

Natural products from Red Algal Genus *Laurencia* as Potential Inhibitors of RdRp and nsp15 Enzymes of SARS-CoV-2: An In Silico Perspective

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Supplementary Information

Genus *Laurencia* Ligand Library (300 Natural products)

	A	B
(-)-3-(E)-bromomethylidene-10beta-bromo-beta-chamigrene	Acetylmajapolene A	Beta Synderol
(+)-3-(Z)-bromomethylidene-10beta-bromo-beta-chamigrene	Acetylmajapolene B	Brasilenol
(3Z)-laurenyne	Aldingenin A	Bromocyclococanol
(5S)-5-Acetoxy-beta-bisabolene	Aldingenin B	Beta cryptoxanthin
(6R,9R,10S)-10-bromo-9-hydroxyhamigra-2,7(14)-diene	Aldingenin C	Beta-sitosterol
(10R)-10-Bromo-alpha-chamigrene	Aldingenin D	Bosseopentanoic acid
1,2-Dehydro-3,4-epoxypalisadin B	Allolaurinterol	Brassicasterol
1-methyl-2,3,5-tribromoindole	Allolaurinterolacetate	Bromlaurenidificin
2-bromospironippol	Aplysinol	Bromophycoic acid A
2-Hydroxyluzofuranone A	Aplysistatin	Bromophycoic acid B
2-Hydroxyluzofuranone B	Aristolan-8-en-1-one.mol	Bromophycoic acid C
3,4-epoxypalisadin B	Aristolan-10-ol-9-one	Bromophycoic acid D
3,7-dihydroxydihydrolaurene	Aristolane	Bromophycoic acid E
3alpha-hydroperoxy-3-epiaplysin	AxinysonB	Bromophycolide A
3alpha-Hydroxydebromoaplysin	Aplysiodiol	Bromophycolide B
3beta-Hydroperoxyaplysin	Aplysiol-7-one	Bromophycolide C

3-Bromo-4, 5-dihydroxybenzaldehyde	Aplysiolic acid	Bromophycolide D
3-Bromobarekoxide	Almadioxide	Bromophycolide E
3-Epi-PerforenoneA	Aromadendrene	Bromophycolide F
3R,4S-luzonolone		Bromophycolide G
3S, 4R-luzonolone		Bromophycolide H
4-Hydroxy-1,8-epi-isotenerone		Bromophycolide I
4-hydroxypalisidin C		Bromophycolide J
5-acetoxyoachamigrene		Bromophycolide K
5-acetoxypalisadin B		Bromophycolide L
5alpha-cholestane-3,6-dione		Bromophycolide M
5alpha-Hydroxyaplysin		Bromophycolide N
5-epi-maneolactone		Bromophycolide O
6,8-cycloeudesmane		Bromophycolide P
6-hydroxycholest-4-en-3-one		Bromophycolide Q
7-acetyl-aplysiol		Bromophycolide R
7-hydroxylaurene		Bromophycolide S
8,10-dibromoisoplysin		Bromophycolide T
9-Deoxyelatol		Bromophycolide U
9-hydroxy-3-epi-perforenone A		Barekoxide
9-octadecanoic acid		Bromocuparene
10-acetoxyangasiol		
10-Bromo-beta-chamigrene		
10-Bromoisoplysin		
10-hydroxyisolaurene		
10-epi-Dehydrothyriferol		
10-Hydroxyaplysin		
11,14-dihydroaplysia-5,11,14,15-Tetrol (AA)		
12-hydroxy Isolaurene		

12-Hydroxypalisadin B		
13-Hydroxyprathyrsenol A		
14-methylpentadecanoic acid		
15-hydroxypalisadin A		
15,16-Dehydrovenustatriol		
15-DehydroxythyrserenolA		
15-Hydroxylarene		
15-Oxolarene		
16-Hydroxydehydrothyrseriferol		
C	D, E, F	G, H, I
Callicladol	Debromoepiaplysinol	Guimarediol
Callophycoic acid A	Debromoisocalenzanol	Halomon
Callophycoic acid B	Debromolaurinterol	Heterocladol
Callophycoic acid C	Debromolaurinterolacetate	Hordenine
Callophycoic acid D	Dendroidiol	Isolaurenidificin
Callophycoic acid E	Dendroidone	Isoafricanol
Callophycoic acid F	Deoxypropacifenol	Isoallolaurinterol
Callophycoic acid G	Deschloroelatol	Isoaplysin
Callophycoic acid H	Dactylyne	Isodactyloxene A
Callophycoic acid I	Debromoaplysin	Isodebromolaurinterol
Callophycoic acid J	Dehydrothyrseriferol	Isolaurenisol
Callophycol A	Dehydrovenustatriol	Isoobtusol
Callophycol B	Elatol	Isopalisol
Campesterol	Epiaplysinol	Isorigidol
Callenzanol	Epibrasilenol	Intricenylene
Chamigrene epoxide	Elatenylene	Isocaespitol
Chamigrene Lactone	Filiformin	Isodehydrothyrseriferol
Chinzallene	Filiforminol	Isodihydrolarene

Compositacin A	Floridoside	Isolaurallene
Compositacin B		Isolaureatin
Compositacin C		Isolaurene
Compositacin D		ItomanindoleA
Compositacin E		
Compositacin F		
Compositacin G		
Compositacin H		
Compositacin I		
Compositacin J		
Compositacin K		
Compositacin L		
Compositacin M		
Compositacin N		
Cycloelatanene A		
Cycloelatanene B		
Cycloisoallolaurinterol		
Chlorofucin		
Cholest-4-en-3,6-dione		
Cholest-4-en-3-one		
Cholest-5-en-3alpha-ol		
Cholest-5-en-3beta-ol		
Cupalaurenol		
Caespitane		
Caespitol		
Caesspitenone		
Cycloeudesmol		
Cyclolaurenol		

J, K, L	M, N, O	P, R, S, T
Japonenyne A	Ma'iliohydrin	Pacifenol
Johnstonol	Mailione	Palisadin A
Kumausallene	Majapolene A	Palisadin B
Lactodehydrothysiferol	Majapolene B	Palisadin C
Laurallene	Mammeisin	Palisadin D
Laureacetal A	Microcladallene A	Pannosane
Laureacetal B	Microcladallene B	Pannosanol
Laureacetal C	Microcladallene C	Perforatone
Laurefurenyne A	Neurymenolide A	Perforenol
Laurefurenyne B	Neurymenolide B	Perforenone A
Laurefurenyne C	Neoirietetraol	Prepacifenol
Laurefurenyne D	Neoisoprelaurefucin	Predehydrovenustatriolacetate
Laurefurenyne E	Neolaurallene	Prelaureatin
Laurefurenyne F	Nidificene	Prethysenol A
Laurencenyne	Notoryne	Pseudo-dehydrothysiferol
Laurencial	Octadecanedioic acid	Rhodophytin
Laurendecumallene A	Obtusane	Saringosterol
Laurendecumallene B	Okamurene A	Scopariol
Laurendecumenyne A	Okamurene B	Seco-Laurokamurone
Laurendecumenyne B	Okamurene C	Spirolaurenone
Laurenenyne	Okamurene D	Stigmasterol
Laurenisol	Okamurene E	Tiomanene
Laurenone A	Omaezallene	Thysenol A
Laureoxanyne	Oxachamigrene	Thysenol B
Laurebiphenyl	Oryzalexin S	Thysiferol
Laurecomin A		Trans-Deacetylkumausyne
Laurecomin B		Trans-Kumausyne

Laurecomin C		Trans-Laurencenyne
Laurecomin D		
Laurencomposidiene		
Laurene		
Laurenokomarin		
Laurentristich-4-ol		
Laureperoxide		
Laurepoxyene		
Laurinterolacetate		
Laurokamurene A		
Laurokamurene B		
Laurokamurene C		
Laurokamurene D		
Luzofuran		
Luzondiol		
Luzonenone		
Luzonensin		
Luzonensol		
Luzonensolacetate		
Laurepinnacin		
Laurinterol		
Lithothamin A		

Table S1: 300 natural products from the red algal Genus *Laurencia* involved in this work

RDRP N-Terminal		
Ligands	Binding affinity ('-4.0 to -4.9)	Interacting amino acids
1-methyl-2,3,5-tribromoindole	-4.8	LYS47 TYR129 HIS133 ASN138 SER709 LYS780 ASN781 SER784
6,8-cycloeudesmane	-4.9	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711
9-octadecanoic acid	-4	TYR32 LYS47 PHE48 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780 ASN781
14-methylpentadecanoic acid	-4.5	LYS47 TYR129 ALA130 HIS133 ASP135 ASN138 CYS139 ASP140 THR141 LEU142 SER709 LYS780 ASN781
Beta Synderol	-4.7	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS780 ASN781
Halomon	-4	ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 GLN773 GLY774 LYS780 ASN781
Luzonensin	-4.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714
Hordenine	-4.5	LYS47 TYR129 ALA130 HIS133 PHE134 ASP135 ASN138 CYS139 ASP140 THR141 LEU142 LYS780
Laurencenyne	-4	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 LYS780
Trans-Laurencenyne	-4.2	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS780

Table S2: Natural products listed under subcategory 1 in low class for RdRp

RDRP N-Terminal		
Ligands	Binding affinity ('-5.0 to -5.9)	Interacting amino acids
(-)-3-(E)-bromomethylidene-10beta-bromo-beta-chamigrene	-5.5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714
(+)-3-(Z)-bromomethylidene-10beta-bromo-beta-chamigrene	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774
(5S)-5-Acetoxy-beta-bisabolene	-5.2	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774
(6R,9R,10S)-10-bromo-9-hydroxychamigra-2,7(14)-diene	-5.9	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711
(10R)-10-Bromo-alpha-chamigrene	-5.2	TYR32 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780
2-bromospironippol	-5.2	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711
(3Z)-laurenyne	-5	ALA46 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS780 ASN781
3,4-epoxypalisadin B	-5.5	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774
3,7-dihydroxydihydrolaurene	-5.7	TYR32 ALA46 LYS47 PHE48 LEU49 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774

3 alpha-Hydroxydebromoaplysin	-5.7	ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS780 ASN781 SER784 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774
3 beta-Hydroperoxyaplysin	-5.7	LEU775 VAL776 ALA777 SER778 LYS780 ASN781
4-Hydroxy-1,8-epi-isotenerone	-5.5	ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780
4-hydroxypalisidin C	-5.7	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 ASP711 LYS714 LYS780
5-acetoxyoachamigrene	-5.5	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774
5-epi-maneolactone	-5.1	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 GLN773 LYS780
7-acetyl-aplysiol	-5.8	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS780 ASN781
7-hydroxylaurene	-5.2	TYR32 ALA46 LYS47 PHE48 SER709 THR710 ASP711 LYS714
8,10-dibromoisoplysin	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 SER772 GLN773
9-Deoxyelatol	-5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714
10-Bromo-beta-chamigrene	-5.2	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLY774 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774
10-Bromosoplyin	-5	SER778 LYS780 ASN781
10-hydroxyisolaurene	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 SER772 GLN773 GLY774
10-Hydroxyaplysin	-5.2	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLY774 LYS780 ASN781
12-hydroxy Isolaurene	-5.2	TYR32 ALA46 LYS47 PHE48 TYR129 ALA706 SER709 THR710 ASP711 TYR32 ALA46 LYS47 TYR129 HIS133 ASN705 ALA706 LEU707 SER709 THR710 ASP711
12-Hydroxypalisadin B	-5.7	GLY774 LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 ALA706 LEU707 SER709 THR710 ASP711 GLN773 GLY774
15-Hydroxylaurene	-5.2	LEU775 ASN781
15-Oxolaurene	-5	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 GLY774 LYS780 ASN781
Almadioxide	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774
Aromadendrene	-5	TYR32 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 ASN705 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 VAL776 SER778
Aldingenin A	-5.5	LYS780 ASN781
Aldingenin B	-5.7	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711

Aldingenin C	-5.9	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 LYS780
Allolaurinterol	-5.5	TYR32 ALA46 LYS47 PHE48 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780
Allolaurinterolacetate	-5.7	TYR32 ALA46 LYS47 PHE48 TYR129 HIS133 SER709 THR710 ASP711 GLN773 GLY774 LYS780 PHE45 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 GLY774 LYS780
Aplysinal	-5.5	ASN781
Aristolan-8-en-1-one	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 LYS780
Aristolane	-5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774
AxinysonB	-5.9	ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS714 GLN773 LYS780
Apysiol-7-one	-5	TYR32 ALA46 LYS47 PHE48 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780
Apysiolic acid	-5.9	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS780 ASN781
(-)-BisezakyneA	-5.5	TYR32 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLY774 LYS780 ASN781
Brasilanol	-5	TYR32 ALA46 LYS47 PHE48 TYR129 ASN138 SER709 ASP711 LYS780
Bromocuparene	-5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 GLN773 ALA46 LYS47 TYR129 ASN705 ALA706 SER709 THR710 ASP711 GLY774 VAL776 SER778
Bromocyclococanol	-5.2	LYS780 ASN781 TYR32 ALA46 LYS47 PHE48 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 GLN773
Bosseopentanoic acid	-5	GLY774 LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Bromlaurenidificin	-5.1	LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773
Caespitane	-5.7	GLY774 VAL776 SER778 LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Caesspitenone	-5.2	LYS780 ASN781
Cycloeudesmol	-5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 TYR129 HIS133 ALA706 SER709 THR710 ALA771 SER772 GLN773 GLY774 VAL776 SER778
Cyclolaurenol	-5.5	LYS780 ASN781 SER78

Callophycoic acid F	-5.8	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 LYS780 ASN781 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774
Callenzanol	-5.5	LYS780 ASN781
Chamigrene epoxide	-5.4	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780
Chinzallene	-5.7	LYS47 TYR129 ALA130 HIS133 ASN138 SER709 THR710 LYS780 ASN781 SER784
Compositacin A	-5.5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780
Compositacin C	-5.9	TYR32 ALA46 LYS47 PHE48 LEU49 TYR129 SER709 THR710 ASP711 LYS714
Compositacin D	-5.7	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780
Compositacin G	-5.5	TYR32 LYS47 PHE48 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLY774 LYS780 LYS47 TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 SER778
Compositacin H	-5.5	LYS780 ASN781
Compositacin J	-5.9	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 TYR129 HIS133 ALA706 SER709 THR710 ALA771 SER772 GLN773 GLY774 SER778 LYS780
Compositacin K	-5.7	ASN781
Compositacin L	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 LYS47 TYR129 HIS133 ASN705 ALA706 SER709 THR710 GLN773 GLY774 SER778 LYS780
Compositacin M	-5.5	ASN781
Cycloelatanene A	-5.5	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLN773 LYS780
Cycloelatanene B	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Cycloisoallolaurinterol	-5.5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714
Chlorofucin	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773
Cupalaurenol	-5.5	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLN773
Dactylyne	-5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780
Debromoaplysin	-5.2	TYR129 HIS133 ALA706 SER709 THR710 ASP711 GLN773 GLY774 LYS780 ASN781 SER784
Debromoepiaplysinol	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Debromolaurinterol	-5.2	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773

Debromolaurinterolacetate	-5.7	ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 GLN773 GLY774 LYS780 ASN781 SER784
Dendroidiol	-5.2	TYR32 ALA46 LYS47 PHE48 LEU49 TYR129 SER709 THR710 ASP711 LYS714 LYS780
Dendroidone	-5.7	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLY774 ASN781
Deoxyprepacifenol	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774
Deschloroelatol	-5.2	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 GLN773 GLY774 LYS780
Elatenyne	-5.5	ASN781
Elatol	-5.7	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780 LYS47 TYR129 HIS133 ASP135 ASN138 SER709 THR710 ASP711 GLN773 GLY774 LYS780
Epiaplysinol	-5.5	ASN781 SER784 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 GLY774 SER778 LYS780 ASN781
Epibrasilenol	-5.2	SER784 TYR129 HIS133 ALA706 SER709 THR710 ASP711 ALA771 GLN773 GLY774 LEU775 VAL776
Floridoside	-5.5	ALA777 SER778 LYS780 ASN781 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 GLN773 GLY774 VAL776 SER778
Filiformin	-5.7	LYS780 ASN781 TYR32 ALA46 LYS47 PHE48 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Filiforminol	-5.7	LYS780 ASN781 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773
Guimarediol	-5.5	GLY774 VAL776 SER778 LYS780 ASN781
Heterocladol	-5.2	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS780
Intricenynne	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 ILE715 ALA716 GLN773 LEU775 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 GLY774 LYS780
Isocaesitol	-5.7	ASN781
Isodihydrolaurene	-5.2	TYR32 ALA46 LYS47 SER709 THR710 ASP711 LYS714
Isolaurallene	-5.5	TYR32 ALA46 LYS47 TYR129 ALA130 HIS133 ASN138 SER709 ASP711 LYS780
Isolaureatin	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 LYS780

Isolaurene	-5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 SER772 GLN773 GLY774 ALA46 LYS47 TYR129 HIS133 ASN705 ALA706 SER709 THR710 ASP711 GLN773 GLY774
ItomanindoleA	-5.2	LYS780 ASN781 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776
Isolaurenidificin	-5.3	SER778 LYS780 ASN781
Isoafricanol	-5.2	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 LYS780
Isoallolaurinterol	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780 TYR129 HIS133 ALA706 SER709 THR710 ALA771 SER772 GLN773 GLY774 SER778 LYS780
Isoaplysin	-5.2	ASN781 SER784
Isodactyloxene A	-5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714
Isodebromolaurinterol	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Isolaurenisol	-5.2	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Isoobtusol	-5.5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Isopalisol	-5	ASN781 TYR32 ALA46 LYS47 PHE48 TYR129 HIS133 ALA706 SER709 THR710 ASP711 GLN773 GLY774
Isorigidol	-5.5	LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 ILE715 ALA716 GLN773
Kumausallene	-5	LEU775
Laurallene	-5	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ILE715 GLN773 GLY774
Laureacetal A	-5.2	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774
Laureacetal B	-5.5	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS714 GLY774 LYS780 ASN781 TYR129 HIS133 ASN138 ASN705 ALA706 SER709 THR710 ASP711 ALA771 GLN773 GLY774
Laurefurenyne A	-5.7	SER778 LYS780 ASN781
Laurefurenyne C	-5.2	TYR32 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLN773 LYS780
Laurefurenyne D	-5.5	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 ILE715 GLN773 LYS780
Laurefurenyne E	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 SER772 GLN773 GLY774
Laurefurenyne F	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 ILE715 GLN773

Laurencial	-5.2	ASN705 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 LYS780 ASN781
Laurendecumallene A	-5.5	TYR32 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780 ASN781
Laurendecumallene B	-5.5	LYS47 TYR129 HIS133 ASN138 ALA706 LEU707 SER709 THR710 ASP711 GLN773 GLY774 LEU775 VAL776 SER778 LYS780 ASN781
Laurendecumenyne A	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774 TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Laurendecumenyne B	-5.5	LYS780 ASN781
Laurenenyne	-5.5	TYR32 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 SER778 LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 GLN773 GLY774 LYS780
Laurenisol	-5.2	ASN781
Laurenone A	-5.2	TYR32 LYS47 TYR129 HIS133 ASN138 SER709 ASP711 LYS780
Laureoxanyne	-5.2	ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS780 ASN781 SER784
Laurecomin B	-5.2	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLN773
Laurecomin C	-5.2	TYR32 LYS47 PHE48 TYR129 ASN138 SER709 THR710 ASP711 GLN773
Laurencomposidiene	-5.2	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 LYS780
Laurene	-5.5	TYR32 ALA46 LYS47 SER709 THR710 ASP711 LYS714 GLN773 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774
Laurentristich-4-ol	-5.5	VAL776 SER778 LYS780 ASN781
Laureperoxide	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 SER772 GLN773 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 ALA771 GLN773 GLY774 SER778
Laurokamurene A	-5.5	LYS780 ASN781
Laurokamurene B	-5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711
Laurokamurene C	-5.5	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 GLY774 LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 ASP711 GLY774 LYS780
Laurokamurene D	-5.5	ASN781
Luzofuran	-5.5	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774

Luzonenone	-5.5	ALA46 LYS47 TYR129 HIS133 ASN705 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLY774 SER778 LYS780 ASN781
Luzonensol	-5.2	TYR32 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 GLY774 ASN781 TYR32 ALA46 LYS47 TYR129 HIS133 ASN705 ALA706 SER709 THR710 ASP711 LYS714 SER778 LYS780 ASN781 SER784
Luzonensolacetate	-5.5	TYR32 ALA46 LYS47 TYR129 ALA130 HIS133 ASN138 SER709 THR710 ASP711 LYS780
Laurepinnacin	-5.5	TYR32 ALA46 LYS47 PHE48 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780
Laurinterol	-5.4	TYR32 ALA46 LYS47 PHE48 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 LYS780
Ma'iliohydrin	-5.7	TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 SER778 LYS780
Mailione	-5.2	ASN781 LYS47 ASP126 TYR129 ALA130 HIS133 PHE134 ASP135 ASN138 CYS139 ASP140 THR141 LEU142 SER709 LYS780
Majapolene B	-5.5	ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 GLN773 GLY774 SER778
Microcladallene A	-5.5	LYS780 ASN781 SER784 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 GLN773 GLY774 SER778
Microcladallene B	-5.5	LYS780 ASN781 SER784 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 ALA771 GLY774 SER778
Microcladallene C	-5.2	LYS780 ASN781 SER784
Neoisoprelaurefucin	-5.2	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 ILE715 SER772 GLN773 TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 SER772 GLN773
Neolaurallene	-5.5	GLY774 ASN781 TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 GLN773 GLY774 LYS780
Nidificene	-5.2	ASN781
Notoryne	-5.5	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS780 ASN781 SER784 TYR32 ALA46 LYS47 TYR129 ALA130 HIS133 PHE134 ASP135 ASN138 CYS139 ASP140 THR141 LEU142 SER709 THR710 ASP711 LYS780
Octadecanedioic acid	-5.1	THR141 LEU142 SER709 THR710 ASP711 LYS780
Obtusane	-5.2	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 GLY774 LYS780 ASN781
Okamurene A	-5.5	TYR32 ALA46 LYS47 SER709 THR710 ASP711 LYS714 GLN773 GLY774

Okamurene B	-5.5	ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS780 ASN781 SER784
Okamurene C	-5.2	TYR32 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 TYR129 HIS133 ASN138 ALA706 SER709 THR710 ALA771 GLN773 GLY774 SER778 LYS780
Okamurene D	-5.5	ASN781 SER784
Okamurene E	-5.5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780 TYR32 ALA46 LYS47 TYR129 ALA130 HIS133 PHE134 ASP135 ASN138 CYS139 THR141
Omaezallene	-5.2	LEU142 SER709 THR710 ASP711 LYS714 LYS780
Oxachamigrene	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714
Palisadin A	-5.6	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774
Palisadin B	-5.5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780 TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 SER772 GLN773
Palisadin C	-5.7	GLY774 ASN781
Pannosane	-5.3	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780
Pannosanol	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780
Perforatone	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 LYS780
Perforenol	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 LYS780
Prepacifenol	-5.7	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 LYS780
Prelaureatin	-5.5	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773
Rhodophytin	-5	TYR32 LYS47 TYR129 SER709 THR710 ASP711 LYS714 GLN773 LYS780
Scopariol	-5.5	TYR32 ALA46 LYS47 PHE48 TYR129 HIS133 SER709 THR710 ASP711 LYS780
Seco-Laurokamurone	-5.5	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 GLN773 GLY774 LYS780 ASN781
Spirolaurenone	-5.7	TYR32 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 GLN773
Trans-Deacetylkumausyne	-5	TYR32 ALA46 LYS47 TYR129 HIS133 ASN138 SER709 ASP711 LYS714 LYS780
Trans-Kumausyne	-5.2	TYR32 LYS47 PHE48 TYR129 ASN138 SER709 THR710 ASP711 LYS714 GLN773 LYS780

Table S3: Natural products listed under subcategory 2 in low class for RdRp

RDRP N-Terminal

Ligands	Binding affinity ('-6.0 to -6.9)	Interacting amino acids
1,2-Dehydro-3,4-epoxypalisadin B	-6.5	ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 ALA771 GLY774 SER778 LYS780 ASN781 SER784
2-Hydroxyluzofuranone A	-6.2	TYR32 ALA46 LYS47 PHE48 TYR129 ALA706 SER709 THR710 ASP711 SER772 GLN773 GLY774 ASN781
2-Hydroxyluzofuranone B	-6.2	TYR129 HIS133 ASN705 ALA706 SER709 THR710 ALA771 SER772 GLN773 GLY774 LYS780 ASN781 SER784 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 VAL776 SER778 LYS780
3 alpha-hydroperoxy-3-epiaplysin	-6	ASN781 ALA46 LYS47 TYR129 HIS133 ALA706 LEU707 SER709 THR710 ASP711 LYS714 ALA771 GLN773 GLY774 LEU775
3-Bromo-4, 5-dihydroxybenzaldehyde	-6.1	VAL776 SER778 LYS780 ASN781
3-Bromobarekoxide	-6	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774
3-Epi-PerforenoneA	-6	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714
3R,4S-luzonolone	-6	TYR32 ALA46 LYS47 TYR129 HIS133 ASN705 ALA706 SER709 THR710 GLY774 LYS780 ASN781 SER784
3S, 4R-luzonolone	-6	TYR32 LYS47 TYR129 ASN705 ALA706 LEU707 SER709 THR710 ASP711 GLN773 GLY774 SER778 LYS780 ASN781 ALA46 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 ASP711 ALA771 GLY774 SER778 LYS780 ASN781
5-acetoxypalisadin B	-6.1	SER784
5alpha-Hydroxyaplystatin	-6.2	TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 GLN773 GLY774
9-hydroxy-3-epi-perforenone A	-6.2	ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 SER772 GLN773 GLY774 LYS780 ASN781 TYR32 LYS47 PHE48 LEU49 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 ALA771 GLN773 GLY774 SER778
11,14-dihydroaplysia-5,11,14,15-Tetrol	-6.9	LYS780 ASN781
15-hydroxypalisadin A	-6.2	ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780 ASN781 TYR32 ALA46 LYS47 PHE48 TYR129 HIS133 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLY774 VAL776 ALA777
Acetylmajapolene A	-6.5	SER778 LYS780 ASN781
Acetylmajapolene B	-6.2	ALA46 LYS47 TYR129 ALA130 HIS133 ASN138 CYS139 ASP140 THR141 LEU142 SER709 THR710 ASP711 LYS780
Aldingenin D	-6	TYR32 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 LYS780 ASN781 SER784
Aplystatin	-6	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLY774 LYS780

Aristolan-10-ol-9-one	-6	TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 VAL776 SER778 LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 ALA130 LEU131 HIS133 PHE134 ASP135 ASN138 CYS139 THR141 SER709 THR710
Aplysiodiol	-6.7	ASP711 LYS780
Barekoxide	-6.5	TYR32 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 GLN773 GLY774 LYS780 ASN781 TYR32 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776 SER778
Beta-sitosterol	-6.9	LYS780 ASN781
Bromophycolide G	-6.7	ASN705 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 SER778 LYS780 ASN781 TYR32 ALA46 LYS47 PHE48 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774
Bromophycolide I	-6.7	VAL776 SER778 LYS780 ASN781
Caespitol	-6	TYR32 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 GLY774 LYS780 ASN781 TYR32 LYS47 TYR129 ASN705 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 SER778
Callophycoic acid A	-6.4	LYS780 ASN781
Callophycoic acid B	-6.1	LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 SER778 LYS780 ASN781
Callophycoic acid G	-6.7	TYR32 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 SER778 LYS780
Callophycoic acid H	-6.7	ASN781 TYR32 ALA46 LYS47 TYR129 HIS133 ASN138 ASN705 ALA706 LEU707 SER709 THR710 ASP711 ALA771 GLY774
Callophycoic acid I	-6.9	VAL776 SER778 LYS780 ASN781
Callophycoic acid J	-6.2	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780
Callophycol A	-6	TYR32 LYS47 TYR129 ALA130 HIS133 ASN138 ALA706 SER709 THR710 ASP711 LYS714 GLY774 LYS780 TYR32 ALA46 LYS47 TYR129 ALA130 HIS133 ASN138 ALA706 SER709 THR710 ASP711 GLN773 GLY774 LYS780
Callophycol B	-6.2	ASN781
Chamigrene Lactone	-6.5	TYR32 ALA46 LYS47 PHE48 TYR129 ASN138 SER709 THR710 ASP711 LYS714 LYS780
Compositacin B	-6.2	ALA46 LYS47 TYR129 SER709 THR710 ASP711 GLN773 GLY774
Compositacin E	-6	TYR32 ALA46 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS780 ASN781
Compositacin F	-6.2	TYR32 ALA46 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS780 ASN781
Compositacin I	-6.2	TYR32 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLY774 LYS780 ASN781
Compositacin N	-6	TYR129 HIS133 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 VAL776 SER778 LYS780 ASN781

Cholest-4-en-3-one	-6.5	TYR32 LYS47 PHE48 TYR129 ASN138 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776 ALA777 SER778 LYS780 ASN781
Cholest-5-en-3alpha-ol	-6.9	TYR32 LYS47 PHE48 LEU49 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 SER778 LYS780 ASN781
Cholest-5-en-3beta-ol	-6.7	TYR32 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776 ALA777 SER778 LYS780 ASN781
Debromoisocalenzanol	-6	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714
JaponenyneA	-6	LYS47 TYR129 ALA130 HIS133 ASP135 ASN138 THR141 SER709 THR710 GLN773 GLY774 SER778 LYS780 ASN781
Johnstonol	-6.2	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS780
Laurecomin A	-6	TYR32 ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 GLY774 LYS780 ASN781
Laurecomin D	-6.2	TYR32 ALA46 LYS47 PHE48 TYR129 ALA706 SER709 THR710 ASP711 LYS714 GLY774 LYS780
Laurenokomarin	-6	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS780
Laurepoxyene	-6	LYS47 TYR129 HIS133 ASN138 ASN705 ALA706 SER709 THR710 ALA771 GLY774 SER778 LYS780 ASN781
Laureacetal C	-6	TYR129 HIS133 ALA706 SER709 THR710 ALA771 SER772 GLN773 GLY774 SER778 LYS780 ASN781 SER784
Laurefurenyne B	-6	LYS47 TYR129 ALA130 HIS133 ASP135 ASN138 CYS139 THR141 LEU142 SER709 THR710 LYS780 ASN781
Laurinterolacetate	-6	ALA46 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 ASP711 GLN773 GLY774 LYS780 ASN781 SER784
Luzondiol	-6	ALA46 LYS47 TYR129 HIS133 ALA706 SER709 THR710 ASP711 GLY774 LYS780 ASN781
Majapolene A	-6.2	TYR32 ALA46 LYS47 TYR129 HIS133 ASN705 ALA706 SER709 THR710 ASP711 LYS780 ASN781 SER784
Oryzalexin S	-6.5	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714
Pacifenol	-6.2	ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 LYS780
Palisadin D	-6.2	ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 VAL776 ALA777 SER778 LYS780 ASN781
Perforenone A	-6	TYR32 ALA46 LYS47 TYR129 SER709 THR710 ASP711 LYS714
Saringosterol	-6.9	LYS47 TYR129 HIS133 PHE134 ASP135 ASN138 CYS139 SER709 THR710 ASP711 LYS714 ILE715 SER772 GLN773 GLY774 LYS780
Tiomanene	-6.2	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLY774 SER778 LYS780 ASN781

Table S4: Natural products listed in lower-moderate class for RdRp

RDRP N-Terminal

Ligands	Binding affinity (⁻ 7.0 to ⁻ 7.9)	Interacting amino acids
5alpha-cholestane-3,6-dione	-7	TYR32 LYS47 TYR129 ASN138 ALA706 SER709 THR710 ASP711 LYS714 ALA771 GLY774 VAL776 ALA777 SER778 LYS780 ASN781 TYR32 LYS47 PHE48 LEU49 TYR129 ASN138 ASN705 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774
6-hydroxycholest-4-en-3-one	-7.1	VAL776 ALA777 SER778 LYS780 ASN781
10-acetoxyangasiol	-7.4	TYR32 ALA46 LYS47 PHE48 TYR129 ALA706 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 TYR32 ALA46 LYS47 PHE48 LEU49 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774
10-epi-Dehydrothyrsiferol	-7.2	SER778 LYS780 ASN781 TYR32 ALA46 LYS47 TYR129 HIS133 ALA706 LEU707 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 LEU775
13-Hydroxyprethyrseanol A	-7	VAL776 SER778 LYS780 ASN781 LYS47 TYR129 HIS133 ASP135 ASN138 ALA706 SER709 THR710 ALA771 SER772 GLN773 GLY774 VAL776 SER778 ILE779 LYS780
15,16-Dehydrovenustatriol	-7.7	ASN781 TYR32 ALA46 LYS47 PHE48 LEU49 TYR129 HIS133 ALA706 SER709 THR710 ASP711 PHE766 ALA771 SER772 GLY774 VAL776
15-DehydroxythyrsenolA	-7.5	SER778 ILE779 LYS780 ASN781 THR801 TYR32 LYS47 PHE48 TYR129 ALA706 SER709 THR710 ASP711 LYS714 PHE766 ALA771 SER772 GLN773 GLY774 SER778 ILE779
16-Hydroxydehydrothyrsiferol	-7.7	LYS780 ASN781 GLU796 THR801 ASP135 GLU136 GLY137 LYS143 PHE157 ASN158 LYS159 LYS160 ASP161 TRP162 TYR163 HIS613 MET615 PHE766 SER768
Beta cryptoxanthin	-7.9	ALA771 SER772 SER778 ILE779 LYS780 LYS783 GLU796 THR801 TYR32 LYS47 ASP126 TYR129 ALA130 HIS133 PHE134 ASP135 ASN138 CYS139 ASP140 THR141 LEU142 SER709 ASP711 LYS714
Brassicasterol	-7.9	LYS780 TYR32 ALA46 LYS47 PHE48 TYR129 ALA130 HIS133 ASP135 ASN138 CYS139 SER709 THR710 ASP711 LYS714 SER772 GLN773
Bromophycoic acid A	-7.5	LYS780 TYR32 ALA46 LYS47 PHE48 TYR129 ASN138 ASN705 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774
Bromophycoic acid D	-7.5	VAL776 SER778 LYS780 ASN781
Bromophycoic acid E	-7.9	TYR32 ALA46 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 ILE715 ALA716 GLN773 LEU775
Bromophycolide A	-7.9	TYR32 ALA46 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780
Bromophycolide B	-7.4	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 LEU775 LYS780 ASN781

Bromophycolide C	-7.5	TYR32 LYS47 ASP126 TYR129 ALA130 LEU131 HIS133 PHE134 ASP135 ASN138 CYS139 ASP140 THR141 LEU142 LYS780 TYR32 LYS47 PHE48 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776 SER778 LYS780
Bromophycolide D	-7.8	ASN781
Bromophycolide F	-7.7	TYR32 ALA46 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 ASP711 GLY774 LYS780 ASN781
Bromophycolide J	-7.5	TYR32 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 ILE715 SER772 GLN773 GLY774 LYS780 TYR129 ASN705 ALA706 LEU707 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 LEU775 VAL776 SER778 LYS780
Bromophycolide M	-7	ASN781
Bromophycolide N	-7.6	TYR32 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 SER772 GLN773 GLY774 SER778 LYS780 ASN781
Bromophycolide O	-7.7	LYS47 TYR129 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 SER778 LYS780 ASN781
Bromophycolide Q	-7.5	TYR32 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ALA771 SER772 GLN773 GLY774 LYS780 ASN781
Bromophycolide T	-7.3	LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 LYS780 ASN781
Bromophycolide U	-7.6	TYR129 HIS133 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 VAL776 ALA777 SER778 LYS780 ASN781
Callophycoic acid C	-7.6	TYR32 ALA46 LYS47 TYR129 HIS133 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 LYS780 ASN781 ALA46 LYS47 TYR129 ASN705 ALA706 SER709 THR710 ASP711 LYS714 ILE715 ALA716 ALA771 SER772 GLN773 GLY774 LEU775
Callophycoic acid D	-7.8	VAL776 SER778 LYS780 ASN781 TYR32 ALA46 LYS47 PHE48 TYR129 SER709 THR710 ASP711 LYS714 ILE715 ALA771 SER772 GLN773 GLY774 SER778 LYS780
Callophycoic acid E	-7.2	ASN781
Campesterol	-7.5	TYR32 LYS47 ASP126 TYR129 ALA130 HIS133 PHE134 ASP135 ASN138 CYS139 THR141 LEU142 SER709 ASP711 LYS714 LYS780 TYR32 LYS47 PHE48 TYR129 ASN138 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776 ALA777
Cholest-4-en-3,6-dione	-7.1	SER778 LYS780 ASN781
Dehydrovenustatriol	-7.7	LYS47 TYR129 HIS133 ASN138 ALA706 SER709 PHE766 ALA771 SER772 GLY774 VAL776 SER778 ILE779 LYS780 ASN781 THR801
Lactodehydrothysiferol	-7.2	TYR32 LYS47 TYR129 ASN138 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774 VAL776 SER778 LYS780 ASN781
Neurymenolide A	-7.1	TYR32 ALA46 LYS47 TYR129 ASN138 ALA706 SER709 THR710 ASP711 LYS714 GLN773 GLY774 SER778 LYS780 ASN781
Neurymenolide B	-7.7	TYR32 ALA46 LYS47 TYR129 ALA130 HIS133 ASP135 ASN138 THR141 SER709 THR710 ASP711 LYS714 GLN773 GLY774 LYS780 TYR32 ALA46 LYS47 PHE48 TYR129 HIS133 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776
Neoirietetraol	-7	SER778 LYS780 ASN781 ALA46 LYS47 TYR129 HIS133 ASN138 MET615 SER709 THR710 ASP711 PHE766 ALA771 SER772 GLN773 GLY774 SER778 ILE779
Predehydrovenustatriolacetate	-7	LYS780 ASN781 THR801

Prethyrserenol A	-7.7	TYR32 ALA46 LYS47 TYR129 ASN705 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776 SER778 ILE779 LYS780 ASN781 GLU796
Pseudodehydrothyrseriferol	-7.2	TYR32 ALA46 LYS47 PHE48 LEU49 TYR129 ALA706 SER709 THR710 ASP711 LYS714 PHE766 SER768 ALA771 SER772 GLN773 GLY774 ALA777 SER778 ILE779 LYS780 ASN781
Stigmasterol	-7	TYR32 LYS47 TYR129 ASN138 SER709 THR710 ASP711 LYS714 ILE715 ALA716 SER772 GLN773 GLY774 LEU775

Table S5: Natural products listed in upper-moderate class for RdRp

RDRP N-Terminal		
Ligands	Binding affinity (⁻ 8.0 and higher)	Interacting amino acids
Bromophycoic acid B	-8.2	TYR32 ALA46 LYS47 PHE48 TYR129 ALA130 HIS133 ASP135 ASN138 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 LEU775 LYS780
Bromophycoic acid C	-8.2	TYR32 LYS47 TYR129 ALA130 HIS133 ASN138 CYS139 SER709 THR710 ASP711 LYS714 ILE715 GLN773 GLY774 LYS780
Bromophycolide E	-8.5	TYR32 ALA46 LYS47 TYR129 ALA130 HIS133 PHE134 ASP135 ASN138 CYS139 ASP140 THR141 LEU142 SER709 THR710 LYS780 ASN781
Bromophycolide H	-8	TYR32 ALA46 LYS47 PHE48 LEU49 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 LYS780 ASN781
Bromophycolide K	-8.2	TYR32 ALA46 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776 SER778 LYS780 ASN781
Bromophycolide L	-8.2	LYS780 ASN781
Bromophycolide P	-8.2	TYR32 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 SER772 GLN773 GLY774 SER778 LYS780 ASN781
Bromophycolide R	-8.2	TYR32 LYS47 TYR129 HIS133 ASN138 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 LYS780 ASN781
Bromophycolide S	-8.7	TYR32 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 ASP711 GLY774 LYS780 ASN781
Callicladol	-8.8	TYR32 LYS47 TYR129 HIS133 ASN138 ALA706 SER709 THR710 ASP711 GLY774 SER778 LYS780 ASN781
Dehydrothyrseriferol	-8.9	ALA46 LYS47 PHE48 TYR129 HIS133 ALA706 SER709 THR710 ASP711 PHE766 SER768 ALA771 SER772 GLN773 GLY774 VAL776 SER778 ILE779 LYS780 ASN781 THR801
Isodehydrothyrseriferol	-8.2	ALA46 LYS47 PHE48 TYR129 HIS133 SER709 THR710 ASP711 PHE766 ALA771 SER772 GLN773 GLY774 VAL776 SER778 ILE779 LYS780 ASN781 THR801

Laurebiphenyl	-8	TYR32 LYS47 ASP126 TYR129 ALA130 HIS133 PHE134 ASP135 ASN138 CYS139 ASP140 THR141 LEU142 SER709 LYS780 TYR32 ALA46 LYS47 TYR129 ASP135 GLY137 ASN138 ALA706 SER709 THR710 ASP711 ALA771 SER772 GLN773 GLY774 SER778
Lithothamin A	-9	ILE779 LYS780 ASN781 GLU796
Mammeisin	-8	TYR32 ALA46 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ILE715 SER772 GLN773 GLY774 SER778 LYS780 ASN781 TYR32 LYS47 TYR129 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 VAL776 ALA777 SER778 ILE779
Thyrsenol A	-8	LYS780 ASN781 GLU796 ALA46 LYS47 TYR129 HIS133 ASN705 ALA706 SER709 THR710 ASP711 LYS714 ALA771 SER772 GLN773 GLY774 SER778 LYS780
Thyrsenol B	-8	ASN781 ALA46 LYS47 PHE48 TYR129 HIS133 ASN138 HIS613 ASN705 ALA706 SER709 THR710 ASP711 PHE766 SER768 ALA771 SER772
Thyrsiferol	-8.2	GLN773 GLY774 VAL776 SER778 LYS780 ASN781

Table S6: Natural products with highest binding affinity for RdRp

C-Terminal catalytic core region RdRp		
Ligands	Binding Affinity (Kcal/mol)	Amino acids involved
Bromophycoic acid B	-8.2	ASP452 LYS551 ARG553 ALA554 ARG555 THR556 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 ARG624 ASP760 PHE793 MET794 SER795 LYS798
Bromophycoic acid C	-7.7	ARG555 ASP618 TYR619 PRO620 LYS621 CYS622 ASN691 SER759 ASP760 ASP761 PHE793 MET794 SER795 LYS798
Bromophycolide E	-7.2	ARG553 ARG555 ASP618 TYR619 PRO620 CYS622 ASP623 THR680 SER682 THR687 ALA688 ASN691 LEU758 SER759 ASP760 ASP761 CYS813
Bromophycolide H	-6.5	ARG553 ARG555 ASP618 LYS621 CYS622 ASP623 LEU758 SER759 ASP760 ASP761 CYS813
Bromophycolide K	-6.5	LYS551 ARG553 ARG555 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 ASN691 SER759 ASP760 ASP761 LYS798
Bromophycolide L	-7.0	ARG553 ARG555 TRP617 ASP618 TYR619 LYS621 CYS622 ASP623 ASN691 LEU758 SER759 ASP760 ASP761 CYS813
Bromophycolide P	-6.5	ARG553 ARG555 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 ASP760 ASP761 SER814
Bromophycolide R	-7.5	ASP164 VAL166 GLU167 LYS551 ARG553 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 ASP760 PHE793 MET794 SER795 LYS798
Bromophycolide S	-7.9	ASP164 VAL166 GLU167 LYS551 ARG553 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 PHE793 MET794 SER795 LYS798 ASP161 ASP164 VAL166 GLU167 LYS551 ARG555 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 THR680 ASN691 SER759 ASP760
Callicladol	-8.2	PHE793 MET794 SER795 LYS798

Dehydrothysiferol	-7.8	ASP164 VAL166 GLU167 LYS551 ARG555 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 THR680 ASN691 SER759 ASP760 PHE793 SER795 LYS798
Isodehydrothysiferol	-7.7	ASP164 VAL166 GLU167 LYS551 ARG553 ARG555 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 ASP760 PHE793 MET794 SER795 LYS798
Laurebiphenyl	-7.2	ASP164 VAL166 GLU167 LYS551 ARG553 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 ASP760 PHE793 SER795 LYS798 LYS551 ARG553 ARG555 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 ARG624 THR680 SER682 THR687 ASN691 LEU758 SER759
Lithothamin A	-8.0	ASP760 ASP761 LYS798 GLU811 CYS813 SER814
Mammeisin	-6.2	LYS551 ARG555 TRP617 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 ASN691 ASP760 ASP761 ALA762 LYS798
Thyrsenol A	-6.9	ARG555 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 THR687 ALA688 ASN691 LEU758 SER759 ASP760 ASP761 CYS813
Thyrsenol B	-7.2	ASP164 VAL166 GLU167 LYS551 ARG553 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 LEU758 ASP760 ASP761 PHE793 MET794 SER795 LYS798 GLU811 CYS813 SER814
Thysiferol	-7.2	ASP164 VAL166 GLU167 LYS551 TRP617 ASP618 TYR619 PRO620 LYS621 CYS622 ASP623 ASP760 ASP761 PHE793 SER795 LYS798 GLU811 CYS813 SER814

Table S7: Outcome of docking the C-terminal catalytic region of RdRP

NSP15 Endoribonuclease		
Ligands	Binding affinity ('-4.0 to -4.9)	Interacting amino acids
9-octadecanoic acid	-4.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
14-methylpentadecanoic acid	-4.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
Bosseopentanoic acid	-4.9	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344
Halomon	-4.2	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Hordenine	-4.7	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Octadecanedioic acid	-4.9	HIS235 ASP240 HIS243 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
Tiomanene	-4.7	ASN75 LEU76 LYS181 GLN188 GLN189 LEU190 PRO191 GLU192 THR322 TYR325 GLU327

Table S8: Natural products listed under subcategory 1 in low class for nsp15

NSP15 Endoribonuclease

Ligands	Binding affinity ('-5.0 to -5.9)	Interacting amino acids
1-methyl-2,3,5-tribromoindole	-5.2	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LEU346
2-bromospironipol	-5.7	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
3,4-epoxypalisadin B	-5.9	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
3alpha-Hydroxydebromoaplysin	-5.7	HIS250 LYS290 VAL292 SER294 MET331 TYR343 PRO344 LYS345 LEU346
4-Hydroxy-1,8-epi-isotenerone	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 THR341 TYR343
5-acetoxyoachamigrene	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
5-acetoxypalisadin B	-5.9	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 LEU346
6,8-cycloeudesmane	-5.2	HIS250 LYS290 VAL292 CYS293 SER294 MET331 TYR343 PRO344 LYS345 LEU346
7-acetyl-aplysiol	-5.9	HIS235 GLN245 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 THR341 TYR343
9-Deoxyelatol	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343
10-Bromo-beta-chamigrene	-5.7	HIS235 LEU246 GLY247 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344
Aristolan-8-en-1-one.mol	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 THR341 TYR343
Aristolan-10-ol-9-one	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 THR341 TYR343
Aristolane	-5.2	HIS235 LEU246 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Almadioxide	-5.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 THR341 TYR343
Aromadendrene	-5.5	GLN245 HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Aplysiol-7-one	-5.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 THR341 TYR343
Aplysiolic acid	-5.9	HIS235 GLN245 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343
Beta Synderol	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344
Brasilanol	-5.5	HIS235 GLN245 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344
(-)-BisezakyneA	-5.7	HIS235 GLY248 HIS250 LYS290 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343
Callenzanol	-5.9	HIS235 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Chamigrene epoxide	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343
Chinzallene	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344 LEU346
Compositacin A	-5.5	HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346

Compositacin D	-5.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344
Compositacin E	-5.9	GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Compositacin F	-5.5	GLN245 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Compositacin G	-5.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344
Compositacin H	-5.7	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Compositacin L	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
Compositacin M	-5.7	HIS235 GLN245 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Compositacin N	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344
Cycloelatanene A	-5.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Cycloelatanene B	-5.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 THR341 TYR343
Cycloeudesmol	-5.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 THR341 TYR343
Cyclolaurenol	-5.7	HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Dactyllyne	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LEU346
Debromoepiaplysinol	-5.9	HIS235 GLY247 GLY248 HIS250 LYS290 TRP333 THR341 TYR343
Dendroidiol	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
Dendroidone	-5.9	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344
Deoxyprepacifenol	-5.7	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Deschloroelatol	-5.9	HIS235 GLY248 HIS250 LYS290 CYS291 VAL292 SER294 THR341 TYR343 LEU346
Elatol	-5.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344
Epibrasilenol	-5.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344
Elatenyne	-5.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Floridoside	-5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 PHE342 TYR343
Guimarediol	-5.9	GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LEU346
Heterocladol	-5.7	HIS235 GLN245 LEU246 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Isolaurenidificin	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Isoafricanol	-5.5	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Isoaplysin	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343
Isodactyloxene A	-5.5	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346

Isoobtusol	-5.5	GLN245 LEU246 HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Isopalisol	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Isorigidol	-5.5	GLN245 HIS250 ASN278 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Intricenyne	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Isolaurallene	-5.5	HIS235 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Itomanindole A	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344 LEU346
Kumausallene	-5.2	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
Laurecomin B	-5.7	HIS250 ASN278 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Laurecomin C	-5.5	HIS235 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Laurenokomarin	-5.7	HIS235 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Luzondiol	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Luzonensin	-5.2	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LYS345
Luzonensol	-5.7	LEU346
Luzonensolacetate	-5.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Laurallene	-5.5	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 MET331 THR341 TYR343 PRO344 LYS345 LEU346
Laureacetal B	-5.9	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344
Laureacetal C	-5.9	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343
Laurefurenyne A	-5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Laurefurenyne B	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Laurefurenyne D	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
Laurefurenyne E	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Laurefurenyne F	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344 LEU346
Laurencenyne	-5.2	HIS235 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Laurencial	-5.7	HIS235 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 LEU346
Laurendecumallene A	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 PHE342 TYR343 PRO344 LYS345 LEU346
Laurendecumallene B	-5.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 PHE342 TYR343 PRO344
Laurendecumenyne B	-5.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343

Laurenenyne	-5.9	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343
Laurenisol	-5.7	HIS235 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 PHE342 TYR343
Laureoxanyne	-5.9	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344
Laurepinnacin	-5.5	HIS235 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344
Mailiohydrin	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Mailione	-5.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 THR341 TYR343
Microcladallene A	-5.2	HIS235 GLN245 LEU246 GLY247 HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Microcladallene B	-5.2	GLN245 LEU246 GLY247 HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Microcladallene C	-5.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Neoisoprelaurefucin	-5.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344
Neolaurallene	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Nidificene	-5.5	GLN245 LEU246 HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Obtusane	-5.7	GLN245 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Okamurene C	-5.9	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Okamurene E	-5.7	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Omaezallene	-5.5	HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Pacifenol	-5.5	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Palisadin B	-5.7	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Palisadin C	-5.7	GLN245 HIS250 LYS290 CYS291 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Palisadin D	-5.5	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Pannosane	-5.5	GLN245 LEU246 HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Perforatone	-5.7	HIS250 LYS290 VAL292 CYS293 SER294 MET331 TYR343 PRO344 LYS345 LEU346
Perforenol	-5.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Prelaureatin	-5.2	GLN245 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Rhodophytin	-5.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LEU346
Scopariol	-5.2	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 THR341 TYR343
Trans-Deacetylkumausyne	-5.7	HIS235 GLY247 GLY248 LEU249 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Trans-Kumausyne	-5.2	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343

Trans-Laurencenyne	-5.2	HIS235 GLY248 HIS250 LYS290 VAL292 VAL315 TRP333 CYS334 GLU340 THR341 TYR343
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Table S9: Natural products listed under subcategory 2 in low class for nsp15

NSP15 Endoribonuclease		
Ligands	Binding affinity (⁻ 6.0 to -6.9)	Interacting amino acids
(-)-3-(E)-bromomethylidene-10beta-bromo-beta-chamigrene	-6	HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
(+)-3-(Z)-bromomethylidene-10beta-bromo-beta-chamigrene	-6	HIS235 LEU246 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343
(5S)-5-Acetoxy-beta-bisabolene	-6	PRO344 LYS345 LEU346
(6R,9R,10S)-10-bromo-9-hydroxychamigra-2,7(14)-diene	-6.5	HIS250 ASN278 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
(10R)-10-Bromo-alpha-chamigrene	-6.2	LEU246 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
1,2-Dehydro-3,4-epoxypalisadin B	-6	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344
2-Hydroxyluzofuranone B	-6.5	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
3,7-dihydroxydihydrolaurene	-6.7	GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341
3 beta-Hydroperoxyaplysin	-6.2	TYR343 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343
3-Bromo-4, 5-dihydroxybenzaldehyde	-6.5	PRO344 LYS345 LEU346
3-Epi-PerforenoneA	-6	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 THR341 TYR343 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341
3R,4S-luzonolone	-6	TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343
3S, 4R-luzonolone	-6.5	PRO344 LYS345 LEU346
(3Z)-laurenyne	-6	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344 LYS345
3-Bromobarekoxide	-6.5	LEU346

4-hydroxypalisidin C	-6	HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
5-epi-maneolactone	-6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
7-hydroxylaurene	-6.7	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343
8,10-dibromoisoplysin	-6	PRO344
9-hydroxy-3-epi-perforenone A	-6.2	GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 CYS293 SER294 THR341
10-acetoxyangasiol	-6.7	TYR343 PRO344 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343
10-Bromosoaplyin	-6	PRO344
10-Hydroxyaplysin	-6	HIS235 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343
10-hydroxyisolaurene	-6.7	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345
12-hydroxy Isolaurene	-6.5	LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345
12-Hydroxypalisadin B	-6.2	LEU346
15-hydroxypalisadin A	-6.7	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 PHE342 TYR343 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345
15-Hydroxylaurene	-6.2	LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345
15-Oxolaurene	-6.5	LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 GLU340 THR341 TYR343 PRO344
Acetylmajapolene A	-6.7	LYS345 LEU346 HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 PRO344
Acetylmajapolene B	-6.7	LYS345 LEU346
Aldingenin A	-6.2	GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Aldingenin B	-6.5	HIS250 ASN278 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Aldingenin C	-6.5	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346

Aldingenin D	-6.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TYR343 PRO344 LYS345 LEU346
Allolaurinterol	-6.9	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Allolaurinterolacetate	-6.2	HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Aplysinol	-6	GLN245 HIS250 ASN278 LYS290 CYS291 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
AxinynoneB	-6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 THR341 TYR343
Aplysiodiol	-6.9	HIS235 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Bromocyclococanol	-6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Bromlaurenidificin	-6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344
Bromocuparene	-6.2	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Callophycoic acid G	-6.9	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Callophycoic acid J	-6.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
Callophycol A	-6.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LEU346
Callophycol B	-6.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LEU346
Chamigrene Lactone	-6.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344
Compositacin B	-6.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 THR341 TYR343
Compositacin C	-6	LEU246 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LEU346
Compositacin I	-6	HIS235 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
Compositacin J	-6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
Compositacin K	-6	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 THR341 TYR343
Cycloisoallolaurinterol	-6.2	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344
Chlorofucin	-6	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346

Cupalaurenol	-6.2	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LEU346
Caespitane	-6.2	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Caespitol	-6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Caesspitenone	-6.2	HIS235 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Debromoisocalenzanol	-6.2	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Debromolaurinterol	-6.5	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Debromolaurinterolacetate	-6	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Debromoaplysin	-6	HIS250 LYS290 VAL292 SER294 MET331 TYR343 PRO344 LYS345 LEU346
Epiaplysinol	-6.5	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LEU346
Filiformin	-6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Filiforminol	-6.7	HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LEU346
Isoallolaurinterol	-6.7	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Isodebromolaurinterol	-6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LEU346
Isolaurenisol	-6.9	GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346 GLN245 LEU246 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345
Isocaespitol	-6	LEU346
Isodihydro laurene	-6.2	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340
Isolaureatin	-6	THR341 TYR343 PRO344
Isolaurene	-6.5	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Japonenyne A	-6	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Johnstonol	-6	GLN245 HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344
Laurecomin A	-6.3	LYS345 LEU346
Laurecomin D	-6.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343

Laurencomposidiene	-6	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344
Laurene	-6.5	LYS345 LEU346
Laurentristich-4-ol	-6.5	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Laureperoxide	-6.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343
Laurepoxyene	-6	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343
Laurinterolacetate	-6.2	PRO344
Laurokamurene A	-6.5	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Laurokamurene B	-6.2	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Laurokamurene C	-6.5	HIS235 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Laurokamurene D	-6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343
Luzofuran	-6.2	PRO344 LYS345
Luzonenone	-6	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 LEU346
Laurinterol	-6.5	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343
Laureacetal A	-6	PRO344
Laurefurenyne C	-6	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343
Laurendecumenyne A	-6.2	PRO344 HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345
Laurenone A	-6.2	LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345
Majapolene A	-6.5	LEU346
Majapolene B	-6.5	HIS235 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 SER294 TRP333 THR341
Mammeisin	-6.9	TYR343 PRO344 LYS345 LEU346

Neoirietetraol	-6.2	HIS235 LEU246 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Notoryne	-6	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 PRO344
Okamurene A	-6.2	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Okamurene B	-6.5	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Okamurene D	-6	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Oxachamigrene	-6	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Oryzalexin S	-6.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343
Palisadin A	-6.5	PRO344
Pannosan	-6.3	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Perforenone A	-6	HIS250 ASN278 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346
Prepacifenol	-6.2	HIS250 LYS290 VAL292 CYS293 SER294 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341 TYR343
Seco-Laurokamurone	-6.5	PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344
Spirolaurenone	-6	LEU346

Table S10: Natural products listed in lower-moderate class for nsp15

NSP15 Endoribonuclease		
Ligands	Binding affinity (⁻ 7.0 to ⁻ 7.9)	Interacting amino acids
2-Hydroxyluzofuranone A	-7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
3 alpha-hydroperoxy-3-epiaplysin	-7.2	HIS235 LEU246 GLY247 GLY248 LEU249 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344
5alpha-Hydroxyaplystatin	-7	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
10-epi-Dehydrothysiferol	-7.7	HIS235 ASP240 HIS243 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343

11,14-dihydroaplysia-5,11,14,15-Tetrol	-7	HIS235 LEU246 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
13-Hydroxyprathyrenol A	-7.5	HIS235 ASP240 HIS243 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
15,16-Dehydrovenustatriol	-7.9	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
Aplysistatin	-7	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 THR341 TYR343
Beta cryptoxanthin	-7.5	HIS250 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 ASP336 GLU340 THR341 TYR343 PRO344
Bromophycoic acid A	-7.7	HIS235 GLN245 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
Bromophycoic acid D	-7.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 SER294 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Bromophycoic acid E	-7.9	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
Bromophycolide A	-7.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 MET331 TRP333 THR341 TYR343 PRO344 LYS345
Bromophycolide B	-7.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 THR341 TYR343
Bromophycolide C	-7.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Bromophycolide D	-7.5	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 LYS345 LEU346
Bromophycolide E	-7.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Bromophycolide F	-7.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343
Bromophycolide H	-7.2	HIS235 HIS243 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 THR341 TYR343
Bromophycolide I	-7.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 SER294 TRP333 THR341 TYR343 LEU346
Bromophycolide J	-7.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 SER294 GLU340 THR341 TYR343 LEU346
Bromophycolide M	-7.7	HIS235 GLN245 LEU246 GLY248 HIS250 LYS290 CYS291 VAL292 SER294 THR341 TYR343 PRO344 LEU346

Bromophycolide N	-7.7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 MET331 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Bromophycolide R	-7.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Barekoxide	-7.2	HIS235 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345
Bromophycolide S	-7.7	LEU346
Callophycoic acid A	-7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 TRP333 GLU340 THR341 TYR343 LEU346 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 CYS291 VAL292 CYS293 SER294 THR341 TYR343
Callophycoic acid C	-7.7	PRO344 LYS345 LEU346
Callophycoic acid D	-7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 THR341 TYR343
Callophycoic acid E	-7	GLY248 HIS250 LYS290 VAL292 CYS293 SER294 MET331 TRP333 THR341 TYR343 PRO344 LYS345
Callophycoic acid F	-7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344
Callophycoic acid H	-7	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 GLU340 THR341 TYR343 PRO344 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 MET331 THR341 TYR343 PRO344
Callophycoic acid I	-7	LYS345 LEU346
Cholest-5-en-3alpha-ol	-7.7	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 MET331 TYR343 PRO344 LYS345 LEU346 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 GLU340 THR341 TYR343 PRO344
Dehydrovenustatriol	-7.2	LYS345 LEU346 HIS235 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345
Isodehydrothyrsiferol	-7.7	LEU346 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 MET331 TRP333 THR341 TYR343 PRO344
Lactodehydrothyrsiferol	-7	LYS345 LEU346 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 PRO344 LYS345
Neurymenolide B	-7.7	LEU346 HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 MET331 TRP333 GLU340 THR341 TYR343 PRO344
Predehydrovenustatriolacetate	-7.2	LYS345 LEU346 HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343
Prethyrsenol A	-7.2	PRO344 LYS345 LEU346

Pseudodehydrothysiferol	-7.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 MET331 TRP333 THR341 TYR343 PRO344 LYS345 LEU346
Saringosterol	-7.5	HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 PRO344

Table S11: Natural products listed in upper-moderate class for nsp15

NSP15 Endoribonuclease		
Ligands	Binding affinity (-8.0 and higher)	Interacting amino acids
5 alpha-cholestane-3,6-dione	-8.6	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344
6-hydroxycholest-4-en-3-one	-8.2	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
15-Dehydroxythysenol A	-8	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
16-Hydroxydehydrothysiferol	-8.2	HIS235 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
Beta-sitosterol	-8	HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344 LEU346
Brassicasterol	-8.5	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344
Bromophycoic acid B	-8.5	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
Bromophycoic acid C	-8.5	HIS235 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
Bromophycolide G	-8.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Bromophycolide K	-8	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL315 MET331 TRP333 GLU340 THR341 TYR343
Bromophycolide L	-8	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 TRP333 THR341 TYR343 LEU346
Bromophycolide O	-8.5	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 TRP333 THR341 TYR343
Bromophycolide P	-8.2	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 CYS291 VAL292 SER294 THR341 TYR343
Bromophycolide Q	-8.2	HIS235 ASP240 HIS243 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 TRP333 GLU340 THR341 TYR343
Bromophycolide T	-8.7	HIS235 GLN245 LEU246 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 THR341 TYR343 PRO344 LEU346
Bromophycolide U	-8	GLN245 LEU246 GLY247 HIS250 LYS290 VAL292 CYS293 SER294 THR341 TYR343 PRO344 LEU346

Callicladol	-8.2	HIS235 LEU246 GLY248 HIS250 LYS290 VAL292 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
Callophycoic acid B	-8.2	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 TRP333 GLU340 THR341 TYR343 PRO344 LYS345 LEU346
Campesterol	-8.2	HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344 HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344
Cholest-4-en-3,6-dione	-8.2	PRO344 HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 GLU340 THR341 TYR343 PRO344 LYS345
Cholest-4-en-3-one	-8	LEU346
Cholest-5-en-3beta-ol	-8.2	HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344 HIS235 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344
Dehydrothyrsiferol	-8.2	LYS345 LEU346
Laurebiphenyl	-8	HIS235 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 MET331 THR341 TYR343 PRO344 LYS345 LEU346
Lithothamin A	-8	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 VAL315 MET331 TRP333 LYS335 GLU340 THR341 TYR343
Neurymenolide A	-8	HIS235 GLN245 LEU246 GLY247 GLY248 HIS250 LYS290 VAL292 SER294 THR341 TYR343 PRO344 LYS345 LEU346
Stigmasterol	-8.3	HIS235 GLY248 HIS250 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341 TYR343 PRO344 HIS235 LEU246 GLY247 GLY248 LEU249 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340
Thyrsenol A	-8.4	THR341 TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341
Thyrsenol B	-8	TYR343 PRO344 LYS345 LEU346 HIS235 LEU246 GLY247 GLY248 HIS250 ASN278 LYS290 VAL292 CYS293 SER294 VAL315 TRP333 CYS334 LYS335 GLU340 THR341
Thyrsiferol	-8.4	TYR343 PRO344 LYS345 LEU346

Table S12: Natural products with highest binding affinity for nsp15

MD simulations for RdRp N-terminal		
Bromophycolide R	Bromophycolide S	Bromophycoic acid C
TYR: 32 - 1.0550	TYR: 32 - 0.3440	TYR: 32 - 0.6340
LYS: 47 - 0.5300	LYS: 47 - 0.3080	LYS: 47 - 0.7850
TYR: 122 - 0.5940	TYR: 122 - 0.8180	TYR: 122 - 0.8310

TYR: 129 - 0.5880	TYR: 129 - 0.1000	TYR: 129 - 0.1690
HIS: 133 - 0.8190	HIS: 133 - 0.1590	HIS: 133 - 0.6030
ASN: 138 - 1.6060	ASN: 138 - 1.0270	ASN: 138 - 1.5620
ASP: 140 - 0.9680	ASP: 140 - 0.8210	ASP: 140 - 0.8730
THR: 141 - 0.7150	THR: 141 - 0.6350	THR: 141 - 0.8220
SER: 709 - 0.6290	SER: 709 - 0.3160	SER: 709 - 0.6330
ASN: 781 - 0.3880	ASN: 781 - 0.2730	ASN: 781 - 0.6380

Table S13: MD Simulations for N-Terminal docked complexes

MD simulations for RdRp C-Terminal			
Bromophycolide E	Bromophycolide H	Bromophycolide P	Thyrsenol A
ASP: 618 - 0.7600	ASP: 618 - 0.7160	ASP: 618 - 0.3580	ASP: 618 - 0.3390
SER: 759 - 0.7200	SER: 759 - 0.9010	SER: 759 - 0.5940	SER: 759 - 0.4980
ASP: 760 - 0.5590	ASP: 760 - 0.6580	ASP: 760 - 0.5140	ASP: 760 - 0.4010
ASP: 761 - 0.1390	ASP: 761 - 0.5400	ASP: 761 - 0.3450	ASP: 761 - 0.2570

Table S14: MD Simulations for C-Terminal docked complexes

MD simulations for nsp15		
Bromophycoic acid B	Bromophycoic acid C	Floridoside
HIS: 242 - 1.8600	HIS: 242 - 2.7260	HIS: 242 - 1.6760
HIS: 234 - 0.4370	HIS: 234 - 0.7460	HIS: 234 - 0.4700
HIS: 235 - 0.3390	HIS: 235 - 0.5010	HIS: 235 - 0.2760
HIS: 249 - 0.7130	HIS: 249 - 0.3880	HIS: 249 - 0.7540
HIS: 250 - 0.4790	HIS: 250 - 0.4230	HIS: 250 - 0.5150
LYS: 289 - 0.5850	LYS: 289 - 0.7520	LYS: 289 - 0.2510
LYS: 290 - 0.5010	LYS: 290 - 0.5080	LYS: 290 - 0.2030
SER: 294 - 0.1720	SER: 294 - 0.4170	SER: 294 - 0.1340

Table S15: MD Simulations for nsp15 docked complexes

Top Ligands	Formulae	SMILES
Bromophycoic acid B	C ₂₇ H ₃₇ BrO ₅	<chem>C[C@@]12CC[C@H]([C@]([C@H]1CC[C@](C2)([C@H]3Cc4cc(ccc4O3)C(=O)O)O)(C)C/C=C/C(C)(C)O)Br</chem>
Bromophycoic acid C	C ₂₇ H ₃₇ BrO ₆	<chem>C[C@@]12CC[C@H]([C@]([C@H]1CC[C@](C2)([C@H]3Cc4cc(ccc4O3)C(=O)O)O)(C)C/C=C/C(C)(C)OO)Br</chem>
Bromophycolide E	C ₂₇ H ₃₆ Br ₂ O ₄	<chem>CC(=C)C1CCC(C(CCC2(C(CCC(=C)C2CC3=C(C=CC(=C3)C(=O)O1)O)Br)C)Br)(C)O</chem>
Bromophycolide H	C ₂₇ H ₃₇ Br ₃ O ₄	<chem>CC1(C(CCC(C(CCC2(C(CCC(=C)C2CC3=C(C=CC(=C3)C(=O)O1)O)Br)C)Br)(C)O)Br)C</chem>
Bromophycolide P	C ₂₇ H ₃₆ Br ₂ O ₄	<chem>CC1(C2CCC(O1)(C(CCC3(C(CCC(=C)C3CC4=C(C=CC(=C4)C(=O)O2)O)Br)C)Br)C)C</chem>
Bromophycolide R	C ₂₇ H ₃₅ BrO ₄	<chem>CC(=C)C1CCC2(C(O2)CCC3(C(CCC(=C)C3CC4=C(C=CC(=C4)C(=O)O1)O)Br)C)C</chem>
Bromophycolide S	C ₂₇ H ₃₆ Br ₂ O ₄	<chem>CC12CCC(OC(=O)C3=CC(=C(C=C3)O)CC4C(=C)CCC(C4(CCC1O2)C)Br)C(C)(C)Br</chem>
Floridoside	C ₉ H ₁₈ O ₈	<chem>C(C1C(C(C(C(O1)OC(CO)CO)O)O)O)O</chem>
Thyrsenol A	C ₃₀ H ₅₁ BrO ₈	<chem>CC1(C(CCC(O1)(C)C2CCC3(C(O2)CC=C(O3)C(CCC(C4(CCC(O4)C(C)(C)O)C)O)(CO)O)C)Br)C</chem>

Table S16: SMILES line notation for selected NPs

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