Targeting 3CLpro and SARS-CoV-2 RdRp by *Amphimedon* sp. metabolites: a computational study

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Table S1. The CDOCKER energy and CDOCKER interaction energy of the virtually screened compounds, Remdesivir and Ligand N3 on RdRp and 3CL pro enzymes.

	RdRp (PDB ID: 6NUR)		**3CL protease (PDB ID: 6LU7).**	
Compound	**CDOCKER energy**	**CDOCKER interaction energy**	**CDOCKER energy**	**CDOCKER interaction energy**
1	-45.4891	-51.245	-56.5311	-48.047
7	-24.9113	-55.4676	-22.9961	-46.8449
8	-14.9527	-33.013	-18.0475	-40.973
9	-34.6093	-36.2722	-39.2038	-39.0384
10	-15.8932	-43.8066	-16.4872	-50.1956
11	-40.4527	-55.0797	-40.2121	-50.9693
12	-33.0222	-57.2272	-26.4258	-47.9309
14	-2.54925	-31.7949	-4.5213	-37.3417
Remdesivir	-30.1162	-59.1337	ND	ND
Ligand N3	ND	ND	-70.8463	-79.0435

Table S2. Different interaction energy types and total binding energies of compounds 1 and 12 with SARS-CoV-2 RdRp (PDB ID 6NUR) and 3CL protease (PDB ID 6LU7).

	Van der Waals (kJ/mol)	**Electrostatic (kJ/mol)**	**Polar Solvation (kJ/mol)**	**SASA (kJ/mol)**	**Binding Energy (kJ/mol)**	**Standard deviation (kJ/mol)**
RdRp						
Remdesivir	-135.85	-94.41	202.29	-16.83	-44.77	± 2.62
Compound 1	-203.89	-32.99	215.63	-23.69	-45.12	± 2.45
Compound 12	-148.28	-135.13	255.7	-20.4	-47.86	± 2.33
3CL protease						
Compound N3	-284.57	-96.25	251.63	-26.83	-156.02	± 2.46
Compound 1	-149.93	-87.39	183.66	-16.02	-69.81	± 2.03
Compound 12	-198.6	-33.42	123.96	-19.02	-127.33	± 1.79

Table S3. Pharmacokinetic properties of compounds.

Property		Compound 1	Compound 7	Compound 8	Compound 9	Compound 10	Compound 11
Absorption	Water Solubility (log mol/L)	-2.94	-6.781	-6.419	-6.309	-7.183	**-5.578**
	Caco2 permeability (log Papp in 10^{-6} cm/s)	0.919	1.127	1.575	1.719	1.565	**1.264**
	Intestinal absorption (%)	88.201	90.9	90.63	92.925	89.723	**86.168**
	Skin permeability (log Kp)	-2.73	-2.758	-2.661	-2.681	-2.758	**-2.734**
	P-glycoprotein substrate	Yes	No	No	No	No	**Yes**
	P-glycoprotein I	No	Yes	No	No	No	**No**
	P-glycoprotein II	Yes	Yes	No	No	Yes	**Yes**
Distribution	VDss (log L/kg)	-0.113	0.566	-0.255	0.237	-0.295	-0.644
	Fraction unbound (Fu)	0.349	0	0.085	0.116	0.034	**0.098**
	BBB permeability (log BB)	-0.477	-0.396	-0.243	0.224	-0.393	**-0.731**
	CNS permeability (log PS)	-2.709	-2.118	-1.831	-1.984	-1.507	**-0.559**
Metabolism	CYP2D6 substrate	Yes	No	No	No	No	No
	CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes	Yes
	CYP1A2 inhibitor	No	No	Yes	Yes	Yes	No
	CYP2C19 inhibitor	No	No	No	No	No	No
	CYP2C9 inhibitor	No	No	No	No	No	No
	CYP2D6 inhibitor	No	No	No	No	No	No
	CYP3A4 inhibitor	No	No	No	No	No	No
Excretion	Total Clearance (log ml/mim/kg)	1.184	1.605	1.784	1.982	1.996	1.985
	Renal OCT2 substrate	No	No	No	No	No	No
Toxicity	AMES toxicity	No	No	No	No	No	No
	Max. tolerated dose (log mg/kg/day)	-0.512	0.238	-0.305	0.317	-0.676	**-1.166**
	hERG I inhibitor	No	No	No	No	No	**No**
	hERG II inhibitor	No	Yes	No	No	Yes	**No**
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.719	2.041	1.754	1.67	1.749	**3.158**
	Oral Rat Chronic Toxicity (LOAEL) (mol/kg_bw/day)	1.823	2.624	3.095	2.727	3.313	**3.86**
	Hepatotoxicity	Yes	No	No	No	No	**No**
	Skin Sensitisation	No	No	Yes	Yes	Yes	**Yes**

	T.Pyriformis toxicity (log µg/L)	0.293	0.336	1.702	1.7	0.932	**0.319**
	Minnow toxicity (log mM)	**-1.235**	**-4.33**	-0.975	-1.335	**-1.607**	**-2.736**

Property		Compound 12	Compound 14			
Absorption	Water Solubility (log mol/L)	**-3.788**	**-3.09**			
	Caco2 permeability (log Papp in 10^{-6} cm/s)	**0.597**	**1.389**			
	Intestinal absorption (%)	**83.364**	**100**			
	Skin permeability (log Kp)	**-2.742**	**-2.733**			
	P-glycoprotein substrate	**Yes**	**No**			
	P-glycoprotein I	**Yes**	**No**			
	P-glycoprotein II	**No**	**Yes**			
Distribution	VDss (log L/kg)	**-1.3**	**0.458**			
	Fraction unbound (Fu)	**0.235**	**0.336**			
	BBB permeability (log BB)	**-1.608**	**0.607**			
	CNS permeability (log PS)	**-3.491**	**-2.057**			
Metabolism	CYP2D6 substrate	**No**	**No**			
	CYP3A4 substrate	**Yes**	**Yes**			
	CYP1A2 inhibitor	**No**	**Yes**			
	CYP2C19 inhibitor	**No**	**Yes**			
	CYP2C9 inhibitor	**No**	**Yes**			
	CYP2D6 inhibitor	**No**	**No**			
	CYP3A4 inhibitor	**No**	**Yes**			
Excretion	Total Clearance (log ml/mim/kg)	**1.762**	**0.835**			
	Renal OCT2 substrate	**No**	**No**			
Toxicity	AMES toxicity	**No**	**No**			
	Max. tolerated dose (log mg/kg/day)	**-0.058**	**0.425**			
	hERG I inhibitor	**No**	**No**			
	hERG II inhibitor	**Yes**	**No**			
	Oral Rat Acute Toxicity (LD50) (mol/kg)	**4.162**	**2.61**			
	Oral Rat Chronic Toxicity (LOAEL) (mol/kg_bw/day)	**4.417**	**0.649**			
	Hepatotoxicity	**Yes**	**Yes**			
	Skin Sensitisation	**No**	**No**			

	T.Pyriformis toxicity (log µg/L)	**0.285**	**0.285**			
	Minnow toxicity (log mM)	**2.319**	**0.612**			