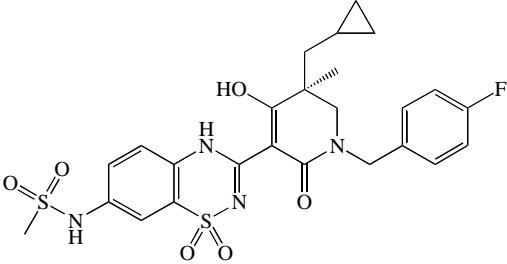
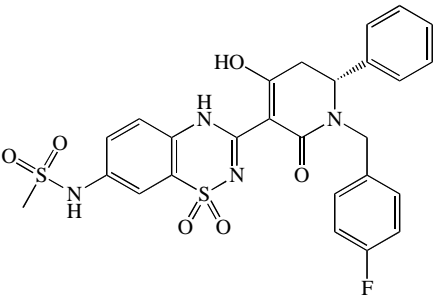
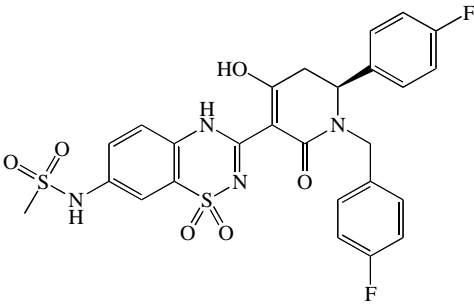
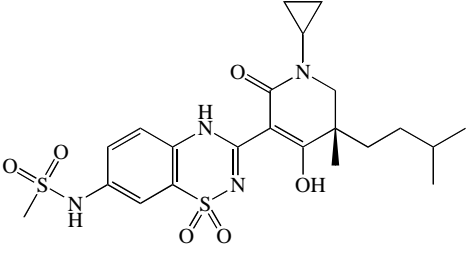
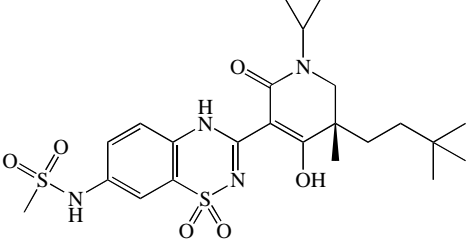
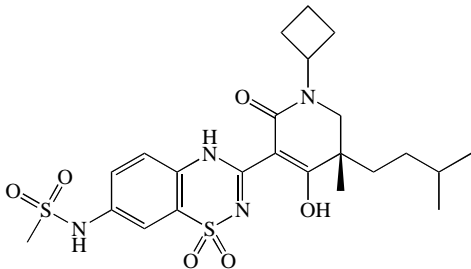
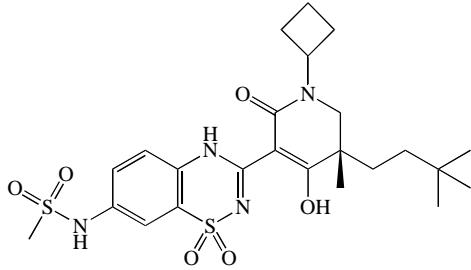
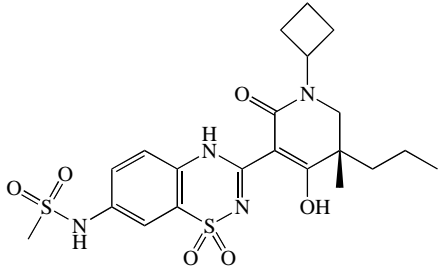
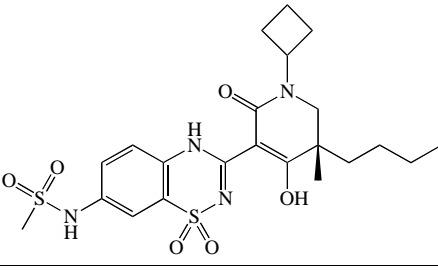
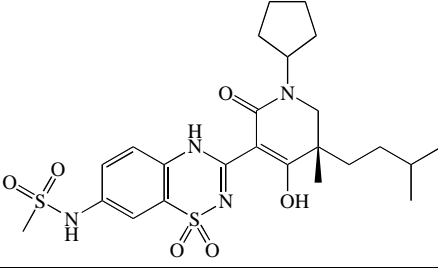
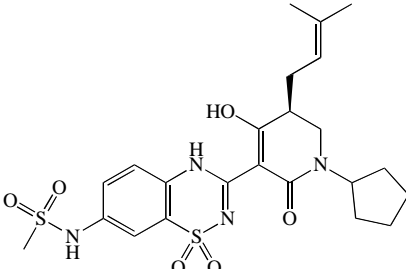


SUPPORTING INFORMATION

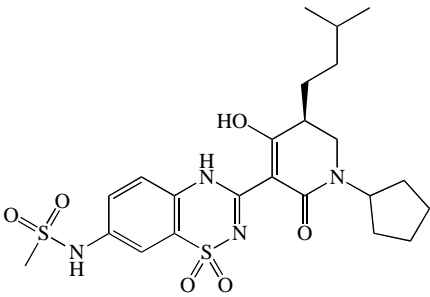
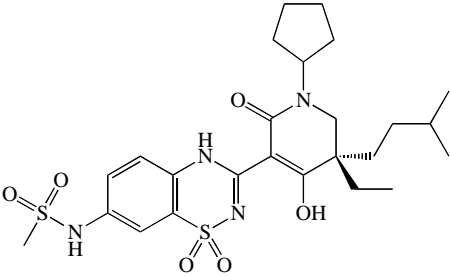
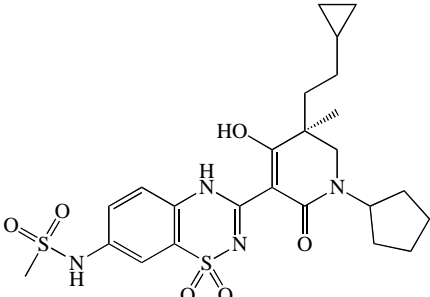
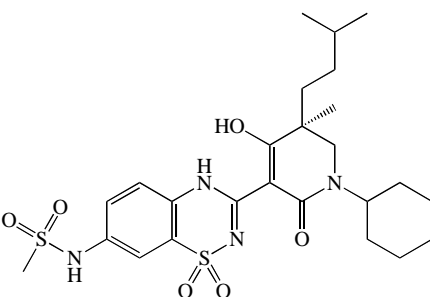
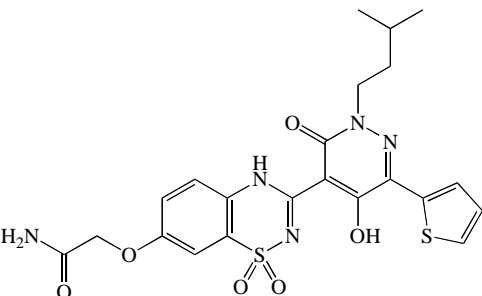
Table S1. The Rest Molecules of Benzothiadiazine Derivatives and Their Binding Affinity IC₅₀ Values

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
5		0.1	1
13		0.17	0.769551
14		0.1	1
16		0.068	1.167491
17		0.075	1.124939

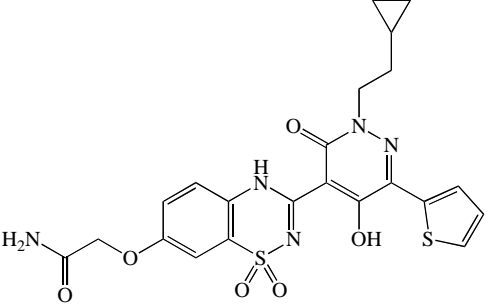
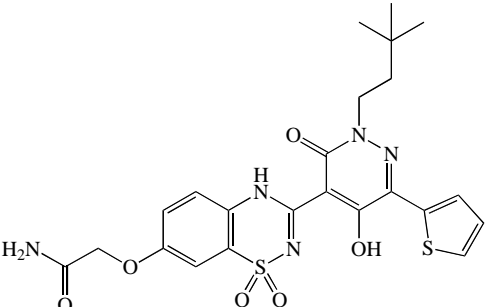
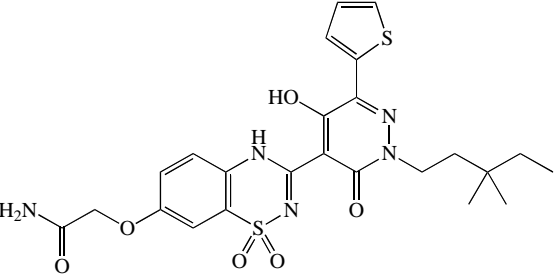
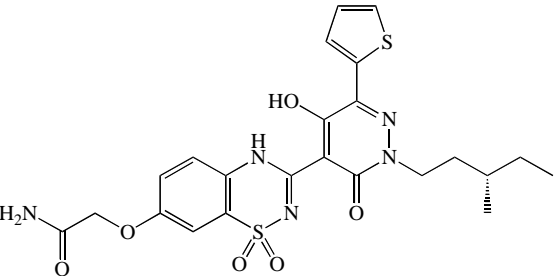
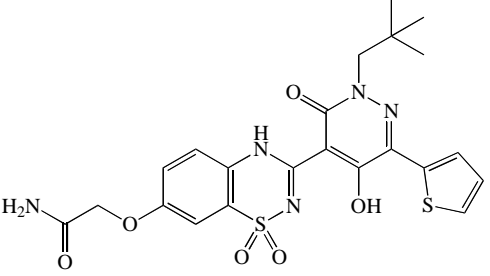
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
18		0.044	1.356547
19*		0.17	0.769551
20		0.11	0.958607
21		0.049	1.309804
22		0.061	1.21467
23*		0.65	0.187087

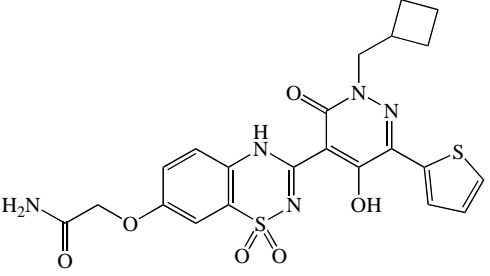
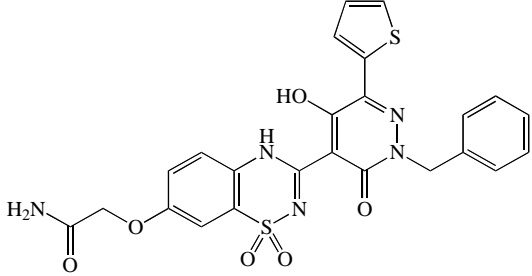
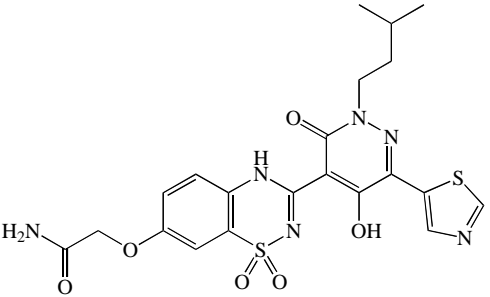
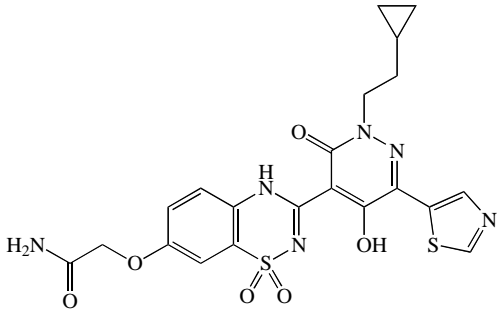
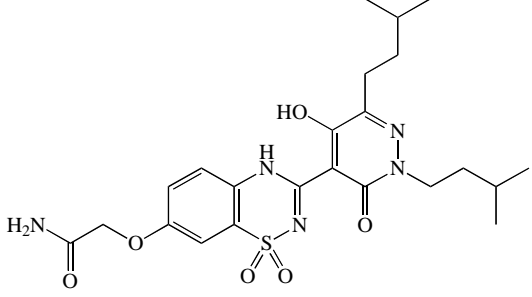
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
24		0.12	0.920819
25		0.048	1.318759
26		0.057	1.244125
27*		0.17	0.769551
28		0.34	0.468521

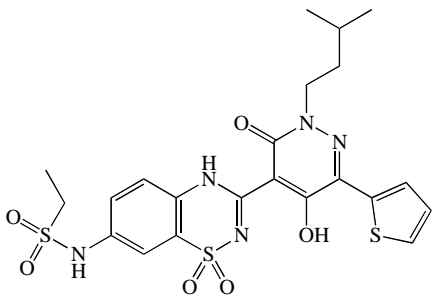
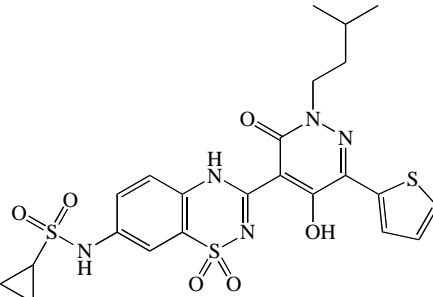
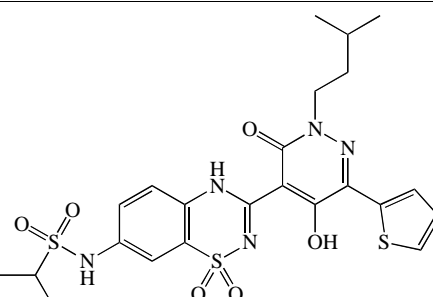
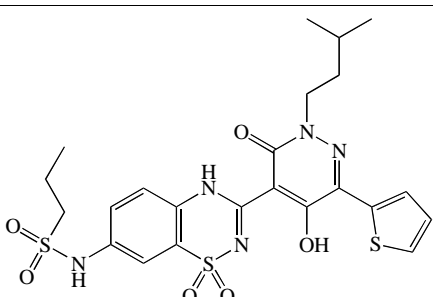
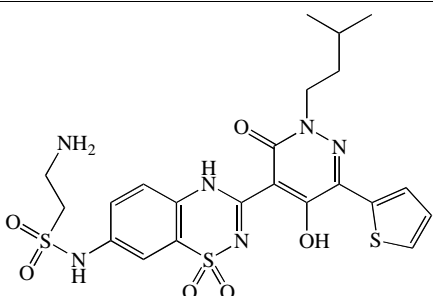
(Table S1). Contd.....

Compound		Genotype-1a NSSB Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
29		0.12	0.920819
30		0.24	0.619789
31*		0.99	0.004365
32		1	0
33		0.84	0.075721

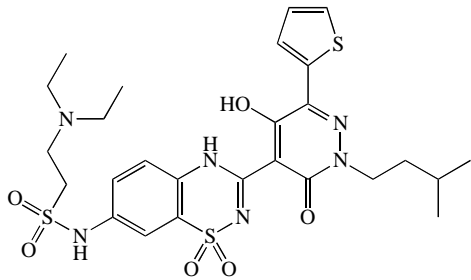
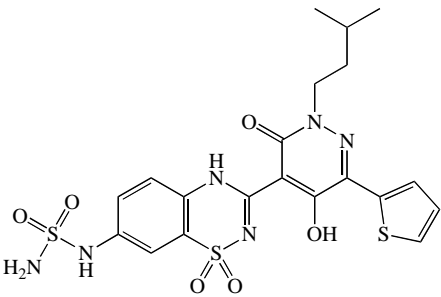
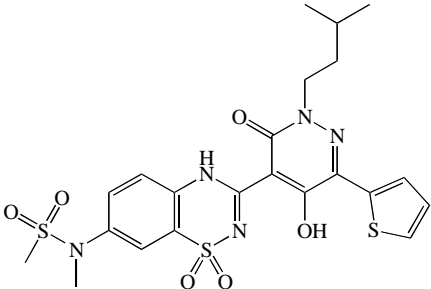
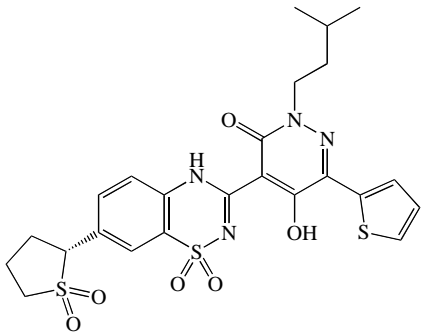
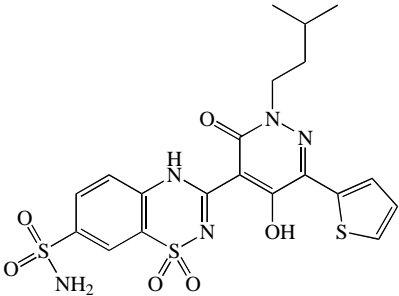
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
34		0.54	0.267606
35*		0.54	0.267606
36		0.15	0.823909
37		0.14	0.853872
38		5.1	-0.70757

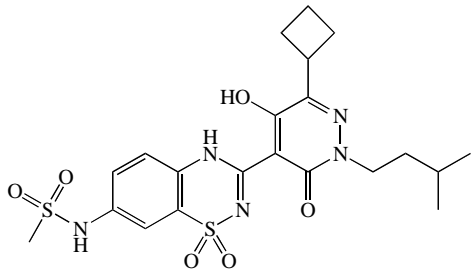
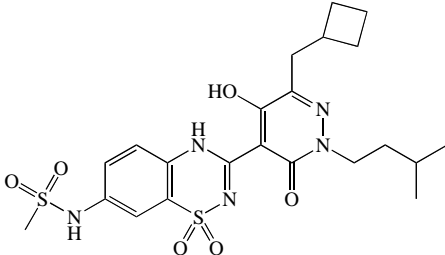
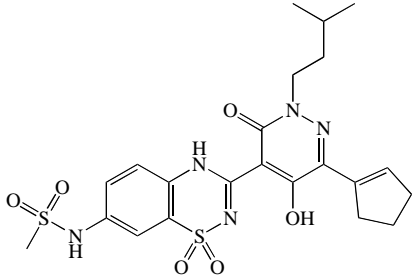
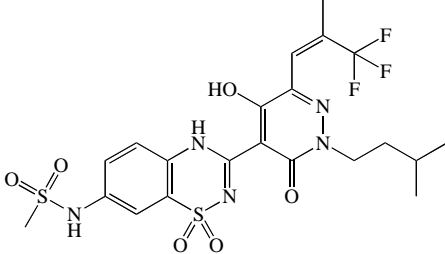
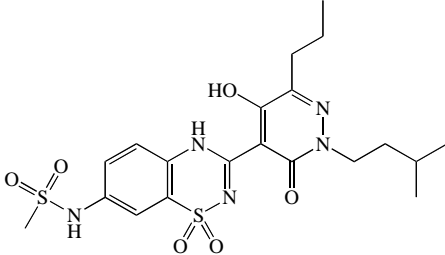
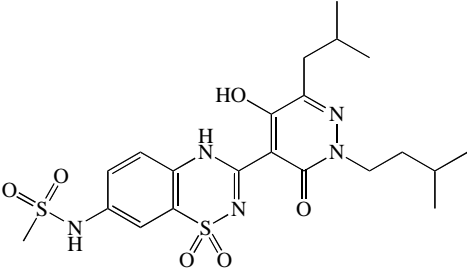
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
39*		0.054	1.267606
40		0.092	1.036212
41		0.16	0.79588
42		0.14	0.853872
43*		0.026	1.585027

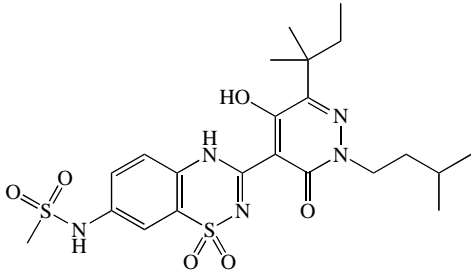
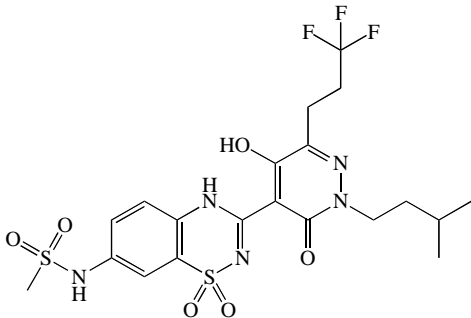
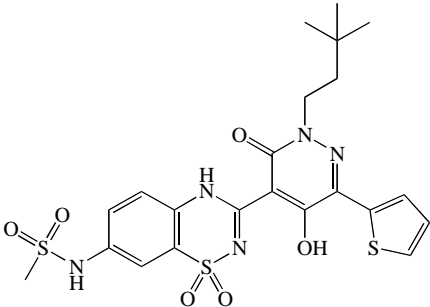
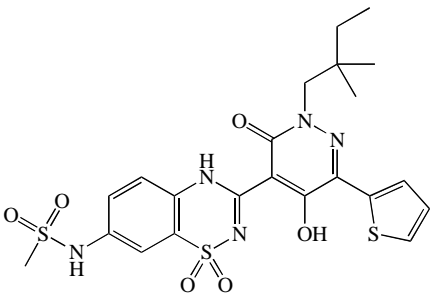
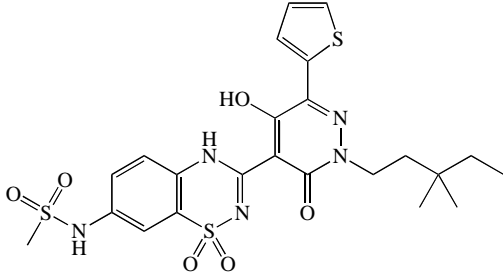
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
44		0.49	0.309804
45		0.028	1.552842
46		0.46	0.337242
47*		0.29	0.537602
48		1.8	-0.25527

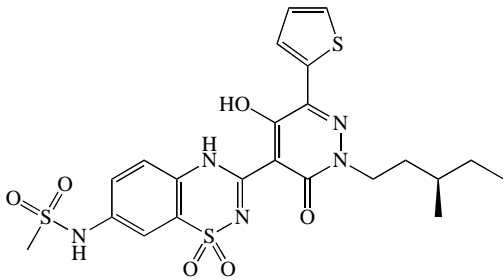
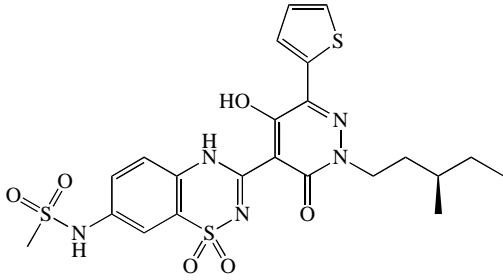
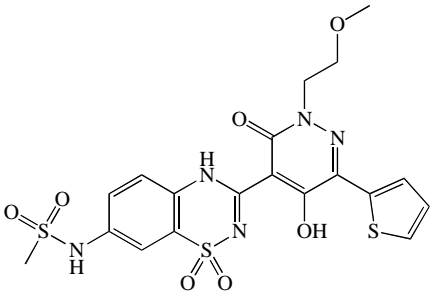
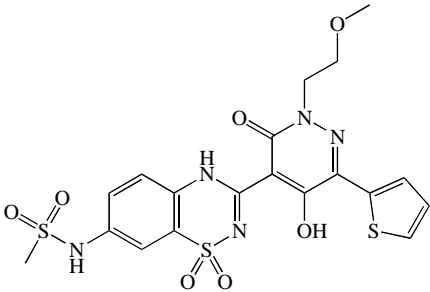
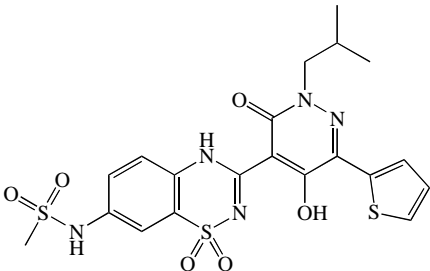
(Table S1). Contd.....

Compound		Genotype-1a NSSB Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
57		0.097	1.013228
58		0.4	0.39794
59*		0.21	0.677781
60		0.3	0.522879
61		0.093	1.031517
62		0.075	1.124939

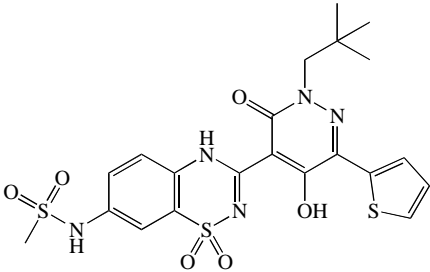
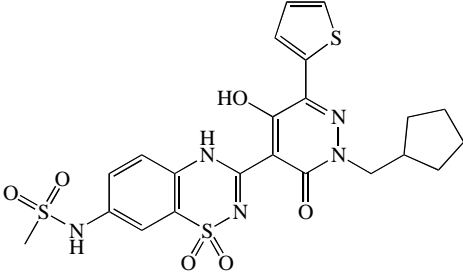
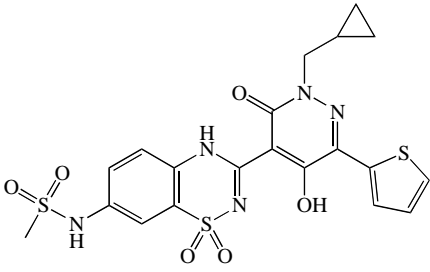
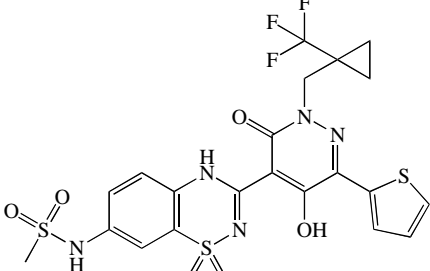
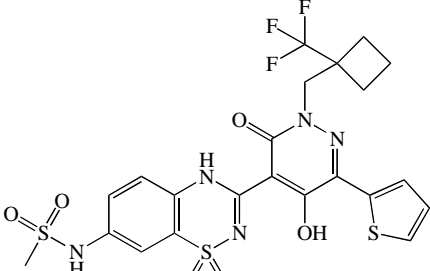
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
63*		0.6	0.221849
64		0.26	0.585027
65		0.059	1.229148
66		0.054	1.267606
67*		0.076	1.119186

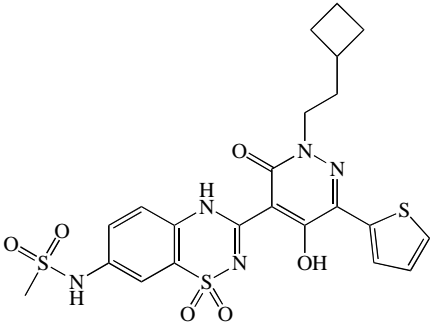
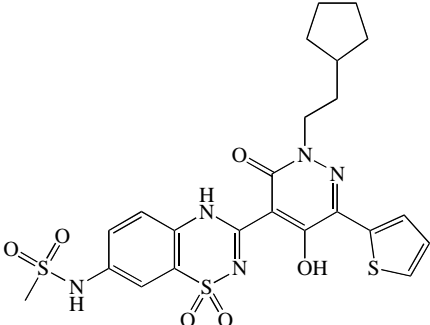
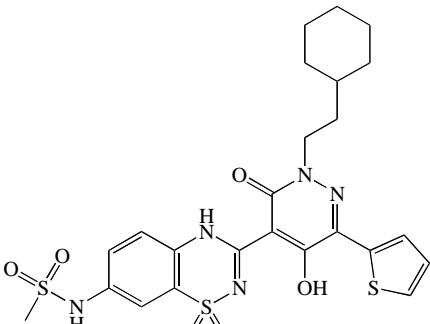
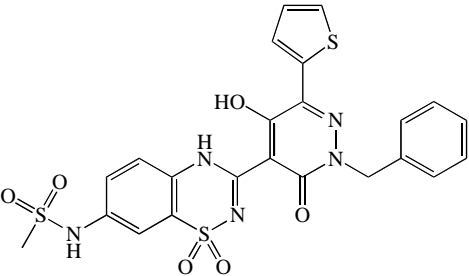
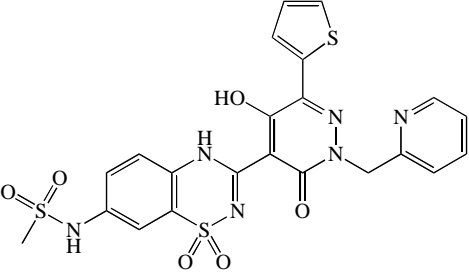
(Table S1). Contd.....

Compound		Genotype-1a NSSB Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
68		0.072	1.142668
69		0.026	1.585027
70		2.5	-0.39794
71*		0.11	0.958607
72		0.3	0.522879

(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
73		0.077	1.113509
74		1.2	-0.07918
75*		0.38	0.420216
76		0.07	1.154902
77		0.1	1

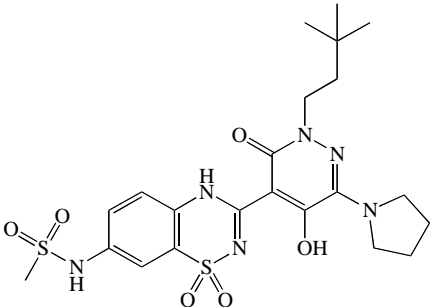
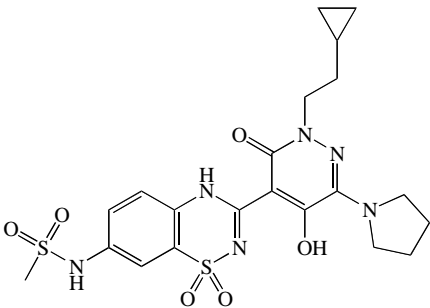
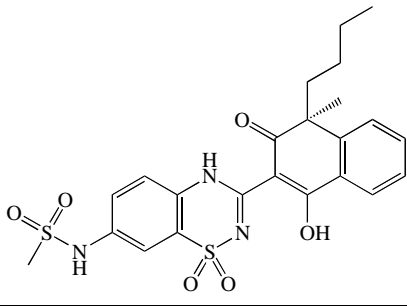
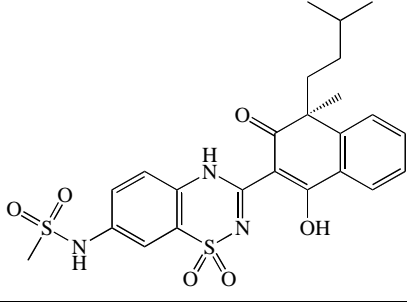
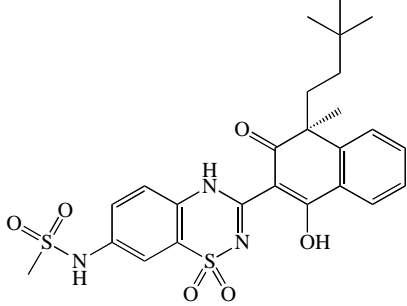
(Table S1). Contd.....

Compound		Genotype-1a NSSB Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
78		0.2	0.69897
79*		0.21	0.677781
80		0.69	0.161151
81		0.45	0.346787
82		0.48	0.318759

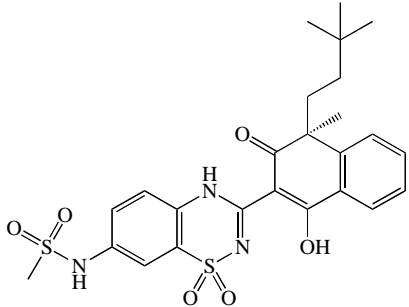
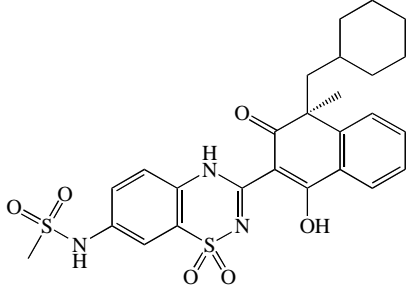
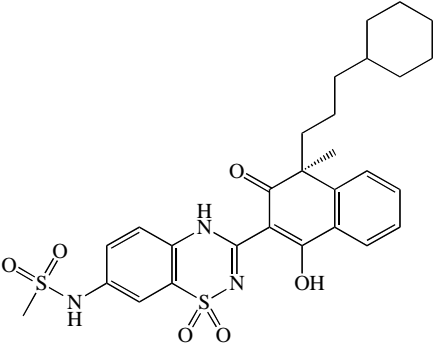
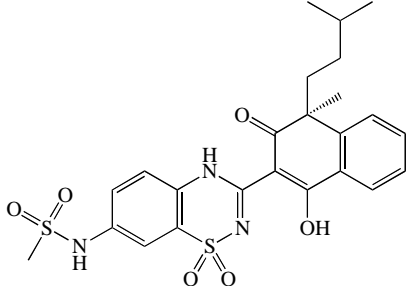
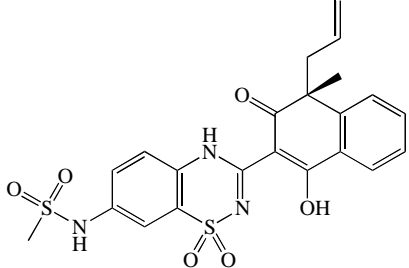
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
83*		0.15	0.823909
84		0.12	0.920819
85		0.091	1.040959
86		0.5	0.30103
87*		0.47	0.327902
88		0.073	1.136677

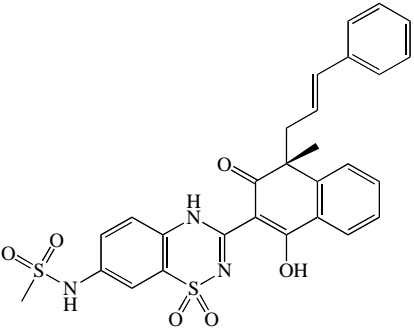
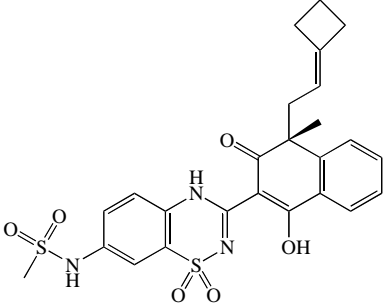
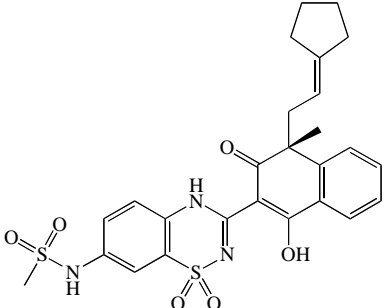
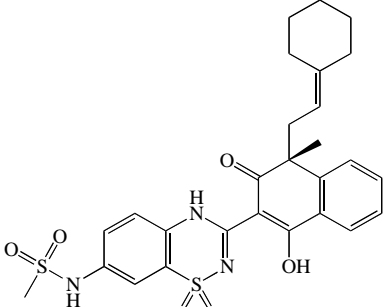
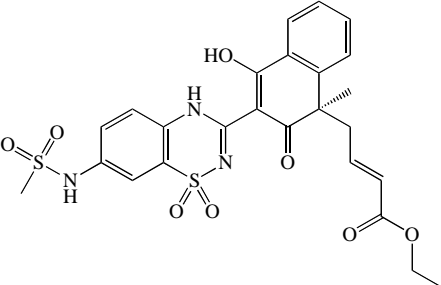
(Table S1). Contd.....

Compound		Genotype-1a NSSB Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
89		0.086	1.065502
90		0.038	1.420216
91*		0.015	1.823909
92		0.007	2.154902
93		0.01	2

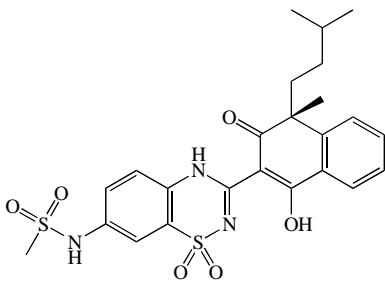
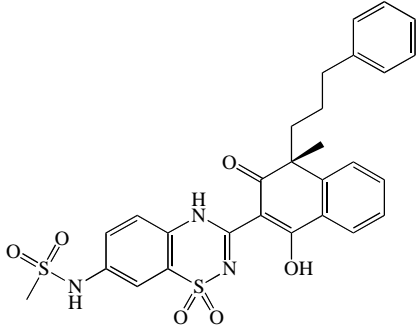
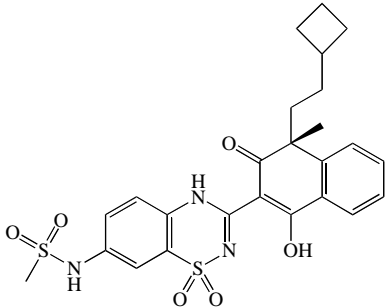
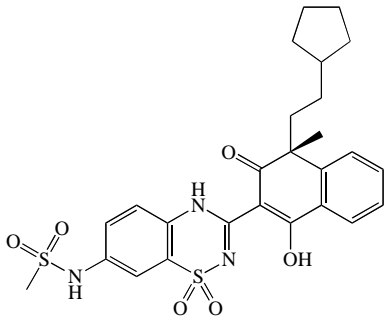
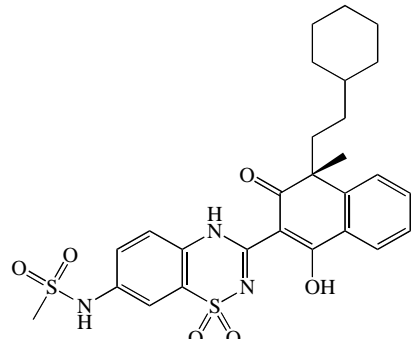
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
94		0.138	0.860121
95*		0.013	1.886057
96		0.791	0.101824
97		0.017	1.769551
98		0.018	1.744727

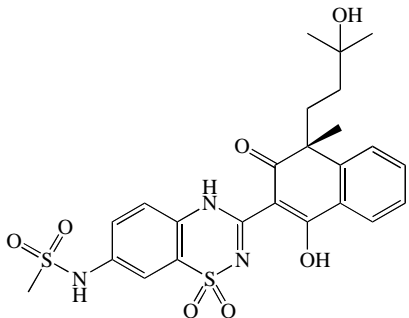
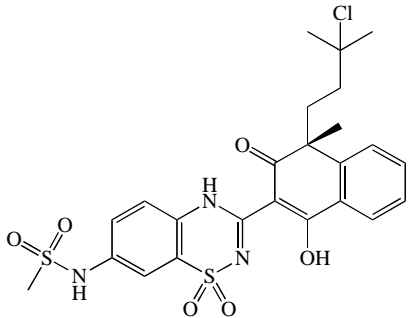
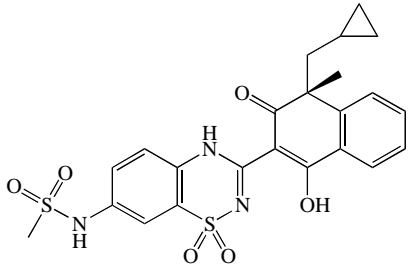
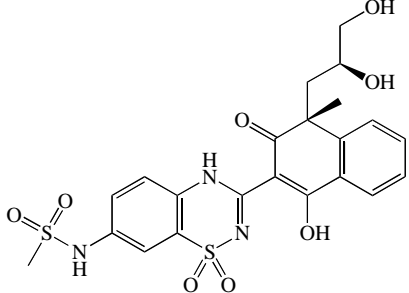
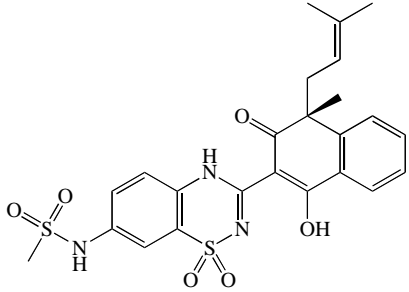
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
99*		0.46	0.337242
100		0.087	1.060481
101		0.093	1.031517
102		0.195	0.709965
103*		1.08	-0.03342

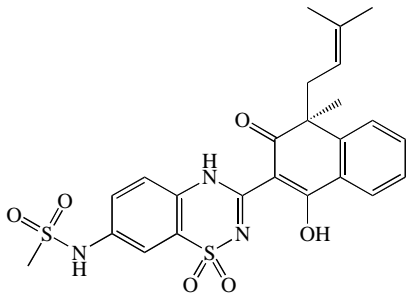
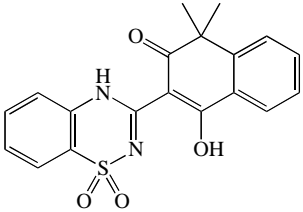
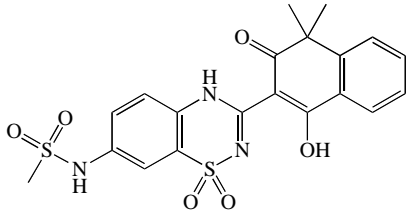
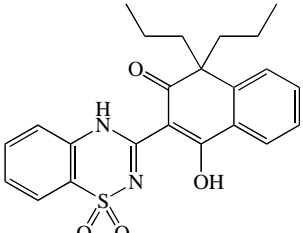
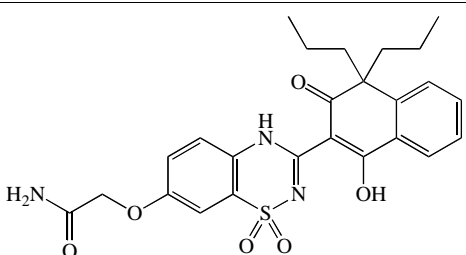
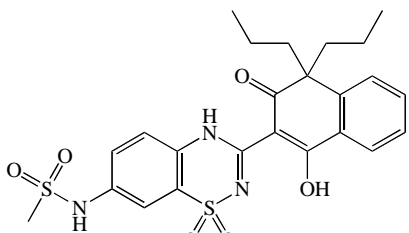
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
104		0.004	2.39794
105		0.115	0.939302
106		0.016	1.79588
107*		0.032	1.49485
108		0.057	1.244125

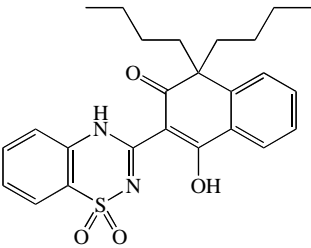
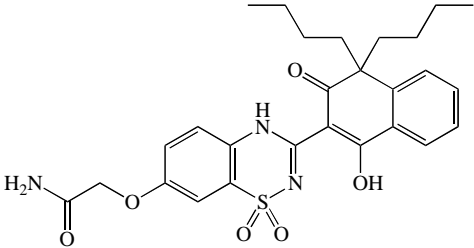
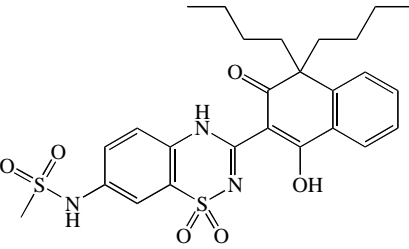
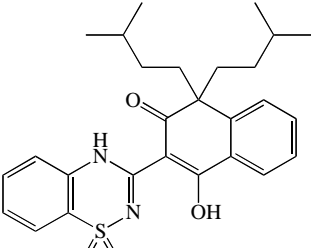
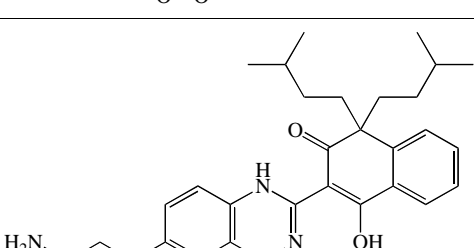
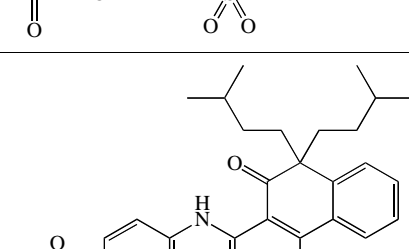
(Table S1). Contd.....

Compound		Genotype-1a NSSB Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
109		0.043	1.366532
110		0.039	1.408935
111*		0.021	1.677781
112		0.45	0.346787
113		0.019	1.721246

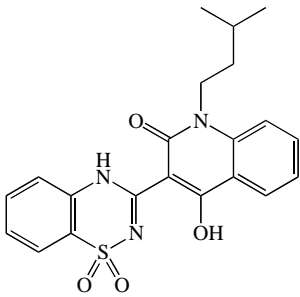
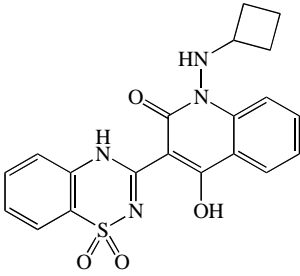
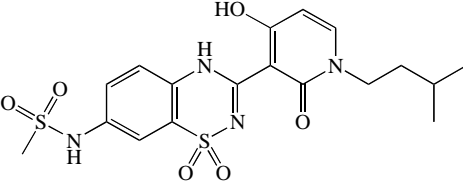
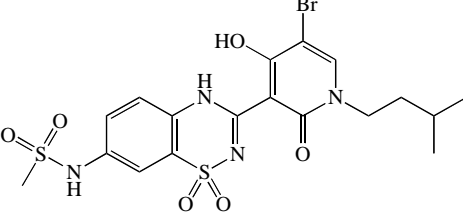
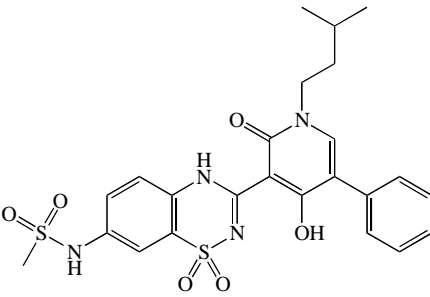
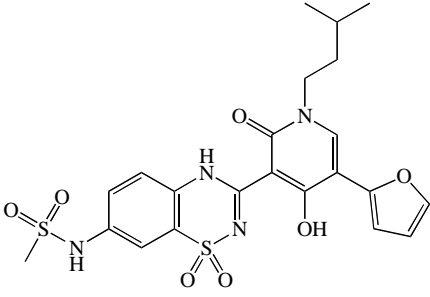
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
114		0.702	0.153663
115*		2.2	-0.34242
116		0.93	0.031517
117		2.2	-0.34242
118		0.24	0.619789
119*		0.099	1.004365

(Table S1). Contd.....

Compound		Genotype-1a NSSB Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
120		0.99	0.004365
121		0.26	0.585027
122		0.01	2
123*		0.82	0.086186
124		0.32	0.49485
125		0.068	1.167491

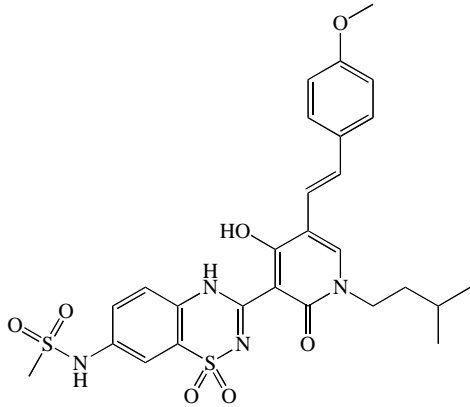
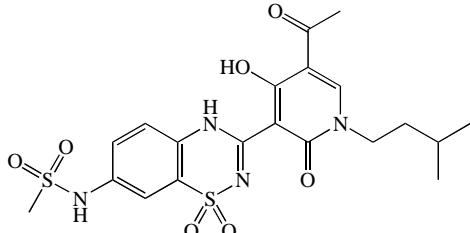
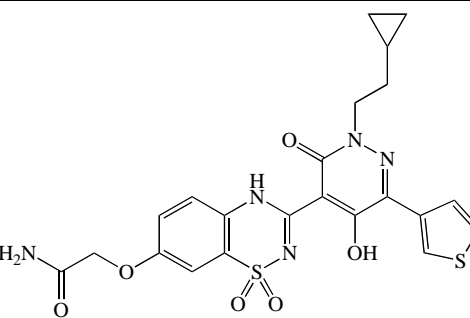
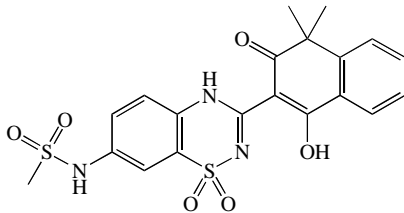
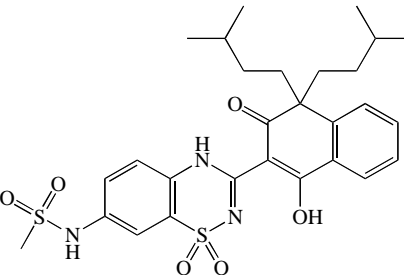
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
126		0.54	0.267606
127*		0.28	0.552842
128		0.274	0.562249
129		0.055	1.259637
130		0.425	0.371611
131*		0.008	2.09691

(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
132		0.011	1.958607
133		0.024	1.619789
134		0.006	2.221849
135*		0.406	0.391474
136		0.067	1.173925

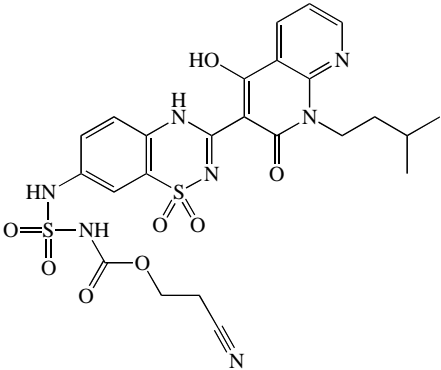
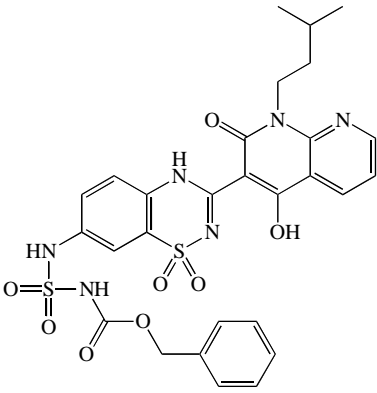
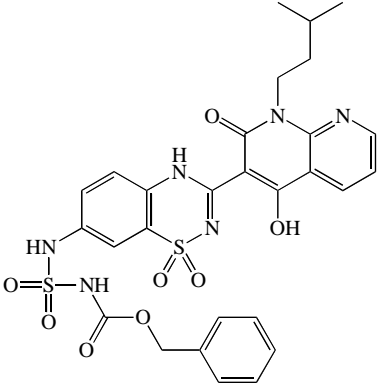
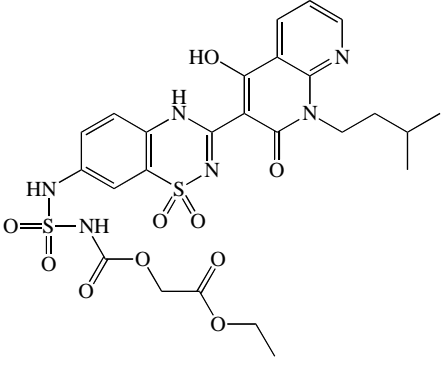
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
137		0.48	0.318759
138		0.28	0.552842
140		0.14	0.853872
141		0.933	0.030118
142		0.068	1.167491

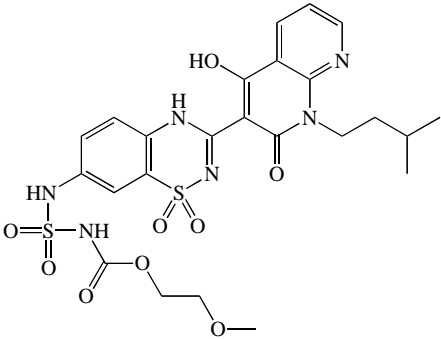
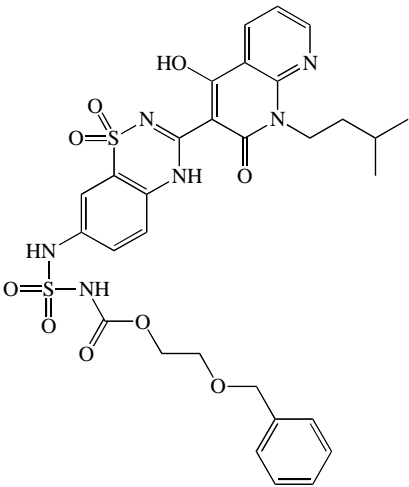
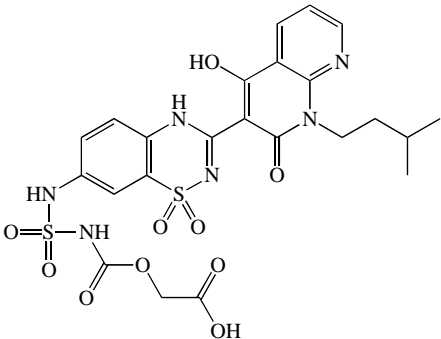
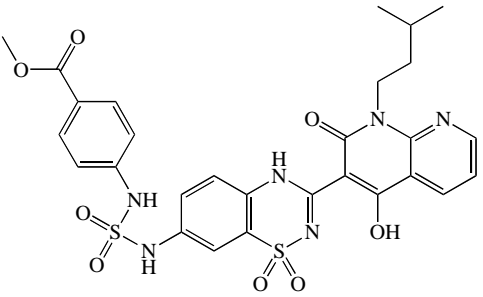
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
143*	<p>Chemical structure of compound 143*: A benzothiazine core with a methylsulfonamide group at position 6, a propyl group at position 4, and a 2-hydroxy-1-phenylethyl group at position 5.</p>	0.02	1.69897
144	<p>Chemical structure of compound 144: A benzothiazine core with a methylsulfonamide group at position 6, a 2-hydroxy-1-(4-pyridyl)ethyl group at position 5, and a 2-methylbutyl group at position 4.</p>	0.063	1.200659
145	<p>Chemical structure of compound 145: A benzothiazine core with a methylsulfonamide group at position 6, a 2-hydroxy-1-(4-pyridyl)ethyl group at position 5, a 2-methylbutyl group at position 4, and a 3-chloropropyl ester group at position 7.</p>	0.189	0.723538
146	<p>Chemical structure of compound 146: A benzothiazine core with a methylsulfonamide group at position 6, a 2-hydroxy-1-(4-pyridyl)ethyl group at position 5, a 2-methylbutyl group at position 4, and an allyl ester group at position 7.</p>	0.088	1.055517
147*	<p>Chemical structure of compound 147*: A benzothiazine core with a methylsulfonamide group at position 6, a 2-hydroxy-1-(4-pyridyl)ethyl group at position 5, a 2-methylbutyl group at position 4, and a propargyl ester group at position 7.</p>	0.072	1.142668

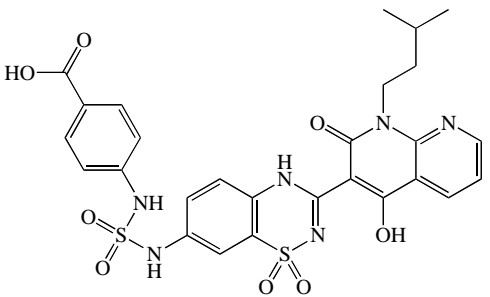
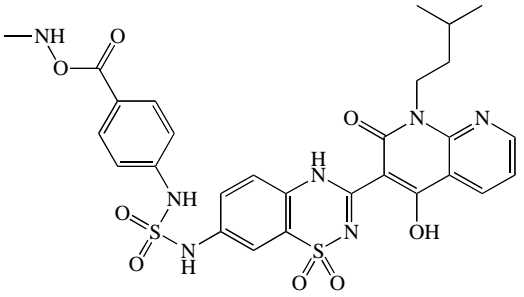
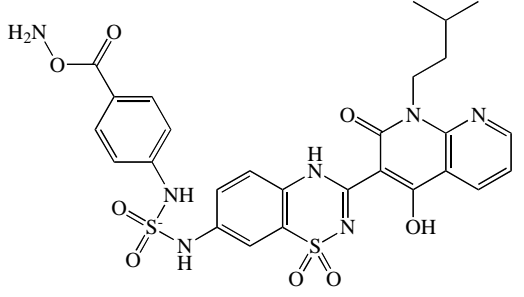
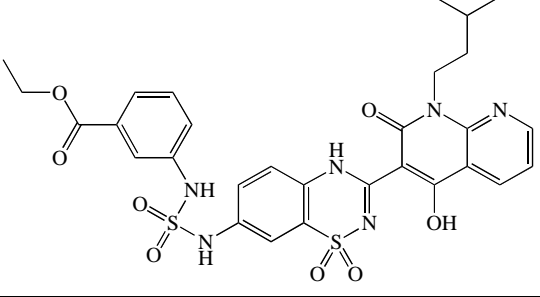
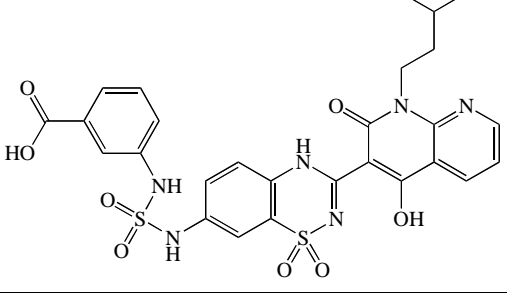
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
148		0.035	1.455932
149		0.058	1.236572
150		0.021	1.677781
151*		0.061	1.21467

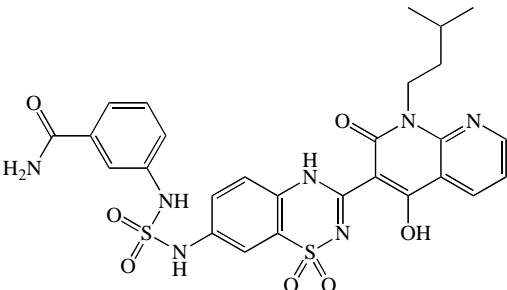
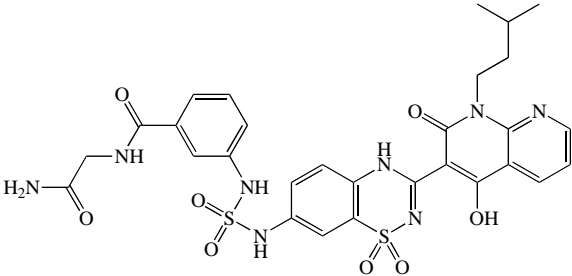
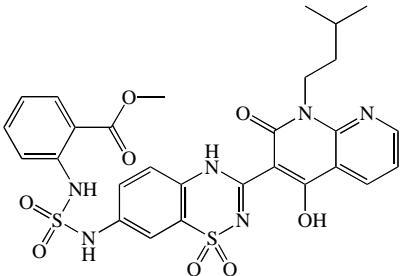
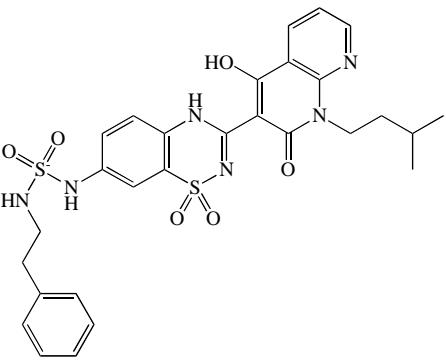
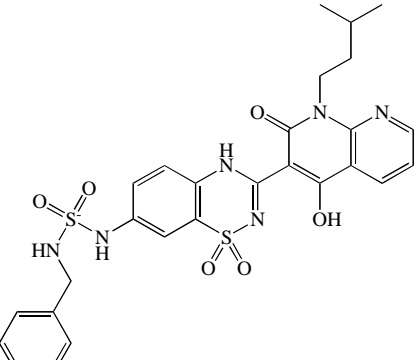
(Table S1). Contd.....

Compound		Genotype-1a NSSB Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
152		0.087	1.060481
153		0.096	1.017729
154		0.05	1.30103
155*		0.048	1.318759

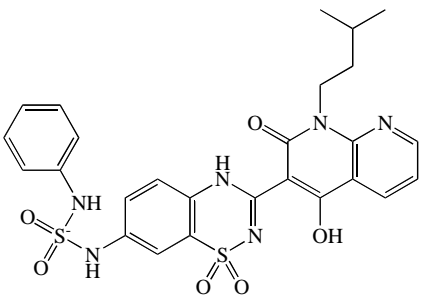
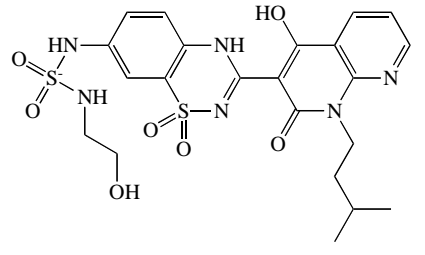
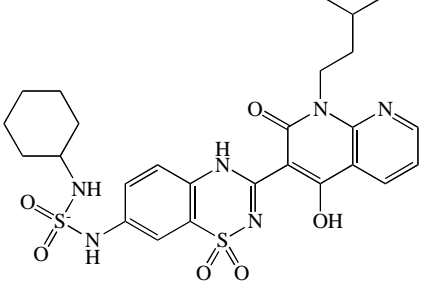
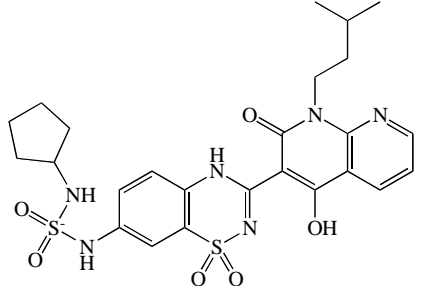
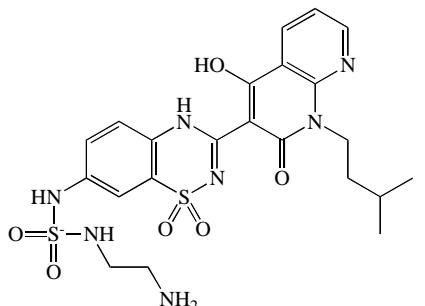
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
156		0.02	1.69897
157		0.043	1.366532
158		0.018	1.744727
159*		0.132	0.879426
160		0.115	0.939302

(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
161		0.043	1.366532
162		0.043	1.366532
163*		0.129	0.88941
164		0.018	1.744727
165		0.0055	2.259637

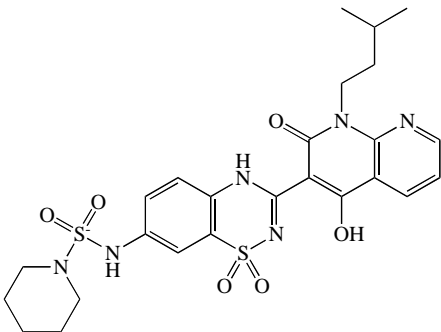
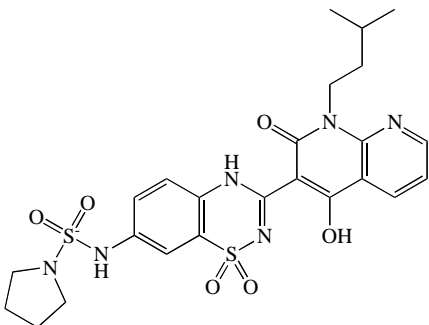
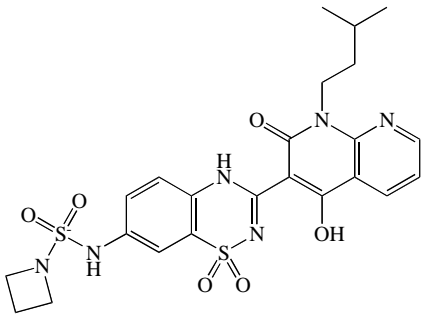
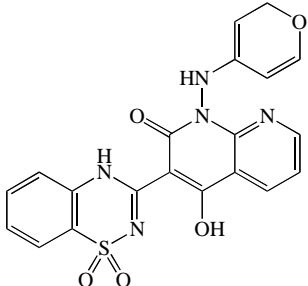
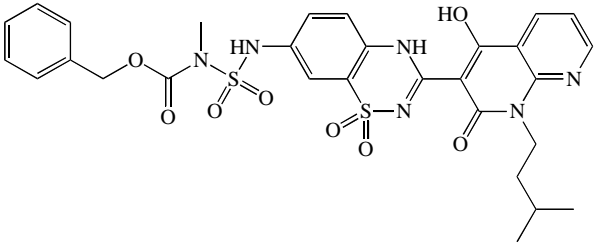
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
166		0.041	1.387216
167*		0.107	0.970616
168		0.067	1.173925
169		0.039	1.408935
170		0.01	2

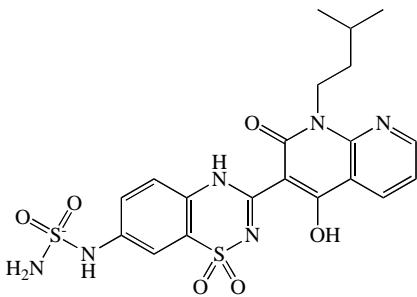
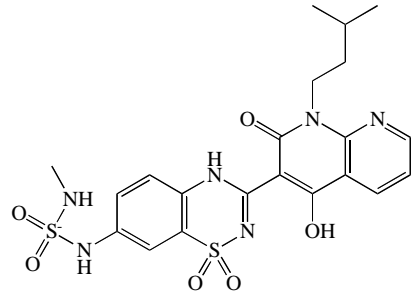
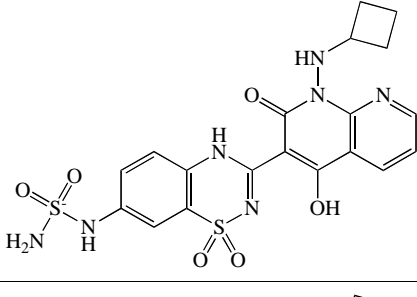
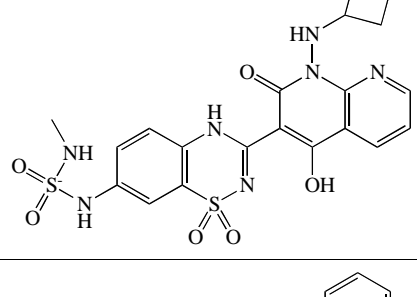
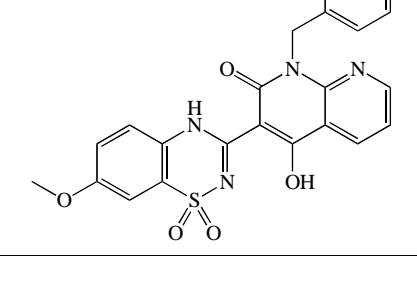
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
171*	<p>Chemical structure of compound 171*: A central benzimidazole ring system. The 2-position is substituted with a piperidine ring via its nitrogen atom. The 4-position is substituted with a sulfonamide group (-NH-SO₂-NH-). The 5-position is substituted with a pyridine ring via its nitrogen atom. The 6-position is substituted with a hydroxyl group (-OH). The 7-position is substituted with a butyl chain attached to the nitrogen atom of a pyridine ring.</p>	0.032	1.49485
172	<p>Chemical structure of compound 172: A central benzimidazole ring system. The 2-position is substituted with a propyl chain ending in a primary amide group (-NH-CH₂-CH₂-NH₂). The 4-position is substituted with a sulfonamide group (-NH-SO₂-NH-). The 5-position is substituted with a pyridine ring via its nitrogen atom. The 6-position is substituted with a hydroxyl group (-OH). The 7-position is substituted with a butyl chain attached to the nitrogen atom of a pyridine ring.</p>	0.02	1.69897
173	<p>Chemical structure of compound 173: A central benzimidazole ring system. The 2-position is substituted with a benzyl group where the benzene ring has a methoxy group (-OCH₃) at the para position. The 4-position is substituted with a sulfonamide group (-NH-SO₂-NH-). The 5-position is substituted with a pyridine ring via its nitrogen atom. The 6-position is substituted with a hydroxyl group (-OH). The 7-position is substituted with a butyl chain attached to the nitrogen atom of a pyridine ring.</p>	0.01	2
174	<p>Chemical structure of compound 174: A central benzimidazole ring system. The 2-position is substituted with a benzyl group where the benzene ring has a methoxy group (-OCH₃) at the para position. The 4-position is substituted with a sulfonamide group (-NH-SO₂-NH-). The 5-position is substituted with a pyridine ring via its nitrogen atom. The 6-position is substituted with a hydroxyl group (-OH). The 7-position is substituted with a butyl chain attached to the nitrogen atom of a pyridine ring.</p>	0.015	1.823909
175*	<p>Chemical structure of compound 175*: A central benzimidazole ring system. The 2-position is substituted with a benzyl group where the benzene ring has a methoxy group (-OCH₃) at the para position. The 4-position is substituted with a sulfonamide group (-NH-SO₂-NH-). The 5-position is substituted with a pyridine ring via its nitrogen atom. The 6-position is substituted with a hydroxyl group (-OH). The 7-position is substituted with a butyl chain attached to the nitrogen atom of a pyridine ring.</p>	0.057	1.244125
176	<p>Chemical structure of compound 176: A central benzimidazole ring system. The 2-position is substituted with a benzyl group where the benzene ring has a nitro group (-NO₂) at the para position. The 4-position is substituted with a sulfonamide group (-NH-SO₂-NH-). The 5-position is substituted with a pyridine ring via its nitrogen atom. The 6-position is substituted with a hydroxyl group (-OH). The 7-position is substituted with a butyl chain attached to the nitrogen atom of a pyridine ring.</p>	0.013	1.886057

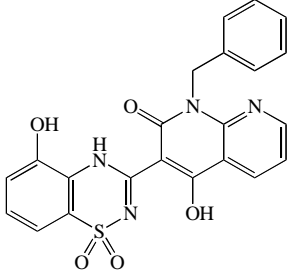
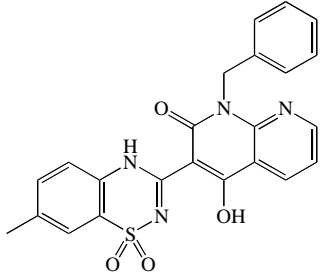
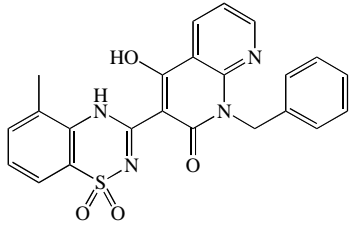
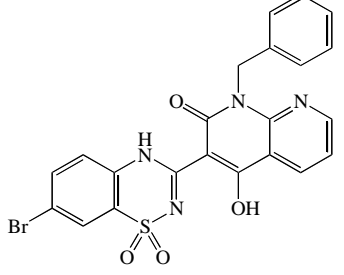
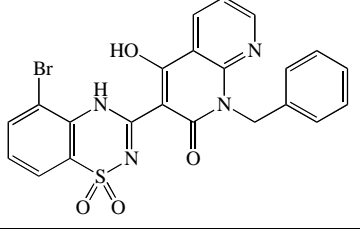
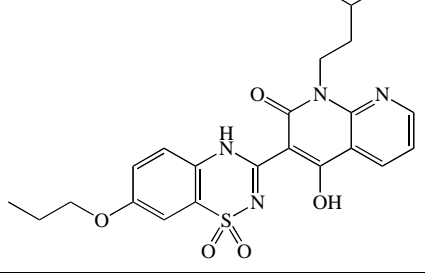
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
177		0.051	1.29243
178		0.027	1.568636
179*		0.024	1.619789
180		4.63	-0.66558
181		0.121	0.917215

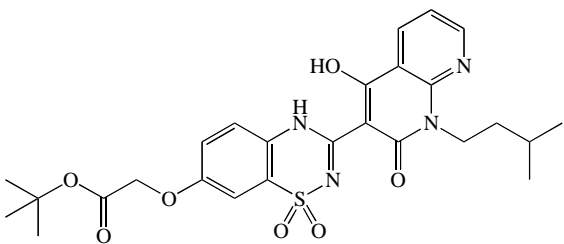
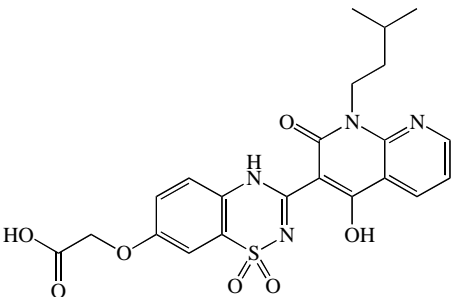
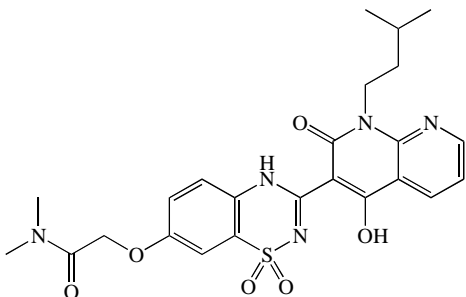
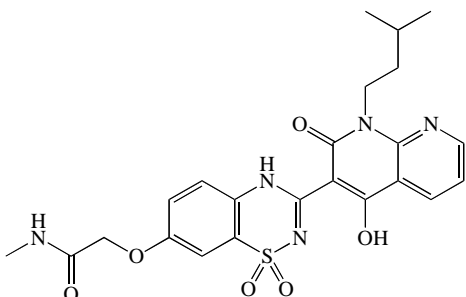
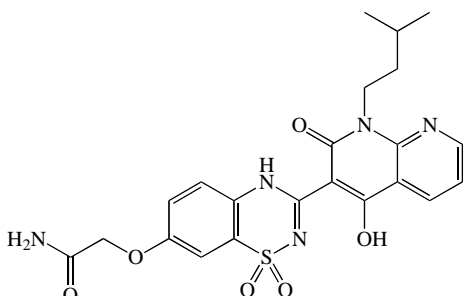
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
182		0.009	2.045757
183*		0.014	1.853872
184		0.0052	2.283997
185		0.0087	2.060481
188		8.31	-0.9196

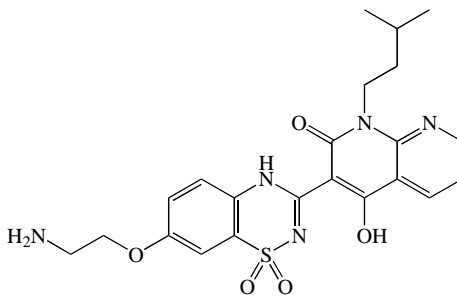
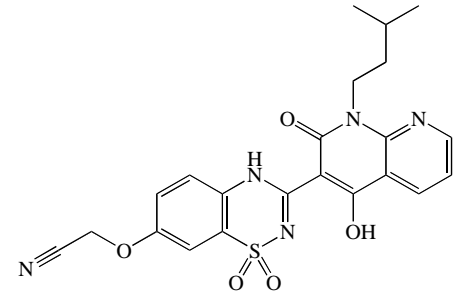
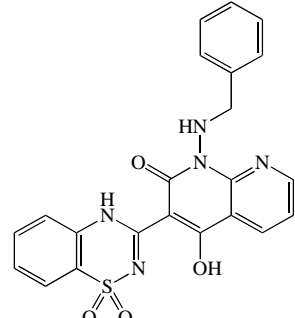
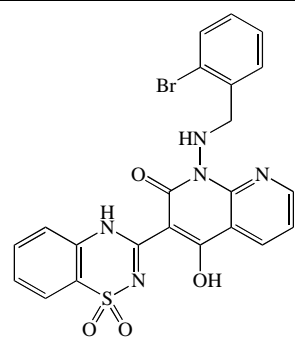
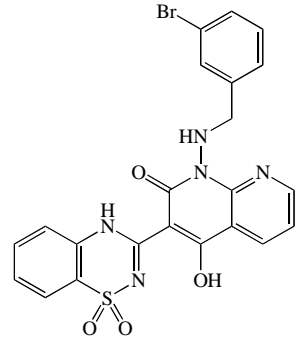
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
189		8.37	-0.92273
190		25.7	-1.40993
191*		6.7	-0.82607
192		16.75	-1.22401
193		6.2	-0.79239
198		1.62	-0.20952

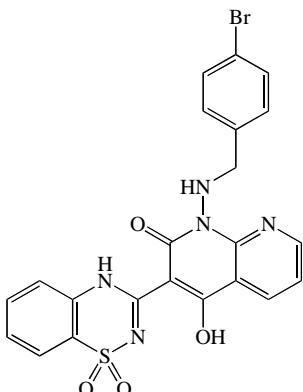
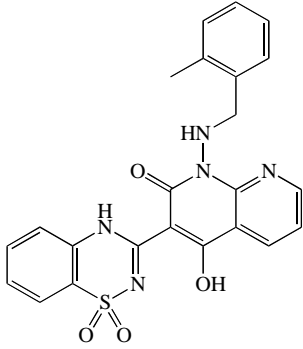
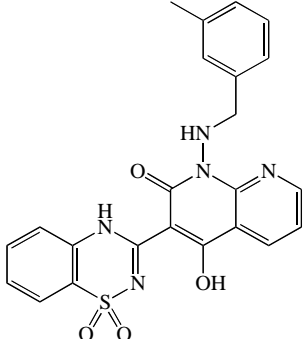
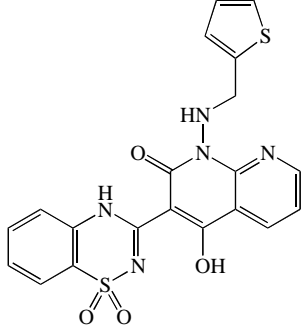
(Table S1). Contd.....

Compound		Genotype-1a NSSB Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
199*		5	-0.69897
200		0.367	0.435334
201		0.934	0.029653
202		0.18	0.744727
203*		0.046	1.337242

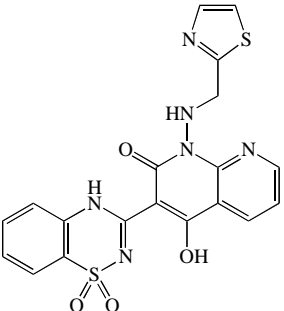
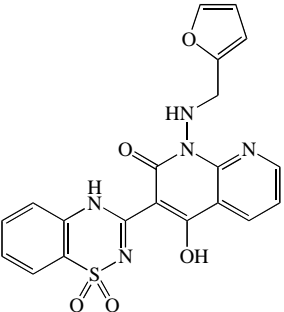
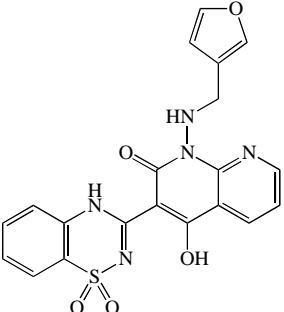
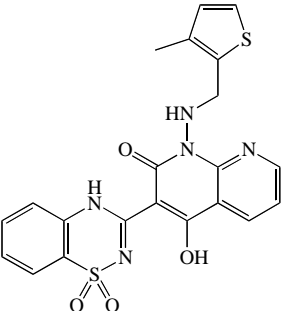
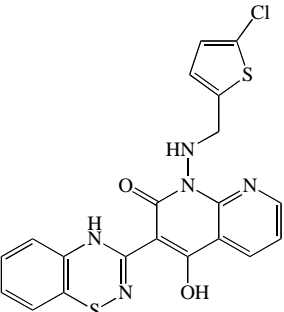
(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
204		0.637	0.195861
205		0.141	0.850781
213		5.09	-0.70672
214*		6.72	-0.82737
215		1.04	-0.01703

(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
216		10.36	-1.01536
217		6.12	-0.78675
218*		8.21	-0.91434
219		2.33	-0.36736

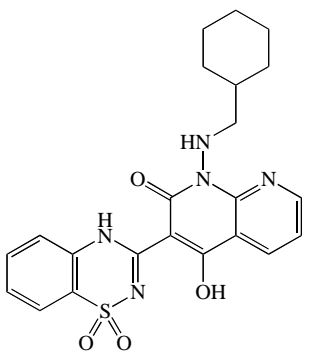
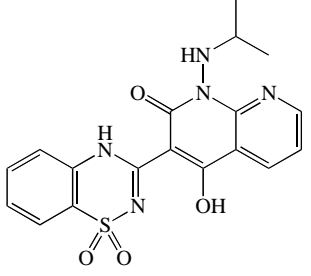
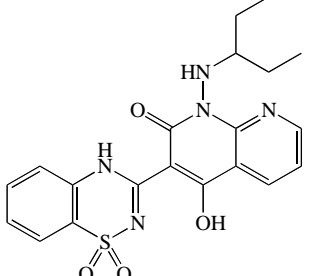
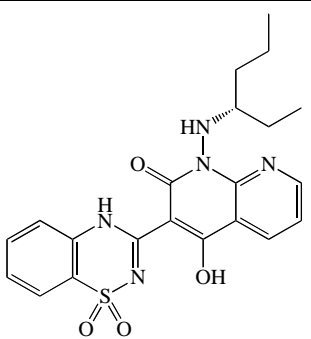
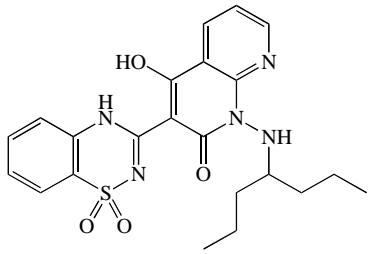
(Table S1). Contd.....

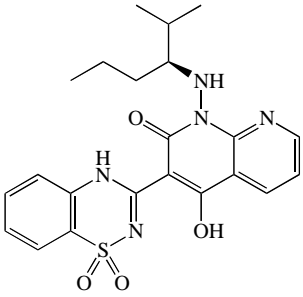
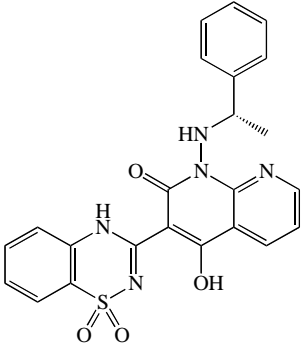
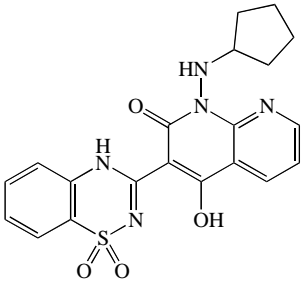
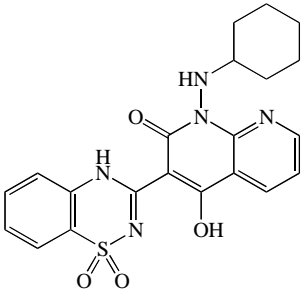
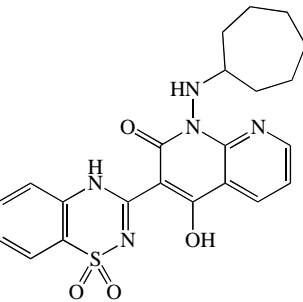
Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
220		35.8	-1.55388
221		3.26	-0.51322
222*		1.55	-0.19033
223		15	-1.17609
224		4.78	-0.67943

(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
225		0.951	0.021819
226*		0.928	0.032452
227		0.629	0.201349
228		0.411	0.386158
229		0.285	0.545155

(Table S1). Contd.....

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μ M)	
		IC ₅₀	pLogIC ₅₀
230*		2.528	-0.40278
231		6.35	-0.80277
232		2.46	-0.39094
233		1.89	-0.27646
234*		2.24	-0.35025

Compound		Genotype-1a NS5B Enzyme IC ₅₀ (μM)	
		IC ₅₀	pLogIC ₅₀
235		6.4	-0.80618
236		16.5	-1.21748
237*		0.747	0.126679
238		0.356	0.44855
239		1.04	-0.01703

*Molecules Belonged to the Test Set. The molecular structures of all 239 Benzothiadiazine Derivatives are deposited in compression file S1.

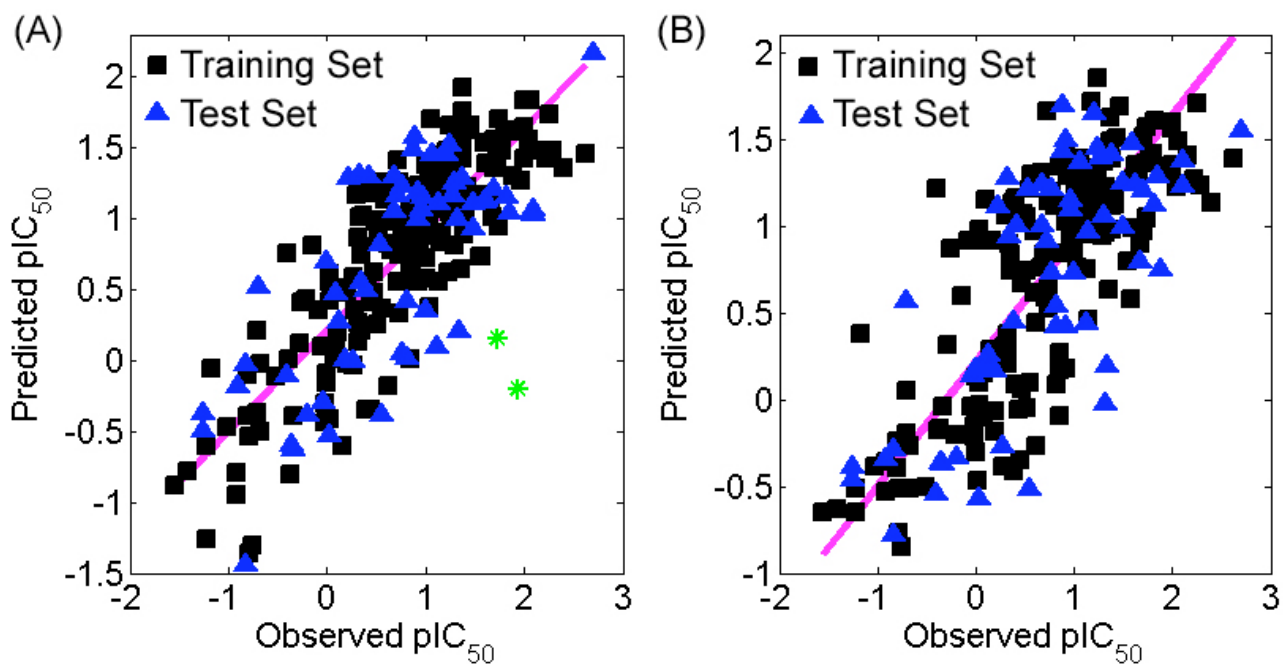


Fig. (S1). The correlation plots of predicted versus actual pIC_{50} values using the training (filled black squares) and test (filled blue triangles) sets based on (A) CoMFA model and (B) CoMSIA model. The solid lines are the regression lines for the fitted and predicted bioactivities of training and test compounds, respectively. The outliers in test set are shown in green asterisks.

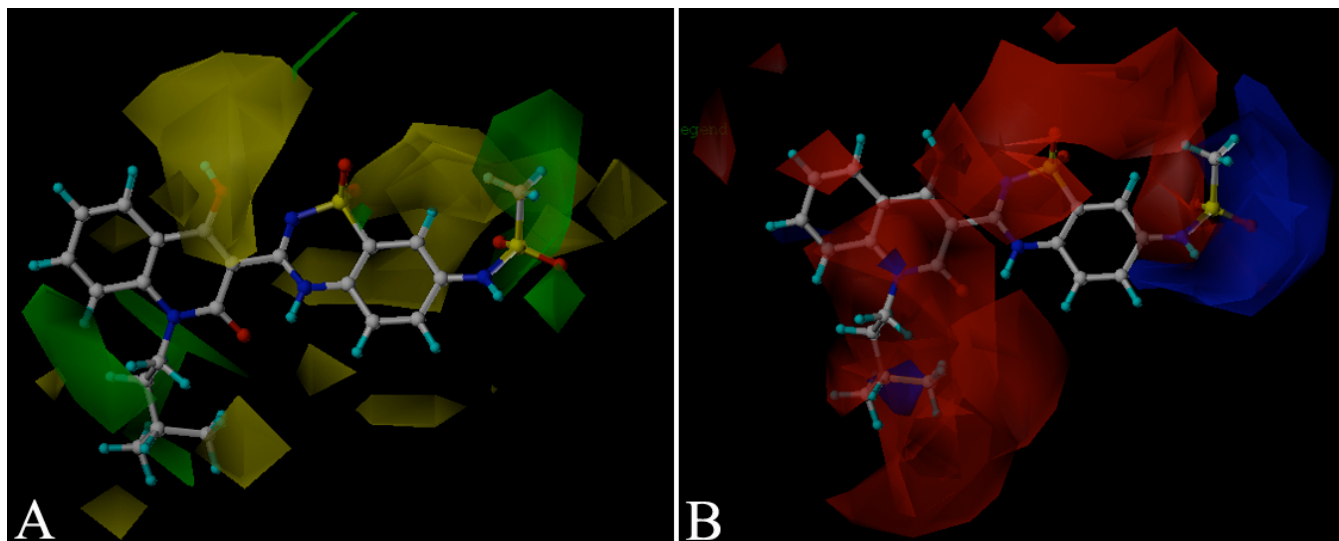


Fig. (S2). CoMFA StDev*Coeff contour plots. (A) steric (green/yellow) contour map combined with compound **139**. Green contours indicate regions where bulky groups increase activity; yellow contours indicate regions where bulky groups decrease activity. (B) electrostatic contour map (red/blue) in combination with compound **139**. Red contours indicate regions where negative charges increase activity; blue contours indicate regions where positive charges increase activity.

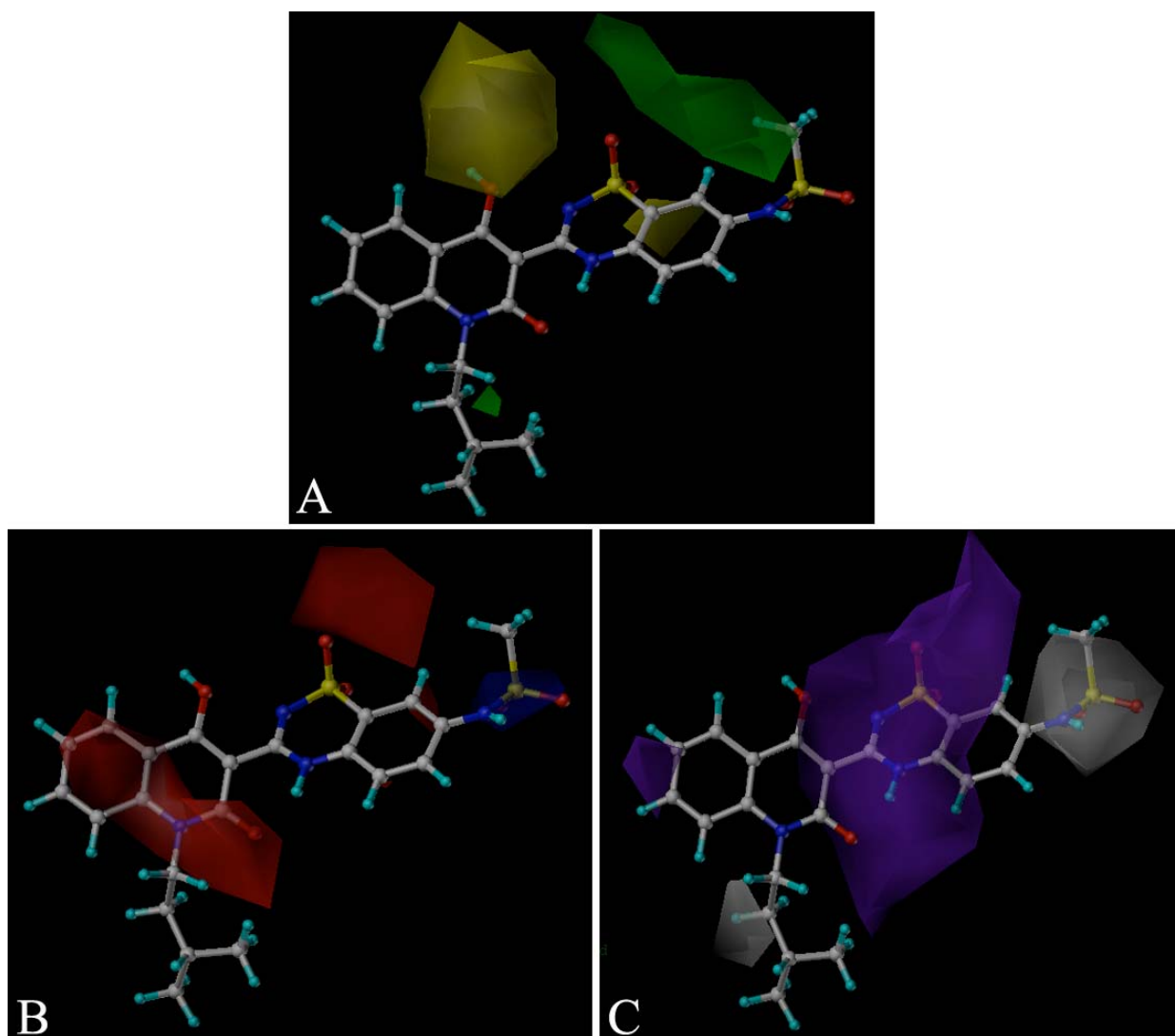


Fig. (S3). CoMSIA StDev*Coeff contour plots. (A) steric (green/yellow) contour map combined with compound **139**. Green contours indicate regions where bulky groups increase activity; yellow contours indicate regions where bulky groups decrease activity. (B) electrostatic contour map (red/blue) in combination with compound **139**. Red contours indicate regions where negative charges increase activity; blue contours indicate regions where positive charges increase activity. (C) hydrophobic contour map (purple/white) in combination with compound **139**. Purple contours indicate regions where hydrophobic substituents enhance activity; white contours indicate regions where hydrophobic substituents decrease activity.