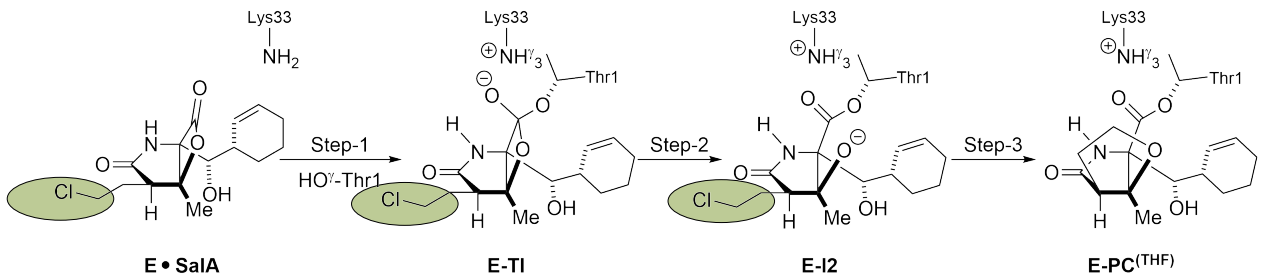




TS structures at M06-2X/MM

Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.
Serrano-Aparicio, N. et al.. **2021,** submitted.

20S PROTEASOME INHIBITION WITH hSalA



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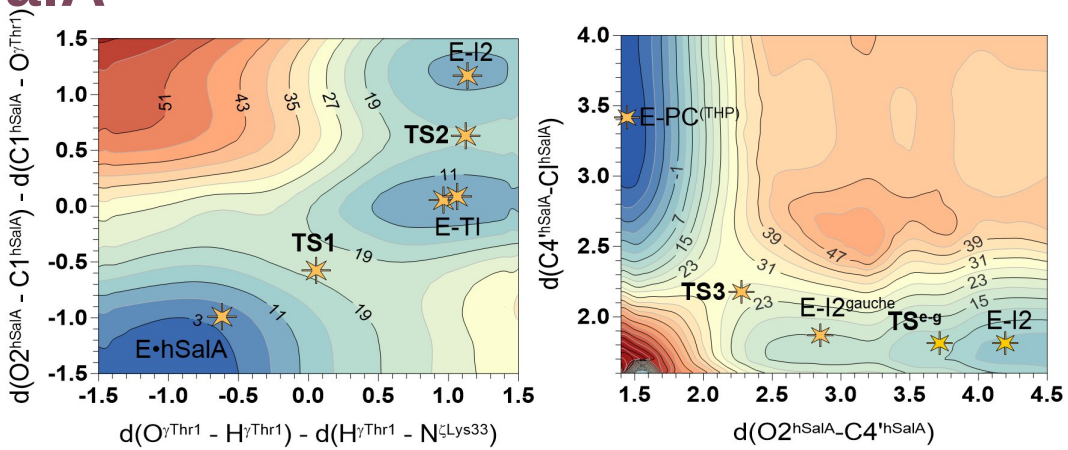

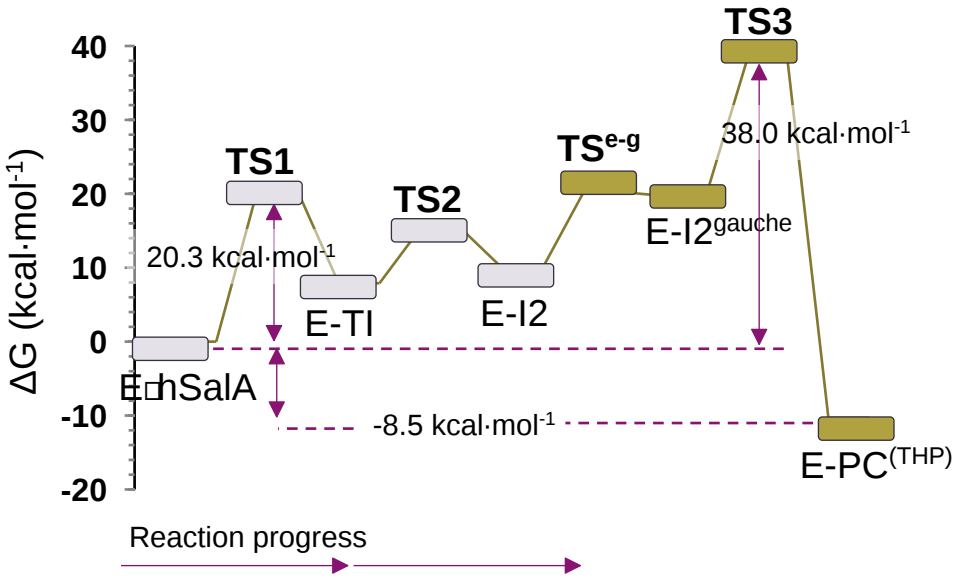

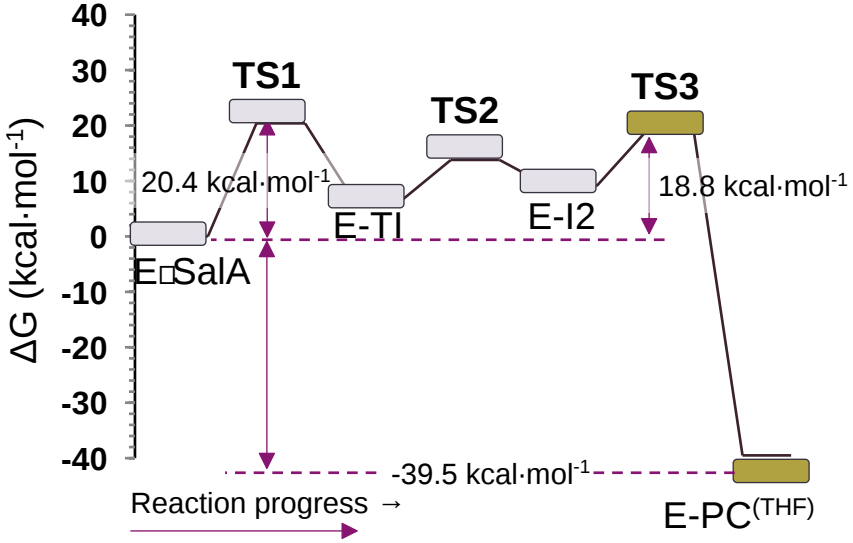

Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.
Serrano-Aparicio, N. et al.. **2021,** submitted.

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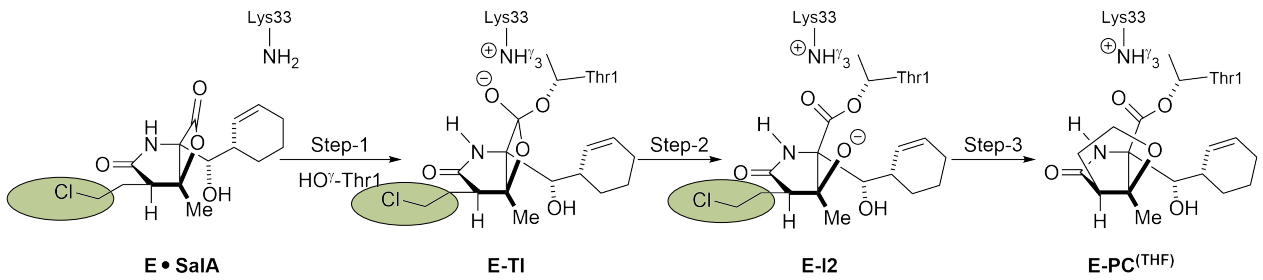
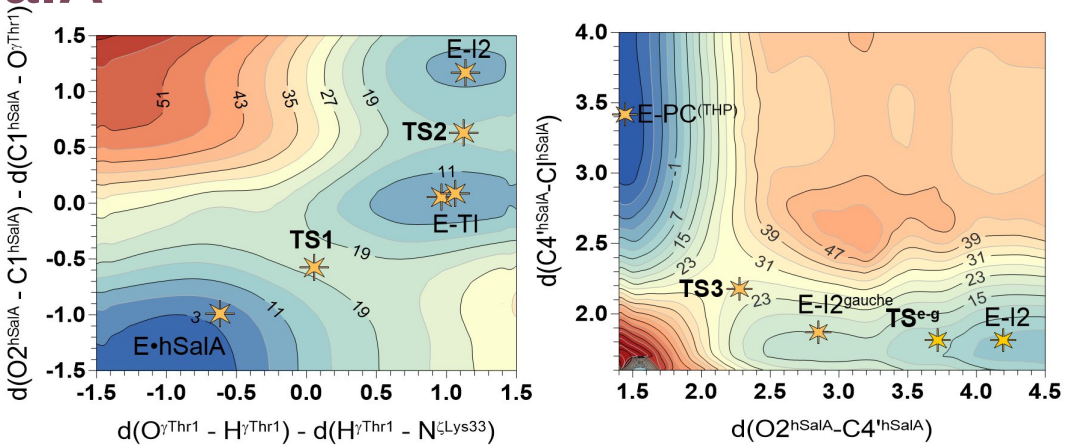
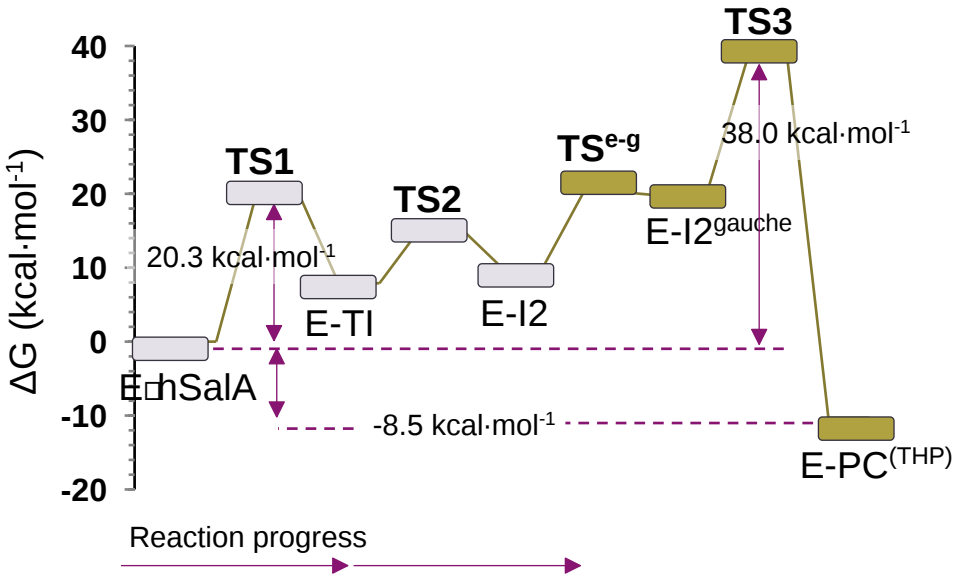


2D-PMF M06-2X:AM1/MM





(i) how is it possible that the final **E-I2 product complex** that corresponds to the one observed in the crystal structure is not thermodynamically stable as deduces from free energy surfaces?;

(ii) is the reversible character of the hSalA inhibitor controlled by **reversible dissociation** of the inhibitor from the active site or is it dictated by an additional step involving **slow hydrolysis of the ester linkage**?

Serrano-Aparicio, N. et al. *ACS Catal.* **2021**, 11, 3575–3589.
Serrano-Aparicio, N. et al.. **2021,** submitted.

FORMATION OF THP vs. THF

The proposed hypothesis explaining the absence of the THP in the crystal structure suggests that **a longer chloro-n-propyl** group of hSalA **adopts an extended conformation** in the active site of proteasome that **can prevent the ring closure**.

However, in the same studies, it was shown that this group is highly flexible, which was confirmed by **experimentally measured high values of B-factor** for this fragment. Therefore, it is expected that **rotation from extended to closed conformer should not be expensive**.

It was found that the gauche conformer is metastable intermediate in the enzyme, which confirms the prediction from experimental studies that assumes a **short half-time** for this inhibitor sidechain orientation.

Free energy computed for THF and THP formation (PC) in the aqueous solution and the active site of the 20S proteasome. Values are given in kcal•mol^{-1}.

	SalA		hSalA	
	water	enzyme	water	enzyme
E-I2^{extended}	-	-	-5.2	-9.7
E-I2/E-I2^{gauche}	0.0	0.0	0.0	0.0
TS	13.1	9.7	16.8	18.3
PC	-45.3	-48.6	-37.2	-30.0

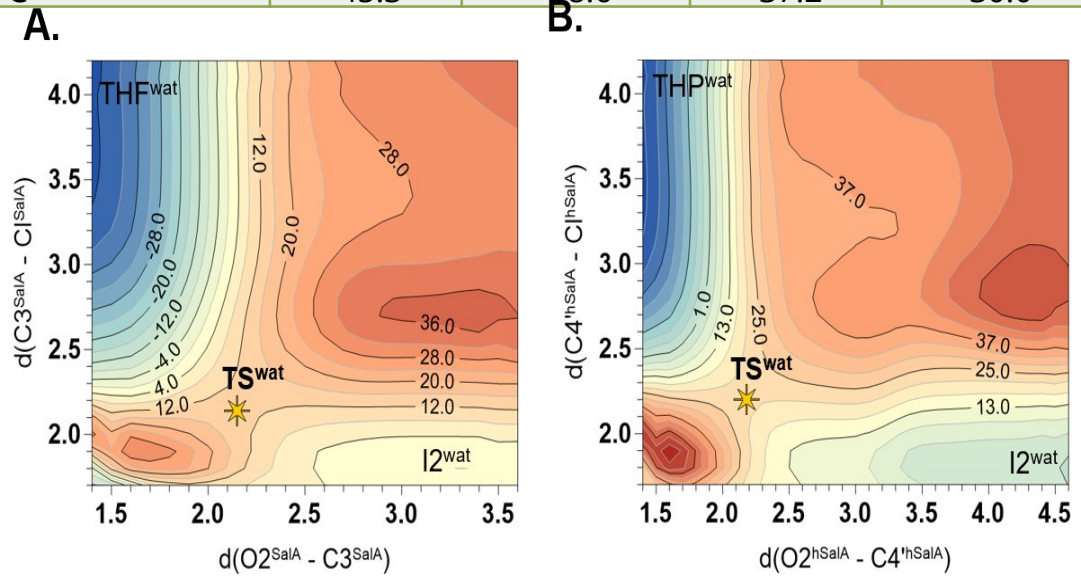
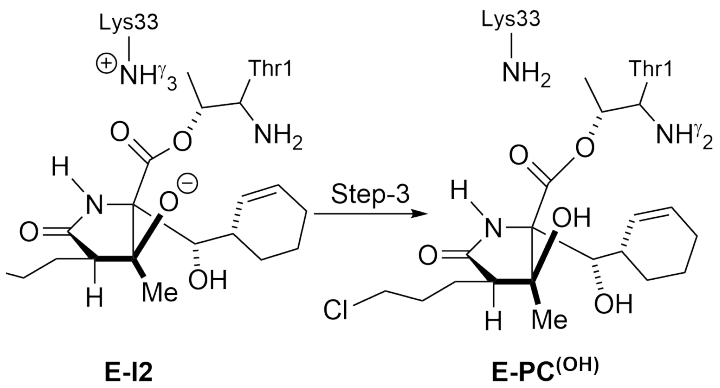
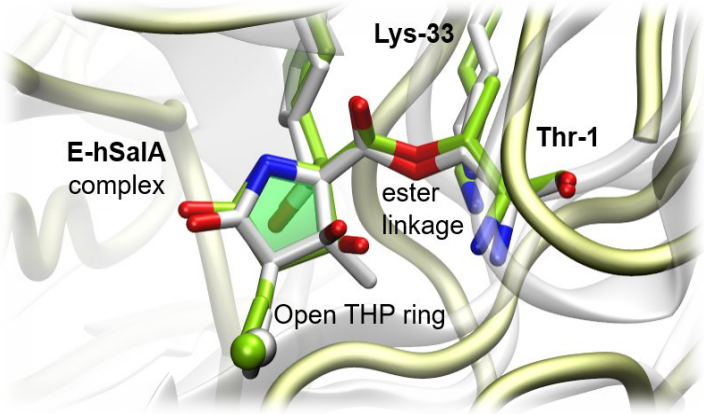


Figure 4. Free energy surfaces for intramolecular cyclization step for **A.** SalA and **B.** hSalA in the aqueous solution.

Groll, M.; et al. *Mar. Drugs* **2018**, *16*, 240–249.

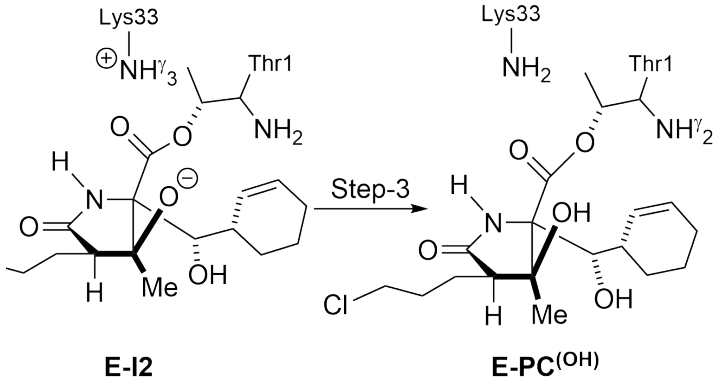
STABILIZATION OF THE FINAL INHIBITION PRODUCT

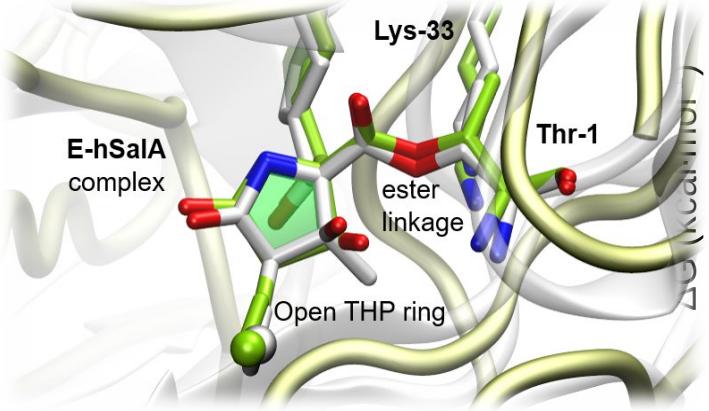


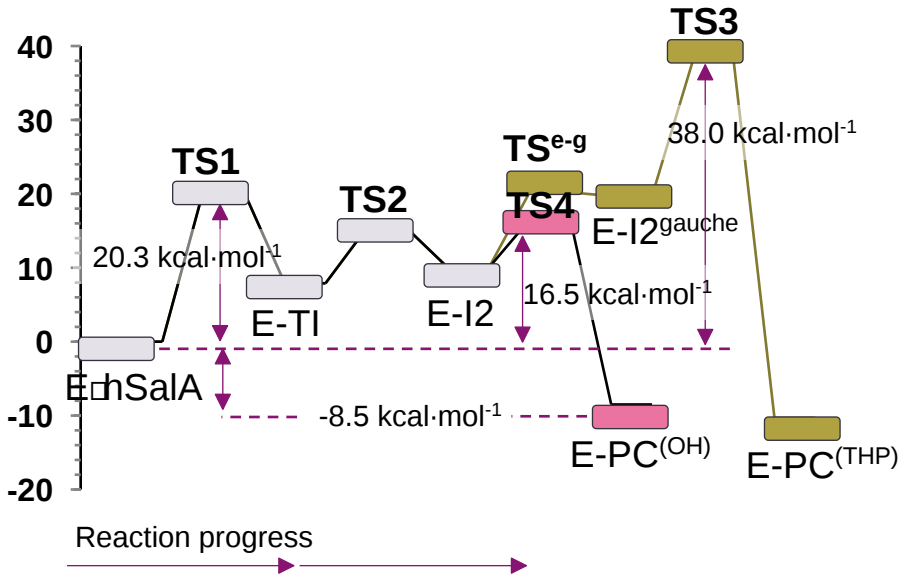


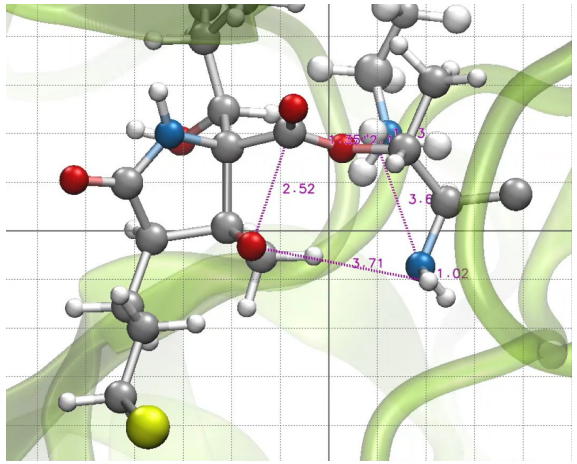
Overlay of the crystal structure of the final product of inhibition of β5-subunit of yeast 20S proteasome (in grey) by hSalA with and human variant delivered from the M06-2X/MM optimization E-PC$^{(OH)}$ (in green).

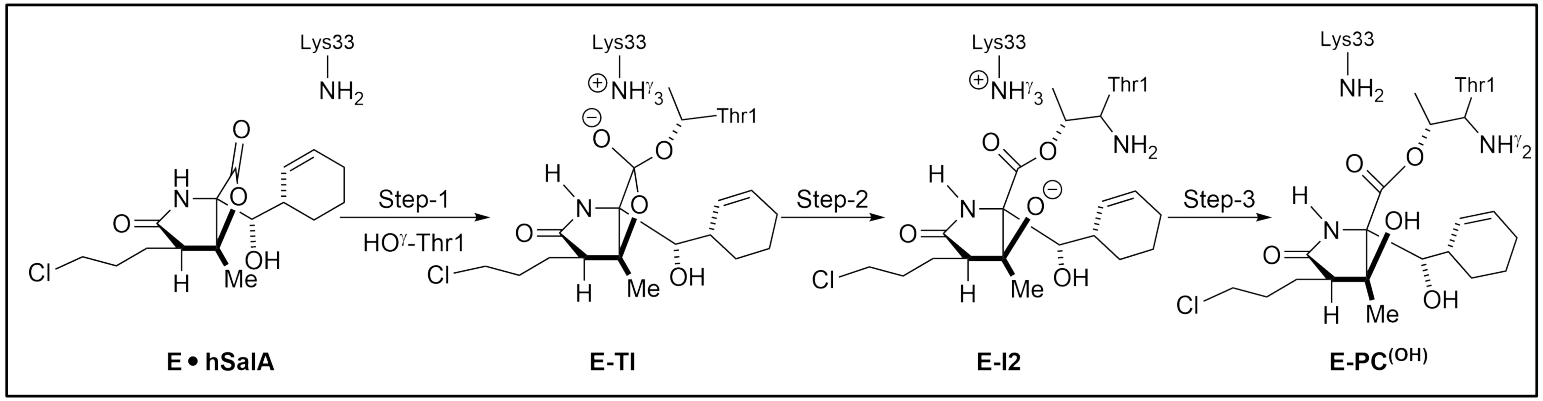
STABILIZATION OF THE FINAL INHIBITION PRODUCT











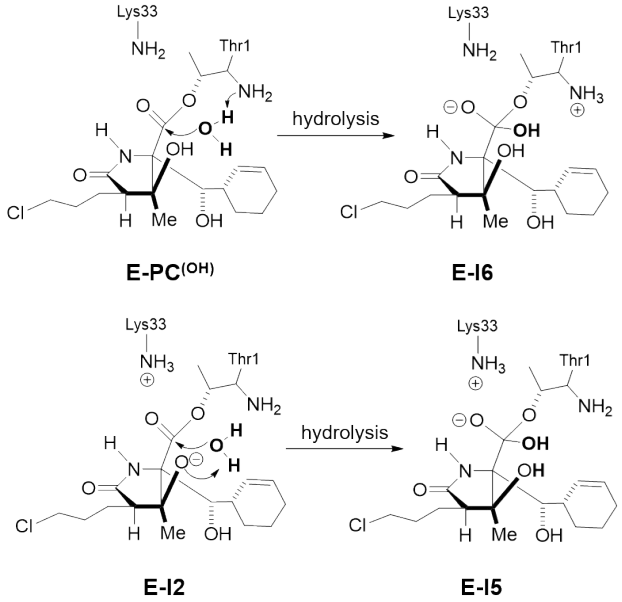
Overlay of the crystal structure of the final product of inhibition of β5-subunit of yeast 20S proteasome (in grey) by hSalA with and human variant delivered from the M06-2X/MM optimization E-PC$^{(OH)}$ (in green).

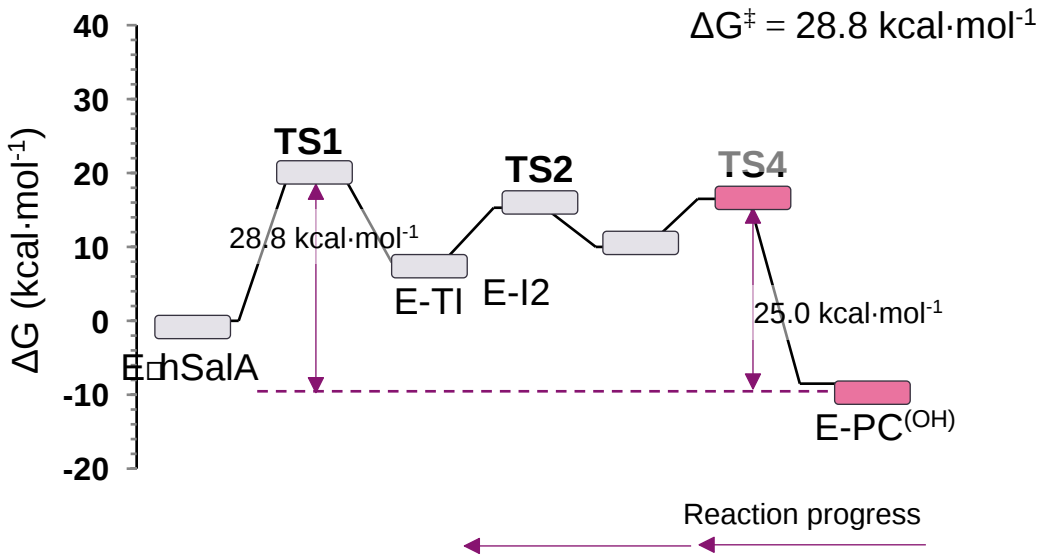
hSalA as COVALENT REVERSIBLE INHIBITOR

Table 1. Covalent inhibition strategy for SalA and hSalA.

	Class of inhibitor	Scheme[a]
Irreversible inhibition	Classical	$E + I \overset{K_i}{\leftrightarrow} E\square I \xrightarrow{k_{inact}} E{-}I$
Reversible inhibition	Covalent reversible	$E + I \overset{K_i}{\leftrightarrow} E\square I \rightleftarrows E{-}I$
	Slow Substrate	$E + I \overset{K_i}{\leftrightarrow} E\square I \longrightarrow E{-}I \underset{slow}{\longrightarrow} E + P$

[a] where the Ki is the inhibition constant that measures binding affinity, and k_{inact} is the inactivation rate constant, that measures chemical reactivity.





hSalA SLOW SUBSTRATE

Table 1. Covalent inhibition strategy for SalA and hSalA.

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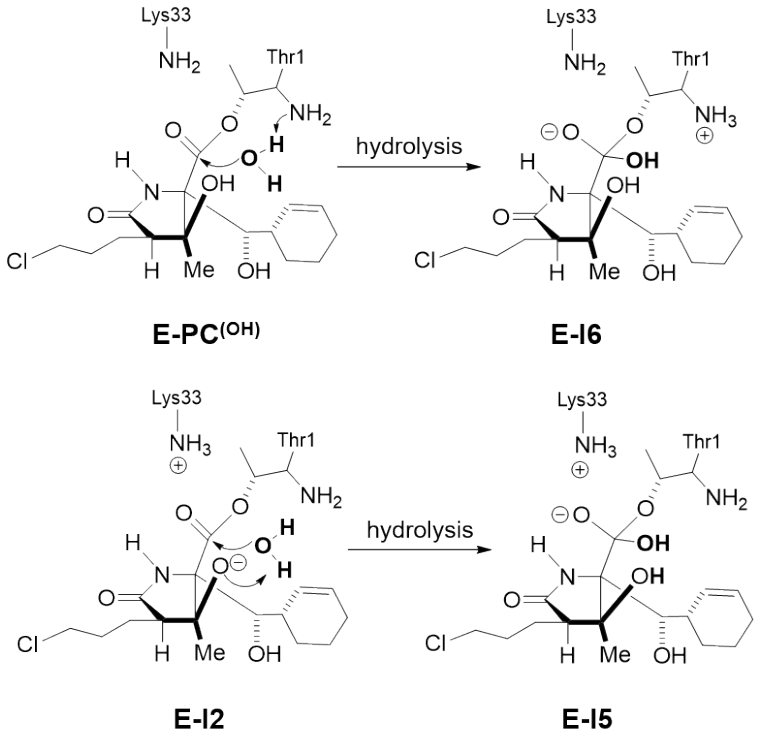
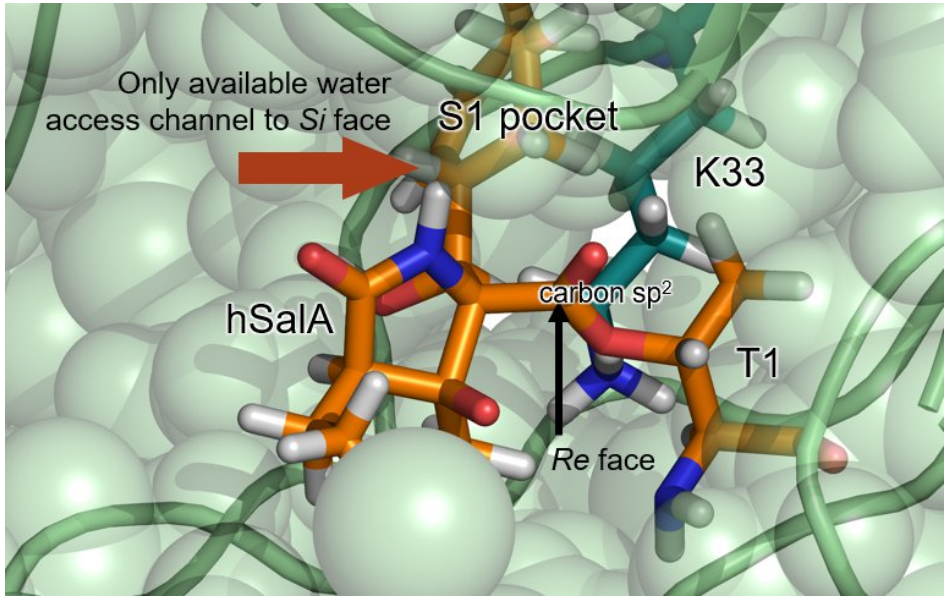
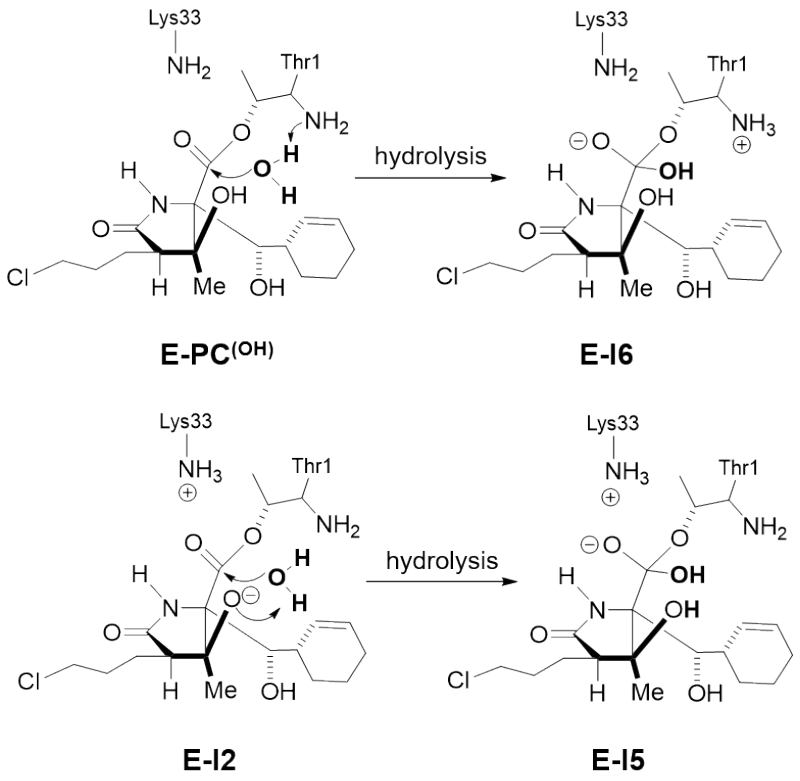
Reversible inhibition	Covalent reversible	$E + I \overset{K_i}{\leftrightarrow} E\square I \rightleftarrows E{-}I$
	Slow Substrate	$E + I \overset{K_i}{\leftrightarrow} E\square I \longrightarrow E{-}I \underset{slow}{\longrightarrow} E + P$

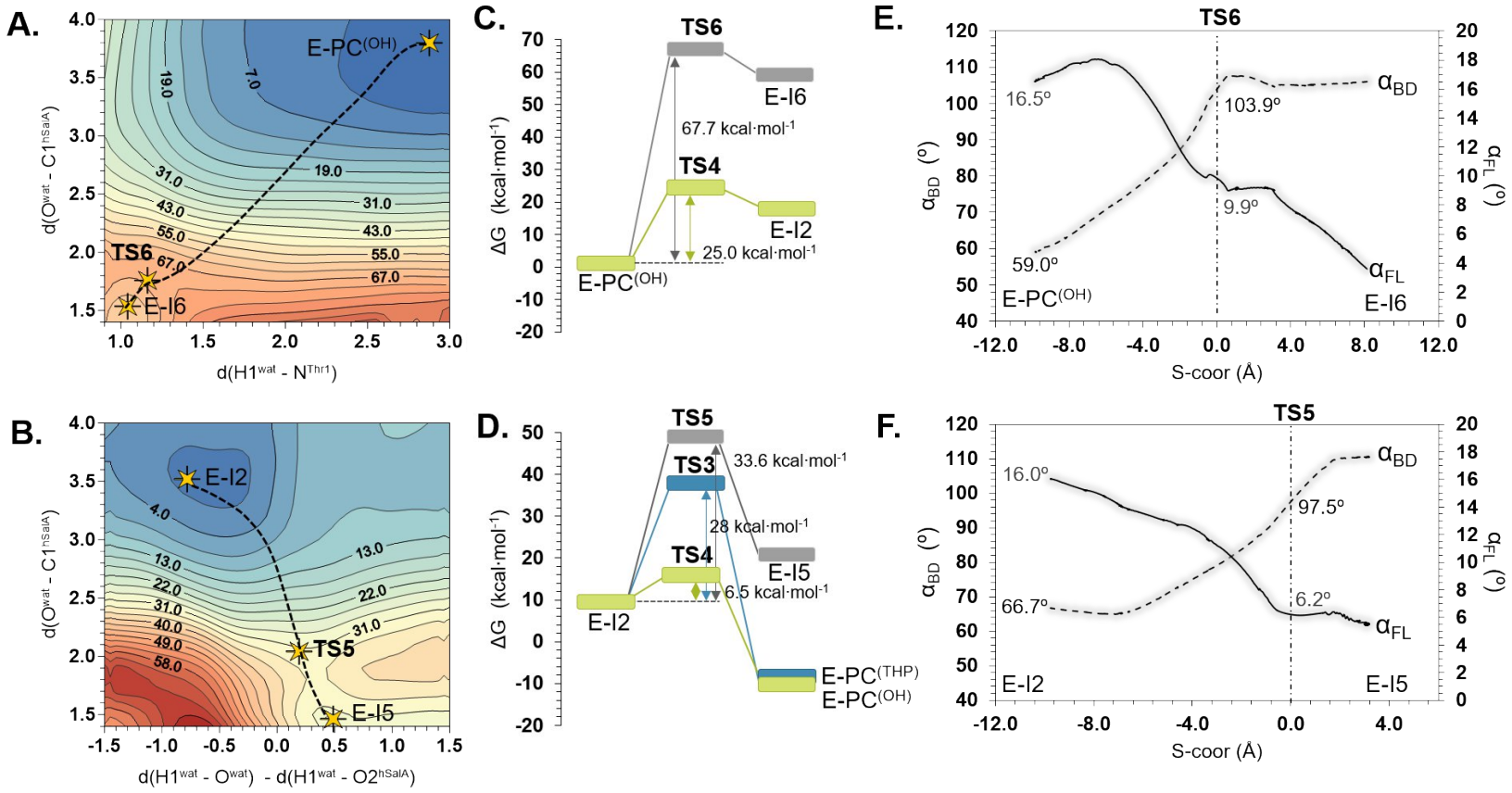
[a] where the Ki is the inhibition constant that measures binding affinity, and k_{inact} is the inactivation rate constant, that measures chemical reactivity.





hSalA as a SLOW SUBSTRATE





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Research Article

Nature of Irreversible Inhibition of *Human* 20S Proteasome by Salinosporamide A. The Critical Role of Lys–Asp Dyad Revealed from Electrostatic Effects Analysis

Natalia Serrano-Aparicio, Vicent Moliner,* and Katarzyna Świderek*

Cite this: *ACS Catal.* 2021, 11, 6, 3575–3589
Publication Date: March 5, 2021
https://doi.org/10.1021/acscatal.0c05313

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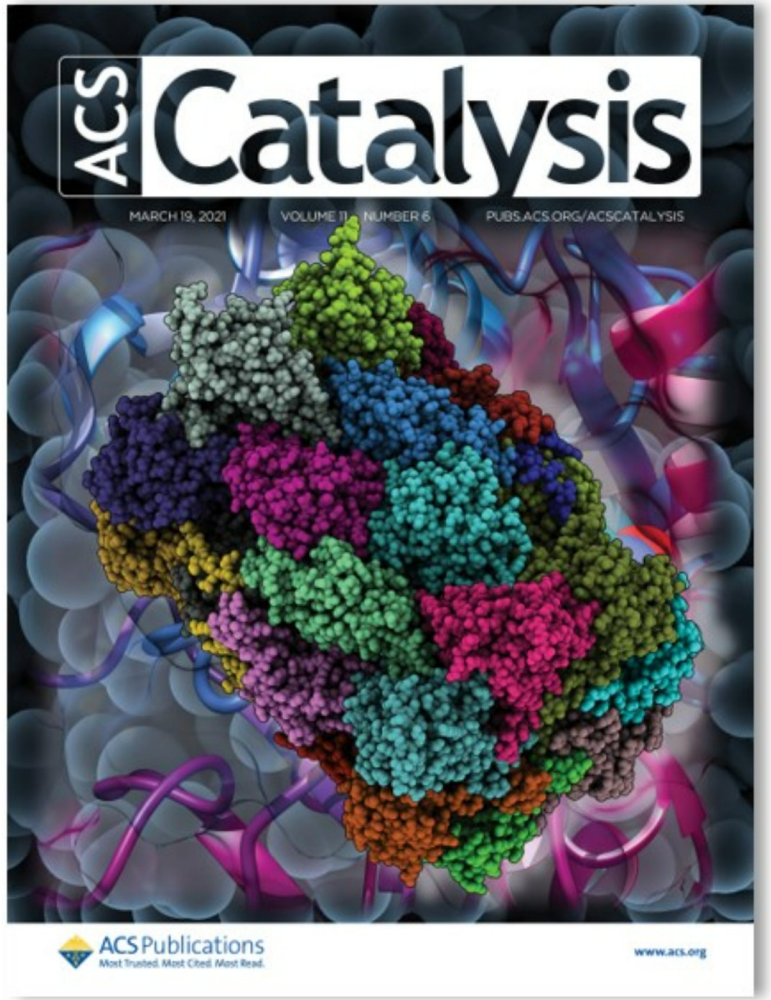
Research Article

On the Origin of the Different Reversible Characters of Salinosporamide A and Homosalinosporamide A in the Covalent Inhibition of the *Human* 20S Proteasome

Natalia Serrano-Aparicio, Vicent Moliner,* and Katarzyna Świderek*

Cite this: *ACS Catal.* 2021, 11, 18, 11806–11819
Publication Date: September 8, 2021
https://doi.org/10.1021/acscatal.1c02614



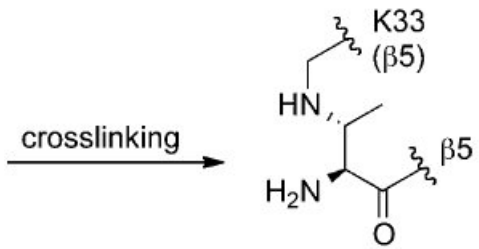
Cover of Issue 6, 2021
ACS Catal., 2021, **11**, 3575–3589

SUMMARY

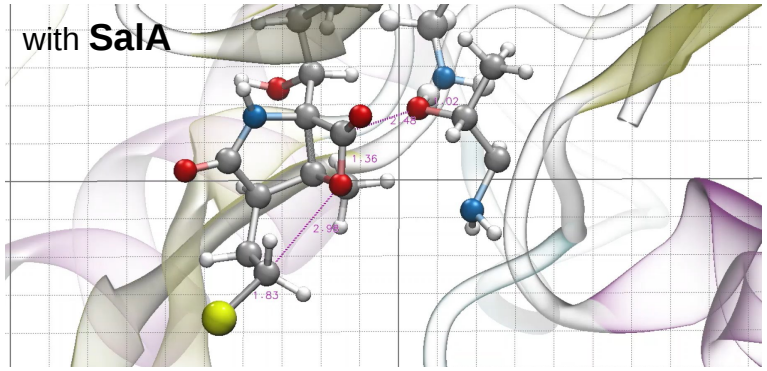
- A **new mechanism of inhibition with SalA** was proposed, that involved the active role of the Lys33-Asp17 diad in the active site of Proteasome 20S.
- **Intramolecular Cyclization Step** Determines the Character of the Human 20S Proteasome Covalent Inhibition with SalA and hSalA.

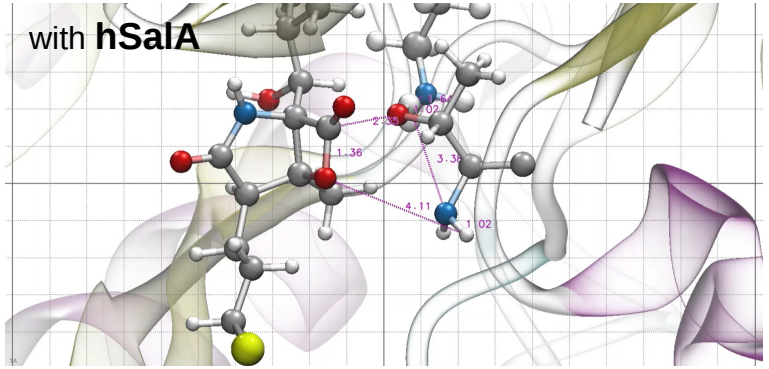
PERSPECTIVES

- Is role of Lys33-Asp17 confirmed for **autolysis and proteolysis** processes?
- How is **K33A variant** still able to catalyze this process with reduced activity?
- A novel reaction mechanism involving irreversible crosslinking of the proteasomal active site (**K33-T1** crosslink)



Mechanism of Covalent Inhibition of β5-subunit of 20S Proteasome





MEPs computed at M06-2X/MM level

- Designing of new inhibitors in collaboration with Dr F. González (UJI,Spain) and Prof. A. Chari (Max Planck Institut, Germany)

ACKNOWLEDGEMENTS

StopProt Research Team:

Natalia Serrano Aparicio, PhD candidate (Univeristat Jaume I, Spain)
Miquel Àngel Galmés, PhD candidate (Univeristat Jaume I, Spain)
Silvia Ferrer, Personal técnico de apoyo, PhD candidate (Univeristat Jaume I, Spain)
Vicent Moliner, Prof. (Universitat Jaume I, Spain)

Alessio Lodola, Dr. (University of Parma, Italy)
Florenci González, Dr. ((Univeristat Jaume I, Spain)
Carmen Domene, Prof.(University of Bath, UK)

Recent fundings and resources:

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN

Ramon y Cajal contract and JIN project (**RYC2020-030596-I** and **PID2019-107098RJ-I00**) Ministerio de Ciencia, Innovación y Universidades, 2020

GENERALITAT VALENCIANA

(SEJI/2020/007)
Subvenciones Excelencia Científica Juniors Investigadores, GVA, GenT-SEJI 2020

Barcelona Supercomputing Center
Centro Nacional de Supercomputación
RES RED ESPAÑOLA DE SUPERCOMPUTACIÓN

Total computational time of **600.8 KHours** granted on Pirineus machine is for period of 4 months 1/11/2020 - 28/02/2021

UNIVERSITAT JAUME I

(UJI-A2019-04)
Universitat Jaume I, 2019

T·R·I·N·I·T·Y cluster: 320 CPUs and 10 Geforce RTX 3090 Turbo 24GB GDDR6X funded by GVA-SEJIGENT program (REF: **SEJI/2020/007**) and Universitat Jaume I from the project of PLA DE PROMOCIÓ DE LA INVESTIGACIÓ (REF: **UJI-A2019-04**).

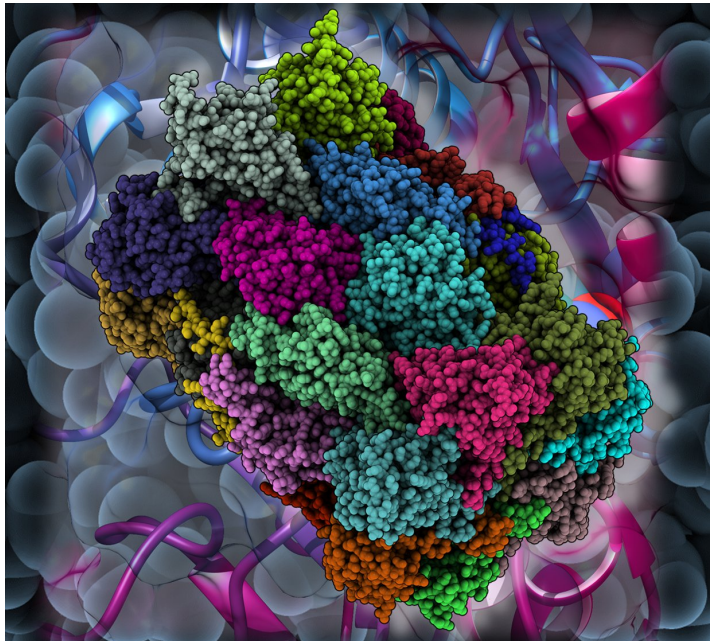
T·R·I·N·I·T·Y

T·R·I·N·I·T·Y cluster: 96 CPUs and 2 NVIDIA RTX 3090 24 GB GDDR6X Blower funded by Ministerio de Ciencia, Innovación y Universidades (REF: **ID2019-107098RJ-I00**)

BioComp group http://www.biocomp.uji.es/
StopProt project http://www.biocomp.uji.es/swiderek/home.html

QM/MM STUDIES ON THE INHIBITION OF *HUMAN* 20S PROTEASOME

THE ROLE OF ELECTROSTATIC EFFECTS IN BIOCATALYSIS



Katarzyna Świderek

Biocomp group, Universitat Jaume I, Spain

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