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Identification of potential bioactive compounds from *Azadirachta indica* (Neem) as inhibitors of SARS-CoV-2 main protease: Molecular docking and molecular dynamics simulation studies

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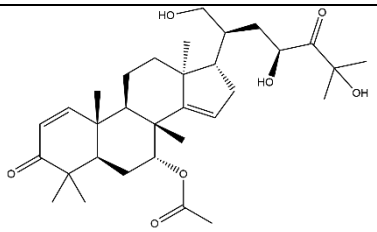
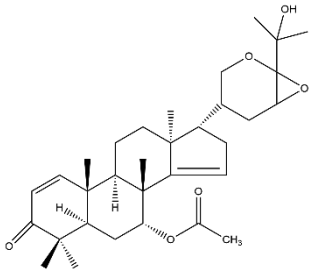
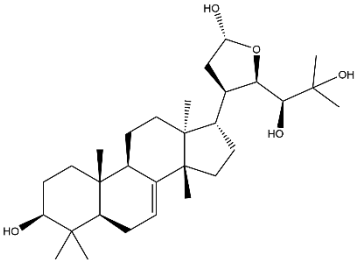
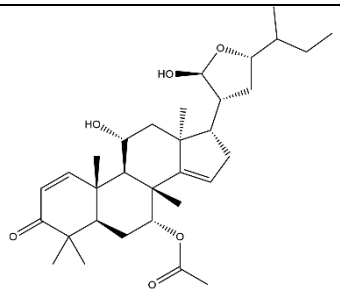
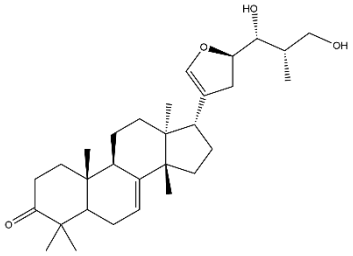
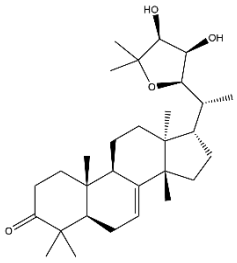
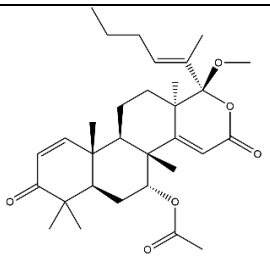
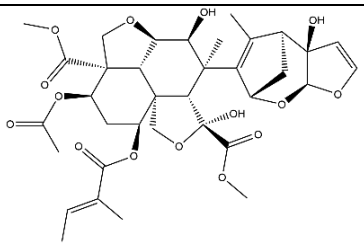
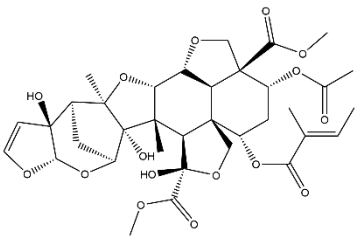
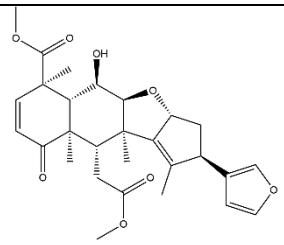
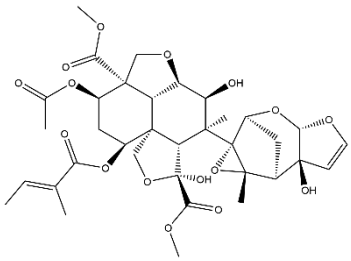
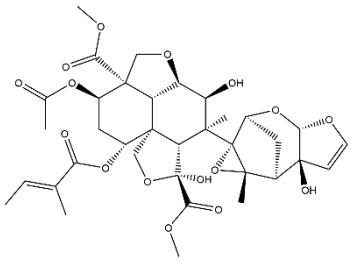
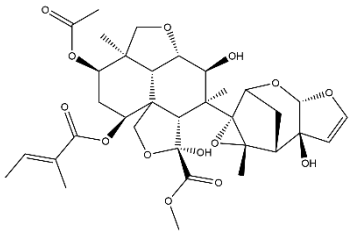
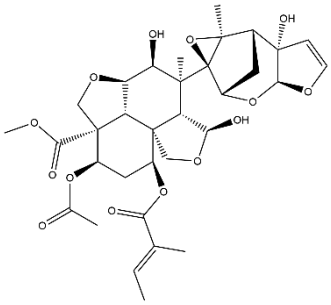
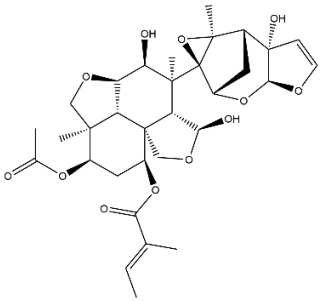
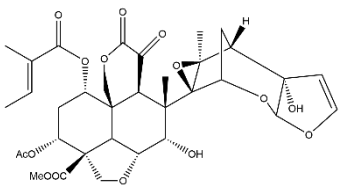
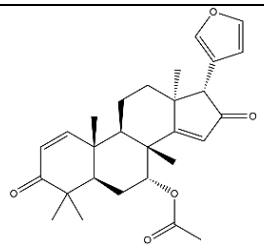
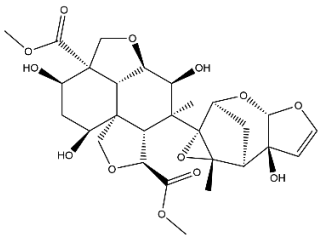
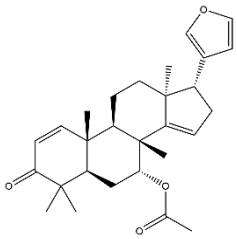
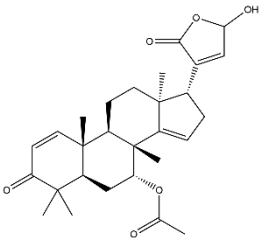
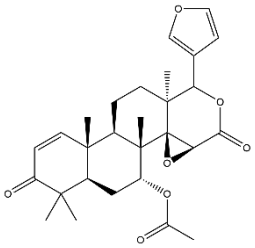
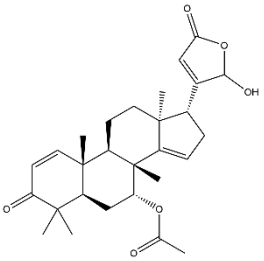
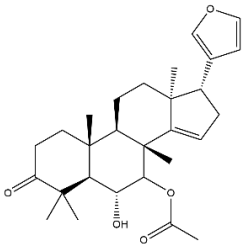
Supplementary Material

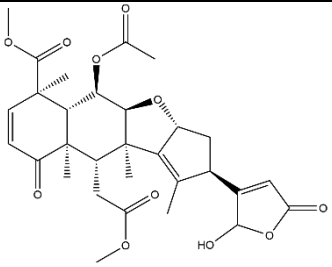
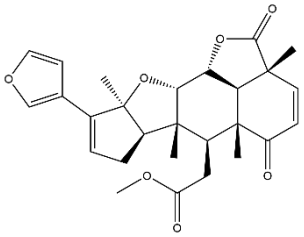
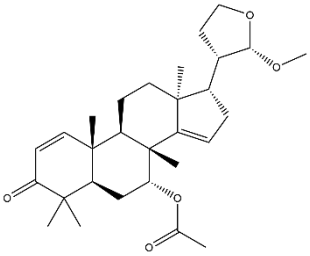
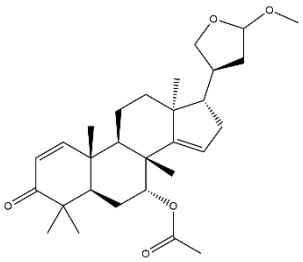
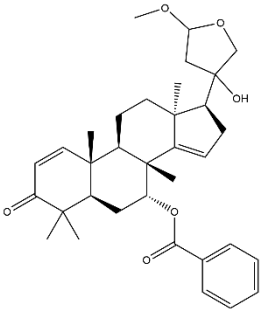
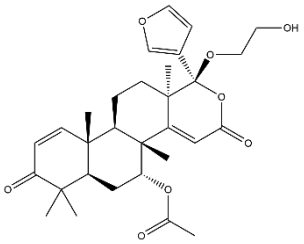
Table S1. Secondary metabolites in *Azadirachta indica* obtained from literature

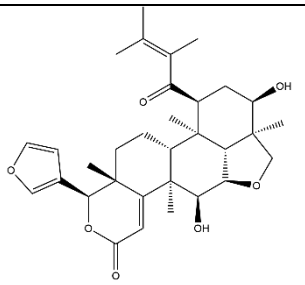
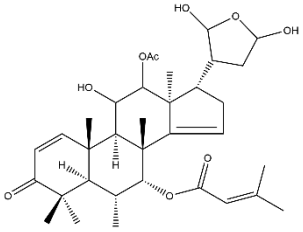
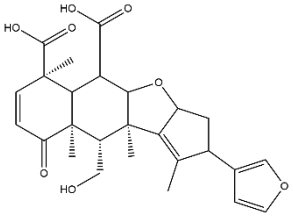
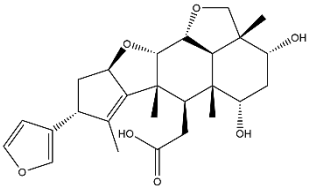
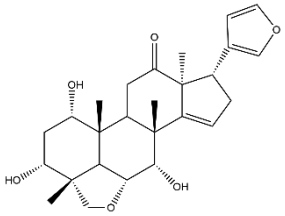
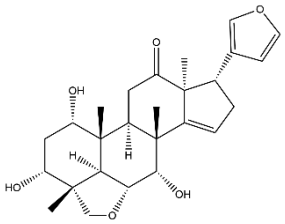
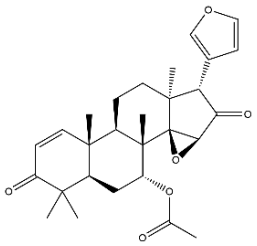
No	Secondary Metabolites	2D Structure	Reference
Protolimonoids			
1	Azadirol		(Siddiqui et al., 2003)
2	Diepoxyazadirol		(Kumar et al., 2014)
3	Meliantriol		(Akhila and Rani, 1999)

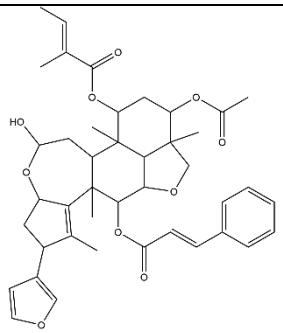
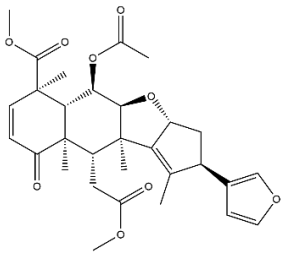
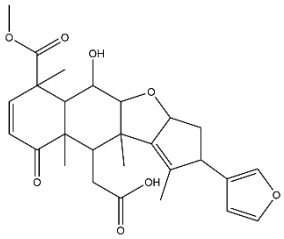
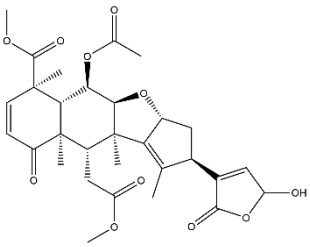
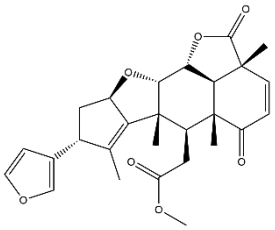
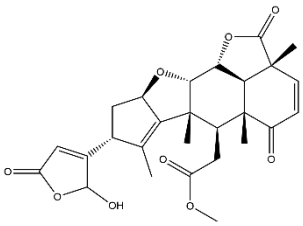
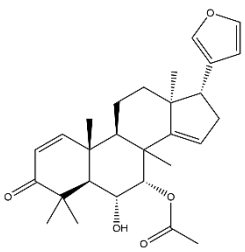
No	Secondary Metabolites	2D Structure	Reference
4	Naheedin		(Atawodi and Atawodi, 2009)
5	Nimbocinone		(Akhila and Rani, 1999)
6	Odoratone		(Luo et al., 2000)
Dinortriterpenoid			
7	Meliacinin		(Singh and Sharma, 2020)
Tetranortriterpenoids			
8	13,14-desepoxyazadirachtin-A		(Govindachari and Geetha, 1997)
9	3-acetyl-1-tigloylazadirachtinin		(Singh and Sharma, 2020)

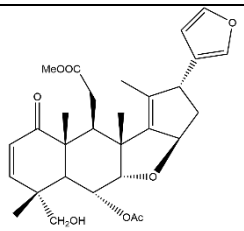
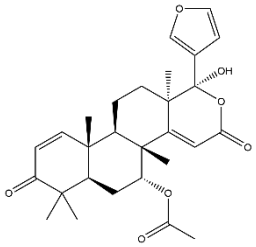
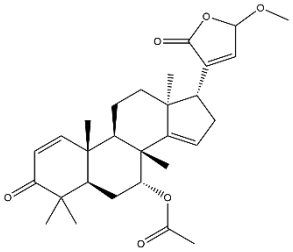
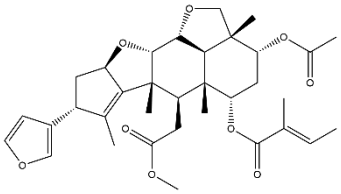
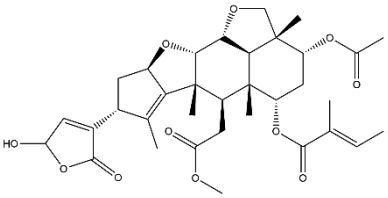
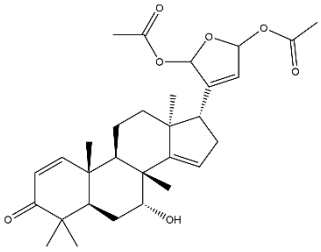
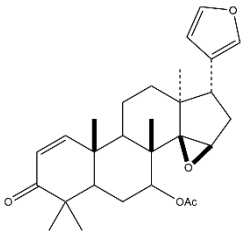
No	Secondary Metabolites	2D Structure	Reference
10	6-deacetylnimbin		(Atawodi and Atawodi, 2009)
11	Azadirachtin A		(Govindachari et al., 1996)
12	Azadirachtin B		(Govindachari et al., 1996)
13	Azadirachtin D		(Govindachari et al., 1996)
14	Azadirachtin H		(Govindachari et al., 1996)
15	Azadirachtin I		(Govindachari et al., 1996)
16	Azadirachtin K		(Akhila and Rani, 1999)

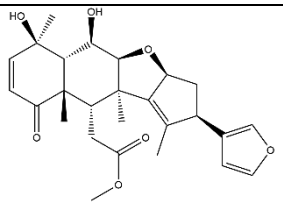
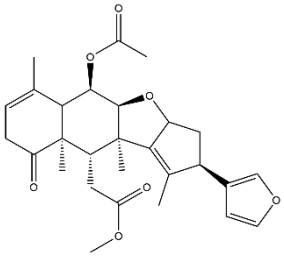
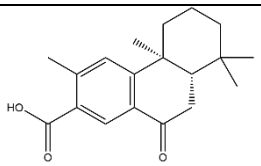
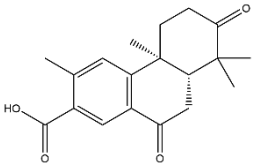
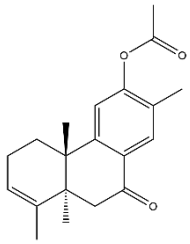
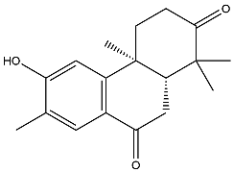
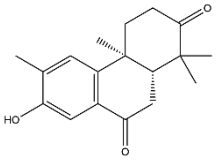
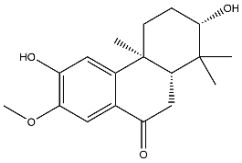
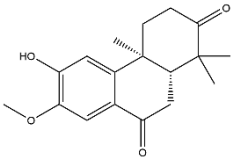
No	Secondary Metabolites	2D Structure	Reference
17	Azadiradione		(Govindachari et al., 2000)
18	Azadirachtol		(Atawodi and Atawodi, 2009)
19	Azadirone		(Atawodi and Atawodi, 2009)
20	Azadironolide		(Atawodi and Atawodi, 2009)
21	Gedunin		(Herrera-Calderon et al., 2019)
22	Isoazadironolide		(Atawodi and Atawodi, 2009)
23	Isomeldenin		(Atawodi and Atawodi, 2009)

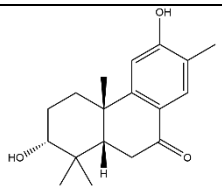
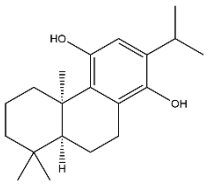
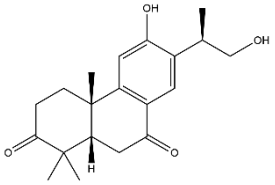
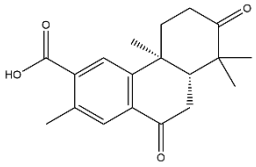
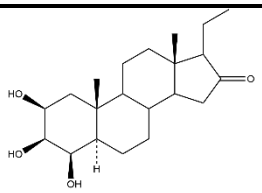
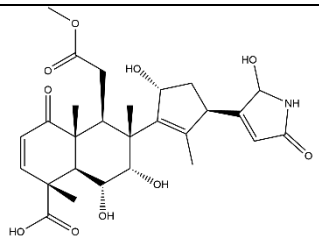
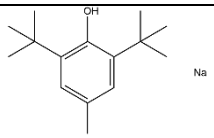
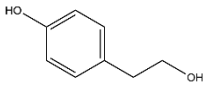
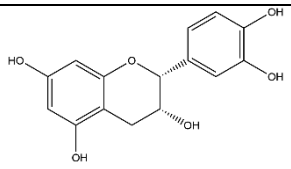
No	Secondary Metabolites	2D Structure	Reference
24	Isonimbinolide		(Akhila and Rani, 1999)
25	Isonimbolide		(Akhila and Rani, 1999)
26	Limocin A		(Akhila and Rani, 1999)
27	Limocin B		(Akhila and Rani, 1999)
28	Limocinin		(Akhila and Rani, 1999)
29	Mahmoodin		(Siddiqui et al., 1992)

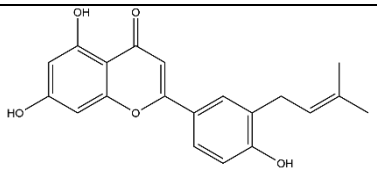
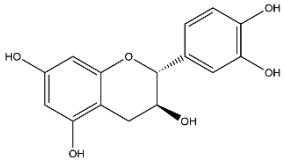
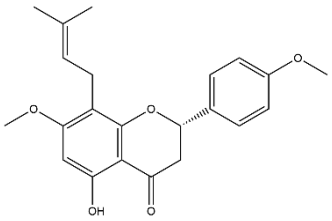
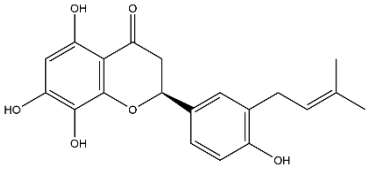
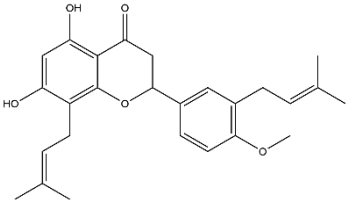
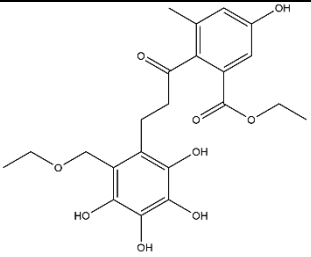
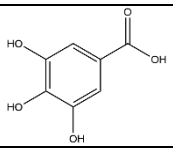
No	Secondary Metabolites	2D Structure	Reference
30	Meliacinol		(Atawodi and Atawodi, 2009)
31	Meliatetraolenone		(Singh, 2009)
32	Nimbic Acid		(Akhila and Rani, 1999)
33	Nimbidic Acid		(Singh and Sharma, 2020)
34	Nimbidin		(Singh and Sharma, 2020)
35	Nimbidinin		(Singh, 2009)
36	Nimbinin		(Singh and Sharma, 2020)

No	Secondary Metabolites	2D Structure	Reference
37	Nimbilin		(Singh and Sharma, 2020)
38	Nimbin		(Atawodi and Atawodi, 2009)
39	Nimbinic Acid		(Singh and Sharma, 2020)
40	Nimbinolide		(Singh and Sharma, 2020)
41	Nimbolide		(Atawodi and Atawodi, 2009)
42	Nimbolide B		(Singh and Sharma, 2020)
43	Nimocinol		(Atawodi and Atawodi, 2009)

No	Secondary Metabolites	2D Structure	Reference
44	Nimbinol		(Akhila and Rani, 1999)
45	Nimolicinol		(Atawodi and Atawodi, 2009)
46	O-methylazadironolide		(Siddiqui et al., 2003)
47	Salannin		(Girish and Shankara, 2008)
48	Salannolide		(Akhila and Rani, 1999)
49	Salimuzzalin		(Singh and Sharma, 2020)
50	Trichilenone Acetate		(Chan et al., 1973)
Pentanortriterpenoids			

No	Secondary Metabolites	2D Structure	Reference
51	Nimbandiol		(Singh and Sharma, 2020)
52	Nimbinene		(Atawodi and Atawodi, 2009)
Diterpenoids			
53	Margolone		(Atawodi and Atawodi, 2009)
54	Margolonone		(Atawodi and Atawodi, 2009)
55	Nimbilicin		(Singh and Sharma, 2020)
56	Nimbinone		(Akhila and Rani, 1999)
57	Nimbione		(Akhila and Rani, 1999)
58	Nimbionol		(Akhila and Rani, 1999)
59	Nimbionone		(Akhila and Rani, 1999)

No	Secondary Metabolites	2D Structure	Reference
60	Nimbisonol		(Singh and Sharma, 2020)
61	Nimbocidin1		(Singh and Sharma, 2020)
62	Nimbocidin2		(Singh and Sharma, 2020)
63	Isomargolonone		(Atawodi and Atawodi, 2009)
Steroid			
64	2β,3β,4β-trihydroxypregnan-16-one		(Luo et al., 2000)
Alkaloid			
65	Nimbic Acid B		(Singh and Sharma, 2020)
Phenolic Constituents			
66	2,6-Bis-(1,1)-dimethylethyl-4-methyl phenol		(Atawodi and Atawodi, 2009)
67	4-(2-hydroxyethyl)phenol		(Siddiqui et al., 2003)
Flavonoids			
68	(-) Epicatechin		(Atawodi and Atawodi, 2009)

No	Secondary Metabolites	2D Structure	Reference
69	3’-prenylnaringenin		(Siddiqui et al., 2003)
70	Catechin		(Atawodi and Atawodi, 2009)
71	Flowerine		(Siddiqui et al., 2003)
72	Flowerone		(Siddiqui et al., 2003)
73	Nimbaflavone		(Siddiqui et al., 2003)
Chalcone			
74	Nimbochalcin		(Singh and Sharma, 2020)
Phenolic Acid			
75	Gallic Acid		(Atawodi and Atawodi, 2009)
Aromatic Ester			

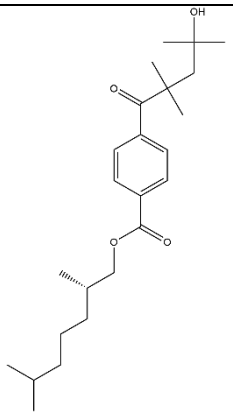
No	Secondary Metabolites	2D Structure	Reference
76	Nimbocetin		(Singh and Sharma, 2020)

Table S2. Estimated free energy of binding ranking from molecular docking results of secondary metabolites in *Azadirachta indica*, reference ligand (FJC), and nirmatrelvir

No.	Ligand	Estimated Free Energy of Binding kcal/mol
1	Odoratone	-11.57
2	Salimuzzalin	-9.83
3	Nimbocidin2	-9.60
4	Nimbocinone	-9.37
5	Limocinin	-9.32
6	Meliacinol	-9.20
7	Nimbisonol	-9.04
8	Naheedin	-8.85
9	Nimbolide B	-8.85
10	Nimbilin	-8.83
11	Azadironolide	-8.79
12	Azadirone	-8.76
13	Nimbolide	-8.67
14	Isonimbinolide	-8.60
15	Nimbocidin1	-8.60
16	Azadiradione	-8.58
17	O-methylazadironolide	-8.50
18	Nimbinin	-8.42
19	Nirmatrelvir	-8.42
20	3’prenylnaringenin	-8.41
21	Limocin B	-8.40
22	Nimocinol	-8.39
23	6-deacetylnimbin	-8.33
24	Trichilenone	-8.33
25	Nimbaflavone	-8.29

No.	Ligand	Estimated Free Energy of Binding kcal/mol
26	Limocin A	-8.26
27	Nimbione	-8.20
28	Gedunin	-8.18
29	Isomeldenin	-8.18
30	Mahmoodin	-8.18
31	Nimbinone	-8.12
32	Azadirol	-8.10
33	Meliacinin	-8.06
34	Meliatetraolenone	-8.05
35	Isonimbolide	-8.04
36	Isoazadironolide	-7.95
37	Nimolicinol	-7.95
38	FJC	-7.93
39	Nimbidinin	-7.92
40	Meliantriol	-7.89
41	Nimbilicin	-7.88
42	Nimbionone	-7.86
43	Diepoxyazadirol	-7.82
44	Isomargolonone	-7.81
45	Margolonone	-7.81
46	Nimbidin	-7.75
47	Flowerone	-7.65
48	Nimbionol	-7.58
49	Margolone	-7.57
50	Flowerine	-7.51
51	Azadirachtin K	-7.50
52	Nimbin	-7.42
53	2β,3β,4β-trihydroxypregnan-16-one	-7.40
54	Azadirachtin I	-7.34
55	Azadirachtol	-7.33
56	Azadirachtin D	-7.31
57	Nimbinene	-7.19
58	Nimbidic Acid	-7.11
59	Azadirachtin H	-7.01
60	(-) Epicatechin	-6.92
61	Nimbinol	-6.89
62	Nimbochalcin	-6.87
63	Nimbandiol	-6.86

No.	Ligand	Estimated Free Energy of Binding kcal/mol
64	Salannolide	-6.84
65	Salannin	-6.82
66	Nimbic Acid B	-6.69
67	Azadirachtin A	-6.67
68	13,14-desepoxyazadirachtin-A	-6.53
69	Nimbinolide	-6.49
70	Catetchin	-6.36
71	2,6-Bis-(1,1)-dimethylethyl-4-methyl phenol	-6.06
72	Nimbocetin	-5.92
73	Nimbic Acid	-5.84
74	3-acetyl-1-tigloylazadirachtinin	-5.61
75	Nimbinic Acid	-5.54
76	Azadirachtin B	-5.37
77	Gallic Acid	-4.99
78	4-(2-hydroxyethyl)phenol	-4.97

Table S3. Lipinski's rule-of-five results for secondary metabolites in *Azadirachta indica*

No.	Secondary Metabolites	Lipinski's Rule of Five				
		Molecular Weight (g/mol)	Log P	H-bond Donor(s)	H-bond Acceptor(s)	Violation(s)
Protolimonoids						
1	Azadirol	544.73	3.29	3	6	1
2	Diepoxyazadirol	526.71	4.79	1	5	1
3	Meliantriol	490.73	4.74	4	5	0
4	Naheedin	528.73	4.77	2	5	1
5	Nimbocinone	470.69	5.43	2	4	1
6	Odoratone	472.71	5.72	2	4	1
Dinortriterpenoids						
7	Meliacinin	512.69	6.17	0	4	2
Tetranortriterpenoids						
8	13,14-desepoxyazadirachtin-A	704.72	0.23	3	11	2
9	3-acetyl-1-tigloylazadirachtinin	720.72	-0.52	3	12	2
10	6-deacetylnimbin	498.57	1.66	1	6	0
11	Azadirachtin A	720.72	-0.52	3	12	2
12	Azadirachtin B	720.72	-0.52	3	12	2
13	Azadirachtin D	676.71	0.15	3	11	2
14	Azadirachtin H	662.69	-0.68	3	11	2

No.	Secondary Metabolites	Lipinski's Rule of Five				
		Molecular Weight (g/mol)	Log P	H-bond Donor(s)	H-bond Acceptor(s)	Violation(s)
15	Azadirachtin I	618.68	-0.01	3	10	1
16	Azadirachtin K	688.68	-1.02	2	11	2
17	Azadiradione	450.58	3.55	0	4	0
18	Azadirachtol	580.58	-2.69	4	11	2
19	Azadirone	436.59	4.75	0	3	0
20	Azadironolide	468.59	4.16	1	4	0
21	Gedunin	482.57	3.10	0	5	0
22	Isoazadironolide	468.59	3.99	1	4	0
23	Isomeldenin	454.61	4.54	1	4	0
24	Isonimbinolide	572.61	1.13	1	7	1
25	Isonimbolide	466.53	2.04	0	5	0
26	Limocin A	470.65	4.67	0	4	0
27	Limocin B	470.65	4.58	0	4	0
28	Limocinin	548.72	5.79	1	5	2
29	Mahmoodin	526.63	3.88	1	6	1
30	Meliacinol	538.68	3.05	2	6	1
31	Meliatetraolenone	600.75	3.94	3	7	1
32	Nimbic Acid	470.52	1.17	3	6	0
33	Nimbidic Acid	458.55	0.70	3	6	0
34	Nimbidin	442.55	1.01	3	6	0
35	Nimbidinin	442.55	1.01	3	6	0
36	Nimbinin	466.57	2.84	0	5	0
37	Nimbilin	714.85	0.00	1	7	1
38	Nimbin	540.61	1.89	0	6	1
39	Nimbinic Acid	484.55	1.40	2	6	0
40	Nimbinolide	572.61	1.30	1	7	1
41	Nimbolide	466.53	1.93	0	5	0
42	Nimbolide B	498.53	1.17	1	6	0
43	Nimocinol	452.59	3.86	1	4	0
44	Nimbinol	512.60	1.49	1	6	1
45	Nimolicinol	482.57	4.04	1	5	0
46	O-methylazadironolide	482.62	4.52	0	4	0
47	Salannin	596.72	2.82	0	6	1
48	Salannolide	628.72	2.23	1	7	1
49	Salimuzzalin	512.64	4.28	1	5	1
50	Trichilenone Acetate	452.59	3.90	0	4	0
Pentanortriterpenoids						
51	Nimbandiol	456.54	0.70	2	6	0

No.	Secondary Metabolites	Lipinski's Rule of Five				
		Molecular Weight (g/mol)	Log P	H-bond Donor(s)	H-bond Acceptor(s)	Violation(s)
52	Nimbinene	482.57	1.63	0	5	0
Diterpenoids						
53	Margolone	300.40	4.30	1	2	0
54	Margolonone	314.38	3.70	1	3	0
55	Nimbilicin	312.41	3.85	0	2	0
56	Nimbinone	286.37	3.75	1	3	0
57	Nimbione	286.37	3.75	1	3	0
58	Nimbionol	304.39	2.65	2	4	0
59	Nimbionone	302.37	3.14	1	4	0
60	Nimbisonol	288.39	3.26	2	3	0
61	Nimbocidin1	302.46	6.07	2	2	1
62	Nimbocidin2	330.42	3.37	2	4	0
63	Isomargolonone	314.38	3.70	1	3	0
Steroids						
64	2β,3β,4β-trihydroxypregnan-16-one	350.50	2.86	3	4	0
Alkaloid						
65	Nimbic Acid B	533.57	-0.68	6	8	2
Phenolic Constituents						
66	2,6-Bis-(1,1)-dimethylethyl-4-methyl phenol	243.35	0.00	1	1	0
67	4-(2-hydroxyethyl)phenol	138.17	1.18	2	2	0
Flavonoids						
68	(-) Epicatechin	442.38	2.46	7	9	1
69	3'-prenylnaringenin	338.36	3.50	3	5	0
70	Catechin	290.27	1.50	5	6	0
71	Flowerine	368.43	3.75	1	5	0
72	Flowerone	356.37	2.84	4	6	0
73	Nimbaflavone	422.52	5.08	2	5	1
Chalchone						
74	Nimbochalcin	434.44	2.43	5	8	0
Phenolic Acid						
75	Gallic Acid	170.12	0.47	4	4	0
Aromatic Ester						
76	Nimbocetin	390.56	6.07	1	3	1

Table S4. Absorption prediction for secondary metabolites in *Azadirachta indica*

No.	Name	Absorption						
		Water Solubility	Caco-2 Permeability	Intestinal Absorption (Human)	Skin Permeability	P-glycoprotein Substrate	P-glycoprotein I Inhibitor	P-glycoprotein II Inhibitor
		log mol/L	log Papp in 10^{-6} cm/s	%Absorbed	log Kp			
1	(-) Epicatechin	-3.117	-0.283	68.829	-2.735	Yes	No	No
2	13,14-desepoxyazadirachtin-A	-4.017	0.614	92.841	-2.735	Yes	Yes	No
3	2,6-Bis-(1,1)-dimethylethyl-4-methyl phenol	-4.834	1.741	91.904	-2.474	No	No	No
4	2β,3β,4β-trihydroxypregnan-16-one	-3.499	1.28	99.374	-3.039	Yes	No	No
5	3’-prenylnaringenin	-3.454	1.056	93.87	-2.735	Yes	No	No
6	3-acetyl-1-tigloylazadirachtinin	-3.846	0.659	86.987	-2.735	Yes	Yes	No
7	4-(2-hydroxyethyl)phenol	-1.146	1.691	85.255	-2.796	No	No	No
8	6-deacetylnimbin	-5.507	0.881	95.803	-3.586	Yes	Yes	Yes
9	Azadirachtin A	-3.79	0.726	90.632	-2.735	Yes	No	No
10	Azadirachtin B	-3.79	0.726	90.632	-2.735	Yes	No	No
11	Azadirachtin D	-4.299	0.744	89.708	-2.734	Yes	Yes	No
12	Azadirachtin H	-4.158	0.778	76.432	-2.735	Yes	Yes	No
13	Azadirachtin I	-4.564	0.796	75.508	-2.731	Yes	Yes	No

No.	Name	Absorption						
		Water Solubility	Caco-2 Permeability	Intestinal Absorption (Human)	Skin Permeability	P-glycoprotein Substrate	P-glycoprotein I Inhibitor	P-glycoprotein II Inhibitor
		log mol/L	log Papp in 10^{-6} cm/s	%Absorbed	log Kp			
14	Azadirachtin K	-3.911	0.673	92.738	-2.735	Yes	Yes	No
15	Azadirachtol	-4.13	0.759	83.753	-2.735	Yes	No	No
16	Azadiradione	-5.07	0.921	99.914	-3.072	No	Yes	Yes
17	Azadirol	-5.164	0.675	81.192	-3.332	Yes	Yes	Yes
18	Azadirone	-6.008	1.382	98.162	-3.003	No	Yes	Yes
19	Azadironolide	-5.362	0.978	97.892	-3.825	No	Yes	Yes
20	Catechin	-3.117	-0.283	68.829	-2.735	Yes	No	No
21	Diepoxyazadirol	-5.441	1.018	98.083	-3.147	Yes	Yes	Yes
22	Flowerine	-5.454	0.587	92.517	-2.734	Yes	Yes	Yes
23	Flowerone	-3.166	0.104	62.027	-2.735	Yes	No	No
24	Gallic Acid	-2.56	-0.081	43.374	-2.735	No	No	No
25	Gedunin	-4.584	0.752	100	-2.998	No	Yes	No
26	Isoazadironolide	-5.362	0.978	97.892	-3.825	No	Yes	Yes
27	Isomargolonone	-2.674	1.027	100	100	No	No	No
28	Isomeldenin	-5.629	0.866	96.618	-3.524	No	Yes	Yes
29	Isonimbinolide	-5.396	0.307	79.624	-2.843	No	Yes	Yes
30	Isonimbolide	-4.815	0.96	100	-3.451	No	Yes	No
31	Limocin A	-5.771	1.345	99.412	-3.248	No	Yes	Yes
32	Limocin B	-5.771	1.345	99.412	-3.248	No	Yes	Yes

No.	Name	Absorption						
		Water Solubility	Caco-2 Permeability	Intestinal Absorption (Human)	Skin Permeability	P-glycoprotein Substrate	P-glycoprotein I Inhibitor	P-glycoprotein II Inhibitor
		log mol/L	log Papp in 10^{-6} cm/s	%Absorbed	log Kp			
33	Limocinin	-6.02	0.76	97.746	-3.078	No	Yes	Yes
34	Mahmoodin	-4.817	0.734	100	-3.108	No	Yes	Yes
35	Margolone	-2.911	1.409	99.903	-2.728	No	No	No
36	Margolonone	-2.507	1.111	100	-2.726	No	No	No
37	Meliacinin	-6.326	0.809	97.396	-3.305	No	Yes	Yes
38	Meliacinol	-4.441	0.876	98.281	-2.932	Yes	Yes	Yes
39	Meliantriol	-5.217	1.033	93.44	-3.382	Yes	Yes	Yes
40	Meliatetraolenone	-4.648	0.554	83.297	-3.165	Yes	Yes	Yes
41	Naheedin	-6.001	0.856	100	-3.964	Yes	Yes	Yes
42	Nimbaflavone	-5.874	0.56	91.484	-2.802	Yes	Yes	Yes
43	Nimbandiol	-4.882	0.823	93.361	-3.988	Yes	Yes	No
44	Nimbic Acid	-2.622	0.607	62.59	-2.735	Yes	No	No
45	Nimbic Acid B	-3.477	-0.299	40.705	-2.735	Yes	No	No
46	Nimbidic Acid	-3.322	0.662	74.168	-2.735	Yes	No	No
47	Nimbidin	-3.999	0.904	86.507	-3.072	Yes	No	No
48	Nimbidinin	-3.999	0.904	86.507	-3.072	Yes	No	No
49	Nimbilicin	-5.387	1.417	98.901	-2.882	No	Yes	No
50	Nimbilin	-4.434	0.884	100	-2.737	No	Yes	Yes
51	Nimbin	-5.754	0.922	100	-3.03	No	Yes	Yes

No.	Name	Absorption						
		Water Solubility	Caco-2 Permeability	Intestinal Absorption (Human)	Skin Permeability	P-glycoprotein Substrate	P-glycoprotein I Inhibitor	P-glycoprotein II Inhibitor
		log mol/L	log Papp in 10^{-6} cm/s	%Absorbed	log Kp			
52	Nimbinene	-5.242	0.957	100	-3.371	No	Yes	Yes
53	Nimbinic Acid	-3.224	0.722	71.251	-2.735	Yes	No	No
54	Nimbinin	-4.235	0.988	100	-3.097	No	Yes	No
55	Nimbinol	-5.486	0.796	100	-3.358	Yes	Yes	Yes
56	Nimbinolide	-5.402	0.289	79.624	-2.829	No	Yes	Yes
57	Nimbinone	-3.233	1.308	93.587	-2.843	Yes	No	No
58	Nimbione	-3.113	1.341	94.016	-2.781	No	No	No
59	Nimbionol	-3.557	1.064	94.893	-3.452	Yes	No	No
60	Nimbionone	-3.627	1.172	95.617	-3.384	No	Yes	No
61	Nimbisonol	-3.496	1.302	93.319	-3.272	Yes	No	No
62	Nimbocetin	-6.406	0.679	91.396	-2.726	No	Yes	Yes
63	Nimbochalcin	-3.458	-0.065	46.722	-2.738	Yes	No	No
64	Nimbocidin1	-4.367	1.054	94.406	-3.023	Yes	No	No
65	Nimbocidin2	-3.816	1.304	92.676	-3.341	Yes	Yes	No
66	Nimbocinone	-5.5	0.743	94.871	-3.172	Yes	Yes	Yes
67	Nimbolide	-5.166	0.92	100	-3.599	No	Yes	Yes
68	Nimbolide B	-5.11	0.976	82.774	-3.278	No	Yes	Yes
69	Nimocinol	-5.537	0.885	97.094	-3.549	No	Yes	Yes
70	Nimolicinol	-4.129	0.821	100	-3.086	No	Yes	Yes

No.	Name	Absorption						
		Water Solubility	Caco-2 Permeability	Intestinal Absorption (Human)	Skin Permeability	P-glycoprotein Substrate	P-glycoprotein I Inhibitor	P-glycoprotein II Inhibitor
		log mol/L	log Papp in 10^{-6} cm/s	%Absorbed	log Kp			
71	Odoratone	-5.853	0.703	95.094	-3.651	No	Yes	Yes
72	O-methylazadironolide	-5.702	0.998	99.877	-3.367	No	Yes	Yes
73	Salannin	-5.518	0.858	100	-2.891	No	Yes	Yes
74	Salannolide	-5.163	0.404	100	-2.822	No	Yes	Yes
75	Salimuzzalin	-5.712	0.934	90.13	-3.416	No	Yes	Yes
76	Trichilenone Acetate	-5.175	0.894	99.423	-3.215	No	Yes	No

Table S5. Disitribution and excretion predictions for secondary metabolites in *Azadirachta indica*

No.	Name	Distribution				Excretion	
		VDss (Human)	Fraction Unbound (Human)	BBB Permeability	CNS Permeability	Total Clearance	Renal OCT2 Substrate
		log L/kg	Fu	log BB	log PS	log ml/min/kg	
1	(-) Epicatechin	-3.117	-0.283	68.829	-2.735	Yes	No
2	13,14-desepoxyazadirachtin-A	-4.017	0.614	92.841	-2.735	Yes	Yes
3	2,6-Bis-(1,1)-dimethylethyl-4-methyl phenol	-4.834	1.741	91.904	-2.474	No	No
4	2β,3β,4β-trihydroxypregnan-16-one	-3.499	1.28	99.374	-3.039	Yes	No
5	3'-prenylnaringenin	-3.454	1.056	93.87	-2.735	Yes	No

No.	Name	Distribution				Excretion	
		VDss (Human)	Fraction Unbound (Human)	BBB Permeability	CNS Permeability	Total Clearance	Renal OCT2 Substrate
6	3-acetyl-1-tigloylazadirachtinin	-3.846	0.659	86.987	-2.735	Yes	Yes
7	4-(2-hydroxyethyl)phenol	-1.146	1.691	85.255	-2.796	No	No
8	6-deacetylnimbin	-5.507	0.881	95.803	-3.586	Yes	Yes
9	Azadirachtin A	-3.79	0.726	90.632	-2.735	Yes	No
10	Azadirachtin B	-3.79	0.726	90.632	-2.735	Yes	No
11	Azadirachtin D	-4.299	0.744	89.708	-2.734	Yes	Yes
12	Azadirachtin H	-4.158	0.778	76.432	-2.735	Yes	Yes
13	Azadirachtin I	-4.564	0.796	75.508	-2.731	Yes	Yes
14	Azadirachtin K	-3.911	0.673	92.738	-2.735	Yes	Yes
15	Azadirachtol	-4.13	0.759	83.753	-2.735	Yes	No
16	Azadiradione	-5.07	0.921	99.914	-3.072	No	Yes
17	Azadirol	-5.164	0.675	81.192	-3.332	Yes	Yes
18	Azadirone	-6.008	1.382	98.162	-3.003	No	Yes
19	Azadironolide	-5.362	0.978	97.892	-3.825	No	Yes
20	Catechin	-3.117	-0.283	68.829	-2.735	Yes	No
21	Diepoxyazadirol	-5.441	1.018	98.083	-3.147	Yes	Yes
22	Flowerine	-5.454	0.587	92.517	-2.734	Yes	Yes
23	Flowerone	-3.166	0.104	62.027	-2.735	Yes	No
24	Gallic Acid	-2.56	-0.081	43.374	-2.735	No	No
25	Gedunin	-4.584	0.752	100	-2.998	No	Yes
26	Isoazadironolide	-5.362	0.978	97.892	-3.825	No	Yes

No.	Name	Distribution				Excretion	
		VDss (Human)	Fraction Unbound (Human)	BBB Permeability	CNS Permeability	Total Clearance	Renal OCT2 Substrate
27	Isomargolonone	-2.674	1.027	100	100	No	No
28	Isomeldenin	-5.629	0.866	96.618	-3.524	No	Yes
29	Isonimbinolide	-5.396	0.307	79.624	-2.843	No	Yes
30	Isonimbolide	-4.815	0.96	100	-3.451	No	Yes
31	Limocin A	-5.771	1.345	99.412	-3.248	No	Yes
32	Limocin B	-5.771	1.345	99.412	-3.248	No	Yes
33	Limocinin	-6.02	0.76	97.746	-3.078	No	Yes
34	Mahmoodin	-4.817	0.734	100	-3.108	No	Yes
35	Margolone	-2.911	1.409	99.903	-2.728	No	No
36	Margolonone	-2.507	1.111	100	-2.726	No	No
37	Meliacinin	-6.326	0.809	97.396	-3.305	No	Yes
38	Meliacinol	-4.441	0.876	98.281	-2.932	Yes	Yes
39	Meliantriol	-5.217	1.033	93.44	-3.382	Yes	Yes
40	Meliatetraolenone	-4.648	0.554	83.297	-3.165	Yes	Yes
41	Naheedin	-6.001	0.856	100	-3.964	Yes	Yes
42	Nimbaflavone	-5.874	0.56	91.484	-2.802	Yes	Yes
43	Nimbandiol	-4.882	0.823	93.361	-3.988	Yes	Yes
44	Nimbic Acid	-2.622	0.607	62.59	-2.735	Yes	No
45	Nimbic Acid B	-3.477	-0.299	40.705	-2.735	Yes	No
46	Nimbidic Acid	-3.322	0.662	74.168	-2.735	Yes	No
47	Nimbidin	-3.999	0.904	86.507	-3.072	Yes	No
48	Nimbidinin	-3.999	0.904	86.507	-3.072	Yes	No

No.	Name	Distribution				Excretion	
		VDss (Human)	Fraction Unbound (Human)	BBB Permeability	CNS Permeability	Total Clearance	Renal OCT2 Substrate
49	Nimbilicin	-5.387	1.417	98.901	-2.882	No	Yes
50	Nimbilin	-4.434	0.884	100	-2.737	No	Yes
51	Nimbin	-5.754	0.922	100	-3.03	No	Yes
52	Nimbinene	-5.242	0.957	100	-3.371	No	Yes
53	Nimbinic Acid	-3.224	0.722	71.251	-2.735	Yes	No
54	Nimbinin	-4.235	0.988	100	-3.097	No	Yes
55	Nimbinol	-5.486	0.796	100	-3.358	Yes	Yes
56	Nimbinolide	-5.402	0.289	79.624	-2.829	No	Yes
57	Nimbinone	-3.233	1.308	93.587	-2.843	Yes	No
58	Nimbione	-3.113	1.341	94.016	-2.781	No	No
59	Nimbionol	-3.557	1.064	94.893	-3.452	Yes	No
60	Nimbionone	-3.627	1.172	95.617	-3.384	No	Yes
61	Nimbisonol	-3.496	1.302	93.319	-3.272	Yes	No
62	Nimbocetin	-6.406	0.679	91.396	-2.726	No	Yes
63	Nimbochalcin	-3.458	-0.065	46.722	-2.738	Yes	No
64	Nimbocidin1	-4.367	1.054	94.406	-3.023	Yes	No
65	Nimbocidin2	-3.816	1.304	92.676	-3.341	Yes	Yes
66	Nimbocinone	-5.5	0.743	94.871	-3.172	Yes	Yes
67	Nimbolide	-5.166	0.92	100	-3.599	No	Yes
68	Nimbolide B	-5.11	0.976	82.774	-3.278	No	Yes
69	Nimocinol	-5.537	0.885	97.094	-3.549	No	Yes
70	Nimolicinol	-4.129	0.821	100	-3.086	No	Yes

No.	Name	Distribution				Excretion	
		VDss (Human)	Fraction Unbound (Human)	BBB Permeability	CNS Permeability	Total Clearance	Renal OCT2 Substrate
71	Odoratone	-5.853	0.703	95.094	-3.651	No	Yes
72	O-methylazadironolide	-5.702	0.998	99.877	-3.367	No	Yes
73	Salannin	-5.518	0.858	100	-2.891	No	Yes
74	Salannolide	-5.163	0.404	100	-2.822	No	Yes
75	Salimuzzalin	-5.712	0.934	90.13	-3.416	No	Yes
76	Trichilenone Acetate	-5.175	0.894	99.423	-3.215	No	Yes

Table S6. Metabolism prediction for secondary metabolites in *Azadirachta indica*

No.	Name	Metabolism						
		CYP2D6 Substrate	CYP3A4 Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
1	(-) Epicatechin	No	No	No	No	No	No	No
2	13,14-desepoxyazadirachtin-A	No	Yes	No	No	No	No	No
3	2,6-Bis-(1,1)-dimethylethyl-4-methyl phenol	No	Yes	Yes	No	No	No	No
4	2β,3β,4β-trihydroxypregnan-16-one	No	Yes	No	No	No	No	No
5	3’-prenylnaringenin	No	Yes	Yes	Yes	Yes	No	No
6	3-acetyl-1-tigloylazadirachtinin	No	Yes	No	No	No	No	No

No.	Name	Metabolism						
		CYP2D6 Substrate	CYP3A4 Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
7	4-(2-hydroxyethyl)phenol	No	No	No	No	No	No	No
8	6-deacetylnimbin	No	Yes	No	No	No	No	Yes
9	Azadirachtin A	No	Yes	No	No	No	No	No
10	Azadirachtin B	No	Yes	No	No	No	No	No
11	Azadirachtin D	No	Yes	No	No	No	No	No
12	Azadirachtin H	No	Yes	No	No	No	No	No
13	Azadirachtin I	No	Yes	No	No	No	No	No
14	Azadirachtin K	No	Yes	No	No	No	No	No
15	Azadirachtol	No	Yes	No	No	No	No	No
16	Azadiradione	No	Yes	No	No	No	No	Yes
17	Azadirol	No	Yes	No	No	No	No	No
18	Azadirone	No	Yes	No	No	No	No	No
19	Azadironolide	No	Yes	No	No	No	No	No
20	Catechin	No	No	No	No	No	No	No
21	Diepoxyazadirol	No	Yes	No	No	No	No	No
22	Flowerine	No	Yes	No	Yes	Yes	No	Yes
23	Flowerone	No	No	No	No	No	No	No
24	Gallic Acid	No	No	No	No	No	No	No
25	Gedunin	No	Yes	No	No	No	No	No
26	Isoazadironolide	No	Yes	No	No	No	No	No
27	Isomargolonone	No	No	No	No	No	No	No
28	Isomeldenin	No	Yes	No	No	No	No	No

No.	Name	Metabolism						
		CYP2D6 Substrate	CYP3A4 Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
29	Isonimbinolide	No	Yes	No	No	No	No	No
30	Isonimbolide	No	Yes	No	No	No	No	Yes
31	Limocin A	No	Yes	No	No	No	No	No
32	Limocin B	No	Yes	No	No	No	No	No
33	Limocinin	No	Yes	No	No	No	No	Yes
34	Mahmoodin	No	Yes	No	No	No	No	Yes
35	Margolone	No	No	No	No	No	No	No
36	Margolonone	No	No	No	No	No	No	No
37	Meliacinin	No	Yes	No	No	No	No	No
38	Meliacinol	No	Yes	No	No	No	No	Yes
39	Meliantriol	No	Yes	No	No	No	No	No
40	Meliatetraolenone	No	Yes	No	No	No	No	No
41	Naheedin	No	Yes	No	No	No	No	Yes
42	Nimbaflavone	No	Yes	No	Yes	Yes	No	Yes
43	Nimbandiol	No	Yes	No	No	No	No	Yes
44	Nimbic Acid	No	Yes	No	No	No	No	No
45	Nimbic Acid B	No	Yes	No	No	No	No	No
46	Nimbidic Acid	No	Yes	No	No	No	No	No
47	Nimbidin	No	Yes	No	No	No	No	No
48	Nimbidinin	No	Yes	No	No	No	No	No
49	Nimbilicin	No	Yes	Yes	Yes	Yes	No	No
50	Nimbilin	No	Yes	No	No	No	No	Yes

No.	Name	Metabolism						
		CYP2D6 Substrate	CYP3A4 Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
51	Nimbin	No	Yes	No	No	No	No	No
52	Nimbinene	No	Yes	No	No	No	No	Yes
53	Nimbinic Acid	No	Yes	No	No	No	No	No
54	Nimbinin	No	Yes	No	No	No	No	Yes
55	Nimbinol	No	Yes	No	No	No	No	Yes
56	Nimbinolide	No	Yes	No	No	No	No	No
57	Nimbinone	No	No	Yes	Yes	No	No	No
58	Nimbione	No	Yes	Yes	Yes	No	No	No
59	Nimbionol	No	No	No	Yes	No	No	No
60	Nimbionone	No	No	No	Yes	No	No	No
61	Nimbisonol	No	No	No	No	No	No	No
62	Nimbocetin	No	Yes	No	Yes	No	No	Yes
63	Nimbochalcin	No	No	No	No	No	No	No
64	Nimbocidin1	No	Yes	Yes	No	No	No	No
65	Nimbocidin2	No	No	No	Yes	No	No	No
66	Nimbocinone	No	Yes	No	No	No	No	No
67	Nimbolide	No	Yes	No	No	No	No	No
68	Nimbolide B	No	Yes	No	No	No	No	No
69	Nimocinol	No	Yes	No	No	No	No	No
70	Nimolicinol	No	Yes	No	No	No	No	Yes
71	Odoratone	No	Yes	No	No	No	No	No
72	O-methylazadironolide	No	Yes	No	No	No	No	No

No.	Name	Metabolism						
		CYP2D6 Substrate	CYP3A4 Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
73	Salannin	No	Yes	No	No	No	No	Yes
74	Salannolide	No	Yes	No	No	No	No	No
75	Salimuzzalin	No	Yes	No	No	No	No	No
76	Trichilenone Acetate	No	Yes	No	No	No	No	Yes

Table S7. Toxicity prediction for secondary metabolites in *Azadirachta indica*

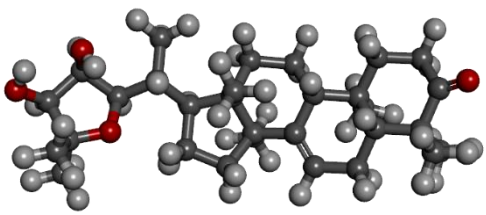
No.	Name	Toxicity									
		AMES Toxicity	Max. Tolerated Dose (Human)	hERG I Inhibitor	hERG II Inhibitor	Oral Rate Acute Toxicity (LD50) mol/kg	Oral Rate Chronic Toxicity (LOAEL) log mg/kg bw/day	Hepato-toxicity	Skin Sensitization	*T. pyriformis* Toxicity log µg/L	Minnow Toxicity log mM
1	(-) Epicatechin	No	0.438	No	No	2.428	2.5	No	No	0.347	3.585
2	13,14-desepoxyazadirachtin-A	No	-0.87	No	Yes	3.376	3.044	No	No	0.285	10.284
3	2,6-Bis-(1,1)-dimethylethyl-4-methyl phenol	No	0.256	No	No	2.586	1.387	No	Yes	1.017	-0.381
4	2β,3β,4β-trihydroxypregnan-16-one	No	-0.635	No	No	2.896	1.463	No	No	0.301	1.097
5	3’-prenylnaringenin	No	0.414	No	No	2.458	2.268	No	No	0.345	1.405

No.	Name	Toxicity									
		AMES Toxicity	Max. Tolerated Dose (Human)	hERG I Inhibitor	hERG II Inhibitor	Oral Rate Acute Toxicity (LD50) mol/kg	Oral Rate Chronic Toxicity (LOAEL) log mg/kg bw/day	Hepato-toxicity	Skin Sensitization	*T. pyriformis* Toxicity log µg/L	Minnow Toxicity log mM
6	3-acetyl-1-tigloylazadirachtinin	No	-0.758	No	Yes	3.136	3.006	No	No	0.285	11.864
7	4-(2-hydroxyethyl)phenol	No	1.396	No	No	1.861	2.331	No	Yes	-0.244	2.207
8	6-deacetylnimbin	No	-0.733	No	No	2.843	1.833	No	No	0.326	1.119
9	Azadirachtin A	No	-0.506	No	Yes	3.249	3.259	No	No	0.285	11.861
10	Azadirachtin B	No	-0.506	No	Yes	3.249	3.259	No	No	0.285	11.861
11	Azadirachtin D	No	-1.098	No	No	3.698	2.919	No	No	0.285	9.456
12	Azadirachtin H	No	-1.12	No	No	3.71	2.858	No	No	0.285	9.192
13	Azadirachtin I	No	-1.506	No	No	4.051	2.52	No	No	0.285	7.18
14	Azadirachtin K	No	-0.524	No	No	3.624	1.793	No	No	0.285	6.374
15	Azadirachtol	No	-0.864	No	No	3.698	3.543	No	No	0.285	8.226
16	Azadiradione	No	-0.101	No	Yes	2.647	0.659	No	No	0.371	-0.746
17	Azadirol	No	-0.838	No	No	2.231	1.745	No	No	0.289	0.316
18	Azadirone	No	-0.178	No	Yes	2.444	1.189	No	No	0.467	-1.184
19	Azadironolide	No	-0.748	No	No	2.16	0.157	No	No	0.32	0.592
20	Catechin	No	0.438	No	No	2.428	2.5	No	No	0.347	3.585
21	Diepoxyazadirol	No	-0.768	No	No	2.579	0.18	No	No	0.298	0.758
22	Flowerine	No	0.554	No	Yes	2.343	1.14	No	No	0.893	1.343

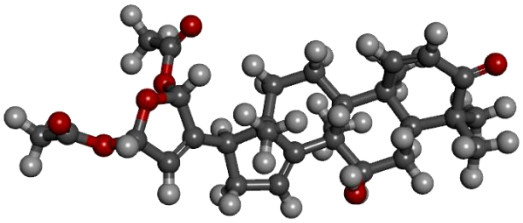
No.	Name	Toxicity									
		AMES Toxicity	Max. Tolerated Dose (Human)	hERG I Inhibitor	hERG II Inhibitor	Oral Rate Acute Toxicity (LD50) mol/kg	Oral Rate Chronic Toxicity (LOAEL) log mg/kg bw/day	Hepato-toxicity	Skin Sensitization	*T. pyriformis* Toxicity log µg/L	Minnow Toxicity log mM
23	Flowerone	No	0.377	No	No	2.546	3.176	No	No	0.287	1.34
24	Gallic Acid	No	0.7	No	No	2.218	3.06	No	No	0.285	3.188
25	Gedunin	No	-0.7	No	No	3.019	0.442	No	No	0.291	-0.107
26	Isoazadironolide	No	-0.628	No	No	2.135	0.157	No	No	0.32	0.592
27	Isomargolonone	No	0.811	No	No	2.321	1.337	No	No	0.31	0.779
28	Isomeldenin	No	-0.485	No	Yes	2.714	0.302	No	No	0.412	-0.44
29	Isonimbinolide	No	-0.642	No	Yes	2.851	1.402	No	No	0.285	3.674
30	Isonimbolide	No	-0.515	No	No	3.002	2.218	Yes	No	0.298	1.126
31	Limocin A	No	-0.546	No	No	2.037	0.295	No	No	0.352	-0.311
32	Limocin B	No	-0.546	No	No	2.037	0.295	No	No	0.352	-0.311
33	Limocinin	No	-0.149	No	No	3.116	2.555	No	No	0.306	-2.337
34	Mahmoodin	No	-0.859	No	No	3.067	0.158	No	No	0.295	1.231
35	Margolone	No	0.297	No	No	2.515	1.675	Yes	No	0.315	0.246
36	Margolonone	No	0.68	No	No	2.376	1.3	No	No	0.31	1.048
37	Meliacinin	No	-0.72	No	No	2.114	1.034	No	No	0.379	0.494
38	Meliacinol	No	-0.529	No	No	3.506	1.687	No	No	0.286	1.007
39	Meliantriol	No	-1.138	No	No	2.811	1.807	No	No	0.301	1.329
40	Meliatetraolenone	No	-1.117	No	No	3.05	2.187	No	No	0.285	2.182
41	Naheedin	No	-1.314	No	No	2.88	1.525	No	No	0.309	1.351

No.	Name	Toxicity									
		AMES Toxicity	Max. Tolerated Dose (Human)	hERG I Inhibitor	hERG II Inhibitor	Oral Rate Acute Toxicity (LD50) mol/kg	Oral Rate Chronic Toxicity (LOAEL) log mg/kg bw/day	Hepato-toxicity	Skin Sensitization	*T. pyriformis* Toxicity log µg/L	Minnow Toxicity log mM
42	Nimbaflavone	No	0.272	No	No	2.495	1.952	No	No	0.44	0.189
43	Nimbandiol	No	-0.604	No	No	2.668	1.927	No	No	0.369	1.478
44	Nimbic Acid	No	0.596	No	No	2.311	2.146	Yes	No	0.285	1.652
45	Nimbic Acid B	No	0.542	No	No	2.395	3.163	Yes	No	0.285	7.474
46	Nimbidic Acid	No	0.799	No	No	2.362	1.953	Yes	No	0.285	1.092
47	Nimbidin	No	-1.154	No	No	3.51	1.206	No	No	0.301	1.363
48	Nimbidinin	No	-1.154	No	No	3.51	1.206	No	No	0.301	1.363
49	Nimbilicin	No	0.544	No	No	2.075	2.016	No	No	1.657	0.29
50	Nimbilin	No	-0.558	No	No	2.949	2.261	Yes	No	0.285	-2.332
51	Nimbin	No	-0.371	No	No	2.48	1.57	No	No	0.295	1.269
52	Nimbinene	No	-0.346	No	No	3.072	0.705	Yes	No	0.318	1.526
53	Nimbinic Acid	No	0.87	No	No	2.599	2.069	Yes	No	0.285	1.409
54	Nimbinin	No	-0.577	No	No	2.716	0.784	No	No	0.304	-0.3
55	Nimbinol	No	-0.325	No	No	2.861	1.644	No	No	0.301	1.722
56	Nimbinolide	No	-0.788	No	Yes	2.804	1.402	No	No	0.285	4.185
57	Nimbinone	No	-0.683	No	No	2.299	1.358	No	No	1.781	0.905
58	Nimbione	No	-0.514	No	No	2.279	1.618	No	No	1.722	0.939
59	Nimbionol	No	-0.409	No	No	2.203	1.663	No	No	0.96	1.422
60	Nimbionone	No	-0.336	No	No	2.113	1.638	No	No	1.07	1.156

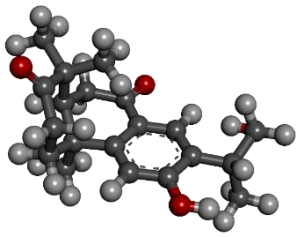
No.	Name	Toxicity									
		AMES Toxicity	Max. Tolerated Dose (Human)	hERG I Inhibitor	hERG II Inhibitor	Oral Rate Acute Toxicity (LD50) mol/kg	Oral Rate Chronic Toxicity (LOAEL) log mg/kg bw/day	Hepato-toxicity	Skin Sensitization	*T. pyriformis* Toxicity log μg/L	Minnow Toxicity log mM
61	Nimbisonol	Yes	-0.645	No	No	2.448	1.537	No	No	1.251	0.878
62	Nimbocetin	No	0.704	No	Yes	2.199	2.336	No	No	1.638	-0.793
63	Nimbochalcin	No	0.67	No	Yes	2.415	2.927	No	No	0.295	1.306
64	Nimbocidin1	No	-0.575	No	No	2.243	2.481	No	No	0.883	-1.385
65	Nimbocidin2	No	-0.526	No	No	2.37	1.89	No	No	1.275	0.567
66	Nimbocinone	No	-0.855	No	No	3.397	1.504	No	No	0.394	1.084
67	Nimbolide	No	-0.476	No	No	2.374	1.554	No	No	0.328	0.318
68	Nimbolide B	No	-0.79	No	No	2.743	1.272	No	No	0.287	2.232
69	Nimocinol	No	-0.489	No	Yes	2.686	0.285	No	No	0.413	-0.361
70	Nimolicinol	No	-1.151	No	No	2.399	0.142	No	No	0.31	0.807
71	Odoratone	No	-0.941	No	No	2.125	1.486	No	No	0.354	-0.405
72	O-methylazadironolide	No	-0.452	No	No	2.077	0.275	No	No	0.32	0.112
73	Salannin	No	-0.378	No	No	2.825	1.066	Yes	No	0.286	0.656
74	Salannolide	No	-1.003	No	No	2.447	1.093	No	No	0.285	4.306
75	Salimuzzalin	No	-0.641	No	No	2.296	0.105	No	No	0.298	-0.839
76	Trichilenone Acetate	No	-0.375	No	No	2.301	0.333	No	No	0.343	-0.519



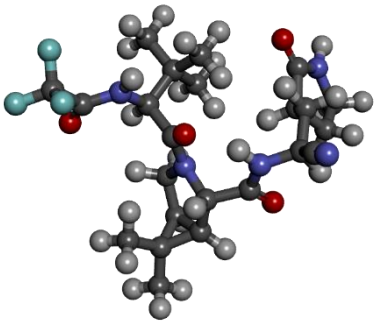
Odoratone



Salimuzzalin



Nimbocidin2



Nirmatrelvir

Figure S1. Geometry optimization results by using PM7 semi-empirical method of nirmatrelvir and the three best secondary metabolites in *Azadirachta indica* from molecular docking studies, odoratone, salimuzzalin, and nimbocidin2

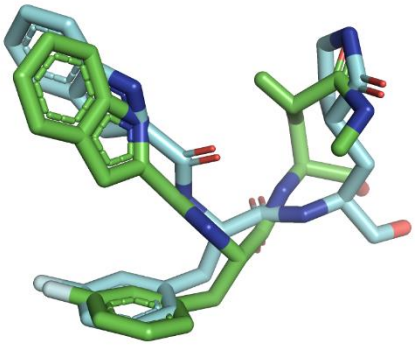
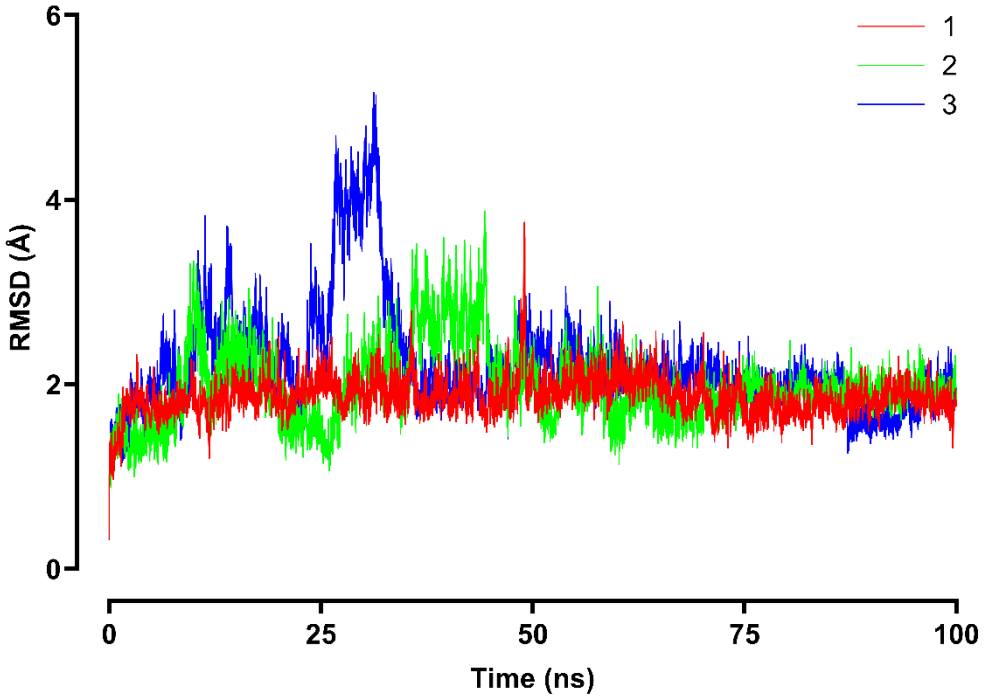
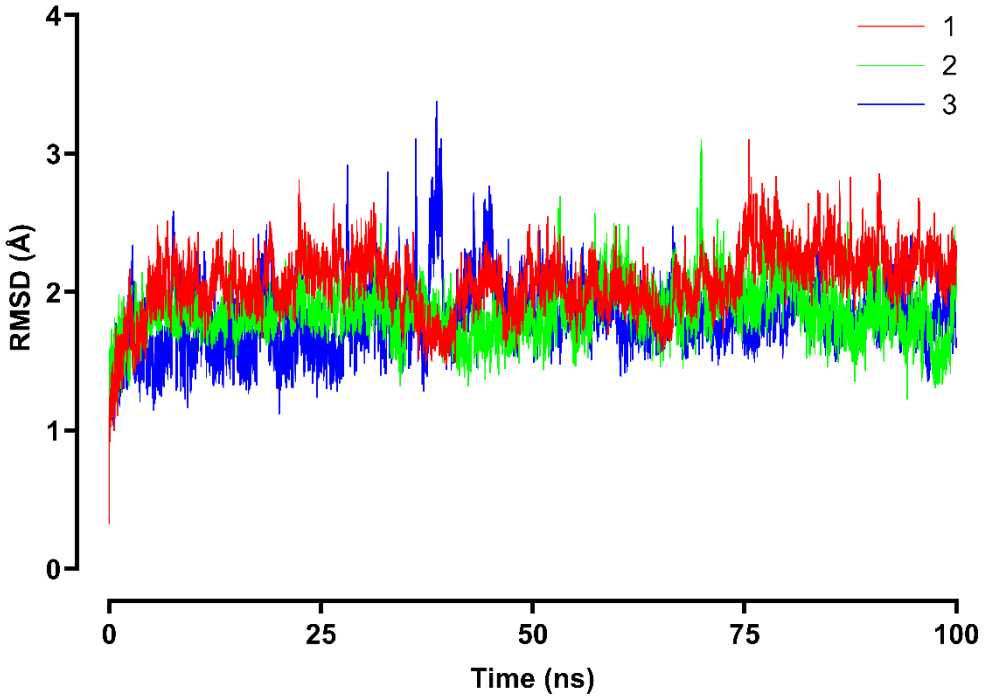


Figure S2. Crystal and redocked structures of reference ligand (FJC) in the overlay. The blue color is crystal structure, while the green color represents redocking structure. The RMSD value of FJC crystal and redocking structures is 1.938 Å

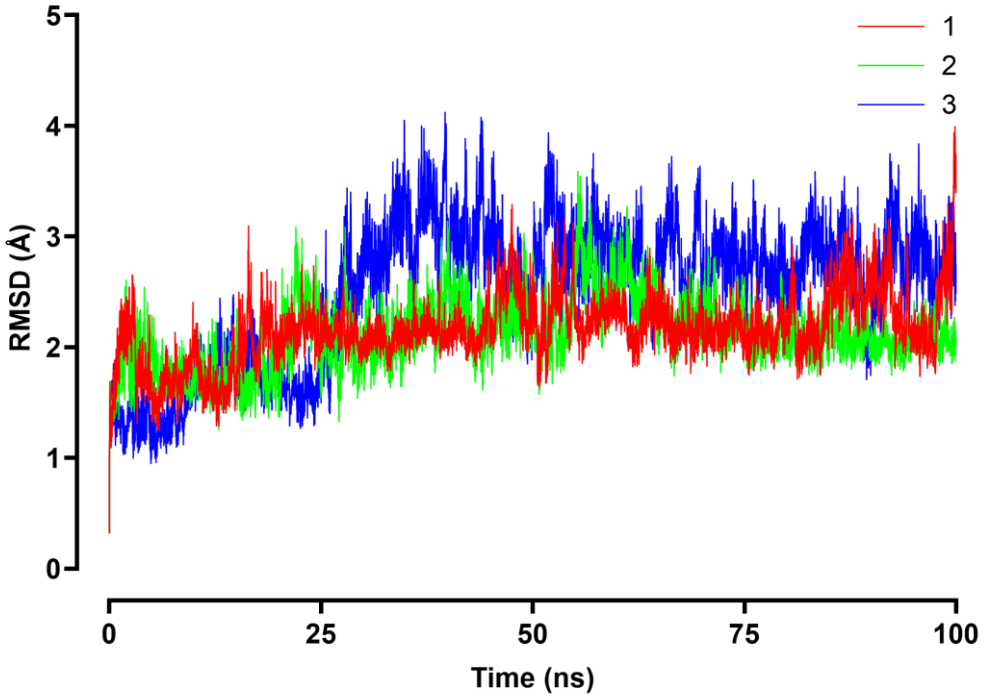


(a)

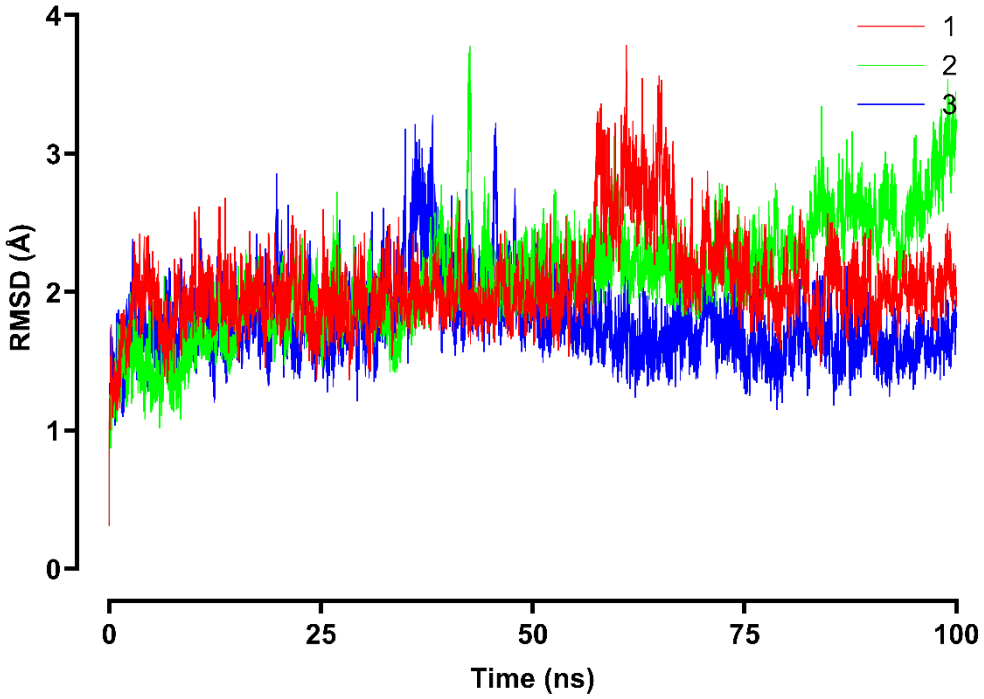


(b)

Figure S3. RMSD plots of SARS-CoV-2 M^{pro} backbone in ligand-unbound and ligand-bound structures of the triplicate MDS runs: odoratone (a) and salimuzzalin (b)

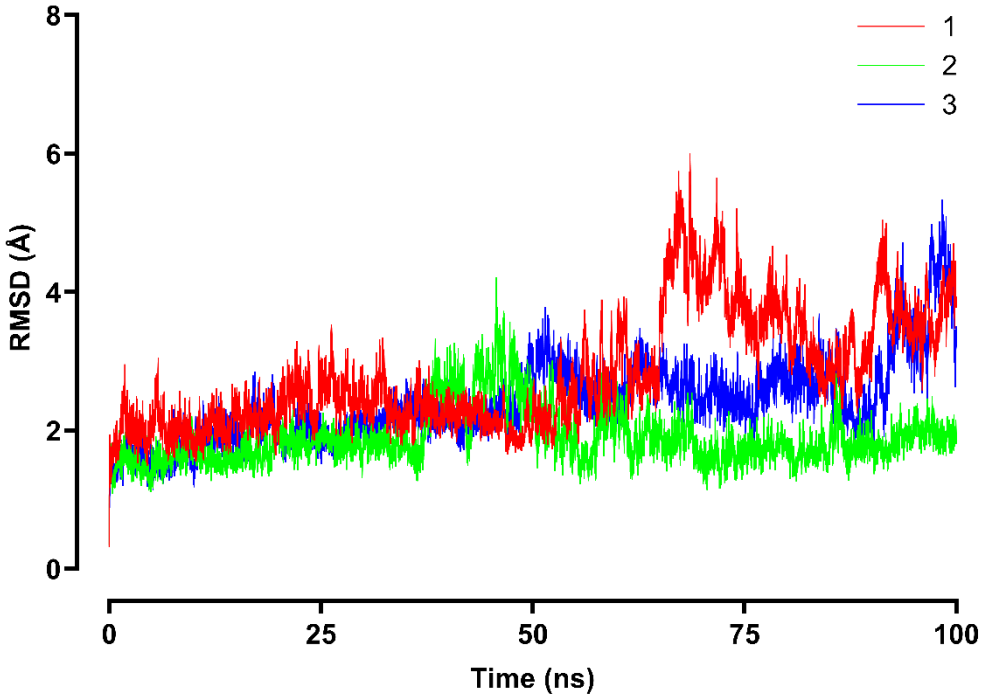


(c)

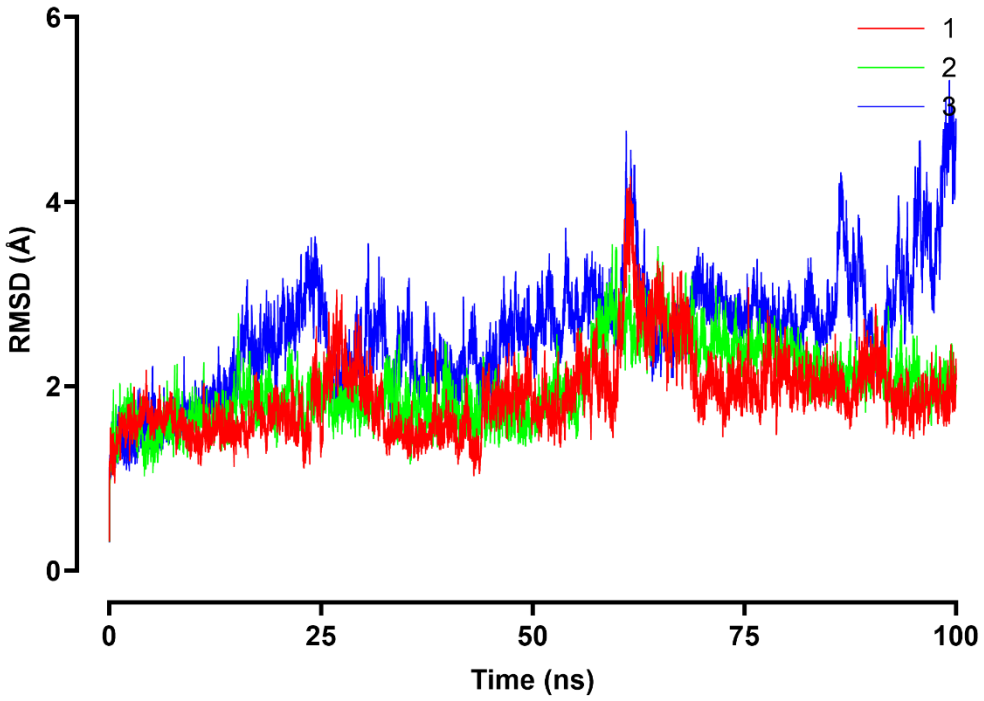


(d)

Figure S3. RMSD plots of SARS-CoV-2 M^{pro} backbone in ligand-unbound and ligand-bound structures of the triplicate MDS runs: nimbocidin (c) and nirmatrelvir (d) (cont.)



(e)



(f)

Figure S3. RMSD plots of SARS-CoV-2 M^{pro} backbone in ligand-unbound and ligand-bound structures of the triplicate MDS runs: FJC (e) and APO (f) (cont.)

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