Supporting information 3

Chemoinformatic Design and Profiling of Derivatives of Dasabuvir, Efavirenz and Tipranavir as Potential Inhibitors of Zika virus RNA-dependent RNA polymerase and methyltransferase

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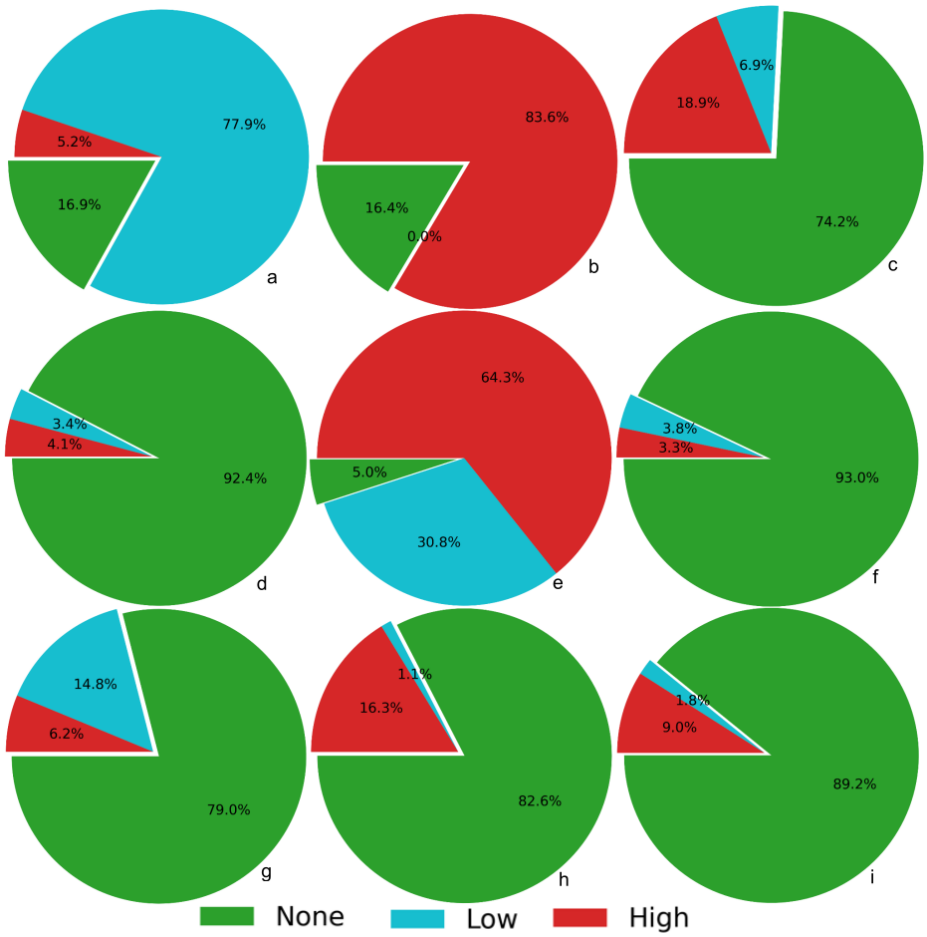


Figure S1: Toxicity prediction of designed compounds with DataWarrior: First panel (a – c) are plots of mutagenic, tumorigenic and irritation risks of derivatives of dasabuvir respectively. Second panel (d – f) are plots of mutagenic, tumorigenic and irritation risks of derivatives of efavirenz respectively. Again, third panel (g – i) are plots of mutagenic, tumorigenic and irritation risks of derivatives of tipranavir respectively.

Table S1: Binding energies of selected designed derivatives of dasabuvir for zika virus RNA-dependent RNA polymerase (RdRP) and methyltransferase (MTase)

Code	ID	Smiles	Binding affinity for RdRP (kcal/mol)	Binding affinity for MTase (kcal/mol)
980	1d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c(cc2cc3)ccc2nc3NS(N)(=O)=O)c1OC	-7.55±0.10	-9.23±0.25
1067	2d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c(cc2cc3)ccc2nc3NS(C)(=O)=O)c1OC	-7.35±0.30	-9.45±0.30
2043	3d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=N)cc(-c(cc2cc3)ccc2nc3NS(C)(=O)=O)c1OC	-7.58±0.55	-9.83±0.42
3515	4d	CC(C)(C)c1cc(N(C=CC(N2)=N)C2=O)cc(-c(cc2cc3)ccc2nc3NS(C)(=O)=O)c1OC	-7.63±0.25	-9.68±0.05
4794	5d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c(cc2cc3)ccc2nc3NS(O)(=O)=O)c1OC	-7.65±0.10	-9.40±0.20
5007	6d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c2cc3ccc(CN)cc3cc2)c1OC	-7.03±0.05	-9.30±0.00
5553	7d	CC(C)(c1cc(N(C=CC(N2)=O)C2=O)cc(-c(cc2cc3)ccc2nc3NS(C)(=O)=O)c1OC)O	-7.38±0.15	-9.50±0.00
5963	8d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c(cc2cc3)ccc2nc3NS(C)(=O)=O)c1NC	-7.33±0.05	-9.25±0.19
6061	9d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c(cc2cc3)ccc2nc3NS(C)(=O)=O)c1SC	-7.60±0.00	-9.25±0.30
6063	10d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c(cc2cc3N)ccc2nc3NS(C)(=O)=O)c1OC	-7.20±0.08	-9.33±0.05
6253	11d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c(cc2cc3)cc(N)c2nc3NS(C)(=O)=O)c1OC	-7.50±0.00	-9.30±0.00
6255	12d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c(cc2c(F)c3)ccc2nc3NS(C)(=O)=O)c1OC	-7.40±0.00	-9.50±0.00
6339	13d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c2ccc(cc(CS(N)(=O)=O)c(C)c3)c3c2)c1OC	-7.00±0.00	-9.40±0.08
6416	14d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c2ncc(cc(CS(N)(=O)=O)cc3)c3c2)c1OC	-6.90±0.00	-9.23±0.10
Dasabuvir	15d	CC(C)(C)C1=CC(=CC(=C1OC)C2=CC3=C(C=C2)C=C(C=C3)NS(=O)(=O)C)N4C=CC(=O)NC4=O	-6.85±0.00	-9.23±0.25
5095	16d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(Cc(cc2cc3)ccc2nc3NS(C)(=O)=O)c1OC	-9.20±0.00	Na
5005	17d	CC(C)(C)c1cc(N(C=CC(N2)=O)C2=O)cc(-c2ccc(ccc(CS(N)(=O)=O)c3)c3c2)c1OC	-8.60±0.00	Na

Table S2: Binding energies of selected designed derivatives of tipranavir for zika virus RNA-dependent RNA polymerase (RdRP) and methyltransferase (MTase)

Codes	ID	Smiles	RdRP: 5U04 (kcal/mol)	Mtase: 5mrk (kcal/mol)
1	1t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CC)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.5±0.54	-9.7±0.00
76	2t	CC[C@H](c1cccc(NS(c2ncc(C(F)(F)F)cc2)(=O)=O)c1)C(C(O[C@](CCC(C)C)(CCc1ccccc1)C1)=O)=C1O	-7.55±0.64	-9.75±0.10
457	3t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](C)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-8.175±0.05	-9.775±0.05
649	4t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CNC)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.85±0.06	-9.7±0.00
718	5t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CN(C)C)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.625±0.56	-9.8±0.00
1068	6t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CF)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.625±0.36	-9.675±0.05
1368	7t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CCCN)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.65±0.06	-9.6±0.00
2007	8t	CC(C)C[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CS)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.5±0.54	-9.75±0.006
2086	9t	CC[C@H](c1cccc(NS(c2ncc(C(F)(F)F)cc2)(=O)=O)c1)C(C(O[C@@](CCc1ccccc1)(CC(C)=C)C1)=O)=C1O	-7.625±0.49	-9.9±0.20
2517	10t	CC[C@H](c1cccc(NS(c2ncc(C(F)(F)F)cc2)(=O)=O)c1)C(C(O[C@@](CCc1ccccc1)(CCC#C)C1)=O)=C1O	-7.6±0.47	-9.6±0.00
2591	11t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CC)c2cccc(NS(c3ncc(C(C)(F)F)cc3)(=O)=O)c2)OC1=O	-7.9±0.14	-9.625±0.05
2769	12t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CC)c2cccc(NS(c3ncc(C(F)(F)F)nc3)(=O)=O)c2)OC1=O	-7.925±0.11	-9.6±0.00

2931	13t	CC[C@H](c1cccc(NS(c2ncc(C(F)(F)F)cc2)(=O)=O)c1)C(C(O[C@@](CCc1ccccc1)(CC#CC)C1)=O)=C1O	-7.8±0.80	-9.85±0.10
3154	14t	CCCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CC)c2cccc(NS(c3nnc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.825±0.21	-9.725±0.05
3217	15t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CC)c2cccc(NS(c3nnc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.8±0.41	-9.7±0.00
3377	16t	CC[C@H](c1cccc(NS(c2ncc(C(F)(F)F)cc2)(=O)=O)c1)C(C(O[C@@](CCc1ccccc1)(C/C=C/C)C1)=O)=C1O	-7.95±0.13	-9.8±0.20
3683	17t	CC[C@H](c1cccc(NS(c2ncc(C(F)(F)F)cc2)(=O)=O)c1)C(C(O[C@](CCC(C)=C)(CCc1ccccc1)C1)=O)=C1O	-7.75±0.13	-9.7±0.00
3828	18t	CC[C@@H](C)C[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CC)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.5±0.61	-9.65±0.06
5262	19t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CF)c2cc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)cnc2)OC1=O	-7.625±0.63	-9.6±0.00
5634	20t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CCCO)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.625±0.11	-9.7±0.00
Tipranavir	21t	CCCC1(CC(=C(C(=O)O1)C(CC)C2=CC(=CC=C2)NS(=O)(=O)C3=NC=C(C=C3)C(F)(F)F)O)CCC4=CC=CC=C4	-7.5±0.34	-9.6±0.00
1510	22t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CC)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)n2)OC1=O	Na	-10.25±0.06
6675	23t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CF)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)n2)OC1=O	Na	-10.2±0.00
5719	24t	CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CCC(O)=O)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	Na	-10.08±0.05
2541	25t	CC[C@H](c1cccc(NS(c2ncc(C(F)(F)F)cc2)(=O)=O)c1)C(C(O[C@@](CCc1ccccc1)(CC#C)C1)=O)=C1O	Na	-10.08±0.05
170	26t	CC[C@H](c1cccc(NS(c2ncc(C(F)(F)F)cc2)(=O)=O)c1)C(C(O[C@@](CCc1ccccc1)(CC(C)C)C1)=O)=C1O	Na	-10±0.00
1186		CCC[C@@](CCc(cc1)ccc1F)(CC(O)=C1[C@H](CC)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	Na	-9.9±0.00
1493		CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CCC#N)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	Na	-9.9±0.00
4435		CC[C@H](c1cc(NS(c2ncc(C(F)(F)F)cc2)(=O)=O)cnc1)C(C(O[C@@](CCc1ccccc1)(CCF)C1)=O)=C1O	-7.925±0.05	Na
264		CCC[C@@](CCc1ccccc1)(CC(O)=C1[C@H](CCO)c2cccc(NS(c3ncc(C(F)(F)F)cc3)(=O)=O)c2)OC1=O	-7.9±0.08	Na

Table S3: Binding energies of selected designed derivatives of tipranavir for zika virus RNA-dependent RNA polymerase (RdRP)

Code	ID	Smiles	RdRP: 5U04 (kcal/mol)
1501	1e	FC([C@](CC#CC1CC1)(c(cc(cc1)Cl)c1N1)OC1=S)(F)F	-6.675±0.05
1436	2e	O=C1O[C@](CC#CC2CC2)(C(F)(F)F)c2cc(Cl)ncc2N1	-6.65±0.06
Efavirenz	3e	C1CC1C#CC2(C3=C(C=CC(=C3)Cl)NC(=O)O2)C(F)(F)F	-6.6±0.00

Table S4: Binding energies of selected designed derivatives of tipranavir for zika virus methyltransferase (MTase)

Code	ID	Smiles	Mtase: 5mrk (kcal/mol)
4403	4e	FC([C@@](c1c(N2)nnc(F)c1)(C#CC1CC1)OC2=S)(F)F	-7.6±0.00
4327	5e	FC([C@@](c1cc(Cl)nnc1N1)(C#CC2CC2)OC1=S)(F)F	-7.5±0.00
Efavirenz	3e	C1CC1C#CC2(C3=C(C=CC(=C3)Cl)NC(=O)O2)C(F)(F)F	-7.425±0.00

Table S5: Bio-activities of selected designed derivatives of dasabuvir for zika virus RNA-dependent RNA polymerase (RdRP) and methyltransferase (MTase)

		MTase					RdRP				
Code	ID	**Average Ki (uM)**	**LE**	**Lescale**	**LELP**	**FQ**	**Average Ki (uM)**	**LE**	**Lescale**	**LELP**	**FQ**
980	1d	0.180067848±0.059893	0.263571	0.287404	11.37149	0.917078	2.911069187±0.449621	0.215714	0.287404	13.8943	0.750562
1067	2d	0.127327876±0.058735	0.270000	0.287404	13.31148	0.939445	4.376737877±1.658545	0.210000	0.287404	17.11476	0.73068
2043	3d	0.076982246±0.067006	0.280714	0.287404	11.38204	0.976725	3.703437534±2.842897	0.216429	0.287404	14.76284	0.753047
3515	4d	0.07970735±0.0070140	0.276429	0.287404	11.5585	0.961813	2.719231219±1.199306	0.217857	0.287404	14.66603	0.758018

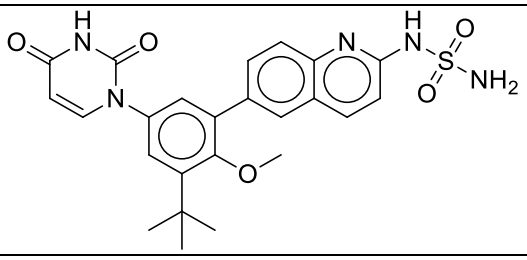
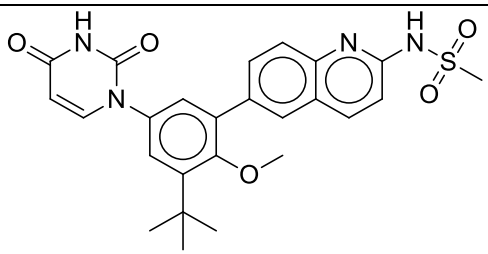
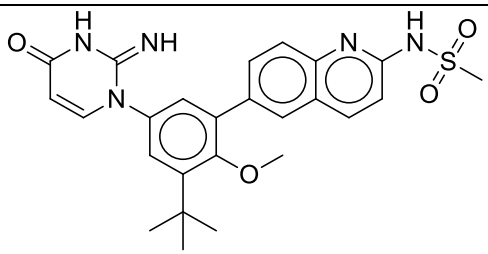
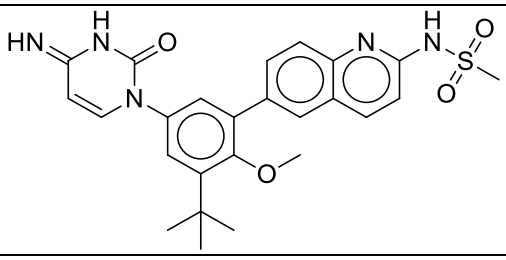
4794	5d	0.132631428±0.051589	0.268571	0.287404	7.46133	0.934475	2.461448198±0.449621	0.218571	0.287404	9.16817	0.760503
5007	6d	0.149790974±0.000000	0.290625	0.315910	14.02942	0.919960	7.015404169±0.567373	0.219531	0.31591	18.57275	0.694916
5553	7d	0.106837052±0.000000	0.271429	0.287404	8.429842	0.944416	3.959587719±0.87415	0.210714	0.287404	10.85878	0.733165
5963	8d	0.169164284±0.050324	0.264286	0.287404	12.52849	0.919563	4.225781837±0.341762	0.209286	0.287404	15.82096	0.728194
6061	9d	0.176561056±0.066907	0.264286	0.287404	15.66978	0.919563	2.648363028±0.00000	0.217143	0.287404	19.07178	0.755533
6063	10d	0.143969195±0.011644	0.259028	0.278385	11.26057	0.930466	5.243256843±0.722934	0.200000	0.278385	14.58400	0.71843
6253	11d	0.149790974±0.000000	0.258333	0.278385	11.29084	0.927972	3.135879681±0.00000	0.208333	0.278385	14.00064	0.748364
6255	12d	0.106837052±0.000000	0.263889	0.278385	14.00173	0.947928	3.713139502±0.00000	0.205556	0.278385	17.97519	0.738386
6339	13d	0.127408935±0.017567	0.261111	0.278385	16.90506	0.937950	7.299090779±0.00000	0.194444	0.278385	22.70109	0.698473
6416	14d	0.171740335±0.028636	0.263571	0.287404	11.9903	0.917078	8.642723911±0.00000	0.197143	0.287404	16.03051	0.685944
Dasabuvir	15d	0.180067848±0.059893	0.263571	0.287404	15.63561	0.917078	9.795009846±3.335809	0.195714	0.287404	21.05672	0.680974
5095	16d	Na	Na	Na	Na	Na	0.177364835±0.0000	0.255556	0.278385	14.67704	0.917994
5005	17d	Na	Na	Na	Na	Na	0.488831033±0.0000	0.245714	0.287404	16.56477	0.854945
6423		0.106837052±0.000	0.271429	0.287404	10.59616	0.944416	Na	Na	Na	Na	Na
5956		0.149790974±0.000	0.265714	0.287404	10.10183	0.924533	Na	Na	Na	Na	Na

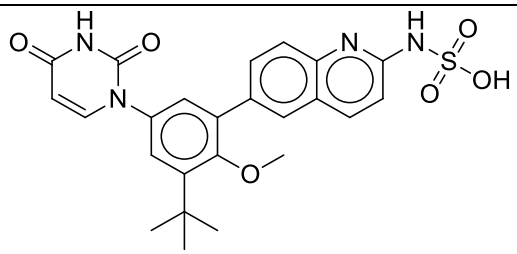
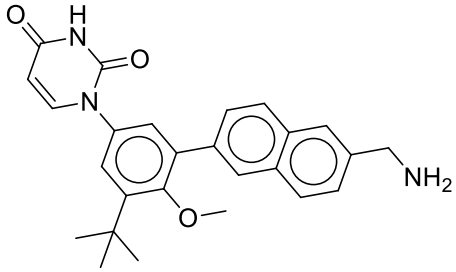
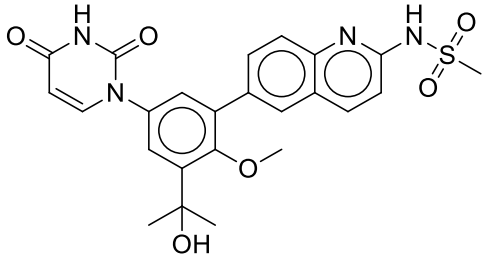
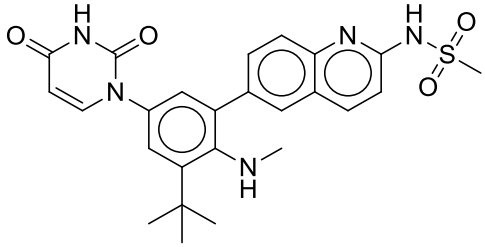
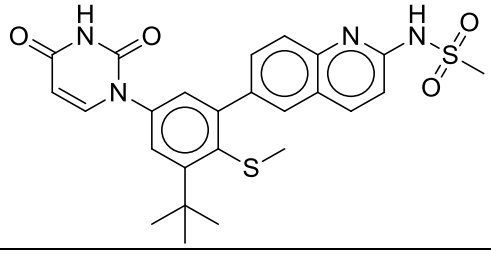
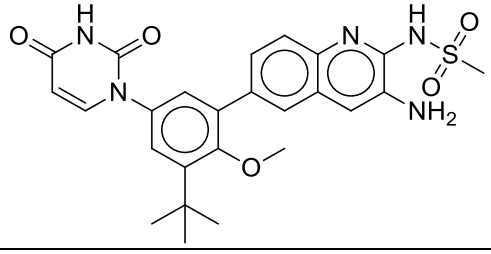
Table S6: Bio-activities of selected designed derivatives of tipranavir for zika virus RNA-dependent RNA polymerase (RdRP) and methyltransferase (MTase)

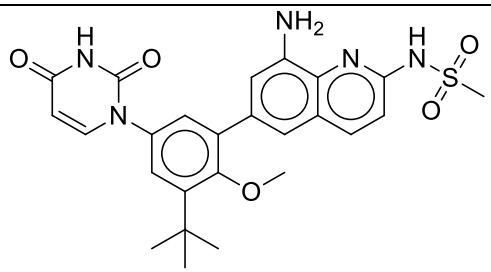
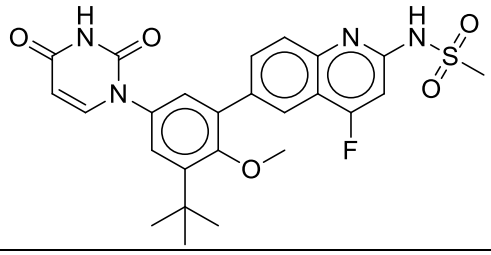
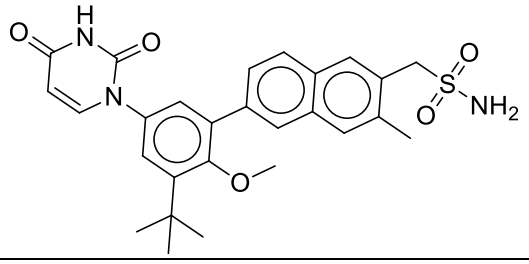
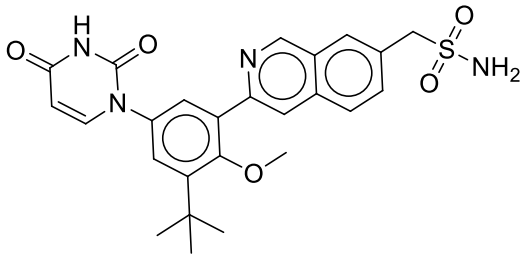
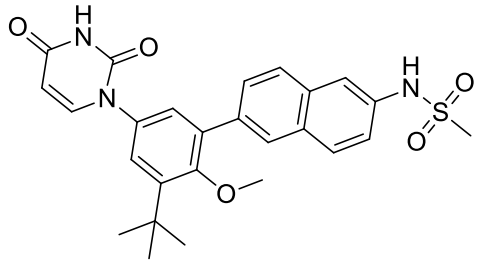
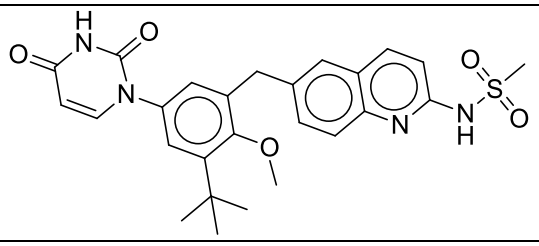
		MTase					**RdRP**				
Code	**ID**	**Average Ki (uM)**	**LE**	**Lescale**	**LELP**	**FQ**	**Average Ki (uM)**	**LE**	**Lescale**	**LELP**	**FQ**
1	1t	0.076200557±0.00000	0.230952	0.228931	25.90274	1.008832	4.197812828±2.986329	0.178571	0.228931	33.50088	0.780024
76	2t	0.070737757±0.010926	0.221591	0.214087	30.03282	1.035049	4.856901424±5.481093	0.171591	0.214087	38.78411	0.801499
457	3t	0.06731572±0.005923	0.238415	0.236647	23.18608	1.007471	1.005139848±0.076595	0.19939	0.236647	27.72402	0.842565
649	4t	0.076200557±0.00000	0.225581	0.221413	20.19182	1.018829	1.742091203±0.14683	0.182558	0.221413	24.95041	0.824516
718	5t	0.064354107±0.00000	0.222727	0.214087	21.6471	1.040357	3.766283534±3.738882	0.173295	0.214087	27.82185	0.809461
1068	6t	0.07970735±0.007014	0.230357	0.228931	23.01774	1.006232	2.971291112±1.857437	0.181548	0.228931	29.20611	0.793025
1368	7t	0.090227728±0.00000	0.218182	0.214087	23.43092	1.019125	2.442500365±0.205863	0.173864	0.214087	29.4035	0.812115
2007	8t	0.070277332±0.00684	0.226744	0.221413	25.04585	1.024080	4.533004358±4.381233	0.174419	0.221413	32.5596	0.787754
2086	9t	0.056981919±0.022164	0.230233	0.221413	27.81188	1.039835	3.22427047±1.983123	0.177326	0.221413	36.10985	0.800883
2517	10t	0.090227728±0.00000	0.223256	0.221413	25.09767	1.008325	3.503956799±2.96929	0.176744	0.221413	31.70232	0.798257
2591	11t	0.086720935±0.007014	0.229167	0.228931	26.36684	1.001031	1.631602639±0.363694	0.188095	0.228931	32.12415	0.821626
2769	12t	0.090227728±0.00000	0.228571	0.228931	22.02988	0.998431	1.544673432±0.223054	0.18869	0.228931	26.68603	0.824226
2931	13t	0.059812156±0.010926	0.22907	0.221413	26.49368	1.034584	4.307728838±5.796847	0.181395	0.221413	33.45676	0.819264
3154	14t	0.073238945±0.005923	0.226163	0.221413	25.03418	1.021454	1.891002645±0.534067	0.181977	0.221413	31.11277	0.82189
3217	15t	0.076200557±0.00000	0.230952	0.228931	22.54751	1.008832	2.321583299±1.673179	0.185714	0.228931	28.03985	0.811225
3377	16t	0.067471279±0.026244	0.227907	0.221413	27.13607	1.029332	1.492310966±0.280452	0.184884	0.221413	33.45075	0.835019
3683	17t	0.076200557±0.000000	0.220455	0.214087	31.10664	1.029741	2.092295784±0.393208	0.176136	0.214087	38.93347	0.822731
3828	18t	0.083214142±0.008099	0.219318	0.214087	30.34404	1.024433	5.017245467±5.391989	0.170455	0.214087	39.04267	0.796191
5262	19t	0.090227728±0.000000	0.228571	0.228931	18.81863	0.998431	4.175242544±4.590815	0.181548	0.228931	23.69296	0.793025
5634	20t	0.076200557±0.000000	0.220455	0.214087	24.99381	1.029741	2.564379529±0.370302	0.173295	0.214087	31.79541	0.809461
Tipranavir	21t	0.090227728±0.000000	0.228571	0.228931	32.04906	0.998431	3.605182303±2.139293	0.178571	0.228931	41.0228	0.780024

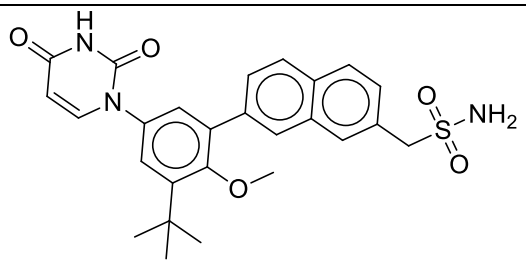
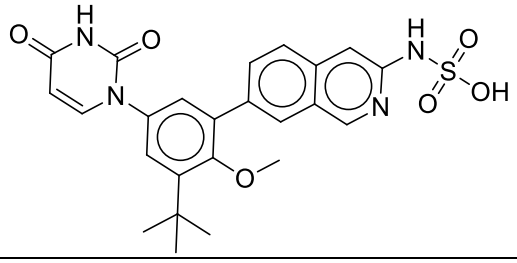
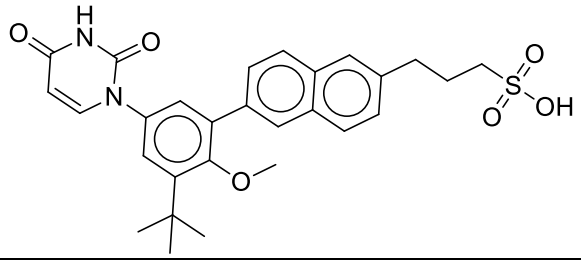
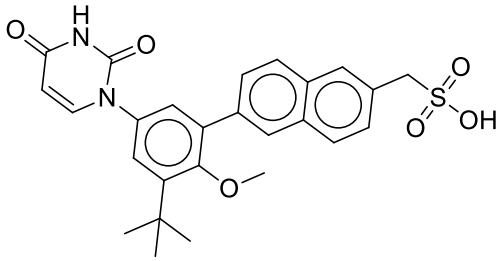
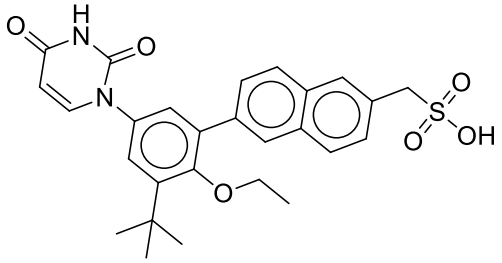
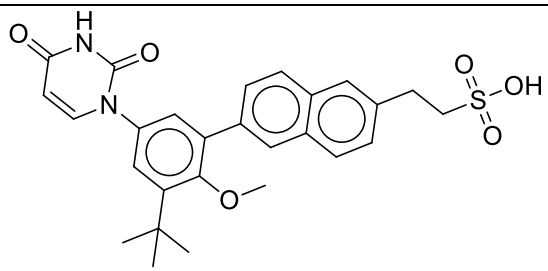
1510	22t	0.030192974±0.002938	0.244048	0.228931	22.07274	1.066033	NA	NA	NA	NA	NA
6675	23t	0.032737746±0.000000	0.242857	0.228931	19.38094	1.060833	NA	NA	NA	NA	NA
5719	24t	0.040548134±0.003568	0.223889	0.20695	23.04893	1.081848	NA	NA	NA	NA	NA
2541	25t	0.040548134±0.003568	0.239881	0.228931	21.46398	1.047833	NA	NA	NA	NA	NA
170	26t	0.045899983±0.000000	0.232558	0.221413	26.66258	1.050339	NA	NA	NA	NA	NA
1186		0.054349355±0.000000	0.230233	0.221413	26.42155	1.039835	NA	NA	NA	NA	NA
1493		0.054349355±0.000000	0.225000	0.214087	25.25467	1.050972	NA	NA	NA	NA	NA
4435		NA	NA	NA	NA	NA	1.533260062±0.124003	0.18869	0.228931	22.79606	0.824226
264		NA	NA	NA	NA	NA	1.606674899±0.221526	0.183721	0.221413	27.51782	0.829768

Table S7: Name and structures of selected designed derivatives of dasabuvir as potential inhibitors of zika virus RNA-dependent RNA polymerase (RdRP) and/or methyltransferase (MTase)

Code	ID	Structure	Name
980	1d		N-{6-[3-tert-butyl-5-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-methoxyphenyl]quinolin-2-yl}aminosulfonamide
1067	2d		N-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide
2043	3d		N-(6-(3-(tert-butyl)-5-(2-imino-4-oxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide
3515	4d		N-(6-(3-(tert-butyl)-5-(4-imino-2-oxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide

4794	5d		(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)sulfamic acid
5007	6d		1-(3-(6-(aminomethyl)naphthalen-2-yl)-5-(tert-butyl)-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione
5553	7d		N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(2-hydroxypropan-2-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide
5963	8d		N-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-(methylamino)phenyl)quinolin-2-yl)methanesulfonamide
6061	9d		N-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-(methylthio)phenyl)quinolin-2-yl)methanesulfonamide
6063	10d		N-(3-amino-6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide

6253	11d		N-(8-amino-6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide
6255	12d		N-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-4-fluoroquinolin-2-yl)methanesulfonamide
6339	13d		(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-3-methylnaphthalen-2-yl)methanesulfonamide
6416	14d		(3-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)isoquinolin-7-yl)methanesulfonamide
Dasa buvir	15d		N-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide
5095	16d		N-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxybenzyl)quinolin-2-yl)methanesulfonamide

5005	17d		(7-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide
2089	18d		(7-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)isoquinolin-3-yl)sulfamic acid
3758	19d		3-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)propane-1-sulfonic acid
3643	20d		(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonic acid
3741	21d		(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-ethoxyphenyl)naphthalen-2-yl)methanesulfonic acid
3742	22d		2-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)ethanesulfonic acid

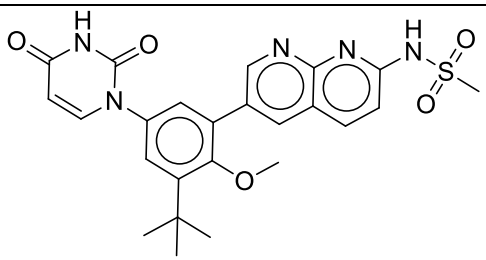
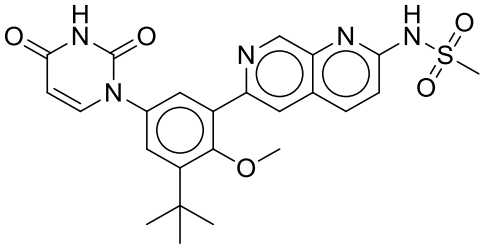
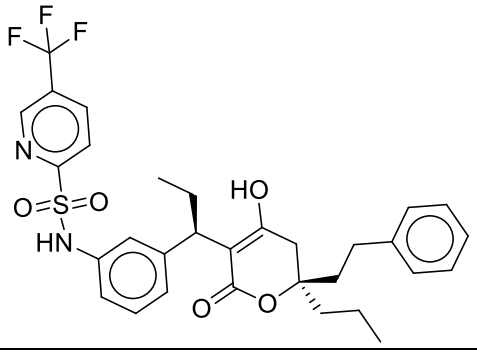
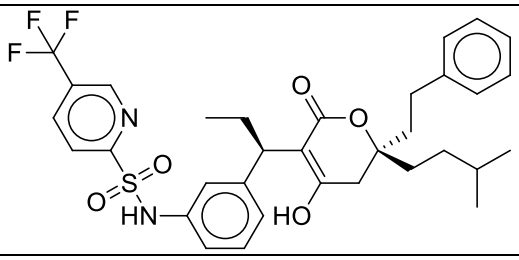
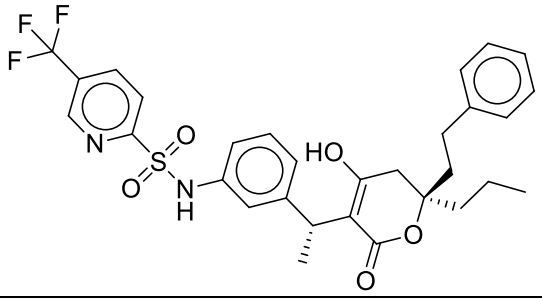
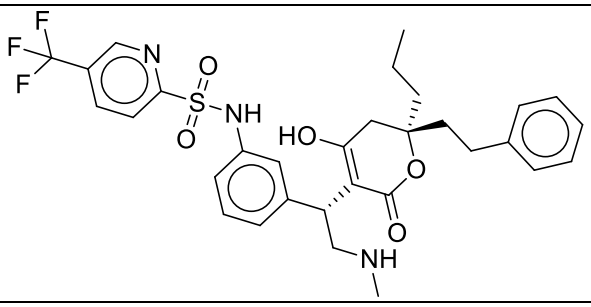
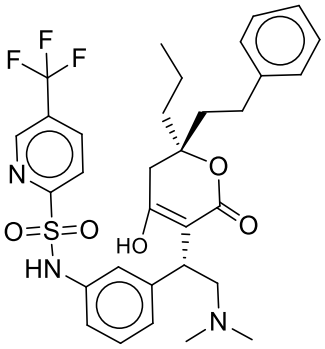
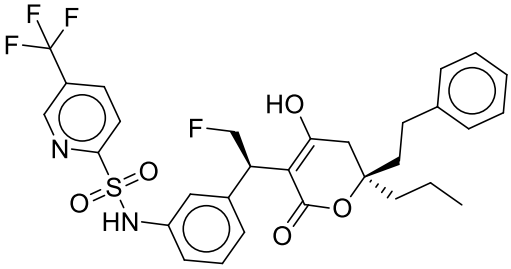
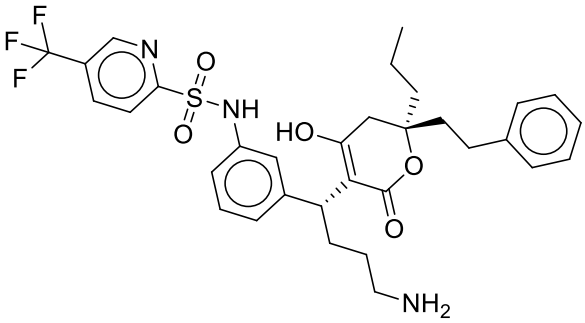
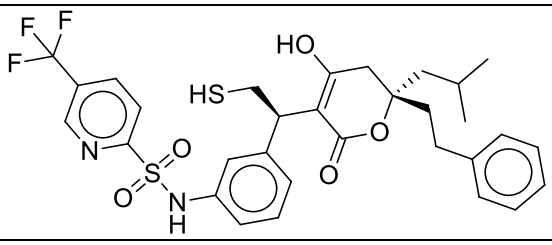
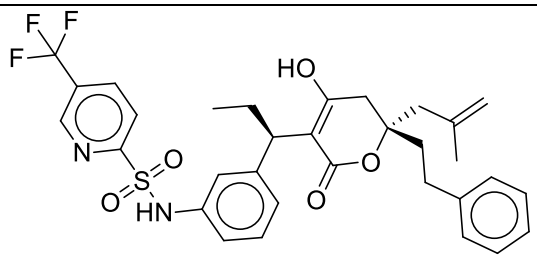
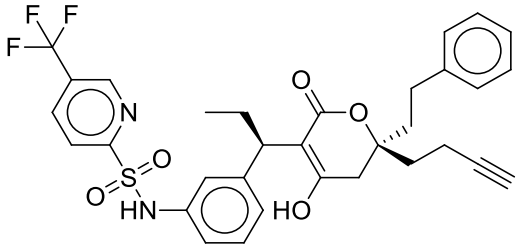
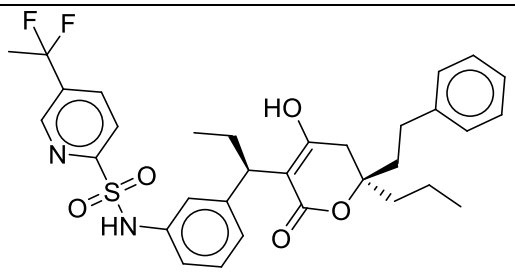
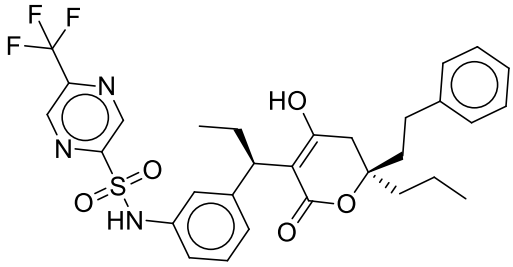
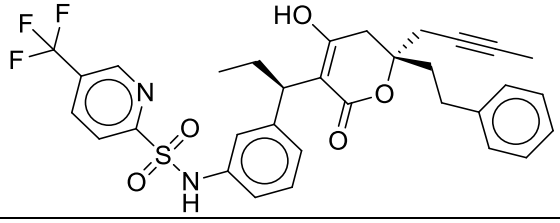
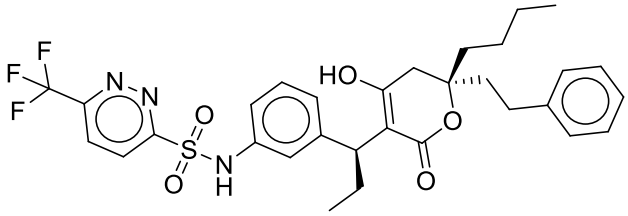
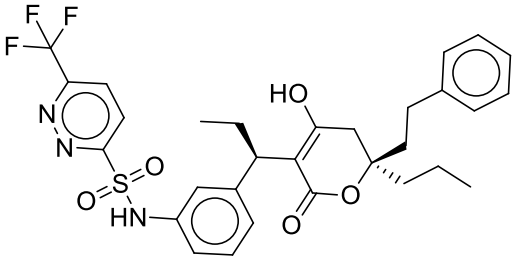
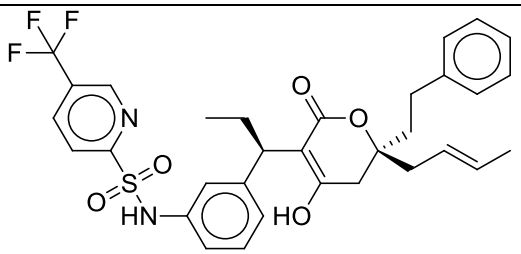
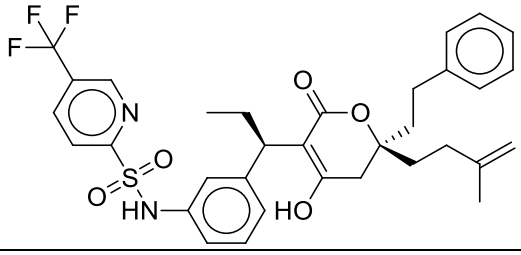
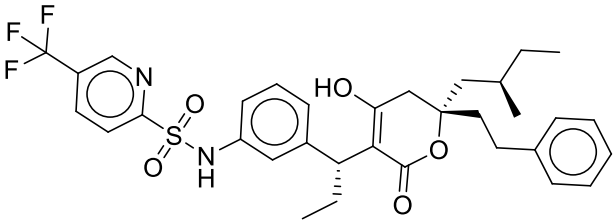
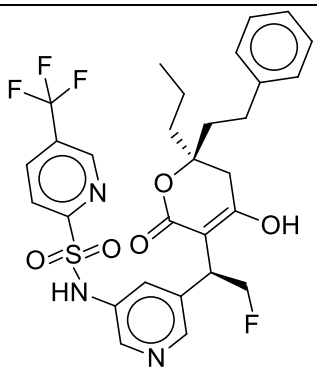
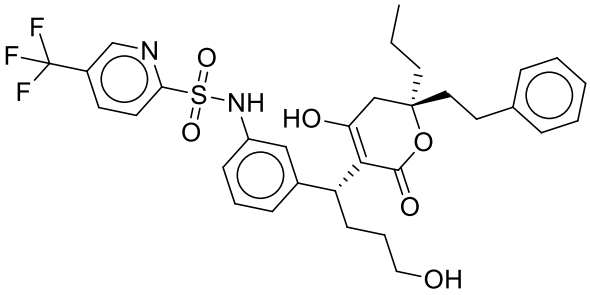
6423			N-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-1,8-naphthyridin-2-yl)methanesulfonamide
5956			N-(6-(3-(tert-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-1,7-naphthyridin-2-yl)methanesulfonamide

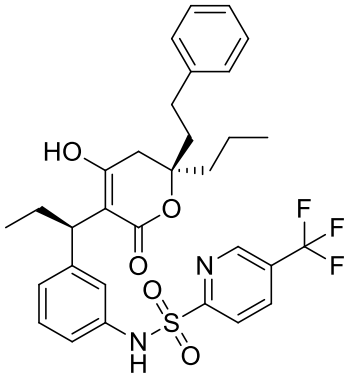
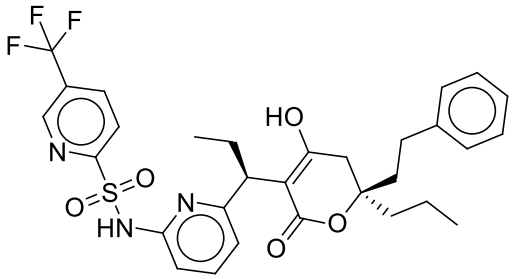
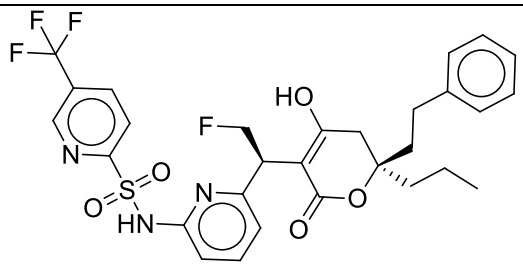
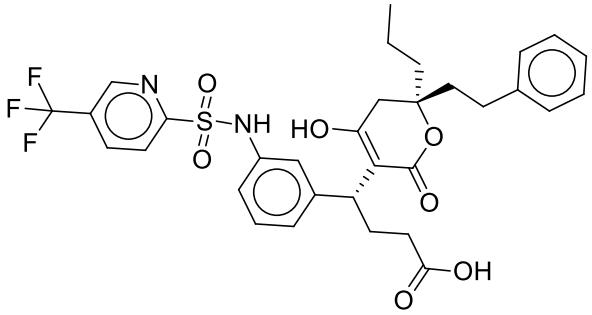
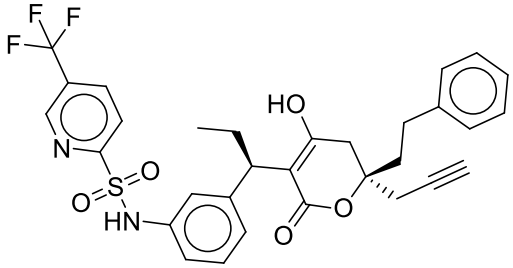
Table S8: Name and structures of selected designed derivatives of tipranavir as potential inhibitors of zika virus RNA-dependent RNA polymerase (RdRP) and/or methyltransferase (MTase)

Codes	ID	Smiles	Name
1	1t		N-(3-((R)-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
76	2t		N-(3-((R)-1-((R)-4-hydroxy-6-isopentyl-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
457	3t		N-(3-((R)-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)ethyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide

649	4t		N-(3-((R)-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-2-(methylamino)ethyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
718	5t		N-(3-((R)-2-(dimethylamino)-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)ethyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
1068	6t		N-(3-((R)-2-fluoro-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)ethyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
1368	7t		N-(3-((R)-4-amino-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)butyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
2007	8t		N-(3-((R)-1-((S)-4-hydroxy-6-isobutyl-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)-2-mercaptoethyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide

2086	9t		N-(3-((R)-1-((S)-4-hydroxy-6-(2-methylallyl)-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
2517	10t		N-(3-((R)-1-((R)-6-(but-3-yn-1-yl)-4-hydroxy-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
2591	11t		5-(1,1-difluoroethyl)-N-(3-((R)-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)pyridine-2-sulfonamide
2769	12t		N-(3-((R)-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyrazine-2-sulfonamide
2931	13t		N-(3-((R)-1-((S)-6-(but-2-yn-1-yl)-4-hydroxy-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
3154	14t		N-(3-((S)-1-((S)-6-butyl-4-hydroxy-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-6-(trifluoromethyl)pyridazine-3-sulfonamide

3217	15t		N-(3-((R)-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-6-(trifluoromethyl)pyridazine-3-sulfonamide
3377	16t		N-(3-((R)-1-((S)-6-((E)-but-2-en-1-yl)-4-hydroxy-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
3683	17t		N-(3-((R)-1-((R)-4-hydroxy-6-(3-methylbut-3-en-1-yl)-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
3828	18t		N-(3-((R)-1-((S)-4-hydroxy-6-((R)-2-methylbutyl)-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
5262	19t		N-(5-((S)-2-fluoro-1-((S)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)ethyl)pyridin-3-yl)-5-(trifluoromethyl)pyridine-2-sulfonamide
5634	20t		N-(3-((R)-4-hydroxy-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)butyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide

Tipranavir	21t		*N*-[3-[(1*R*)-1-[(2*R*)-4-hydroxy-6-oxo-2-(2-phenylethyl)-2-propyl-3*H*-pyran-5-yl]propyl]phenyl]-5-(trifluoromethyl)pyridine-2-sulfonamide Obtained from pubchem N-(3-((R)-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide Obtained with ChemDraw
1510	22t		N-(6-((S)-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)propyl)pyridin-2-yl)-5-(trifluoromethyl)pyridine-2-sulfonamide
6675	23t		N-(6-((S)-2-fluoro-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)ethyl)pyridin-2-yl)-5-(trifluoromethyl)pyridine-2-sulfonamide
5719	24t		(R)-4-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-4-(3-(5-(trifluoromethyl)pyridine-2-sulfonamido)phenyl)butanoic acid
2541	25t		N-(3-((R)-1-((S)-4-hydroxy-2-oxo-6-phenethyl-6-(prop-2-yn-1-yl)-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide

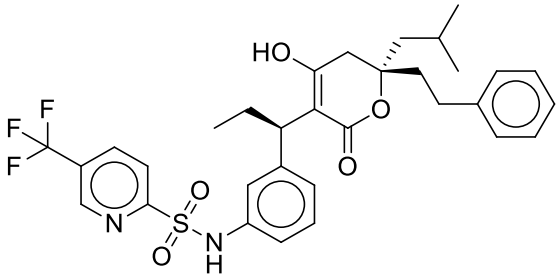
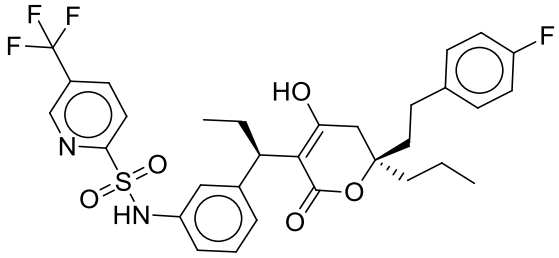
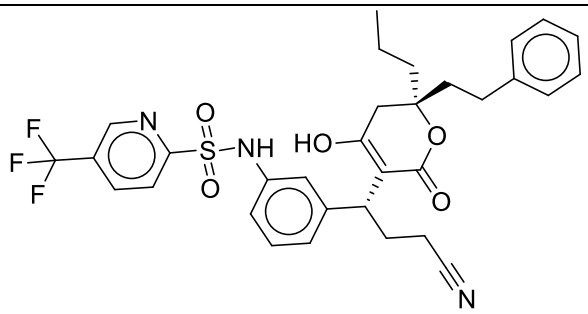
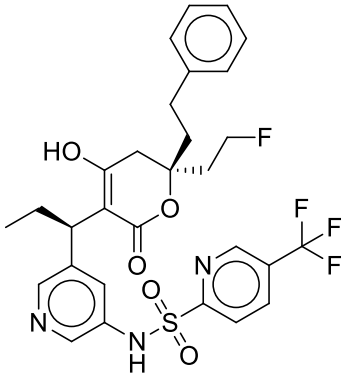
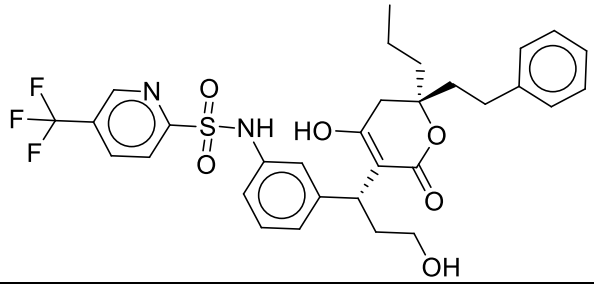
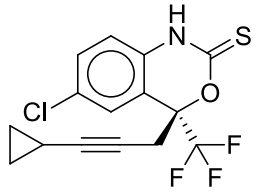
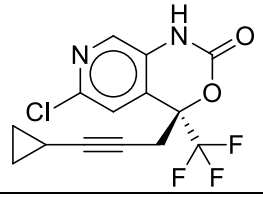
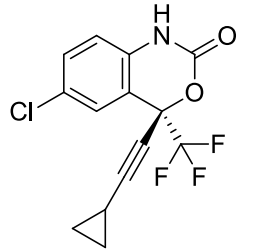
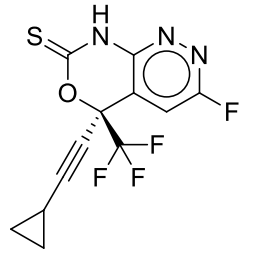
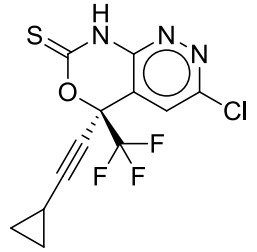
170	26t		N-(3-((R)-1-((S)-4-hydroxy-6-isobutyl-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
1186	27t		N-(3-((R)-1-((R)-6-(4-fluorophenethyl)-4-hydroxy-2-oxo-6-propyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
1493	28t		N-(3-((R)-3-cyano-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide
4435	29t		N-(5-((R)-1-((R)-6-(2-fluoroethyl)-4-hydroxy-2-oxo-6-phenethyl-5,6-dihydro-2H-pyran-3-yl)propyl)pyridin-3-yl)-5-(trifluoromethyl)pyridine-2-sulfonamide
264	30t		N-(3-((R)-3-hydroxy-1-((R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)propyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide

Table S9: Name and structures of selected designed derivatives of efavirenz as potential inhibitors of zika virus RNA-dependent RNA polymerase (RdRP) or methyltransferase (MTase)

Code	ID	Smiles	Name
1501	1e		(S)-6-chloro-4-(3-cyclopropylprop-2-yn-1-yl)-4-(trifluoromethyl)-1H-benzo[d][1,3]oxazine-2(4H)-thione
1436	2e		(S)-6-chloro-4-(3-cyclopropylprop-2-yn-1-yl)-4-(trifluoromethyl)-1H-pyrido[3,4-d][1,3]oxazin-2(4H)-one
Efavirenz	3e		(S)-6-chloro-4-(cyclopropylethynyl)-4-(trifluoromethyl)-1H-benzo[d][1,3]oxazin-2(4H)-one
4403	4e		(S)-5-(cyclopropylethynyl)-3-fluoro-5-(trifluoromethyl)-5H-pyridazino[3,4-d][1,3]oxazine-7(8H)-thione
4327	5e		(S)-3-chloro-5-(cyclopropylethynyl)-5-(trifluoromethyl)-5H-pyridazino[3,4-d][1,3]oxazine-7(8H)-thione

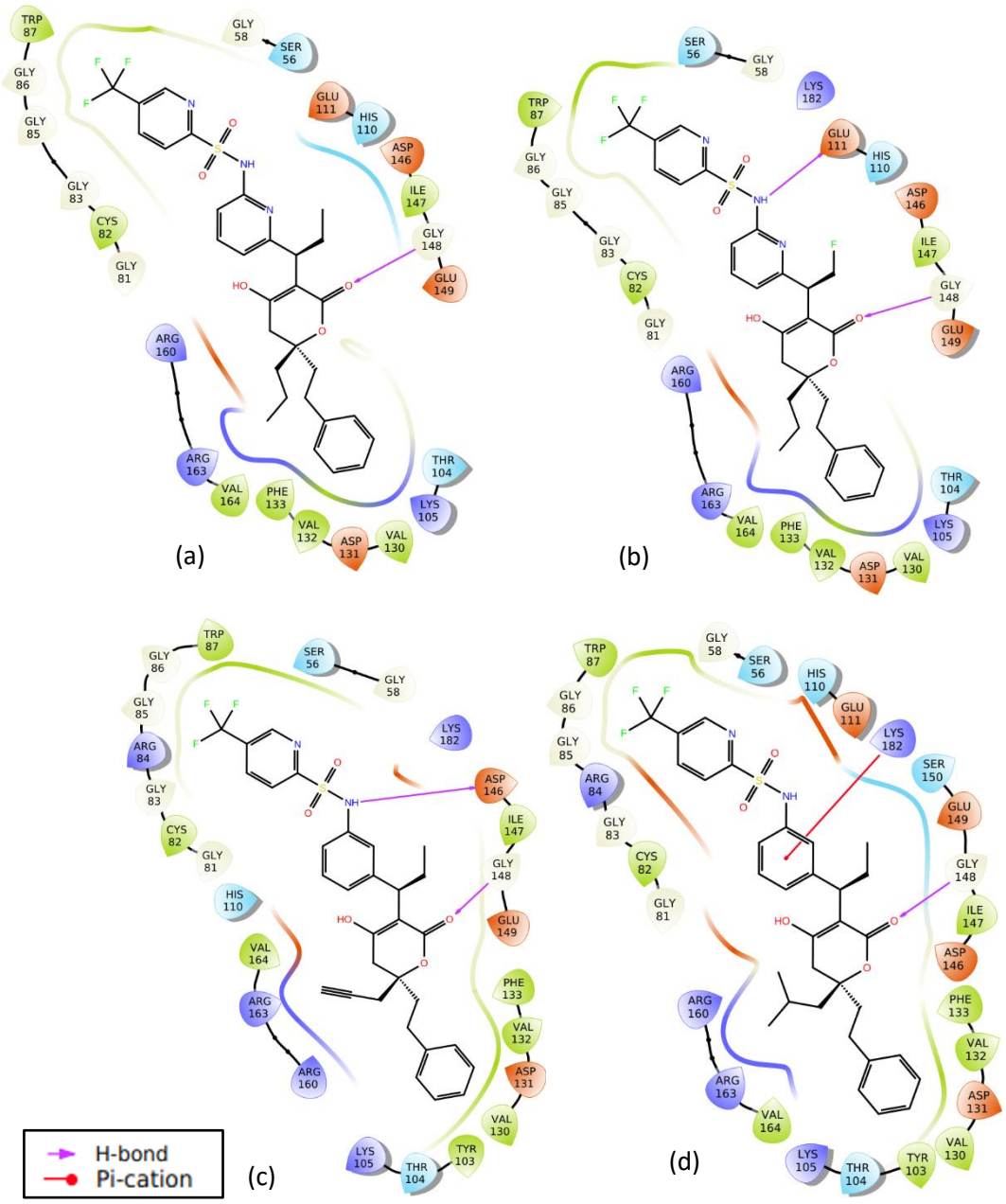


Figure S2: Molecular interactions of **22t** (a), **23t** (b), **25t** (c) and **26t** (d) with zika virus NS5-methyltransferase.

Table S10: Drug-likeness and pharmacokinetic parameters of derivatives of dasabuvir with high GI absorption

ID	MW	#Rotatable bonds	#H-bond acceptors	#H-bond donors	TPSA	Consensus Log P	GIA	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski #violations	Bioavailability Score	PAINS #alerts	Synthetic Accessibility
23d	507.6	7	6	2	118.64	3.72	High	No	No	Yes	Yes	No	Yes	1	0.55	0	3.59
24d	492.59	6	5	1	106.61	4.25	High	No	No	Yes	Yes	No	Yes	0	0.55	0	3.57
6d	429.51	5	4	2	90.11	3.94	High	Yes	No	No	Yes	No	Yes	0	0.55	0	3.26
15d	493.57	6	5	2	118.64	3.8	Low	No	No	Yes	Yes	No	Yes	0	0.55	0	3.46

Derivatives of dasabuvir (**23d**, **24d** and **6d**) that showed high GI absorption, better binding energies and Ki compared with dasabuvir. This dasabuvir derivatives show NO to BBB just like the parent compound. The derivatives of efavirenz (**1e, 2e, 4e** and **5e**) showed high GI absorption like the parent compound (efavirenz) with only 1e, 2e showing YES for BBB.

Table S11: Predicted toxicity of designed derivatives of dasabuvir with high GI absorption

ID	Formula	AMES toxicity	Max. tolerated dose (human) (Log mg/kg/day)	hERG I inhibitor	hERG II inhibitor	Oral rat acute Toxicity (LD_{50}) (mol/kg)	Oral rat chronic toxicity (LOAEL) (Log mg/kg_bw/day)	Hepato toxicity	Skin Sensitization
23d	$C_{27}H_{29}N_3O_5S$	Yes	0.233	No	Yes	2.932	1.502	Yes	No
24d	$C_{27}H_{28}N_2O_5S$	Yes	0.126	No	Yes	3.011	0.796	Yes	No
6d	$C_{26}H_{27}N_3O_3$	Yes	0.375	No	Yes	2.566	1.658	Yes	No
15d	$C_{26}H_{27}N_3O_5S$	No	0.149	No	Yes	3.081	3.139	Yes	No

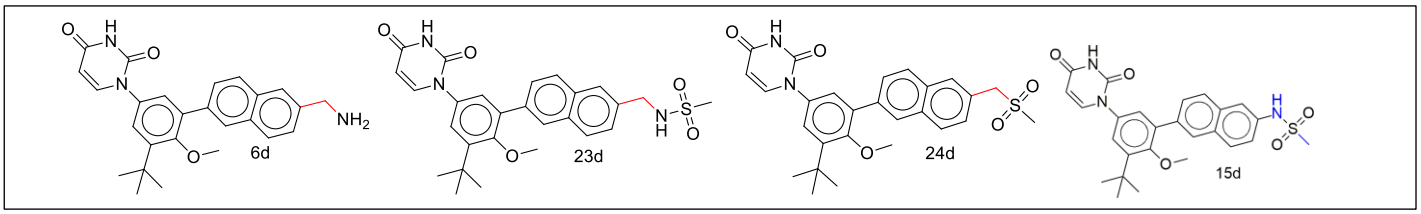


Figure S3: Structural determinant of high Gastrointestinal absorption (GIA) for derivatives of dasabuvir. Compounds **6d**, **23d** and **24d** are compounds with high GIA compared with dasabuvir (**15d**) with low GIA.

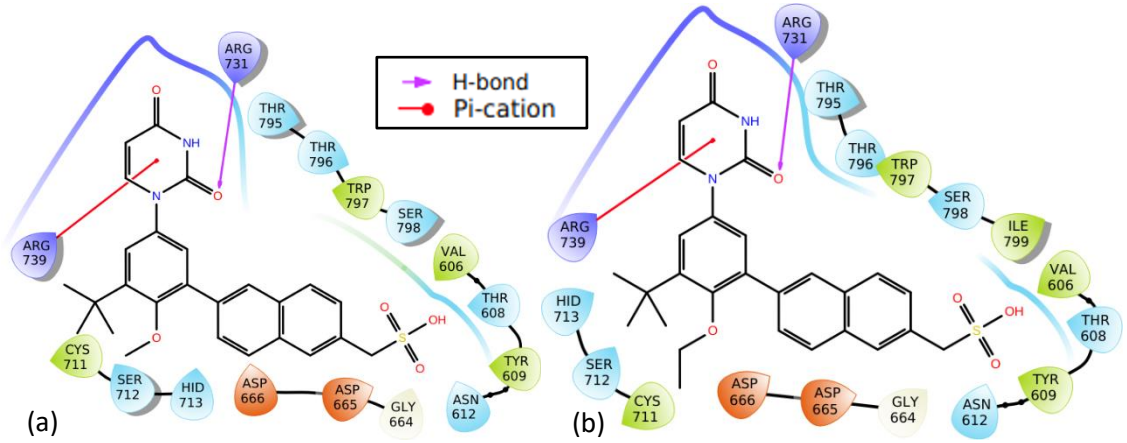


Figure S4: Molecular interactions of designed derivatives of dasabuvir (**20d** and **21d**) with zika virus RNA-dependent RNA polymerase. Interactions of **20d** (a) and **21d** (b) with RNA-dependent RNA polymerase

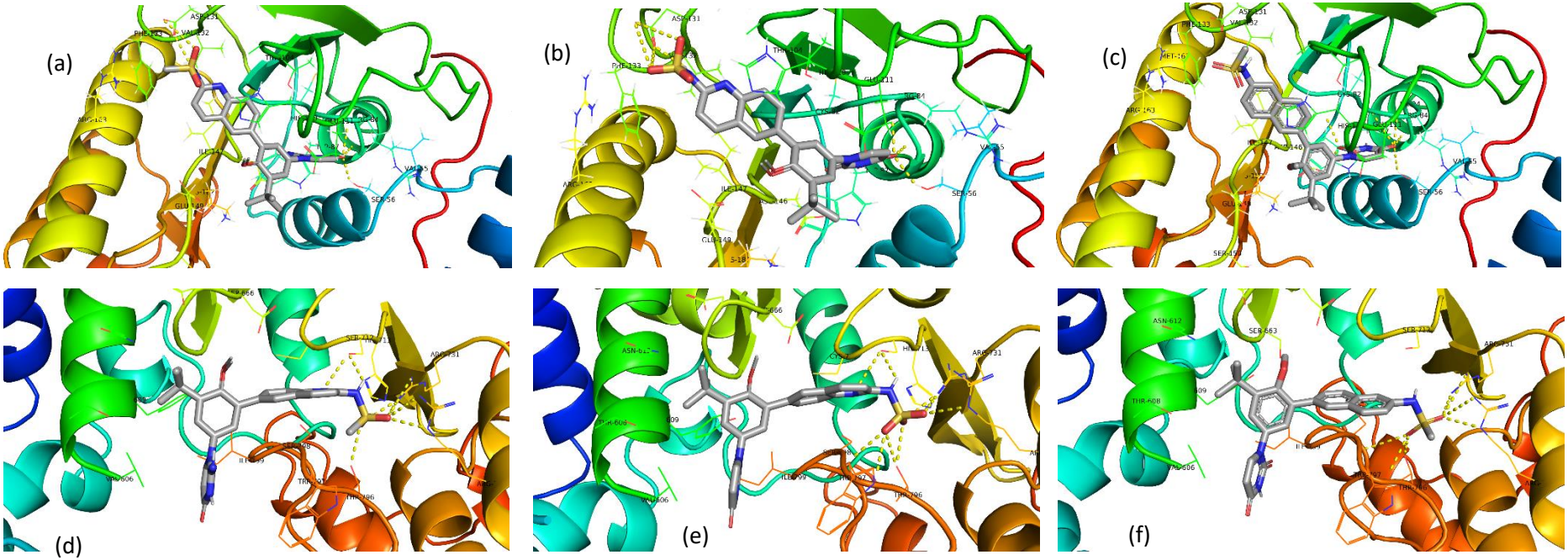


Figure S5: Three-dimensional molecular interactions of two representatives of derivatives of dasabuvir and dasabuvir, **15d** with zika virus methyltransferase and RNA-dependent RNA polymerase. First panel (a-c) is the interactions of **3d**, **5d** and dasabuvir respectively with methyltransferase while the second panel (d-f) is that of interactions with RNA-dependent RNA polymerase respectively.

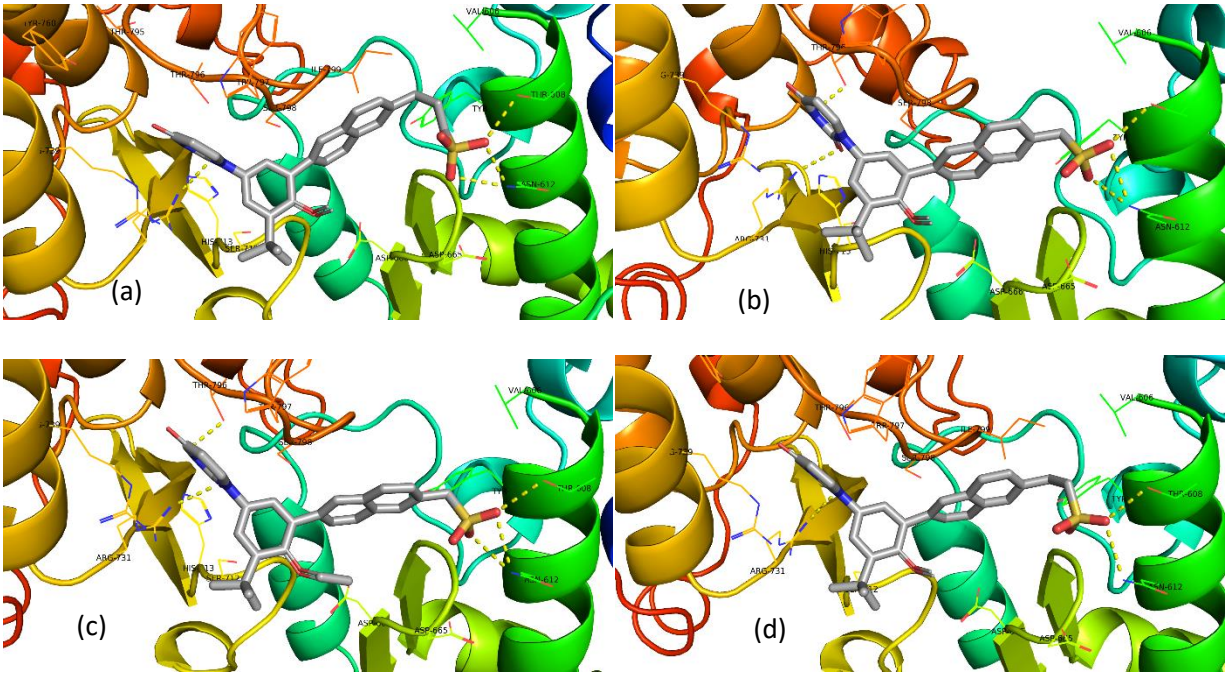


Figure S6: Three-dimensional molecular interactions of **19d, 20d, 21d, 22d** with zika virus RNA-dependent RNA polymerase. First panel (a-b) is the interactions of **19d**, **20d** while the second panel (c-d) is that of interactions 21d and 22d with the RNA-dependent RNA polymerase respectively.

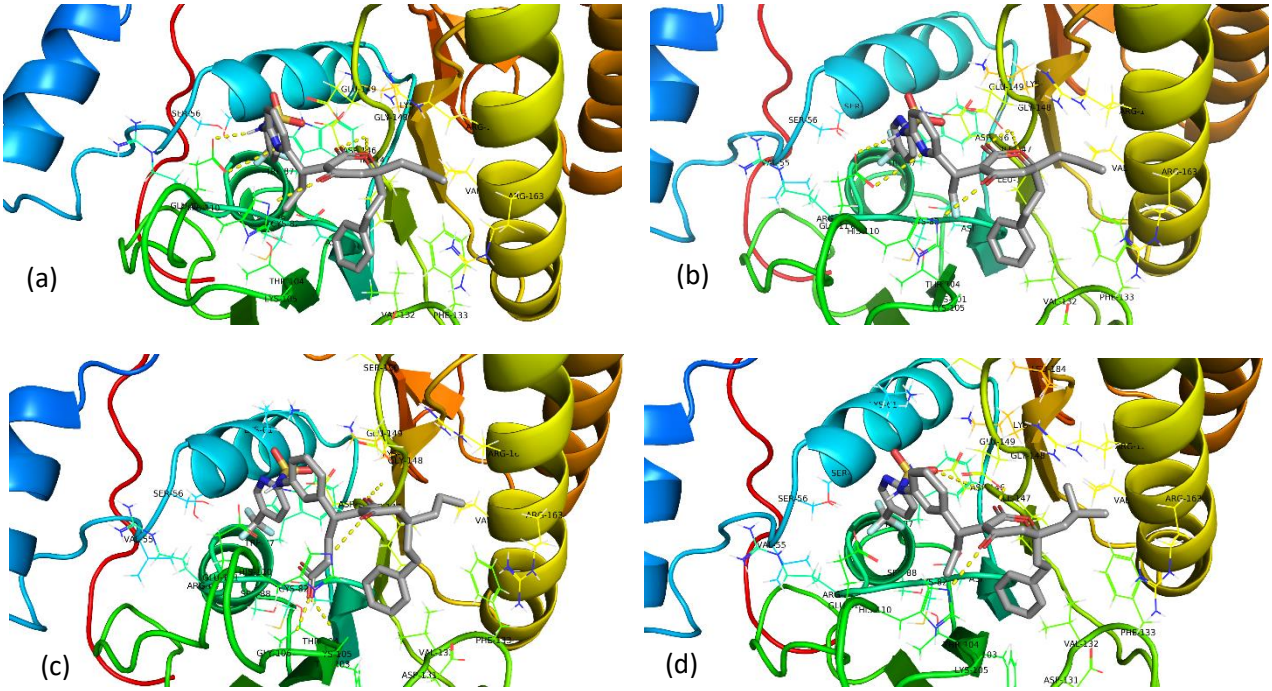


Figure S7: Three-dimensional molecular interactions of **22t, 23t, 24t, 26t** with zika virus methyltransferase. First panel (a-b) is the interactions of **22t**, **23t** while the second panel (c-d) is that of interactions **24t** and **26t** with the methyltransferase respectively.

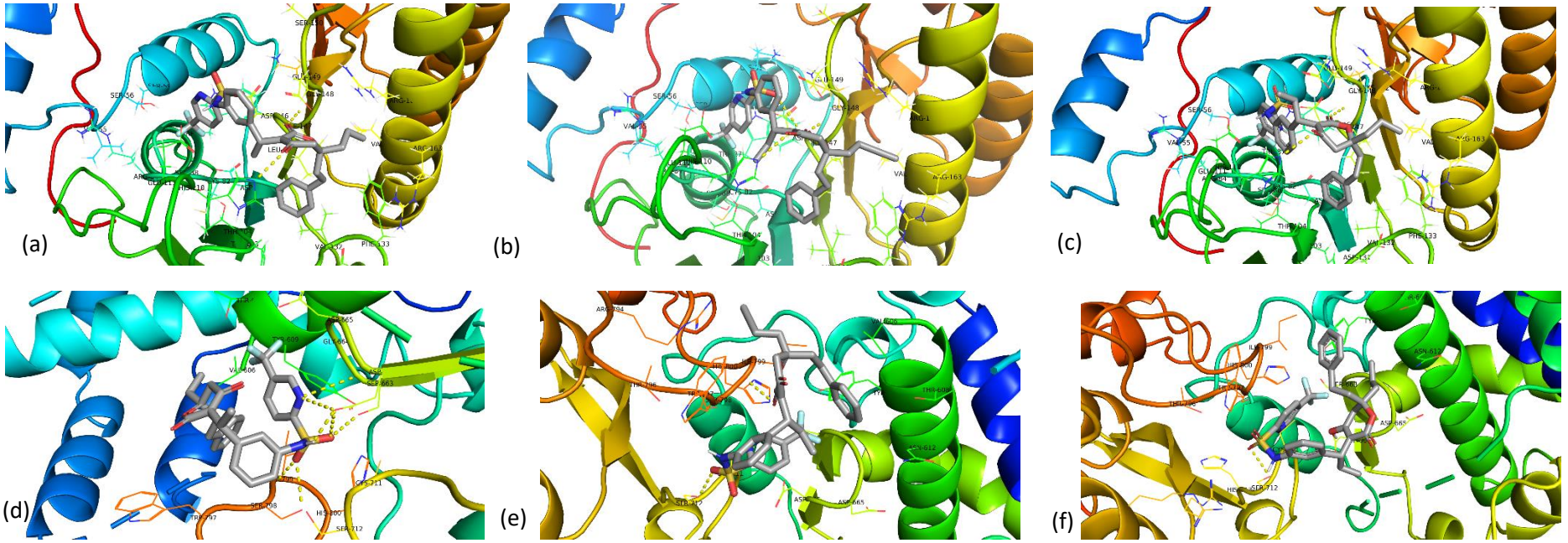


Figure S8: Three-dimensional Molecular interactions of two representatives of derivatives of tipranavir (**3t** and **10t**) and tipranavir, **21t** with zika virus methyltransferase and RNA-dependent RNA polymerase. First panel (a-c) is the interactions of **3t**, **10t** and tipranavir respectively with methyltransferase while the second panel (d-f) is that of interactions with RNA-dependent RNA polymerase respectively