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An integrated theoretical study on natural alkaloids as SARS-CoV-2 main protease inhibitors: A step toward discovery of potential drug candidate with anti-covid-19 activity

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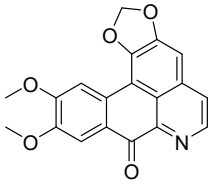
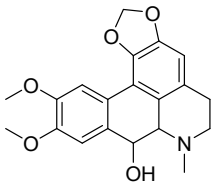
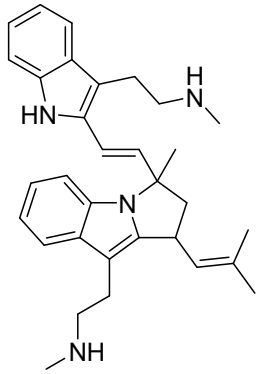
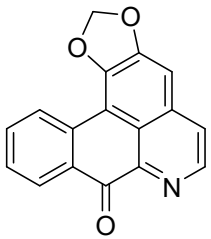
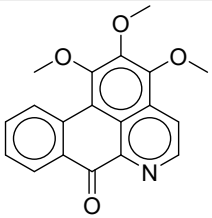
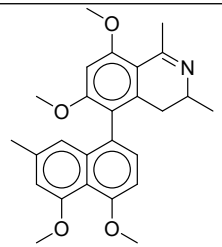
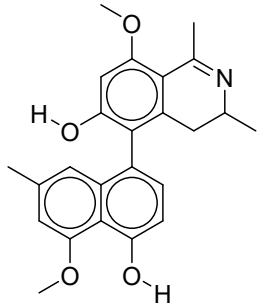
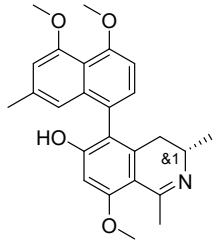
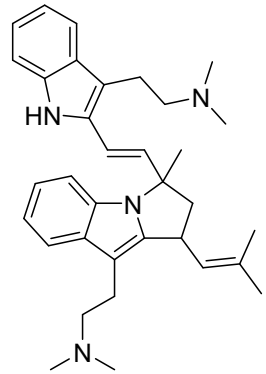
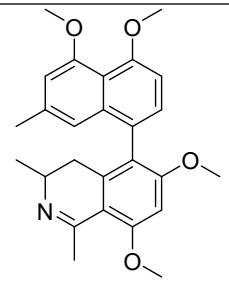
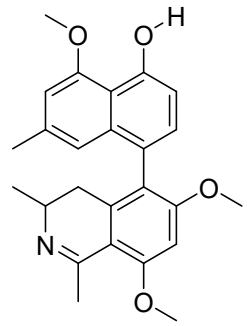
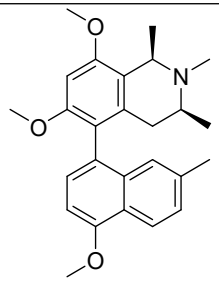
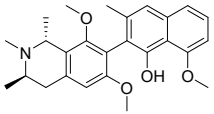
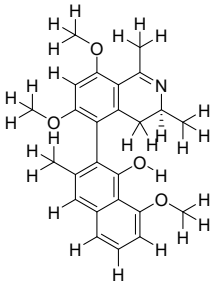
Table S-1: Dataset of antiparasitic natural alkaloids with their IC_{50} values and their sources

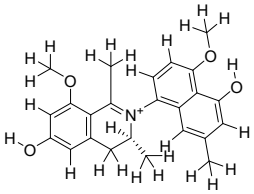
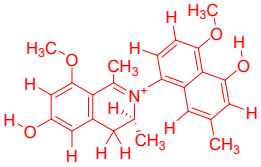
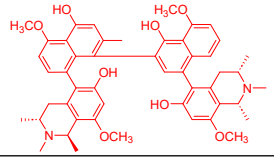
S No	Name	Formula	Smiles	Activity	Structure	IC50/ EC50 µM / nm / µg/mL / mM	Source	Reference
1	Dicentrinone	C19H13NO5	COC1=C(C=C2C(=C1)C3=C4C(=CC5=C3OCO5)C=CN=C4C2=O)OC	Against free trypomastigotes of the Ystrain of T.cruzi		16.4 µM	fresh leaves of Ocotea puberula	(Fernández *et al.*, 2021a).

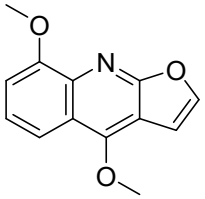
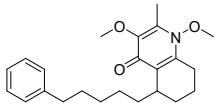
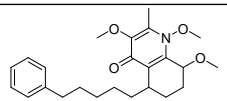
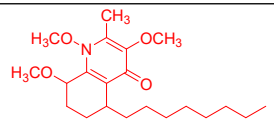
2	Duguetine	C20H21NO5	CN1CCC2=CC3=C(C4=C2C1C(C5=CC(=C(C=C54)OC)OC)O)OCO3	Against free trypomastigotes of the Ystrain of T.cruzi		9.32 µM	fresh leaves of Ocotea puberula	(Fernández *et al.*, 2021a).
3	Flinderole A	C32H40N4	CC(=CC1CC(N2C1=C(C3=CC=CC=C32)CCNC)(C)C=CC4=C(C5=CC=CC=C5N4)CCNC)C	against P. falciparum 3D7 strain		0.75 µM	Australian species Flindersia acuminata	(Fernandez *et al.*, 2010).
4	Liriodenine	C17H9NO3	C1OC2=C(O1)C3=C4C(=C2)C=CN=C4C(=O)C5=CC=CC=C53	against the trypomastigote of T.cruzi		14.5 µM	Annona foetida	(Fernández *et al.*, 2021a).
5	O-methylmoschatoline	$C_{19}H_{15}NO_4$	COc1c2ccnc3c2c(c(c1OC)OC)-c4ccccc4C3=O	against the trypomastigote of T.cruzi		11.83 µM	Annona foetida	(Fernández *et al.*, 2021a).

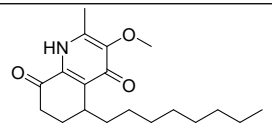
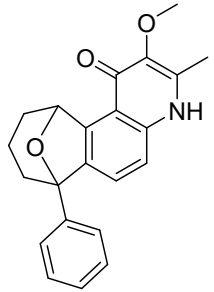
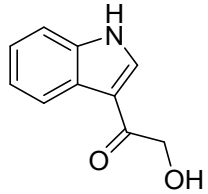
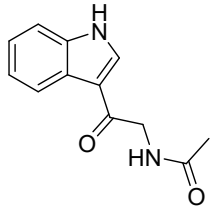
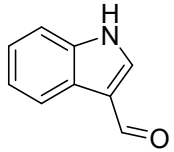
6	ancistroealaine A	$C_{26}H_{29}NO_4$	Cc1cc2c(ccc(c2c(c1)OC)OC)c3c(cc(c4c3CC(N=C4C)C)OC)OC	against trypomastigotes (Tulahuen C4, L6 cells		5.6 µM	isolated from lianas from the Ancistrocladus genus	(Fernández *et al.*, 2021a).
7	6,5 ′-O,O-didemethylancistroealaine A	C24H25NO4	Cc(c1)cc(OC)c2c1c(c3c(CC(C)N=C4C)c4c(OC)cc3O[H])ccc2O[H]	against trypomastigotes (Tulahuen C4, L6 cells		16.3 µM	isolated from lianas from the Ancistrocladus genus	(Fernández *et al.*, 2021a).
8	6-O-demethylancistroealaine A	$C_{25}H_{27}NO_4$	OC1=C(C2=C3C=C(C)C=C(OC)C3=C(OC)C=C2)C(C[C@H](C)N=C4C)=C4C(OC)=C1	against trypomastigotes (Tulahuen C4, L6 cells		25.9 µM	isolated from lianas from the Ancistrocladus genus	(Fernández *et al.*, 2021a).

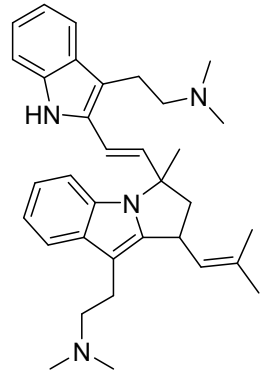
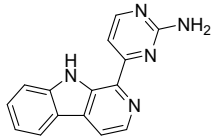
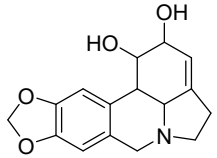
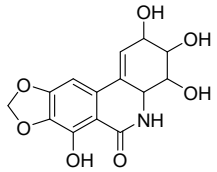
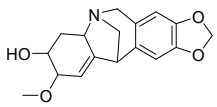
9	Flinderole B	C34H44N4	CC(=CC1CC(N2C1=C(C3=CC=CC=C32)CCN(C)C)(C)C=CC4=C(C5=CC=CC=C5N4)CCN(C)C)C	against P. falciparum 3D7 strain		0.21 µM	*F. amboinensis*	(Fernandez *et al.*, 2010).
10	ancistrotanzanine B	C26H29NO4	CC1CC2=C(C(=CC(=C2C(=N1)C)OC)OC)C3=C4C=C(C=C(C4=C(C=C3)OC)OC)C	against β-gal Tulahuen trypomastigotes		3.58 µM	isolated from lianas from the *Ancistrocladus genus*	(Fernández *et al.*, 2021a).
11	ancistectorine D	C25H27NO4	CC1CC2=C(C3=C4C=C(C)C=C(OC)C4=C(O[H])C=C3)C(OC)=CC(OC)=C2C(C)=N1	against T. cruzi		4.439 µM	isolated from lianas from the *Ancistrocladus genus*	(Fernández *et al.*, 2021a).

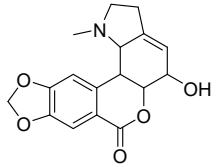
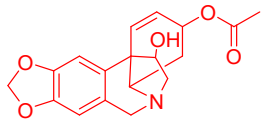
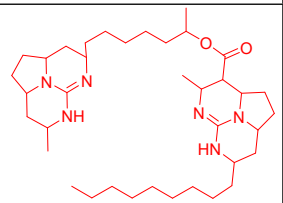
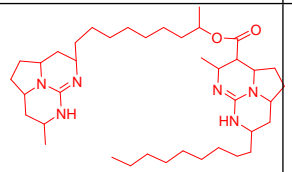
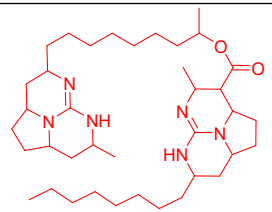
12	5-epi-4′-O-demethylancistrobertsonine C	$C_{26}H_{31}NO_4$	CC1=CC=C2C(OC)=CC=C(C3=C(OC)C=C(OC)C4=C3C[C@H](C)N(C)[C@@H]4C)C2=C1	against T. cruzi		11.1 µM	isolated from lianas from the Ancistrocladus genus	(Fernández *et al.*, 2021a).
13	Ancistotectorine	$C_{26}H_{31}NO_4$	COC1=CC=CC2=CC(C)=C(C(O)=C12)C1=C(OC)C2=C(C[C@@H](C)N(C)[C@@H]2C)C=C1OC	against T. cruzi		10.2 µM	isolated from lianas from the Ancistrocladus genus	(Fernández *et al.*, 2021a).
14	.Ancistrotanzanine A	$C_{25}H_{27}NO_4$	[H]OC1=C2C(OC([H])([H])[H])=C([H])C([H])=C([H])C2=C([H])C(=C1C1=C(OC([H])([H])[H])C([H])=C(OC([H])([H])[H])C2=C1C([H])([H])[C@@]([H15])(N=C2C([H])([H])[H])C([H])([H])[H])C([H])([H])[H]	against T. cruzi		4.20 µM	isolated from lianas from the Ancistrocladus genus	(Fernández *et al.*, 2021a).
15	4′-O-demethylancistrocl	$C_{25}H_{28}NO_4$	[H]OC1=C(C(C([H])([H])[H])=	against Tulahuen C4		0.03µM	isolated from lianas from the	(Fernández *et al.*, 2021a).

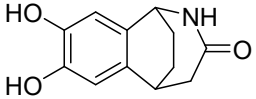
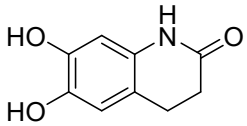
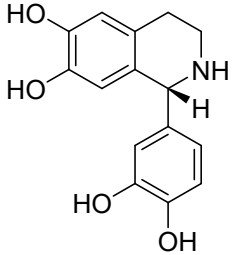
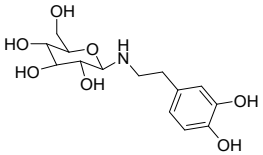
	adinium A		C(C2=C([N+]3=C(C([H])([H])[H])C4=C(C([H])([C@@]3(C([H])([H])[H])[H])[H])C([H])=C(C([H])=C4OC([H])([H])[H])O[H])C([H])=C(C(OC([H])([H])[H])=C12)[H])[H])[H]	trypomastigotes of T. cruzi			Ancistrocladus genus	
16	6,4′-O-didemethylancistrocladinium A	C24H26NO4+	[H]OC1=C(C(C([H])([H])[H])=C(C2=C([N+]3=C(C([H])([H])[H])C4=C(C([H])([C@@]3(C([H])([H])[H])[H])[H])C([H])=C(C([H])=C4OC([H])([H])[H])O[H])C([H])=C(C(OC([H])([H])[H])=C12)[H])[H])[H]	against Tulahuen C4 trypomastigotes of T. cruzi		6.0 µM	isolated from lianas from the Ancistrocladus genus	(Fernández *et al.*, 2021a).
17	Mbandakamine B2	C49H54N2O8	OC1=CC(C)=C(C2=CC(C3=C(O)C=C(OC)C4=C3C[C@H](C	against Tulahuen C4 trypomastigotes of T.		2.98 µM	isolated from lianas from the Ancistrocladus genus	(Fernández *et al.*, 2021a).

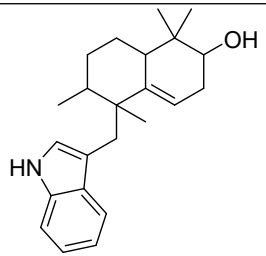
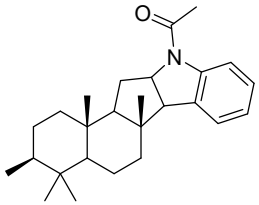
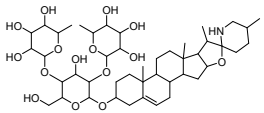
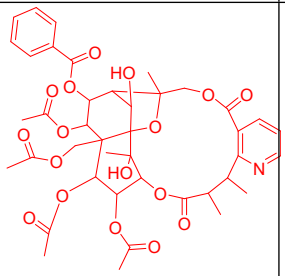
			)N(C)[C@@H]4C)=C(C=CC=C5OC)C5=C2O)C6=C(C7=C(O)C=C(OC)C8=C7C[C@@H](C)N(C)[C@@H]8C)C=CC(OC)=C61	cruzi				
18	γ-fagarine	$C_{13}H_{11}NO_3$	COC1=CC=CC2=C1N=C1OC=CC1=C2OC	against epimastigotesof the Y strain of T.cruzi		33.4 µM	isolated from lianas from the Ancistrocladus genus	(Fernández *et al.*, 2021a).
19	Waltherione G	$C_{23}H_{31}NO_3$	CC1=C(C(=O)C2=C(N1OC)CCCC2CCCCCC3=CC=CC=C3)OC	against amastigotes (Tuluhaen C2C4 (LacZ))		0.02 µM	aerial parts and roots of Waltheria indicas	(Fernández *et al.*, 2021a).
20	Waltheriones H	$C_{24}H_{33}NO_4$	CC1=C(C(=O)C2=C(N1OC)C(CCC2CCCCCC3=CC=CC=C3)OC)OC	against amastigotes (Tuluhaen C2C4 (LacZ))		0.04 µM	aerial parts and roots of Waltheria indicas	(Fernández *et al.*, 2021a).
21	Waltheriones K	$C_{21}H_{35}NO_4$	CCCCCCCCC1CCC(C2=C1C(=O)C(=C(N2OC)C)OC)OC	against amastigotes (Tuluhaen C2C4 (LacZ))		0.04 µM	aerial parts and roots of Waltheria indicas	(Fernández *et al.*, 2021a).

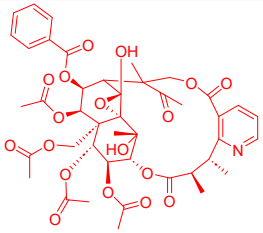
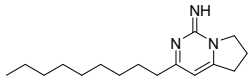
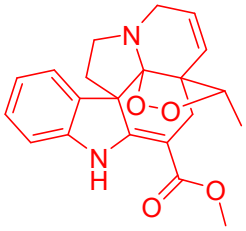
22	Antidesmone	C19H29NO3	CCCCCCCCC1CCC(=O)C2=C1C(=O)C(=C(N2)C)OC	against amastigotes (Tuluhaen C2C4 (LacZ))		0.062 µM	aerial parts and roots of Waltheria indicas	(Fernández *et al.*, 2021a).
23	Waltherione C	$C_{22}H_{21}NO_3$	CC1=C(C(=O)C2=C(N1)C=CC3=C2C4CCCC3(O4)C5=CC=CC=C5)OC	against amastigotes (Tuluhaen C2C4 (LacZ))		1.93 µM	aerial parts and roots of Waltheria indicas	(Fernández *et al.*, 2021a).
24	3-hydroxyacetylindole	$C_{10}H_9NO_2$	C1=CC=C2C(=C1)C(=CN2)C(=O)CO	amastigotes (Tulahuen β-gal)		20.6 µM	black coral Antipathes sp.	(Fernández *et al.*, 2021a).
25	N-acetyl-β-oxotryptamine	$C_{12}H_{12}N_2O_2$	CC(=O)NCC(=O)C1=CNC2=CC=CC=C12	amastigotes (Tulahuen β-gal)		19.4 µM	black coral Antipathes sp.	(Fernández *et al.*, 2021a).
26	3-formylindole	C_9H_7NO	C1=CC=C2C(=C1)C(=CN2)C=O	amastigotes (Tulahuen β-gal)		26.9 µM	black coral Antipathes sp.	(Fernández *et al.*, 2021a).

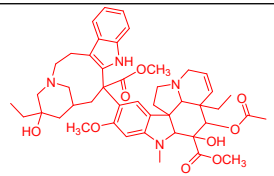
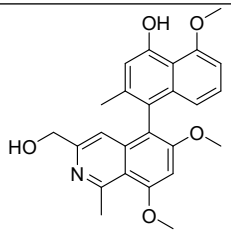
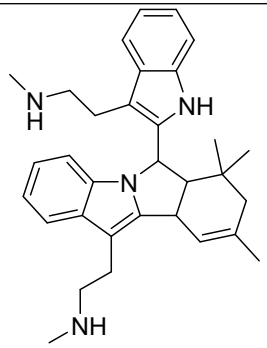
27	Flinderole C	C34H44N4	CC(=CC1CC(N2C1=C(C3=CC=CC=C32)CCN(C)C)(C)C=CC4=C(C5=CC=CC=C5N4)CCN(C)C)C	against P. falciparum FCR3 strain		0.36 µM	F. amboinensis	(Fernández *et al.*, 2021b).
28	Annomontine	$C_{15}H_{11}N_5$	C1=CC=C2C(=C1)C3=C(N2)C(=NC=C3)C4=NC(=NC=C4)N	trypomastigotes (Y strain) of T.cruzi		16.08 µM	branches of Annona foetida	(Fernández *et al.*, 2021a).
29	Lycorine	$C_{16}H_{17}NO_4$	C1CN2CC3=CC4=C(C=C3C5C2C1=CC(C5O)O)OCO4	anti-T. cruzi activity		0.70 µM	isolated from extracts of different Narcissus species	(Fernández *et al.*, 2021a).
30	Narciclasine	$C_{14}H_{13}NO_7$	C1OC2=C(O1)C(=C3C(=C2)C4=CC(C(C(C4NC3=O)O)O)O)O	anti-T. cruzi activity		0.49 µM	isolated from extracts of different Narcissus species	(Fernández *et al.*, 2021a).
31	Montanine	$C_{17}H_{19}NO_4$	COC1C=C2C(CC1O)N3CC2C4=CC5=C(C=C4C3)OCO5	anti-T. cruzi activity		1.99 µM	isolated from extracts of different Narcissus species	(Fernández *et al.*, 2021a).

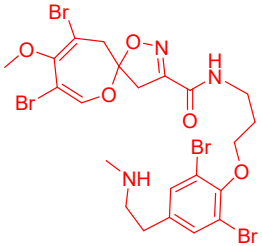
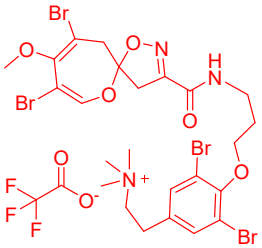
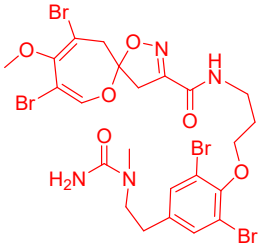
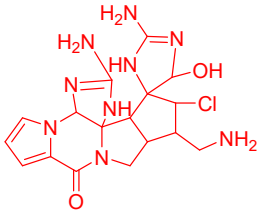
32	Hippeastrine	$C_{17}H_{17}NO_5$	CN1CCC2=CC(C3C(C21)C4=CC5=C(C=C4C(=O)O3)OCO5)O	anti-T. cruzi activity		3.31 µM	isolated from extracts of different Narcissus species	(Fernández *et al.*, 2021a).
33	3-O-acetylhamayne	$C_{18}H_{19}NO_5$	CC(=O)OC1CC2C3(C=C1)C(CN2CC4=CC5=C(C=C34)OCO5)O	against the amastigote form (Tulahuen β-gal C2C4 strain)		25.2 µM	fresh bulbs of Crinum amabile	(Fernández *et al.*, 2021a).
34	Batzelladine F	$C_{37}H_{64}N_6O_2$	CCCCCCCCCC1CC2CCC3N2C(=NC(C3C(=O)OC(C)CCCCCC4CC5CCC6N5C(=N4)NC(C6)C)C)N1	trypomastigotes(Ystrain) of T.cruzi		5 µM	marine sponge Monanchora arbuscula	(Fernández *et al.*, 2021a).
35	Batzelladine L	$C_{39}H_{68}N_6O_2$	CCCCCCCCCC1CC2CCC3N2C(=NC(C3C(=O)OC(C)CCCCCCCC4CC5CCC6N5C(=N4)NC(C6)C)C)N1	trypomastigotes(Ystrain) of T.cruzi		2 µM	marine sponge Monanchora arbuscula	(Fernández *et al.*, 2021a).
36	nor-batzelladine L	$C_{38}H_{66}N_6O_2$	CCCCCCCCC1CC2CCC3N2C(=NC(C3C(=O)OC(C)CCCCCCCC4CC5CCC	trypomastigotes(Ystrain) of T.cruzi		7 µM	marine sponge Monanchora arbuscula	(Fernández *et al.*, 2021a).

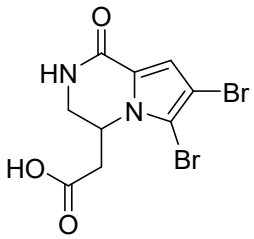
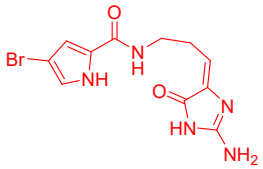
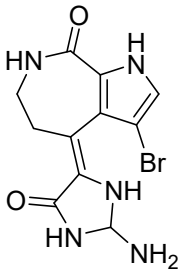
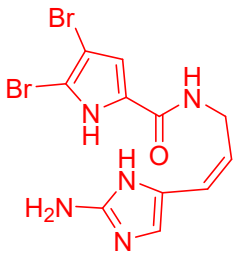
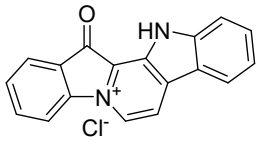
			6N5C(=N4)NC(C6)C)C)N1					
37	Alternamide A	C12H13NO3	O=C1CC2C3=CC(O)=C(O)C=C3C(CC2)N1	Against free trypomastigotes (Ystrain) of T.cruzi		0.61 µM	aerial parts of Alternanthera littoralis	(Fernández *et al.*, 2021a).
38	Alternamide B	C9H9NO3	O=C1CCC2=CC(O)=C(O)C=C2N1	Against free trypomastigotes (Ystrain) of T.cruzi		10 µM	aerial parts of Alternanthera littoralis	(Fernández *et al.*, 2021a).
39	Alternamine A	C15H15NO4	OC1=C(O)C=C([C@](C2=CC(O)=C(O)C=C2)([H])NCC3)C3=C1	Against free trypomastigotes (Ystrain) of T.cruzi		0.23 µM	aerial parts of Alternanthera littoralis	(Fernández *et al.*, 2021a).
40	Alternamine B	C14H21NO7	OC1=CC(CCN[C@@H]2O[C@H](CO)[C@@H](O)C(O)[C@H]2O)=CC=C1O	Against free trypomastigotes (Ystrain) of T.cruzi		0.82 µM	aerial parts of Alternanthera littoralis	(Fernández *et al.*, 2021a).

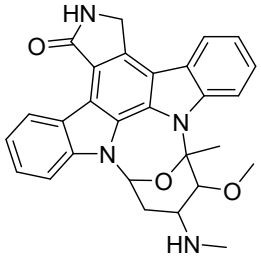
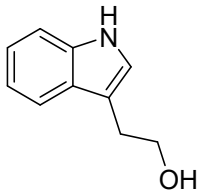
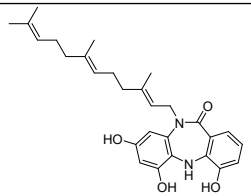
41	Polyalthenol	$C_{23}H_{31}NO$	CC1CCC2C(=CCC(C2(C)C)O)C1(C)CC3=CNC4=CC=CC=C43	against trypomastigotes (Tulahuen strain) of T.cruzi		8.4 µM	Root bark of Greenwayodendron suaveolens	(Fernández *et al.*, 2021a).
42	N-acetyl-polyveoline	C26H37NO	CC1(C)[C@@H](C)CC[C@@]2(C)C1CC[C@]3(C)C2CC4C3C(C=CC=C5)=C5N4C(C)=O	against trypomastigotes (Tulahuen strain)		8.4 µM	Root bark of Greenwayodendron suaveolens	(Fernández *et al.*, 2021a).
43	Solamargine	$C_{45}H_{73}NO_{15}$	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CC=C6C5(CCC(C6)OC7C(C(C(C(O7)CO)OC8C(C(C(C(O8)C)O)O)O)O)OC9C(C(C(C(O9)C)O)O)O)C)C)C)NC1	against epimastigotes of the Y strain of T.cruzi		17.63µM	isolated from Solanum palinacanthum	(Fernández *et al.*, 2021a).
44	Ilicifoliunines A	C41H47NO17	CC1C(C(=O)OC2C(C(C3(C(C(C4C(C3(C2(C)O)OC4(COC(=O)C5=C1N=CC=C5)C)O)OC(=O)C6=CC=CC=C6)OC(=O)C)COC(=O)C)OC(	against the epimastigotes (Y strain) of T.cruzi		27.7 µM	root bark of Maytenus ilicifolia	(Fernández *et al.*, 2021a).

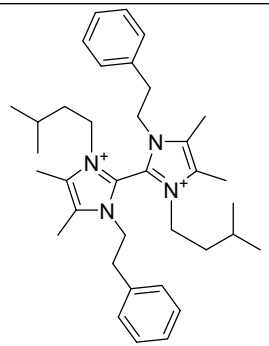
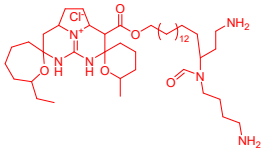
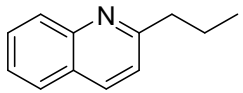
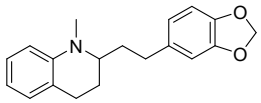
			=O)C)OC(=O)C)C					
45	Aquifoliunine E-I	$C_{43}H_{49}NO_{18}$	C[C@@H]1[C@@H](C)C(=O)O[C@@H]2[C@@H](OC(C)=O)[C@H](OC(C)=O)[C@@]3(COC(C)=O)[C@@H](OC(C)=O)[C@@H](OC(=O)C4=CC=CC=C4)[C@H]4[C@H](OC(C)=O)[C@@]3(O[C@]4(C)COC(=O)C3=C1N=CC=C3)[C@@]2(C)O	against the epimastigotes (Y strain) of T.cruzi		41.9 µM	root bark of Maytenus ilicifolia	(Fernández *et al.*, 2021a).
46	Monalidine A	$C_{16}H_{27}N_3$	CCCCCCCCCC1=NC(=N)N2CCCC2=C1	against free trypomastigotes (Y strain) of T.cruzi		8 µM	isolated from the marine sponge Monanchora arbuscula	(Fernández *et al.*, 2021a).
47	Catharoseumine	$C_{21}H_{22}N_2O_4$	CC1C23CC(=C4C5(C2(N(CC5)CC=C3)OO1)C6=CC=CC=C6N4)C(=O)OC	against protozoan parasite falcipain-2		4.06 µM	whole plant of C. roseus	(Almagro *et al.*, 2015).

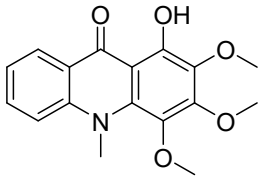
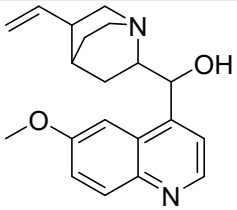
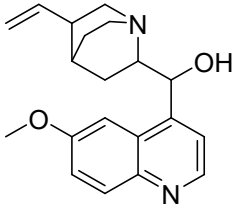
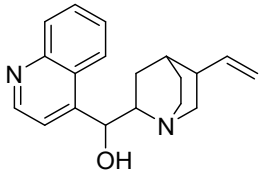
48	Vinblastine	$C_{46}H_{58}N_4O_9$	CCC1(CC2CC(C3=C(CCN(C2)C1)C4=CC=CC=C4N3)(C5=C(C=C6C(=C5)C78CCN9C7C(C=CC9)(C(C(C8N6C)(C(=O)OC)O)OC(=O)C)CC)OC)C(=O)OC)O	against Trypanosoma cruzi		15 µM	whole plant of C. roseus	(Dey *et al.*, 2020).
49	ancistrobenomine A	$C_{25}H_{25}NO_5$	COC1=CC=CC2=C(C(C)=CC(O)=C12)C1=C2C=C(CO)N=C(C)C2=C(OC)C=C1OC	against T. cruzi		11.45 µM	isolated from lianas from the Ancistrocladus genus	(Dey *et al.*, 2020).
50	Isoborreverine	C32H40N4	CC1=CC2C(CN3C2=C(C4=CC=CC=C43)CCNC)C5=C(C6=CC=CC=C6N5)CCNC)C(C1)(C)C	against P. falciparum 3D7 strain		0.24 µM	Australian species Flindersia acuminata	(Fernandez *et al.*, 2010).
51	psammaplysin F	C22H25Br4N3O5	CNCCC1=CC(=C(C(=C1)Br)OCCCNC(=O)	against T. cruzi		5.6 µM	Hyatella sp.	(Tempone *et al.*, 2021).

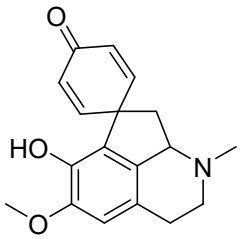
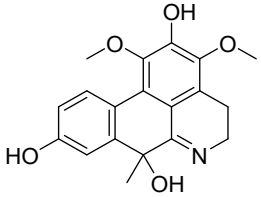
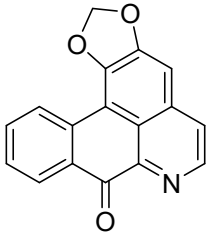
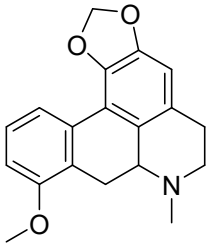
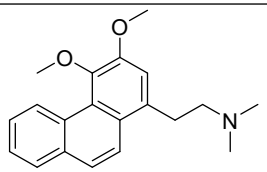
			C2=NOC3(C2)CC(=C(C(=CO3)Br)OC)Br)Br					
52	Psammaplysin H	C26H30Br4F3N3O8	C[N+](C)(C)CCC1=CC(=C(C(=C1)Br)OCCCNC(=O)C2=NOC3(C2O)C=C(C(C(=CO3)Br)OC)Br)Br.C(=O)(C(F)(F)F)[O-]	against the P. falciparum strain 3D7		0.4 µM	Pseudoceratina sp.	(Tempone *et al.*, 2021).
53	psammaplysins G	C23H26Br4N4O7	CN(CCC1=CC(=C(C(=C1)Br)OCCCNC(=O)C2=NOC3(C2O)C=C(C(C(=CO3)Br)OC)Br)Br)C(=O)N	against the P. falciparum strain 3D7		5.2 µM	Pseudoceratina sp.	(Tempone *et al.*, 2021).
54	Palauamine	C17H22ClN9O2	C1C2C(C(C3(C2C45N1C(=O)C6=CC=CN6C4N=C(N5)N)C(N=C(N3)N)O)Cl)CN	against T. b. rhodesiense and L. donovani		0.4 µg/mL 1.1 µg/mL	sponges of the Agelas and Axinella genera	(Tempone *et al.*, 2021).

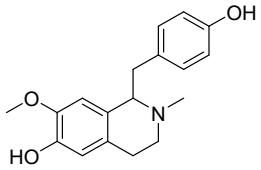
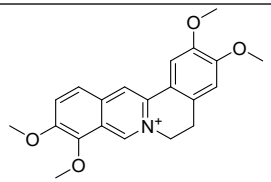
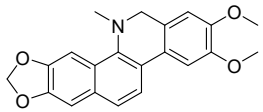
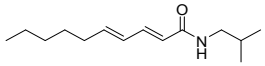
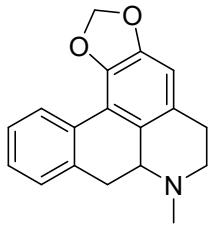
55	longamide B	C9H8Br2N2O3	C1C(N2C(=CC(=C2Br)Br)C(=O)N1)CC(=O)O	against T. b. rhodesiense and L. donovani		1.5 µg/mL 3.8 µg/mL	sponges of the Agelas and Axinella genera	(Tempone *et al.*, 2021).
56	dispacamide B	C11H12BrN5O2	C1=C(NC=C1Br)C(=O)NCCC=C2C(=O)NC(=N2)N	against P. falciparum		1.3 µM	sponges of the Agelas and Axinella genera	(Tempone *et al.*, 2021).
57	spongiacidin B	C11H12BrN5O2	C1CNC(=O)C2=C(C1=C3C(=O)NC(N3)N)C(=CN2)Br	against P. falciparum		1.1 µM	sponges of the Agelas and Axinella genera	(Tempone *et al.*, 2021).
58	Oroidin	C11H11Br2N5O	C1=C(NC(=C1Br)Br)C(=O)NCC=CC2=CN=C(N2)N	inhibition of the P. falciparum enoyl-ACP reductase (PfFabI) enzyme		0.77 µM	sponges of the Agelas and Axinella genera	(Tempone *et al.*, 2021).
59	Fascaplysin	C18H11ClN2O	C1=CC=C2C(=C1)C3=C(N2)C4=[N+](C=C3)C5=CC=CC=C	against T. b. rhodesiense		0.17 µg/mL	sponge Hyrtios cf. erecta	(Tempone *et al.*, 2021).

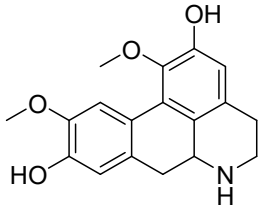
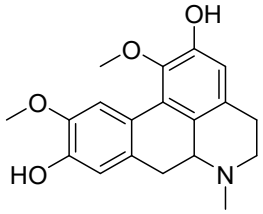
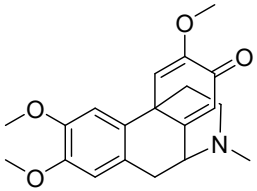
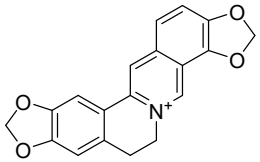
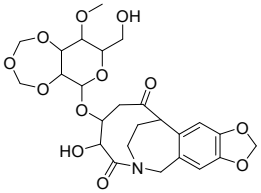
			5C4=O.[Cl-]					
60	Staurosporine	C28H26N4O3	CC12C(C(CC(O1)N3C4=CC=CC=C4C5=C6C(=C7C8=CC=CC=C8N2C7=C53)CNC6=O)NC)OC	against L. major promastigotes, against T. b. brucei		5.3 µM 20 nM	sponge associated actinomycetes Streptomyces sp.	(Tempone *et al.*, 2021).
61	Tryptophol	C10H11NO	C1=CC=C2C(=C1)C(=CN2)CCO	against L. donovani amastigotes		9.6 µg/mL	Spongia sp., Ircinia sp.	(Tempone *et al.*, 2021).
62	Diazepinomicin	C28H34N2O4	CC(=CCCC(=CCCC(=CCN1C2=C(C(=CC(=C2)O)O)NC3=C(C1=O)C=CC=C3O)C)C)C	against T. b. brucei trypomastigotes inhibit the T. b. brucei protease rhodesain		13.6 µM	Micromonospora sp.	(Tempone *et al.*, 2021).

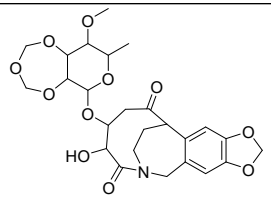
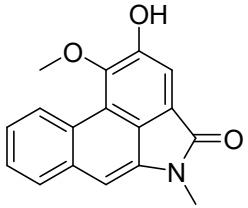
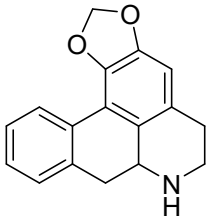
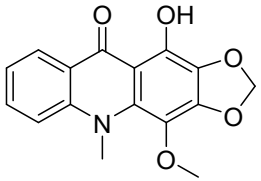
63	paenidigyamycin A	C36H52N4+2	CC1=C([N+](=C(N1CCC2=CC=CC=C2)C3=[N+](C(=C(N3CCC4=CC=CC=C4)C)C)CCC(C)C)CCC(C)C)C	Against (T. b. brucei trypomastigotes Against P. falciparum		0.78 µM 9.1 µM	mangrove rhizosphere soils	(Tempone *et al.*, 2021).
64	Ptilomycalin A	C45H83ClN6O5	CCC1CCCCC2(O1)CC3CCC4[N+]3=C(N2)NC5(C4C(=O)OCCCCCCCCCCCCCCC(=O)N(CCCCN)CCCN)CCCC(O5)C.[Cl-]	against P. falciparum		0.1 µM	sponge Monanchora arbuscula	(Tempone *et al.*, 2021).
65	2-n-propylquinoline	C12H13N	CCCC1=NC2=CC=CC=C2C=C1	against the promastigote forms of L. braziliensis and the epimastigote forms of T. cruzi		0.29 mM	Galipea longiflora K. Krause	(Osorio *et al.*, 2008).
66	Galipinine	C19H21NO2	CN1C(CCC2=CC=CC=C21)CCC3=CC4=C(C=C3)OCO4	Against chloroquine-resistant strains of P.		6.12 µM	Galipea officinalis Hancock	(Osorio *et al.*, 2008).

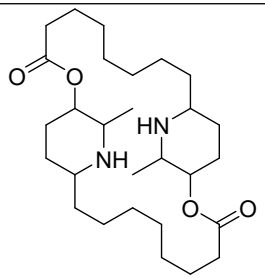
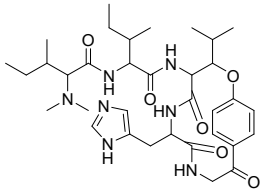
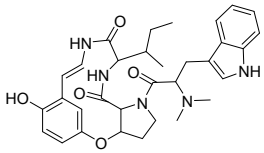
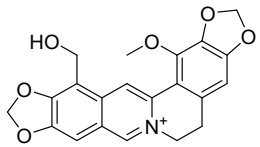
				falciparum				
67	Normelicopicine	C17H17NO5	CN1C2=CC=CC=C2C(=O)C3=C1C(=C(C(=C3O)OC)OC)OC	against both chloroquine-sensitive (HB3) and chloroquine-resistant (K1) strains of P. falciparum		14.7 µM	Teclea trichocarpas	(Osorio *et al.*, 2008).
68	Quinine	C20H24N2O2	COC1=CC2=C(C=CN=C2C=C1)C(C3CC4CCN3CC4C=C)O	Against T. b. brucei		4.9 µM	cinchona bark	(Osorio *et al.*, 2008).
69	Quinidine	C20H24N2O2	COC1=CC2=C(C=CN=C2C=C1)C(C3CC4CCN3CC4C=C)O	Against T. b. brucei		0.8 µM	cinchona bark	(Osorio *et al.*, 2008).
70	Cinchonine	C19H22N2O	C=CC1CN2CCC1CC2C(C3=CC=NC4=CC=CC=C34)O	Against T. b. brucei		1.2 µM	cinchona bark	(Osorio *et al.*, 2008).

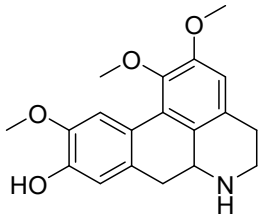
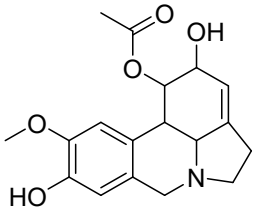
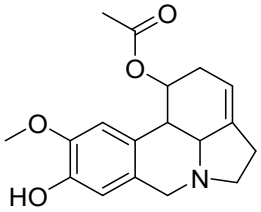
71	Crotsparine	C18H19NO3	CN1CCC2=CC(=C(C3=C2C1CC34C=CC(=O)C=C4)O)OC	against the chloroquine-resistant FcB1 strain		7.41 µM	Uvaria klaineana	(Osorio *et al.*, 2008).
72	isoguattouregidine	C19H19NO5	CC1(C2=C(C=CC(=C2)O)C3=C(C(=C(C4=C3C1=NCC4)OC)O)OC)O	against the promastigote forms of L. donovani and L. amazonensis		0.29 mM	genus Guatteria	(Osorio *et al.*, 2008).
73	Liriodenine	C17H9NO3	C1OC2=C(O1)C3=C4C(=C2)C=CN=C4C(=O)C5=CC=CC=C53	Against P. falciparum		26.2 µM	Stephania dinklagei	(Osorio *et al.*, 2008).
74	Stephanine	C19H19NO3	CN1CCC2=CC3=C(C4=C2C1CC5=C4C=CC=C5OC)OCO3	against the T9/94 strain of P. falciparum		0.38 µM	Stephania venosa	(Osorio *et al.*, 2008).
75	Atherosperminine	C20H23NO2	CN(C)CCC1=CC(=C(C2=C1C=CC3=CC=CC=C32)OC)OC	against a chloroquine-resistant strain of P. falciparum		5.80 µM	stem bark of Cryptocarya nigra	(Uzor, 2020b).

				(K1 strain)				
76	(+)-N-methylisococlaurine	C18H21NO3	CN1CCC2=CC(=C(C=C2C1CC3=CC=C(C=C3)O)OC)O	against a chloroquine-resistant strain of P. falciparum (K1 strain)		5.40 µM	stem bark of Cryptocarya nigra	(Uzor, 2020b).
77	Palmatine	C21H22NO4+	COC1=C(C2=C[N+]3=C(C=C2C=C1)C4=CC(=C(C=C4CC3)OC)OC)OC	against P. falciparum K1 strain		0.080 µg/mL	leaves of Annickia kummeriae	(Uzor, 2020b).
78	Dihydronitidine	C21H19NO4	CN1CC2=CC(=C(C=C2C3=C1C4=CC5=C(C=C4C=C3)OCO5)OC)OC	antiparasitic activity		25 nM	Zanthoxylum heitzii (Rutaceae) bark	(Uzor, 2020b).
79	Pellitorine	C14H25NO	CCCCCC=CC=CC(=O)NCC(C)C	antiparasitic activity		9.7 µM	Zanthoxylum heitzii (Rutaceae) bark	(Uzor, 2020b).
80	Roemerine	C18H17NO2	CN1CCC2=CC3=C(C4=C2C1CC5=CC=CC=C54)OCO3	inhibitory activity against the growth of P. falciparum 3D7 clone		1.49 µg/mL	leaves of Phoebe tavoyana (Meissn.) Hook f. (Lauraceae)	(Uzor, 2020b).

81	Laurolitsine	C18H19NO4	COC1=C(C=C2CC3C4=C(C2=C1)C(=C(C=C4CCN3)O)OC)O	inhibitory activity against the growth of P. falciparum 3D7 clone		1.65 µg/mL	leaves of Phoebe tavoyana (Meissn.) Hook f. (Lauraceae)	(Uzor, 2020b).
82	boldine	C19H21NO4	CN1CCC2=CC(=C(C3=C2C1CC4=CC(=C(C=C43)OC)O)OC)O	inhibitory activity against the growth of P. falciparum 3D7 clone		2.76 µg/ml	leaves of Phoebe tavoyana (Meissn.) Hook f. (Lauraceae)	(Uzor, 2020b).a
83	Sebiferine	C20H23NO4	CN1CCC23C=C(C(=O)C=C2C1CC4=CC(=C(C=C34)OC)OC)OC	against P. falciparum KI strain		22.46 µM	Dehaasia longipedicellata	(Uzor, 2020b).
84	Coptisine	C19H14NO4+	C1C[N+]2=C(C=C3C=CC4=C(C3=C2)OCO4)C5=CC6=C(C=C51)OCO6	inhibitor of Plasmodium falciparum dihydroorotate dehydrogenase		1.83 µM	Coptidis rhizoma	(Uzor, 2020b).
85	cripowellin A	C25H31NO12	COC1C(OC(C2C1OCOCO2)OC3CC(=O)C4CCN(CC5=CC6=C(C=C45)OCO	antiplasmodial activity		30 nM	swamp lily Crinum erubescens	(Uzor, 2020b).

			6)C(=O)C3O)CO					
86	Cripowellin C	C25H31NO11	CC1C(C2C(C(O1)OC3CC(=O)C4CCN(CC5=CC6=C(C=C45)OCO6)C(=O)C3O)OCOCO2)OC	antiplasmodial activity		26 nM	swamp lily Crinum erubescens	(Uzor, 2020b).
87	Sauristolactam	C17H13NO3	CN1C2=CC3=CC=CC=C3C4=C2C(=CC(=C4OC)O)C1=O	Against a chloroquine-sensitive P.falciparum line(3D7)		9.0 µM	aerial parts of Goniothalamus australis	(Uzor, 2020b).
88	(-)-anonaine	C17H15NO2	C1CNC2CC3=CC=CC=C3C4=C2C1=CC5=C4OCO5	Against a chloroquine-sensitive P.falciparum line 3D7		7.0 µM	aerial parts of Goniothalamus australis	(Uzor, 2020b).
89	Normelicopidine	C16H13NO5	CN1C2=CC=CC=C2C(=O)C3=C1C(=C4C(=C3O)OCO4)OC	parasite P. falciparum Dd_2		18.9 ug/mL	root bark of Zanthoxylum simullans	(Uzor, 2020b).

90	Carpaine	C28H50N2O4	CC1C2CCC(N1)CCCCCCCC(=O)OC3CCC(CCCCCCCC(=O)O2)NC3C	strains of P. falciparum 3D7		4.21 µM	Carica papaya L	(Uzor, 2020b).
91	hymenocardine-H	C34H51N7O6	CCC(C)C(C(=O)NC1C(OC2=CC=C(C=C2)C(=O)CNC(=O)C(NC1=O)CC3=CN=CN3)C(C)C)NC(=O)C(C(C)CC)N(C)C	antiplasmodial activity		27.9 µM	root barkofHymenocardiaacida	(Uzor, 2020b).
92	O-desmethylnummularine-R	C32H39N5O5	CCC(C)C1C(=O)NC=CC2=C(C=CC(=C2)OC3CCN(C3C(=O)N1)C(=O)C(CC4=CNC5=CC=CC=C54)N(C)C)O	antiplasmodial activity against P. falciparum K1		3.2 µM	Roots of Ziziphus oxyphylla	(Uzor, 2020b).
93	simplicifolianine	C21H18NO6+	COC1=C2C(=CC3=C1OCO3)CC[N+]4=CC5=CC6=C(C(=C5C=C24)CO)OCO6	antiplasmodial activity against the P. falciparum strains, TM4/8.2		0.78 µg/mL 1.29 µg/mL	aerial parts of Meconopsis simplicifolia (D. Don) Walpers (Papaveraceae)	(Uzor, 2020b).

				(chloroquine -antifolate-sensitive strain) and K1CB1 (multidrug-resistant strain)				
94	(+)-laurotetanine	C19H21NO4	COC1=C(C2=C3C(CC4=CC(=C(C=C42)OC)O)NCCC3=C1)OC	Antiplasmodialactivity		0.189 µM	Alseodaphne corneri.	(Uzor, 2020b).
95	Sternbergine	C18H21NO5	CC(=O)OC1C(C=C2CCN3C2C1C4=CC(=C(C=C4C3)O)OC)O	Against P. falciparum strain D10		3.9 µg/mL	B. radulosa	(Nair and van Staden, 2019).
96	1-O-Acetylnorpluviine	C18H21NO4	CC(=O)OC1CC=C2CCN3C2C1C4=CC(=C(C=C4C3)O)OC	Against P. falciparum strain D10		28.3 µg/mL	B. radulosa	(Nair and van Staden, 2019).

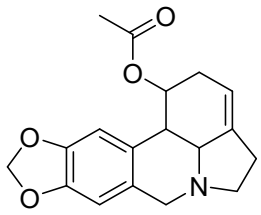
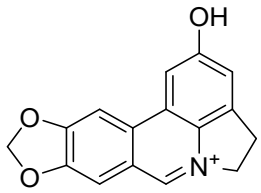
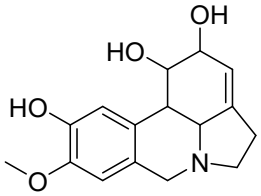
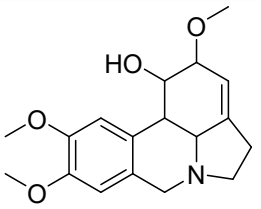
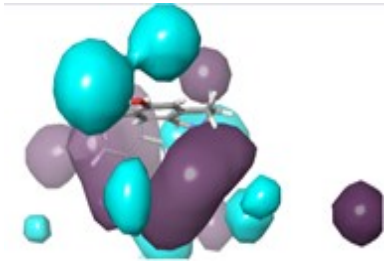
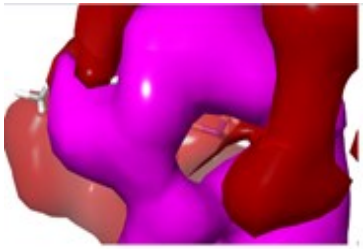
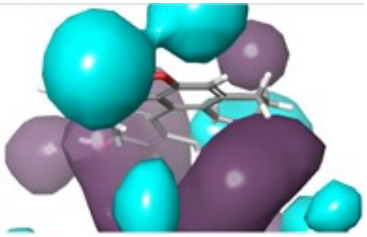
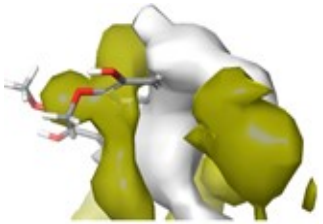
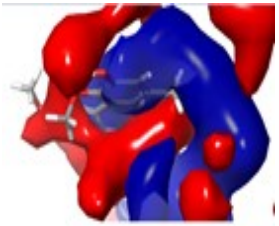
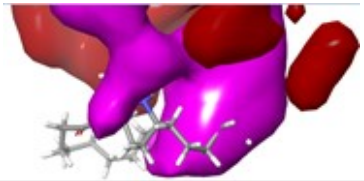
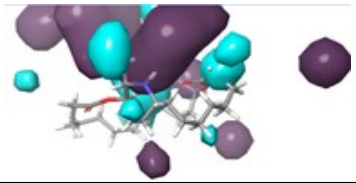
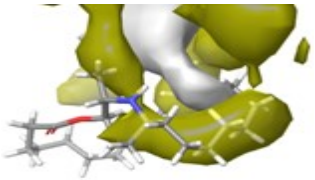
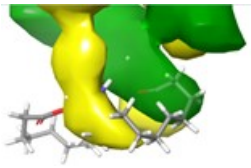
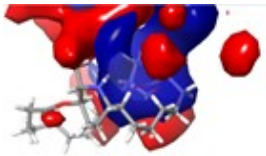
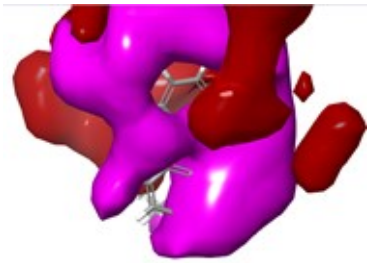
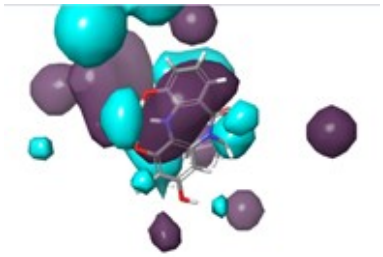
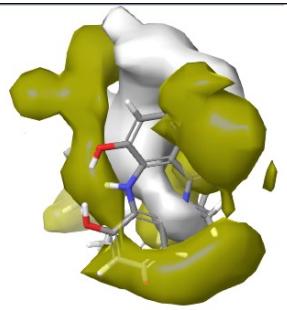
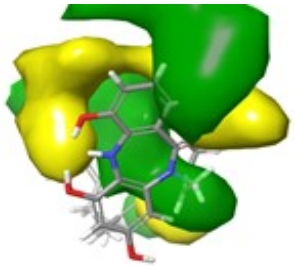
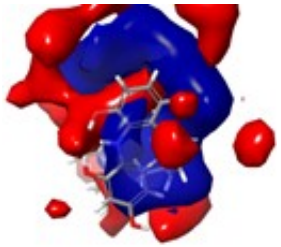
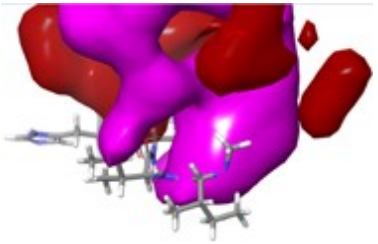
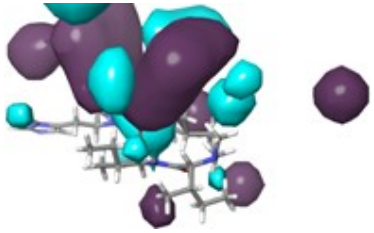
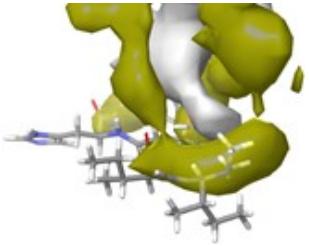
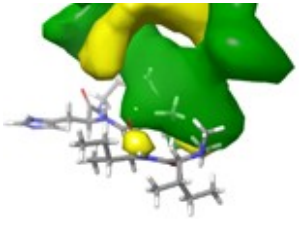
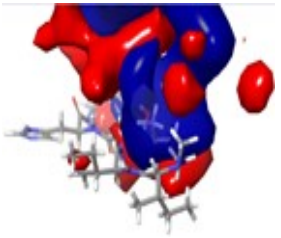
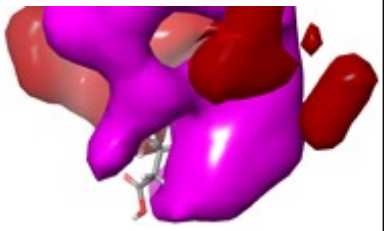
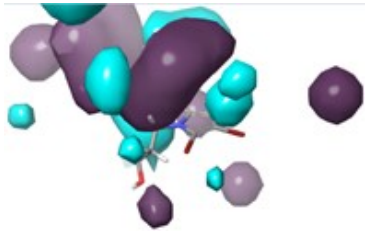
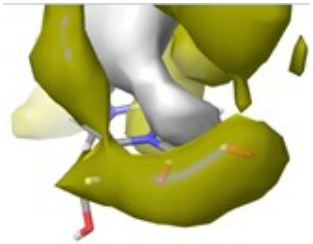
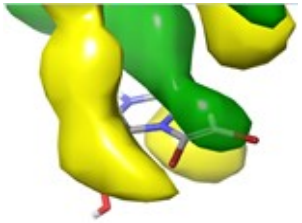
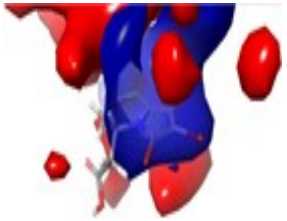
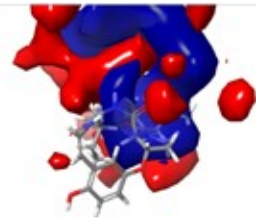
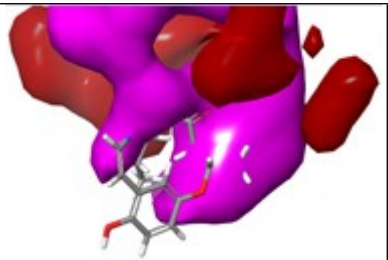
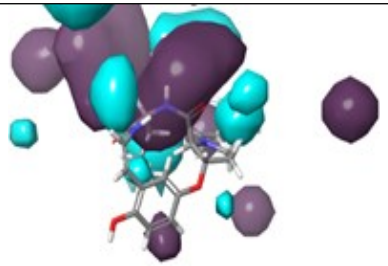
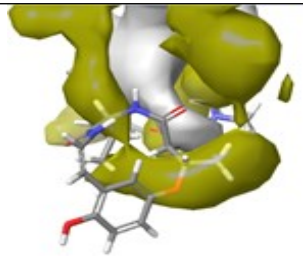
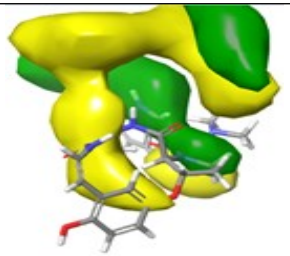
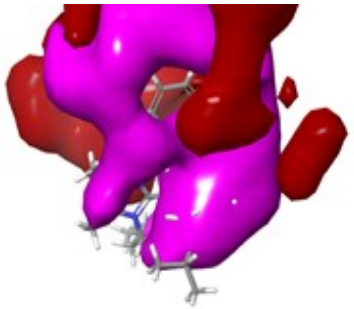
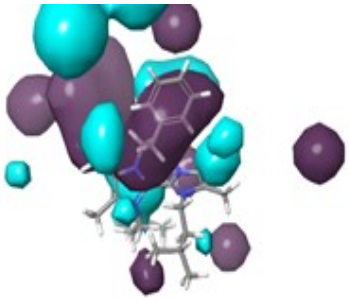
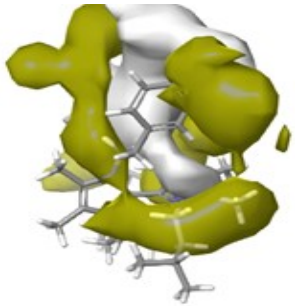
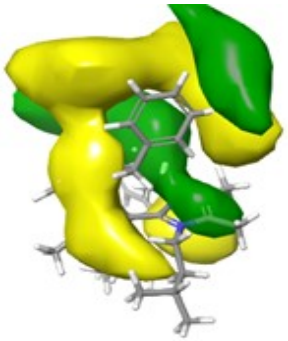
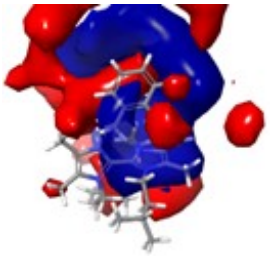
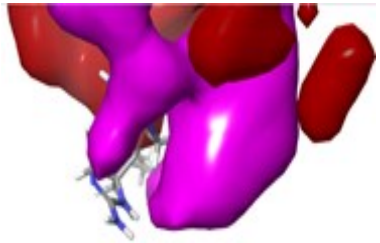
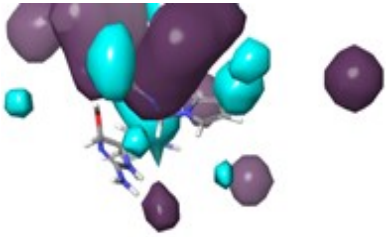
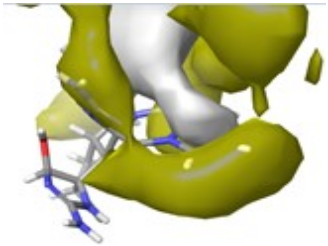
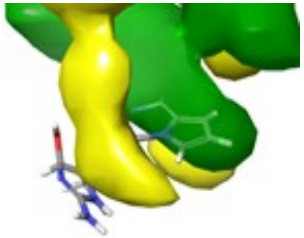
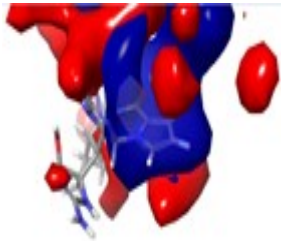
97	Acetylcaranine	C18H19NO4	CC(=O)OC1CC=C2CCN3C2C1C4=CC5=C(C=C4C3)OCO5	Against P. falciparum strain Dd2		1.1 µg/mL	A. belladonna	(Nair and van Staden, 2019).
98	Ungeremine	C16H12NO3+	C1C[N+]2=CC3=CC4=C(C=C3C5=CC(=CC1=C52)O)OCO4	Against P. falciparum strain K1		0.088 µg/mL	Phaedranassa dubia	(Nair and van Staden, 2019).
99	Pseudolycorine	C16H19NO4	COC1=C(C=C2C3C(C(C=C4C3N(CC4)CC2=C1)O)O)O	Against P. falciparum strain K1		0.24 µg/mL	P. dubia	(Nair and van Staden, 2019).
100	Galanthine	C18H23NO4	COC1C=C2CCN3C2C(C1O)C4=CC(=C(C=C4C3)OC)OC	Against P. falciparum strain K1		0.2 µg/mL	Z. citrina	(Nair and van Staden, 2019).

Table S-2: Visualization of Contour Maps from the Field-Based QSAR Study.

Compound	**Gaussian**	**Gaussian**	**Gaussian**	**Gaussian**	**Gaussian**

	H-bond acceptor	**H-bond donor**	**Hydrophobic**	**Steric**	**Electrostatic**
(+)-N-methylisococlaurine					
Boldine					
Carpaine					

diazepinomicin					
hymenocardine-H					
longamide B					
O-desmethylnummularine-R					

					
paenidigyamycin A					
Palauamine					
spongiacidin B					

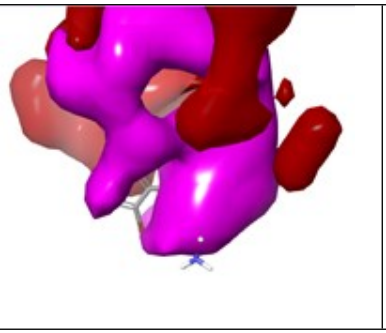
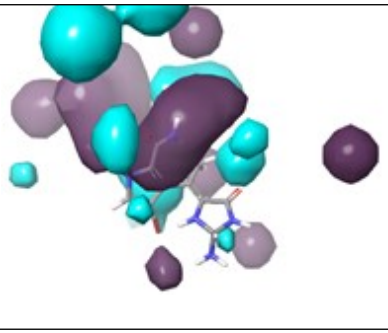
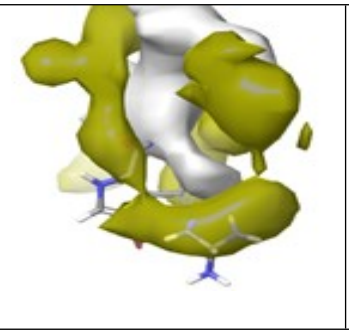
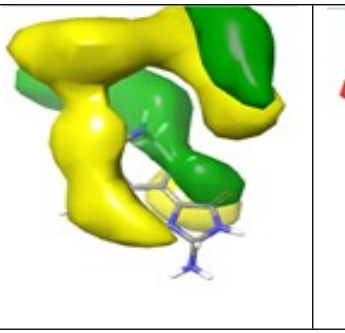
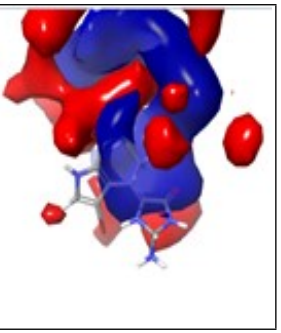
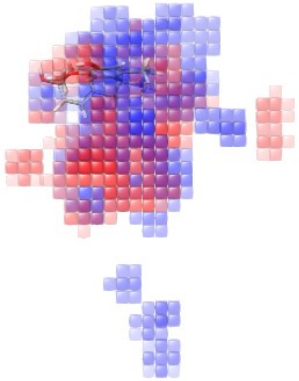
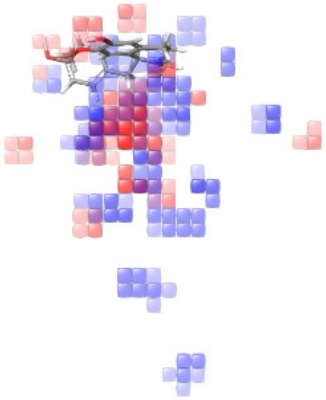
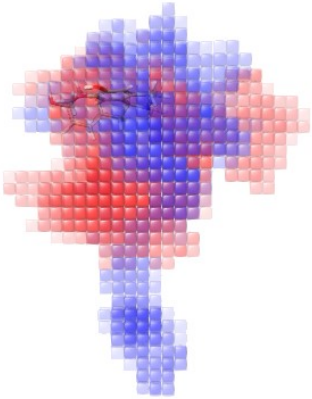
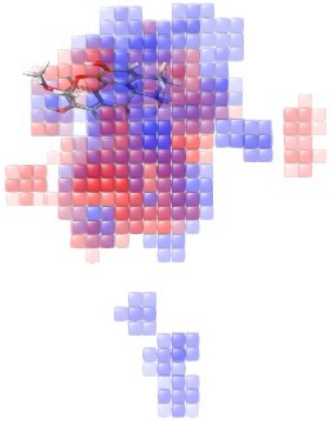
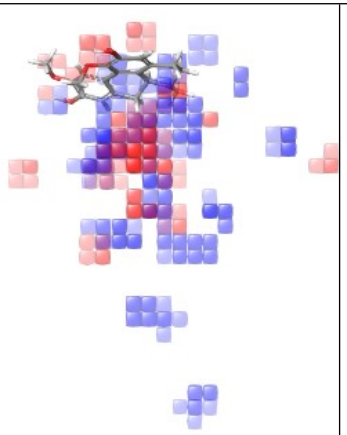
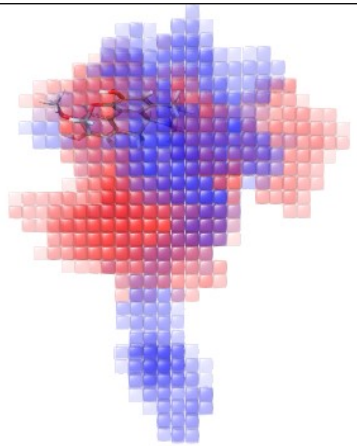
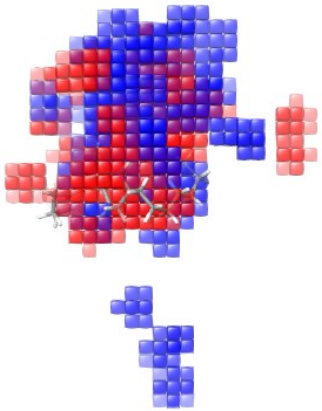
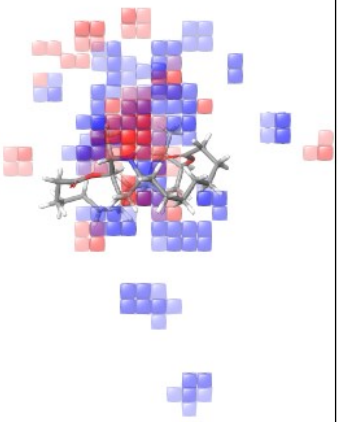
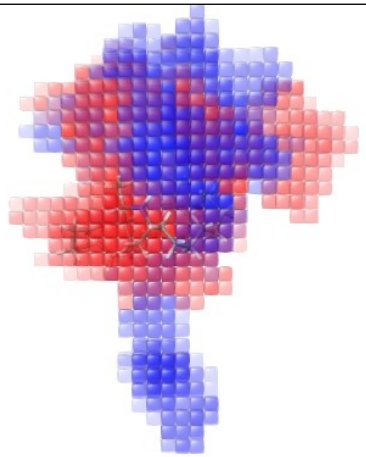
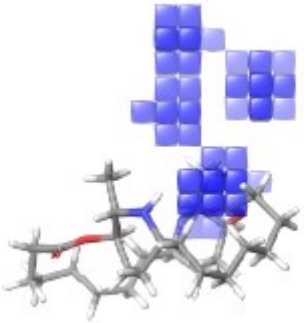
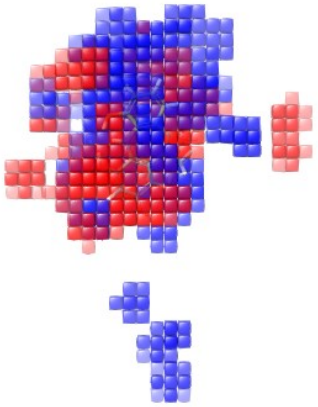
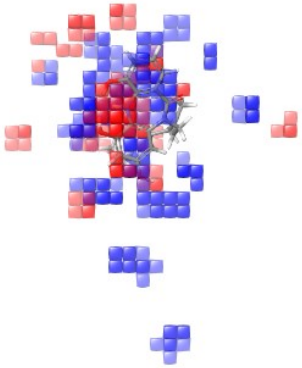
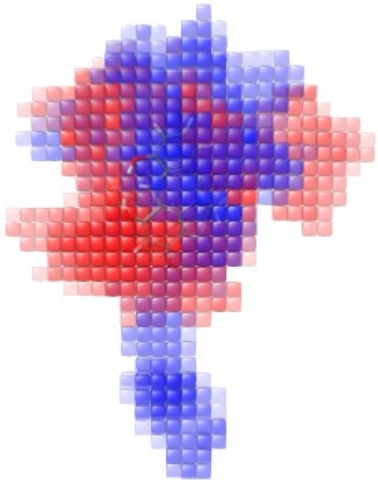
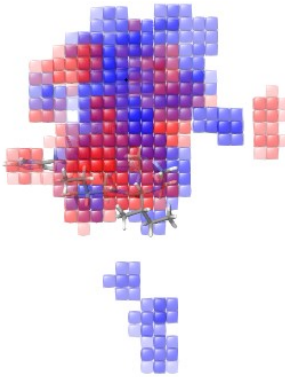
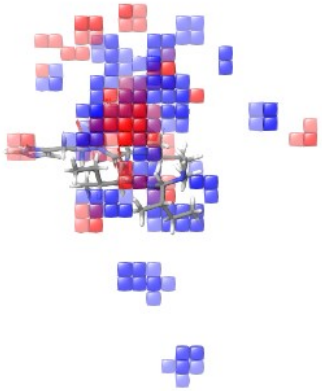
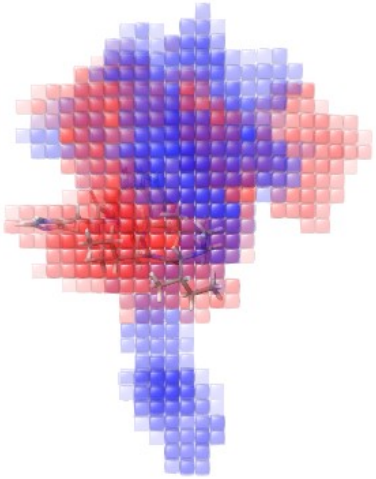
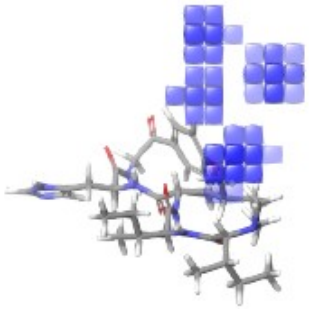
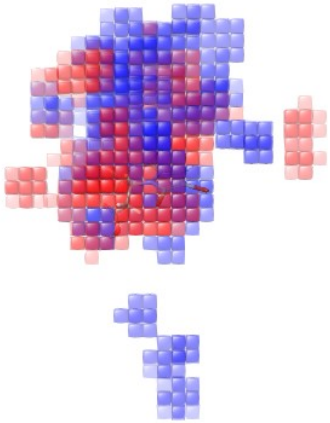
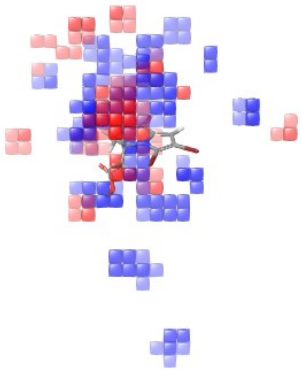
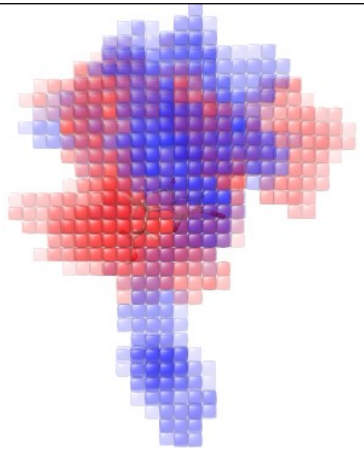
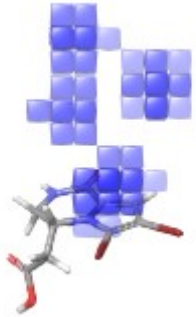
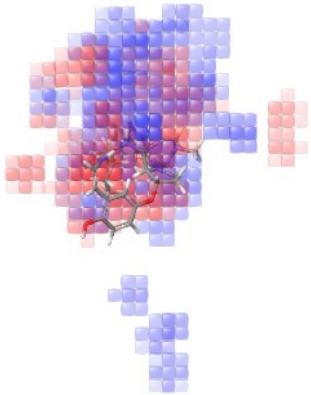
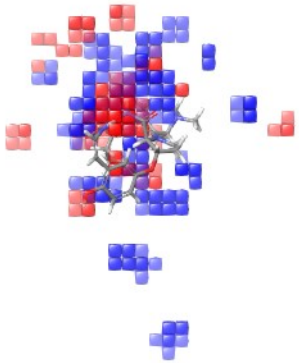
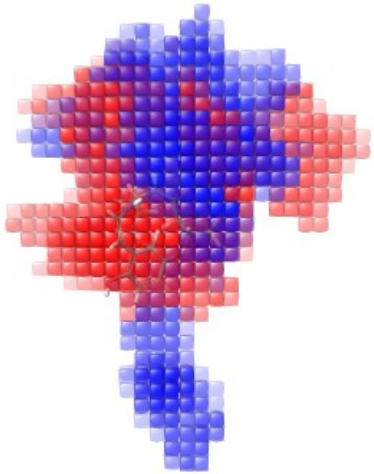
					

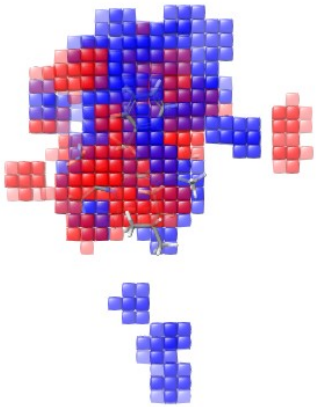
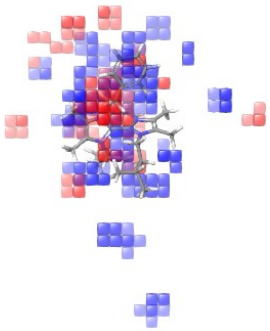
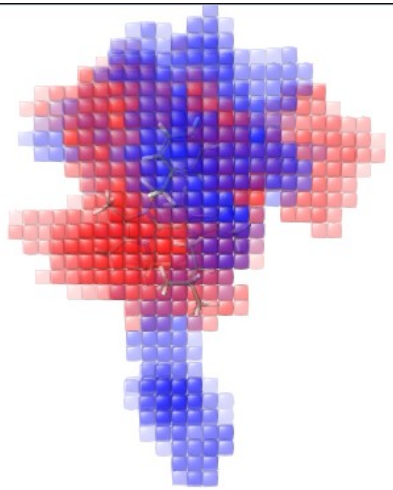
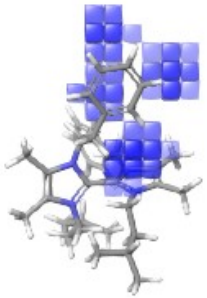
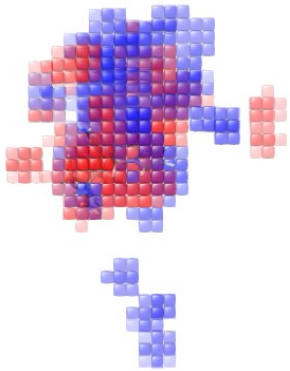
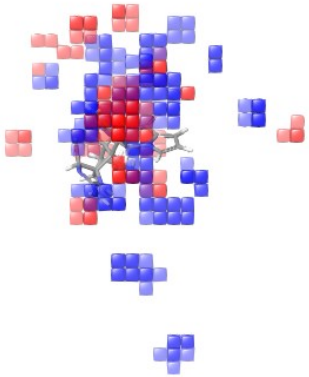
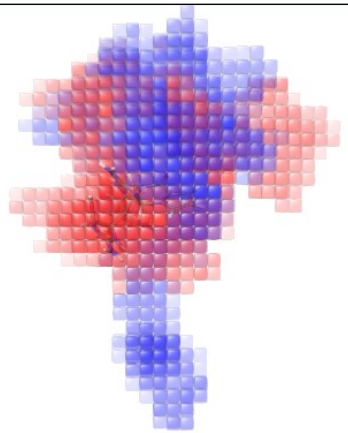
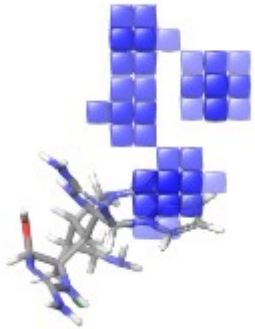
Table S-3: Atom-Based QSAR Contour Map Visualization

Compound	**Electron withdrawing**	**H-bond donor**	**Hydrophobic**	**Positive ionic**
(+)-N-methylisococlaurine				

Boldine				
Carpaine				

Diazepinomicin				
hymenocardine-H				

longamide B				
O-desmethylnummularine-R				

paenidigyamycin A				
Palauamine				

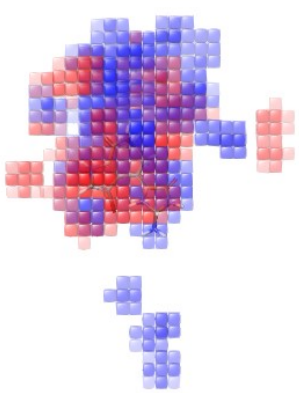
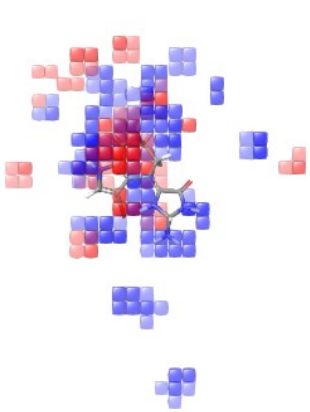
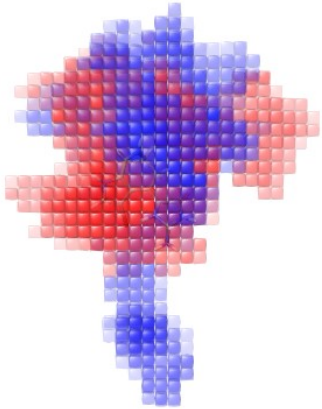
spongiacidin B				

Table S-4: Ramachandran Plot Statistics

Ramachandran Plot	**PDB ID**											
Plot statistics	**7AVT**	**6SFR**	**6YNE**	**6W8H**	**7JX2**	**7JWR**	**7JVY**	**7JZ5**	**7JWD**	**6W81**	**6VF1**	**6UX9**
Residues in most favored regions	778=93.8%	770=93.0%	1049=91.1%	335=93.1%	112=90.3%	232=92.4%	228=91.9%	229=92.3%	230=92.0%	479=92.1%	267=94.3%	519=92.0%
Residues in Additional Allowed regions	51= 6.2%	58=7.0%	95=8.2%	23=6.4%	11=8.9%	17=6.8%	18=7.3%	17=6.9%	18=7.2%	38=7.3%	16=5.7%	43=7.6%
Residues in generously allowed regions	0=0.0%	0=0.0%	4=0.3%	2=0.6%	1=0.8%	2=0.8%	2=0.8%	2=0.8%	2=0.8%	1=0.2%	0=0.0%	2=0.4%
Residues in disallowed regions	0=0.0%	0=0.0%	4=0.3%	0=0.0%	0=0.0%	0=0.0%	0=0.0%	0=0.0%	0=0.0%	2=0.4%	0=0.0%	0=0.0%

Number of non-glycine and non-proline residues	829=100.0%	828=100.0%	1152=100.0%	360=100.0%	124=100.0%	251=100.0%	248=100.0%	248=100.0%	250=100.0%	520=100.0%	283=100.0%	564=100.0%
Number of end-residues	7	7	4	3	2	4	3	3	4	4	22	13
Number of glycine residues	29	29	132	14	9	18	18	18	18	66	26	24
Number of proline residues	64	64	48	20	0	1	1	1	1	12	18	27
Total number of residues	929	928	1336	397	135	274	270	270	273	602	349	628

Table S-5: Docking score and interactions of compounds with their respective proteins

Protein	Compounds name	No. of interactions	Residues	Types of protein-ligand interaction by	Distance	Docking score	H-bond
6UX9	(+)-N-methylisococlaurine	1 1	ASP 359 PHE 134	H-bonding Pi-pi stacking	2.14 4.29	-7.727	1
	spongiacidin B	1 1	ASN 198 ASN 124	H-Bonding H-bonding	1.92 1.85	-6.736	2
	Diazepinomicin	1 1 1 1	LYS 228 ASP 211 LYS 234 GLU 225	Pi-cation H-bonding H-bonding H-bonding	4.46 1.71 2.35 1.72	-6.431	3
	Boldine	1	ASN 198	H-bonding	2.02	-5.972	1
	longamide B	1 1 1	VAL 199 PHE 200 LYS 209	Halogen bond Pi-pi stacking H-bonding	2.46 1.84	-5.279	1
	Palauamine	1 1 1	ASP 359 ALA 132 GLU 225	H-bonding H-bonding H-bonding	2.13 1.95 1.65	-4.455	3

	Oseltamivir	1 1 1	VAL-199 ASP-359 LYS—145	H-bonding H-bonding H-bonding	1.69 2.47 2.68	-7.119	3
6VF1	(+)-N-methylisococlaurine	1 2	GOA 506 MG 502 MG 502	H-bonding Metal-coordination Metal-coordination	1.58 2.10 2.38	-8.672	1
	Palauamine	1 1 1	ASP 418 MG 502 MG 501	H-bonding Metal coordination Metal coordination	2.46 2.06 2.22	-8.258	1
	longamide B	1 2 1	GOA 506 MG 502 MG 502 MG 501	H-bonding Metal coordination Metal coordination Metal coordination	2.00 1.99 2.36 2.25	-7.86	1
	Boldine	1 1	MG 502 MG 501	Metal coordination Metal coordination	2.24 2.07	-7.588	0
	spongiacidin B	1 1 1	GOA 506 MG 502 MG 501	H-bonding Metal coordination Metal coordination	2.50 2.06 2.27	-7.087	1
	Diazepinomicin	1 1	MG 501 TRP 434	Metal coordination Pi-pi stacking	2.28 3.96	-6.499	0
	Carpaine	1	MG 502	Metal coordination	2.13	-6.238	0
	hymenocardine-H	1 1	MG 501 MG 502	Metal coordination Metal coordination	2.42 2.04	-5.898	0
	Oseltamivir	1 1 1 1	GOA 506 GLY 433 MG 501 MG 502	H-bonding H-bonding Metal coordination Metal coordination	1.79 1.89 2.27 2.06	-7.833	2
6W81	hymenocardine-H	2 1	GLU 165 GLU 165 HIE 162	H-bonding H-bonding H-bonding	2.29 1.60 1.91	-7.635	3
	(+)-N-methylisococlaurine	1	GLN 191	H-bonding	1.90	-7.043	1
	Palauamine	1 2 1	PRO 188 GLN 191 GLN 191 GLU 165	H-bonding H-bonding H-bonding H-bonding	2.73 1.96 2.05 2.12	-6.988	4
	Boldine	1	GLU 165	H-bonding	1.81	-6.764	1

	spongiacidin B	1 1 1	HIE 162 ILE 140 GLY 142	H-bonding H-bonding H-bonding	1.99 1.93 2.14	-6.698	3
	Diazepinomicin	1 1	GLU 165 THR 189	H-bonding H-bonding	2.52 1.81	-6.332	2
	paenidigyamycin A	1	HIE 41	Pi-pi stacking	5.36	-5.766	0
	longamide B	1	GLU 165	Halogen bond	3.22	-5.543	0
	O-desmethylnummularine-R	1 1 1	GLU 165 ALA 143 GLY 142	H-bonding H-bonding H-bonding	2.71 2.68 2.36	-5.355	3
	Carpaine	1	GLY 142	H-bonding	2.33	-5.053	1
	Oseltamivir	1 1	GLN 187 GLY 167	H-bonding H-bonding	1.99 2.51	-5.131	2
7JWD	Diazepinomicin	1 1 1	GLU 72 ASP 78 TYR 19	H-bonding H-bonding Pi-pi stacking	1.69 2.43 5.03	-8.068	2
	Boldine	1 1	ASP 78 PHE 16	H-bonding Pi-pi stacking	2.13 5.01	-7.823	1
	(+)-N-methylisococlaurine	1	PHE 16	Pi-pi stacking	5.35	-7.512	0
	spongiacidin B	-	-	-	-	-7.262	0
	longamide B	1 1	THR 53 PHE 16	H-bonding Pi-pi stacking	2.04 5.15	-6.897	1
	Oseltamivir	-	-	-	-	-5.591	0
7JZ5	Boldine	1	TYR 19	H-bonding	1.98	-9	1
	Diazepinomicin	1 1 1 1	THR 51 ARG 104 TYR 60 TYR 19	H-bonding H-bonding Pi-pi stacking Pi-pi stacking	2.51 2.25 5.20 5.18	-8.623	2
	(+)-N-methylisococlaurine	1 1	LYS 40 PHE 16	H-bonding Pi-pi stacking	2.37 5.11	-7.467	1
	spongiacidin B	-	-	-	-	-7.252	0
	longamide B	1 1 1 1 1	GLN 38 GLN 108 GLN 97 LYS 40 GLU 72	Halogen bond H-bonding H-bonding H-bonding H-bonding	2.76 2.06 1.79 1.95 2.58	-6.936	4

	Oseltamivir	1 1	LYS 40 ARG 104	H-bonding H-bonding	2.02 2.39	-6.632	2
7JVY	Diazepinomicin	1	ASP 78	H-bonding	1.80	-8.351	1
	Boldine	1	PHE 16	Pi-pi stacking	5.45	-8.117	0
	(+)-N-methylisococlaurine	1	PHE 16	Pi-pi stacking	5.49	-7.982	0
	spongiacidin B	-	-	-	-	-7.081	0
	longamide B	1 1 1 1 1 1	GLN 97 GLU 72 GLN 108 LYS 40 LYS 40 GLN 38	H-bonding H-bonding H-bonding H-bonding Halogen bond Halogen bond	1.94 2.27 2.42 1.83 2.69 2.87	-7.08	4
	Oseltamivir	1	GLN 38	H-bonding	2.63	-6.355	1
7JWR	Diazepinomicin	-	-	-	-	-9.417	0
	Boldine	1	TYR 19	H-bonding	2.13	-9.152	1
	(+)-N-methylisococlaurine	1	TYR 19	H-bonding	2.15	-8.091	1
	spongiacidin B	1	TYR 19	H-bonding	2.10	-7.317	1
	longamide B	1 1	THR 53 PHE 16	H-bonding Pi-pi stacking	1.88 5.32	-6.932	1
	Oseltamivir	-	-	-	-	-6.329	0
7jx2	(+)-N-methylisococlaurine	1	TYR 19	H-bonding	2.68	-7.607	1
	Diazepinomicin	1 1	THR 53 PHE 16	H-bonding Pi-pi stacking	2.20 5.14	-7.384	1
	longamide B	1 1 1 1 1 1	GLN 108 LYS 40 GLU 72 GLN 97 LYS 40 GLN 38	H-bonding H-bonding H-bonding H-bonding Halogen bond Halogen bond	2.14 2.00 2.49 1.78 2.48 3.11	-7.217	4
	spongiacidin B	1 1	GLN 38 PHE 16	H-bonding Pi-pi stacking	2.26 5.08	-6.953	1
	Boldine	1	PHE 16	Pi-pi stacking	4.73	-6.824	0
	Oseltamivir	1 1	ARG 58 THR 53	H-bonding H-bonding	2.41 1.90	-6.674	2

6W8H	Diazepinomicin	3	GSH 201 GSH 201 GSH 201	H-bonding H-bonding H-bonding	1.88 1.90 1.67	-7.948	3
	Boldine	1	GSH 201	H-bonding	1.97	-7.192	1
	(+)-N-methylisococlaurine	2	TRP 104 TRP 104	Pi-pi stacking Pi-pi stacking	4.30 4.33	-6.339	0
	Palauamine 2	1 1	TRP 104 GLN 36	H-bonding Halogen bond	1.80 2.20	-5.485	1
	spongiacidin B	1	ARG 14	Halogen bond	2.72	-5.482	0
	paenidigyamycin A	2 1 2	TRP 104 TRP 104 PHE 16 LYS 112 LYS 112	Pi-pi stacking Pi-pi stacking Pi-pi stacking Pi-cation Pi-cation	3.73 3.93 5.17 3.44 6.45	-4.785	0
	longamide B	-	-	-	-	-4.341	0
	Oseltamivir	1	GLN 36	H-bonding	2.02	-4.229	1
6YNE	Diazepinomicin	1 1	ASN 136 PHE 131	H-bonding Pi-pi stacking	2.15 5.03	-5.664	1
	Palauamine	1 1	LYS 219 MET 130	H-bonding H-bonding	2.15 2.03	-4.958	2
	(+)-N-methylisococlaurine	1	SER 125	H-bonding	2.20	-4.921	1
	spongiacidin B	1 1	ASN 136 LYS 139	H-bonding H-bonding	2.08 2.66	-4.913	2
	Boldine	1 1 1	ASN 136 LYS 219 ASP 127	H-bonding H-bonding H-bonding	2.32 2.19 1.79	-4.781	3
	longamide B	1 1 1	LYS 219 LYS 139 LYS 139	H-bonding H-bonding H-bonding	1.60 2.61 2.58	-4.521	3
	Oseltamivir	1	ASN 136	H-bonding	2.30	-3.941	1
6SFR	(+)-N-methylisococlaurine	1	GLU 909	H-bonding	1.66	-6.181	1
	spongiacidin B	1 1	TYR 884 ASN 879	Pi-pi stacking H-bonding	4.93 1.94	-5.906	1
	Boldine	1 1 1	ASN 879 TYR 884 IMD 1102	H-bonding Pi-pi stacking Pi-pi stacking	1.79 5.36 5.08	-5.767	1

	longamide B	1 1	LEU 901 IMD 1102	H-bonding Pi-pi stacking	1.70 5.30	-5.616	1
	O-desmethylnummularine-R	1 1 1 1	TYR 884 TYR 884 ASN 879 GLU 902	Pi-pi stacking H-bonding H-bonding H-bonding	5.47 2.39 1.94 2.22	-5.179	3
	Palauamine	1 1 1 1	GLU 906 GLU 902 HIE 905 TYR 884	H-bonding H-bonding Pi-pi stacking Pi-pi stacking	2.28 2.70 5.28 5.46	-4.942	2
	Diazepinomicin	1 1	ASN 879 HIE 905	H-bonding Pi-pi stacking	1.67 3.92	-4.747	1
	paenidigyamycin A	1 1 1 1 1	GLU 909 GLU 906 HIE 905 IMD 1102 IMD 1102	Salt-bridge Salt-bridge Pi-pi stacking Pi-pi stacking Pi-pi stacking	4.86 3.99 4.08 4.83 4.99	-4.66	0
	Oseltamivir	1	TYR 884	H-bonding	2.11	-4.764	1
7AVT	hymenocardine-H	1 1	ASP 887 TYR 884	H-bonding H-bonding	1.51 2.04	-5.866	2
	Boldine	1 1	ASN 879 TYR 884	H-bonding Pi-pi stacking	1.79 5.25	-5.364	2
	(+)-N-methylisococlaurine	1	GLU 906	H-bonding	1.79	-5.244	
	Diazepinomicin	1 2	GLU 909 GLU 906 GLU 906	H-bonding H-bonding H-bonding	2.25 1.61 1.69	-5.102	3
	Spongiacidin B	1	TYR 884	Pi-pi stacking	5.13	-5.095	1
	Longamide B	1 1	TYR 884 LEU 901	Pi-pi stacking H-bonding	5.46 1.60	-4.915	1
	O-desmethylnummularine-R	1 1 1	TYR 884 ASN 879 TYR 884	Pi-pi stacking H-bonding H-bonding	5.50 1.89 2.57	-4.793	2
	Palauamine	1 1 1	IMD 1102 GLU 909 GLU 902	Pi-pi stacking H-bonding H-bonding	5.05 1.80 2.23	-4.593	2
	Oseltamivir	1	GLU 902	H-bonding	2.09	-3.773	1

Table S-6: Binding free energies of all docked complexes

Proteins	Compounds	MM-GBSA dG Bind	MM-GBSA dG Bind Coulomb	MMGBSA dG Bind vdW	MMGBSA dG Bind Lipo
6UX9	(+)-N-methylisococlaurine	-69.99	-20.77	-41.78	-29.15
	oseltamivir	-66.66	-12.51	-49.61	-20.82
	spongiacidin B	-49.15	-23.68	-36.2	-11.08
	diazepinomicin	-76.73	-22.14	-58.29	-29.3
	Boldine	-66.4	-19.52	-40.59	-28.21
	longamide B	-52.04	-14.7	-35.81	-10.49
	palauamine	-50.67	-28.05	-40.04	-14.9
	Carpaine	-35.97	-2.29	-47.29	-15.29
7JX2	(+)-N-methylisococlaurine	-70.2	-0.14	-43.66	-32.72
	diazepinomicin	-80.96	-6.92	-63.82	-41.21
	Longamide B	-42.81	-20.46	-32.42	-9.18
	Spongiacidin B	-36.37	-1.07	-32.32	-11.38
	Boldine	-71.42	4.45	-56.34	-36.8
	oseltamivir	-54.32	0.58	-50.06	-20.26
6SFR	(+)-N-methylisococlaurine	-34.89	-4.1	-25.72	-16
	Spongiacidin B	-26.51	-0.55	-32.61	-9.39
	Boldine	-37.41	6.95	-36.56	-21.15
	Longamide B	-36.03	-7.81	-31.27	-6.57
	O-desmethylnummularine-R	-35.37	-7.83	-47	-17.02
	palauamine	-8.73	-11.96	-35.03	-11.01
	oseltamivir	-35.22	-9.58	-30.66	-11.13
	diazepinomicin	-26.83	4.13	-37.67	-16.7
	paenidigyamycin A	-60.21	-4.13	-45.9	-22.64
	hymenocardine-H	-26.48	-35.14	-34.46	-8.71
	Carpaine	-24.89	-14.29	-35.61	-12.94
6W81	hymenocardine-H	-72.59	-49.52	-55.22	-18.27
	(+)-N-methylisococlaurine	-51.04	-23.72	-30.75	-14.91

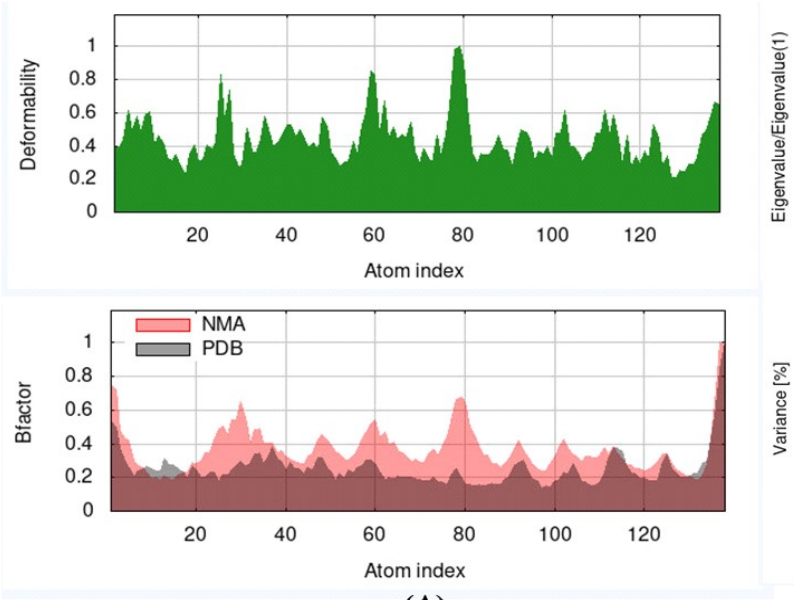
	palauamine	-57.48	-34	-24.74	-9.24
	Boldine	-51.9	-17.83	-39.46	-14.46
	spongiacidin B	-45.22	-39.16	-46.28	-5.07
	Diazepinomicin	-44.6	-9.68	-45.96	-11.23
	paenidigyamycin A	-66.97	-67.5	-56.87	-20.51
	longamide B	-30.37	-28	-19.14	-3.13
	O-desmethylnummularine-R	-57.79	-14.7	-57.81	-20.47
	oseltamivir	-45.46	-28.73	-22.36	-7.07
	Carpaine	-53.52	-15.97	-57.61	-13.45
7AVT	hymenocardine-H	-34.93	-11.49	-45.02	-15.48
	Boldine	-44.27	-18.45	-35.48	-19.24
	(+)-N-methylisococlaurine	-37.42	-20.09	-28.63	-15.67
	diazepinomicin	-35.34	-9.9	-35.07	-13.26
	Spongiacidin B	-30.89	-2.5	-34.18	-9.37
	Longamide B	-35.38	-15.9	-33.84	-6.08
	O-desmethylnummularine-R	-46.9	-17.78	-44.33	-16.49
	palauamine	-24.5	-15.04	-33.79	-9.94
	paenidigyamycin A	-63.86	-1.99	-44.68	-24.34
	oseltamivir	-37.82	-15.55	-34.24	-12.43
6W8H	Diazepinomicin	-69.55	-21.57	-50.64	-19.84
	Boldine	-67.73	-19.07	-37.23	-26.06
	(+)-N-methylisococlaurine	-62	-19.18	-35.87	-23.65
	palauamine	-56.84	-29.8	-40.38	-13.48
	spongiacidin B	-43.16	-32.55	-43.44	-12.61
	paenidigyamycin A	-64.33	42.83	-51.82	-31.39
	longamide B	-39.52	-0.95	-33.67	-8.1
	oseltamivir	-39.85	-13.44	-35.58	-16.51
	O-desmethylnummularine-R	-57.96	-3.62	-54.34	-22.26
	hymenocardine-H	-55.53	-8.24	-53.3	-20.84
	Carpaine	-48.85	9.19	-45.77	-17.43
6YNE	diazepinomicin	-71.21	-34.78	-21.03	-37.66

	palauamine	-43.83	-21.13	-7.96	-33.61
	(+)-N-methylisococlaurine	-42.87	-27.05	-14.99	-27.25
	spongiacidin B	-31.4	-17.19	-6.3	-25.02
	Boldine	-46.89	-17.36	-13.93	-27.83
	longamide B	-33.73	-19.62	-4.21	-22.53
	oseltamivir	-40.27	-18.83	-9.35	-31.26
	hymenocardine-H	-49.46	-25.18	-12.46	-44.83
	paenidigyamycin A	-46.35	63.19	-17.05	-38.19
	Carpaine	-35.69	-6.93	-8.71	-31.9
	O-desmethylnummularine-R	-23.78	7.61	-8.59	-34.51
7JVY	Diazepinomicin	-70.98	-3.51	-52.13	-38.75
	Boldine	-47.49	14.22	-36.44	-25.09
	(+)-N-methylisococlaurine	-41.19	14.45	-32.16	-24.12
	spongiacidin B	-25.99	-0.97	-25.93	-2.2
	longamide B	-25.68	-15.88	-10.3	0.82
	oseltamivir	-38.17	-3.27	-27.9	-10.43
7JWD	Diazepinomicin	-68.22	3.69	-56.3	-35.85
	Boldine	-64.23	-12.84	-47.01	-32.3
	(+)-N-methylisococlaurine	-58.51	2.69	-50.06	-31.52
	spongiacidin B	-43.11	-4.68	-41.35	-10.45
	longamide B	-50.73	4.63	-47.27	-10.2
	oseltamivir	-60.98	-8.77	-49.02	-18.57
6VF1	(+)-N-methylisococlaurine	1641.94	-4.31	462.43	-22.64
	boldine	125.75	5.16	9.08	-21.17
	carpaine	1389.57	77.14	426.37	-3.16
	diazepinomicin	91.49	20.42	1.64	-17.97
	hymenocardine-H	439.83	28.98	127.17	-18.54
	longamide B	78.69	10.16	-7.91	-6.62
	O-desmethylnummularine-R	85.46	-0.6	14.64	-28.38
	oseltamivir	46.24	46.05	-8.71	-12.79
	paenidigyamycin A	3293.07	216.57	1011.98	-24.2

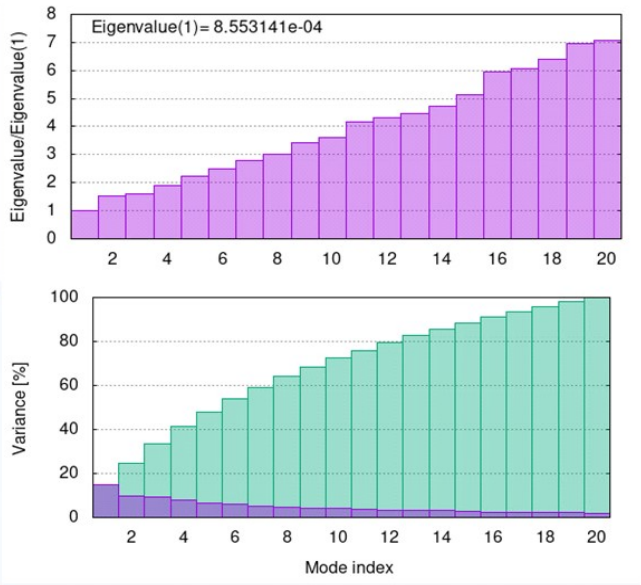
	palauamine	2155.23	12.36	593.8	-10.78
	spongiacidin B	20.97	-9.98	3.07	-5.18
7JWR	Diazepinomicin	-67.53	0.2	-54.92	-31.57
	Boldine	-74.74	-6.01	-45.14	-33.36
	(+)-N-methylisococlaurine	-69.66	-11.13	-40.87	-33.02
	spongiacidin B	-44.14	-22.01	-35.27	-12.63
	longamide B	-52.3	-14.33	-43.73	-11.14
	oseltamivir	-58.5	-3.43	-49.87	-21.18

Table S-7: ADMET Pharmacokinetic Properties of the top three compounds

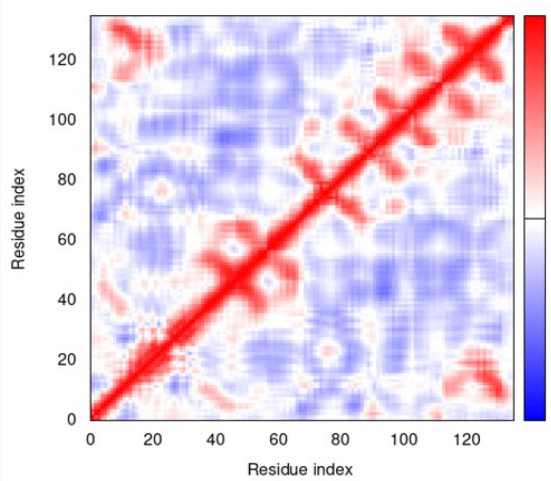
Variant	CNS	mol MW	Donor HB	Accpt HB	logP	logS	QPPCaco	QPlogBB	QPPMDCK	logKp	QPlogKhsa	Percent Human Oral Absorption	Rule Of Five
(+)-N-methylisococlaurine	1	299.369	2	4.25	32.19	-2.912	244.511	-0.312	119.413	-4.353	0.238	84.536	0
Diazepinomicin	-2	462.588	4	5.75	50.627	-7.244	209.925	-2.13	91.534	-2.957	0.943	100	0
hymenocardine-H	-2	653.82	2.75	14	65.658	-3.908	96.477	-1.057	71.97	-4.162	-0.703	46.753	2


Deformability
Atom index
Bfactor
NMA
PDB
Atom index

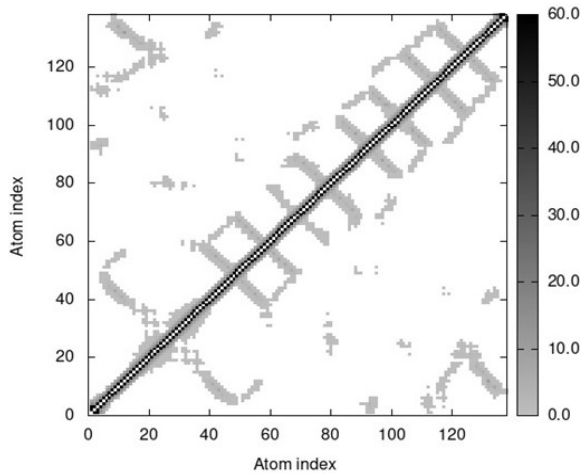
(A)


Eigenvalue(1)= 8.553141e-04
Eigenvalue/Eigenvalue(1)
Variance [%]
Mode index

(B)


Residue index
Residue index

(C)


Atom index
Atom index

(D)

Figure S1: results of MD stimulation (A) Deformability and B-factor, (B) Eigenvalue and variance, (C) residue index, (D) atom index of 7JWR-diazepinomicin

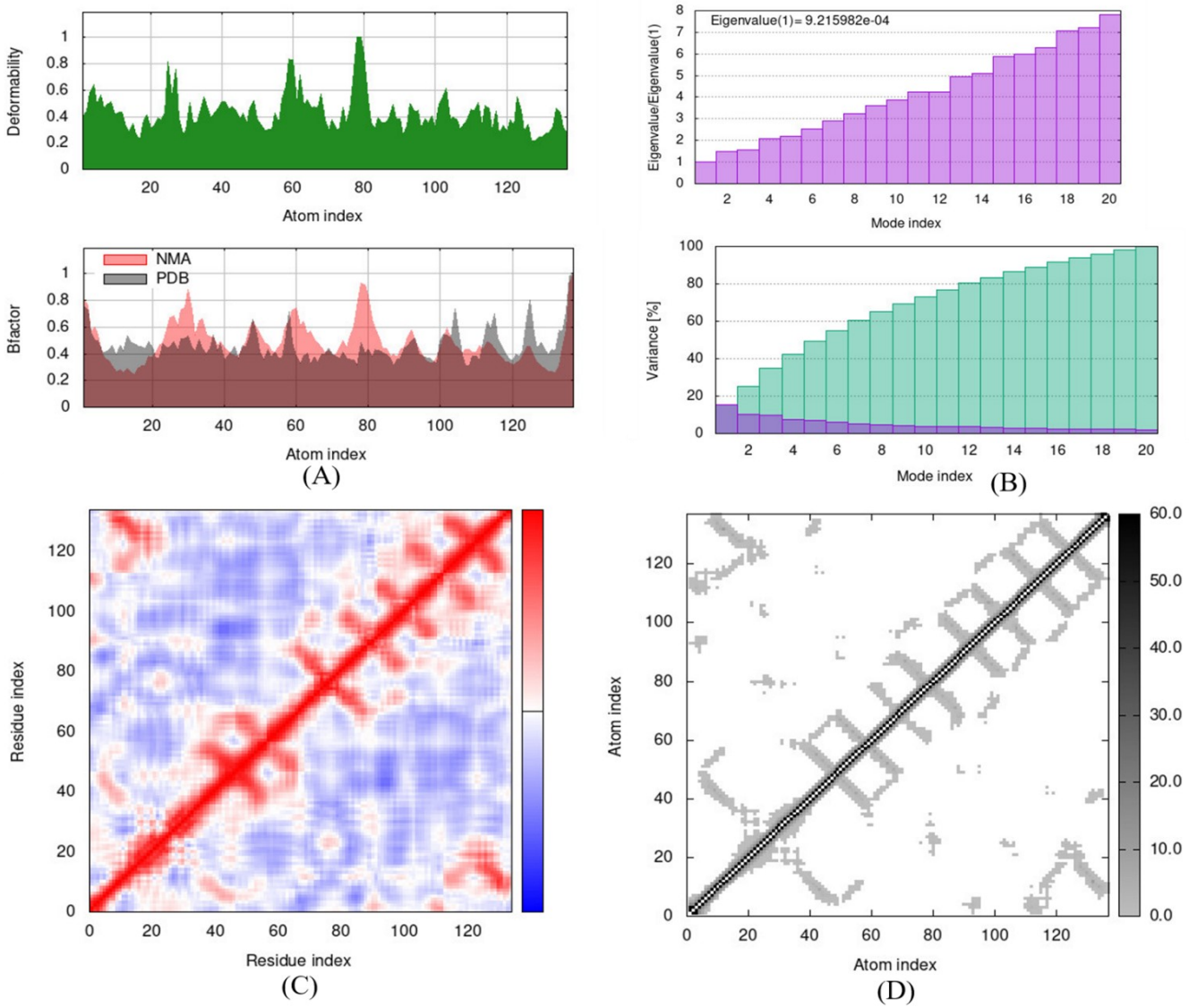
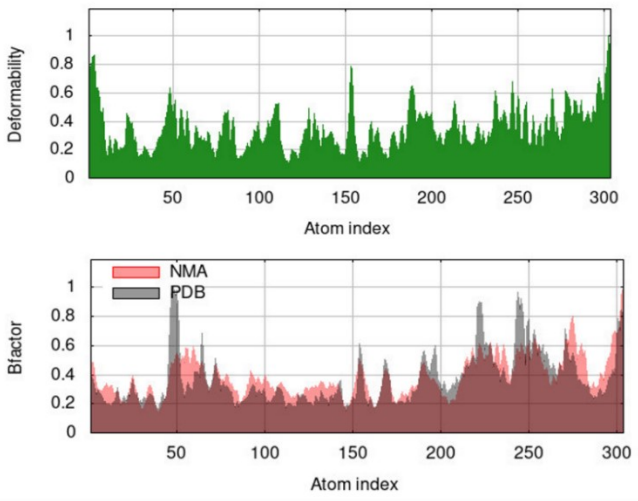
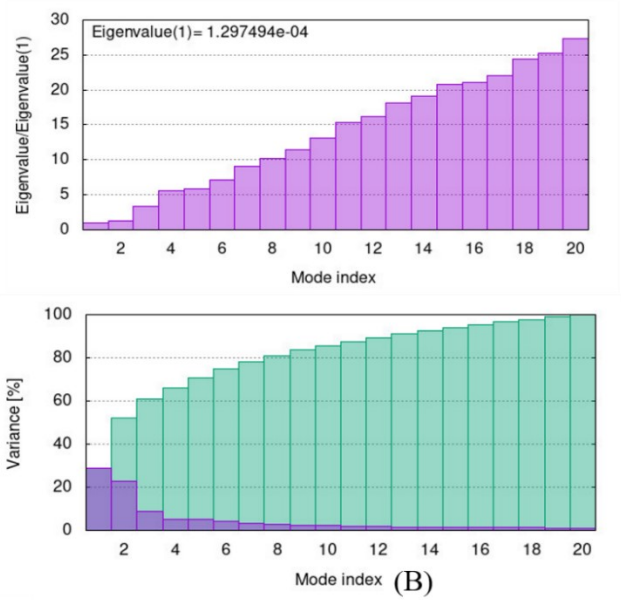

Deformability
Atom index
Bfactor
NMA
PDB
Atom index
(A)
Eigenvalue(1)= 9.215982e-04
Eigenvalue/Eigenvalue(1)
Mode index
Variance [%]
Mode index
(B)
Residue index
Residue index
(C)
Atom index
Atom index
(D)

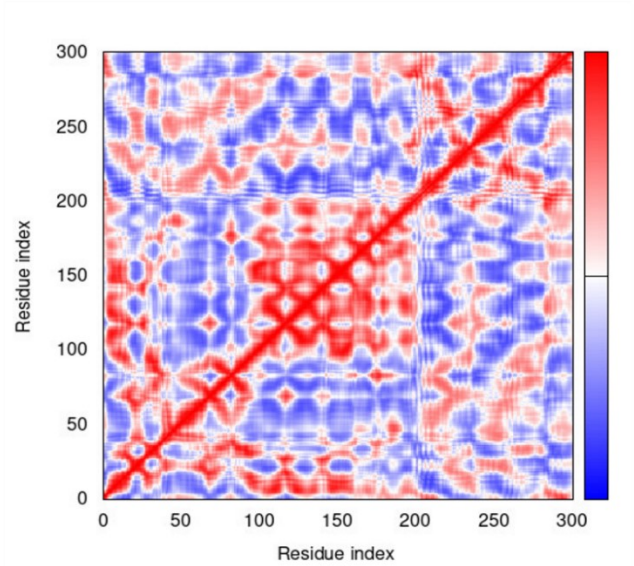
Figure S2: results of MD stimulation (A) Deformability and B-factor, (B) Eigenvalue and variance, (C) residue index, (D) atom index of 7JX2-(+)-N-methylisococlaurine


Deformability
Atom index
Bfactor
NMA
PDB
Atom index

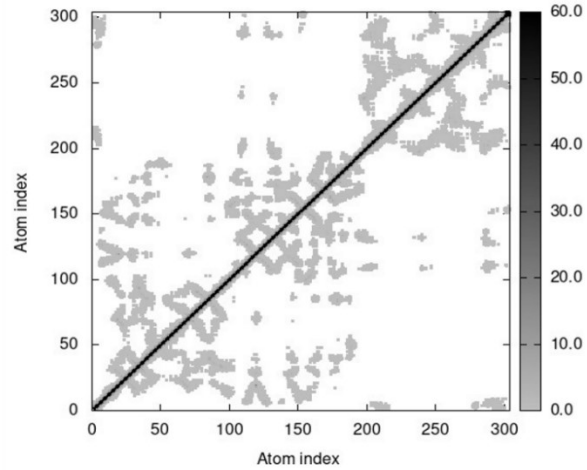
(A)


Eigenvalue(1)= 1.297494e-04
Eigenvalue/Eigenvalue(1)
Mode index
Variance [%]
Mode index

(B)


Residue index
Residue index

(C)


Atom index
Atom index

(D)

Figure S3**:** results of MD stimulation (A) Deformability and B-factor, (B) Eigenvalue and variance, (C) residue index, (D) atom index of 6W81- hymenocardine-H