Supplementary file 1

Inhibition of hepatitis C virus by *Avicennia marina* (Forssk.) Vierh. leaves extract: Liquid chromatography-high-resolution mass spectrometry, network pharmacology, molecular simulation, and *in vitro* study

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Table S1 Compounds identified from AM extract as revealed by High Resolution-Liquid Chromatography Mass Spectrometry (HR-LCMS) analysis. Compounds violated more than one Lipinsky rule of 5 was assigned as red colors.

No	Compound	Molecular Formula	Calc MW	m/z	RT(min)	Area (max)
1	(1S)-6-O-(5 Aminopentyl)-1,5 anhydro-2,3,4-tri-O benzyl-1-[2-(1H indol-3-yl)ethyl]-D glucitol	$C_{42}H_{50}N_2O_5$	662.37212	663.38	33.56	2.30E+06
2	(2R,3R,4R,5S)-1-(2-ethoxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol	$C_{10}H_{21}NO_5$	235.14189	236.15	0.75	1.15E+06
3	(2R,3R,4R,5S)-2-(hydroxymethyl)-1-(2-methoxyethyl)piperidine-3,4,5-triol	$C_9H_{19}NO_5$	221.12650	222.13	0.67	2.20E+07
4	(2S,3R,4R,5S)-1-(5-butoxypentyl)-2-(hydroxymethyl)piperidine-3,4,5-triol	$C_{15}H_{31}NO_5$	305.22048	306.28	13.32	5.51E+06
5	2-[(5S,7R)-3-hydroxy-1-adamantyl]acetic acid	$C_{12}H_{18}O_3$	210.12558	211.13	38.06	1.00E+06
6	(3R)-3-(hexadecanoylamino)-4-(trimethylazaniumyl)butanoate	$C_{23}H_{46}N_2O_3$	398.35116	399.35	21.25	1.26E+08
7	(4R,5S)-4,5-dihydroxy-3-[(E)-prop-1-enyl]cyclopent-2-en-1-one	$C_8H_{10}O_3$	154.06304	155.07	38.08	2.52E+05
8	(2R)-1,1,1-trifluoroheptan-2-ol	$C_7H_{13}F_3O$	170.09270	171.09	0.82	5.65E+06
9	(2R)-4-methylpentan-2-amine	$C_6H_{15}N$	101.12047	102.12	38.11	6.62E+07
10	1-piperidin-1-yldecan-1-one	$C_{15}H_{29}NO$	239.22508	240.23	15.78	8.70E+07
11	1-dodecyl-3-(2,2,3,3-tetramethylbutyl)urea	$C_{21}H_{44}N_2O$	340.34551	341.35	19.3	1.15E+07
12	1-pentylpyrrolidin-2-imine	$C_9H_{18}N_2$	154.14691	155.15	33.41	1.00E+06
13	1-Vinyl-2pyrrolidone	C_6H_9NO	111.06850	144.10	38.13	1.52E+07
14	2,4-Xylidine	$C_8H_{11}N$	121.08917	122.09	38.11	1.68E+08
15	2,6-dioctylpyridine	$C_{21}H_{37}N$	303.29283	304.30	38.13	2.75E+07
16	2-(1-Dodecyl-4 piperidinyl)-1 propanol	$C_{20}H_{41}NO$	311.31880	312.32	33.55	3.78E+06

17	2-(1-piperidinyl)cyclohexanol	$C_{11}H_{21}NO$	183.16248	184.17	10.03	1.83E+07
18	2-(3,4-dimethoxyphenyl)-N-[(2S)-4-(2,4-dimethoxyphenyl)butan-2-yl]acetamide	$C_{22}H_{29}NO_5$	387.20470	388.22	23.36	4.74E+07
19	2-(cyclopropylmethyl)guanidine	$C_5H_{11}N_3$	113.09531	114.10	38.41	3.34E+07
20	2-amino-1,3,4-octadecanetriol	$C_{18}H_{39}NO_3$	317.29323	318.30	15.22	5.39E+06
21	2-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]acetic acid	$C_9H_{14}O_2$	154.09940	155.10	38.07	2.00E+06
22	2-oxa-4-azatetracyclo[6.3.1.1~6,10~.0~1,5~]trid ecan-3-one	$C_{11}H_{15}NO_2$	193.11041	194.11	38.13	8.15E+07
23	23D6XVI233	$C_{19}H_{38}N_2O_3$	342.28842	343.29	15.78	3.53E+08
24	(3R)-3-(tetradecanoylamino)-4-(trimethylazaniumyl)butanoate	$C_{21}H_{42}N_2O_3$	370.31976	371.32	18.4	1.82E+08
25	3-Cyclopentyl-1-phenyl-1H-pyrazol-5-amine	$C_{14}H_{17}N_3$	227.14243	228.14	10.03	2.00E+06
26	3-ethoxy-1-[4-[(2R)-2-hydroxy-3,3-dimethylbutyl]piperazin-1-yl]propan-1-one	$C_{15}H_{30}N_2O_3$	286.22588	287.23	1.1	3.00E+07
27	3-Methyl-5-isoxazoleacetic acid	$C_6H_7NO_3$	141.04271	174.07	8.67	3.00E+05
28	3-Methyl-N-(4- morpholinylcarbonyl)-L-valyl-N~2~- (cyclopentylmethyl) -N-hydroxyglycinamide	$C_{19}H_{34}N_4O_5$	398.25195	399.25	30.33	1.20E+07
29	4-(Bicyclo[2.2.1]hept-2-yl)-1,2 cyclohexanediol	$C_{13}H_{22}O_2$	210.16206	228.19	25.92	1.56E+06
30	4-[4-(3-benzhydryloxypropoxy)but-2-ynyl]morpholine	$C_{24}H_{29}NO_3$	379.21587	380.22	38.11	2.29E+05
31	5K8XI641G3	$C_6H_{10}N_2$	110.08443	111.09	13.13	4.53E+07
32	7-[carbamoyl(nonyl)amino]heptanoic acid	$C_{17}H_{34}N_2O_3$	314.25714	315.26	18.91	2.98E+07
33	9-[(RS)-2,3 bis(Pivaloyloxy)propyl]adenine	$C_{18}H_{27}N_5O_4$	377.20519	378.21	1.08	1.20E+07

34	ALLYLBENZENE	C_9H_{10}	118.07839	119.08	30.33	2.22E+07
35	Bavachinin	$C_{21}H_{22}O_4$	338.15053	339.157	0.73	4.22E+07
36	betaine	$C_5H_{11}NO_2$	117.07900	118.08	18.87	3.43E+09
37	Bis(4 ethylbenzylidene)sorbitol	$C_{24}H_{30}O_6$	414.20436	415.21	25.96	6.28E+06
38	C12E3	$C_{18}H_{38}O_4$	318.27724	319.28	25.93	7.01E+07
39	C12E4	$C_{20}H_{42}O_5$	362.30346	363.31	24.58	5.24E+07
40	C6 Urea Ceramide	$C_{25}H_{50}N_2O_3$	426.38237	427.38	4.47	2.21E+08
41	Caprolactam	$C_6H_{11}NO$	113.08413	114.09	0.69	1.12E+07
42	Choline	$C_5H_{14}NO^+$	103.09977	104.10	24.22	1.42E+08
43	Citroflex 4	$C_{18}H_{32}O_7$	360.21483	383.20	15.27	2.43E+07
44	Cyprodenate	$C_{13}H_{25}NO_2$	227.18871	228.19	12.72	2.70E+07
45	Diisopropyl Fumarate	$C_{10}H_{16}O_4$	200.10504	442.24	23.18	4.21E+04
46	Dipropyleneglycol dibenzoate	$C_{20}H_{22}O_5$	342.14675	365.13	8.15	4.83E+07
47	Ethyl (8-syn)-8-({2- [(4-morpholinylcarbonyl)amino]ethyl}amin o)-3-azabicyclo[3.2.1]oct ane-3-carboxylate	$C_{17}H_{30}N_4O_4$	354.22560	355.23	25	2.01E+07
48	Ethyl palmitoleate	$C_{18}H_{34}O_2$	282.25591	283.26	38.77	1.02E+07
49	heptanediimidamide	$C_7H_{16}N_4$	156.13758	157.14	0.62	5.98E+08
50	Iminodimethanethiol	$C_2H_7NS_2$	109.00151	110.00	8.92	3.66E+07
51	L-gamma-Glutamyl-L-leucyl- N~6~-(4-aminobutyl)-L- lysine	$C_{21}H_{41}N_5O_6$	459.30470	460.31	10.03	5.23E+06
52	Laureth-5	$C_{22}H_{46}O_6$	406.32974	424.36	25.84	
53	Laurolactam	$C_{12}H_{23}NO$	197.17816	198.18	14.8	5.09E+07
54	Menetryl	$C_{12}H_{19}NO$	193.14660	194.15	13.57	1.02E+07
55	Methyl (6S,14S)-6 (4-aminobutyl)-14 benzyl-2,2 dimethyl-4,7,12 trioxo-10	$C_{25}H_{38}F_3N_5O_6$	561.27867	562.28	19.73	8.37E+05

	(trifluoromethyl)-3 oxa-5,8,9,13 tetraazapentadecan 15-oate					
56	Methylene blue	$C_{16}H_{17}N_3S$	283.11458	284.12	10.21	8.70E+06
57	MMDMA	$C_{12}H_{17}NO_3$	223.12102	224.12	1.1	5.31E+06
58	N,N'-1,2-Ethanediylbis(2- ethylbutanamide)	$C_{14}H_{28}N_2O_2$	256.21514	257.22	12.66	1.25E+07
59	N-(11Z,14Z)-eicosadienoylethano lamine	$C_{22}H_{41}NO_2$	351.31396	352.32	27.25	2.82E+05
60	N-(3-aminopropyl)hexadecanamide	$C_{19}H_{40}N_2O$	312.31423	313.32	17.17	1.50E+07
61	N-[2-(4-Methyl-3-cyclohexen-1-yl)-2-propanyl]acetamide	$C_{12}H_{21}NO$	195.16248	196.16	14.85	2.25E+07
62	N-Tetradecylacrylamid e	$C_{17}H_{33}NO$	267.25643	268.26	18.4	3.19E+07
63	NP-019498	$C_{28}H_{32}O_{16}$	624.16949	625.17	9.09	2.94E+07
64	N~1~- (Dispiro[cyclohexan e-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.1~3,7~]decan]-4- ylmethyl)-N~4~-(6-methoxy-5-phenyl- 8-quinolinyl)-1,4-pentanediamine	$C_{38}H_{49}N_3O_5$	627.36754	628.37	35.08	4.97E+06
65	pemerid	$C_{15}H_{32}N_2O$	256.25170	257.25	12.56	1.27E+07
66	Phthalic anhydride	$C_8H_4O_3$	148.01605	149.02	24.18	6.29E+06
67	pyrrolizidine	$C_7H_{13}N$	111.10483	112.11	38.11	1.05E+07
68	Safingol	$C_{18}H_{39}NO_2$	301.29836	302.30	17.25	5.06E+06
69	Stearamide	$C_{18}H_{37}NO$	283.28774	284.29	31.17	7.57E+06
70	Succinylacetone	$C_7H_{10}O_4$	158.05798	159.06	40.7	9.18E+06
71	Tetrahydrofurfuryl methacrylate	$C_9H_{14}O_3$	170.09432	358.22	38.07	3.38E+04
72	Triphenylphosphine oxide	$C_{18}H_{15}OP$	278.08608	279.09	15.42	4.08E+06

73	Tris(2-butoxyethyl) phosphate	$C_{18}H_{39}O_7P$	398.24343	399.25	23.16	2.25E+08
74	UNII:6S7S02945H	$C_{13}H_{25}NO$	211.19376	212.201	13.13	1.18E+07

Table S2 The drug-likeness properties of all compounds. Compounds violated more than one Lipinsky rule of 5 was assigned as red colors.

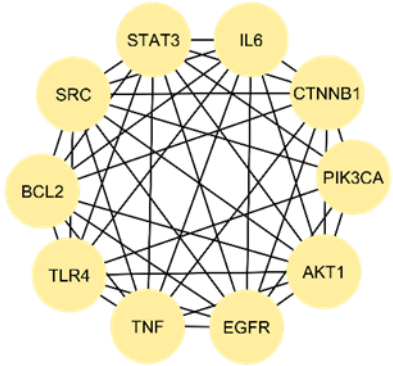
No	Compound	Molecular Formula	Lipinski Rule of 5	MW (g/mol)	MlogP	Hbond Aceptor	Hbond Donor
1	(1S)-6-O-(5 Aminopentyl)-1,5 anhydro-2,3,4-tri-O benzyl-1-[2-(1H indol-3-yl)ethyl]-D glucitol	$C_{42}H_{50}N_2O_5$	1 violation	662,86	3.18	6	2
2	(2R,3R,4R,5S)-1-(2-ethoxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol	$C_{10}H_{21}NO_5$	0 violation	235,28	-1.85	6	4
3	(2R,3R,4R,5S)-2-(hydroxymethyl)-1-(2-methoxyethyl)piperidine-3,4,5-triol	$C_9H_{19}NO_5$	0 violation	221.25	-2.16	6	4
4	(2S,3R,4R,5S)-1-(5-butoxypentyl)-2-(hydroxymethyl)piperidine-3,4,5-triol	$C_{15}H_{31}NO_5$	0 violation	305,41	-0.49	6	4
5	(3 Hydroxyadamantan 1-yl)acetic acid	$C_{12}H_{18}O_3$	0 violation	210,27	1.88	3	2
6	(3R)-3-(hexadecanoylamino)-4-(trimethylazaniumyl)butanoate	$C_{23}H_{46}N_2O_3$	0 violation	398,62	-0.16	3	1
7	(4R,5S)-4,5-dihydroxy-3-[(E)-prop-1-enyl]cyclopent-2-en-1-one	$C_8H_{10}O_3$	0 violation	154,16	-0.33	3	2
8	(2R)-1,1,1-trifluoroheptan-2-ol	$C_7H_{13}F_3O$	0 violation	170,17	2.38	4	1
9	1,3 Dimethylbutylamine	$C_6H_{15}N$	0 violation	101,19	1.53	1	1
10	1-piperidin-1-yldecan-1-one	$C_{15}H_{29}NO$	0 violation	239,40	3.151	1	0

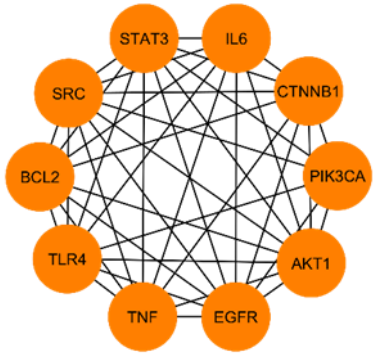
11	1-dodecyl-3-(2,2,3,3-tetramethylbutyl)urea	$C_{21}H_{44}N_2O$	1 violation	340,59	4.88	1	2
12	1-pentylpyrrolidin-2-imine	$C_9H_{18}N_2$	0 violation	154,25	1.88	1	1
13	1-Vinyl-2pyrrolidone	C_6H_9NO	0 violation	111,14	0.37	1	0
14	2,4-Xylidine	$C_8H_{11}N$	0 violation	121,18	2.14	0	1
15	2,6-dioctylpyridine	$C_{21}H_{37}N$	1 violation	303,53	4.88	1	0
16	2-(1-Dodecyl-4 piperidinyl)-1 propanol	$C_{20}H_{41}NO$	1 violation	311.55	4.73	1	0
17	2-(1-piperidinyl)cyclohexanol	$C_{11}H_{21}NO$	0 violation	183,29	1.81	2	1
18	2-(3,4-dimethoxyphenyl)-N-[(2S)-4-(2,4-dimethoxyphenyl)butan-2-yl]acetamide	$C_{22}H_{29}NO_5$	0 violation	387,47	2.33	5	1
19	2-(cyclopropylmethyl)guanidine	$C_5H_{11}N_3$	0 violation	113,16	0.03	1	2
20	2-amino-1,3,4-octadecanetriol	$C_{18}H_{39}NO_3$	0 violation	317,51	2.28	4	4
21	2-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]acetic acid	$C_9H_{14}O_2$	0 violation	154,21	1.88	2	1
22	2-oxa-4- azatetracyclo[6.3.1.1~6,10~.0~1,5~]tridecan-3-one	$C_{11}H_{15}NO_2$	0 violation	193,24	1.48	2	1
23	23D6XVI233	$C_{19}H_{38}N_2O_3$	0 violation	342,52	-1.04	3	1
24	(3R)-3-(tetradecanoylamino)-4-(trimethylazaniumyl)butanoate	$C_{21}H_{42}N_2O_3$	0 violation	370,57	-0.59	3	1
25	3-Cyclopentyl-1-phenyl-1H-pyrazol-5-amine	$C_{14}H_{17}N_3$	0 violation	227,30	2.94	1	1
26	3-ethoxy-1-[4-[(2R)-2-hydroxy-3,3-dimethylbutyl]piperazin-1-yl]propan-1-one	$C_{15}H_{30}N_2O_3$	0 violation	286,41	1.63	4	1
27	3-Methyl-5-isoxazoleacetic acid	$C_6H_7NO_3$	0 violation	142,12	-0.29	4	1
28	3-Methyl-N-(4- morpholinylcarbony l)-L-valyl-N~2~- (cyclopentylmethyl) -N-hydroxyglycinamide	$C_{19}H_{34}N_4O_5$	0 violation	398,50	0.6	5	3
29	4-(Bicyclo[2.2.1]hept- 2-yl)-1,2-cyclohexanediol	$C_{13}H_{22}O_2$	0 violation	210,31	2.37	2	2

30	4-[4-(3-benzhydryloxypropoxy)but-2-ynyl]morpholine	$C_{24}H_{29}NO_3$	0 violation	379,49	4.94	4	0
31	5K8XI641G3	$C_6H_{10}N_2$	0 violation	110,16	0.32	1	1
32	7-[carbamoyl(nonyl)amino]heptanoic acid	$C_{17}H_{34}N_2O_3$	0 violation	314,46	2.99	3	2
33	9-[(RS)-2,3 bis(Pivaloyloxy)pro pyl]adenine	$C_{18}H_{27}N_5O_4$	0 violation	377,44	0.83	7	1
34	Allylbenzene	C_9H_{10}	0 violation	118,18	4.08	0	0
35	Bavachinin	$C_{21}H_{22}O_4$	0 violation	338,40	2.61	4	1
36	betaine	$C_5H_{11}NO_2$	0 violation	117,15	-3.67	2	0
37	Bis(4 ethylbenzylidene)sorbitol	$C_{24}H_{30}O_6$	3 violation	414,2	5.83	12	7
38	C12E3	$C_{18}H_{38}O_4$	0 violation	318,49	2.28	4	1
39	C12E4	$C_{20}H_{42}O_5$	0 violation	362,54	1.91	5	1
40	C6 Urea Ceramide	$C_{25}H_{50}N_2O_3$	0 violation	426,68	3.95	3	4
41	Caprolactam	$C_6H_{11}NO$	0 violation	113,16	0.47	1	1
42	Choline	$C_5H_{14}NO^+$	0 violation	104,17	-3.46	1	1
43	Citroflex 4	$C_{18}H_{32}O_7$	0 violation	360,44	1.92	7	1
44	Cyprodenate	$C_{13}H_{25}NO_2$	0 violation	227,34	2.15	7	3
45	Diisopropyl Fumarate	$C_{10}H_{16}O_4$	0 violation	200,23	1.46	6	4
46	Dipropyleneglycol dibenzoate	$C_{20}H_{22}O_5$	0 violation	342,39	3.3	5	0
47	Ethyl (8-syn)-8-({2- [(4-morpholinylcarbony l)amino]ethyl}amin o)-3-azabicyclo[3.2.1]oct ane-3-carboxylate	$C_{17}H_{30}N_4O_4$	0 violation	354,44	0.6	5	2
48	Ethyl palmitoleate	$C_{18}H_{34}O_2$	1 violation	282,46	4.57	2	0
49	heptanediimidamide	$C_7H_{16}N_4$	0 violation	158,24	0.6	0	4
50	Iminodimethanethiol	$C_2H_7NS_2$	0 violation	109.21	-0.23	1	1
51	L-gamma-Glutamyl-L-leucyl- N~6~-(4-aminobutyl)-L-lysine	$C_{21}H_{41}N_5O_6$	2 violation	459,30	5.6	2	2
52	Laureth-5	$C_{22}H_{46}O_6$	0 violation	406,	1.54	6	1
53	Laurolactam	$C_{12}H_{23}NO$	0 violation	197,32	2.35	1	1

54	Menetryl	$C_{12}H_{19}NO$	0 violation	193,29	2.14	2	1
55	Methyl (6S,14S)-6 (4-aminobutyl)-14 benzyl-2,2 dimethyl-4,7,12 trioxo-10 (trifluoromethyl)-3 oxa-5,8,9,13 tetraazapentadecan 15-oate	$C_{25}H_{38}F_3N_5O_6$	1 violation	561,39	1.54	10	5
56	Methylene blue	$C_{16}H_{17}N_3S$	0 violation	321,87	2.06	2	1
57	MMDMA	$C_{12}H_{17}NO_3$	0 violation	223,27	1.22	4	1
58	N,N'-1,2-Ethanediylbis(2- ethylbutanamide)	$C_{14}H_{28}N_2O_2$	0 violation	256,38	2.74	2	2
59	N-(11Z,14Z)-eicosadienoylethano lamine	$C_{22}H_{41}NO_2$	2 violation	351,57	5.6	6	7
60	N-(3-aminopropyl)hexadecanamide	$C_{19}H_{40}N_2O$	0 violation	312,53	3.62	2	2
61	N-[2-(4-Methyl-3-cyclohexen-1-yl)-2- propanyl]acetamide	$C_{12}H_{21}NO$	0 violation	195,30	2.25	1	1
62	N-Tetradecylacrylamid e	$C_{17}H_{33}NO$	0 violation	267,45	3.92	1	1
63	NP-019498	$C_{28}H_{32}O_{16}$	0 violation	624,54	-3.96	10	4
64	N~1~- (Dispiro[cyclohexan e-1,3'-[1,2,4,5]tetroxane-6',2''-tricyclo[3.3.1.1~3,7~]decan]-4- ylmethyl)-N~4~-(6- methoxy-5-phenyl- 8-quinolinyl)-1,4-pentanediamine	$C_{38}H_{49}N_3O_5$	2 violation	627,81	5.08	7	2
65	pemerid	$C_{15}H_{32}N_2O$	0 violation	256,43	2	3	0
66	Phthalic anhydride	$C_8H_4O_3$	0 violation	148,12	1.65	3	0
67	pyrrolizidine	$C_7H_{13}N$	0 violation	111,18	1.49	1	0
68	Safingol	$C_{18}H_{39}NO_2$	0 violation	301,51	3.13	3	3
69	Stearamide	$C_{18}H_{37}NO$	0 violation	283,29	4.27	1	1
70	Succinylacetone	$C_7H_{10}O_4$	0 violation	158,15	-0.31	4	1
71	Tetrahydrofurfuryl methacrylate	$C_9H_{14}O_3$	0 violation	170,21	0.9	3	0

72	Triphenylphosphine oxide	$C_{18}H_{15}OP$	0 violation	278,28	2.5	3	2
73	Tris(2-butoxyethyl) phosphate	$C_{18}H_{39}O_7P$	0 violation	398,47	1.31	7	0
74	UNII:6S7S02945H	$C_{13}H_{25}NO$	0 violation	211,34	2.63	1	1





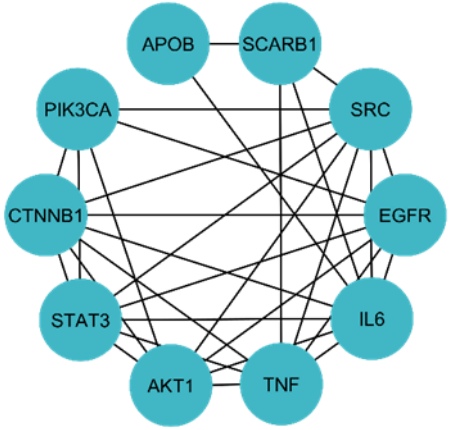
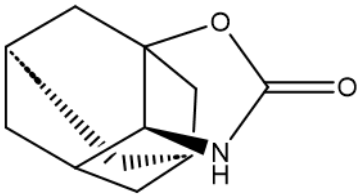
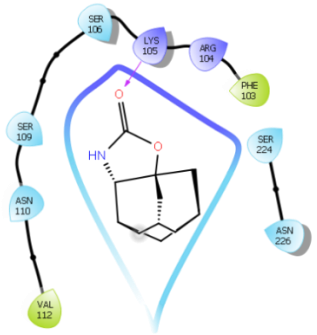


Figure S1 The core targets based on degree (yellow), betweenness (orange), closeness (blue).

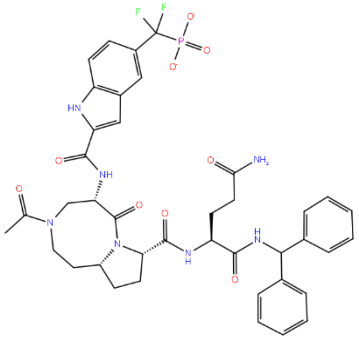


2-oxa-4-azatetracyclo[6.3.1. 1~6,10~.0~1,5~]tridecan-3-one
(Comp22)

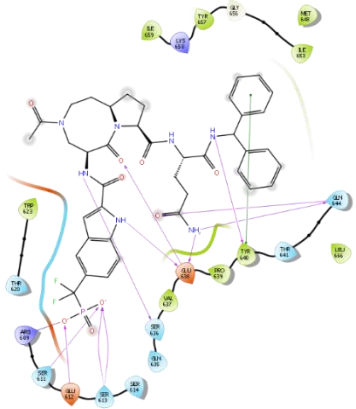


Binding energy: -1.665 kcal/mol

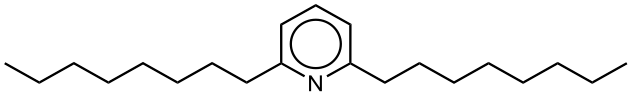
Figure S2 The structures of Comp22 and its docking conformation to IL-6.



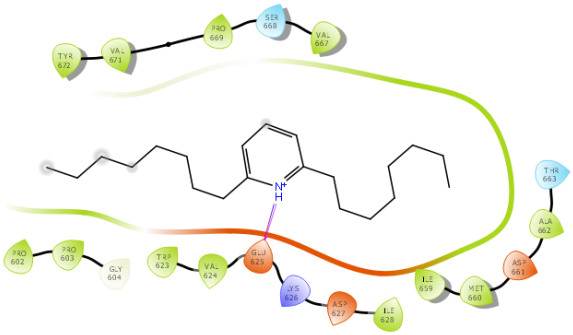
KQV (Native ligand)



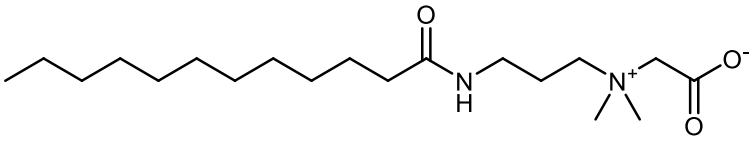
Binding energy: -10.616 kcal/mol



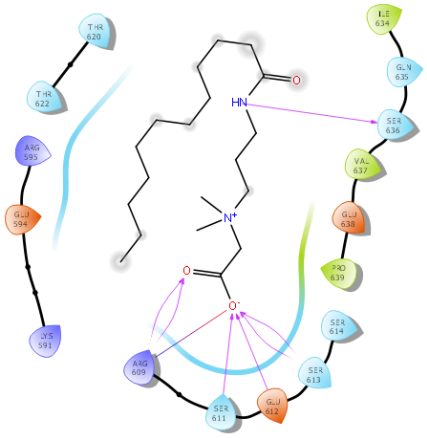
2,6-Dioctylpyridine (Comp15)



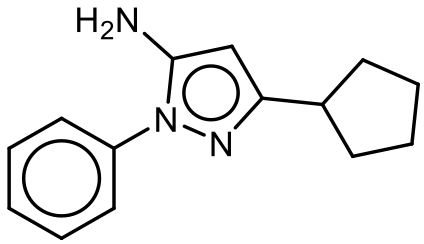
Binding energy: -4.192 kcal/mol



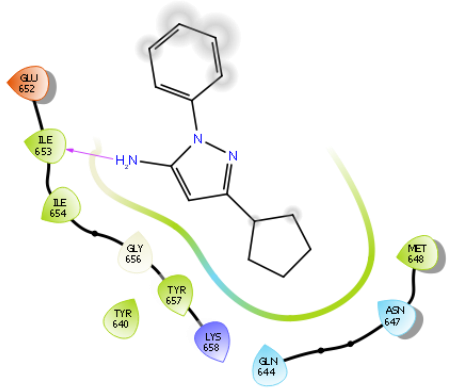
23D6XVI233
(Comp23)



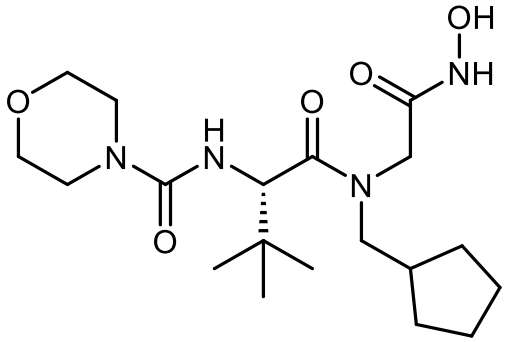
Binding energy: -4.385 kcal/mol



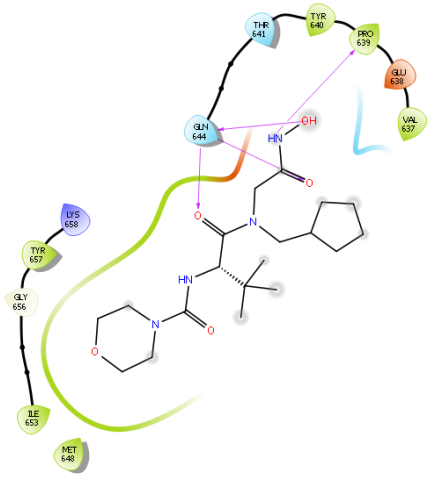
3-Cyclopentyl-1-phenyl-1H-pyrazol-5-amine
(Comp25)



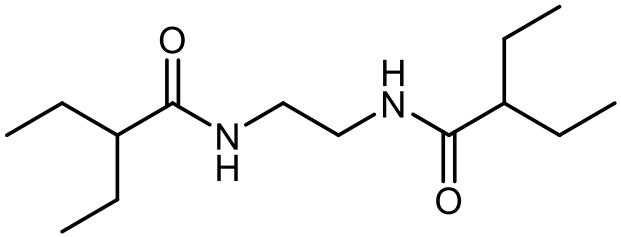
Binding energy: -2.546 kcal/mol



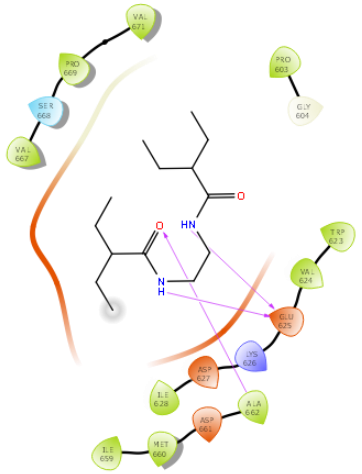
3-Methyl-N-(4- morpholinylcarbony l)-L-valyl-N~2~- (cyclopentylmethyl) -N-hydroxyglycinamide (Comp28)



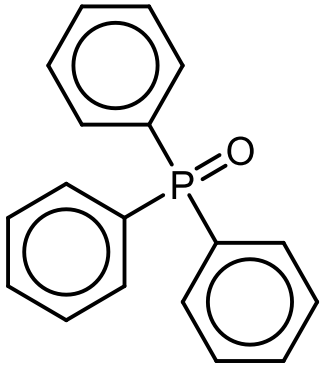
Binding energy: -4.182 kcal/mol



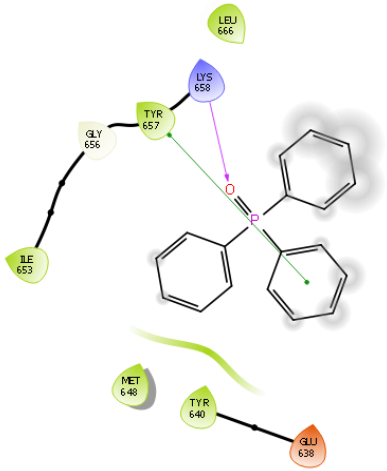
N,N'-1,2 Ethanediylbis(2-ethylbutanamide) (Comp58)



Binding energy: -1.692 kcal/mol

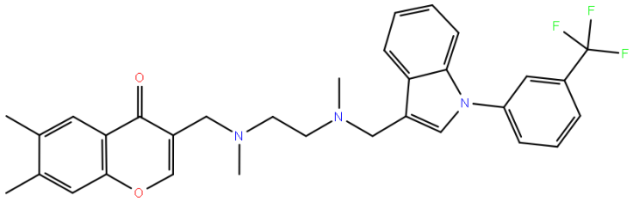


Triphenylphosphine oxide
(Comp72)

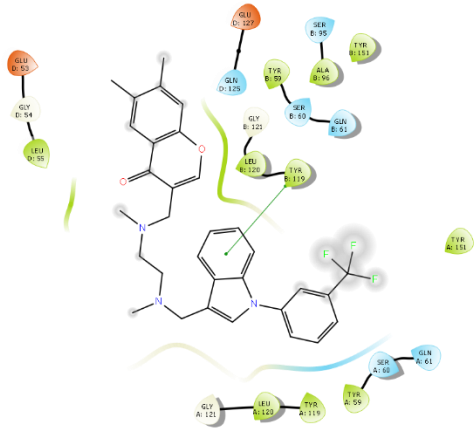


Binding energy: -2.893 kcal/mol

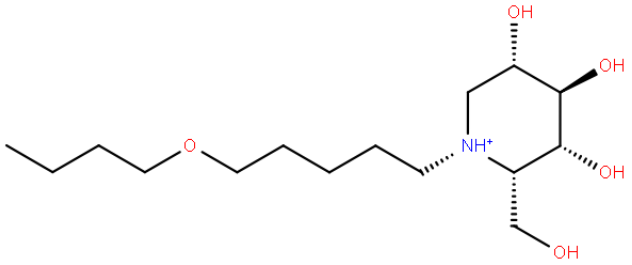
Figure S3 The structures of the 6 compounds and their docking conformation to STAT3.



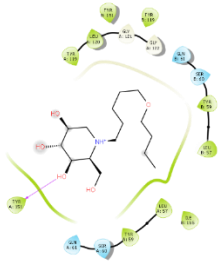
307 (Native ligand)



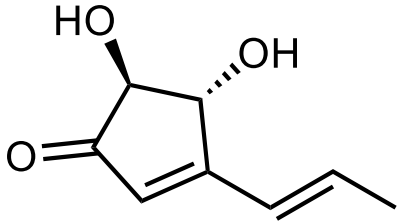
Binding energy: -6.102 kcal/mol



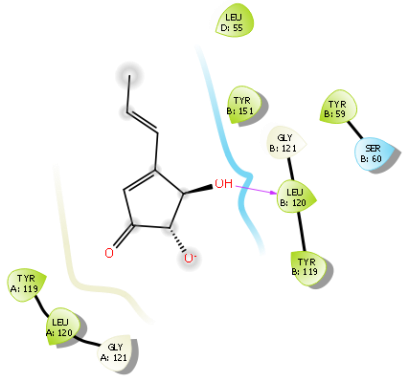
(2S,3R,4R,5S)-1-(5-butoxypentyl)-2-(hydroxymethyl)piperidine-3,4,5-triol (Comp4)



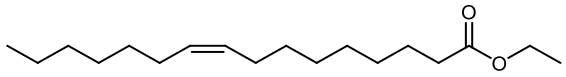
Binding energy: -6.405 kcal/mol



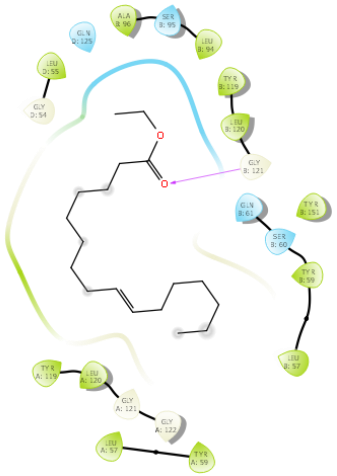
(4R,5S)-4,5 Dihydroxy-3-[(1E) 1-propen-1-yl]-2 cyclopenten-1-one
(Comp7)



Binding energy: -4.097 kcal/mol



Ethyl palmitoleate
(Comp48)



Binding energy: -4.798 kcal/mol

Figure S4 The structures of the 3 compounds and their docking conformation to TNF-α.

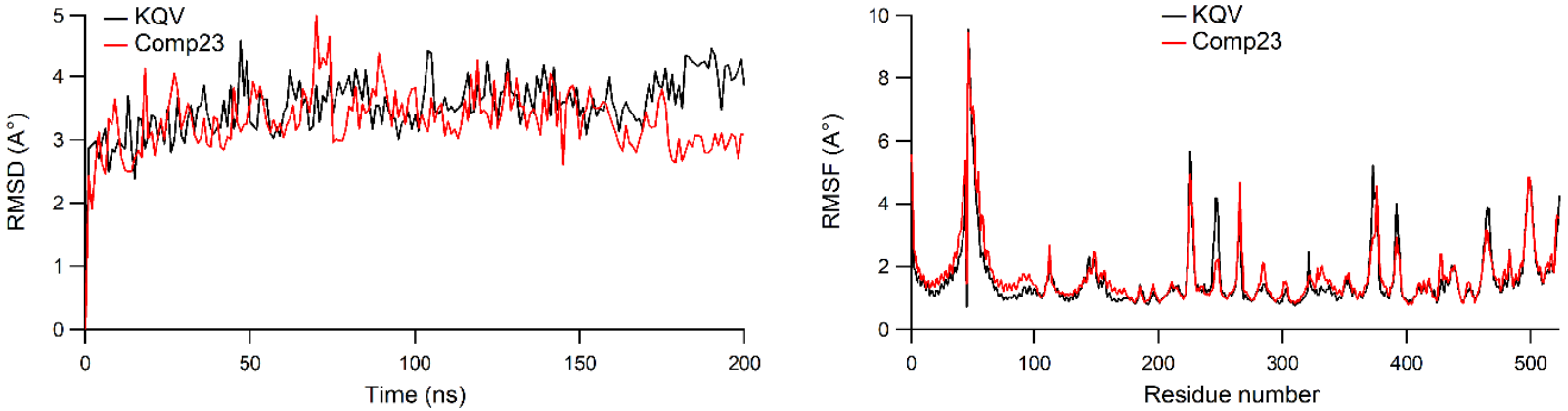
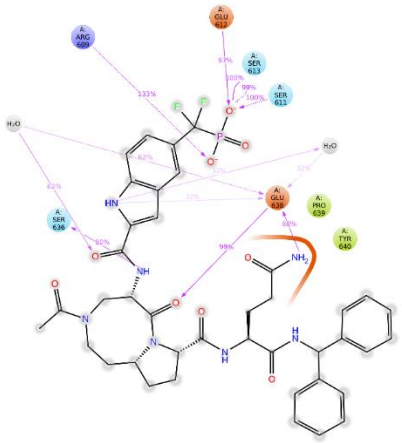
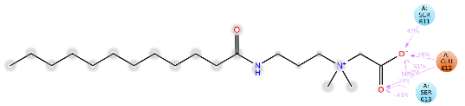


Figure S5 The RMSD (left) and RMSF (right) plots of protein Cα in KQV and Comp23 systems.

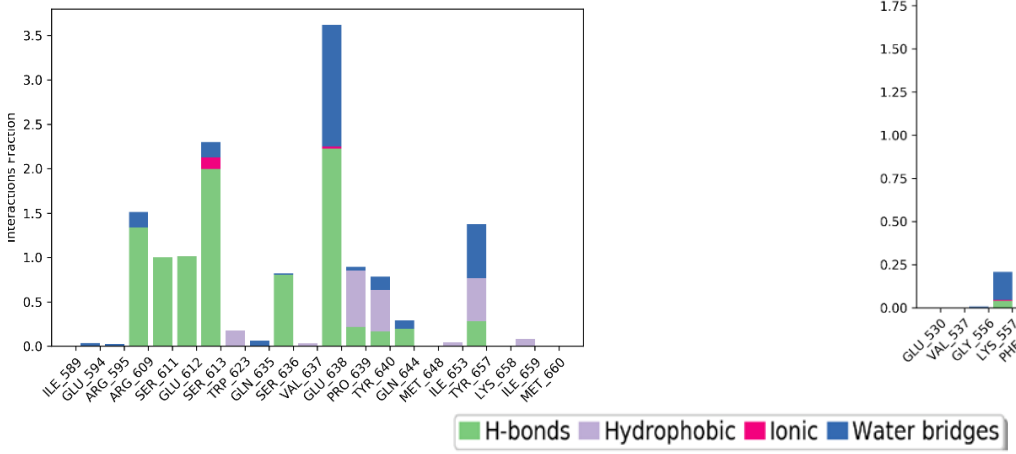
(a)



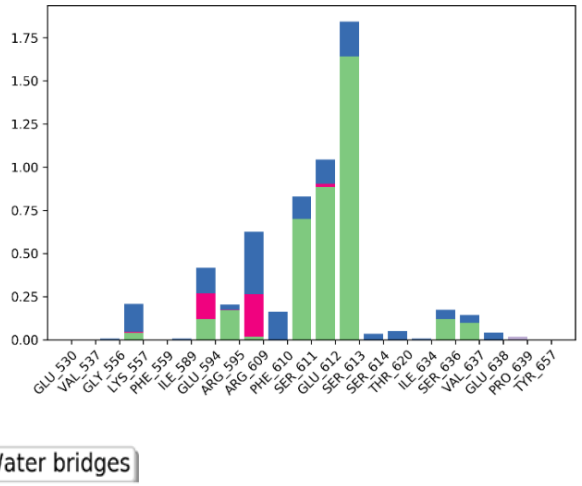
(b)



(c)


Interactions fraction
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
ILE_589
GLU_594
ARG_595
ARG_609
SER_611
GLU_612
SER_613
TRP_623
GLN_635
SER_636
VAL_637
GLU_638
PRO_639
TYR_640
GLN_644
MET_648
ILE_653
TYR_657
LYS_658
ILE_659
MET_660

(d)


0.00
0.25
0.50
0.75
1.00
1.25
1.50
1.75
GLU_530
VAL_537
GLY_556
LYS_557
PHE_559
ILE_589
GLU_594
ARG_595
ARG_609
PHE_610
SER_611
GLU_612
SER_613
SER_614
THR_620
ILE_634
SER_636
VAL_637
GLU_638
PRO_639
TYR_657

H-bonds
Hydrophobic
Ionic
Water bridges

Figure S6 The 2D ligand protein interaction diagram recorded during MD simulations for KQV **(a)** and Comp23 **(b)** systems. Protein-Ligand contacts during MD simulations for for KQV **(c)** and Comp23 **(d)** systems. Interaction fraction greater than 1 is because of multiple contacts on one residue.