Ligand selectivity between ADP-ribosylating toxins. An inverse docking study for multi-target drug discovery.

Patricia Saenz-Méndez[1,2], Martin Eriksson[1] and Leif A. Eriksson[1*]

[1]*Department of Chemistry and Molecular Biology, University of Gothenburg, 405 30 Göteborg, Sweden*

[2]*Computational Chemistry and Biology Group, Facultad de Química, Universidad de la República, 11800 Montevideo, Uruguay*

*corresponding author: leif.eriksson@chem.gu.se

Table of Contents

Table S1: Known ligands selected to optimize the docking box size and crystal structures used as references

Toxin	PDB id	Ligand
ETA	1AER	β-TAD
ETA	1XK9	PJ34
DT	1DTP	APU
CT	3Q9O	NAD^+
CT	3ESS	1,8-naphthalimide
CT	3NY6	V30
CT	3KI0	GPD
CT	3KI1	GPF
CT	3KI2	GPG
CT	3KI3	GPH
CT	3KI4	GPP
CT	3KI5	GPM
CT	3KI6	GPL
CT	3KI7	GPI

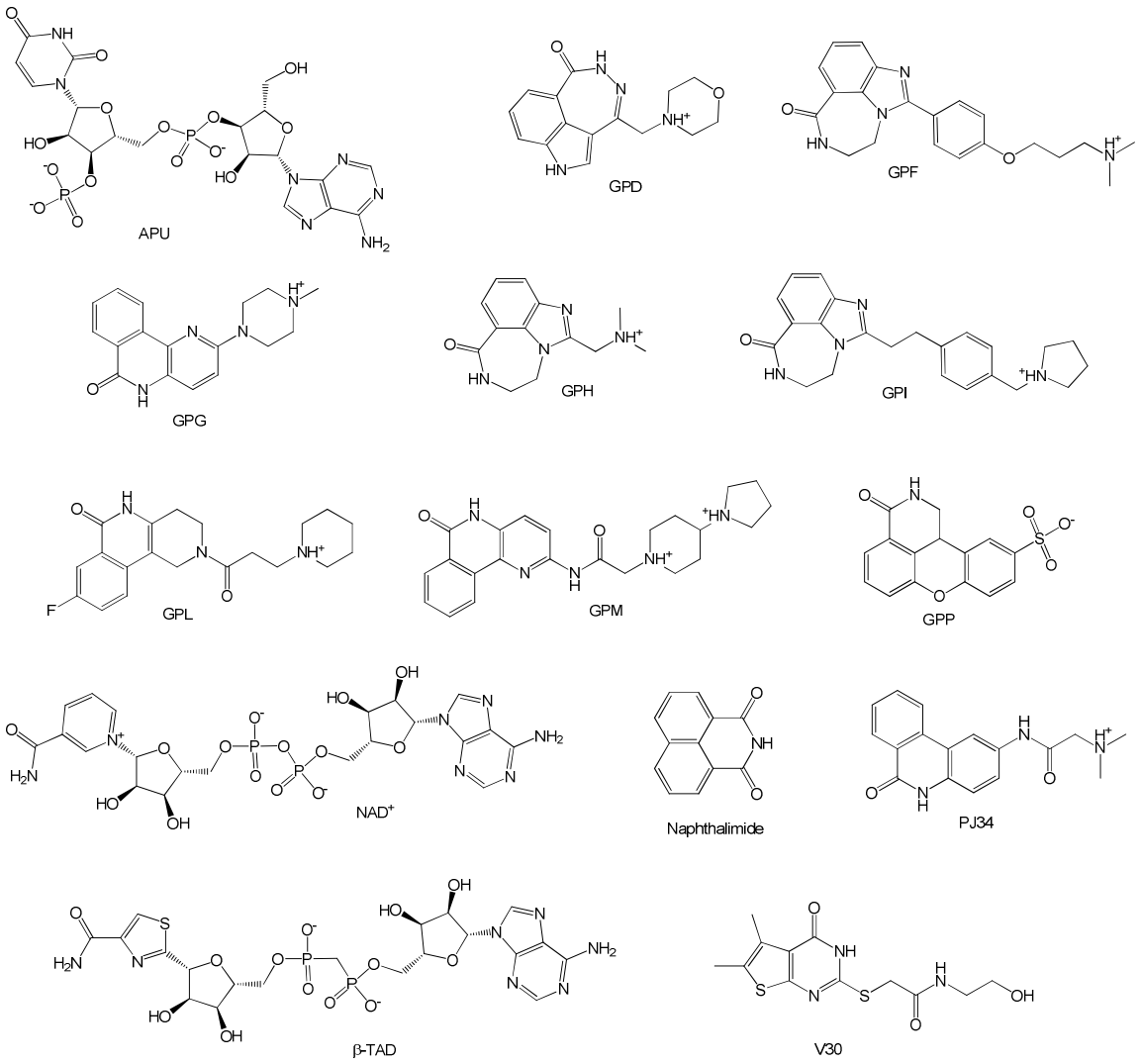

Figure S1. Structures of the ligands selected for benchmarking docking against toxins

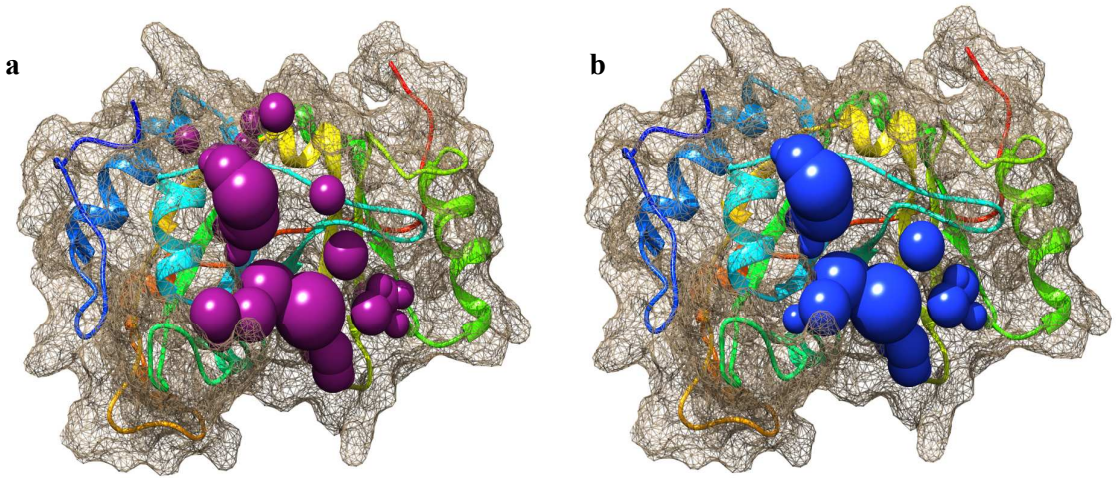

Figure S2. ETA represented with ribbons, including the molecular surface of the protein. (a) Selected spheres corresponding to an 8Å box are represented in magenta. (b) Selected spheres corresponding to a 6Å box are represented in blue.

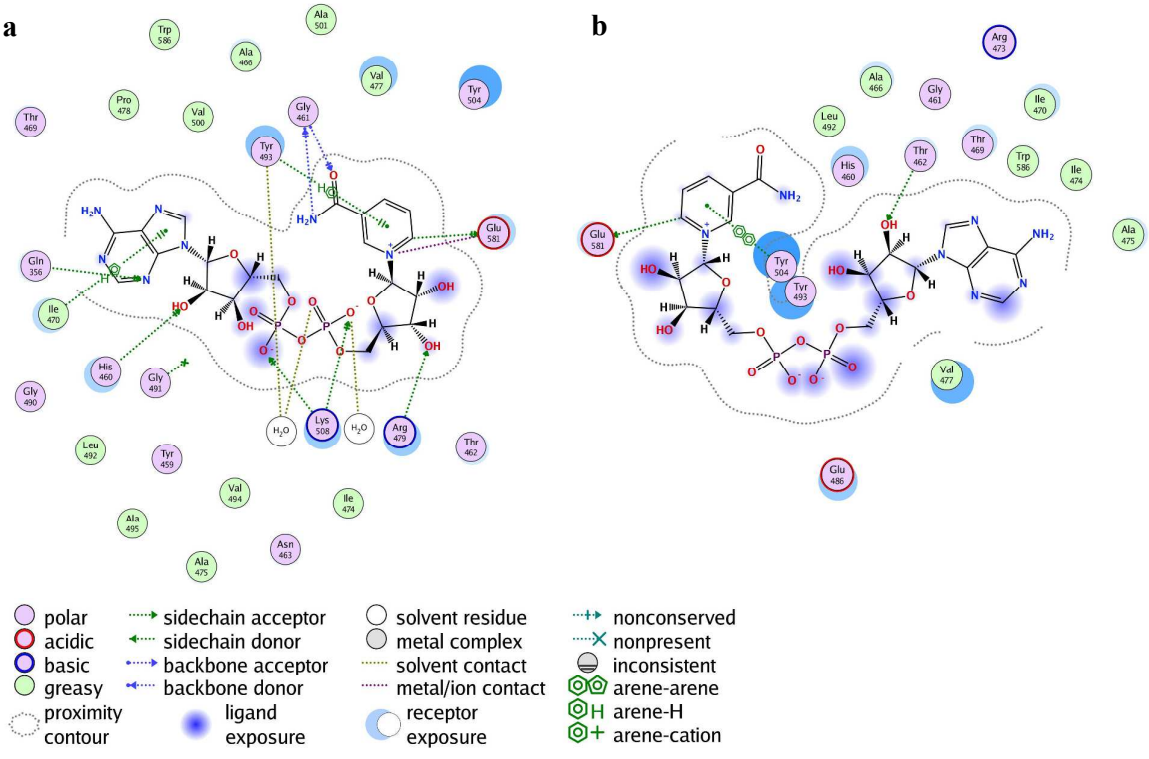

Figure S3. Ligand interactions between CT and NAD^+. (a) Crystal structure (3Q9O[1]). (b) Docking results using 2Q6M [2] as target. The 2D representations were prepared using MOE 2015.10 [3].

Table S2: RMSD values of the heavy atoms for each docked ligand with respect to the crystal structure, when employing an 8 Å or a 6 Å sphere selecting radius.

PDB id (reference crystal structure)	Ligand	RMSD values	
		8 Å	**6** Å
3ESS	1,8-naphthalimide	2.43	2.39
3NY6	V30	7.73	5.60
3KI0	GPD	3.19	0.69
3KI1	GPF	11.77	7.15
3KI2	GPG	1.18	0.31
3KI3	GPH	2.94	0.94
3KI4	GPP	0.82	0.72
3KI5	GPM	4.97	4.81
3KI6	GPL	5.03	3.02
3KI7	GPI	3.28	1.04

References:

1. Jorgensen, R., Purdy, A. E., Fieldhouse, R. J., Kimber, M. S., Bartlett, D. H., and Merrill, A. R. Cholix toxin, a novel ADP-ribosylating factor from Vibrio cholerae. *J. Biol. Chem.*, **2008**. *283*(16), 10671-10678.
2. Fieldhouse, R. J., Jorgensen, R., Lugo, M. R., and Merrill, A. R. The 1.8 A Cholix Toxin Crystal Structure in Complex with NAD+ and Evidence for a New Kinetic Model. *J. Biol. Chem.*, **2012**. *287*(25), 21176-21188.
3. *Molecular Operating Environment (MOE)*. 2015, Chemical Computing Group: Montreal, Canada.