

(**I**)

wherein

A and **B** rings are each independently a single or fused aromatic or heteroaromatic ring system, or a single or fused C_3-C_{10} cycloalkyl or a single or fused C_3-C_{10} heterocyclic ring;

$\mathbf{R_1}$ and $\mathbf{R_2}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH, R_8-SH, -R_8-O-R_{10}, CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$, R_9-R_8-$N(R_{10})(R_{11})$ $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} NHCO-$N(R_{10})(R_{11})$ COOH, -C(O)Ph, C(O)O-R_{10}, R_8-C(O)-R_{10}, C(O)H, C(O)-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$, SO_2R, $SO_2N(R_{10})(R_{11})$, C_1-C_5 linear or branched, substituted or unsubstituted alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 linear, branched or cyclic alkoxy optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_3-C_8 heterocyclic ring, substituted or unsubstituted aryl, $CH(CF_3)(NH\text{-}R_{10})$;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring;

$\mathbf{R_3}$ is C_2-C_5 linear or branched haloalkyl, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)\text{-}CH(CH_3)_2$, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_3-C_8 heterocyclic ring;

$\mathbf{R_4}$ is H, F, Cl, Br, I, OH, SH, R_8-OH, R_8-SH, -R_8-O-R_{10}, CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$, R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10}, NHCO-$N(R_{10})(R_{11})$, COOH, -C(O)Ph, C(O)O-R_{10}, R_8-C(O)-R_{10}, C(O)H, C(O)-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$, SO_2R, $SO_2N(R_{10})(R_{11})$, C_1-C_5 linear or branched, substituted or unsubstituted alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 linear, branched or cyclic alkoxy, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_3-C_8 heterocyclic ring, substituted or unsubstituted aryl, $CH(CF_3)(NH\text{-}R_{10})$;

or $\mathbf{R_3}$ and $\mathbf{R_4}$ are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring;

$\mathbf{R_5}$ is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl, C_1-C_5 linear or branched haloalkyl, R_8-aryl, substituted or unsubstituted heteroaryl;

$\mathbf{R_6}$ is H, C_1-C_5 linear or branched alkyl;

$\mathbf{R_8}$ is $[CH_2]_p$

wherein **p** is between 1 and 10;

$\mathbf{R_9}$ is $[CH]_q$, $[C]_q$

wherein **q** is between 2 and 10;

$\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are each independently H, C_1-C_5 linear or branched alkyl, C(O)R, or $S(O)_2R$;

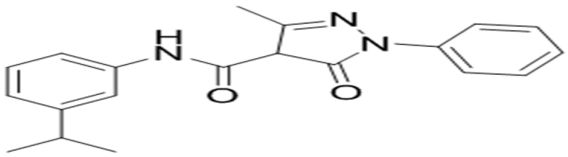
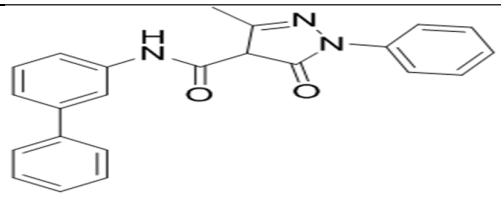
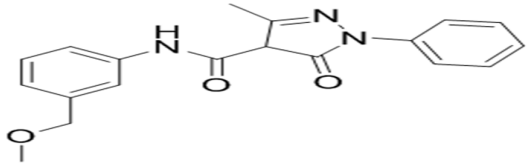
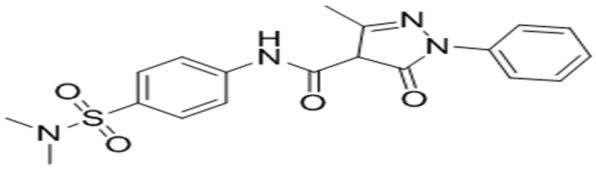
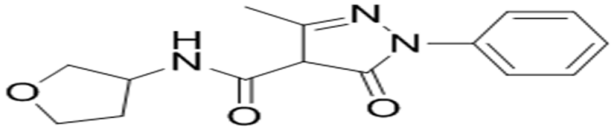
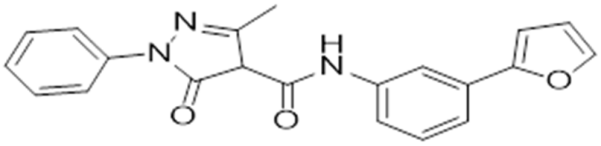
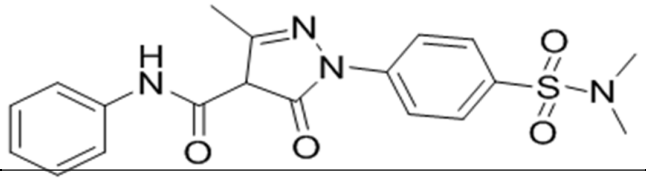
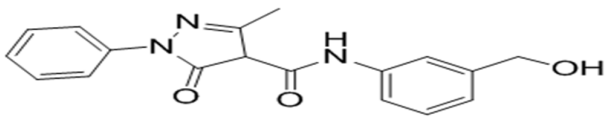
R is H, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkoxy, phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

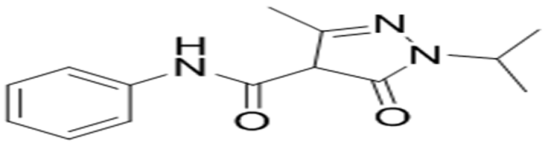
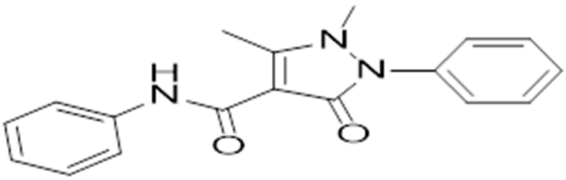
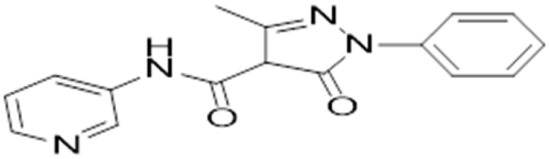
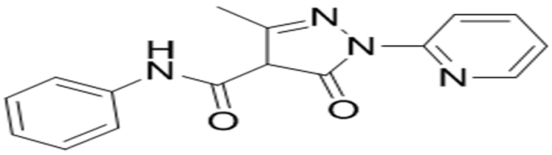
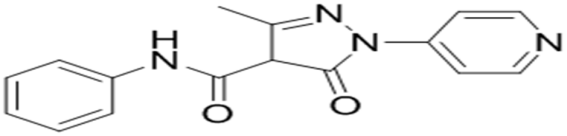
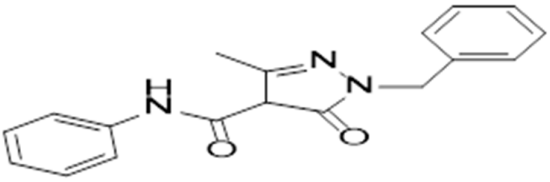
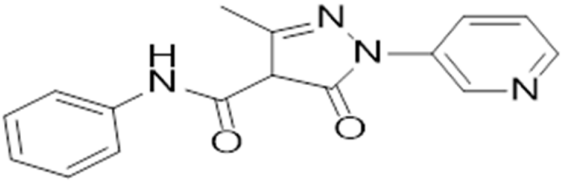
m, **n**, **l** and **k** are each independently an integer between 0 and 4;

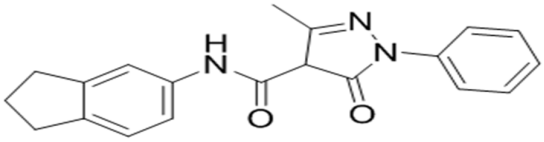
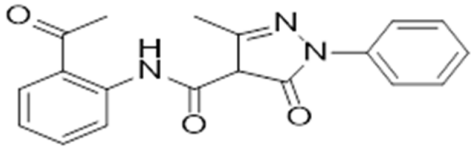
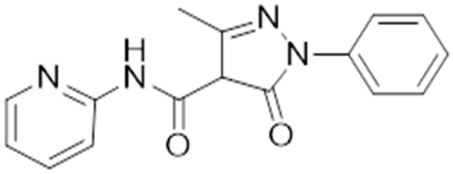
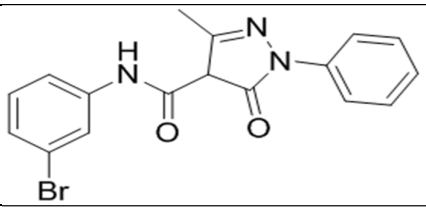
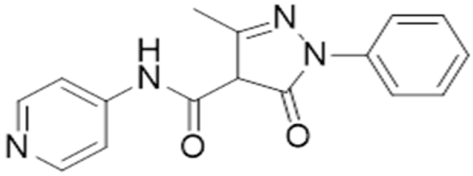
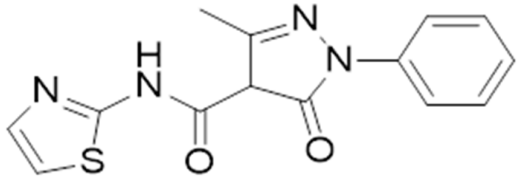
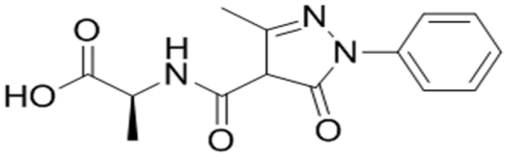
$\mathbf{Q_1}$ and $\mathbf{Q_2}$ are each independently S or O;

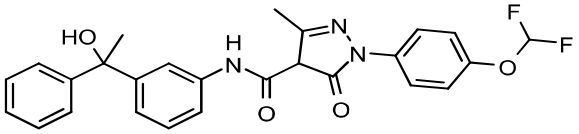
or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, isotopic variant, pharmaceutical product or any combination thereof.

[0014b] In one aspect, the present disclosure refers to a compound represented by the following structures:

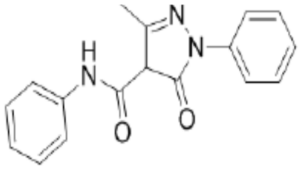
Compound name	Structure
100	
102	
103	
105	
106	
108	
110	
111	

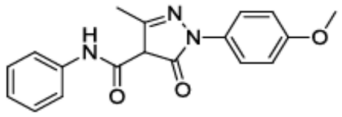
187	
190	
191	
192	
193	
194	
195	

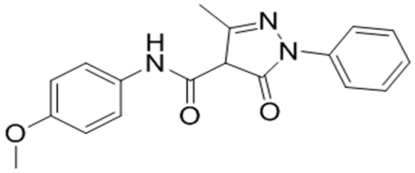
209	
213	
214	
215	
216	
217	
218	

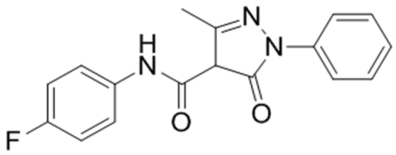
337	

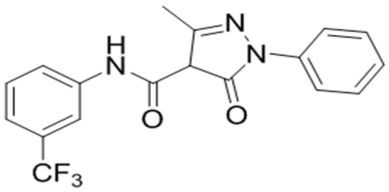
[0014c] In one aspect, the present disclosure refers to use of a compound represented by the following structures:

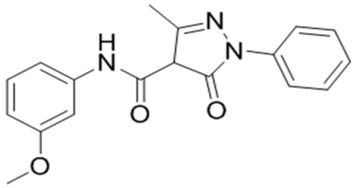


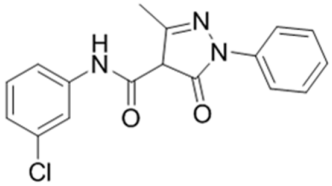
182 ;  **197** ;

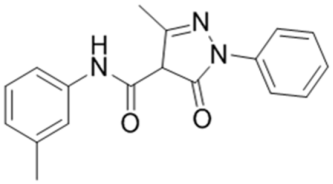


188 ;  **189**



209 ;  **211**



210 ;  **212** ;

in the manufacture of a medicament for:

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a viral infection, such as human cytomegalovirus (HCMV) infection, in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting alcoholic steatohepatitis (ASH) in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non alcoholic fatty liver disease (NAFLD) in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non-alcoholic steatohepatitis (NASH) in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a metabolic disorder such as obesity, weight gain, hepatic steatosis and fatty liver disease in a subject;

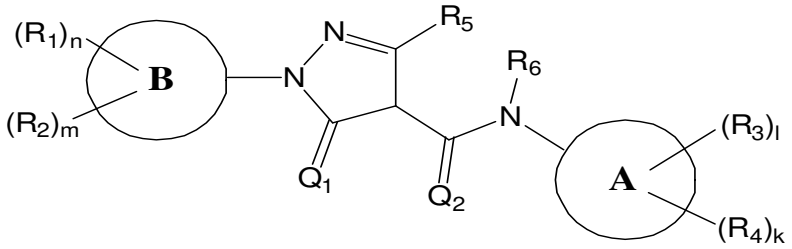
treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a neuropsychiatric disease or disorder such as anxiety, depression, schizophrenia, autism and post-traumatic stress disorder in a subject; and/or

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject.

[0015] This disclosure further provides a pharmaceutical composition comprising a compound or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable carrier.

WHAT IS CLAIMED:

1. A compound represented by the structure of formula (I):



(**I**)

wherein

A and **B** rings are each independently a single or fused aromatic or heteroaromatic ring system, or a single or fused C_3-C_{10} cycloalkyl or a single or fused C_3-C_{10} heterocyclic ring;

R_1 and **R_2** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH, R_8-SH, -R_8-O-R_{10}, CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, N(R)$_2$, R_8-N(R_{10})(R_{11}), R_9-R_8-N(R_{10})(R_{11}) B(OH)$_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R_{10} NHCO-N(R_{10})(R_{11}) COOH, -C(O)Ph, C(O)O-R_{10}, R_8-C(O)-R_{10}, C(O)H, C(O)-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -C(O)NH_2, C(O)NHR, C(O)N(R_{10})(R_{11}), SO_2R, SO_2N(R_{10})(R_{11}), C_1-C_5 linear or branched, substituted or unsubstituted alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 linear, branched or cyclic alkoxy optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_3-C_8 heterocyclic ring, substituted or unsubstituted aryl, CH(CF_3)(NH-R_{10});

or **R_2** and **R_1** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring;

R_3 is C_2-C_5 linear or branched haloalkyl, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_3-C_8 heterocyclic ring;

R_4 is H, F, Cl, Br, I, OH, SH, R_8-OH, R_8-SH, -R_8-O-R_{10}, CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, N(R)$_2$, R_8-N(R_{10})(R_{11}), R_9-R_8-N(R_{10})(R_{11}), B(OH)$_2$, -OC(O)CF_3, -OCH_2Ph, -NHCO-R_{10}, NHCO-N(R_{10})(R_{11}), COOH, -C(O)Ph, C(O)O-R_{10}, R_8-C(O)-R_{10}, C(O)H, C(O)-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -C(O)NH_2, C(O)NHR, C(O)N(R_{10})(R_{11}), SO_2R, SO_2N(R_{10})(R_{11}), C_1-C_5 linear or branched, substituted or unsubstituted alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 linear, branched or cyclic alkoxy, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_3-C_8 heterocyclic ring, substituted or unsubstituted aryl, CH(CF_3)(NH-R_{10});

or **R_3** and **R_4** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring;

R_5 is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl, C_1-C_5 linear or branched haloalkyl, R_8-aryl, substituted or unsubstituted heteroaryl;

R_6 is H, C_1-C_5 linear or branched alkyl;

R_8 is $[CH_2]_p$

wherein **p** is between 1 and 10;

R_9 is $[CH]_q$, $[C]_q$

wherein **q** is between 2 and 10;

R_{10} and **R_{11}** are each independently H, C_1-C_5 linear or branched alkyl, C(O)R, or $S(O)_2R$;

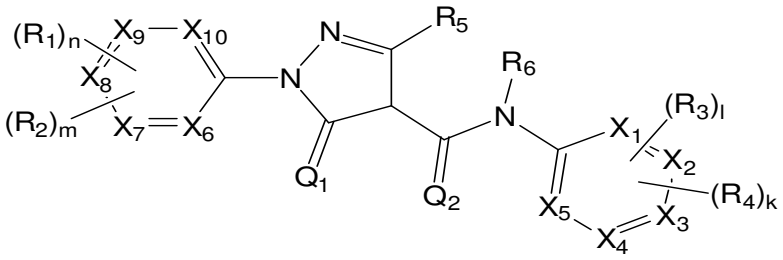
R is H, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkoxy, phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

m, **n, l** and **k** are each independently an integer between 0 and 4;

Q_1 and **Q_2** are each independently S or O;

or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, isotopic variant, pharmaceutical product or any combination thereof.

2. The compound of claim 1, represented by the structure of formula (II):



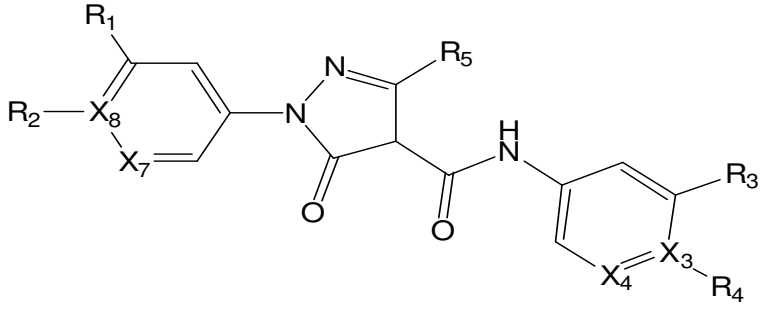
(II)

wherein

R_1, R_2, R_3, R_4, **R_5**, **R_6, R_8, R_{10}**, **R_{11}, R, m**, **n, l, k, Q_1** and **Q_2** are as defined in claim 1; and

X_1, **X_2**, **X_3**, **X_4**, **X_5**, **X_6**, **X_7**, **X_8**, **X_9** or **X_{10}** are each independently C or N;

or represented by the structure of formula (IV):



(IV)

wherein

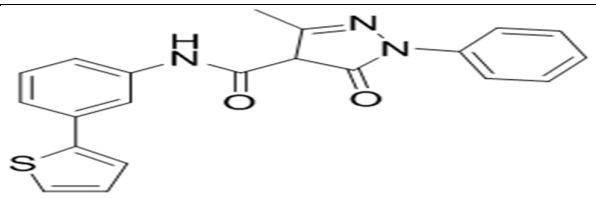
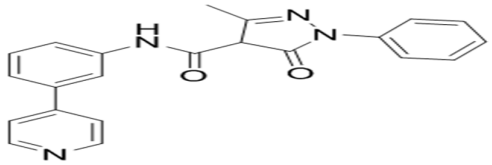
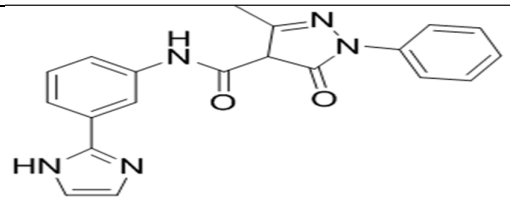
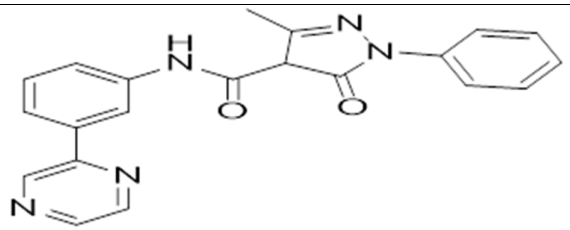
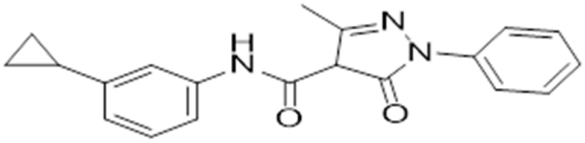
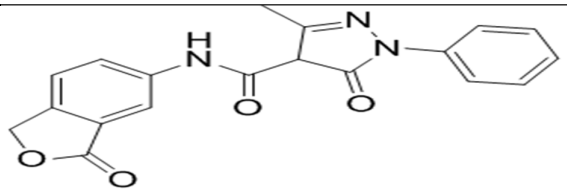
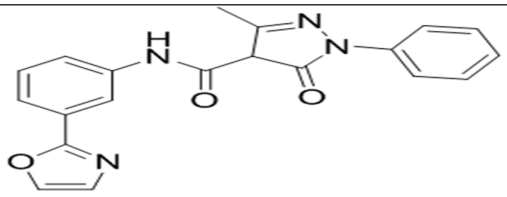
R_1, R_2, R_3, R_4, and **R_5** are as defined in claim 1; and

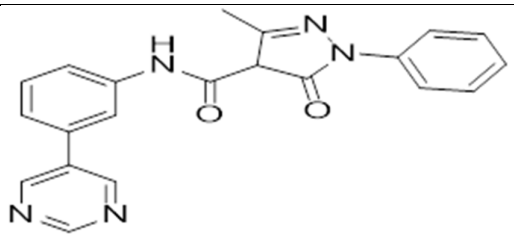
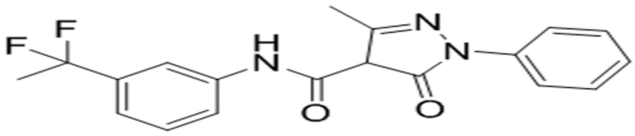
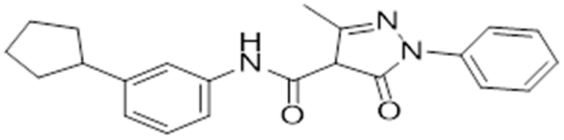
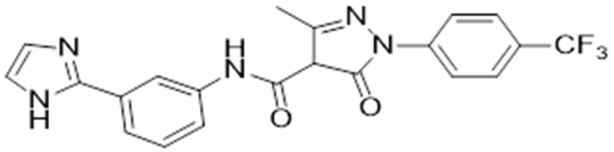
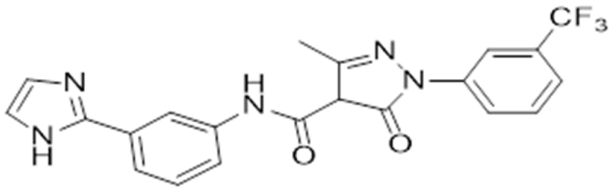
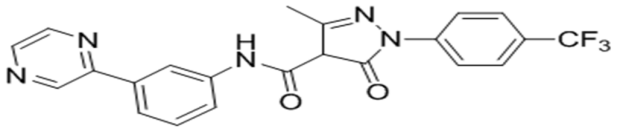
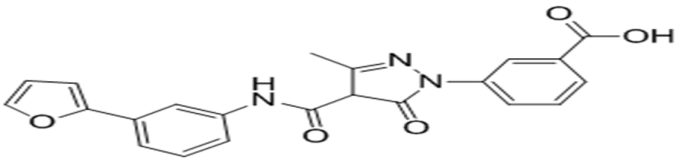
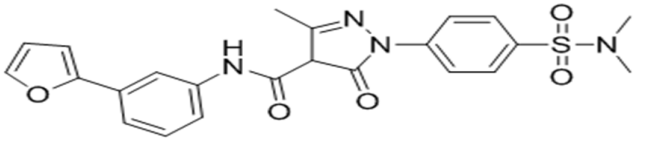
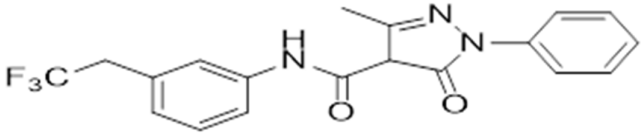
X_3, **X_4**, **X_7**, and **X_8** are each independently C or N;

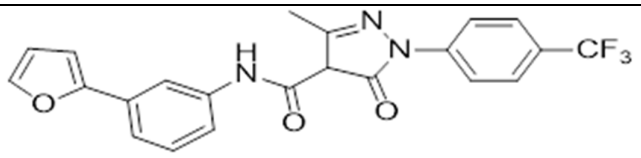
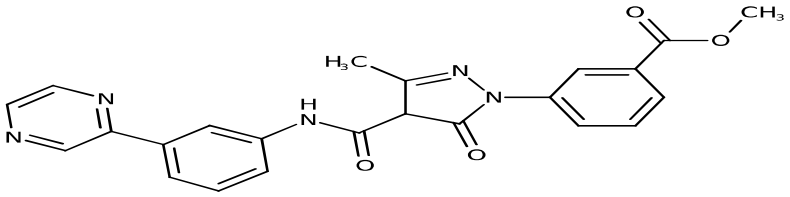
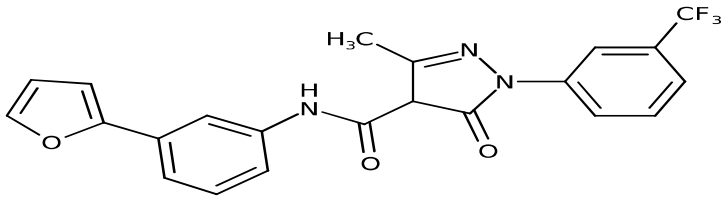
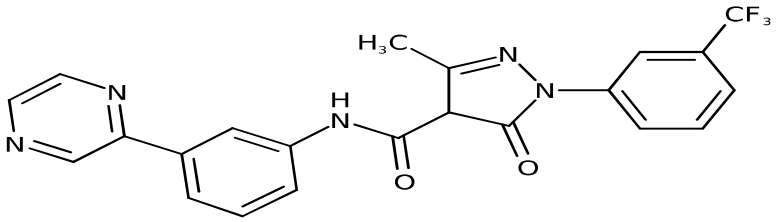
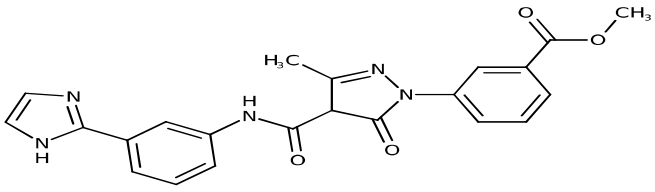
wherein if X_3 is N, then R_4 is absent; and

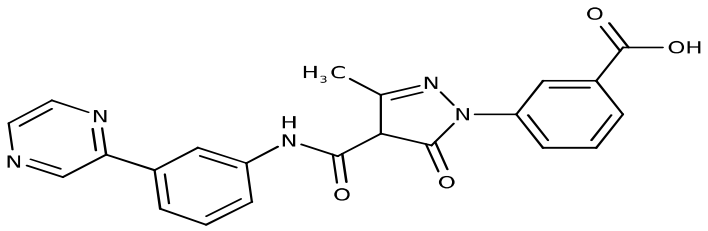
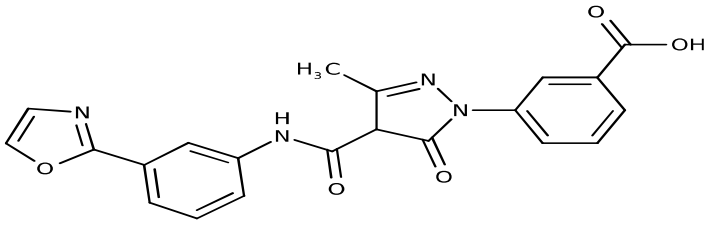
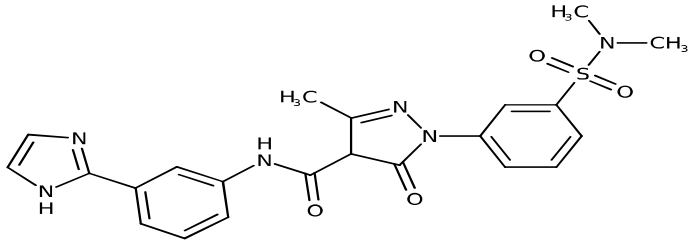
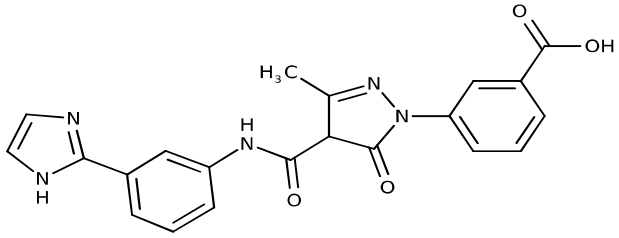
wherein if X_8 is N, then R_2 is absent.

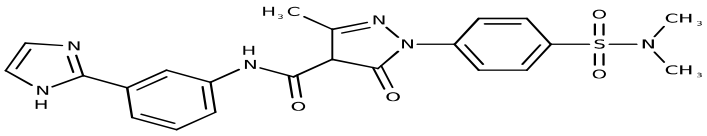
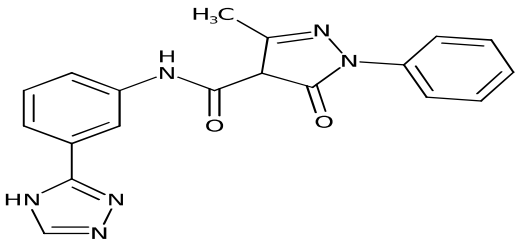
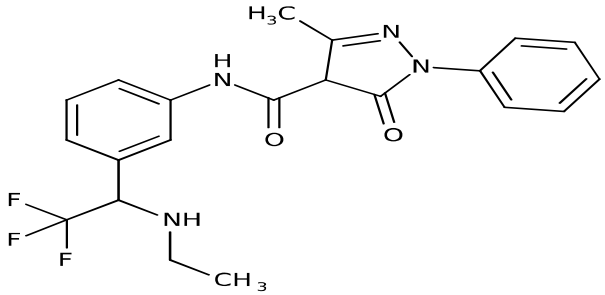
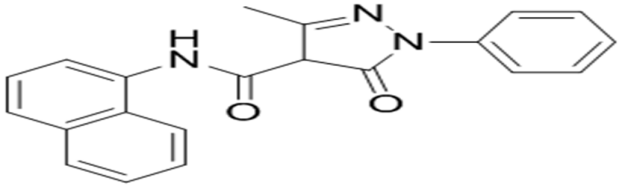
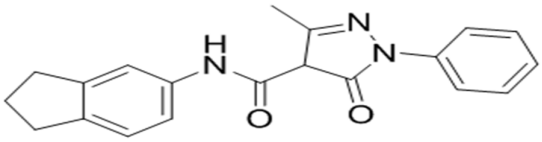
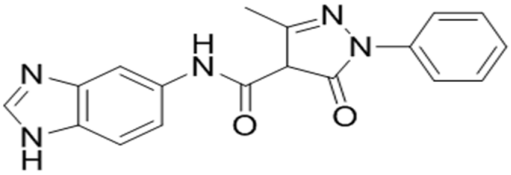
3. The compound of claim 1, selected from the following:

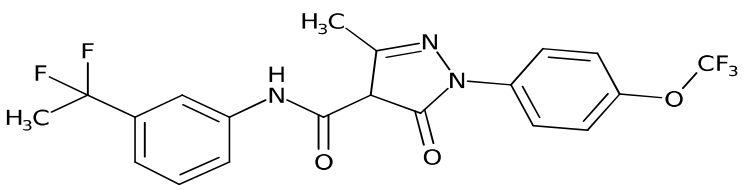
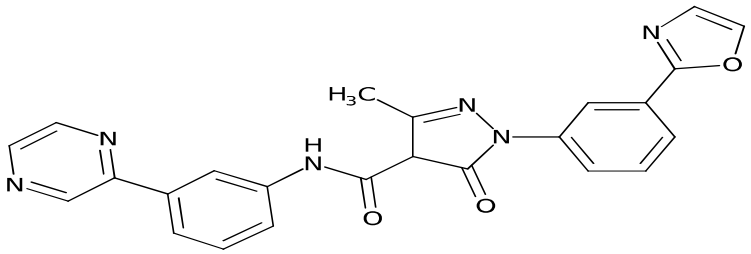
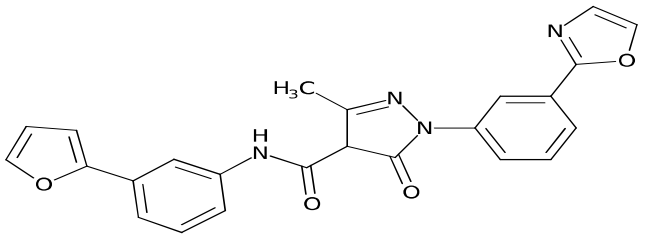
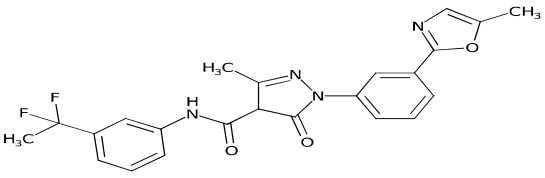
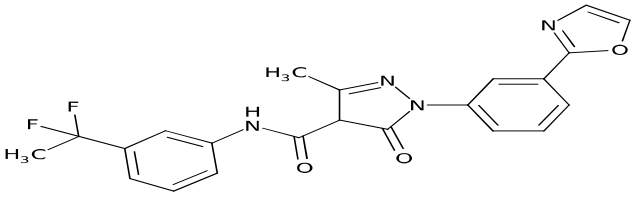
Compound name	Structure
101	
104	
107	
109	
119	
122	
124	

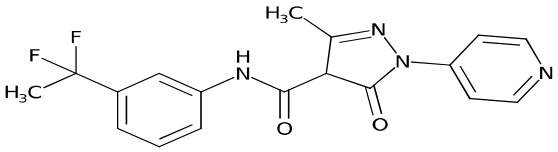
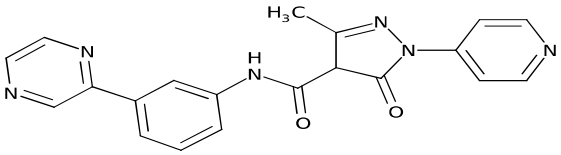
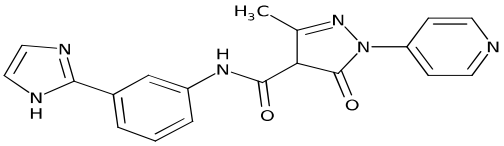
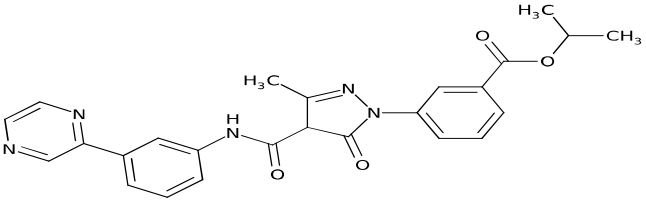
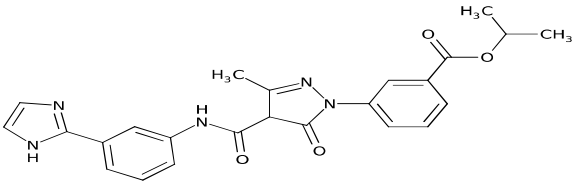
132	
141	
146	
148	
149	
150	
159	
160	
161	

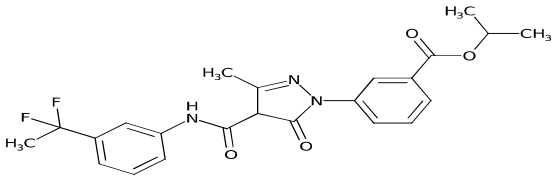
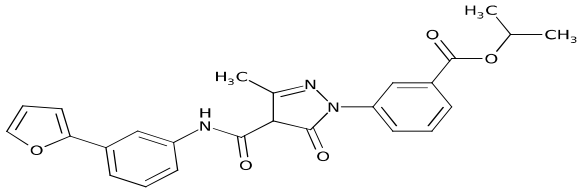
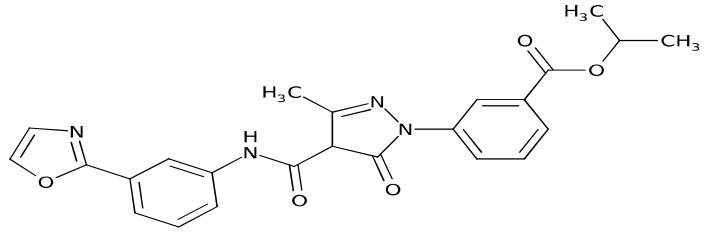
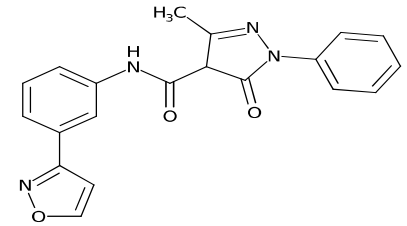
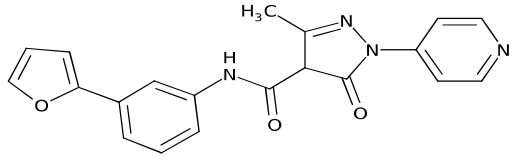
162	
164	
165	
166	
167	

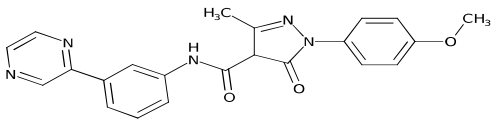
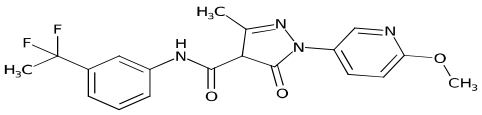
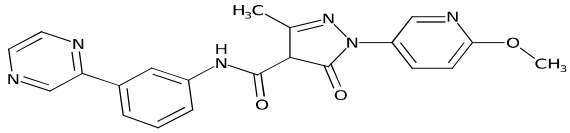
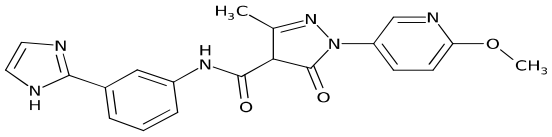
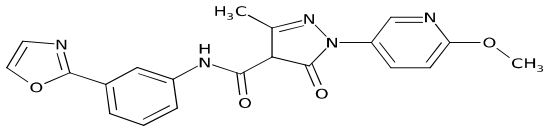
169	
170	
171	
172	

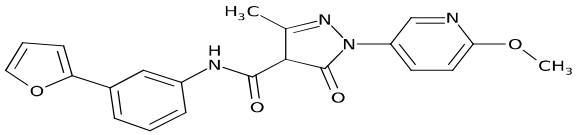
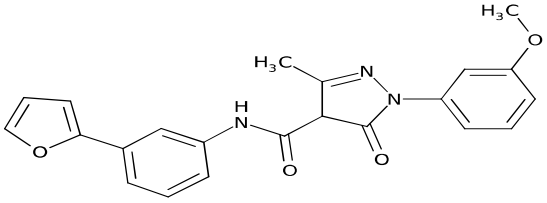
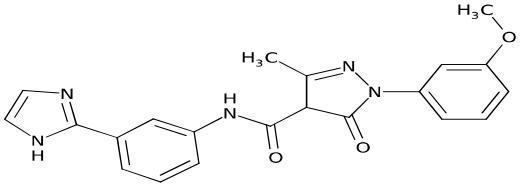
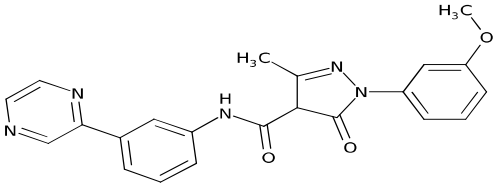
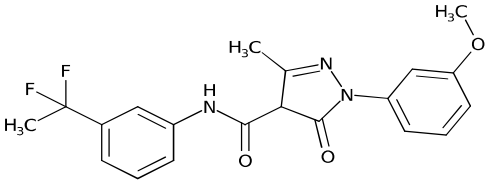
173	
174	
176	
185	
209	
219	

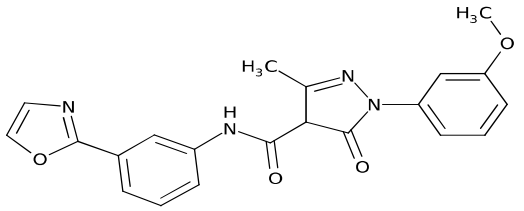
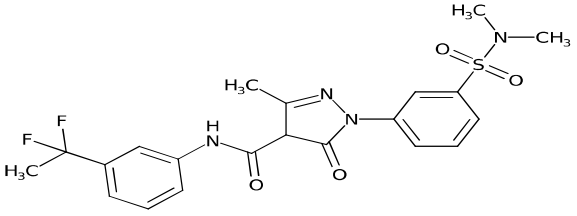
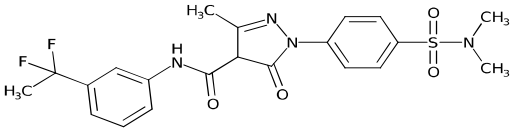
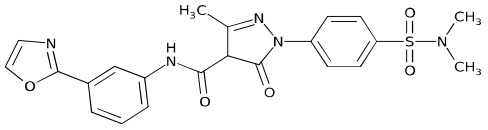
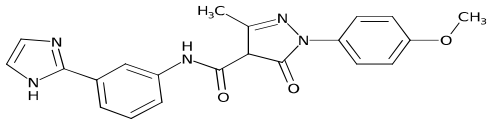
226	
227	
228	
229	
230	

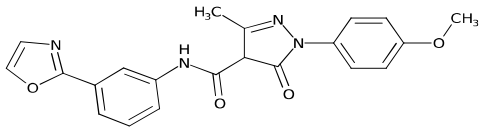
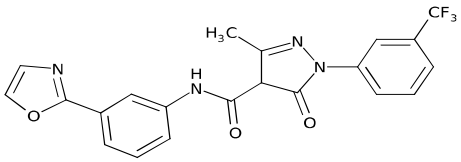
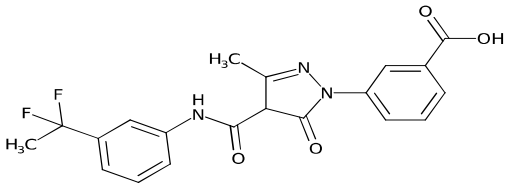
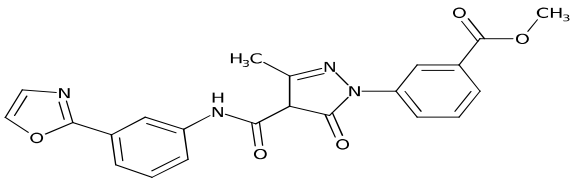
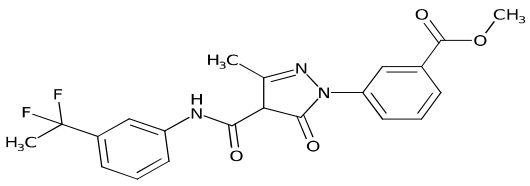
231	
232	
233	
234	
235	

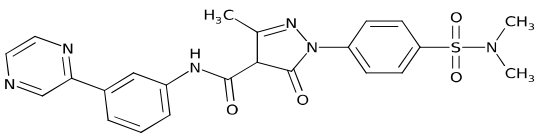
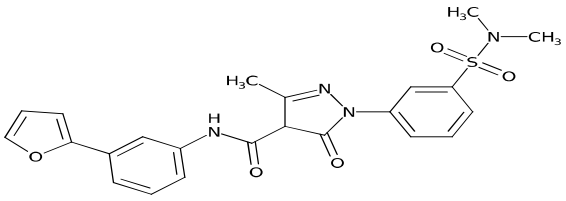
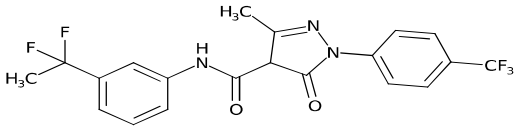
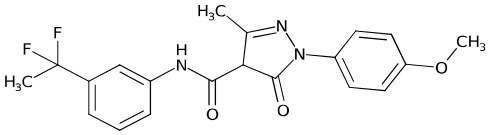
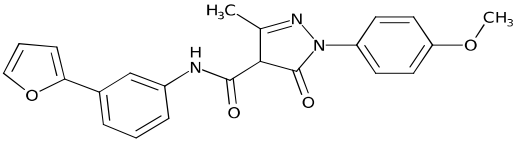
236	
237	
238	
239	
240	

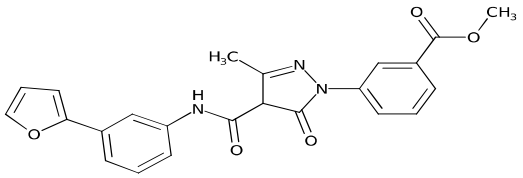
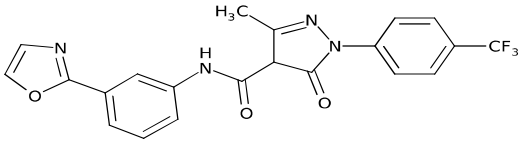
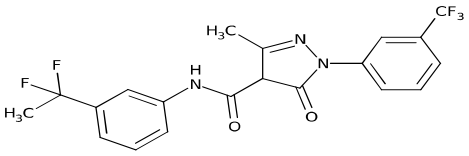
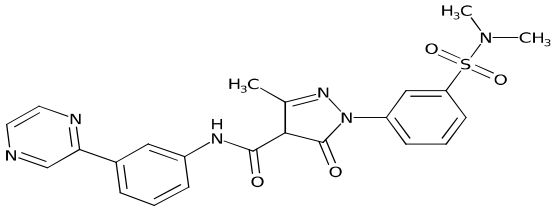
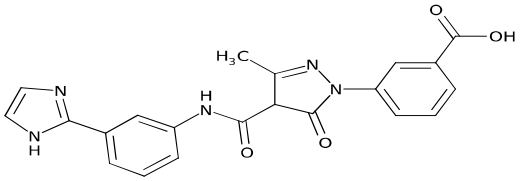
241	
242	
243	
244	
245	

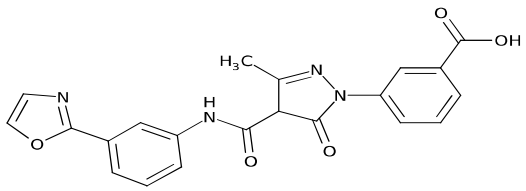
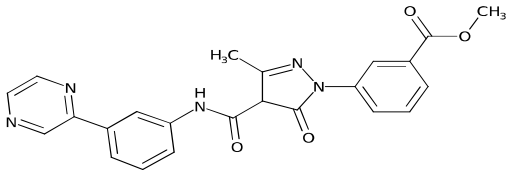
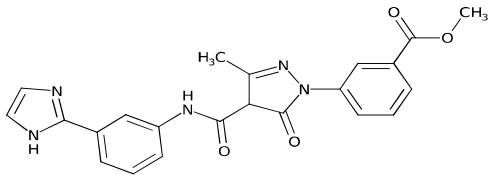
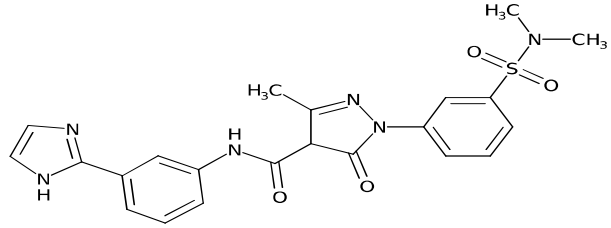
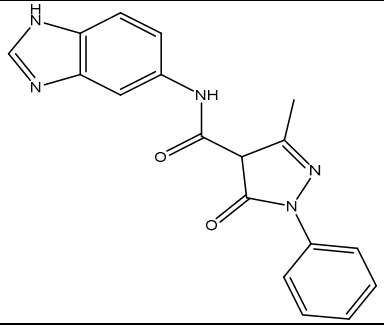
246	
247	
248	
249	
250	

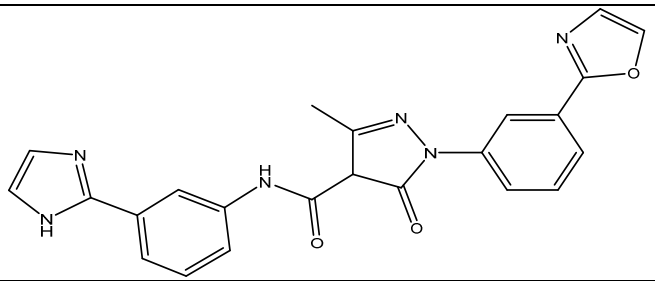
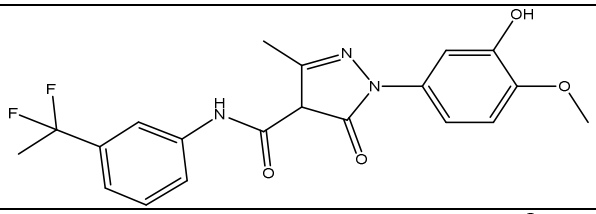
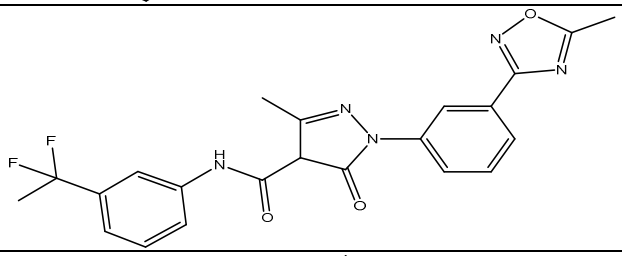
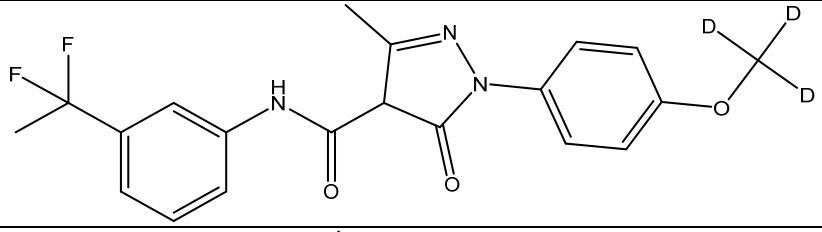
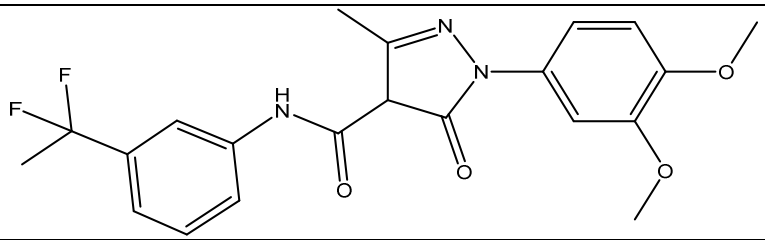
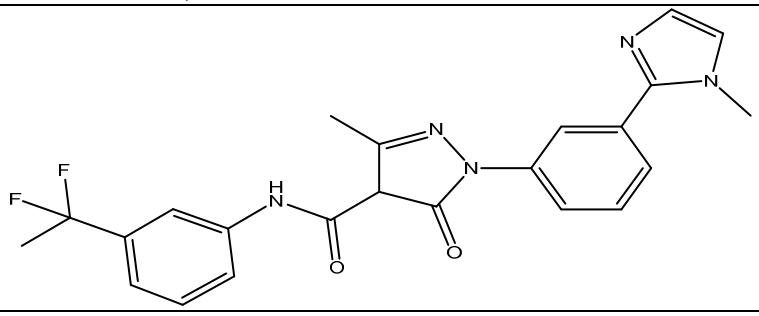
251	
252	
253	
254	
255	

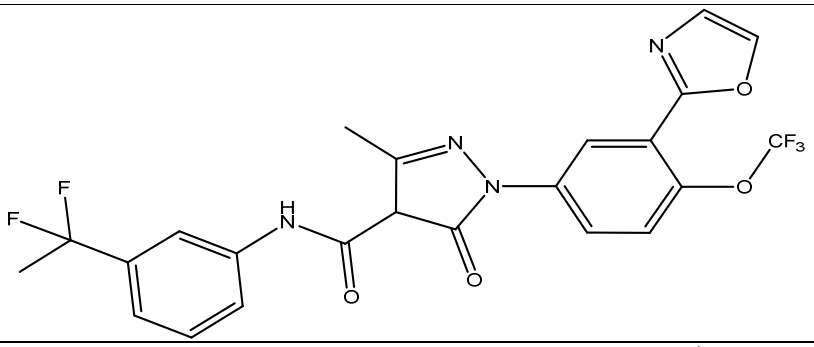
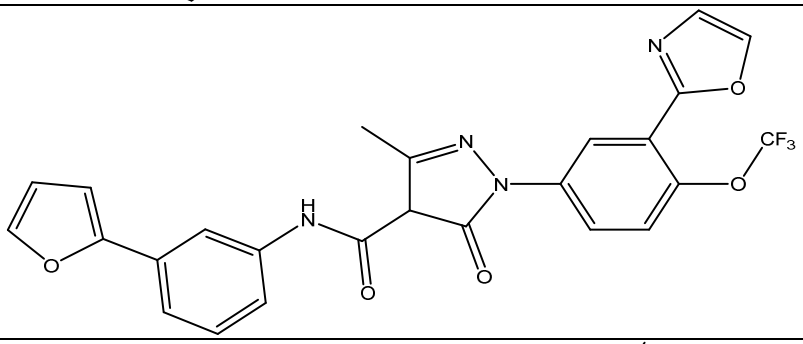
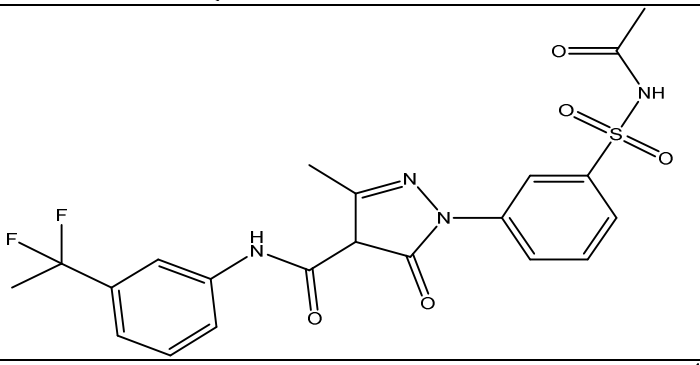
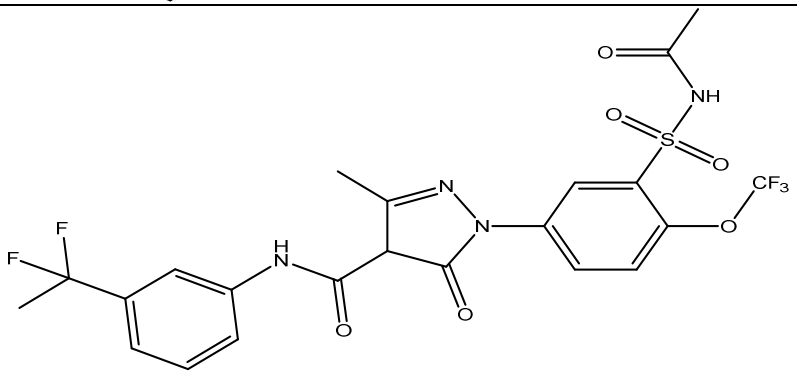
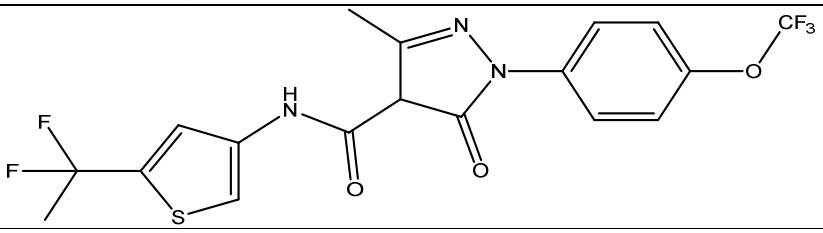
256	
257	
258	
259	
261	

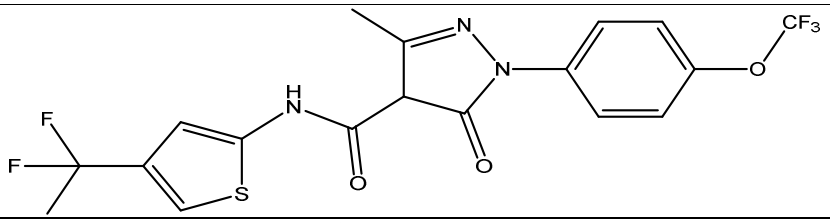
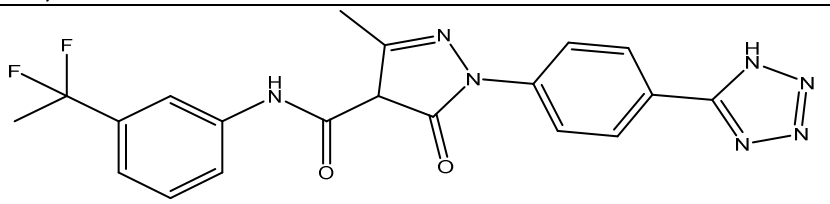
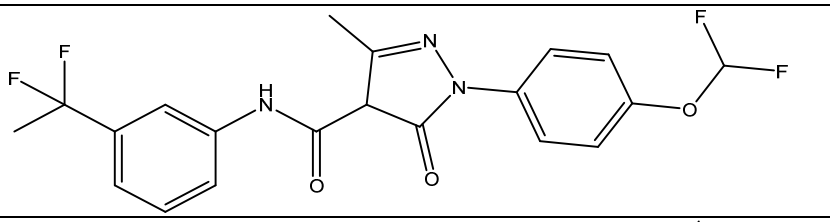
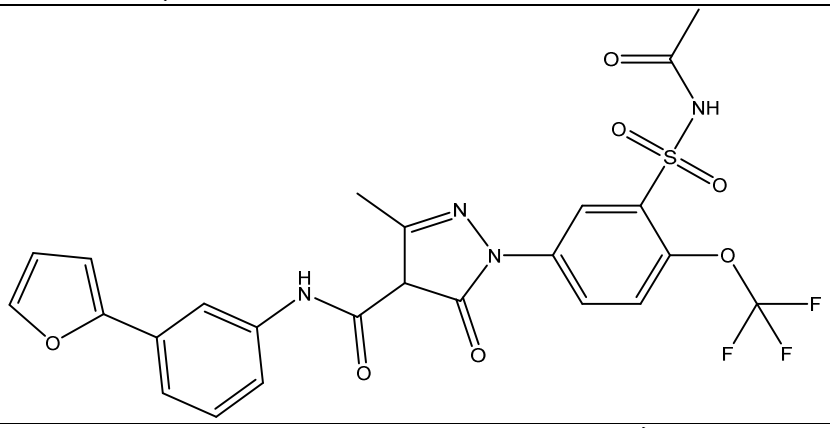
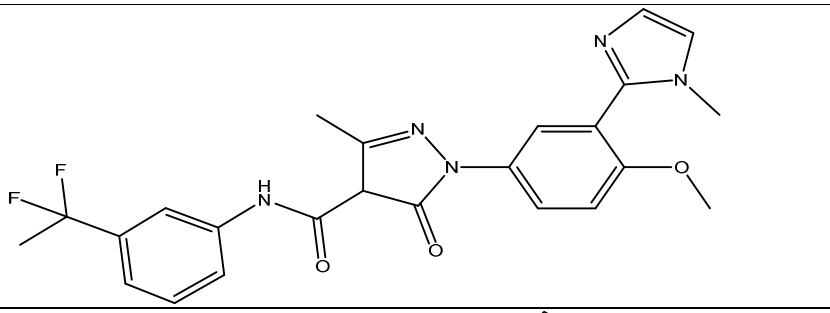
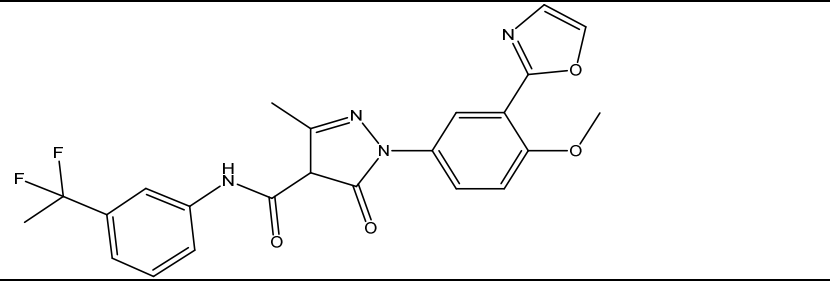
262	
263	
264	
265	
266	

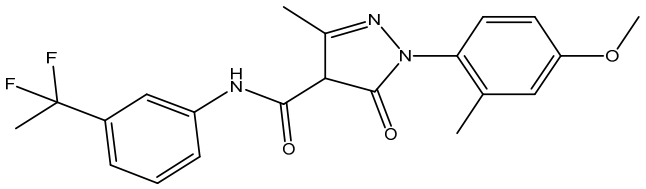
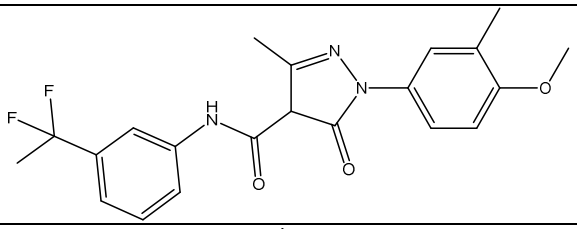
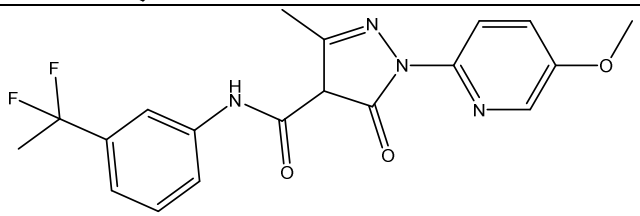
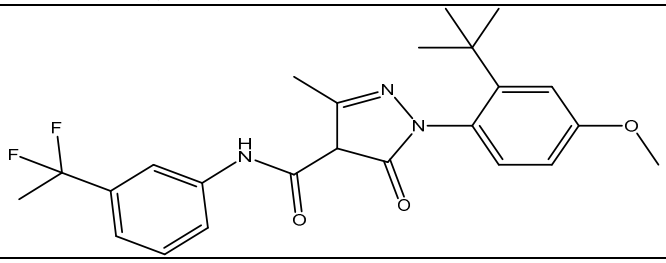
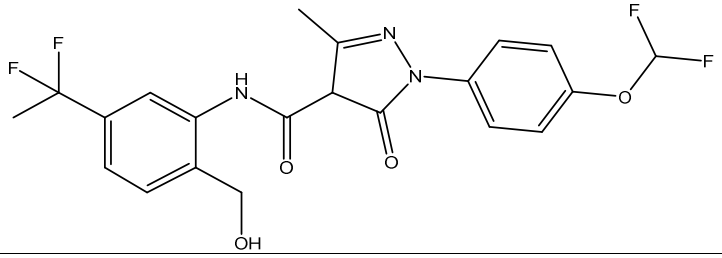
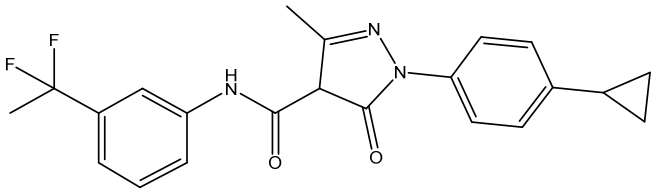
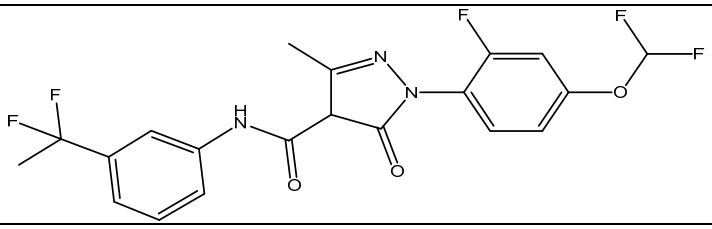
269	
270	
271	
272	
273	

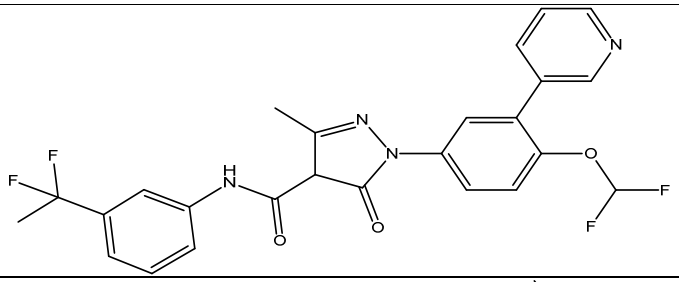
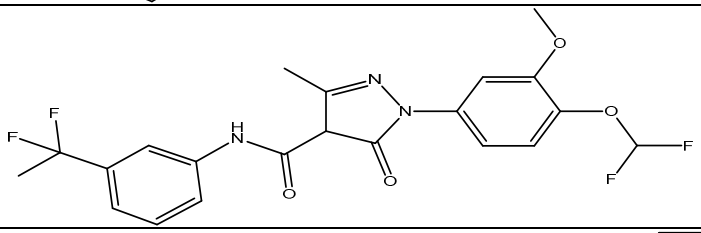
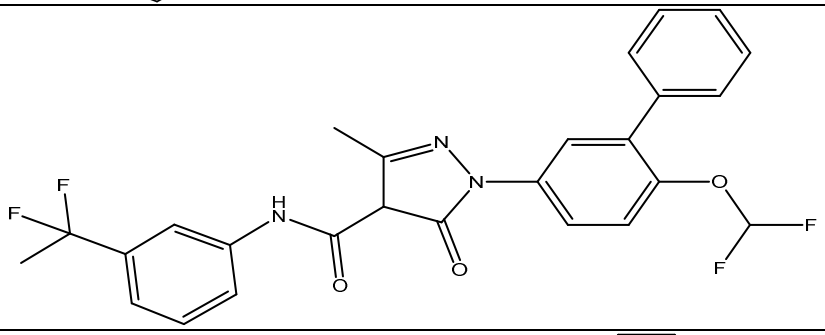
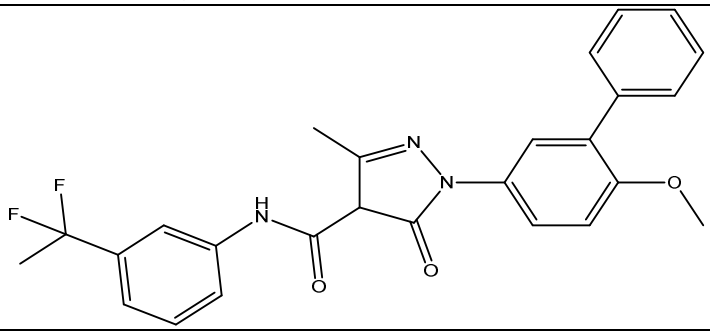
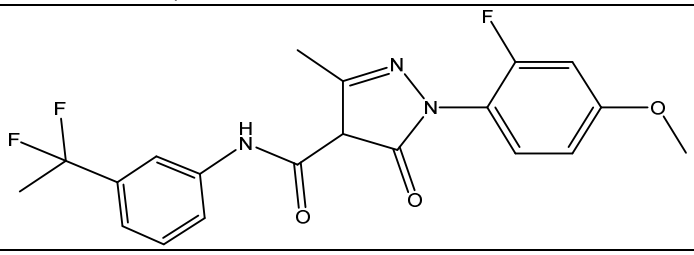
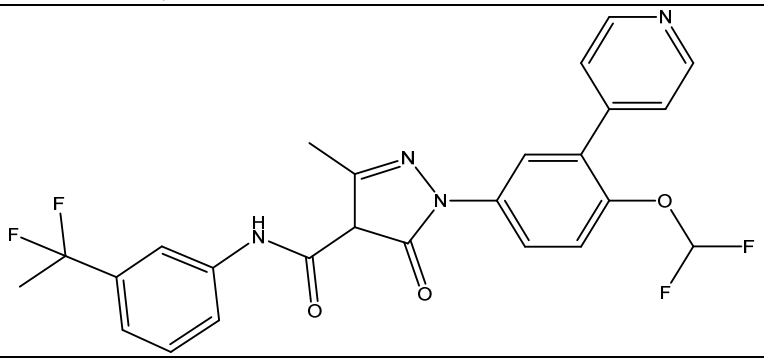
274	
275	
276	
277	
278	

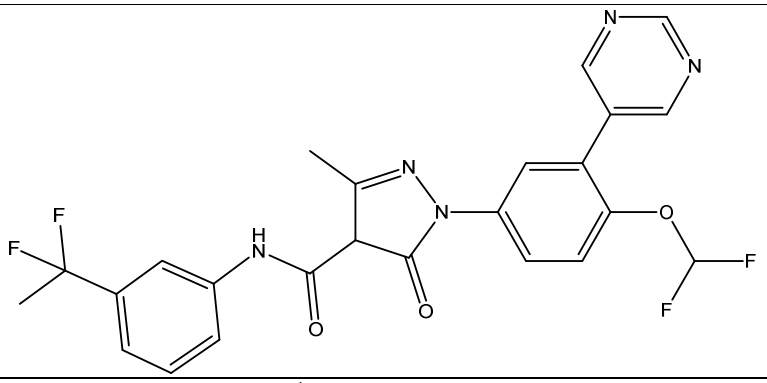
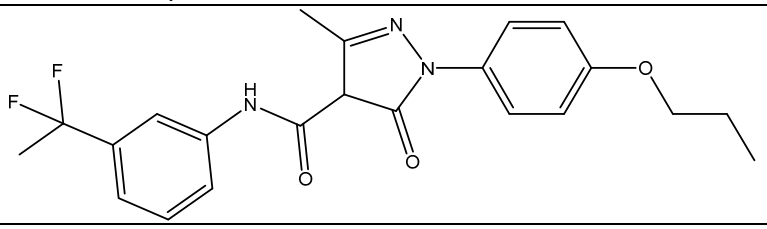
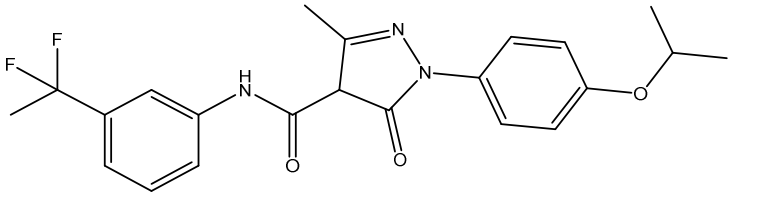
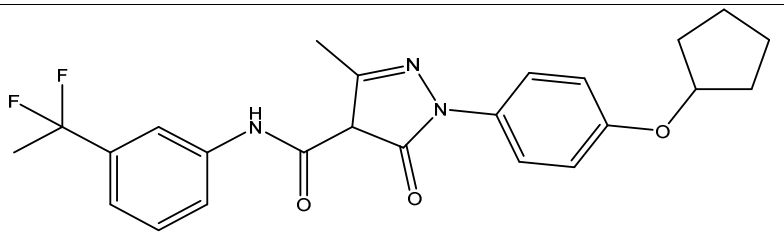
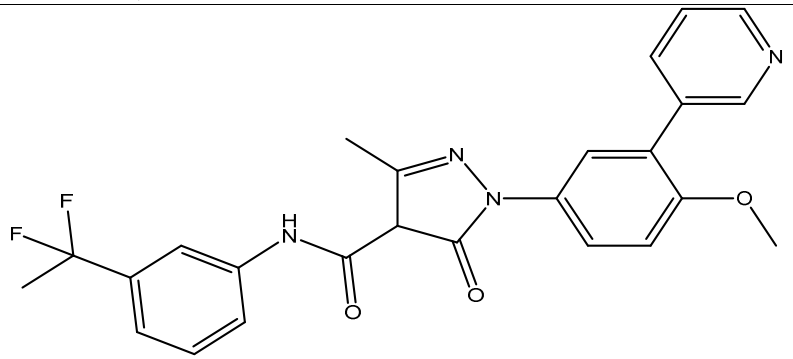
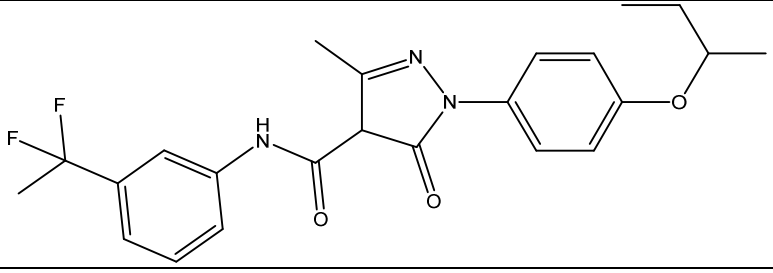
279	
280	
281	
282	
286	
287	
289	

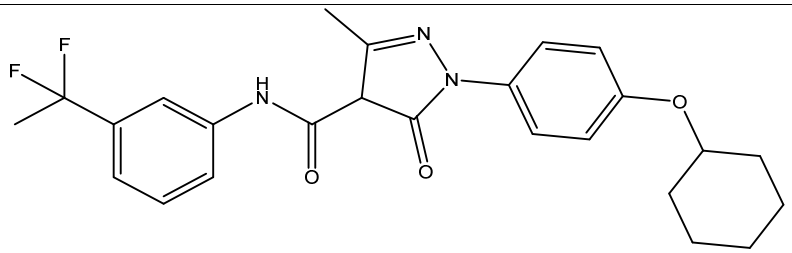
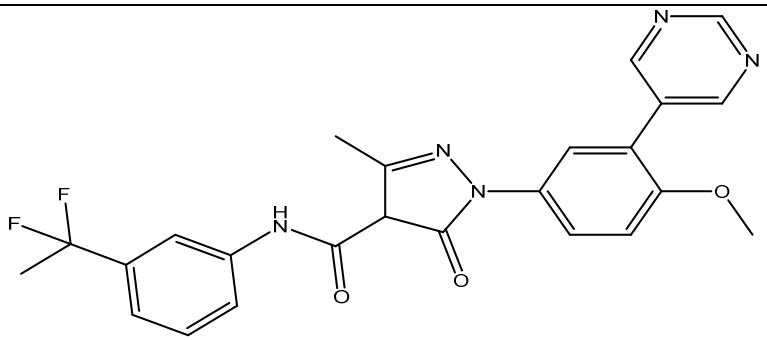
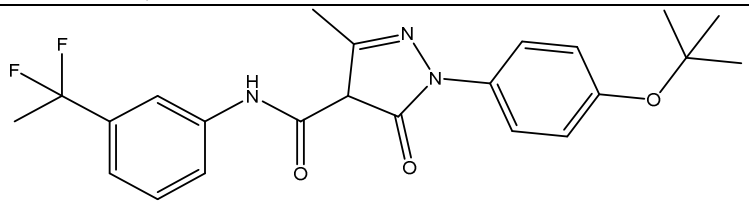
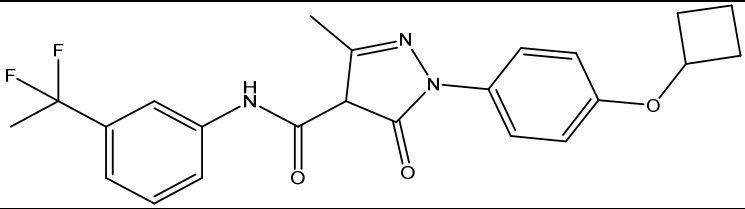
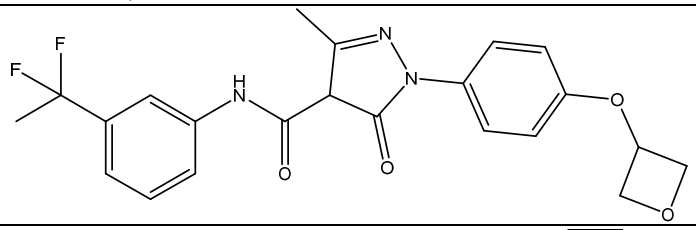
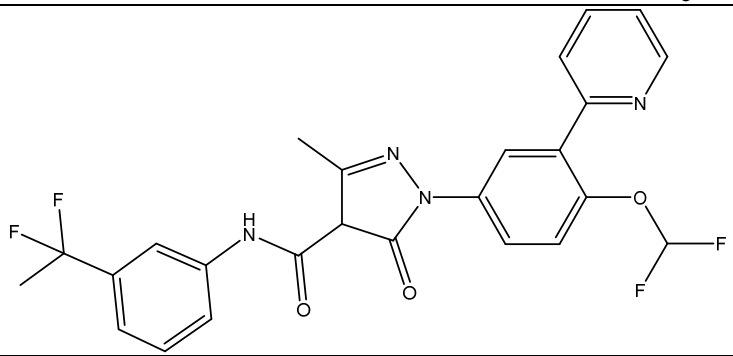
291	
292	
293	
294	
295	

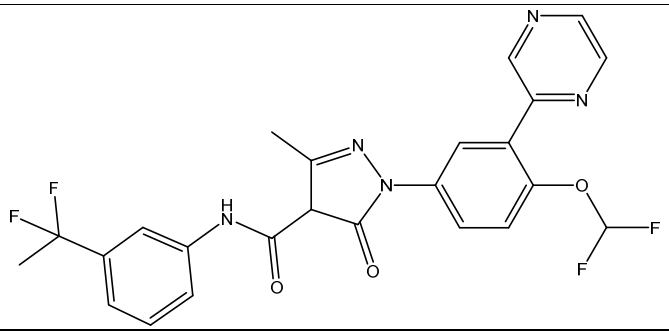
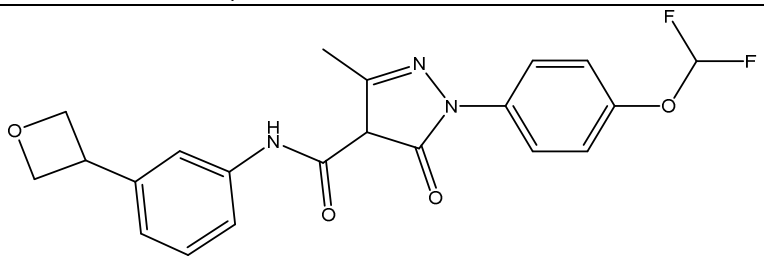
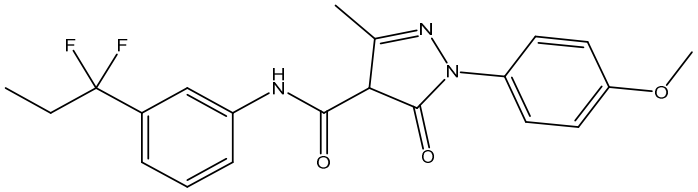
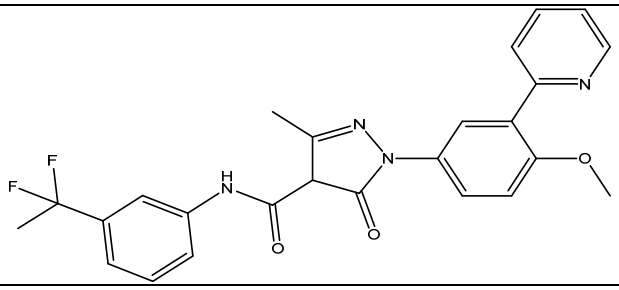
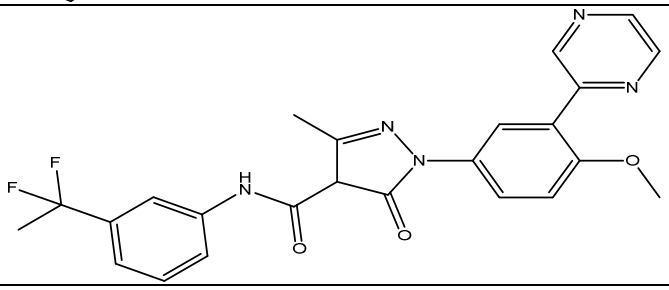
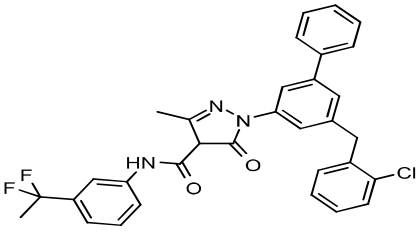
296	
297	
298	
299	
300	
301	

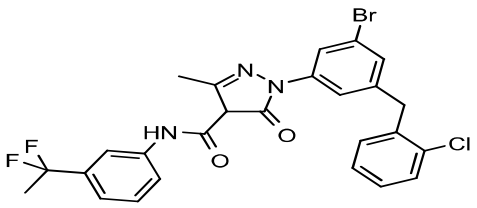
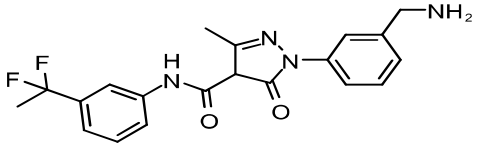
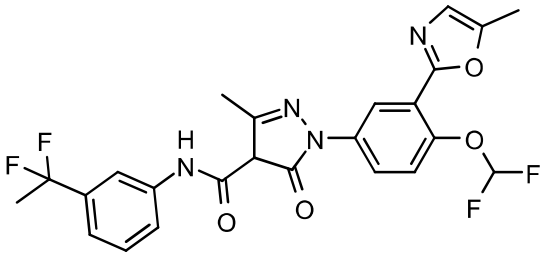
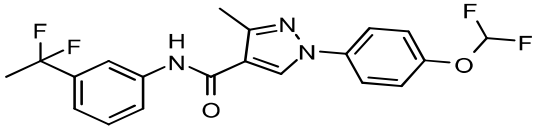
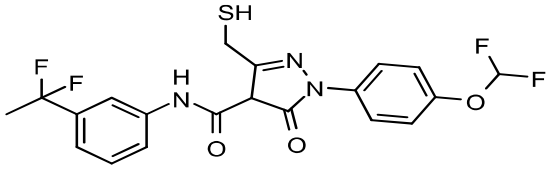
302	
303	
304	
305	
306	
308	
309	

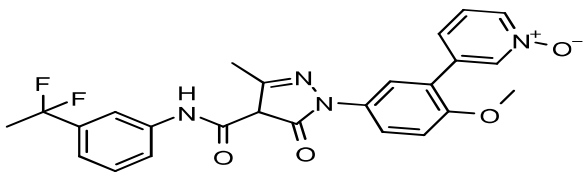
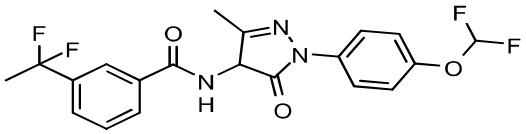
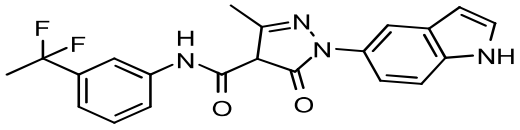
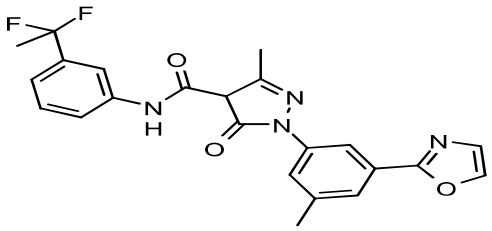
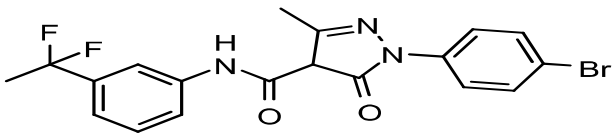
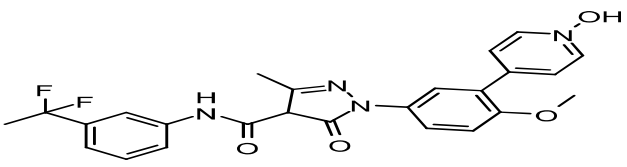
310	
311	
312	
313	
314	
315	

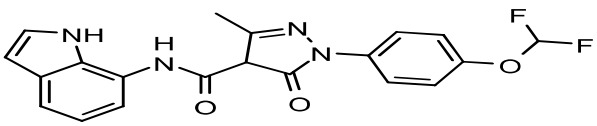
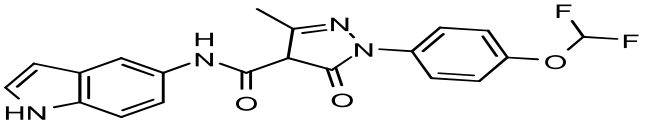
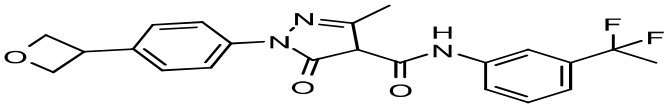
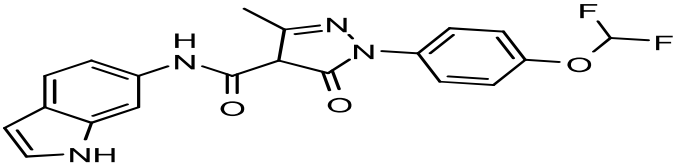
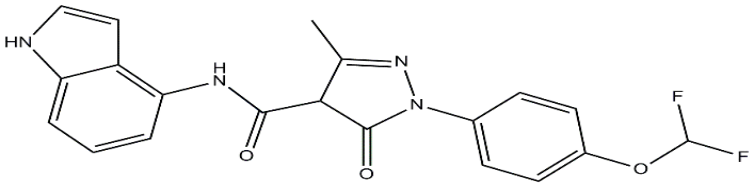
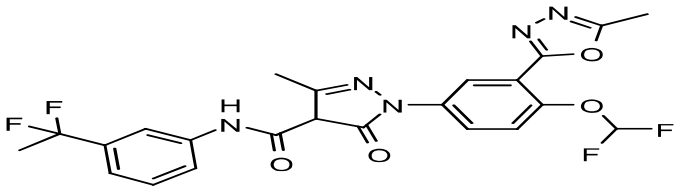
316	
317	
318	
319	
320	
321	

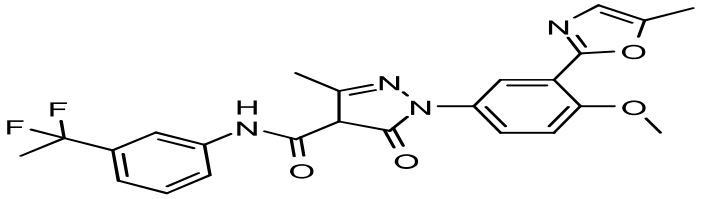
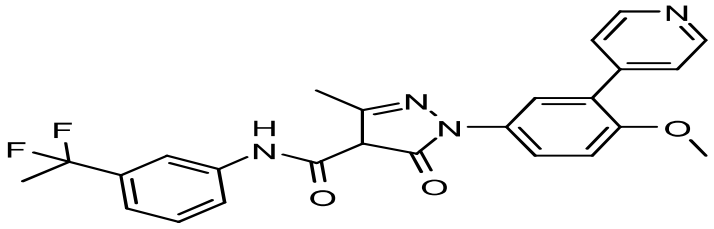
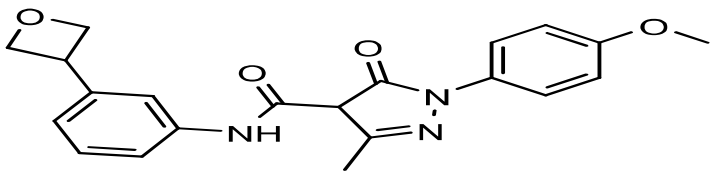
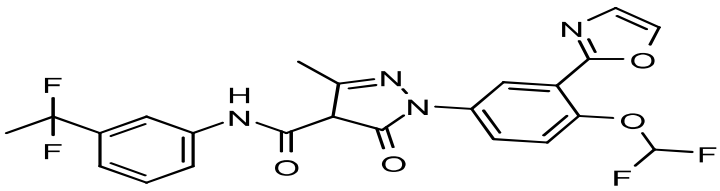
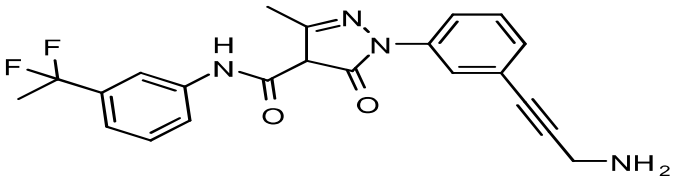
322	
323	
324	
325	
326	
327	

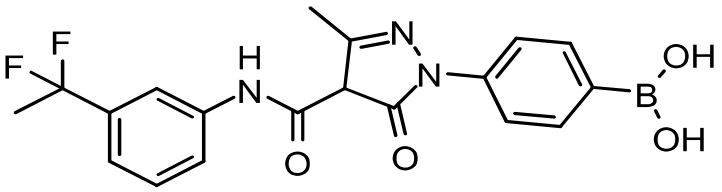
328	
329	
330	
331	
332	
333	

334	
335	
336	
338	
339	

340	
341	
342	
343	
344	
345	

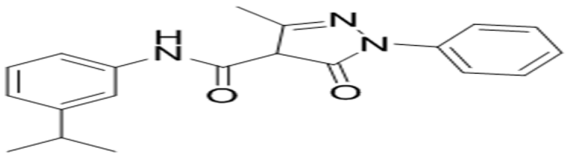
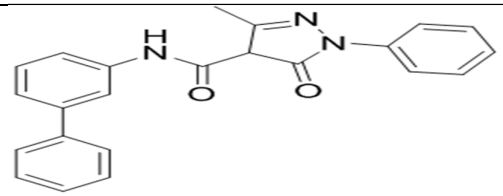
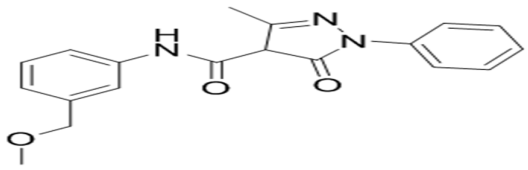
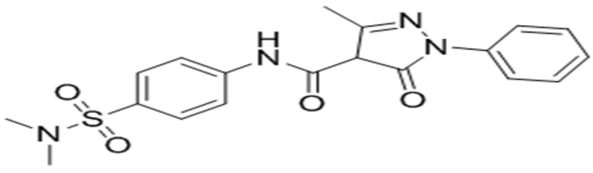
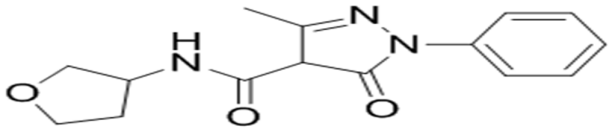
346	
347	
348	
349	
350	
351	

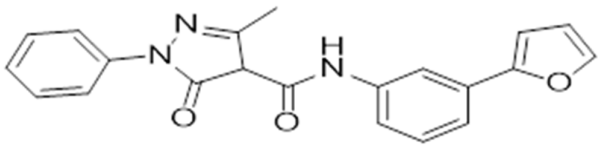
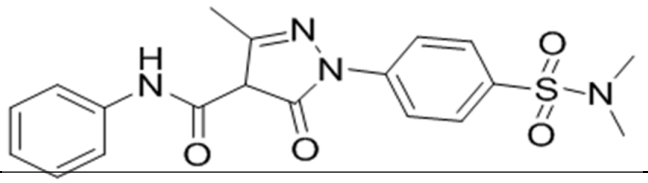
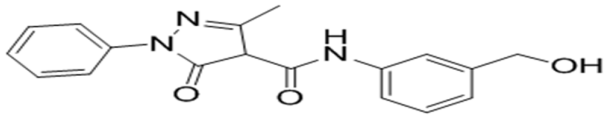
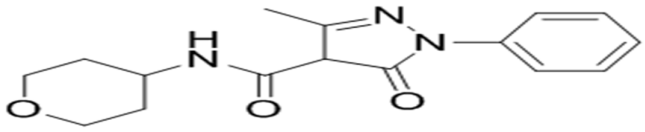
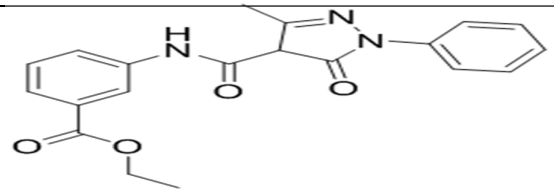
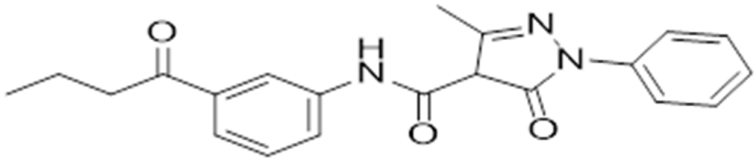
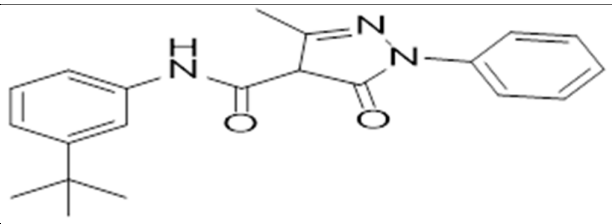
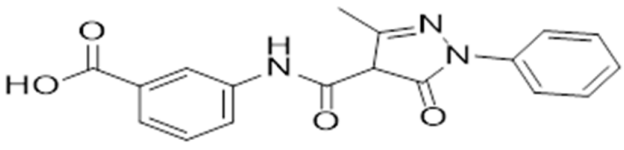
352	
353	
354	
355	
356	 HCl

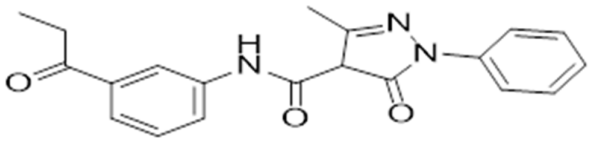
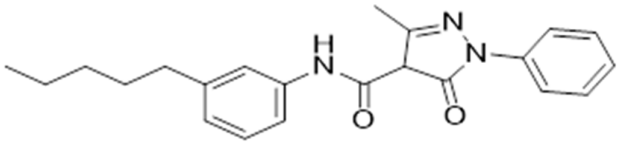
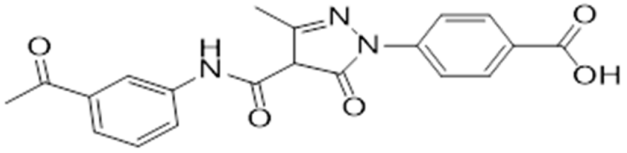
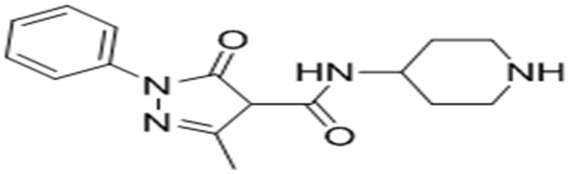
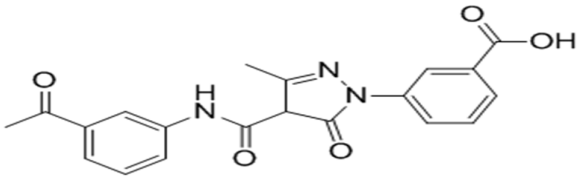
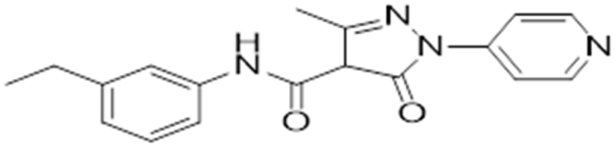
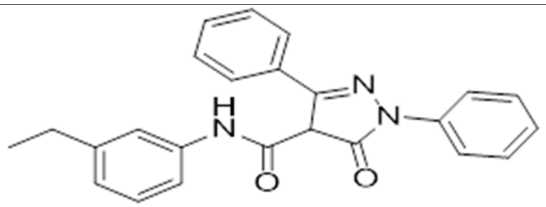
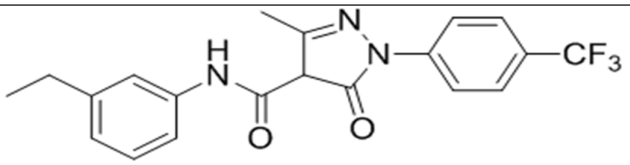
357	

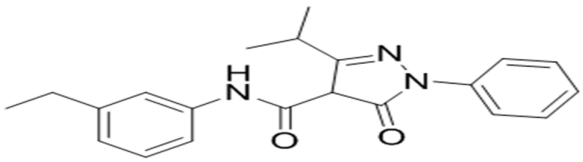
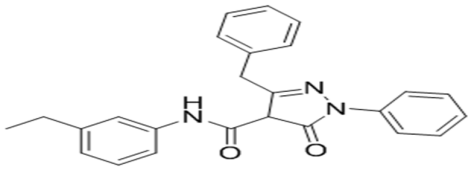
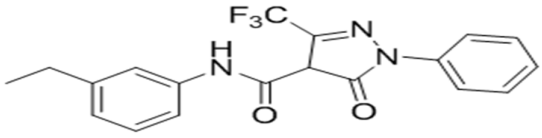
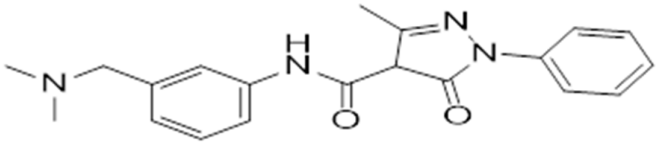
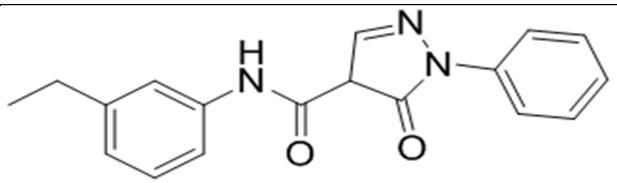
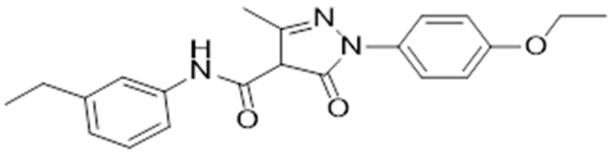
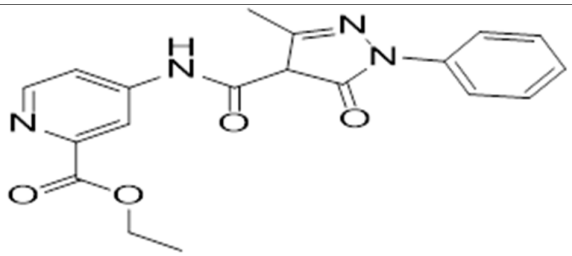
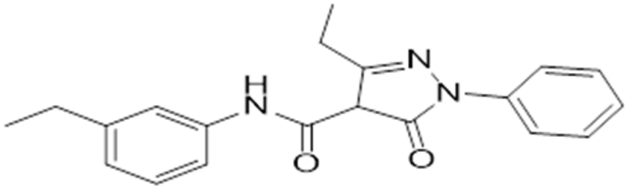
or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, isotopic variants (e.g., deuterated analog), pharmaceutical product or any combination thereof.

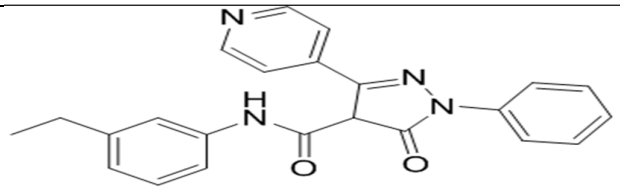
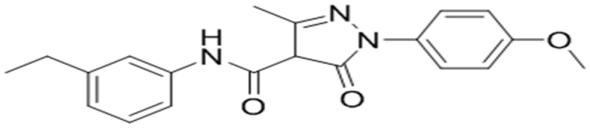
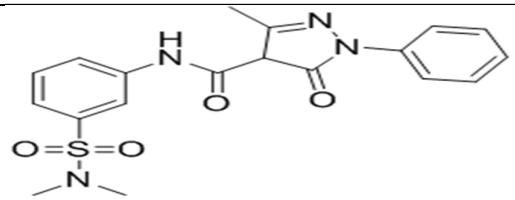
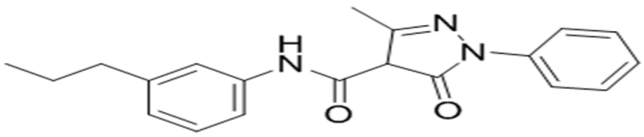
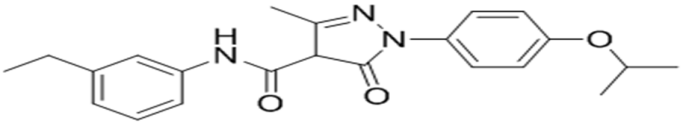
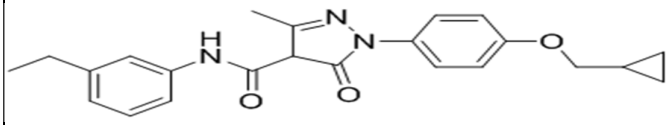
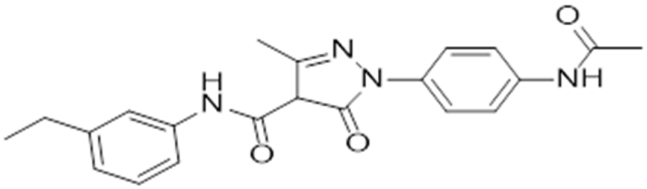
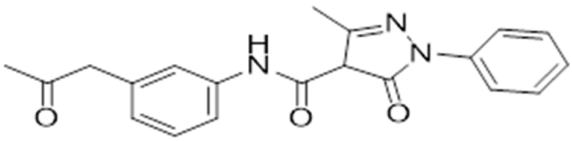
4. A compound represented by the following structures:

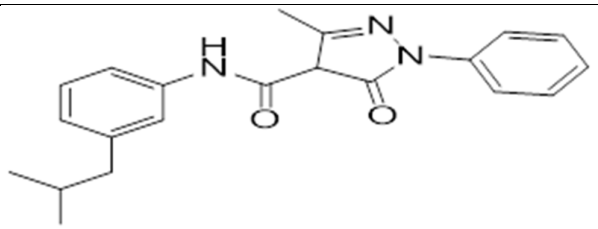
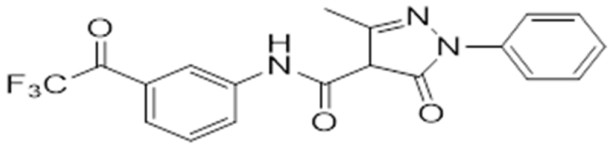
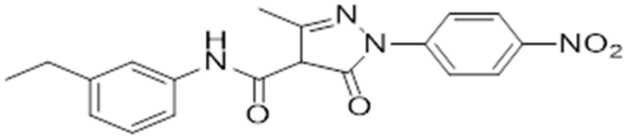
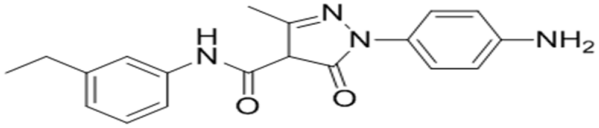
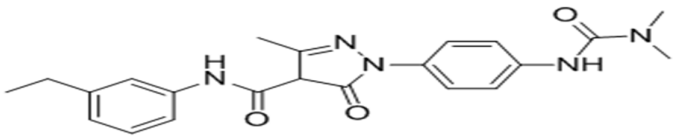
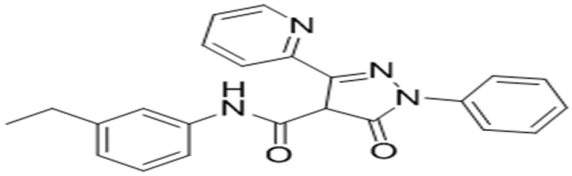
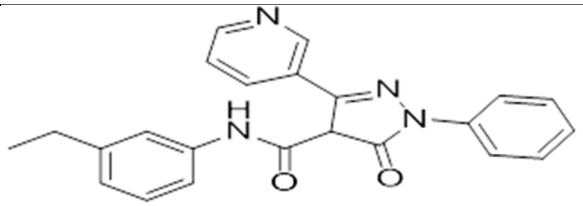
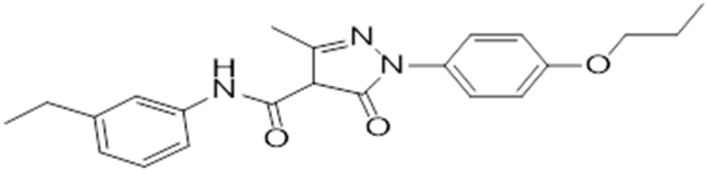
Compound name	Structure
100	
102	
103	
105	
106	

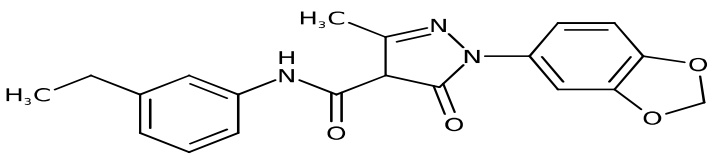
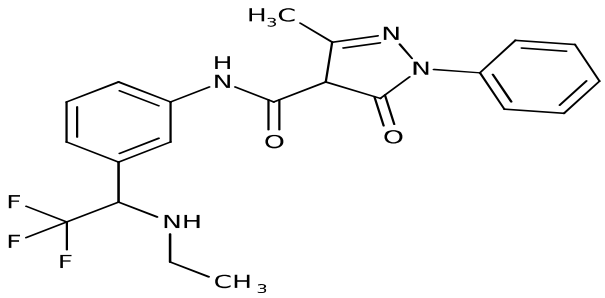
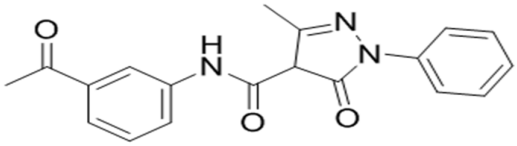
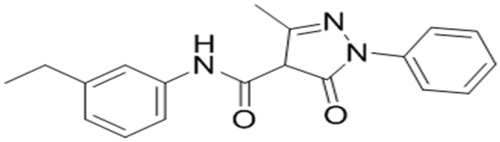
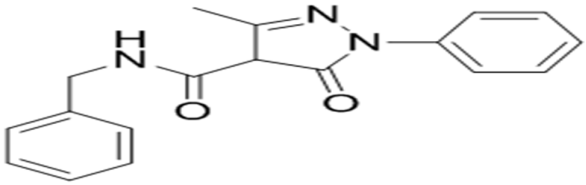
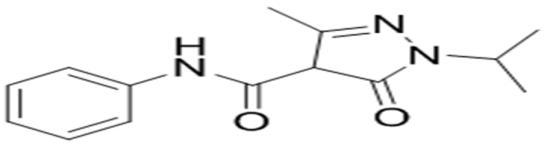
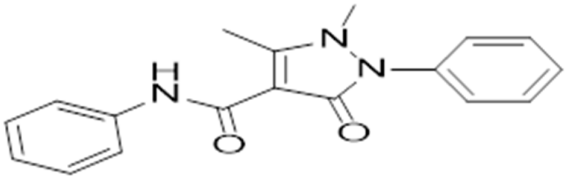
108	
110	
111	
112	
113	
114	
115	
116	

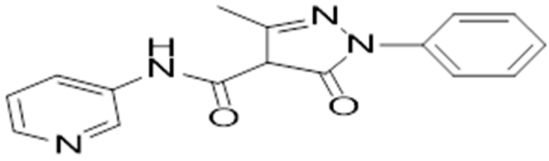
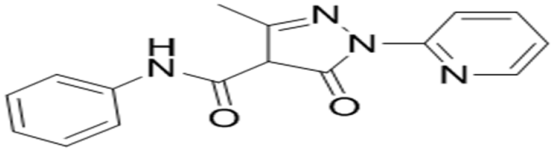
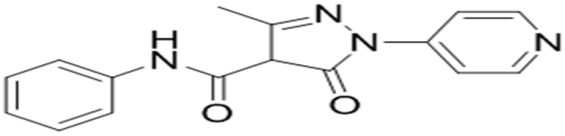
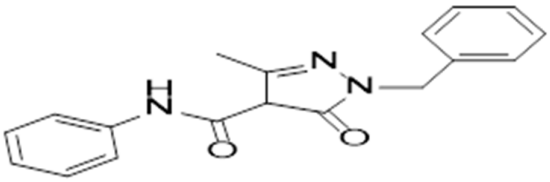
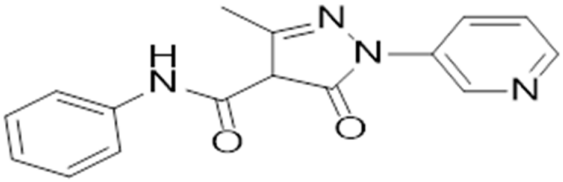
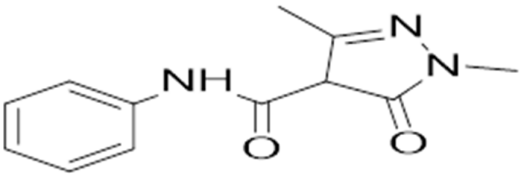
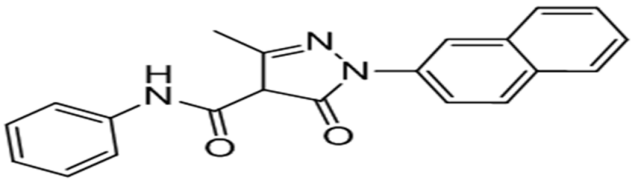
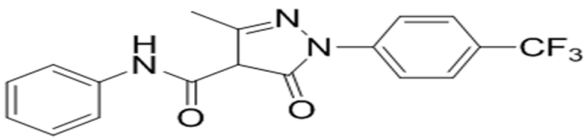
117	
118	
120	
121	
123	
125	
126	
127	

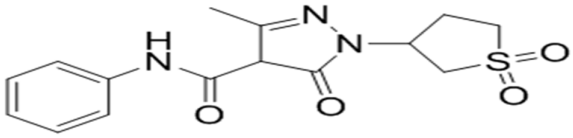
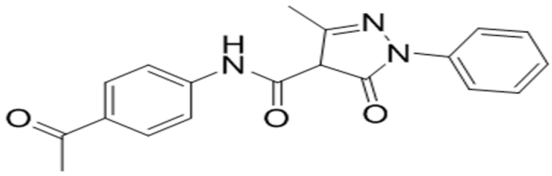
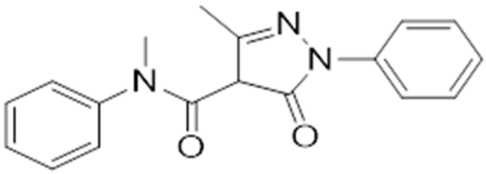
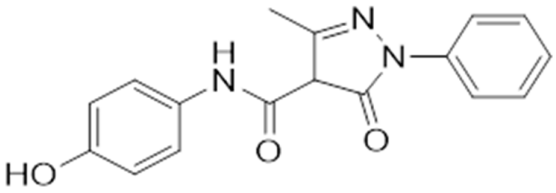
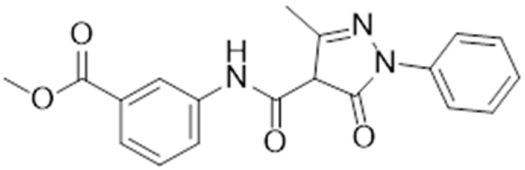
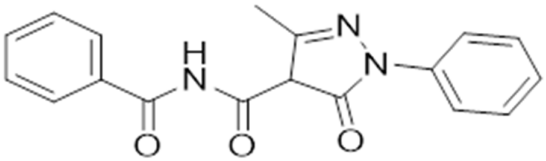
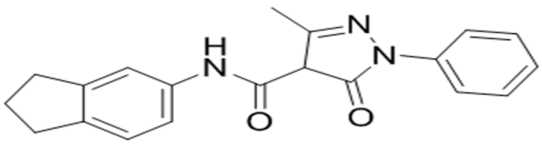
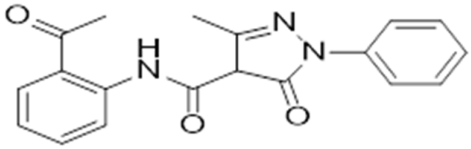
128	
129	
130	
131	
133	
134	
135	
136	

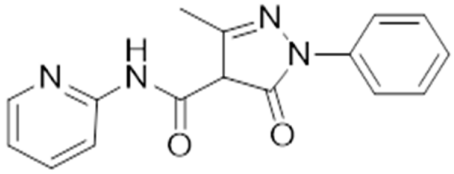
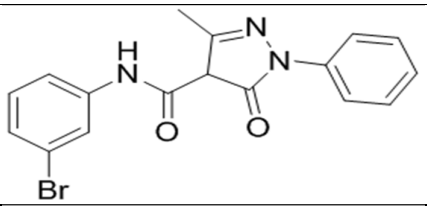
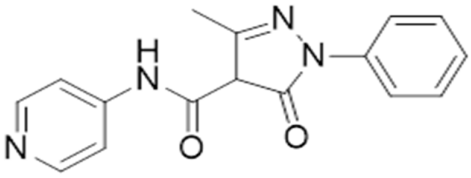
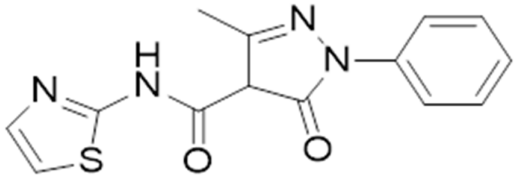
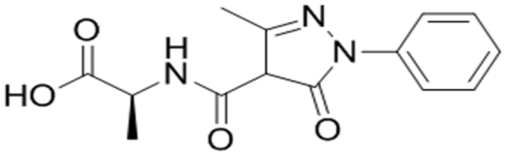
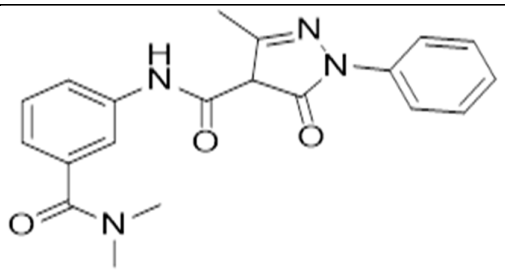
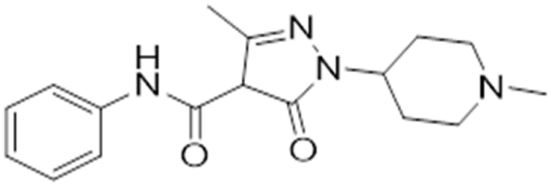
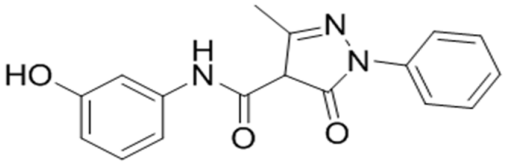
137	
138	
139	
140	
142	
143	
144	
145	

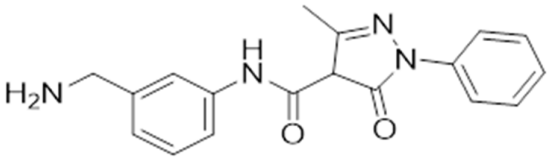
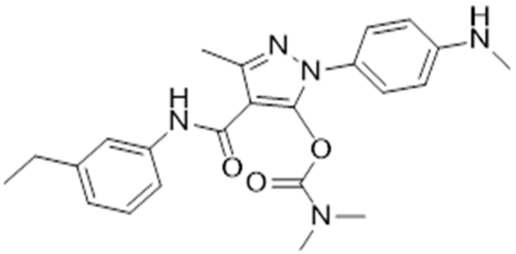
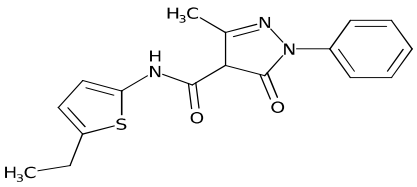
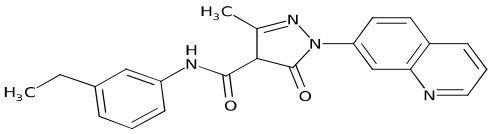
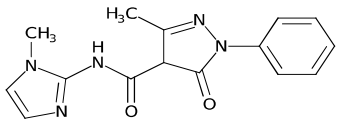
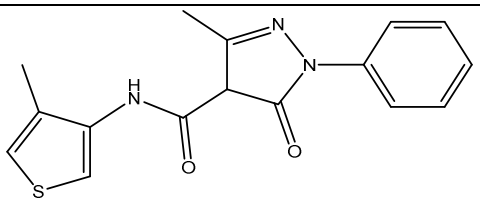
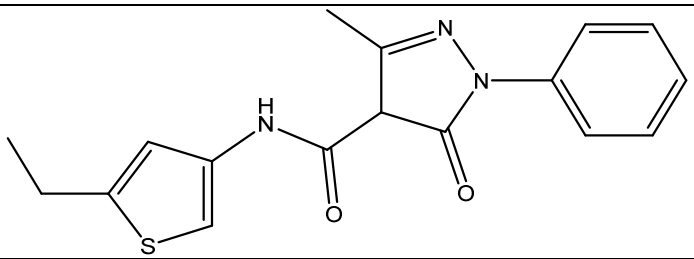
147	
152	
153	
154	
155	
156	
157	
158	

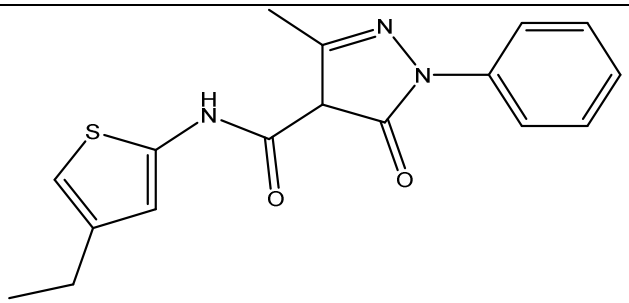
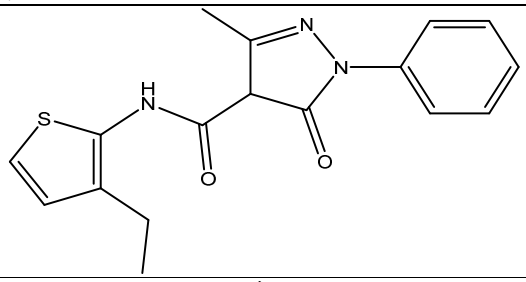
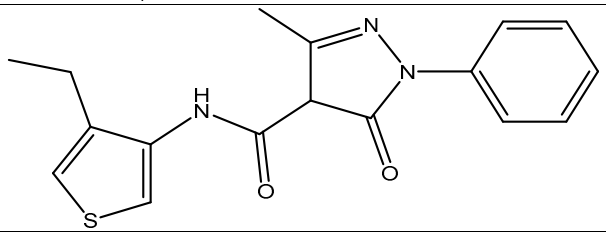
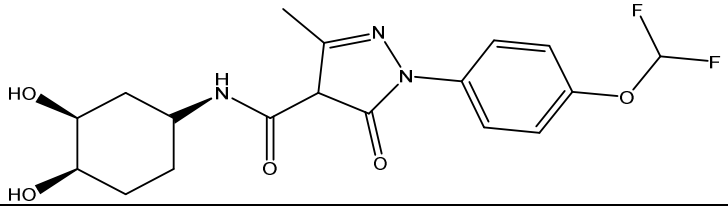
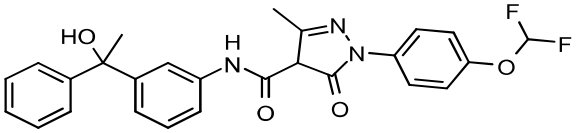
168	
176	
183	
184	
186	
187	
190	

191	
192	
193	
194	
195	
196	
198	
201	

202	
203	
204	
205	
206	
207	
209	
213	

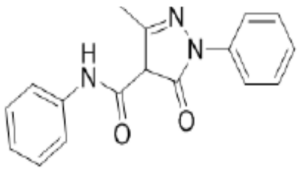
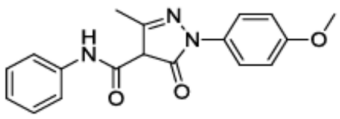
214	
215	
216	
217	
218	
220	
221	
222	

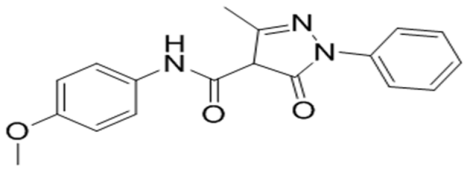
223	
224	
260	
267	
268	
283	
284	

285	
288	
290	
307	
337	

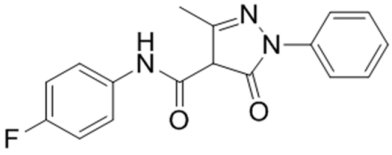
5. The compound of any one of the preceding claims, wherein the compound is an Acyl-CoA Synthetase Short-Chain Family Member 2 (ACSS2) inhibitor.

6. Use of a compound represented by the following structures:

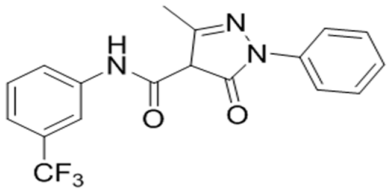
 **182** ;  **197** ;



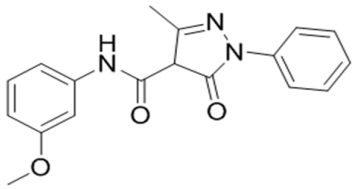
188 ;



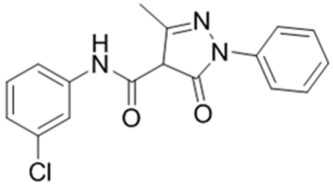
189



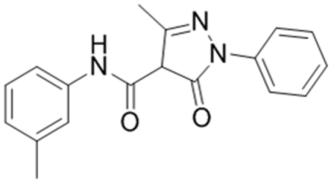
208 ;



211



210 ;



212 ;

in the manufacture of a medicament for:

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a viral infection, such as human cytomegalovirus (HCMV) infection, in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting alcoholic steatohepatitis (ASH) in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non alcoholic fatty liver disease (NAFLD) in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non-alcoholic steatohepatitis (NASH) in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a metabolic disorder such as obesity, weight gain, hepatic steatosis and fatty liver disease in a subject;

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a neuropsychiatric disease or disorder such as anxiety, depression, schizophrenia, autism and post-traumatic stress disorder in a subject; and/or

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.
8. A compound according to any of claims 1-6 for use as a medicament.
9. Use of a compound according to any of claims 1-6 in the manufacture of a medicament for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer in a subject.
10. The use according to claim 9, wherein the cancer is selected from hepatocellular carcinoma, melanoma (e.g., BRAF mutant melanoma), glioblastoma, breast cancer (e.g., invasive ductal carcinomas of the breast, triple-negative breast cancer), prostate cancer, liver cancer, brain cancer, ovarian cancer, lung cancer, Lewis lung carcinoma (LLC), colon carcinoma, pancreatic cancer, renal cell carcinoma and mammary carcinoma, and/or

    wherein the cancer is early cancer, advanced cancer, invasive cancer, metastatic cancer, drug resistant cancer or any combination thereof, and/or

    wherein the subject has been previously treated with chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof, and/or

    wherein the compound is to be administered in combination with an anti-cancer therapy, such as chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof.
11. Use of a compound according to any of claims 1-6 in the manufacture of a medicament for suppressing, reducing or inhibiting tumour growth in a subject.
12. The use according to claim 11, wherein the tumor growth is enhanced by increased acetate uptake by cancer cells of said cancer, for example:

    wherein the increased acetate uptake is mediated by ACSS2, and/or

    wherein the tumour cells are under hypoxic stress, or

    wherein the tumor growth is suppressed due to suppression of lipid (e.g., fatty acid) synthesis and/or regulating histones acetylation and function induced by ACSS2 mediated acetate metabolism to acetyl-CoA.
13. An *in vitro* method of suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and function in a cell such as a cancer cell; or

    of suppressing, reducing or inhibiting acetyl-CoA synthesis, such as ACSS2-mediated acetyl-CoA synthesis, from acetate in a cell such as a cancer cell; or

    of suppressing, reducing or inhibiting acetate metabolism, such as ACSS2-mediated acetate metabolism, in a cancer cell, optionally wherein the cancer cell is under hypoxic stress,

    the method comprising contacting the cell with a compound according to any one of claims 1 to 6.
14. An *in vitro* method of binding an ACSS2 inhibitor compound to an ACSS2 enzyme, comprising the step of contacting an ACSS2 enzyme with an ACSS2 inhibitor compound according to any one of claims 1 to 6, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme.

15. Use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject, or

for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a viral infection, such as human cytomegalovirus (HCMV) infection, in a subject, or

for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting alcoholic steatohepatitis (ASH) in a subject, or

for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non alcoholic fatty liver disease (NAFLD) in a subject, or

for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non-alcoholic steatohepatitis (NASH) in a subject, or

for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a metabolic disorder such as obesity, weight gain, hepatic steatosis and fatty liver disease in a subject, or

for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a neuropsychiatric disease or disorder such as anxiety, depression, schizophrenia, autism and post-traumatic stress disorder in a subject, or

for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting inflammatory condition in a subject, or

for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject.