

Antiviral Potential of *Antillogorgia americana* and *elisabethae* Natural Products against nsp16-nsp10 complex, nsp13, and nsp14 Proteins of SARS-CoV-2: An In silico Investigation

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Supplementary Information

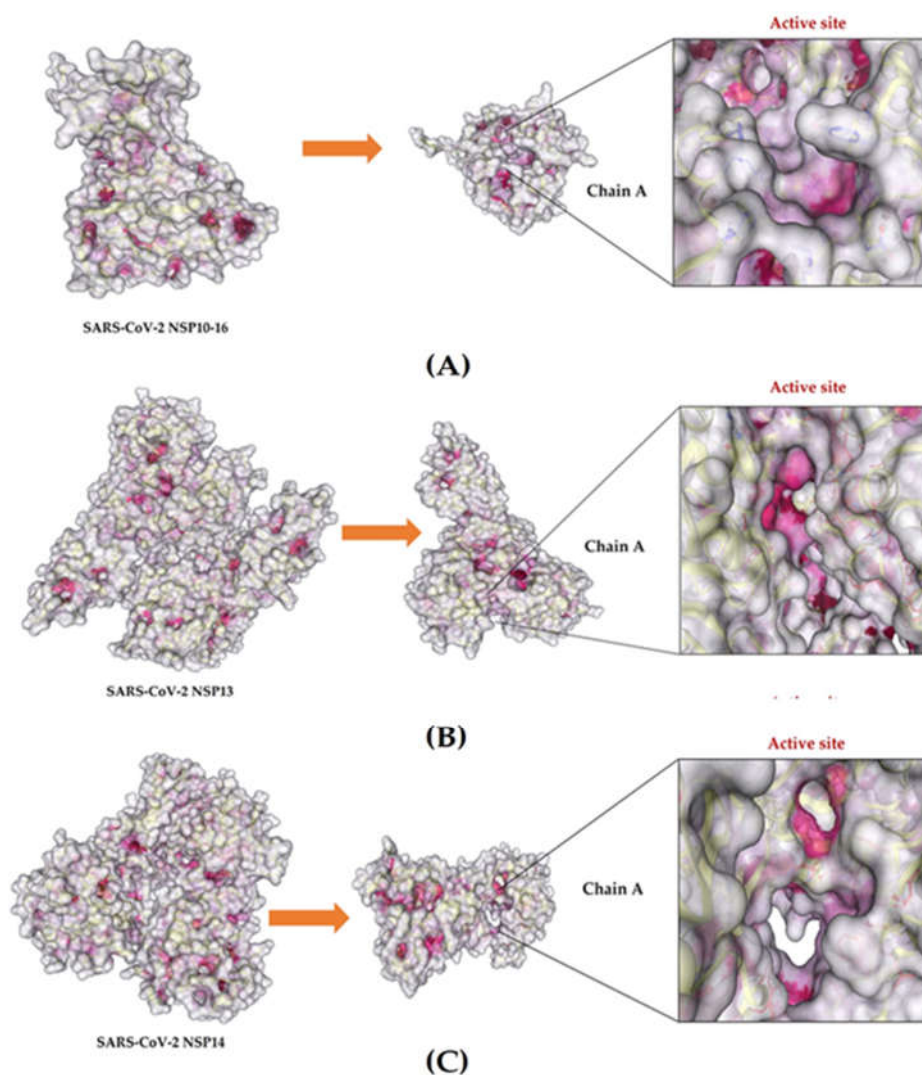


Figure S1: Protein crystal structures and their respective active sites (A) nsp16-nsp10 complex (B) nsp13 (C) nsp14.

Natural products – Genus <i>Antilloorgia</i>	
<i>Americana</i>	<i>Elisabethae</i>
1-monoacetate	3-epi-Elisabanolide
1 β ,3 β -dihydroxy-5 α ,6 α -epoxy-9-oxo-9,11-secogorgostan-11-ol	3-O-Methylquercetin
3 β -Hydroxy-5 α ,6 α -epoxy-9-oxo-9,11-secogorgostan-11-ol	4-Acetylaphilectolide
5-Hydroperoxyicosa-2,4,6,8-tetraenoic acid	7-Hydroxyerogorgiaene
8-epi-Americanolide C	7-Hydroxyerogorgiaenone
8-epi-Methoxyamericanolide A	7, 14-erogorgiaenediol
10-epiamericanolide C	12-Acetoxypseudopterolide
10-epi-Methoxyamericanolide A	15 α -(Angeloyloxy) kaura-16-ene-18-oic acid
Ameristerol A	(+)-Aristolone
Ameristerenol A and B	(+)- α -Terpineol
Americanolide A-F	Aberrarone
Beta-Gorgonene	Amphilectolide
(-)-beta-Chamigrene	Amphiphenalene
(-)-Curcuquinone	Amphilectosin A and B
Calamenene	Biformene
Caridiene	Bis-7-hydroxyerogorgiaene
Curcuhydroquinone	Bicyclogermacrene
Furanogermacrene	Beta-Eudesmol
Furanoguaian-4-ene	Beta-Selinene
Furanotriene	Caribenol A and B
Gamma-Maaliene	Colombiasin A
Germacrene D	Cumbiasin A-C
Iso-furanotriene	Cyperene
Methoxyamericanolide A	Elisabanolide
Methoxyamericanolide B	Elisabatin A-C
Methoxyamericanolide E	Elisabethadienol
Methoxyamericanolide G	Elisabethadione
Methoxyamericanolide H	Elisabethamine
Methoxyamericanolide I	Elisabethatrienol
Preclavulone A	Elisabethin A-H
Secogorgosterol	Elisabethin A acetate
	Elisabethin D acetate
	Elisabetholide
	Elisabethol
	Elisapterosin A-F
	Erogorgiaene
	Ent-Kaur-16-en-19-ol
	Grandifloric acid
	Homopseudopteroxazole

	Hypersodie
	Ileabethin
	Ileabethoxazole
	Isopseudopterosin E
	Isoquercitrin
	Ichthyothereol acetate
	Kaempferol
	Kaurenoic acid
	Kaurane-16,18-diol 18-acetate
	O-methylelisabethadione
	O-methyl-nor-elisabethadione
	Pseudopterolide
	Pseudopteroxazole
	Pseudopterosin A- Z
	Pseudopterosin E - MA
	Pseudopterosin G-J aglycone
	Quercetin
	Quercetin 3-O-beta-D-arabinofuranoside
	Sandresolide A-C
	Seco-pseudopterosin A-K
	Seco-pseudopteroxazole
	Taxifolin
	CMNPD 11416, 12137, 12138, 12139, 12140, 12142, 16184, 16185, 16186, 16187, 17188, 5089.

Table S1: List of NPs from *Antillogorgia Americana* and *Antillogorgia Elisabethae*.

Ligands	Binding affinity ('-4 to -5.9)	Interacting amino acids
5-Hydroperoxyicosa-2,4,6,8-tetraenoic acid	-5.3	SER74 ASP75 ASP99 LEU100 ASN101 ASP130 MET131 TYR132 PRO134 LYS170 THR172 ASN198 SER201 GLU203
(+)-Aristolone	-5.7	CYS25 ASP26 LEU27 TYR30 LYS137 GLU173 HIS174 SER200 SER201 SER202 GLU203
(+)-alpha-Terpineol	-5.2	CYS25 ASP26 LEU27 TYR30 LYS137 GLU173 HIS174 SER200 SER201 SER202
(-)-beta-Chamigrene	-5.5	CYS25 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
β -gorgonene	-5.2	CYS25 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Beta-Selinene	-5.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER202
Calarene	-5.2	LEU22 GLU23 LYS24 CYS25 ASN138 VAL139 LYS141 GLU142 ASN143 GLU173 HIS174
Cumbiasin B	-4.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Cumbiasin C	-4.2	LYS46 TYR132 PRO134 LYS137 LYS170 THR172 ASN198 SER201 SER202 GLU203
Cyperene	-5.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Elisabethadienol	-5.9	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Elisabethatrienol	-5.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Elisabethin B	-5	LEU27 TYR30 TYR132 LYS137 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Elisabethin C	-5.7	TYR30 TYR132 LYS137 GLU173 ASN198 SER200 SER201 SER202 GLU203
Elisabethin D	-5.9	LEU27 TYR30 TYR132 LYS137 LYS170 THR172 ASN198 SER200 SER201 SER202 GLU203
Elisabethin G	-5.5	TYR30 TYR132 LYS137 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Elisabetholide	-5.5	CYS25 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Elisapterosin A	-5.7	TYR30 LYS46 TYR132 LYS137 LYS170 THR172 ASN198 SER200 SER201 SER202 GLU203
furanotriene	-5.9	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER201 SER202
Gamma-Maaliene	-5.7	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 SER201 SER202
Ichthyothereol acetate	-5.9	GLU203
Preclavulone A	-5.5	CYS25 LEU27 TYR30 LYS46 TYR132 LYS137 LYS170 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203

Table S2: Low affinity NPs for target nsp16-nsp10.

Ligands	Binding affinity ('-6 to -6.9)	Interacting amino acids
1-monoacetate	-6.7	CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203 TYR30 ASN43 LYS46 GLY73 SER74 ASP75 ASP130 TYR132 PRO134 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
3 β -Hydroxy-5 α ,6 α -epoxy-9-oxo-9,11-secogorgostan-11-ol	-6.7	GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
3-epi-Elisabanolide	-6.5	TYR30 LYS46 TYR132 LYS137 LYS170 THR172 ASN198 SER200 SER201 SER202 GLU203
4-Acetylamphilectolide	-6.2	TYR30 LYS46 TYR132 LYS137 LYS170 THR172 ASN198 SER201 SER202 GLU203
7-Hydroxyerogorgiaene	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
7-Hydroxyerogorgiaenone	-6.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202 GLU203
7,14-erogorgiaenediol	-6.6	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202 GLU203
8-epi-Americanolide C	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202
8-epi-Methoxyamericanolide A	-6.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
10-epi-Americanolide C	-6.5	LYS24 CYS25 LEU27 TYR30 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
10-epi-Methoxyamericanolide A	-6.5	GLU203
12-Acetoxypseudopterolide	-6.2	LYS24 CYS25 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 SER200 SER201 SER202
Aberrarone	-6.7	TYR30 LYS46 TYR132 LYS137 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Ameristerenol B	-6.7	ASN198 SER200 SER201 SER202 GLU203
Americanolide A	-6.7	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Americanolide B	-6.5	LYS24 CYS25 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202 GLU203
Americanolide C	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 GLU173 SER200 SER201 SER202
Amphilectolide	-6.7	CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 SER200 SER201 SER202 GLU203
beta-Eudesmol	-6.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 GLU173 SER200 SER201 SER202
Bicyclogermacrene	-6.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Biformene	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 GLU173 HIS174 SER200 SER201 SER202
Caribenol B	-6.8	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER202

Calamenene	-6	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER202
Caridiene	-6.5	CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Curcuhydroquinone	-6	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 GLU173 SER200 SER201 SER202 GLU203
(-)-Curcuquinone	-6.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 GLU173 SER200 SER201 SER202 GLU203
Colombiasin A	-6.7	TYR30 TYR132 LYS137 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Cumbiasin A	-6.9	ASN43 LYS46 TYR132 PRO134 LYS137 LYS170 THR172 ASN198 SER201 GLU203
CMNPD5089	-6.7	LYS24 CYS25 ASP26 LEU27 GLN28 TYR30 LYS137 ASN138 VAL139 GLU173 SER200 SER202 LYS24 CYS25 ASP26 LEU27 TYR30 ASP32 LYS137 VAL139 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
CMNPD11416	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
CMNPD12137	-6.2	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 LYS170 THR172 GLU173 SER200 SER201 SER202 GLU203
CMNPD12138	-6.7	LYS24 CYS25 ASP26 LEU27 TYR30 MET42 TYR132 PRO134 LYS137 VAL139 LYS170 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
CMNPD12139	-6.9	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202
CMNPD16185	-6.9	TYR30 MET42 ASN43 LYS46 GLY71 GLY73 ASP130 TYR132 PRO134 LYS137 LYS170 THR172 ASN198 SER200 SER201 SER202 GLU203
CMNPD16187	-6.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
CMNPD17188	-6.9	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 GLU173 HIS174 SER200 SER201 SER202
Ent-Kaur-16-en-19-ol	-6.7	TYR30 LYS46 TYR132 LYS137 LYS170 THR172 ASN198 SER200 SER201 SER202 GLU203
Elisabanolide	-6.7	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Elisabethamine	-6.2	CYS25 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Elisabethin A	-6.7	TYR30 TYR132 PRO134 LYS137 THR172 GLU173 SER200 SER201 SER202 GLU203
Elisabethin E	-6.2	CYS25 LEU27 TYR30 TYR132 PRO134 LYS137 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Elisabethin F	-6.2	

		LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202 GLU203
Elisabethin H	-6.5	
Elisapterosin B	-6.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Elisapterosin C	-6.7	LEU27 TYR30 TYR132 PRO134 LYS137 THR172 GLU173 SER200 SER201 SER202 GLU203 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Elisapterosin D	-6.2	
Elisapterosin E	-6	MET42 ASN43 LYS46 TYR132 LYS137 LYS170 THR172 ASN198 SER201 GLU203
Erogorgiaene	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
furanogermacrene	-6	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202
Furanoguaian-4-ene	-6.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202
Germacrene D	-6	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202
Isofuranotriene	-6	LEU27 TYR30 TYR132 LYS137 THR172 SER200 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Kaurane-16,18-diol18-acetate	-6.5	
Kaurenoicacid	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 GLU173 SER200 SER201 SER202
Methoxyamericanolide A	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Methoxyamericanolide E	-6.5	
Methoxyamericanolide G	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Methoxyamericanolide H	-6.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202 GLU203
Methoxyamericanolide I	-6	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER202
Pseudopterolide	-6	ASN43 LYS46 TYR132 PRO134 LYS137 LYS170 THR172 ASN198 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS135 LYS137 VAL139 THR172 GLU173 SER200 SER201 SER202 GLU203
Pseudopterrosin S	-6.5	
Pseudopterrosin-MA	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202 MET42 ASN43 LYS46 GLY71 GLY73 ASP130 MET131 TYR132 LYS137 LYS170 THR172 ASN198 SER201 SER202 GLU203
Quercetin3-O-beta-D-arabinofuranoside	-6.5	

Seco-pseudopterosin B	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 PRO134 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Seco-pseudopterosin J	-6.9	LYS24 CYS25 LEU27 TYR30 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Secogorgosterol	-6.5	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 ILE171 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203

Table S3: Lower-moderate affinity NPs for target nsp16-nsp10.

Ligands	Binding affinity ('-7 to -7.9)	Interacting amino acids
1 β ,3 β -dihydroxy-5 α ,6 α -epoxy-9-oxo-9,11-secogorgostan-11-ol	-7.7	LYS24 CYS25 ASP26 LEU27 TYR30 MET42 ASN43 LYS46 ASP130 TYR132 LYS137 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
3-O-Methylquercetin	-7	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203 ASN233
15 α -(Angeloyloxy)kaura-16-ene-18-oicacid	-7	ASN43 LYS46 ASP130 TYR132 LYS137 LYS170 THR172 ASN198 SER201 SER202 GLU203
Ameristerol A	-7	CYS25 ASP26 LEU27 TYR30 MET42 ASN43 LYS46 ASP130 TYR132 PRO134 LYS137 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Ameristerenol A	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 ASP130 TYR132 LYS137 LYS170 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Amphilectosin A	-7	TYR30 MET42 ASN43 LYS46 GLY71 GLY73 SER74 ASP75 ASP99 ASP130 TYR132 PRO134 LYS137 LYS170 THR172 GLU173 ASN198 SER201 SER202 GLU203
Amphilectosin B	-7.2	CYS25 ASP26 LEU27 TYR30 MET42 ASN43 LYS46 ASP130 TYR132 LYS137 LYS170 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Americanolide D	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Americanolide E	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202

Americanolide F	-7	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202 GLU203
Amphiphenalone	-7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 PRO134 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Bis-7-hydroxyerogorgiaene	-7.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER202
Caribenol A	-7.5	CYS25 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 SER200 SER201 SER202 GLU203
CMNPD12140	-7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202
CMNPD12142	-7.5	CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202 GLU203
CMNPD16184	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER201 SER202
CMNPD16186	-7.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER202
Elisabethol	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202 GLU203
Elisabatin A	-7.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER202
Elisabatin B	-7.9	LYS24 CYS25 ASP26 LEU27 GLN28 TYR30 LYS137 VAL139 GLU173 SER200 SER202
Elisabatin C	-7.2	CYS25 LEU27 TYR30 TYR132 PRO134 LYS137 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Elisabethin A acetate	-7	CYS25 LEU27 TYR30 TYR132 PRO134 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Elisabethin D acetate	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Elisapterosin F	-7.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 GLU173 HIS174 SER200 SER201 SER202
Grandifloric acid	-7.2	CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 LYS137 LYS170 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Homopseudopteroxazole	-7.5	CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 ASN138 VAL139 THR172 GLU173 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 ASN138 VAL139 THR172 GLU173 HIS174 SER201 SER202 GLU203
Hyperoside	-7	
Isoquercitrin	-7.2	

Ileabethin	-7.1	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 SER200 SER201 SER202 LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202
Ileabethoxazole	-7.2	GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198
Iso-pseudopterosin E	-7.2	SER200 SER201 SER202 GLU203
Kaempferol	-7	TYR30 LYS46 ASP130 TYR132 LYS137 LYS170 THR172 GLU173 ASN198 SER201 SER202 GLU203
Methoxyamericanolide B	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202 GLU203
O-methylelisabethadione	-7	CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203 LYS24 CYS25 LEU27 TYR30 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 SER200 SER201
O-methyl-nor-elisabethadione	-7.2	SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 MET42 LYS46 TYR132 LYS137 VAL139 LYS170 THR172 GLU173
Pseudopterosin B	-7.9	ASN198 SER200 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 MET42 LYS46 TYR132 LYS137 VAL139 THR172 GLU173 ASN198
Pseudopterosin C	-7.8	SER200 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 ASP32 SER33 TYR132 LYS137 VAL139 GLU173 ASN198 SER200
Pseudopterosin D	-7.9	SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 VAL139 THR172 GLU173 HIS174 SER200
Pseudopterosin E	-7.8	SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 VAL139 THR172 GLU173 HIS174 ASN198
Pseudopterosin F	-7.5	SER200 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 ASN198
Pseudopterosin G	-7.7	SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 ASN43 LYS46 TYR132 LYS137 VAL139 LYS170 ILE171 THR172
Pseudopterosin J	-7.5	GLU173 ASN198 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 VAL139 THR172 GLU173 HIS174 SER200
Pseudopterosin K	-7.5	SER201 SER202

Pseudopterosin L	-7.7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER201 SER202 GLU203
Pseudopterosin M	-7.9	LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin N	-7.5	LYS24 CYS25 LEU27 TYR30 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin O	-7.5	LYS24 CYS25 LEU27 TYR30 ASP32 MET42 LYS46 TYR132 LYS137 VAL139 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin P	-7.5	CYS25 LEU27 TYR30 ASN43 LYS46 TYR132 PRO134 LYS137 VAL139 LYS170 ILE171 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin Q	-7.7	LYS24 CYS25 LEU27 TYR30 LYS46 TYR132 LYS137 ASN138 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin U	-7.5	CYS25 LEU27 TYR30 MET42 ASN43 LYS46 TYR132 LYS137 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin W	-7.7	LYS24 CYS25 LEU27 TYR30 LYS46 TYR132 PRO134 LYS137 VAL139 LYS170 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin Z	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 MET42 ASN43 LYS46 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin G-J aglycone	-7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER200 SER201 SER202
Pseudopteroxazole	-7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 GLU173 HIS174 SER201 SER202
Quercetin	-7.5	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 SER200 SER201 SER202 GLU203 LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 THR172 GLU173 HIS174 SER200 SER201
Taxifolin	-7.5	SER202 GLU203 LEU27 TYR30 MET42 ASN43 LYS46 GLY73 SER74 ASP130 TYR132 LYS137 LYS170 THR172 GLU173
Seco-pseudopterosin A	-7.2	ASN198 SER200 SER201 SER202 GLU203 LEU27 TYR30 MET42 ASN43 LYS46 ASP130 TYR132 LYS137 LYS170 THR172 GLU173 ASN198 SER200
Seco-pseudopterosin C	-7	SER201 SER202 GLU203

Seco-pseudopterosin D	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Seco-pseudopterosin E	-7	LEU27 TYR30 MET42 ASN43 LYS46 GLY71 GLY73 ASP99 ASP130 MET131 TYR132 PRO134 LYS137 LYS170 THR172 ASN198 SER200 SER201 SER202 GLU203
Seco-pseudopterosin F	-7.2	CYS25 ASP26 LEU27 TYR30 MET42 ASN43 LYS46 TYR132 PRO134 LYS137 LYS170 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203
Seco-pseudopterosin G	-7.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 LYS137 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Seco-pseudopterosin H	-7	LYS24 CYS25 LEU27 TYR30 ASP32 MET42 LYS46 TYR132 LYS137 ASN138 VAL139 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Seco-pseudopterosin I	-7	LYS24 CYS25 LEU27 TYR30 LYS46 TYR132 LYS137 VAL139 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Seco-pseudopterosin K	-7.5	LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 LYS137 VAL139 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Sandresolide A	-7.5	CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 SER200 SER201 SER202 GLU203
Sandresolide C	-7	LYS24 CYS25 ASP26 LEU27 TYR30 LYS137 VAL139 THR172 GLU173 SER200 SER201 SER202 GLU203
Seco-pseudopteroxazole	-7	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 VAL139 THR172 GLU173 SER200 SER201 SER202 GLU203

Table S4: Upper-moderate affinity NPs for nsp16-nsp10 protein complex

Ligands	Binding affinity ('-8.0 and above)	Interacting amino acids
Pseudopterosin A	-8	LYS24 CYS25 ASP26 TYR30 LYS46 ASP130 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER201 SER202 GLU203
Pseudopterosin H	-8.2	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 VAL139 LYS170 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin I	-8.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 PRO134 LYS137 VAL139 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin R	-8.2	LYS24 CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 LYS137 VAL139 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203

Pseudopterosin T	-8	CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 LYS170 ILE171 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin V	-8.2	LYS24 CYS25 ASP26 LEU27 TYR30 TYR132 PRO134 LYS137 LYS170 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin X	-8	LEU27 TYR30 MET42 ASN43 LYS46 ASP130 TYR132 LYS137 LYS170 THR172 GLU173 ASN198 SER200 SER201 SER202 GLU203
Pseudopterosin Y	-8	CYS25 ASP26 LEU27 TYR30 LYS46 TYR132 PRO134 LYS137 THR172 GLU173 HIS174 ASN198 SER200 SER201 SER202 GLU203
Sandresolide B	-8	CYS25 ASP26 LEU27 TYR30 TYR132 LYS137 THR172 GLU173 HIS174 SER200 SER201 SER202 GLU203

Table S5: High affinity NPs for nsp16-nsp10 enzyme complex.

Ligands	Binding affinity ('-5 to -5.9)	Interacting amino acids
5-Hydroperoxyicosa-2,4,6,8-tetraenoic acid	-5.5	PRO284 LYS288 SER289 ALA316 GLU319 LYS320 ASP374 GLU375 ILE376 SER377 MET378 ILE399 GLY400 ASP401 GLN404 LEU405 ARG443 GLN537 GLY538 SER539 GLU540 ARG567 PRO284 GLY285 GLY287 LYS288 SER289 ALA313 ALA316 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 GLU540 ARG567
7,14-erogorgiaenediol	-5.7	GLU540 ARG567
12-Acetoxypseudopterolide	-5	ASN179 CYS309 SER310 HIS311 ALA312 ARG339 VAL340 GLU375 MET378 THR532 ASP534 SER535 GLN537
(+)-alpha-Terpineol	-5.2	LYS288 ALA312 ALA313 ALA316 ASP374 GLU375 ILE376 SER377 ILE399 GLY400 ASP401 GLN404 GLN537 GLY538
Beta-Eudesmol	-5.9	LYS288 SER289 ALA312 ALA313 VAL314 ALA316 LEU317 ASP374 GLU375 ARG443 GLY538
Beta-Selinene	-5.7	GLY287 LYS288 SER289 ALA313 ALA316 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538
Bicyclogermacrene	-5.5	GLY285 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538
β -gorgonene	-5	GLY285 THR286 GLY287 LYS288 SER289 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLY538 SER539 ARG567
Cyperene	-5.7	LYS288 SER289 ALA312 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538
Calamenene	-5.7	PRO284 GLY285 LYS288 SER289 ALA313 ALA316 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
Calarene	-5	GLY285 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG443 GLY538 GLU540 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ALA313 ALA316 ASP374 GLU375 GLN404 ARG443 GLN537
Caridiene	-5.7	GLY538 HIS311 ALA312 ALA313 ASP315 ALA316 GLU319 VAL340 GLU341 GLN531 SER535 SER536 GLN537 GLY538 SER539
CMNPD12139	-5.5	GLU540 TYR541
CMNPD16184	-5.2	SER310 HIS311 ALA312 ASP315 VAL340 GLU341 GLU375 MET378 GLN531 ASP534 SER535 SER536 GLN537

CMNPD16185	-5.2	ALA312 ALA313 ASP315 ALA316 GLU319 PHE343 SER535 GLN537 GLY538 SER539
Elisabethol	-5.5	HIS311 ALA312 ALA313 ASP315 ALA316 GLU319 GLU341 PHE343 SER535 GLN537 GLY538 SER539 GLU540
Elisabethin A acetate	-5.2	ALA312 ALA313 ASP315 ALA316 GLU319 GLN531 SER535 GLN537 GLY538 SER539 GLU540 TYR541
Elisabethin B	-5.5	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540
Elisabethin C	-5.5	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ASP374 ARG443 GLY538 GLU540
Elisabethin D acetate	-5.7	ASN179 CYS309 SER310 HIS311 ALA312 ALA313 GLU375 MET378 ASP534 SER535 GLN537 GLY538
Elisabethin E	-5.5	SER289 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540
Elisabethin G	-5.7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ASP374 ARG443 GLY538 GLU540
Elisabetholide	-5.2	ASN179 CYS309 SER310 HIS311 ALA312 ALA313 ARG339 GLU375 MET378 GLN531 ASP534 SER535 GLN537
furanogermacrene	-5.2	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG443 GLY538 GLU540
furanotriene	-5.9	PRO284 GLY285 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 ARG443 GLN537 GLY538
Gamma-Maaliene	-5.5	GLY285 THR286 GLY287 LYS288 SER289 ALA316 LYS320 ASP374 ARG443 GLY538 GLU540
Germacrene D	-5.2	GLY287 LYS288 SER289 HIS290 ALA316 LEU317 GLU319 LYS320 ASP374 ARG443 GLY538
Grandifloric acid	-5.5	SER310 HIS311 ALA312 VAL340 GLU375 MET378 ASP534 SER535 SER536 GLN537 GLY538
Ichthyothereol acetate	-5.7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA316 GLU319 ASP374 ARG443 GLY538
Isofuranotriene	-5.5	PRO284 GLY285 GLY287 LYS288 SER289 HIS290 ALA313 ALA316 LEU317 ASP374 GLN404 ARG443 GLY538 ARG567
Kaurane-16,18-diol18-acetate	-5.2	VAL181 SER310 HIS311 ALA312 ARG339 VAL340 GLU375 MET378 ASP534 SER535 GLN537
Pseudopterolide	-5.5	HIS311 ALA312 ASP315 ALA316 GLU319 VAL340 GLU341 CYS342 PHE343 GLN531 SER535 GLN537 GLY538 SER539 CYS309 SER310 ALA312 ASP315 ALA316 GLU319 VAL340 GLU341 GLU375 MET378 GLN531 ASP534 SER535 SER536
Pseudopterosin D	-5.7	GLN537 GLY538 SER539
Pseudopterosin G	-5.9	GLY285 LYS288 SER289 ALA312 ALA313 ALA316 LEU317 GLU319 ASP374 ARG443 GLY538 SER539 GLU54
Pseudopterosin-MA	-5.0	LYS288 ALA312 ASP315 ALA316 GLU319 GLU341 CYS342 PHE343 GLN404 GLN531 SER535 GLY538 SER539
Sandresolide A	-5.5	HIS311 ALA312 ALA313 ASP315 ALA316 GLU319 CYS342 PHE343 ASP344 GLN531 SER535 GLN537 GLY538 SER539

Table S6: Low affinity NPs for target nsp13.

Ligands	Binding affinity ('-6 to -6.9)	Interacting amino acids
1-monoacetate	-6.2	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 ASP374 GLU375 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538
1β,3β-dihydroxy-5α,6α-epoxy-9-oxo-9,11-secogorgostan-11-ol	-6	PRO284 GLY285 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 GLU319 LYS320 ASP374 GLU375 GLN404 ARG443 GLY538 SER539 GLU540 ARG567
3β-Hydroxy-5α,6α-epoxy-9-oxo-9,11-secogorgostan-11-ol	-6.7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ASP315 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540
3-O-Methyl Quercetin	-6.2	GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 GLU319 ASP374 GLU375 ILE399 GLY400 GLN404 ARG443 GLN537 GLY538 GLU540
7-Hydroxyerogorgiaene	-6.5	PRO284 GLY285 GLY287 LYS288 SER289 ALA313 ALA316 GLU319 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
7-Hydroxyerogorgiaenone	-6.2	PRO284 GLY285 GLY287 LYS288 SER289 ALA313 ALA316 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 GLU540 ARG567
8-epi-Americanolide C	-6.5	GLY282 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG443 GLY538
8-epi-Methoxyamericanolide A	-6.2	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG443 GLY538 SER539 GLU540
10-epi-Methoxyamericanolide A	-6.7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 GLU319 LYS320 ARG443 GLY538 GLU540
15α-(Angeloyloxy)kaura-16-ene-18-oicacid	-6.7	GLY285 THR286 GLY287 LYS288 SER289 ALA312 ASP315 ALA316 GLU319 ASP374 ARG443 GLY538 SER539 GLU540 ARG567
(+)-Aristolone	-6.5	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ASP374 ARG443 GLY538 GLU540
Amersiterol A	-6.5	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ASP315 ALA316 LEU317 GLU319 LYS320 ARG443 GLY538 SER539 GLU540

Ameristerenol A	-6.9	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA312 ALA313 ASP315 ALA316 GLU319 LYS320 ARG443 GLN537 GLY538 SER539 GLU540 PRO284 GLY285 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 ARG567 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538
Americanolide C	-6.7	GLY285 GLY287 LYS288 SER289 HIS290 ALA316 GLU319 LYS320 ASP374 ARG443 GLY538 SER539 PRO284 GLY285 LYS288 SER289 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567 GLY285 LYS288 SER289 SER310 ALA312 ALA313 ALA316 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
Americanolide D	-6.2	SER289 HIS311 ALA312 ALA313 ASP315 ALA316 LEU317 GLU319 LYS320 GLU341 ASP374 ARG443 GLN537 GLY538 SER539 TYR541
Americanolide E	-6	LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA316 ASP374 GLU375 SER377 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538 PRO283 PRO284 GLY285 THR286 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 SER377 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538
Americanolide F	-6.5	GLY285 LYS288 SER289 ALA316 LEU317 LYS320 ARG443 GLY538 SER539 GLU540 PRO284 GLY285 GLY287 LYS288 SER289 HIS290 ALA316 LEU317 LYS320 ASP374 ARG443 GLY538 SER539 GLU540 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ALA313 VAL314 ALA316 LEU317 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ALA313 ALA316 LYS320 ASP374 GLU375 ILE399 ARG443 GLN537 GLY538 SER539
Biformene	-6	
Bis-7-hydroxyerogorgiaene	-6.2	
(-)-beta-Chamigrene	-6	
(-)-Curcuquinone	-6.5	
Curcuhydroquinone	-6	
Cumbiasin C	-6.7	
Caribenol A	-6.7	
Caribenol B	-6.9	
CMNPD5089	-6	
CMNPD11416	-6.2	

CMNPD12137	-6.5	GLY285 THR286 GLY287 LYS288 SER289 ALA316 ASP374 GLU375 ILE376 SER377 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538
CMNPD12138	-6.5	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 SER310 ALA312 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 ARG567
CMNPD12140	-6.9	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG443 GLY538 SER539 GLU540 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375
CMNPD17188	-6.5	GLY400 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Elisabanolide	-6.7	GLY285 SER289 ASP315 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540 PRO284 GLY285 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537
Elisabatin B	-6.7	GLY538 ARG567
Elisabatin C	-6.7	GLY282 PRO283 PRO284 GLY285 THR286 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
Elisabethadienol	-6.5	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA313 ALA316 LEU317 LYS320 ASP374 GLU375 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538 SER539 GLU540
Elisabethamine	-6.2	GLY282 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ASP315 ALA316 GLU319 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
Elisabethatrienol	-6	PRO284 GLY285 LYS288 SER289 SER310 ALA312 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 ARG567
Elisabethin A	-6.2	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LEU317 GLU319 LYS320 ARG443 GLY538 SER539 GLU540
Elisabethin D	-6.5	GLY285 LYS288 SER289 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375
Elisabethin F	-6.2	GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Elisabethin H	-6	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 ASP374 GLN404 ARG443 GLY538 SER539 GLU540 ARG567
Elisapterosin C	-6.5	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540

Ent-Kaur-16-en-19-ol	-6.5	GLY285 THR286 GLY287 LYS288 SER289 ALA316 LYS320 ASP374 GLU375 ARG443 GLY538 GLU540 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443
Erogorgiaene	-6.2	GLN537 GLY538 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375
Furanoguaian-4-ene	-6.2	GLN404 ARG443 GLN537 GLY538 ARG56 LYS288 ALA312 ALA313 ASP315 ALA316 ASP374 GLU375 GLN404 GLN531 SER535 GLN537 GLY538
Homopseudopteroxazole	-6.2	SER539 TYR541 ASN179 SER310 HIS311 ALA312 ARG339 VAL340 GLU375 MET378 GLN531 THR532 ASP534 SER535
Hyperoside	-6.2	SER536 GLN537 GLY538 SER539
Iso-pseudopterosin E	-6.2	SER289 ALA312 ASP315 ALA316 LEU317 GLU319 LYS320 PHE343 ARG443 GLY538 SER539 GLU540 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA316 GLU319 LYS320 ARG443 GLY538
Methoxyamericanolide A	-6.5	GLU540
Methoxyamericanolide B	-6.7	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 GLU319 LYS320 ARG443 GLY538 GLU540
Methoxyamericanolide E	-6.2	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA316 LYS320 ARG443 GLY538 GLU540 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404
Methoxyamericanolide G	-6.7	ARG443 GLN537 GLY538 GLU540 ARG567 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG443 GLY538 SER539
Methoxyamericanolide H	-6.7	GLU540 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LEU317 LYS320 ARG443
Methoxyamericanolide I	-6.2	GLY538 SER539 GLU540 GLY285 GLY287 LYS288 SER289 ALA312 ALA313 ASP315 ALA316 GLU319 ASP374 GLU375 ARG443
O-methylelisabethadione	-6	GLN537 GLY538 SER539 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 SER310 ALA312 ALA313 ALA316
Preclavulone A	-6.2	ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 ARG567 SER310 HIS311 ALA312 ALA313 ASP315 ARG339 VAL340 GLU341 GLU375 MET378 GLN531 ASP534
Pseudopterosin A	-6.7	SER535 SER536 GLN537 GLY538

Pseudopterosin B	-6	ASN179 CYS309 SER310 HIS311 ALA312 ALA313 GLU375 MET378 ASP383 PRO406 ALA407 GLN531 ASP534 SER535 SER536 GLN537 GLY538 SER539 PRO283 PRO284 GLY285 THR286 LYS288 SER289 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540 TYR541
Pseudopterosin C	-6.2	CYS309 SER310 HIS311 ARG339 VAL340 THR359 VAL360 ASN361 GLU375 MET378 THR380 ASP383 ALA407 ASP534 SER535 GLN537
Pseudopterosin E	-6.2	SER310 HIS311 ALA312 ALA313 ARG339 VAL340 GLU341 GLU375 MET378 LEU405 GLN531 VAL533 ASP534 SER535 SER536 GLN537 SER539
Pseudopterosin F	-6.7	PRO284 GLY285 THR286 LYS288 SER289 ALA312 ALA313 ALA316 LEU317 GLU319 LYS320 ASP374 ARG443 GLN537 GLY538 SER539 GLU540
Pseudopterosin H	-6.2	PRO284 GLY285 LYS288 SER289 ALA312 ALA316 GLU319 ASP374 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Pseudopterosin I	-6.5	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ALA313 ALA316 GLU319 ASP374 ARG443 GLY538 SER539 GLU540
Pseudopterosin J	-6.9	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ASP315 ALA316 GLU319 LYS320 PHE343 ASP374 ARG443 GLY538 SER539 GLU540 ARG567
Pseudopterosin L	-6.2	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA312 ALA313 ASP315 ALA316 LEU317 GLU319 LYS320 ASP374 GLU375 ARG443 GLY538 SER539 GLU540
Pseudopterosin M	-6.5	GLY285 THR286 GLY287 LYS288 SER289 ALA312 ALA313 ASP315 ALA316 GLU319 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 GLU540
Pseudopterosin N	-6	LYS288 SER310 ALA312 ALA313 ASP315 ALA316 GLU319 GLU341 ASP374 GLU375 GLN404 SER535 GLN537 GLY538 SER539
Pseudopterosin O	-6.5	SER310 HIS311 ALA312 ALA313 ASP315 ALA316 VAL340 GLU375 MET378 GLN531 ASP534 SER535 GLN537 GLY538 SER539
Pseudopterosin P	-6.2	ASN179 VAL181 SER310 HIS311 ALA312 ALA313 ALA316 VAL340 GLU341 GLU375 MET378 GLN531 THR532 ASP534 SER535 GLN537 GLY538 SER539
Pseudopterosin Q	-6	

Pseudopterosin R	-6.9	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA312 ASP315 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540
Pseudopterosin S	-6.9	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ASP315 ALA316 GLU319 LYS320 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Pseudopterosin W	-6.7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ALA313 ASP315 ALA316 GLU319 LYS320 ASP374 GLU375 GLN404 ARG443 SER535 SER536 GLN537 GLY538 SER539 GLU540
Pseudopterosin X	-6.5	ASN179 CYS309 SER310 HIS311 ALA312 ALA313 ASP315 ARG339 VAL340 GLU341 GLU375 MET378 PRO406 ALA407 GLN531 ASP534 SER535 SER536 GLN537
Pseudopterosin Y	-6.2	VAL181 CYS309 SER310 HIS311 ALA312 ALA313 ARG339 VAL340 GLU375 MET378 VAL533 ASP534 SER535 SER536 GLN537 GLY538
Pseudopterosin Z	-6.5	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA312 ALA313 ALA316 LYS320 ARG443 GLN537 GLY538 SER539 GLU540 TYR541 ARG567
Pseudopterosin G-J aglycone	-6.5	GLY282 PRO283 PRO284 GLY285 THR286 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
Secogorgosterol	-6.2	GLY282 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA312 ASP315 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540
Seco-pseudopterosin A	-6.2	SER310 HIS311 ALA312 ALA313 ASP315 ALA316 VAL340 GLU341 GLU375 MET378 GLN531 ASP534 SER535 SER536 GLN537 GLY538 SER539
Seco-pseudopterosin B	-6.9	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA312 ALA313 ALA316 LYS320 ARG442 ARG443 GLN537 GLY538 SER539 GLU540
Seco-pseudopterosin C	-6.7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ASP315 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540
Seco-pseudopterosin D	-6.5	GLY285 GLY287 LYS288 SER289 ALA312 ALA313 ASP315 ALA316 GLU319 LYS320 PHE343 ASP374 GLU375 GLN404 ARG443 GLY538 SER539 GLU540
Seco-pseudopterosin J	-6.9	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 HIS311 ALA312 ASP315 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540

Seco-pseudopteroxazole	-6.7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA316 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Sandresolide B	-6.2	GLY282 PRO284 GLY285 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 SER377 MET378 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538 ARG567

Table S7: Moderate affinity NPs for target nsp13.

Ligands	Binding affinity ('-7 to -8.2)	Interacting amino acids
3-epi-Elisabanolide	-7.5	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 GLU319 LYS320 ASP374 ARG443 GLY538 SER539 GLU540 PRO283 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LEU317 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
4-Acetylamphilectolide	-7.2	PRO284 GLY285 LYS288 SER289 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
10-epi-Americanolide C	-7.2	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA316 GLU319 LYS320 ARG443 GLY538 GLU540
Aberrarone	-7.5	PRO284 GLY285 LYS288 SER289 ALA312 ASP315 ALA316 GLU319 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 TYR541 ARG567
Ameristerenol B	-7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538
Americanolide A	-7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA316 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Americanolide B	-7	GLY282 PRO283 PRO284 GLY285 LYS288 SER289 ALA312 ALA313 ASP315 ALA316 LEU317 GLU319 LYS320 ASP374 GLU375 GLY400 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Amphilectosin A	-7.2	

Amphilectosin B	-7.2	GLY282 PRO284 GLY285 LYS288 SER289 ALA312 ALA313 ASP315 ALA316 LEU317 GLU319 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Amphilectolide	-7.5	PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 GLU540 ARG567
Amphiphenalone	-7	GLY282 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
Colombiasin A	-7.2	GLY285 THR286 GLY287 LYS288 SER289 HIS290 LYS320 ASP374 ARG442 ARG443 GLY538 SER539 GLU540
Cumbiasin A	-7	PRO283 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG442 ARG443 GLY538 GLU540
Cumbiasin B	-7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG442 ARG443 GLY538 GLU540
CMNPD12142	-7.7	PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 GLU540 ARG567
CMNPD16186	-7.7	PRO283 PRO284 GLY285 THR286 LYS288 SER289 ALA313 ALA316 LEU317 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
CMNPD16187	-8.2	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 SER310 ALA312 ALA313 ASP315 ALA316 GLU319 ASP374 GLU375 ARG443 GLN537 GLY538 SER539 GLU540
Elisabatin A	-7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ALA313 ALA316 LEU317 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
Elisapterosin A	-7.2	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG443 GLY538 SER539 GLU540
Elisapterosin B	-7	PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 GLU319 LYS320 ASP374 ARG443 GLY538 GLU540
Elisapterosin D	-7	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 GLU319 LYS320 ARG443 GLY538 SER539 GLU540
Elisapterosin E	-7.5	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG443 GLY538 SER539 GLU540 ARG567
Elisapterosin F	-7.2	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA316 LYS320 ARG443 GLY538 SER539 GLU540
Ileabethin	-7.2	PRO283 PRO284 GLY285 LYS288 SER289 ALA313 ALA316 LEU317 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
Ileabethoxazole	-8.2	PRO283 PRO284 GLY285 LYS288 SER289 ALA313 ALA316 LEU317 GLU319 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 ARG567

Isoquercitrin	-7.5	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA313 ALA316 LEU317 GLU319 LYS320 ASP374 GLU375 ASP401 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA316 LYS320 ASP374 GLU375 SER377 GLN404 ARG443 GLN537 GLY538 SER539 ARG567
Kaempferol	-7.2	GLY285 THR286 GLY287 LYS288 SER289 ALA316 LYS320 ASP374 ARG443 GLY538 GLU540
Kaurenoicacid	-7	GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LEU317 GLU319 ASP374 GLU375 SER377 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538 SER539 GLU540
O-methyl-nor-elisabethadione	-7.2	GLY282 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA313 ALA316 LEU317 ASP374 GLU375 ILE376 SER377 ILE399 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538 GLU540 ARG567
Pseudopterosin K	-7.5	GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA313 ALA316 GLU319 LYS320 ASP374 GLU375 ILE399 GLN404 ARG443 GLN537 GLY538 SER539 GLU540
Pseudopterosin T	-8	GLY282 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 GLU319 LYS320 ASP374 GLU375 SER377 MET378 ILE399 GLY400 ASP401 GLN404 LEU405 ARG443 GLN537 GLY538 SER539 GLU540
Pseudopterosin U	-7.9	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ALA316 GLU319 LYS320 GLN404 ARG443 GLY538 SER539 GLU540 TYR541 ARG567
Pseudopterosin V	-7	PRO283 PRO284 GLY285 LYS288 SER289 ALA313 ALA316 LEU317 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 ARG567
Pseudopteroxazole	-7	GLY282 PRO284 GLY285 LYS288 SER289 ALA313 ALA316 LEU317 GLU319 LYS320 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 GLU540 ARG567
Quercetin	-7.2	GLY282 PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA313 ALA316 LEU317 GLU319 ASP374 GLU375 ILE399 LEU438 ARG443 GLY538 GLU540
Quercetin3-O-beta-D-arabinofuranoside	-7.5	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA312 ALA313 ALA316 GLU319 LYS320 ARG443 SER535 GLN537 GLY538 SER539 GLU540 ARG567
Seco-pseudopterosin E	-7.7	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA312 ASP315 ALA316 GLU319 LYS320 GLU341 CYS342 PHE343 ASP344 ARG443 GLY538 SER539 GLU540 ARG567
Seco-pseudopterosin F	-7	GLY285 GLY287 LYS288 SER289 ALA312 ASP315 ALA316 GLU319 LYS320 GLU341 CYS342 PHE343 ASP374 GLU375 GLN404 ARG443 GLN537 GLY538 SER539 GLU540
Seco-pseudopterosin G	-7.5	

Seco-pseudopterosin H	-7.9	PRO283 PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA316 GLU319 LYS320 ASP374 GLU375 ILE376 SER377 ILE399 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Seco-pseudopterosin I	-7.2	PRO283 PRO284 GLY285 LYS288 SER289 ALA313 ALA316 LEU317 GLU319 ASP374 GLU375 GLY400 GLN404 ARG443 GLN537 GLY538 SER539 GLU540 ARG567
Seco-pseudopterosin K	-8	PRO284 GLY285 THR286 GLY287 LYS288 SER289 HIS290 ALA312 ALA313 ALA316 LYS320 ASP374 GLU375 GLN404 ARG443 SER535 GLN537 GLY538 SER539 GLU540 ARG567
Sandresolide C	-7	GLY282 PRO284 GLY285 LYS288 SER289 HIS290 ALA313 ALA316 LEU317 ASP374 GLU375 ILE376 SER377 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538 SER539 ARG567
Taxifolin	-7	PRO284 GLY285 THR286 GLY287 LYS288 SER289 ALA313 ALA316 LYS320 ASP374 GLU375 SER377 GLY400 ASP401 GLN404 ARG443 GLN537 GLY538 SER539 ARG567

Table S8: High affinity NPs for target nsp13.

Ligands	Binding affinity ('-6.5 to -7.9)	Interacting amino acids
1-monoacetate	-7.5	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
5-Hydroperoxyicosa-2,4,6,8-tetraenoic acid	-6.7	PHE286 VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 ALA425 PHE426 HIS427 THR428 PHE506
8-epi-Methoxyamericanolide A	-7.7	VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 ASN386 CYS387 ASN388 PHE426 HIS427
10-epi-Methoxyamericanolide A	-7.7	TRP292 ASN306 ARG310 GLY333 ASN334 PRO335 LYS336 TRP385 ASN386 ASN422 LYS423 HIS424 PHE426
Americanolide E	-7.5	VAL287 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 TRP385 ASN386 CYS387 ASN388 PHE426 HIS427
Americanolide F	-7.7	VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 TRP385 ASN386 PHE401 TYR420 ASN422 PHE426 PHE506
(+)-alpha-Terpineol	-6.5	ASN306 CYS309 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 THR428 PHE506
(+)-Aristolone	-7.2	TRP292 ILE305 ASN306 CYS309 ARG310 TRP385 ASN386 TYR420 ASN422 LYS423 PHE426 PHE506
(-)-beta-Chamigrene	-7	ILE305 ASN306 CYS309 ARG310 ASN386 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
beta-Eudesmol	-7.5	TRP292 ASN306 ARG310 GLY333 PRO335 TRP385 ASN386 CYS387 TYR420 ASN422 PHE426 PHE506
beta-Selinene	-7.7	ILE305 ASN306 ARG310 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 PHE426 THR428 PHE506

β-gorgonene	-7.2	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 TYR420 ASN422 HIS424 PHE426 PHE506
Bicyclogermacrene	-7	TRP292 ASN306 CYS309 ARG310 GLY333 TRP385 ASN386 TYR420 ASN422 PHE426 PHE506
Calarene	-6.7	TRP292 ILE305 ASN306 CYS309 ARG310 TRP385 ASN386 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Cyperene	-7.5	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 TYR420 ASN422 HIS424 PHE426 PHE506
Curcuhydroquinone	-7.2	TRP292 ASN306 CYS309 ARG310 LYS336 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
(-)-Curcuquinone	-7.7	ASN306 ARG310 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506 VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 ASN386 CYS387 ASN388 PHE426
Ent-Kaur-16-en-19-ol	-7.7	TRP292 ASN306 ARG310 LYS336 TRP385 ASN386 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Elisabethin C	-6.7	PHE286 VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 PHE367 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 THR428 PRO429
Elisabethin D	-7.7	PHE286 VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 TRP385 ASN386 CYS387 ASN388 PHE426 HIS427
Elisabethin F	-7.9	TRP292 ASN306 CYS309 ARG310 GLY333 ASN334 PRO335 LYS336 TRP385 ASN386 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Elisabethin G	-7.2	TRP292 ASN306 ARG310 GLY333 PRO335 TRP385 ASN386 CYS387 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Elisabethin H	-7.2	TRP292 ASN306 ARG310 TRP385 ASN386 PHE401 TYR420 ASN422 LYS423 PHE426 PHE506
Furanogermacrene	-7.5	TRP292 ILE305 ASN306 CYS309 ARG310 TRP385 ASN386 TYR420 ASN422 LYS423 PHE426 PHE506
Furanotriene	-7.2	TRP292 ASN306 ARG310 TRP385 ASN386 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Gamma-Maaliene	-7.5	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 PHE506
Germacrene D	-7	VAL290 TRP292 ASN306 CYS309 ARG310 ASP352 ALA353 GLN354 TRP385 ASN386 TYR420 ASN422 PHE426 PHE506
Ichthyothereol acetate	-7.2	VAL287 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TYR368 CYS387 HIS427 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TYR368 TRP385 ASN386 CYS387 ASN388 VAL389 PHE426
Isofuranotriene	-6.9	TRP292 ASN306 CYS309 ARG310 GLY333 TRP385 ASN386 ASN388 TYR420 ASN422 HIS424 PHE426 PHE506
Kaurane-16,18-diol18-acetate	-7.9	
Methoxyamericanolide A	-7.5	

Preclavulone A	-7.2	TRP292 ASN306 ARG310 GLN313 GLY333 ASN334 PRO335 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
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Table S9: Medium affinity NPs for target nsp14.

Ligands	Binding affinity ('-8.0 to -9.9)	Interacting amino acids
1 β ,3 β -dihydroxy-5 α ,6 α -epoxy-9-oxo-9,11-secogorgostan-11-ol	-9	VAL287 ARG289 VAL290 TRP292 ARG310 GLY333 ASN334 PRO335 ASP352 PHE367 TRP385 ASN386 CYS387 ASN388 TYR420 PHE426 HIS427 THR428 PRO429 PHE506
3 β -Hydroxy-5 α ,6 α -epoxy-9-oxo-9,11-secogorgostan-11-ol	-8.2	VAL287 LYS288 ARG289 VAL290 TRP292 ARG310 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 PHE426 HIS427 PRO429
3-O-Methylquercetin	-8.9	GLU302 ASN306 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 HIS427 THR428 PHE506
3-epi-Elisabanolide	-8.5	LYS288 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TYR368 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427
4-Acetylamphilectolide	-9.7	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
7-Hydroxyerogorgiaene	-9	VAL290 TRP292 ASN306 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 HIS427 THR428 PHE506
7-Hydroxyerogorgiaenone	-8.7	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
7,14-erogorgiaenediol	-8.7	TRP292 ASN306 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 HIS427 THR428 PHE506
8-epi-Americanolide C	-9	TRP292 ASN306 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PHE506
10-epi-Americanolide C	-8.2	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 TYR420 ASN422 PHE426 PHE506
12-Acetoxypseudopterolide	-8.2	LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 THR428 PRO429

15alpha-(Angeloyloxy)kaura-16-ene-18-oicacid	-8.2	VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 PHE426 HIS427 PRO429
Aberrarone	-8.5	VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 PHE426 HIS427
Ameristerenol A	-9.5	VAL287 VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 ALA353 PHE367 TRP385 ASN386 CYS387 ASN388 VAL389 TYR420 ASN422 PHE426 HIS427 PRO429 PHE506
Ameristerenol B	-9.5	PHE286 VAL287 LYS288 ARG289 VAL290 TRP292 ARG310 GLY333 ASN334 PRO335 ASP352 ALA353 PHE367 TRP385 ASN386 CYS387 ASN388 VAL389 TYR420 PHE426 HIS427 PHE506
Americanolide A	-8	ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 ASN386 CYS387 ASN388 PHE426 HIS427
Americanolide B	-8	TRP292 ILE305 ASN306 CYS309 ARG310 TRP385 ASN386 TYR420 ASN422 PHE426 PHE506
Americanolide C	-8	TRP292 ASN306 CYS309 ARG310 GLY333 TRP385 ASN386 CYS387 TYR420 PHE426 PHE506
Americanolide D	-8.2	TRP292 ASN306 CYS309 ARG310 GLN313 GLY333 PRO335 TRP385 ASN386 ASN388 TYR420 ASN422 PHE426 PHE506
Amphilectolide	-9.2	VAL290 TRP292 ARG310 GLY333 PRO335 ASP352 TRP385 ASN386 ASN388 PHE401 TYR420 PHE426 THR428 PHE506
Amphiphenalone	-9	VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 HIS424 PHE426 PHE506
Bis-7-hydroxyerogorgiaene	-9.5	VAL290 TRP292 LEU303 ASN306 ALA307 CYS309 ARG310 GLY333 PRO335 ASP352 ALA353 GLN354 TRP385 ASN386 CYS387 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Biformene	-8.7	TRP292 ILE305 ASN306 ARG310 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Calamenene	-8.2	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 THR428 PHE506
Caridiene	-8.2	TRP292 ASN306 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 THR428 PHE506
Colombiasin A	-8.7	PHE286 VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TYR368 ASN386 CYS387 VAL389 PHE426 HIS427

Cumbiasin A	-9	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 TYR420 ASN422 LYS423 PHE426 PHE506
Cumbiasin B	-8	VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TYR368 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 PRO429
Caribenol A	-9	TRP292 ASN306 CYS309 ARG310 GLY333 TRP385 ASN386 CYS387 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Caribenol B	-8.7	TRP292 ASN306 ARG310 GLY333 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
CMNPD5089	-8.7	TRP292 ASN306 ARG310 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
CMNPD11416	-9	TRP292 ILE305 ASN306 CYS309 ARG310 GLN313 ASP331 GLY333 ASN334 PRO335 ILE338 TRP385 ASN386 PHE401 TYR420 ASN422 PHE426 PHE506
CMNPD12137	-9.2	VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 TRP385 ASN386 ASN388 TYR420 ASN422 PHE426 THR428 PHE506
CMNPD12138	-9	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 PHE426 HIS427 THR428 PHE506
CMNPD12139	-9.2	VAL290 TRP292 ILE305 ASN306 CYS309 ARG310 GLY333 PRO335 LYS336 ASP352 TRP385 ASN386 CYS387 ASN388 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
CMNPD12140	-9	LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 ASN386 CYS387 ASN388 PHE426 HIS427
CMNPD12142	-9.5	VAL290 TRP292 ASN306 CYS309 ARG310 GLY333 PRO335 TRP385 ASN386 CYS387 ASN388 TYR420 PHE426 THR428 PHE506
CMNPD16184	-8.2	ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 THR428 PRO429
CMNPD16185	-9.5	VAL290 TRP292 ASN306 ARG310 GLY333 ASN334 PRO335 LYS336 ASP352 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 PHE426 THR428 PHE506
CMNPD16187	-9.2	VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 ALA353 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 HIS427 THR428 PHE506

CMNPD17188	-9	VAL290 TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PHE506
Elisabethol	-9.2	VAL290 TRP292 ASN306 ARG310 GLY333 ASN334 PRO335 LYS336 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 PHE426 THR428 PHE506
Elisabanolide	-8.7	VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 PRO429
Elisabethadienol	-8.5	TRP292 ILE305 ASN306 ARG310 TRP385 ASN386 ASN388 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Elisabethamine	-8.2	VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Elisabethatrienol	-8.5	TRP292 ILE305 ASN306 CYS309 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Elisabethin A	-8	VAL287 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 THR428
Elisabethin A acetate	-8	VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TYR368 ASN386 CYS387 ASN388 VAL389 ASP390 PHE426 HIS427
Elisabethin B	-8.2	TRP292 ASN306 CYS309 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Elisabethin D acetate	-9	VAL287 LYS288 ARG289 VAL290 TRP292 ILE332 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TYR368 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427
Elisabethin E	-8	VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TYR368 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427
Elisabetholide	-8	VAL287 LYS288 ARG289 VAL290 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TYR368 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 THR428 PRO429
Elisapterosin B	-8.2	VAL287 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 PHE426 HIS427

Elisapterosin C	-8.2	VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427
Elisapterosin D	-8.9	VAL287 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427
Elisapterosin E	-8.5	VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 PHE367 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 THR428 PRO429
Elisapterosin F	-8.7	LYS288 ARG289 VAL290 TRP292 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 PHE426 HIS427 THR428 PRO429
Erogorgiaene	-9	TRP292 ASN306 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Furanoguaian-4-ene	-8.5	TRP292 ASN306 ARG310 GLY333 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 PHE426 PHE506 VAL287 LYS288 ARG289 VAL290 TRP292 GLY333 ASN334 PRO335 ASP352 ALA353 PHE367 ASN386 CYS387 ASN388 PHE426 HIS427 THR428 PRO429
Grandifloric acid	-8.2	VAL290 TRP292 ASN306 ARG310 GLN313 ASP331 GLY333 ASN334 PRO335 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 HIS427 THR428 PHE506
Hyperoside	-9.7	VAL290 TRP292 ASN306 CYS309 ARG310 GLN313 ASP331 GLY333 ASN334 PRO335 LYS336 ILE338 ASP352 TRP385 ASN386 CYS387 ASN388 ASN422 LYS423 HIS424 PHE426
Isoquercitrin	-8.5	TRP292 ASN306 CYS309 ARG310 GLY333 PRO335 LYS336 ASP352 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 THR428 PHE506
Ileabethin	-9.9	GLU302 ASN306 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Kaempferol	-9	VAL287 ARG289 VAL290 TRP292 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 ASN386 CYS387 ASN388 PHE426 HIS427 THR428 PRO429
Kaurenoicacid	-8	TRP292 ASN306 ARG310 GLY333 TRP385 ASN386 ASN388 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Methoxyamericanolide B	-8.2	TRP292 ILE305 ASN306 CYS309 ARG310 GLY333 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Methoxyamericanolide E	-9.5	LYS423 HIS424 PHE426 PHE506

Methoxyamericanolide G	-9	TRP292 ILE305 ASN306 CYS309 ARG310 TRP385 ASN386 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Methoxyamericanolide H	-8	TRP292 ASN306 CYS309 ARG310 GLY333 PRO335 TRP385 ASN386 ASN422 LYS423 HIS424 PHE426 ARG289 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387
Methoxyamericanolide I	-8	ASN388 PHE426 HIS427 TRP292 ASN306 ARG310 GLN313 ASP331 GLY333 ASN334 PRO335 ILE338 TRP385 ASN386 ASN388
O-methylelisabethadione	-8.7	PHE401 TYR420 ASN422 PHE426 THR428 PHE506 TRP292 ASN306 ARG310 GLN313 ASP331 GLY333 ASN334 PRO335 ILE338 TRP385 ASN386 CYS387
O-methyl-nor-elisabethadione	-8.7	ASN388 PHE401 TYR420 ASN422 PHE426 THR428 PHE506 VAL290 TRP292 ARG310 GLN313 ASP331 GLY333 ASN334 PRO335 LYS336 ILE338 ASP352 TRP385
Pseudopterosin B	-9.5	ASN386 CYS387 ASN388 PHE426 HIS427 THR428 VAL290 TRP292 ARG310 GLN313 ASP331 ILE332 GLY333 ASN334 PRO335 LYS336 ILE338 CYS340
Pseudopterosin C	-9.6	ASP352 LEU383 TRP385 ASN386 CYS387 ASN388 PHE426 HIS427 THR428 VAL290 TRP292 ARG310 GLN313 ASP331 ILE332 GLY333 ASN334 PRO335 ASP352 PHE384 TRP385
Pseudopterosin F	-9.8	ASN386 CYS387 ASN388 TYR420 PHE426 HIS427 THR428 PHE506 ARG289 VAL290 TRP292 ASN306 ILE332 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 TRP385
Pseudopterosin H	-9.8	ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 ALA425 PHE426 HIS427 THR428 PHE506 ARG289 VAL290 TRP292 ARG310 GLN313 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 PHE367
Pseudopterosin K	-9.5	TRP385 ASN386 CYS387 ASN388 TYR420 PHE426 HIS427 THR428 PHE506 VAL287 LYS288 ARG289 VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 ALA353 GLN354
Pseudopterosin L	-9	LEU366 PHE367 TRP385 ASN386 CYS387 ASN388 TYR420 ASN422 PHE426 HIS427 THR428 PHE506 VAL290 TRP292 ARG310 GLN313 GLY333 PRO335 PHE367 TRP385 ASN386 CYS387 ASN388 VAL389
Pseudopterosin V	-9.9	PHE401 TYR420 PHE426 HIS427 THR428 PRO429 PHE506 VAL290 TRP292 ARG310 GLN313 GLY333 ASN334 PRO335 TRP385 ASN386 ASN388 PHE401 TYR420
Pseudopterosin G-J aglycone	-9.2	PHE426 HIS427 THR428 PHE506 VAL290 TRP292 ASN306 ARG310 GLN313 GLY333 PRO335 TRP385 ASN386 CYS387 ASN388 PHE401
Pseudopterosin-MA	-9	TYR420 PHE426 HIS427 THR428 PHE506

Quercetin	-9	GLU302 ASN306 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 HIS427 THR428 PHE506
Quercetin3-O-beta-D-arabinofuranoside	-9	VAL290 TRP292 ASN306 ARG310 GLN313 ASP331 GLY333 ASN334 PRO335 LYS336 ALA337 ASP352 TRP385 ASN386 CYS387 ASN388 TYR420 ASN422 PHE426 THR428 PHE506
Seco-pseudopterosin A	-9.7	VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TYR368 TRP385 ASN386 CYS387 ASN388 VAL389 TYR420 PHE426 HIS427 THR428 PHE506
Seco-pseudopterosin B	-9.8	VAL287 VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 GLN354 PHE367 TYR368 TRP385 ASN386 CYS387 ASN388 VAL389 PHE401 TYR420 PHE426 HIS427 THR428 PRO429 PHE506
Seco-pseudopterosin C	-9.7	VAL290 TRP292 GLY333 PRO335 ASP352 ALA353 PHE367 TYR368 TRP385 ASN386 CYS387 ASN388 VAL389 ASP390 TYR420 PHE426 HIS427 THR428 PRO429 PHE506
Seco-pseudopterosin D	-9.7	VAL287 VAL290 TRP292 ILE332 GLY333 PRO335 ASP352 ALA353 LEU366 PHE367 TYR368 TRP385 ASN386 CYS387 ASN388 VAL389 TYR420 PHE426 HIS427 THR428 PRO429 PHE506
Seco-pseudopterosin I	-9.7	VAL290 TRP292 ASN306 ARG310 GLN313 ASP331 ILE332 GLY333 ASN334 PRO335 LYS336 ALA337 ILE338 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PHE506
Seco-pseudopterosin J	-9.7	VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 ALA353 GLN354 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Seco-pseudopterosin K	-8.2	TRP292 ASN306 ALA307 CYS309 ARG310 GLN313 ASP331 ILE332 GLY333 ASN334 PRO335 LYS336 ILE338 TRP385 ASN386 ASN422 LYS423 HIS424 PHE426
Sandresolide A	-9	TRP292 ASN306 CYS309 ARG310 GLY333 PRO335 ASP352 TRP385 ASN386 CYS387 ASN388 TYR420 ASN422 PHE426 PHE506
Sandresolide B	-8.5	LYS288 ARG289 VAL290 TRP292 ILE332 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 PHE426
Secogorgosterol	-8.5	PHE286 VAL287 LYS288 ARG289 VAL290 TRP292 ASN306 CYS309 ARG310 GLY333 PRO335 ASP352 PHE367 TRP385 ASN386 CYS387 ASN388 TYR420 PHE426 HIS427 PHE506
Seco-pseudopteroxazole	-9.2	VAL290 TRP292 GLY333 PRO335 ASP352 TRP385 ASN386 CYS387 ASN388 TYR420 PHE426 HIS427 THR428 PHE506

Taxifolin	-9.2	ASN306 ARG310 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
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Table S10: High affinity NPs for target nsp14.

Ligands	Binding affinity -10.0 and above	Interacting amino acids
Amphilectosin A	-10.2	VAL290 TRP292 ASN306 ARG310 GLN313 ASP331 ILE332 GLY333 ASN334 PRO335 LYS336 ILE338 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PHE506
Amphilectosin B	-10	TRP292 ASN306 ARG310 GLN313 ASP331 ILE332 GLY333 ASN334 PRO335 LYS336 ILE338 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Amersiterol A	-10	VAL290 TRP292 ARG310 ILE332 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TYR368 TRP385 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 PRO429
Cumbiasin C	-10.2	TRP292 ASN306 CYS309 ARG310 GLY333 TRP385 ASN386 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506 VAL290 TRP292 ASN306 ARG310 GLN313 GLY333 PRO335 TRP385 ASN386 ASN388 PHE401 TYR420 PHE426 HIS427 THR428 PHE506
CMNPD16186	-10.2	VAL290 TRP292 ASN306 ARG310 GLN313 GLY333 ASN334 PRO335 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PHE506
Elisabatin A	-10.5	VAL290 TRP292 ILE305 ASN306 CYS309 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PHE506
Elisabatin B	-11.2	VAL290 TRP292 ILE305 ASN306 CYS309 GLY333 ASN386 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PHE506
Elisabatin C	-11.2	VAL287 LYS288 ARG289 VAL290 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 THR428 PRO429
Elisapterosin A	-10.7	PHE286 VAL287 LYS288 ARG289 VAL290 TRP292 ARG310 GLN313 GLY333 ASN334 PRO335 TRP385 ASN386 ASN388 PHE401 TYR420 PHE426 HIS427 THR428 PHE506
Homopseudopteroxazole	-10	VAL290 TRP292 ARG310 GLN313 GLY333 ASN334 PRO335 LYS336 ASP352 TRP385 ASN386 ASN388 PHE401 TYR420 PHE426 HIS427 THR428 PHE506
lLeabethoxazole	-10.5	VAL290 TRP292 ILE305 ASN306 CYS309 ARG310 ILE332 GLY333 ASN334 PRO335 ASP352 ALA353 TRP385 ASN386 CYS387 ASN388 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506
Iso-pseudopterosin E	-10.2	

Pseudopterosin A	-10	TRP292 ILE305 ASN306 CYS309 ARG310 GLN313 ASP331 ILE332 GLY333 ASN334 PRO335 LYS336 ILE338 CYS340 LEU383 PHE384 TRP385 ASN386 CYS387 TYR420 ASN422 LYS423 HIS424 PHE426 PHE506 VAL290 TRP292 ASN306 ALA307 CYS309 ARG310 GLY333 PRO335 ASP352 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420
Pseudopterosin D	-10	ASN422 LYS423 HIS424 PHE426 HIS427 THR428 PHE506 VAL290 TRP292 ASN306 ARG310 GLY333 ASN334 PRO335 ASP352 ALA353 TRP385 ASN386 CYS387 ASN388 ARG400 PHE401
Pseudopterosin E	-10	TYR420 ASN422 PHE426 HIS427 THR428 PHE506 VAL290 TRP292 ASN306 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420
Pseudopterosin G	-10	ASN422 LYS423 PHE426 HIS427 THR428 PHE506 ARG289 VAL290 TRP292 ASN306 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 TRP385 ASN386 CYS387 ASN388 PHE401
Pseudopterosin I	-10.2	TYR420 ASN422 LYS423 PHE426 HIS427 THR428 PHE506 LYS288 VAL290 TRP292 ASN306 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388
Pseudopterosin J	-10.7	PHE401 TYR420 ASN422 LYS423 PHE426 HIS427 THR428 PHE506 VAL287 VAL290 TRP292 ARG310 GLN313 GLY333 PRO335 ASP352 ALA353 PHE367 TRP385 ASN386 CYS387 ASN388 PHE401
Pseudopterosin M	-10	TYR420 PHE426 HIS427 THR428 PRO429 PHE506 PHE286 VAL287 LYS288 ARG289 VAL290 TRP292 ARG310 GLY333 ASN334 PRO335 ALA353 PHE367 TRP385 ASN386 CYS387
Pseudopterosin N	-11	ASN388 VAL389 PHE401 TYR420 PHE426 HIS427 THR428 PHE506 VAL290 TRP292 ASN306 ARG310 GLN313 ASP331 ILE332 GLY333 ASN334 PRO335 LYS336 ILE338 LEU383 PHE384 TRP385 ASN386
Pseudopterosin O	-11.2	CYS387 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PHE506 VAL290 TRP292 ASN306 ARG310 GLY333 ASN334 PRO335 LYS336 ASP352 ALA353 GLN354 TRP385 ASN386 CYS387 ASN388
Pseudopterosin P	-10.2	ARG400 PHE401 TYR420 ASN422 PHE426 THR428 PHE506 VAL290 TRP292 ASN306 ARG310 GLY333 ASN334 PRO335 LYS336 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387
Pseudopterosin Q	-10.4	ASN388 ARG400 PHE401 TYR420 ASN422 PHE426 THR428 PHE506 PHE286 VAL287 LYS288 ARG289 VAL290 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TYR368 SER369
Pseudopterosin R	-10.5	ASN386 CYS387 ASN388 VAL389 ASP390 HIS427 PRO429 VAL290 TRP292 ARG310 GLN313 GLY333 ASN334 PRO335 ASP352 ALA353 PHE367 TRP385 ASN386 CYS387 ASN388 PHE401
Pseudopterosin S	-10.2	TYR420 PHE426 HIS427 THR428 PRO429 PHE506

Pseudopterosin T	-10	VAL290 TRP292 ARG310 GLN313 GLY333 ASN334 PRO335 PHE367 TRP385 ASN386 CYS387 ASN388 VAL389 PHE401 TYR420 PHE426 HIS427 THR428 PRO429 PHE506
Pseudopterosin U	-10	VAL290 TRP292 ARG310 GLN313 GLY333 PRO335 ALA353 PHE367 TYR368 TRP385 ASN386 CYS387 ASN388 VAL389 PHE401 TYR420 PHE426 HIS427 THR428 PHE506
Pseudopterosin W	-10.7	LYS288 ARG289 VAL290 TRP292 ARG310 GLY333 ASN334 PRO335 ASP352 ALA353 GLN354 PHE367 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 PHE426 HIS427 THR428 PHE506
Pseudopterosin X	-11	VAL287 VAL290 TRP292 ARG310 GLY333 ASN334 PRO335 ASP352 ALA353 PHE367 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 PHE426 HIS427 THR428 PRO429 PHE506
Pseudopterosin Y	-10.7	VAL287 VAL290 TRP292 ASN306 ARG310 GLY333 ASN334 PRO335 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 PHE426 HIS427 THR428 PRO429 PHE506
Pseudopterosin Z	-11	VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Pseudopteroxazole	-10.5	VAL290 TRP292 ARG310 GLN313 GLY333 ASN334 PRO335 TRP385 ASN386 ASN388 PHE401 TYR420 PHE426 HIS427 THR428 PHE506
Pseudopterolide	-10.2	VAL290 TRP292 ILE332 GLY333 PRO335 TYR351 ASP352 ALA353 LEU366 PHE367 TYR368 ASN386 CYS387 ASN388 VAL389 PHE426 HIS427 THR428 PRO429
Seco-pseudopterosin E	-10	ARG289 VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 GLN354 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 PHE426 HIS427 THR428 PHE506
Seco-pseudopterosin F	-10	PHE286 VAL287 VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 ALA353 PHE367 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PRO429 PHE506
Seco-pseudopterosin G	-10.2	VAL290 TRP292 ASN306 ARG310 GLY333 PRO335 ASP352 ALA353 GLN354 LEU366 PHE367 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506
Seco-pseudopterosin H	-10	VAL290 TRP292 ASN306 ARG310 GLN313 ASP331 GLY333 ASN334 PRO335 LYS336 ILE338 TRP385 ASN386 CYS387 ASN388 PHE401 TYR420 ASN422 PHE426 HIS427 THR428 PHE506
Sandresolide C	10	TRP292 ILE305 ASN306 CYS309 ARG310 TRP385 ASN386 ASN388 PHE401 TYR420 ASN422 LYS423 HIS424 PHE426 THR428 PHE506

Table S11: Very high affinity NPs for target nsp14.

Top Ligands	Formulae	SMILES
Amphilectosin A	C ₂₅ H ₃₆ O ₆	<chem>CC1CCC(C2=C1C(=C(C(=C2)C)OC3C(C(C(CO3)O)O)O)O)C(C)C=CC=C(C)C</chem>
Amphilectosin B	C ₂₅ H ₃₆ O ₆	<chem>CC1CCC(C2=C1C(=C(C(=C2)C)OC3C(C(C(CO3)O)O)O)O)C(C)C=CC=C(C)C</chem>
Ameristerenol A	C ₃₀ H ₄₈ O ₂	<chem>C[C@@H]([C@H]1CC[C@@H]2[C@@]1(CCOC3=C2CC=C4[C@@]3(CC[C@H](C4)O)C)C)[C@H]5CC5(C)[C@H](C)C(C)C</chem>
Ameristerol A	C ₃₀ H ₄₈ O ₃	<chem>C[C@@H]([C@H]1CC[C@H]([C@]1(C)CCO)[C@@H]2CC=C3C[C@H](CC[C@@]3(C2=O)C)O)[C@H]4CC4(C)C(=C)C(C)C</chem>
Elisapterosin A	C ₂₀ H ₂₈ O ₅	<chem>CC1CCC2C(CC3C24C1(C(=O)C5(C(C3C(O5)(C)C)(C4=O)C)O)O)C</chem>
Elisabatin A	C ₂₀ H ₂₂ O ₃	<chem>CC1CC(C2=C(C(=O)C(=O)C3=C2C1=C(C=C3C)O)C)C=C(C)C</chem>
Pseudopterosin A	C ₂₅ H ₃₆ O ₆	<chem>CC1CCC2C(CC(C3=C(C(=C(C1=C23)OC4C(C(C(CO4)O)O)O)O)C)C=C(C)C)C</chem>
Pseudopterosin R	C ₂₈ H ₄₀ O ₇	<chem>CC1CCC2C(CC(C3=C(C(=C(C1=C23)O)OC4C(C(C(CO4)C)O)OC(=O)C)O)C)C=C(C)C)C</chem>
Pseudopterolide	C ₂₁ H ₂₂ O ₆	<chem>CC(=C)C1CC2=C(C=C(O2)C(C3C=C(C4C1O4)C(=O)O3)C(=C)C)C(=O)OC</chem>
Pseudopteroxazole	C ₂₁ H ₂₇ NO	<chem>CC1CCC2C(CC(C3=C(C4=C(C1=C23)OC=N4)C)C)C=C(C)C)C</chem>
Sandresolide B	C ₁₉ H ₂₈ O ₄	<chem>CC1CCC2C(CC(C(C3(C2=C1C(=O)O3)O)(C)O)C)C=C(C)C)C</chem>
Seco-Pseudopterosin A	C ₂₅ H ₃₈ O ₆	<chem>CC1CCC(C2=C1C(=C(C(=C2)C)O)OC3C(C(C(CO3)O)O)O)C(C)CCC=C(C)C</chem>

Table S12: Smiles line notations for filtered NPs.