PMMB **2025**, *8*, 1: a0000467. doi: 10.36877/pmmb.a0000469

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Supplementary materials

Table S1. Protein-ligand binding site coordinates.

Protein	PDB ID	UniProt ID	Binding Site Coordinates	
NFCYP51	7RKW	-	Site 1	16.0, -5.0, 16.0
			Site 2	11.0, 6.0, 30.0
			Site 3	20.0, 3.0, 8.0
	7RKT	-	Site 1	12.0, 3.0, 30.0
			Site 2	4.0, 11.0, 13.0
			Site 3	24.0, 3.0, 8.0
Cathepsin B	-	X5D761	Site 1	-14.0, 15.0, 10.0
			Site 2	-10.0, 13.0, 12.0
			Site 3	7.0, 0.0, -23.0
Serine Carboxypeptidase NF314	-	P42661	Site 1	18.0, 8.0, 1.0
			Site 2	2.0, 10.0, -1.0
			Site 3	-2.0, 9.0, -21.0
Rab Family Small GTPase	-	D2VS55	Site 1	12.0, 8.0, -7.0
			Site 2	-4.0, -9.0, 8.0
			Site 3	0.0, 4.0, 16.0

PMMB **2025**, *8*, 1: a0000467. doi: 10.36877/pmmb.a0000469

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Table S2. Docking results on the 3 binding sites in CB-DOCK2 and DINC.

Receptor	Binding Site	Malabaricone A	Malabaricone B	Malabaricone C	Amphotericin B
DINC					
NFCYP51 (7RKW)	**Site 1**	**-9.50**	**-9.50**	**-9.50**	**-8.70**
	Site 2	-7.30	-7.40	-7.60	-7.80
	Site 3	-6.00	-6.40	-6.50	-8.20
CB-Dock2					
NFCYP51 (7RKW)	**Site 1**	**-7.90**	**-7.80**	**-7.80**	**-5.60**
	Site 2	-6.80	-6.90	-7.30	-8.30
	Site 3	-6.20	-6.60	-6.70	-7.20
DINC					
NFCYP51 (7RKT)	Site 1	-7.80	-7.80	-7.40	-9.40
	Site 2	-7.00	-7.40	-7.50	-8.80
	Site 3	-5.90	-6.80	-6.60	-9.80
CB-Dock2					
NFCYP51 (7RKT)	Site 1	-6.50	-7.50	-7.30	-7.10
	Site 2	-6.30	-5.30	-5.40	-8.00
	Site 3	-5.30	-5.30	-5.70	-7.50
DINC					
Cathepsin B	Site 1	-7.80	-7.60	-7.90	-8.40
	Site 2	-7.30	-7.90	-6.70	-8.30
	Site 3	-6.40	-6.70	-6.70	-8.30
CB-Dock2					

Cathepsin B	Site 1	-5.70	-5.60	-5.80	-7.30
	Site 2	-5.40	-5.70	-5.90	-7.70
	Site 3	-5.30	-6.20	-5.90	-7.50
DINC					
Serine Carboxypeptidase NF314	**Site 1**	**-9.10**	**-9.30**	**-9.20**	**-7.50**
	Site 2	-6.70	-7.10	-7.10	-8.90
	Site 3	-6.50	-6.60	-6.50	-8.60
CB-Dock2					
Serine Carboxypeptidase NF314	**Site 1**	**-7.80**	**-8.50**	**-7.80**	**-5.90**
	Site 2	-6.10	-6.50	-6.00	-8.00
	Site 3	-5.40	-5.20	-5.70	-6.70
DINC					
Rab Family Small GTPase	**Site 1**	**-8.50**	**-8.40**	**-8.50**	**-7.60**
	Site 2	-7.10	-6.90	-6.60	-8.60
	Site 3	-6.40	-6.50	-6.20	-8.20
CB-Dock2					
Rab Family Small GTPase	**Site 1**	**-8.00**	**-8.00**	**-7.50**	**-6.20**
	Site 2	-5.40	-4.80	-6.00	-8.40
	Site 3	-5.10	-5.70	-5.70	-7.00

PMMB **2025**, *8*, 1; a0000467. doi: 10.36877/pmmb.a0000469

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PMMB 2025, 8, 1: a0000467. doi: 10.36877/pmmb.a0000469

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Table S3. Free binding energy, ΔG_{bind}, of the complexes calculated using MM/PBSA and MM/GBSA from Gromacs MD simulation trajectories.

	MM/GBSA in kJ/mol		MM/PBSA in kJ/mol	
Complex	$\bar{x} \pm CI^a$	**se**	$\bar{x} \pm CI$	**se**
CYP-MA	-30.616 ± 0.201	0.103	1.846 ± 0.383	0.195
CYP-MB	-29.901 ± 0.263	0.134	11.569 ± 0.411	0.209
CYP-MC	-31.018 ± 0.294	0.150	5.279 ± 0.480	0.245
R-MA	-14.872 ± 0.356	0.181	4.288 ± 0.453	0.231
R-MB	-27.288 ± 0.556	0.283	**-3.263 ± 0.585**	**0.298**
R-MC	-19.764 ± 0.486	0.247	5.034 ± 0.770	0.392
S-MA	-40.114 ± 0.476	0.242	**-4.873 ± 0.967**	**0.492**
S-MB	-40.552 ± 0.441	0.225	**-2.229 ± 0.596**	**0.303**
S-MC	-42.820 ± 0.408	0.208	**-1.217 ± 0.531**	**0.270**

Standard error, se; NFCYP51, CYP; serine carboxypeptidase Nf314, S; Rab family small GTPase, R; malabaricone A, MA; malabaricone B, MB; malabaricone C, MC.

[a]At α=0.05

PMMB **2025**, *8*, 1; a0000467. doi: 10.36877/pmmb.a0000469

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Table S4. Summary of toxicity predictions for malabaricone A, B, C and amphotericin B using ADMETLab3.0, ProTox, and vnn-ADMET models.

		Malabaricone A			Malabaricone B			Malabaricone C			Amphotericin B		
		ADMET Lab	**ProTox**	**vnn-ADMET**	**ADMET Lab**	**ProTox**	**vnn-ADMET**	**ADMET Lab**	**ProTox**	**vnn-ADMET**	**ADMETLab**	**ProTox**	**vnn-ADMET**
hERG blocker	<50%	28%		No	23%		No	15%		No	0%		Maybe not
Cardiotoxicity	<50%		active			active			active			active	
Ames Toxicity	<50%	23%		Maybe not	23%		No	29%		Maybe not	56%		No
Mutagenicity	<50%		inactive			inactive			inactive			inactive	
Carcinogenicity	<50%	10%	inactive		15%	inactive		13%	inactive		2%	inactive	
ROA / cytotoxicity	<50%	22%	inactive	Maybe not	24%	inactive	Maybe not	27%	inactive	Maybe not	<1%	inactive	Maybe not
Nephrotoxicity	<50%	34%	Active, 61%		23%	Active, 63%		10%	Active, 61%		100%	Active, 77%	
Hepatotoxicity / DILI	<50%	7%	inactive	Yes	4%	inactive	maybe yes	10%	inactive	No	53%	inactive	No
Neurotoxicity	<50%	16%	inactive		14%	inactive		2%	inactive		0%	inactive	
Respiratory irritation	<50%	94%	inactive		94%	active		92%	inactive		0%	active	

Progress in Microbes and Molecular Biology

PMMB **2025**, *8*, 1: a0000467. doi: 10.36877/pmmb.a0000469

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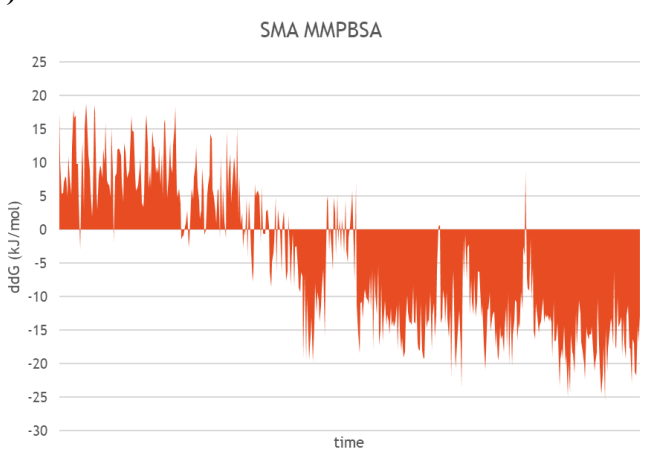

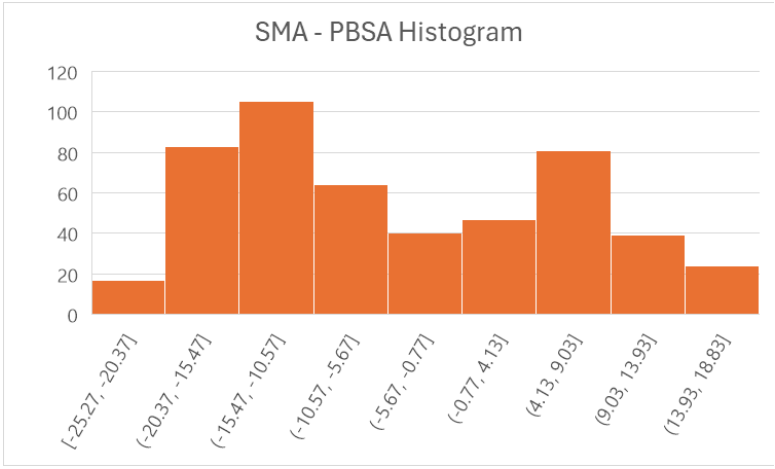

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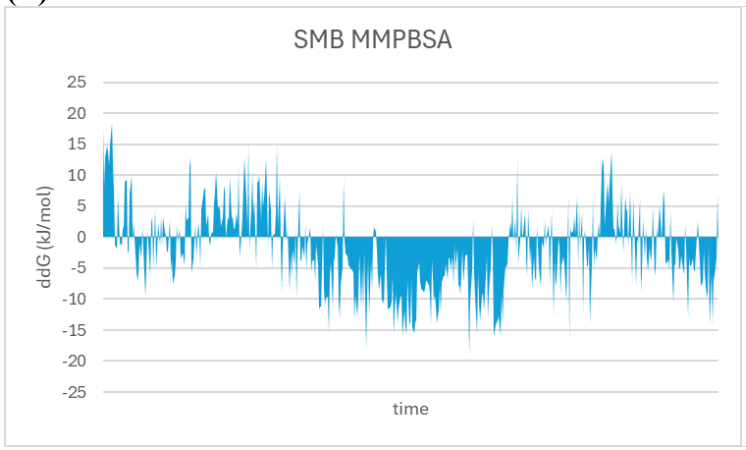

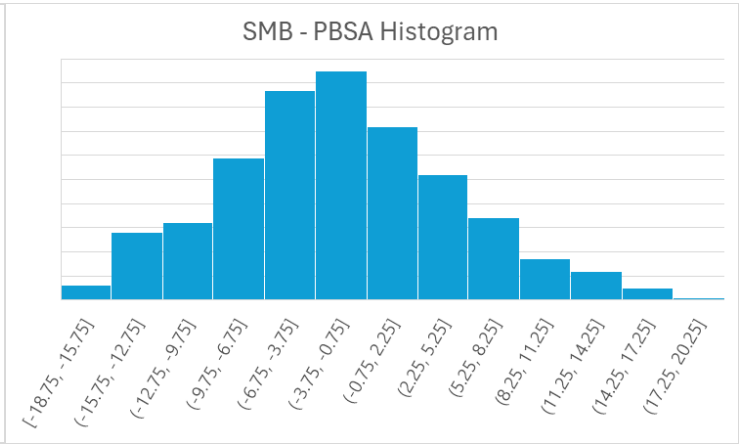

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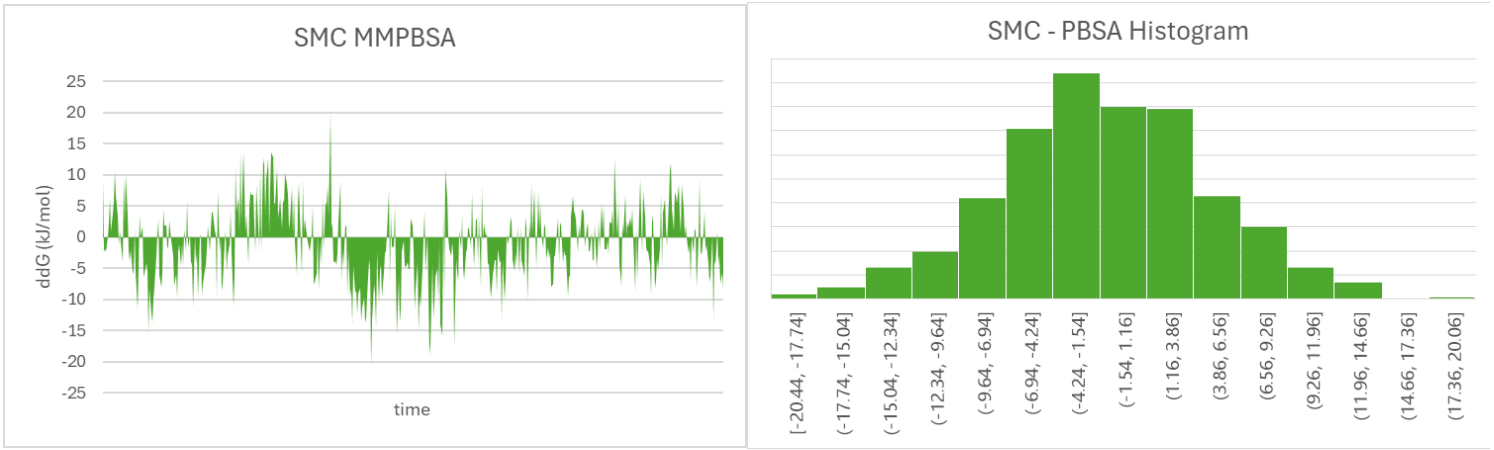

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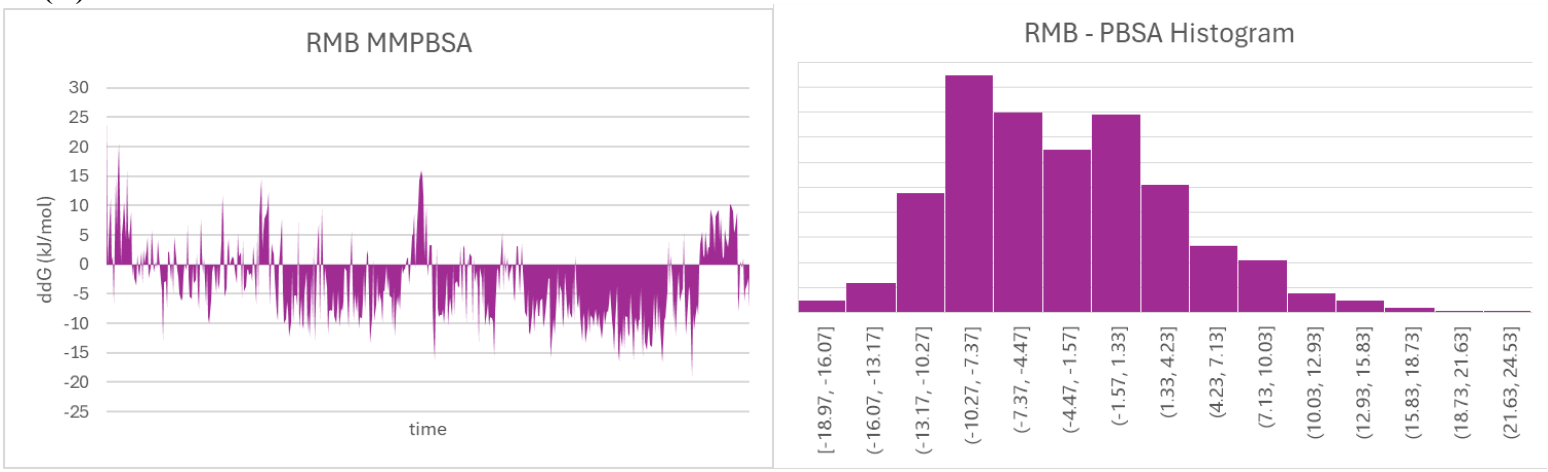

Figure S1. ΔG_{bind} fluctuations during the simulations (left) and distribution of ΔG_{bind} values (right) for the complexes of serine carboxypeptidase with **(A)** malabaricone A, **(B)** malabaricone B, **(C)** malabaricone C; and **(D)** Rab-family GTPase with malabaricone B.

Progress in Microbes and Molecular Biology
HH PUBLISHER

PMMB 2025, 8, 1; a0000467. doi: 10.36877/pmmb.a0000469

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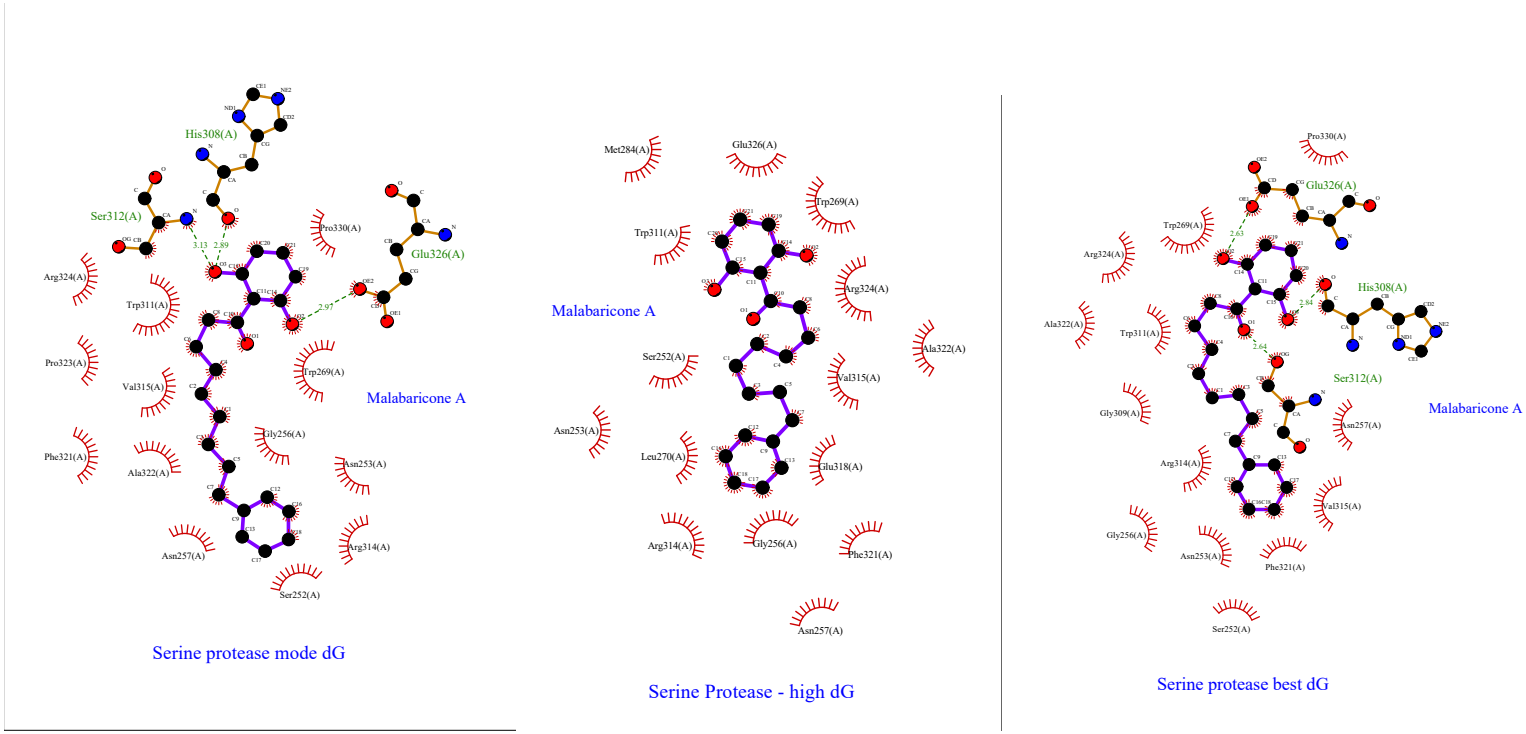

Figure S2. Intermolecular interactions of malabaricone A with serine carboxypeptidase visualized in 2D using LigPlot+.

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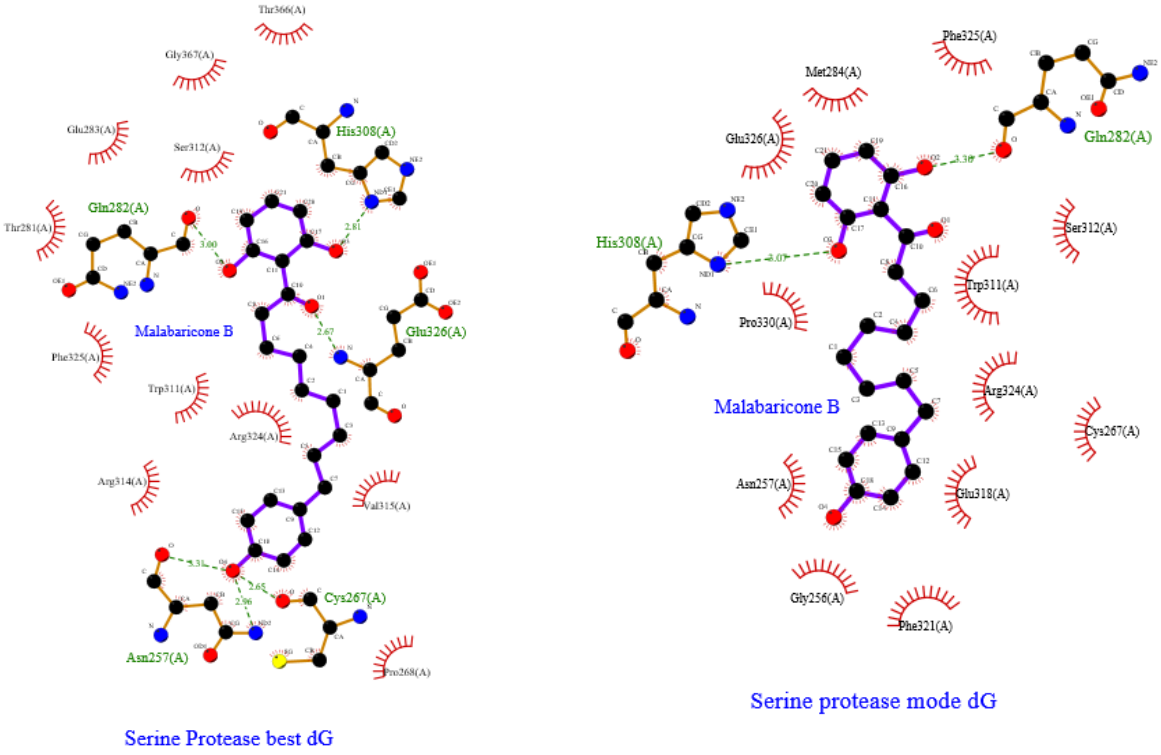

Figure S3. Intermolecular interactions of malabaricone B with serine carboxypeptidase visualized in 2D using LigPlot+.

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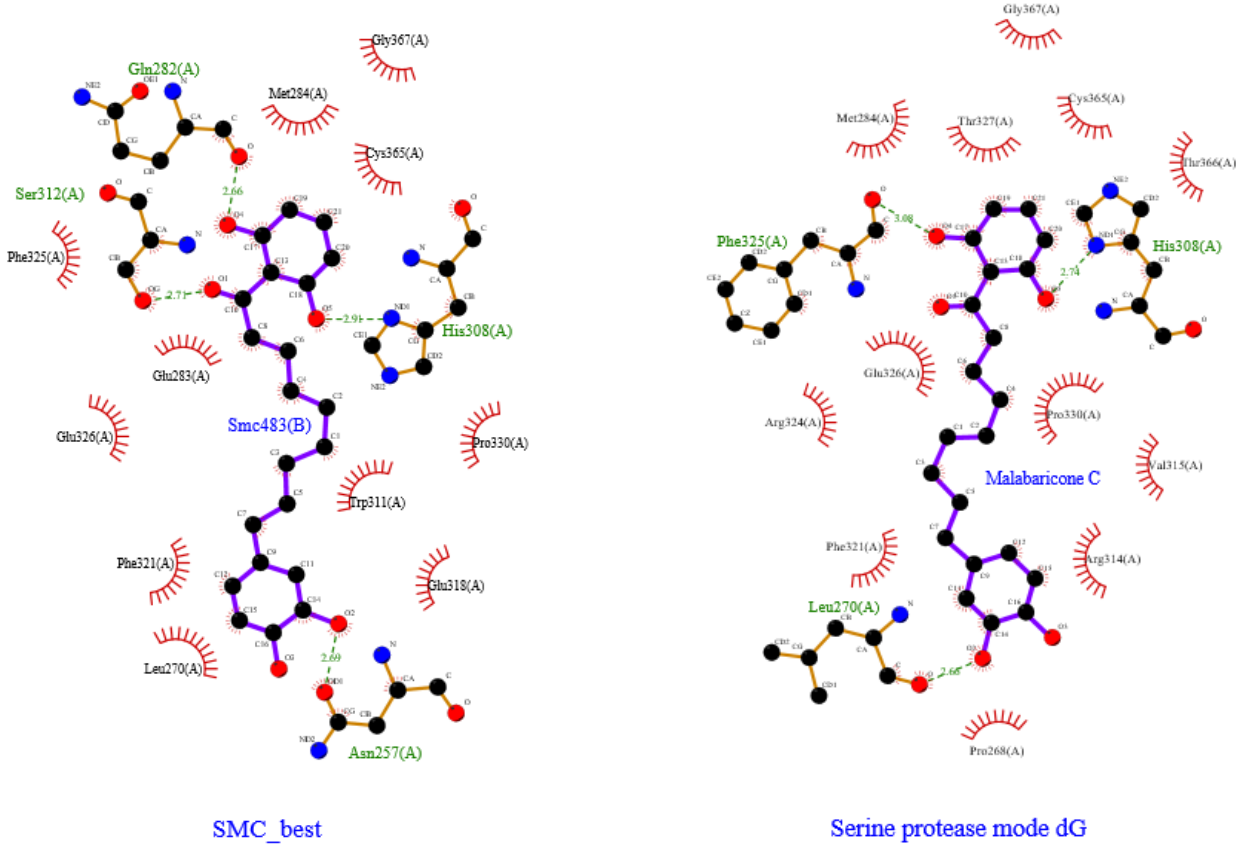

Figure S4. Intermolecular interactions of malabaricone C with serine carboxypeptidase visualized in 2D using LigPlot+.

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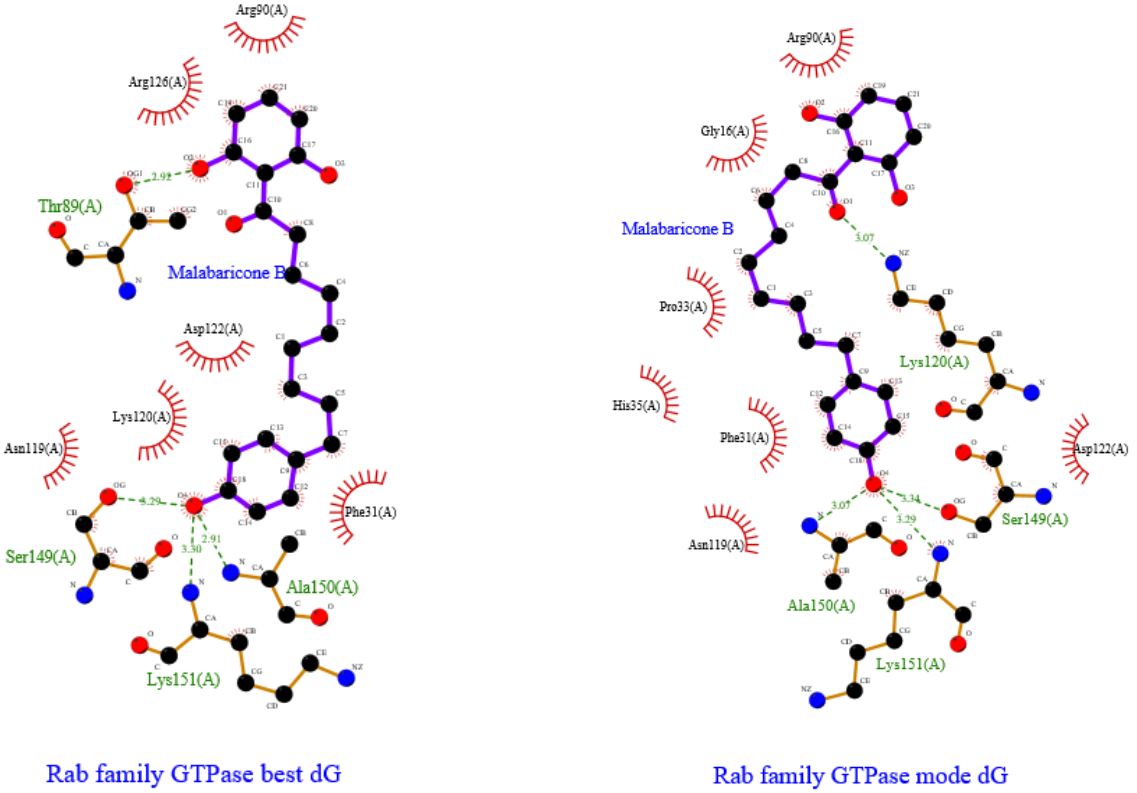

Figure S5. Intermolecular interactions of malabaricone B with Rab Family GTPase visualized in 2D using LigPlot+.