have a better safety profile than ACC inhibitors since they are expected only to affect the flux from Acetate that is not a major source for Ac-CoA in normal conditions (Harriman G *et. al*., **2016**. "Acetyl-CoA carboxylase inhibition by ND-630 reduces hepatic steatosis, improves insulin sensitivity, and modulates dyslipidemia in rats" *PNAS*). In addition, mice lacking ACSS2 showed reduced body weight and hepatic steatosis in a diet-induced obesity model (Z. Huang et al., ACSS2 promotes systemic fat storage and utilization through selective regulation of genes involved in lipid metabolismPNAS 115, (40), E9499-E9506, 2018).

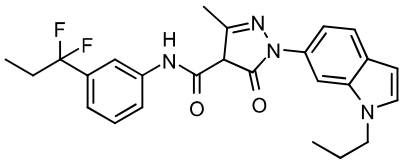
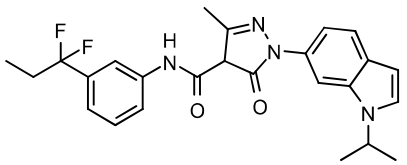
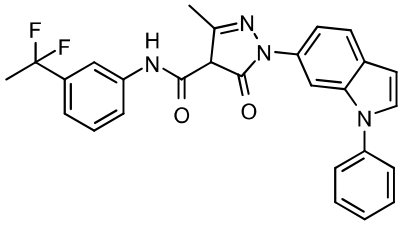
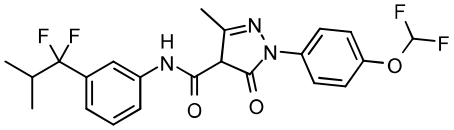
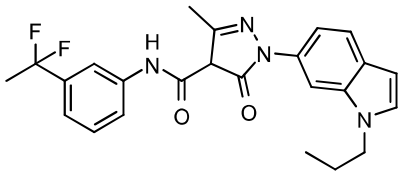
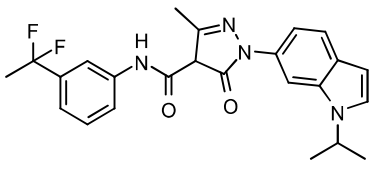
[0012] ACSS2 is also shown to enter the nucleus under certain condition (hypoxia, high fat etc.) and to affect histone acetylation and crotonylation by making available acetyl-CoA and crotonyl-CoA and thereby regulate gene expression. For example, ACSS2 decrease is shown to lower levels of nuclear acetyl-CoA and histone acetylation in neurons affecting the the expression of many neuronal genes. In the hippocampus such reductions in ACSS2 lead to effects on memory and neuronal plasticity (Mews P, et al., Nature, Vol 546, 381, 2017). Such epigenetic modifications are implicated in neuropsychiatric diseases such as anxiety, PTSD, depression etc. (Graff, J et al. Histone acetylation: molecular mnemonics on chromatin. Nat Rev. Neurosci. 14, 97-111 (2013)). Thus, an inhibitor of ACSS2 may find useful application in these conditions.

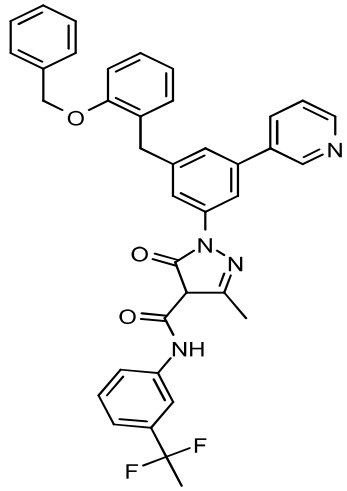
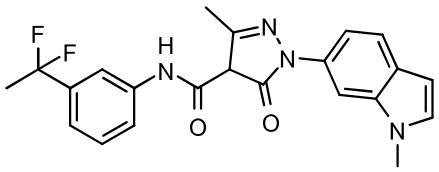
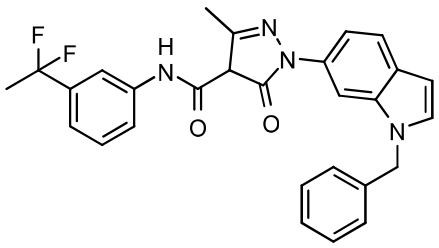
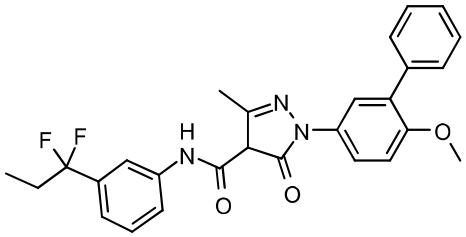
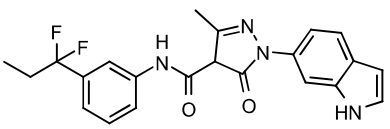
[0013] Nuclear ACSS2 is also shown to promote lysosomal biogenesis, autophagy and to promote brain tumorigenesis by affecting Histone H3 acetylation (Li, X et al.: Nucleus-Translocated ACSS2 Promotes Gene Transcription for Lysosomal Biogenesis and Autophagy, Molecular Cell 66, 1-14, 2017). In addition, nuclear ACSS2 is shown to activate HIF-2alpha by acetylation and thus accelerate growth and metastasis of HIF2alpha-driven cancers such as certain Renal Cell Carcinoma and Glioblastomas (Chen, R. et al. Coordinate regulation of stress signaling and epigenetic events by ACSS2 and HIF-2 in cancer cells, Plos One,12 (12) 1-31, 2017).

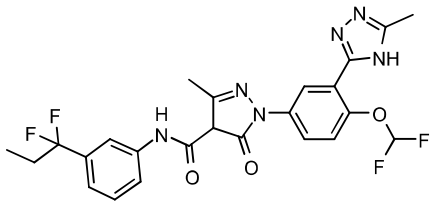
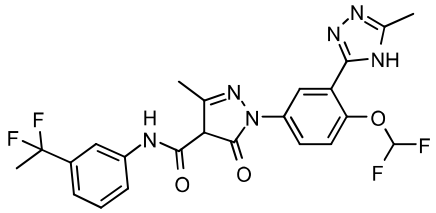
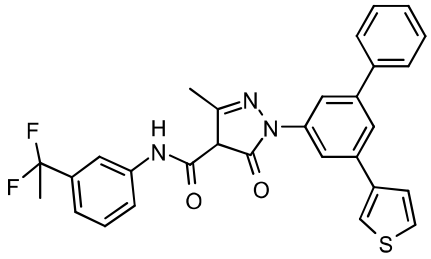
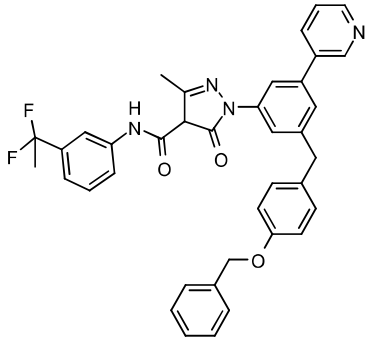
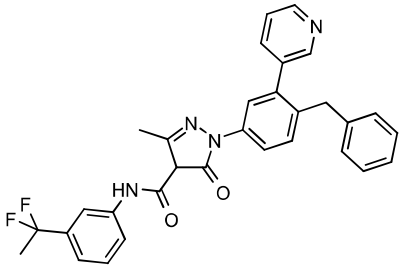
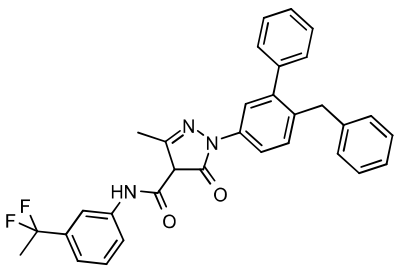
SUMMARY

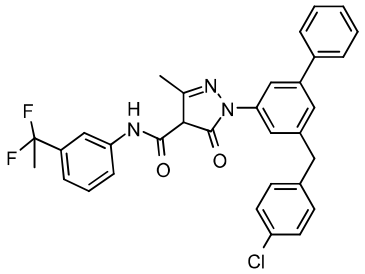
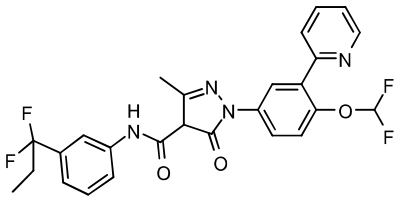
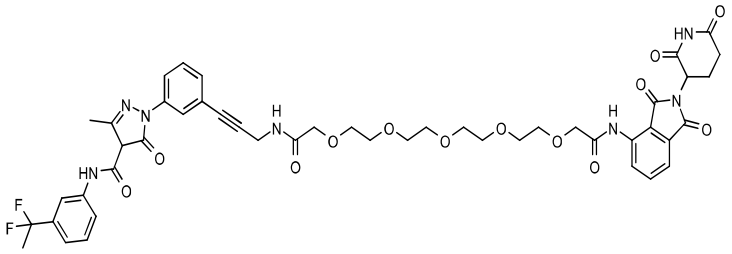
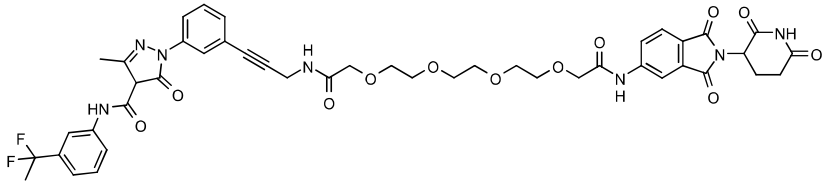
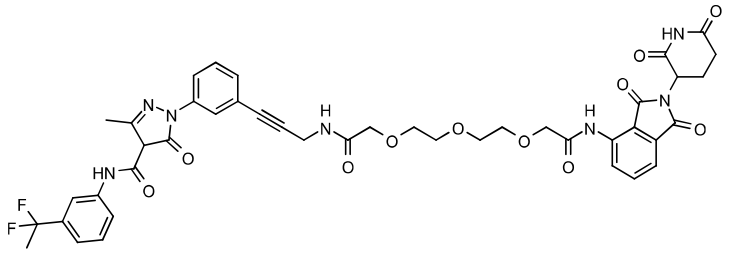
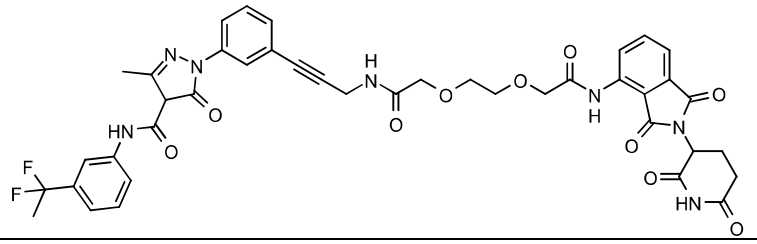
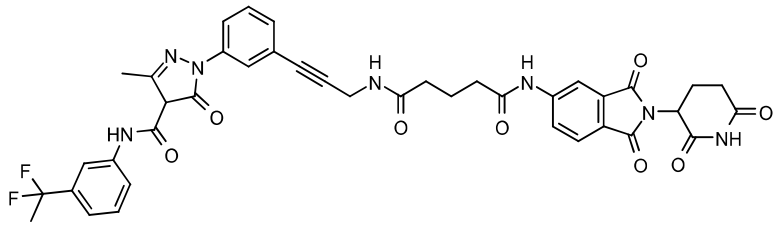
[0014] This disclosure provides a compound or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below. In various examples, the compound is an Acyl-CoA Synthetase Short-Chain Family Member 2 (ACSS2) inhibitor.

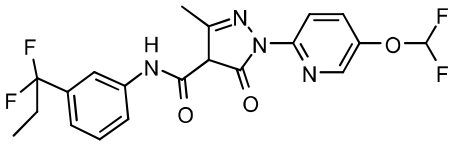
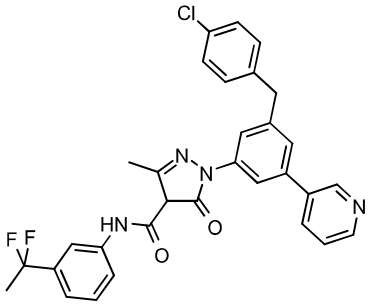
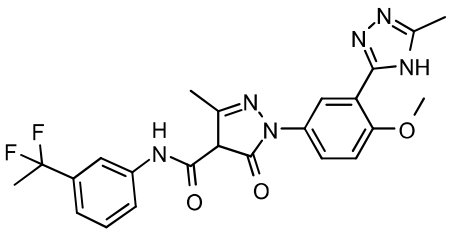
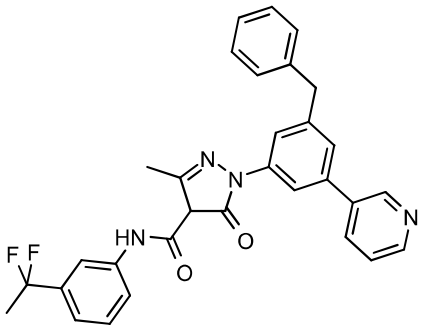
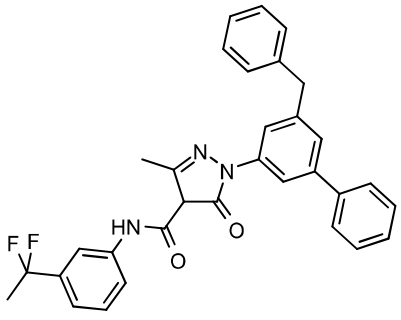
[0014a] In one aspect, the present disclosure refers to a compound represented by the following structures:

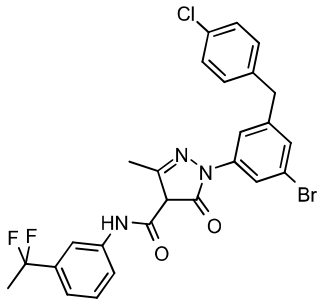
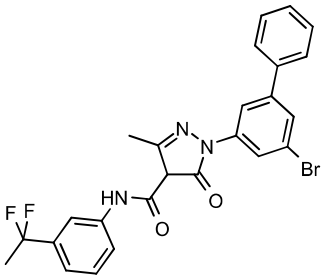
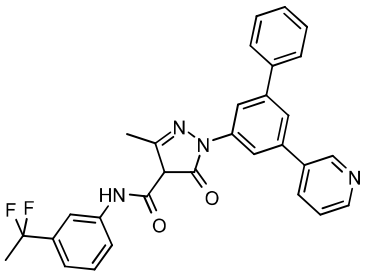
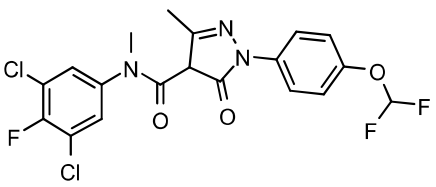
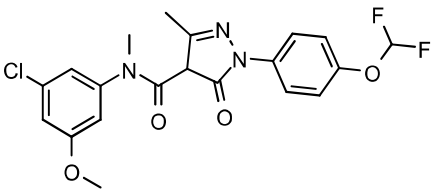
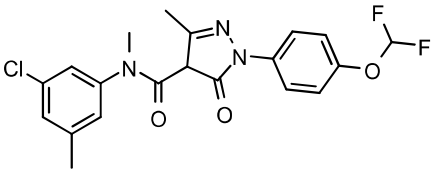
Compound name	Structure
359	
360	
361	
362	
363	
364	

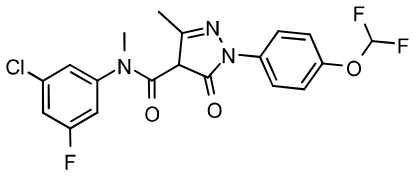
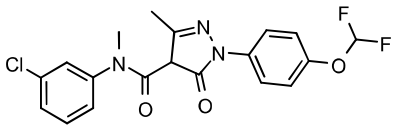
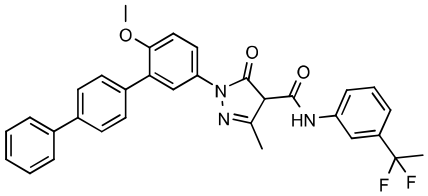
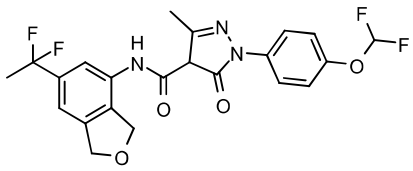
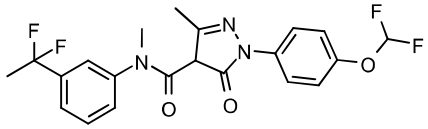
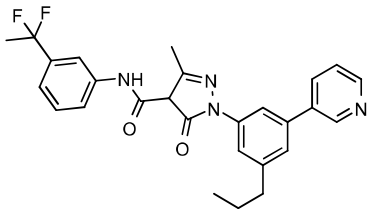
365	
366	
367	
368	
369	

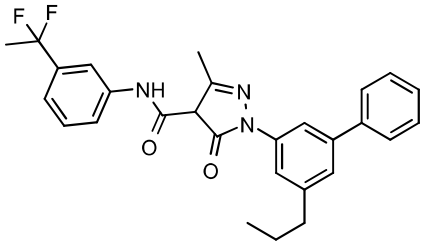
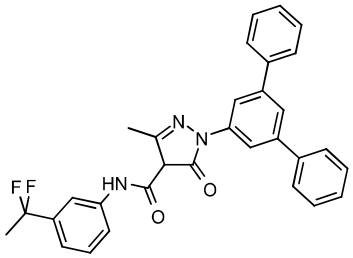
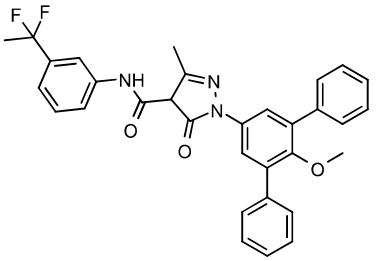
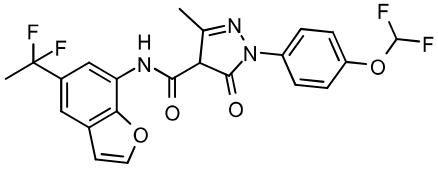
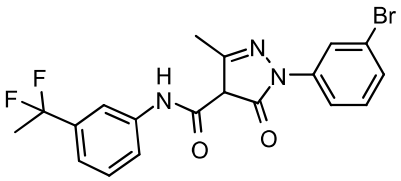
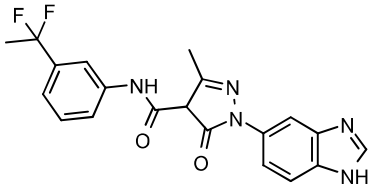
370	
371	
372	
373	
374	
375	

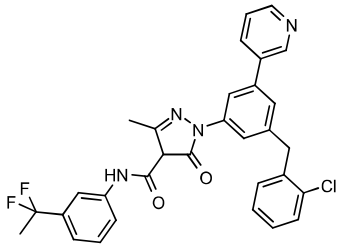
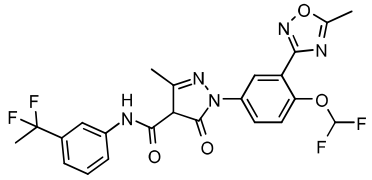
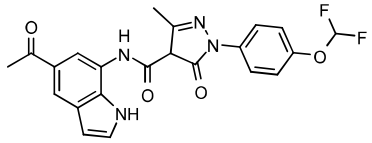
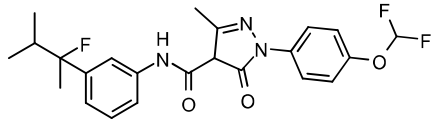
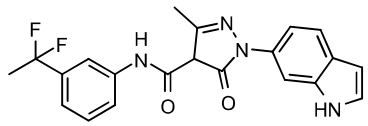
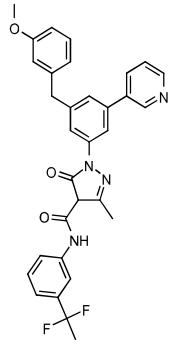
376	
377	
378	
379	
380	
381	
382	

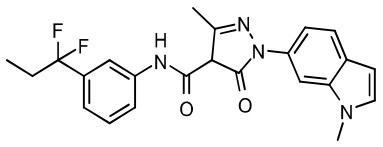
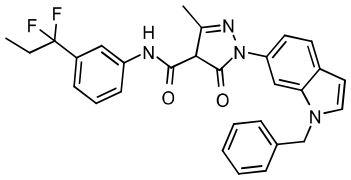
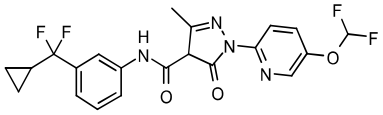
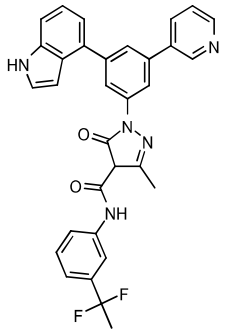
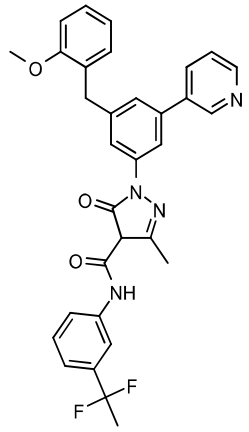
383	
384	
385	
386	
387	

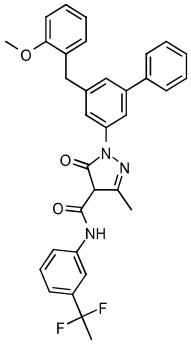
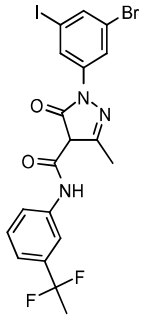
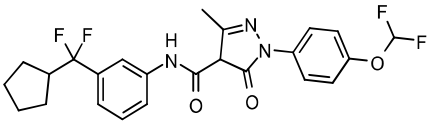
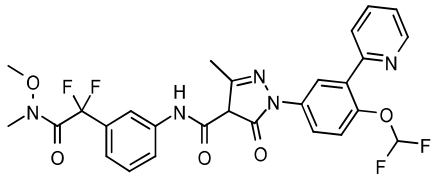
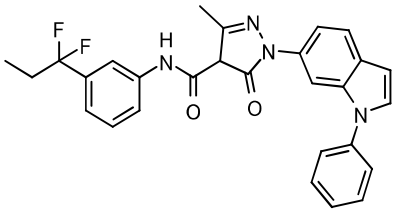
388	
389	
390	
391	
392	
393	

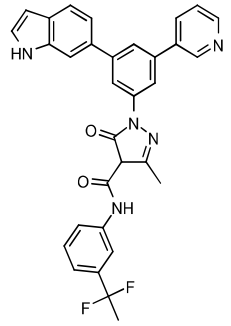
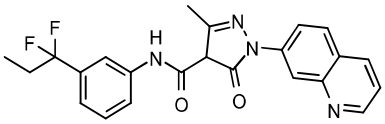
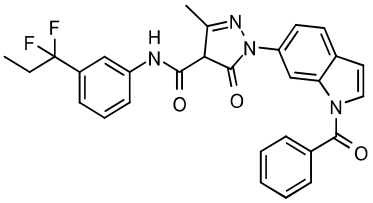
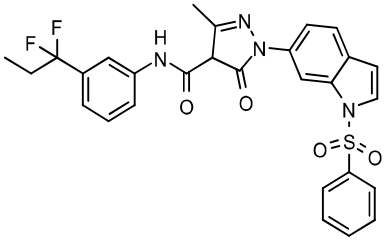
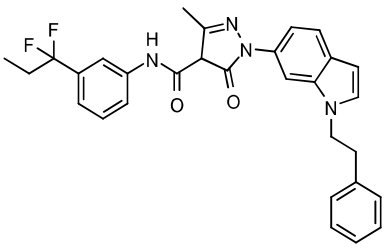
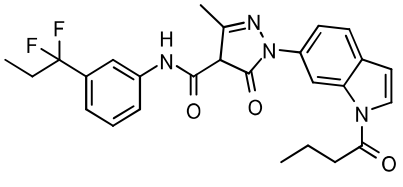
394	
395	
396	
397	
398	
399	

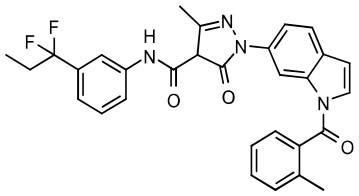
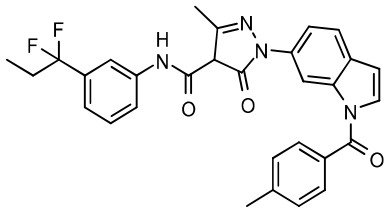
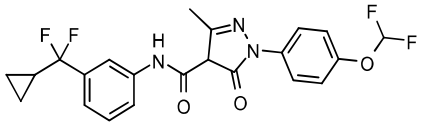
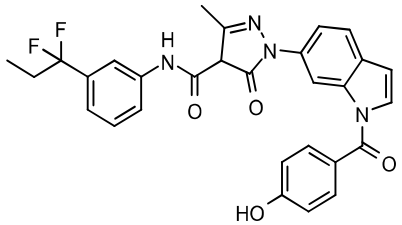
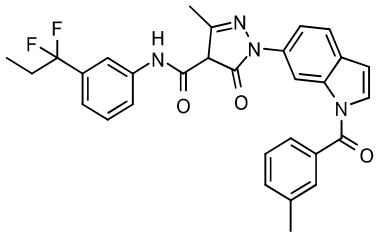
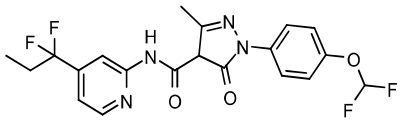
400	
401	
402	
403	
404	
405	

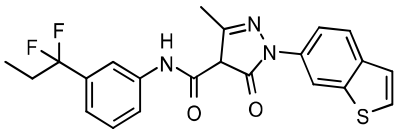
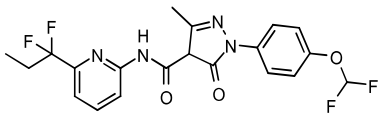
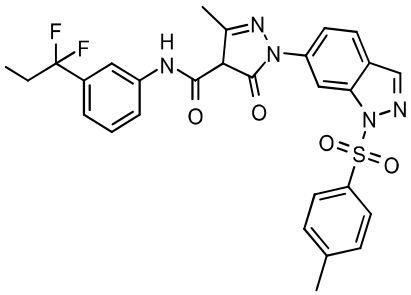
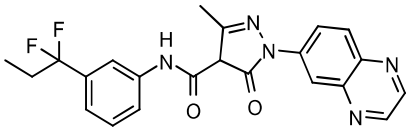
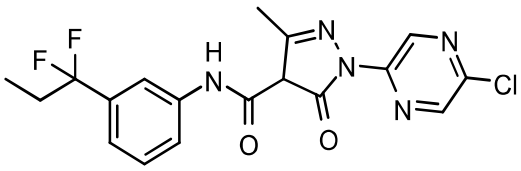
406	
407	
408	
409	
410	
461	

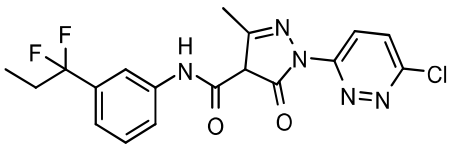
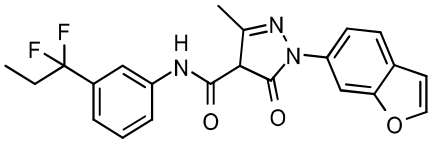
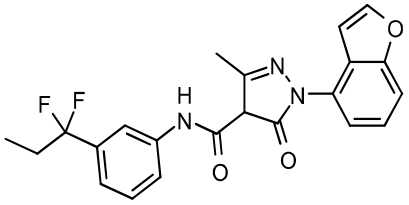
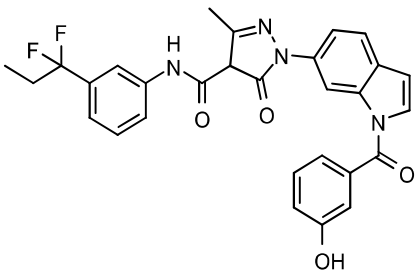
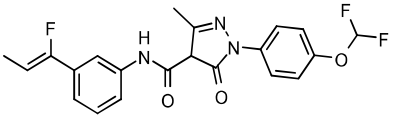
462	
463	
464	
465	
466	

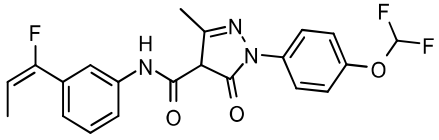
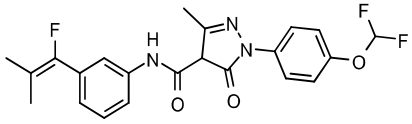
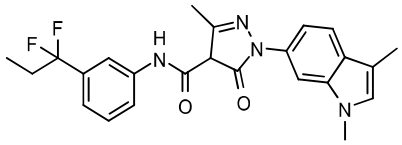
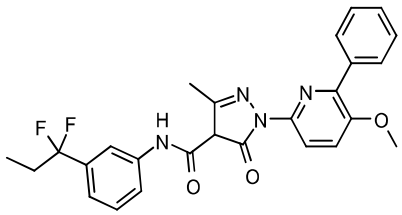
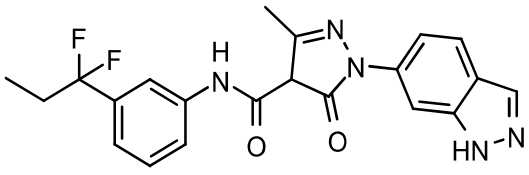
467	
468	
470	
471	
472	

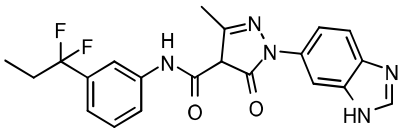
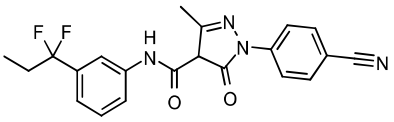
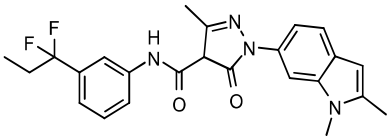
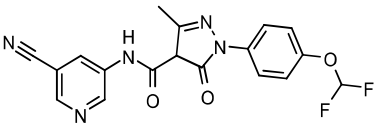
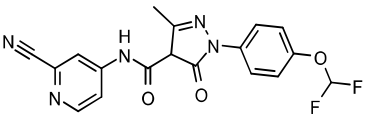
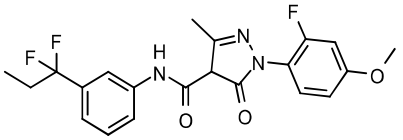
473	
474	
475	
476	
477	
478	

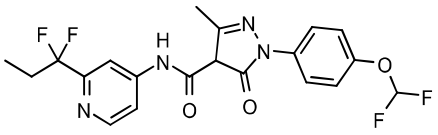
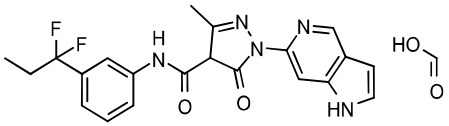
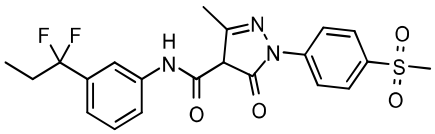
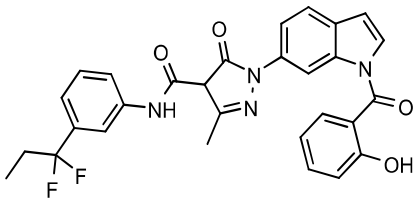
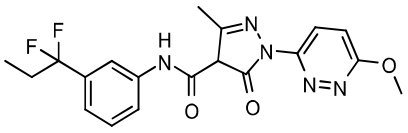
479	
480	
481	
482	
483	
484	

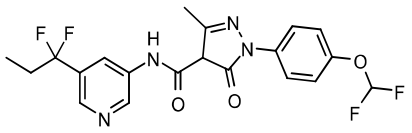
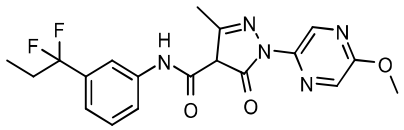
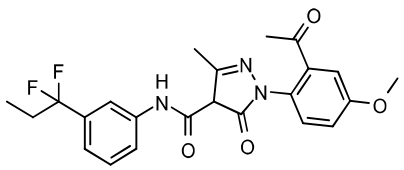
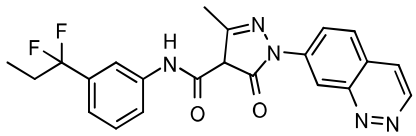
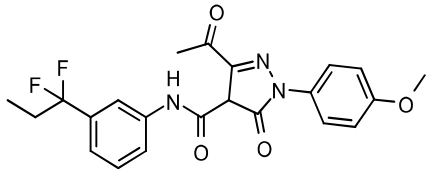
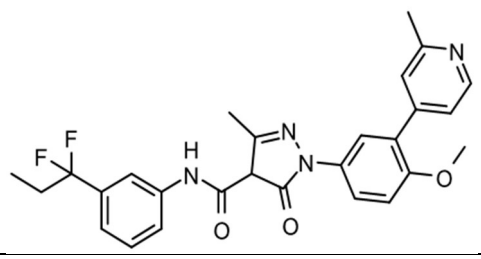
485	
486	
487	
488	
489	

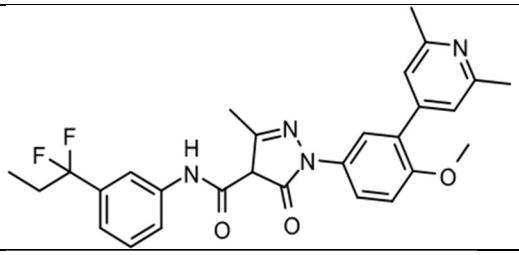
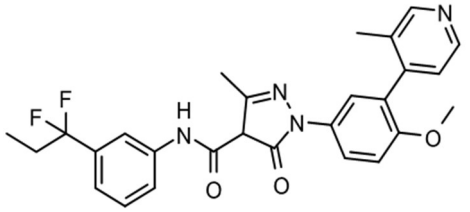
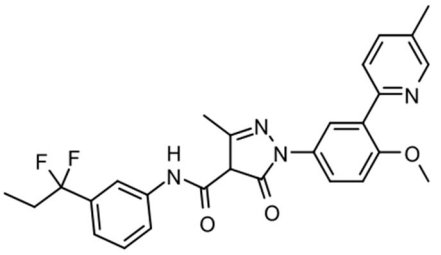
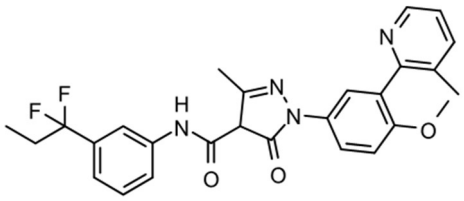
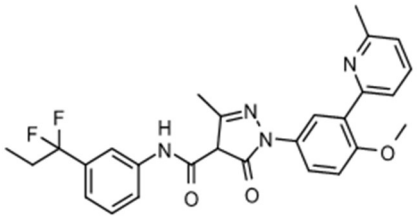
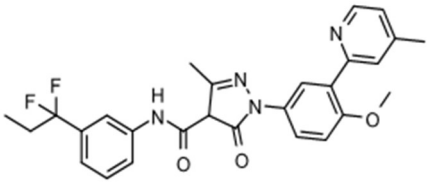
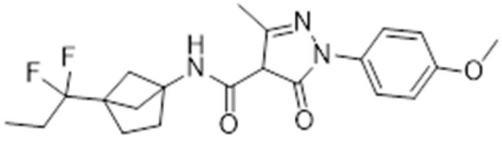
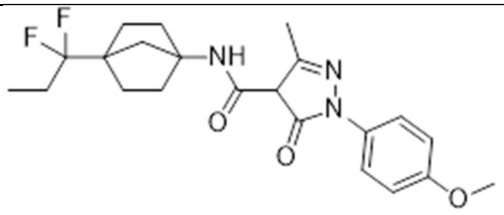
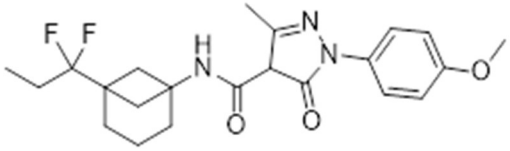
490	
491	
492	
493	
494	

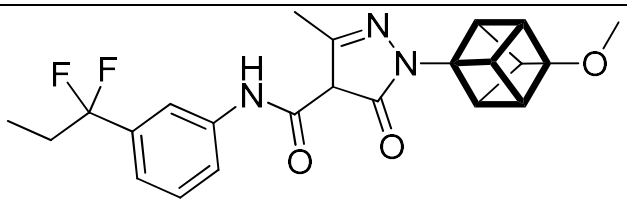
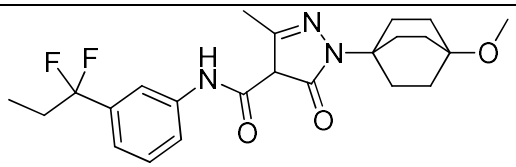
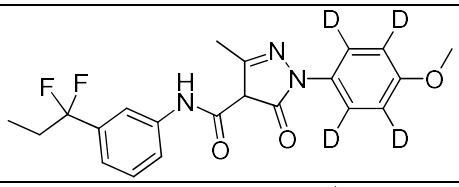
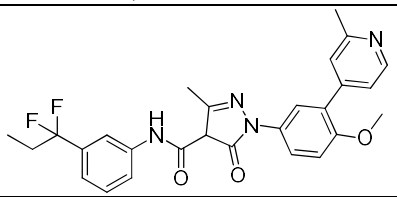
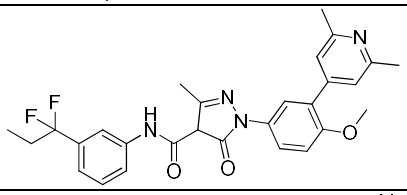
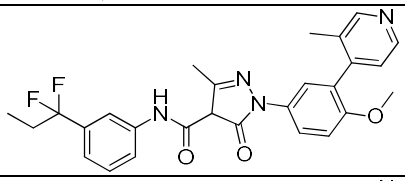
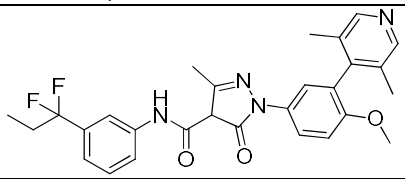
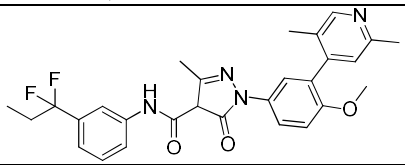
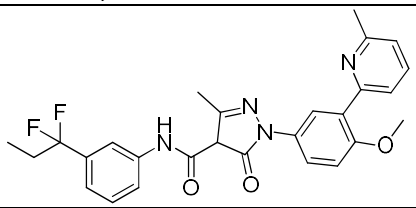
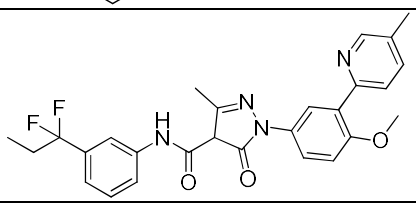
495	
496	
497	
498	
499	

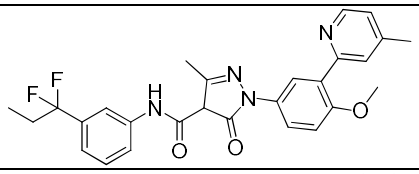
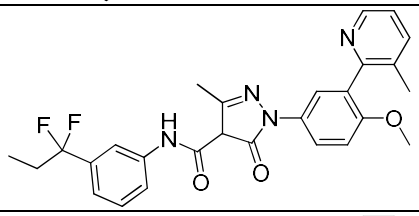
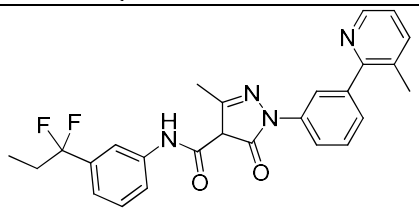
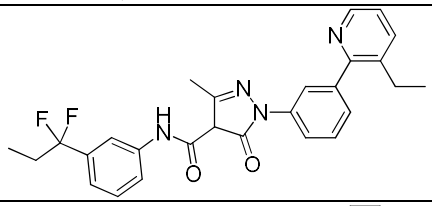
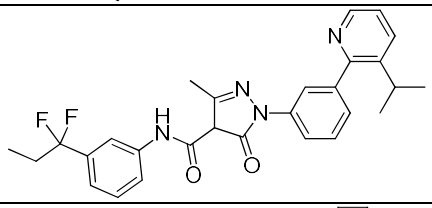
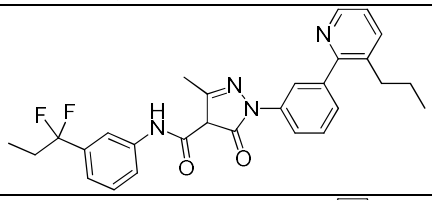
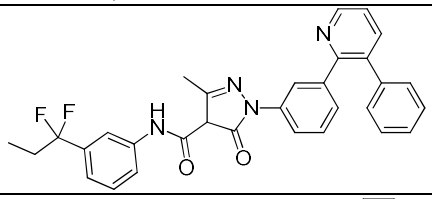
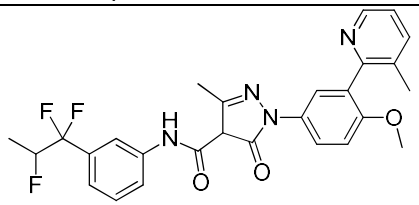
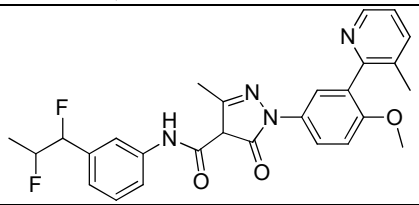
500	
501	
502	
503	
504	
505	

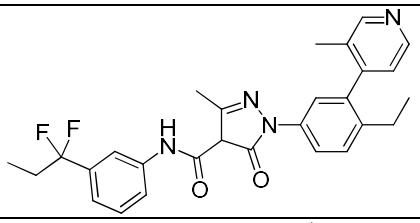
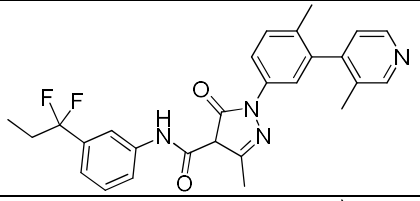
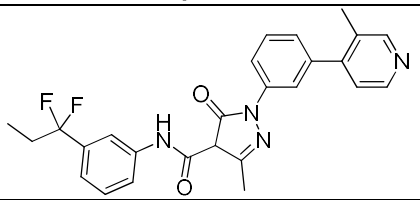
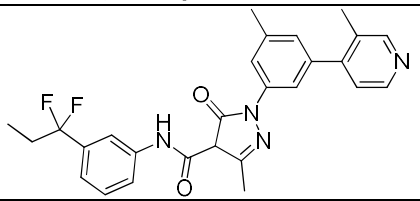
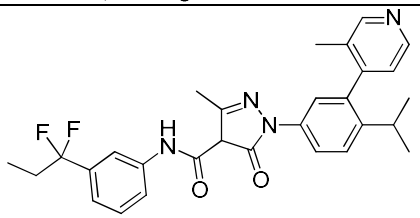
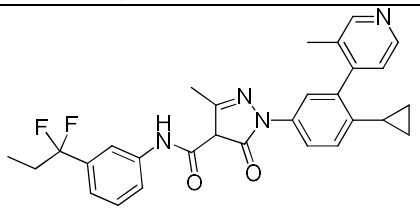
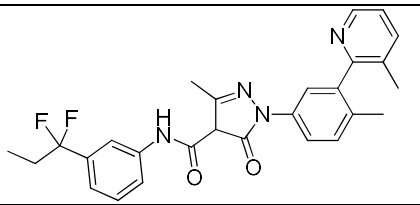
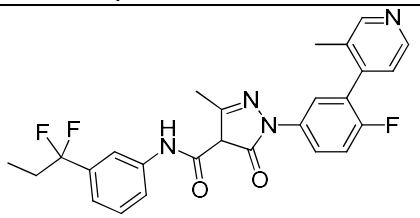
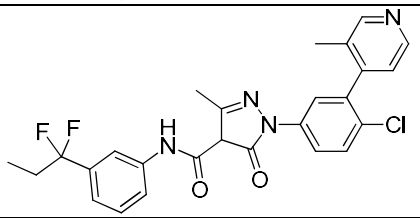
506	
507	
508	
509	
510	

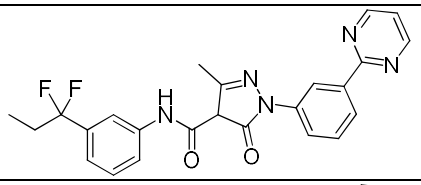
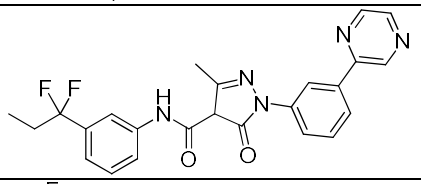
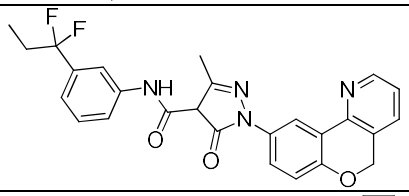
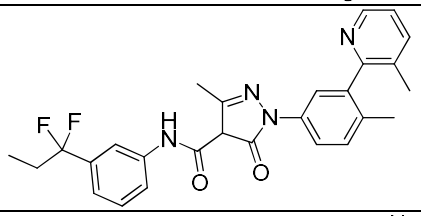
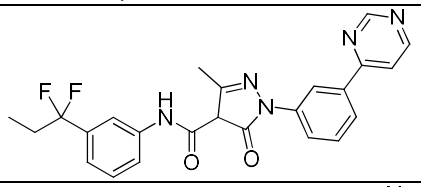
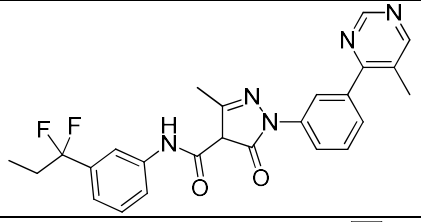
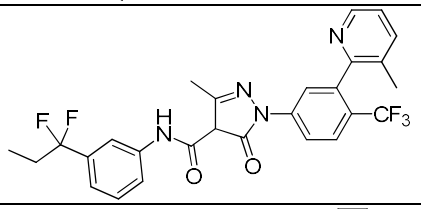
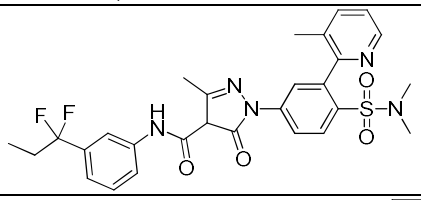
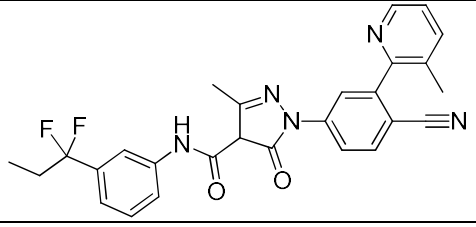
511	
512	
516	
524	
529	
530	

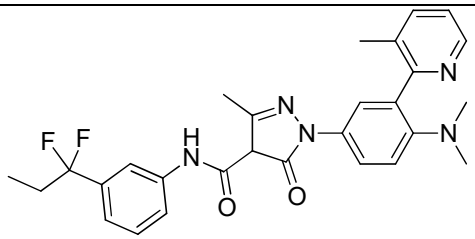
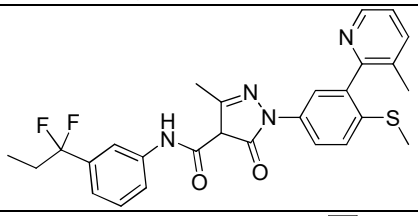
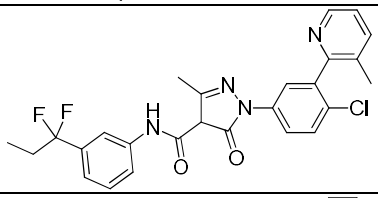
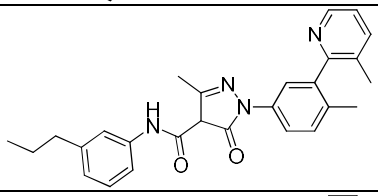
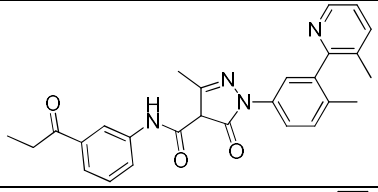
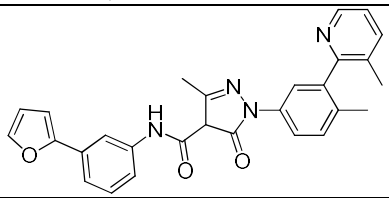
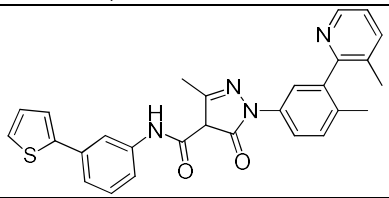
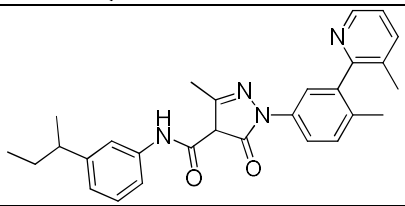
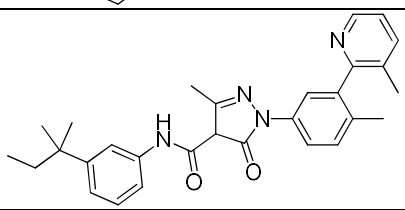
531	
532	
534	
535	
536	
537	
538	
539	
540	

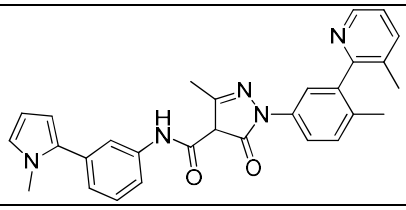
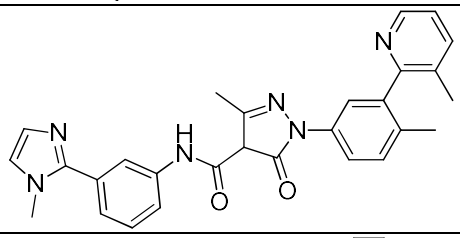
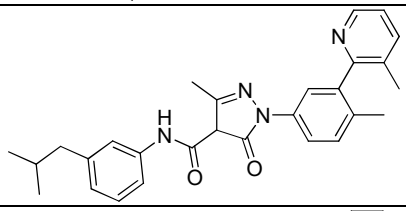
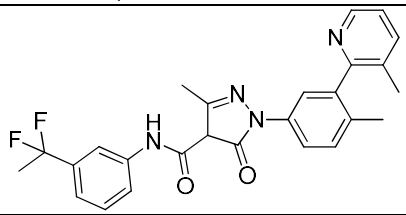
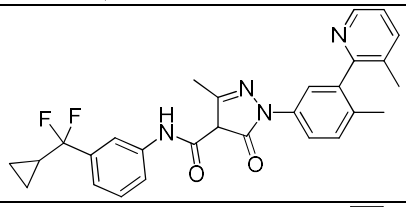
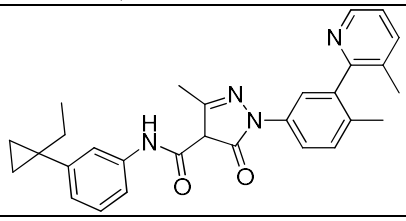
541	
542	
543	
544	
545	
546	
547	
548	
549	
550	

551	
552	
553	
554	
555	
556	
557	
558	
559	

560	
561	
562	
563	
564	
565	
566	
567	
568	

569	
570	
571	
572	
573	
574	
575	
576	
577	

578	
579	
580	
581	
582	
583	
584	
585	
586	

587	
588	
589	
590	
591	
592	

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

[0015] This disclosure further provides a pharmaceutical composition comprising a compound or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, 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.

[0015a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

[0016] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a

subject suffering from cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit said cancer. In various examples, the cancer is selected from the list of: 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. In various examples, the cancer is early cancer, advanced cancer, invasive cancer, metastatic cancer, drug resistant cancer or any combination thereof. In various examples, the subject has been previously treated with chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof. In various examples, the compound is administered in combination with an anti-cancer therapy. In various examples, the anti-cancer therapy is chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof.

[0016a] In one aspect, the present disclosure refers to the use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a disease or condition selected from: cancer, human alcoholism, a viral infection, an alcoholic steatohepatitis (ASH), a non alcoholic fatty liver disease (NAFLD), a non-alcoholic steatohepatitis (NASH), a metabolic disorder, a neuropsychiatric disease or disorder, an inflammatory condition and an autoimmune disease or disorder in a subject.

[0017] This disclosure further provides a method of suppressing, reducing or inhibiting tumour growth in a subject, comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a subject suffering from cancer under conditions effective to suppress, reduce or inhibit said tumour growth in said subject. In various examples, the tumor growth is enhanced by increased acetate uptake by cancer cells of said cancer. In various examples, the increased acetate uptake is mediated by ACSS2. In various examples, the cancer cells are under hypoxic stress. In various examples, the tumor growth is suppressed due to suppression of lipid (e.g., fatty acid) synthesis and/or histones synthesis induced by ACSS2 mediated acetate metabolism to acetyl-CoA. In various examples, the tumor growth is suppressed due to suppressed regulation of histones acetylation and function induced by ACSS2 mediated acetate metabolism to acetyl-CoA.

[0017a] In one aspect, the present disclosure refers to the use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament in suppressing, reducing or inhibiting tumor growth in a subject.

[0018] This disclosure further provides a method of suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and functionin a cell, comprising contacting a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, with a cell under conditions effective to suppress, reduce or inhibit lipid synthesis and/or regulating histones acetylation and function in said cell. In various examples, the cell is a cancer cell.

[0018a] In one aspect, the present disclosure refers to the use of a compound disclosed herein, in the manufacture of a medicament for suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and function in a cell.

[0019] This disclosure further provides a method of binding an ACSS2 inhibitor compound to an ACSS2 enzyme, comprising the step of contacting an ACSS2 enzyme with an ACSS2 inhibitor compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme.

[0019a] In one aspect, the present disclosure refers to 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 disclosed herein, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme.

[0020] This disclosure further provides a method of suppressing, reducing or inhibiting acetyl-CoA synthesis from acetate in a cell, comprising contacting a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, with a cell, under conditions effective to suppress, reduce or inhibit acetyl-CoA synthesis from acetate in said cell. In

various examples, the cell is a cancer cell. In various examples, the synthesis is mediated by ACSS2.

[0020a] In one aspect, the present disclosure refers to the use of a compound disclosed herein, in the manufacture of a medicament for suppressing, reducing or inhibiting acetyl-CoA synthesis from acetate in a cell.

[0021] This disclosure further provides a method of suppressing, reducing or inhibiting acetate metabolism in a cancer cell, comprising contacting a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, with a cancer cell, under conditions effective to suppress, reduce or inhibit acetate metabolism in said cells. In various examples, the acetate metabolism is mediated by ACSS2. In various examples, the cancer cell is under hypoxic stress.

[0021a] In one aspect, the present disclosure refers to the use of a compound disclosed herein, in the manufacture of a medicament for suppressing, reducing or inhibiting acetate metabolism in a cancer cell.

[0022] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject, comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a subject suffering from alcoholism under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit alcoholism in said subject.

[0023] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a viral infection in a subject, comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a subject suffering from a viral infection under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the viral infection in said subject. In various examples, the viral infection is human cytomegalovirus (HCMV) infection.

[0024] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a non-alcoholic steatohepatitis (NASH) in a subject, comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a subject suffering from non-alcoholic steatohepatitis (NASH) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the non-alcoholic steatohepatitis (NASH) in said subject.

[0025] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an alcoholic steatohepatitis (ASH) in a subject, comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a subject suffering from an alcoholic steatohepatitis (ASH) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the alcoholic steatohepatitis (ASH) in said subject.

[0026] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a metabolic disorder in a subject, comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a subject suffering from metabolic disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit metabolic disorder in said subject. In various example, the metabolic disorder is selected from: obesity, weight gain, hepatic steatosis and fatty liver disease.

[0027] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a neuropsychiatric disease or disorder in a subject, comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a subject suffering from neuropsychiatric disease or disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit neuropsychiatric disease or disorder in said subject. In some examples, the neuropsychiatric disease or disorder is selected from: anxiety, depression, schizophrenia, autism and post-traumatic stress disorder.

[0028] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting inflammatory condition in a subject, comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a subject suffering from inflammatory condition under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit inflammatory condition in said subject.

[0029] This disclosure further provides amethod of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject, comprising administering a compound represented by the structure of formula (I)-(V), and by the structures listed in Table 1, as defined herein below, to a subject suffering from an autoimmune disease or disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the autoimmune disease or disorder in said subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features, and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanying drawings in which:

[0031] **Figure 1** depicts a general synthetic scheme for compounds of the invention.

[0032] **Figure 2** depicts a synthetic scheme for compound **204**.

[0033] **Figure 3** depicts a synthetic scheme for compound **133**.

[0034] **Figure 4** depicts the oral pharmacokinetic profile of compound **265** in mice.

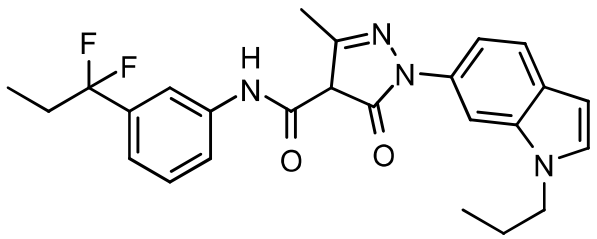
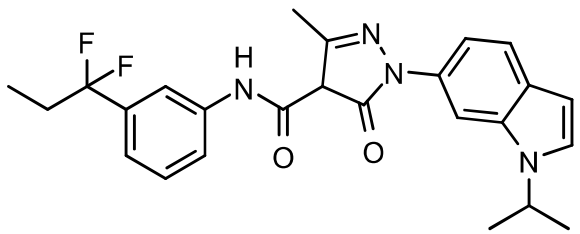
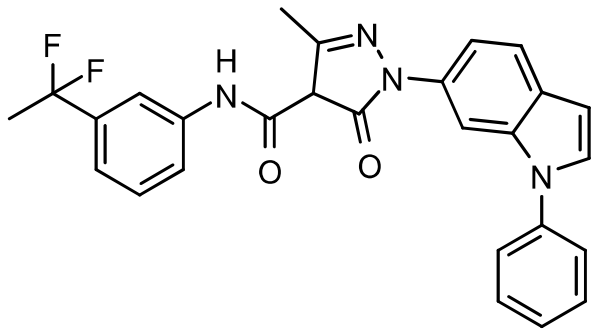
[0035] **Figure 5** depicts an *in-vivo* efficacy study of compound **265** and **298** in MDA-MB-468 breast cancer cells xenograft mouse model.

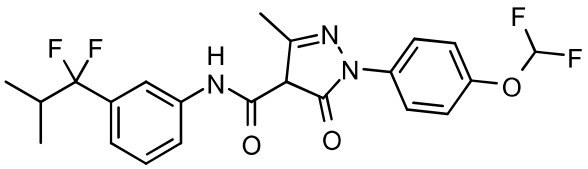
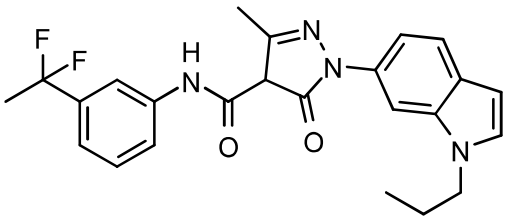
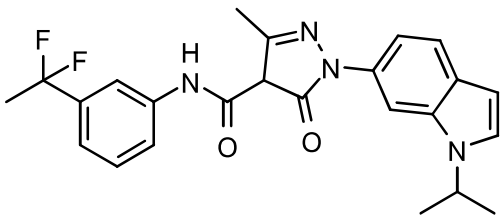
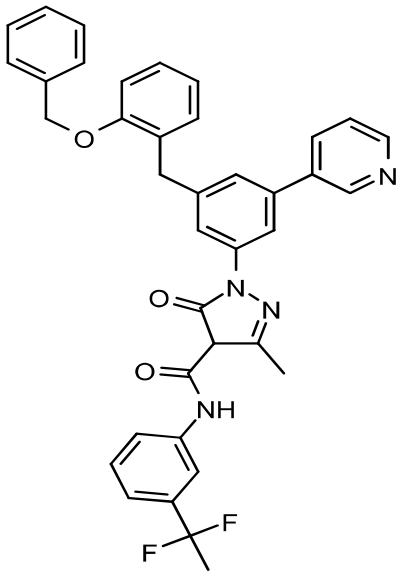
[0036] It will be appreciated that for simplicity and clarity of illustration, elements shown in the figures have not necessarily been drawn to scale. For example, the dimensions of some of the elements may be exaggerated relative to other elements for clarity. Further, where considered appropriate, reference numerals may be repeated among the figures to indicate corresponding or analogous elements.

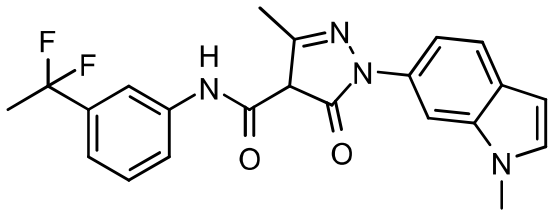
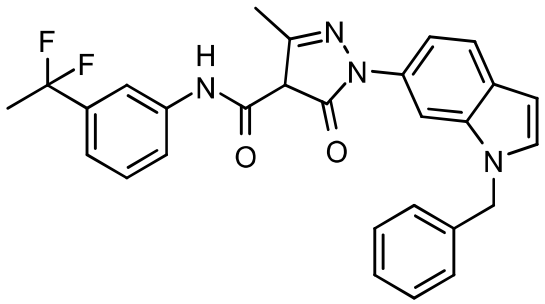
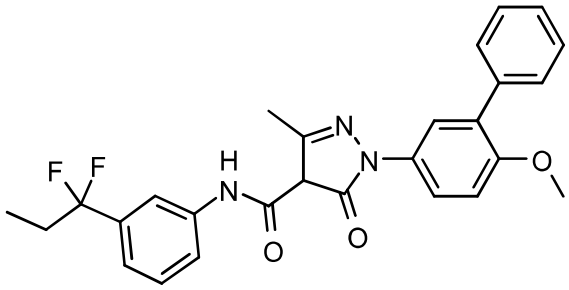
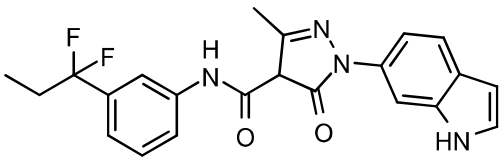
DETAILED DESCRIPTION OF THE INVENTION

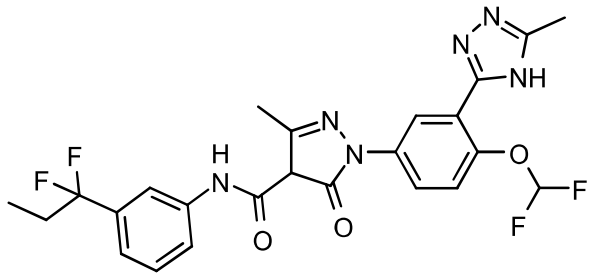
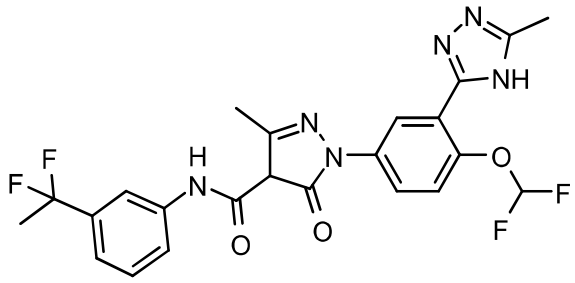
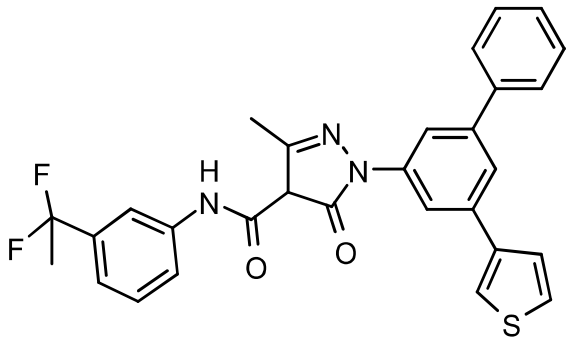
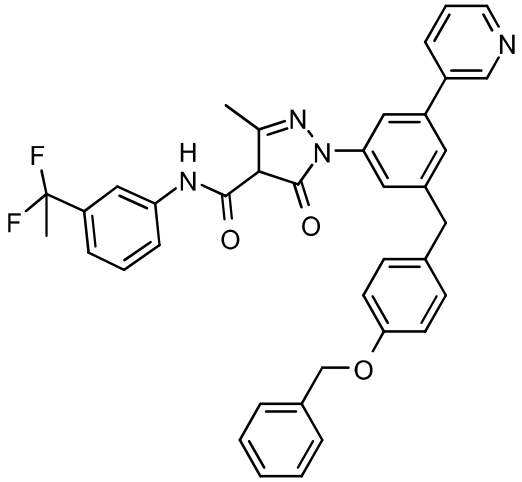
WHAT IS CLAIMED:

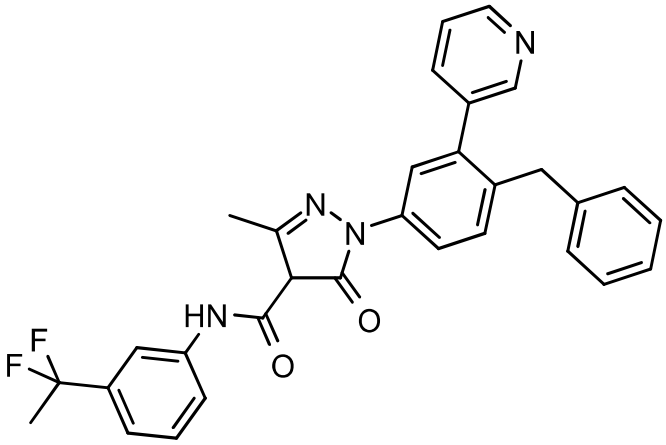
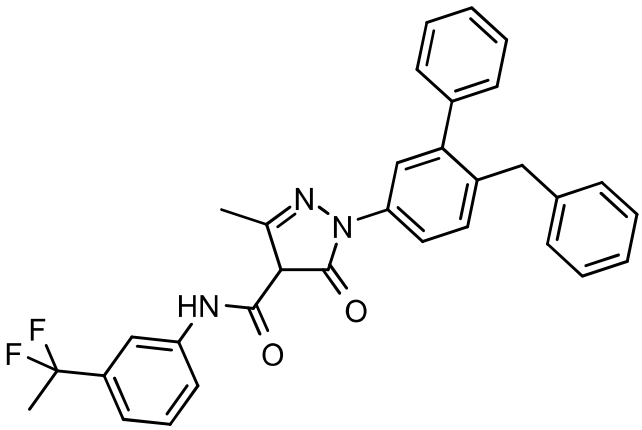
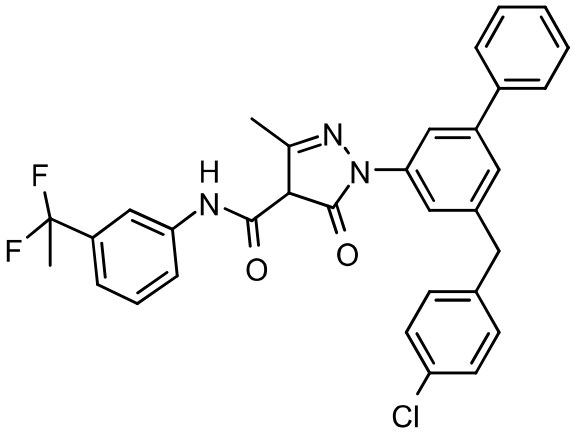
1. A compound represented by the following structures:

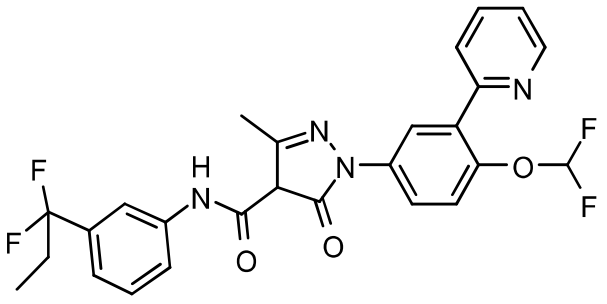
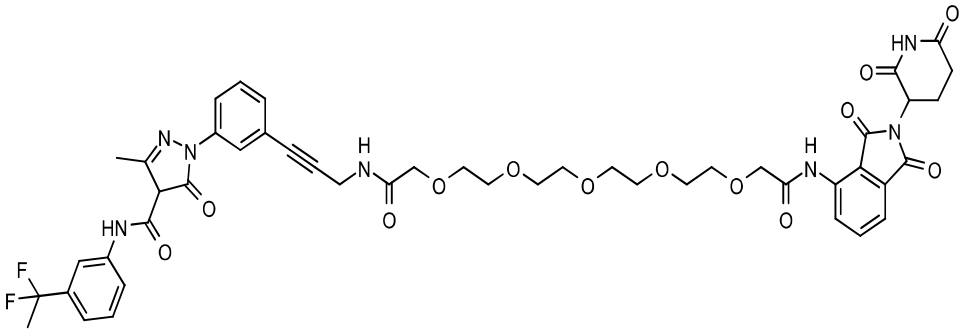
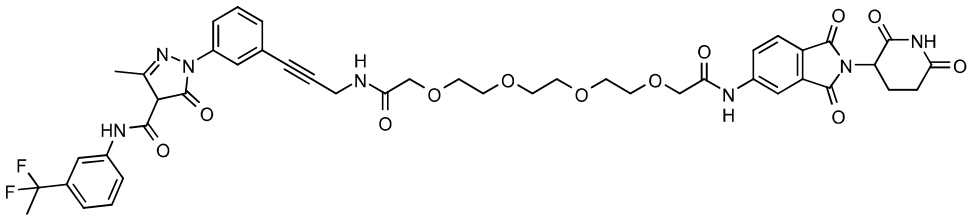
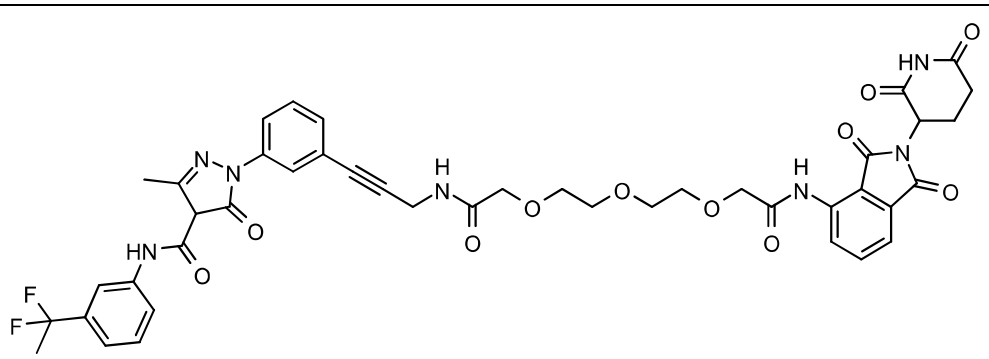
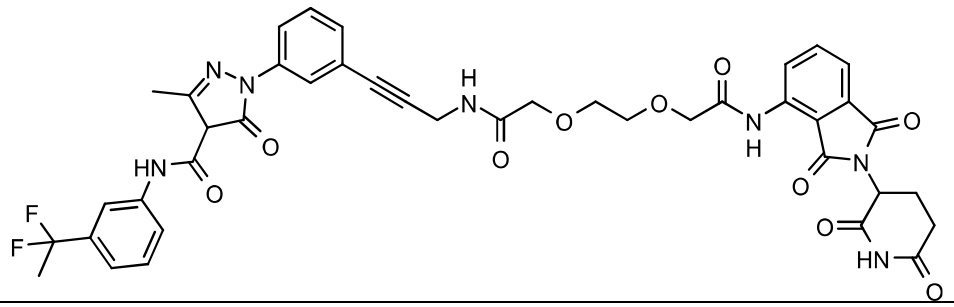
Compound name	Structure
359	
360	
361	

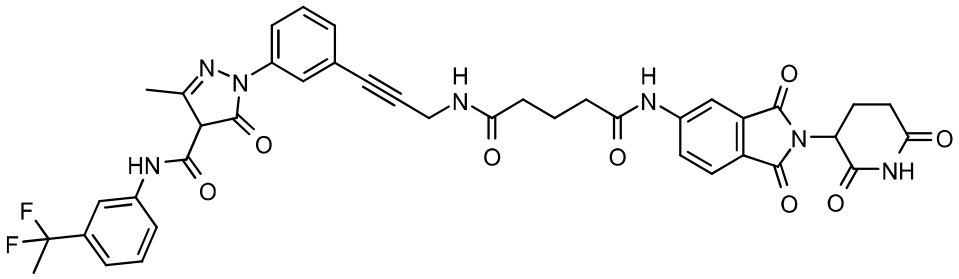
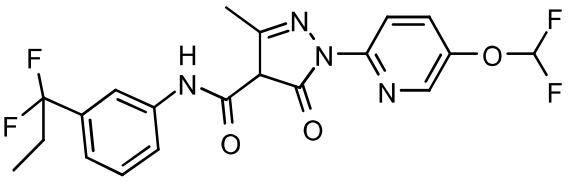
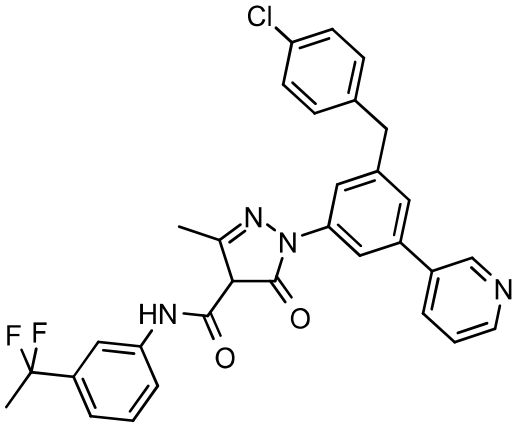
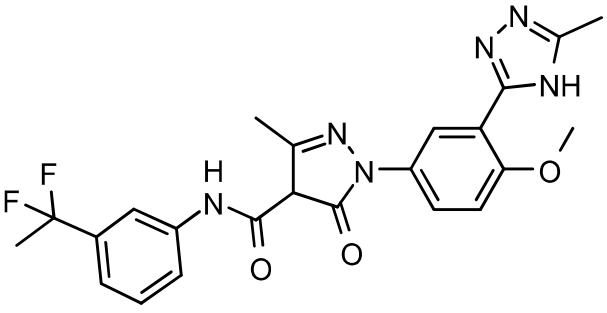
362	
363	
364	
365	

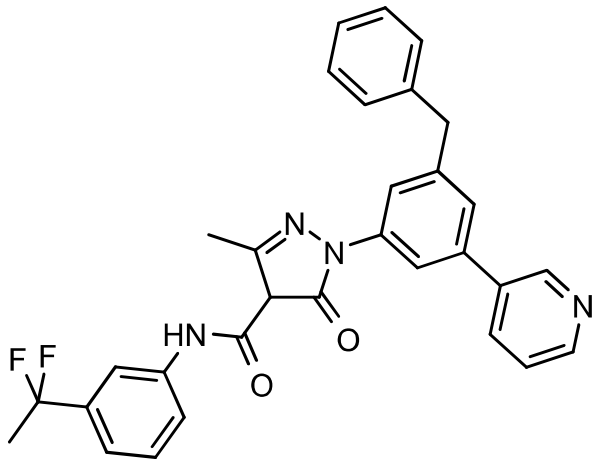
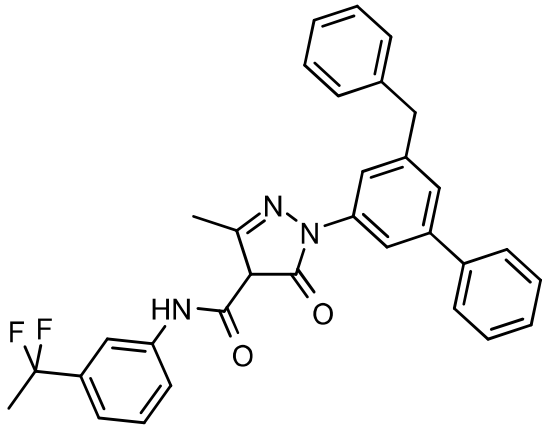
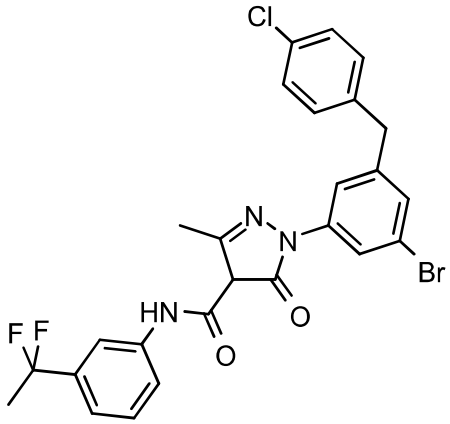
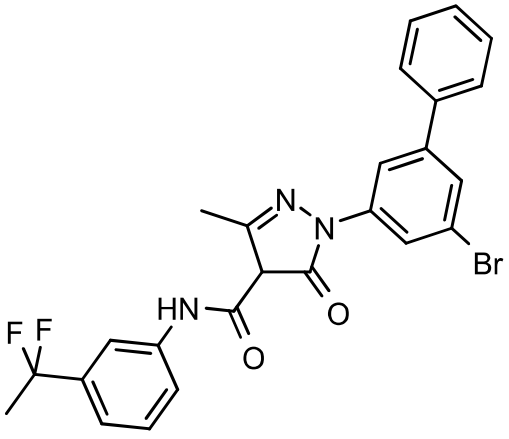
366	
367	
368	
369	

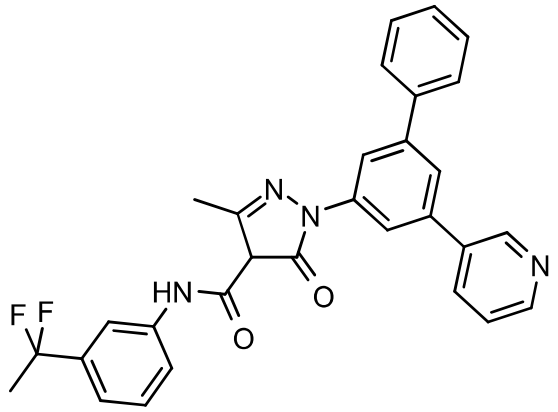
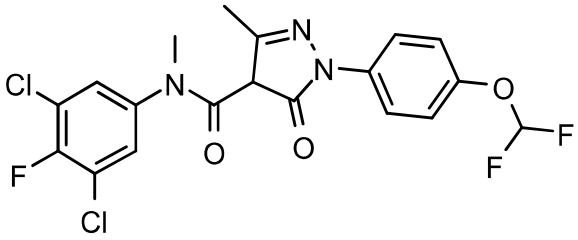
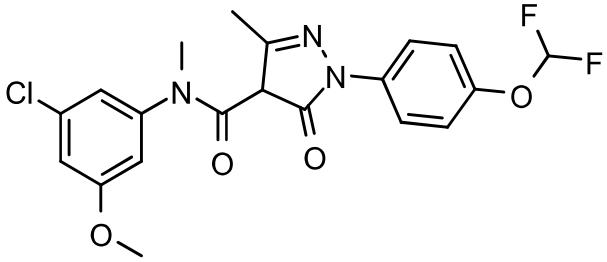
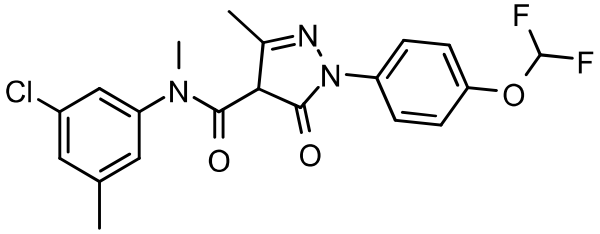
370	
371	
372	
373	

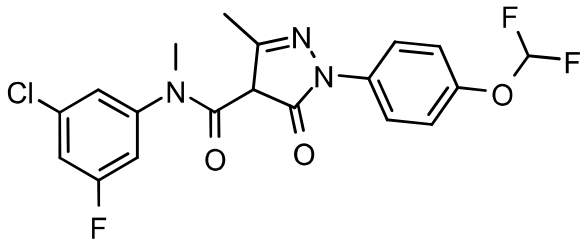
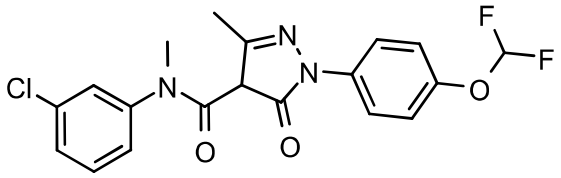
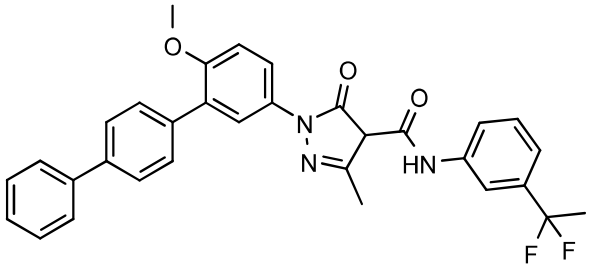
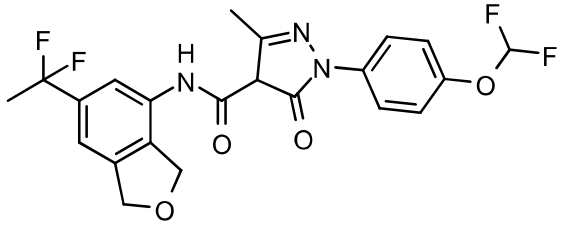
374	
375	
376	

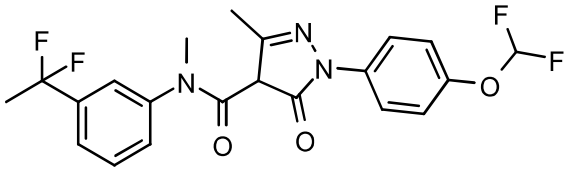
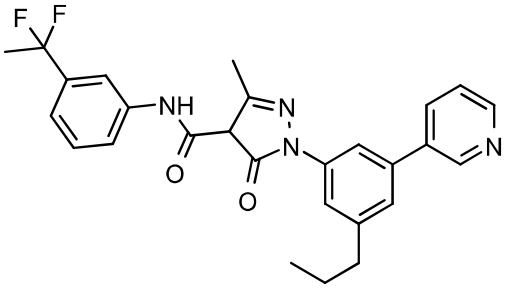
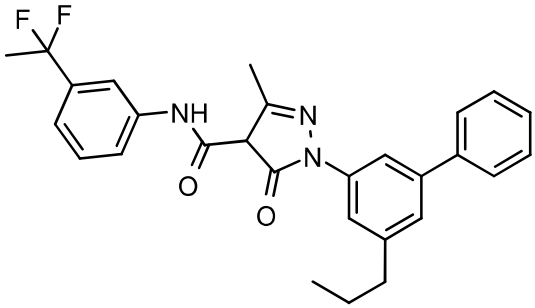
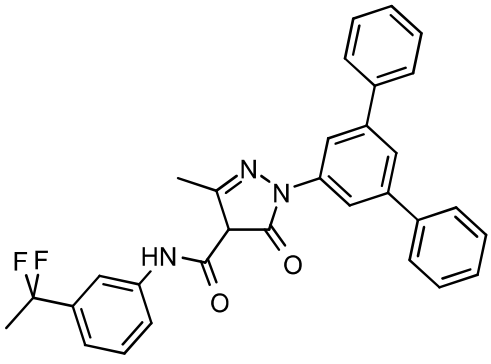
377	
378	
379	
380	
381	

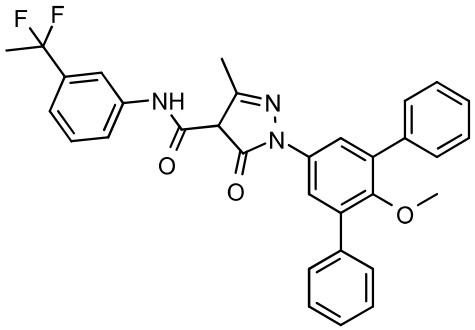
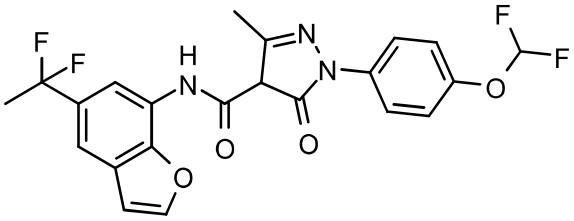
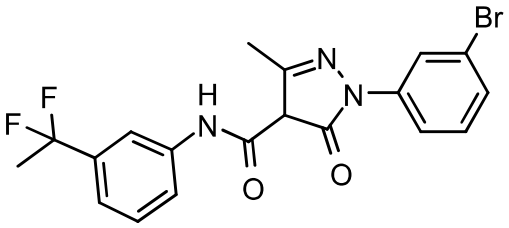
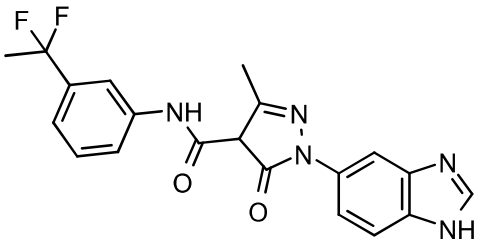
382	
383	
384	
385	

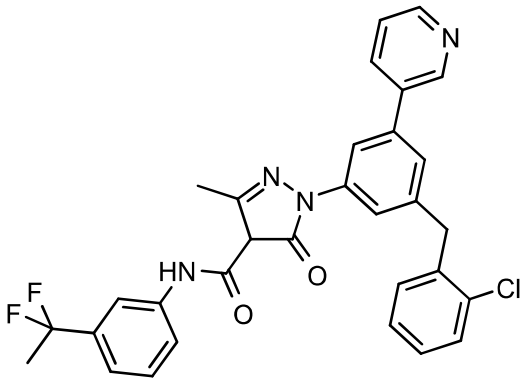
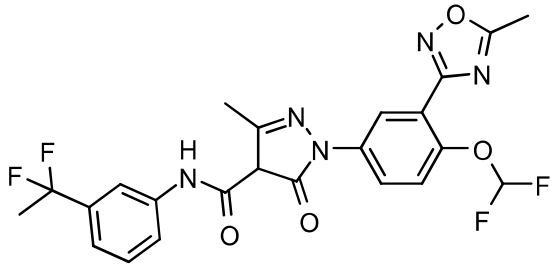
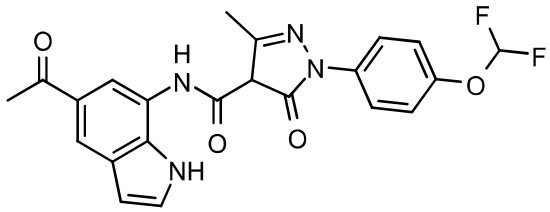
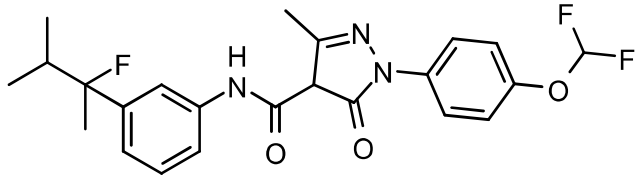
386	
387	
388	
389	

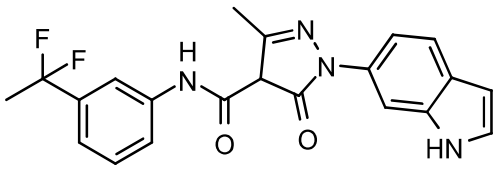
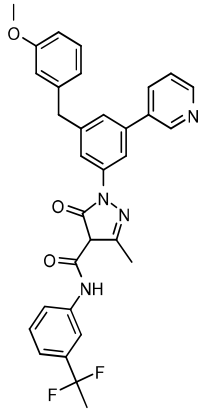
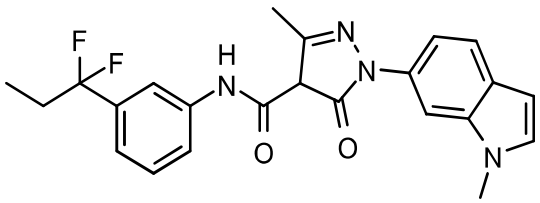
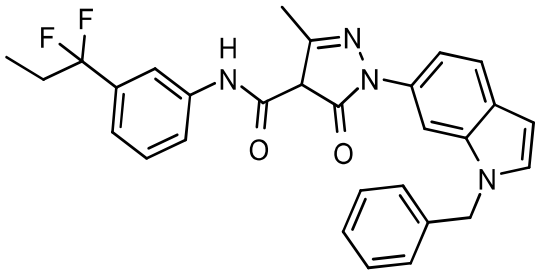
390	
391	
392	
393	

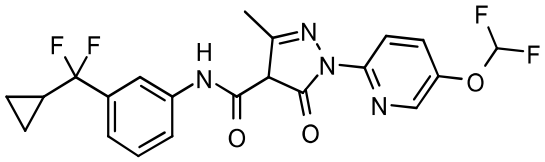
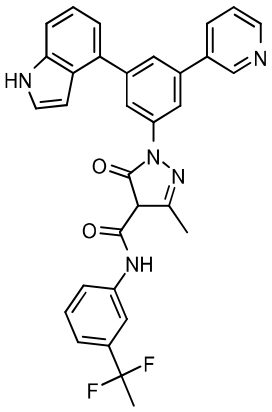
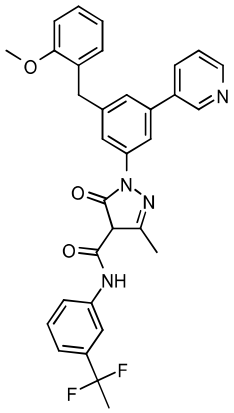
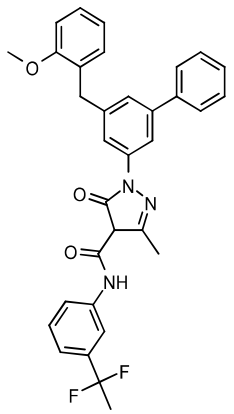
394	
395	
396	
397	

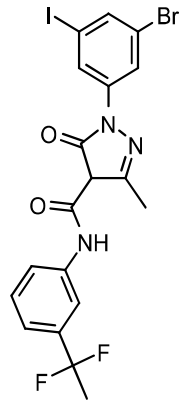
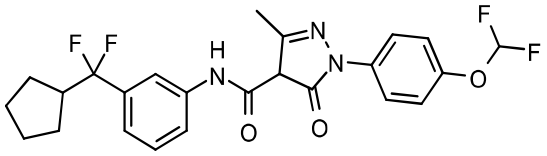
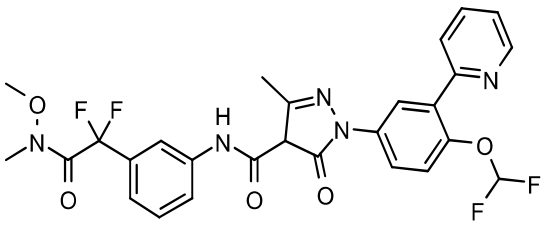
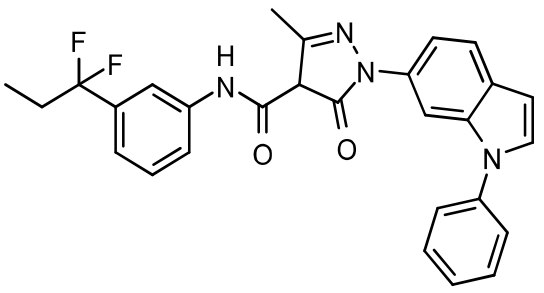
398	
399	
400	
401	

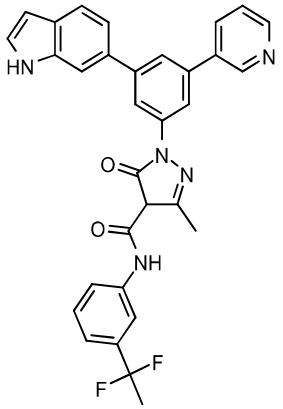
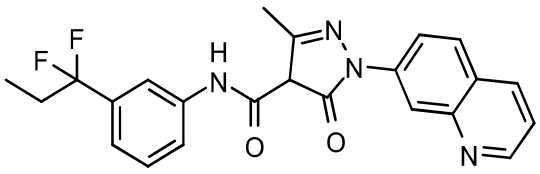
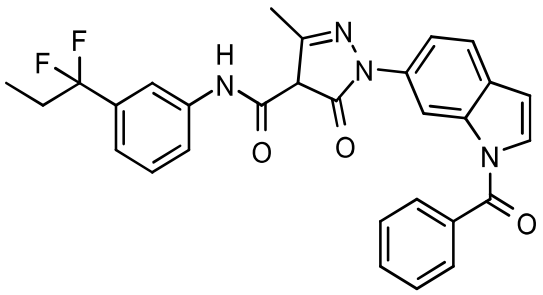
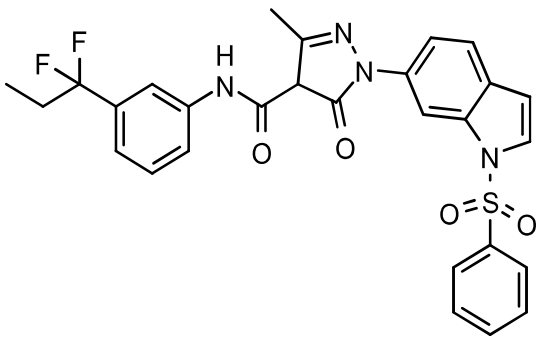
402	
403	
404	
405	

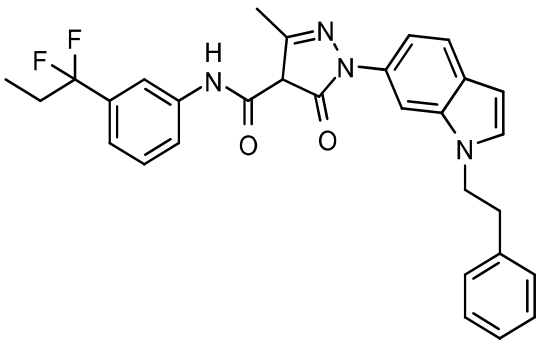
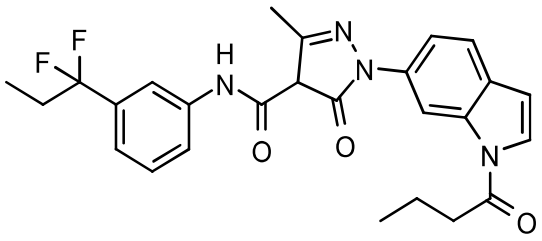
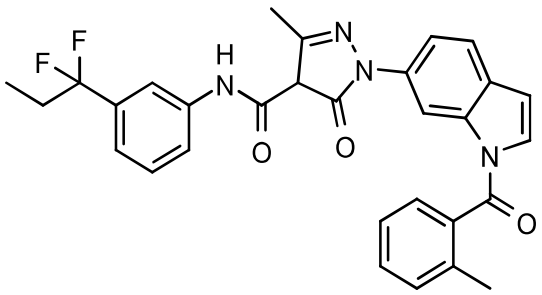
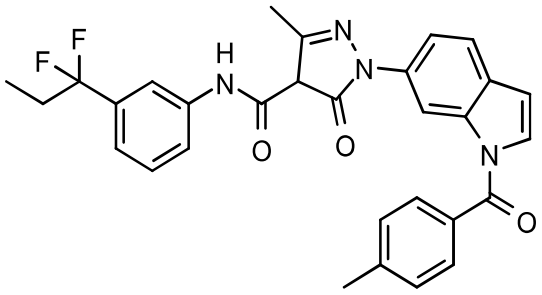
406	
407	
408	
409	

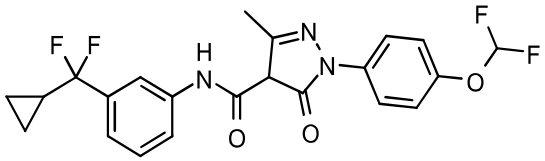
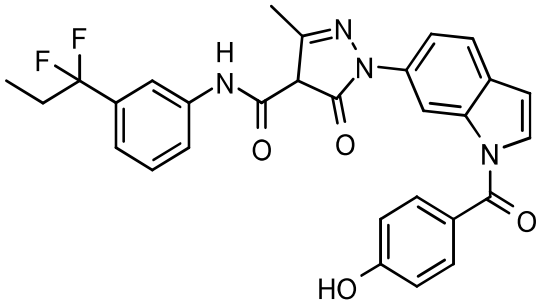
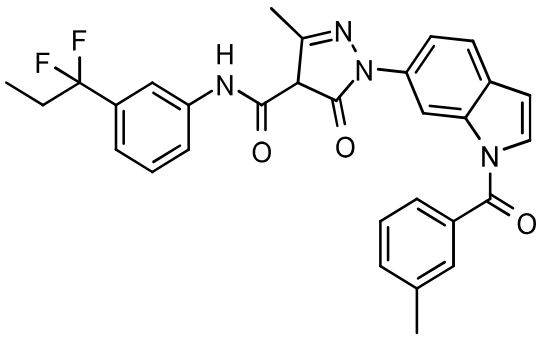
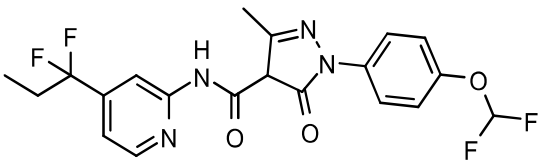
410	
461	
462	
463	

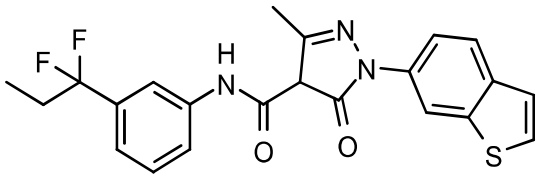
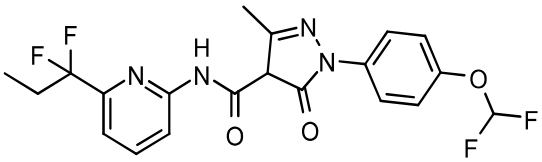
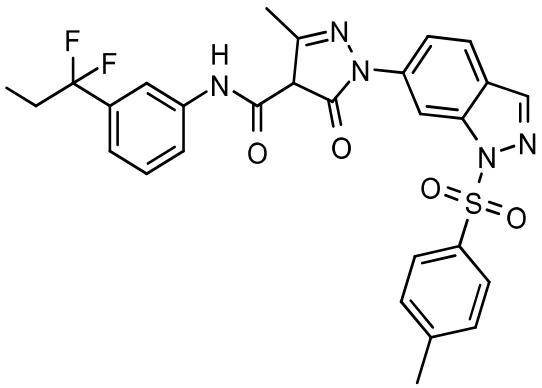
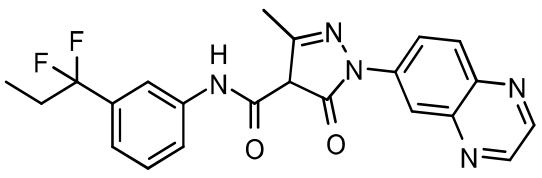
464	
465	
466	
467	

468	
470	
471	
472	

473	
474	
475	
476	

477	
478	
479	
480	

481	
482	
483	
484	

485	
486	
487	
488	

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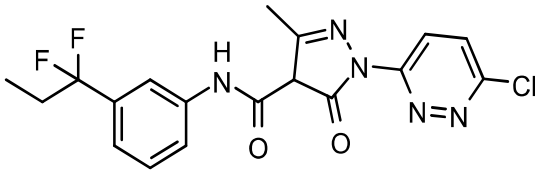
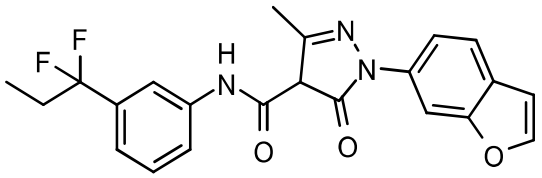
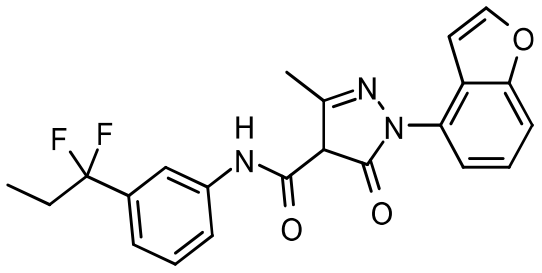
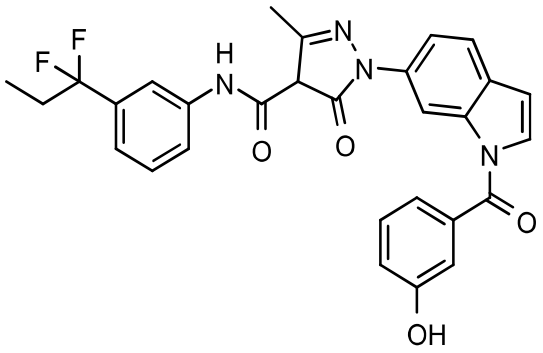
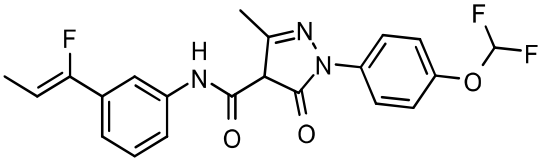
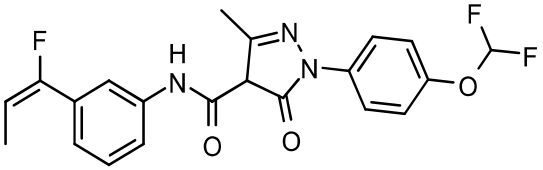
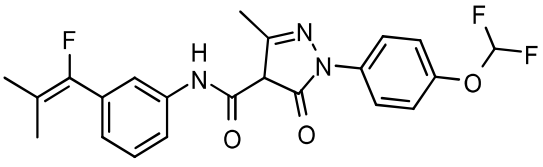
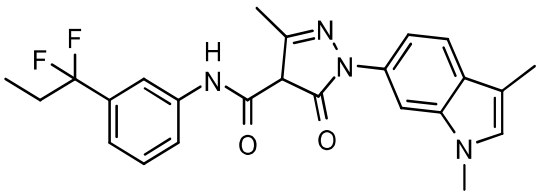
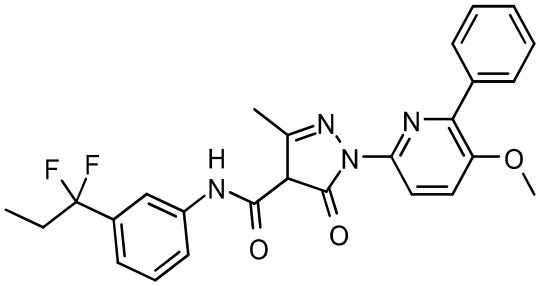
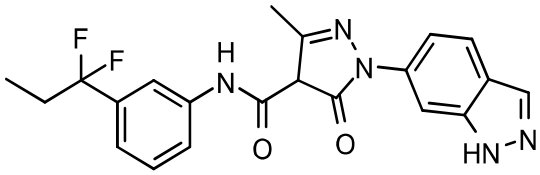
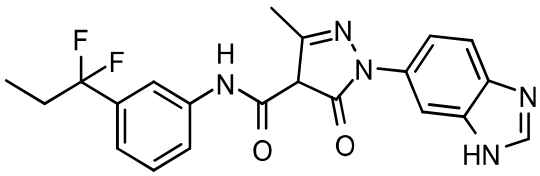
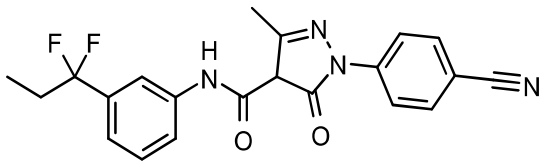
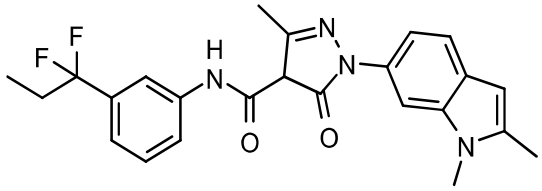
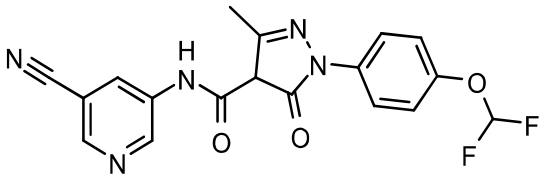
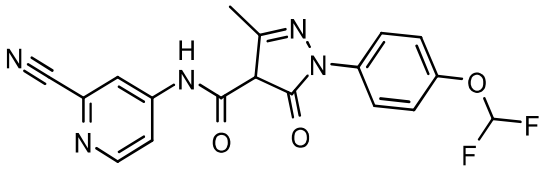
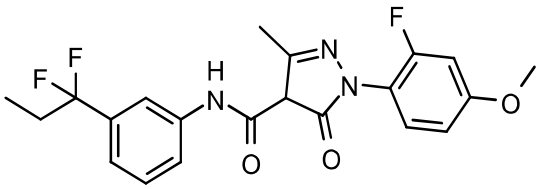
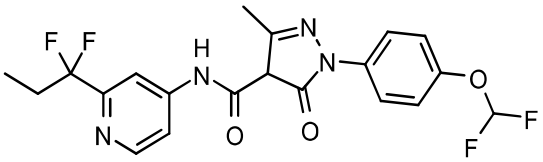
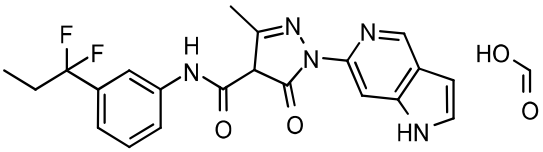
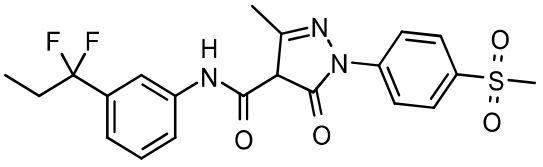
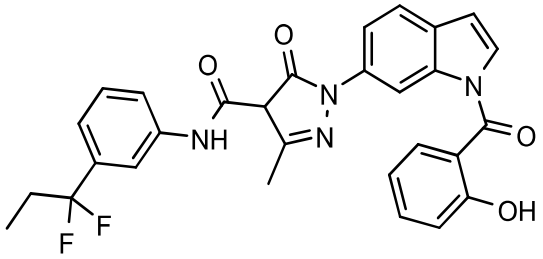
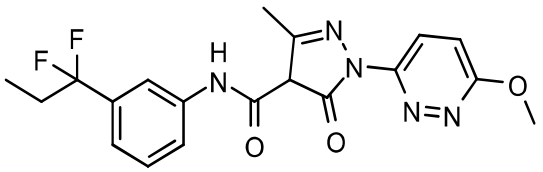
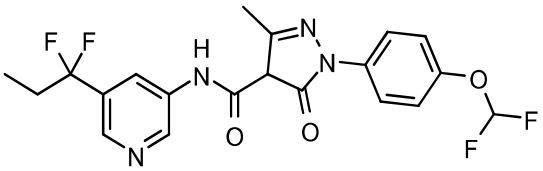
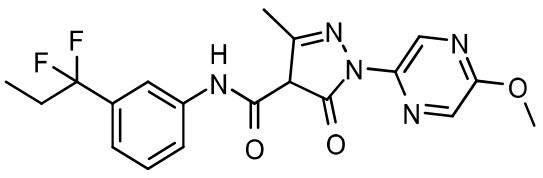
490	
491	
492	

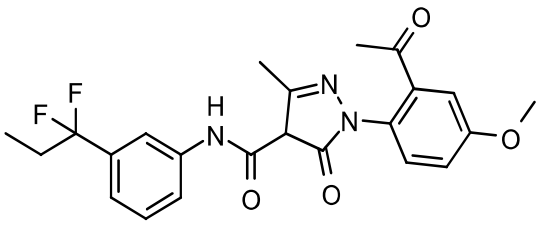
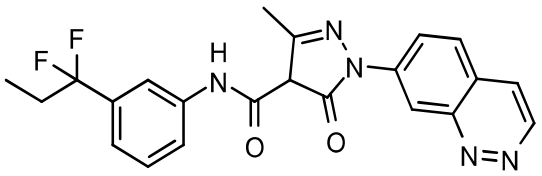
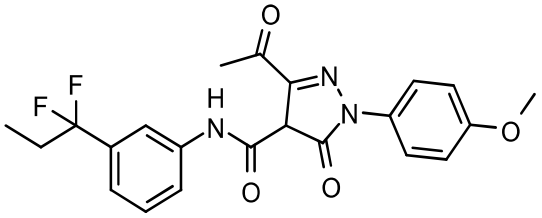
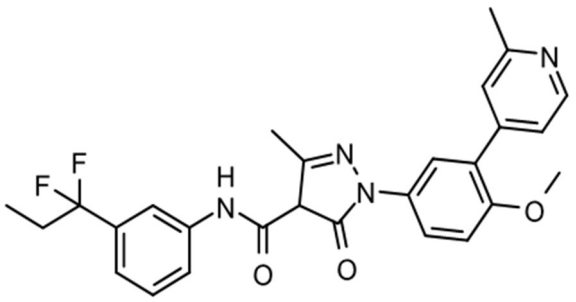
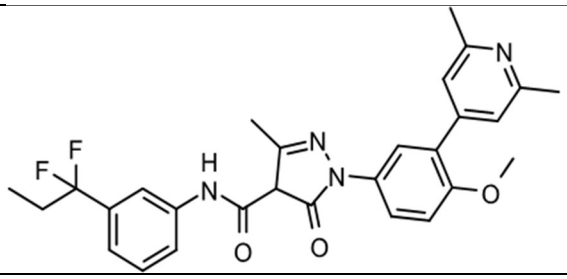
493	
494	
495	
496	

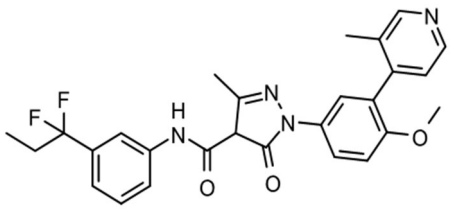
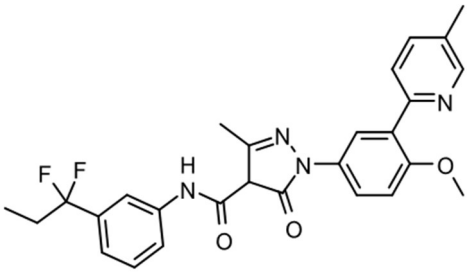
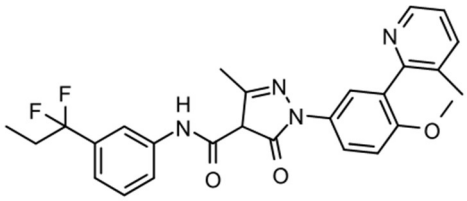
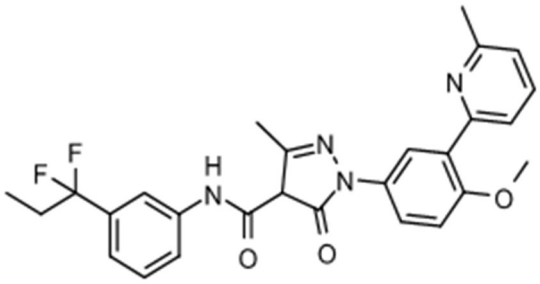
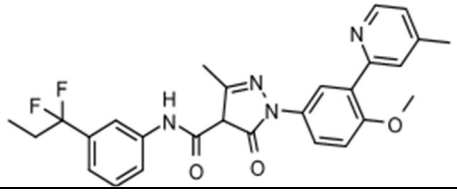
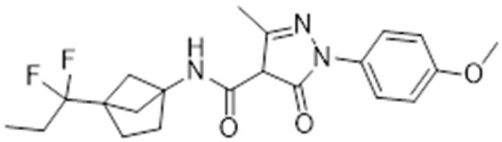
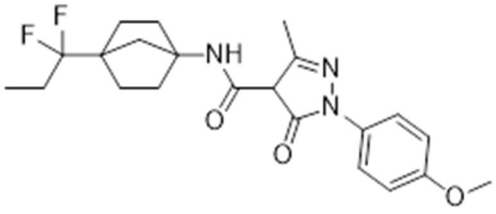
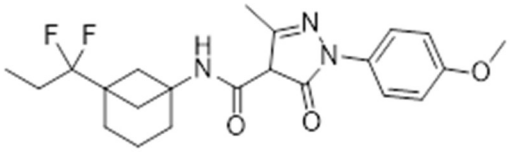
497	
498	
499	
500	

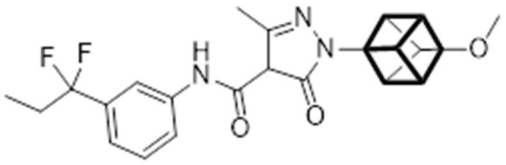
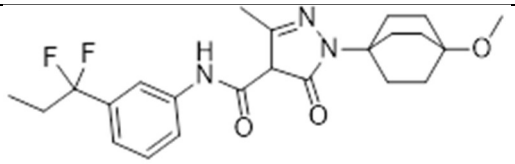
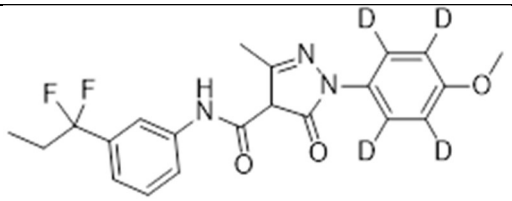
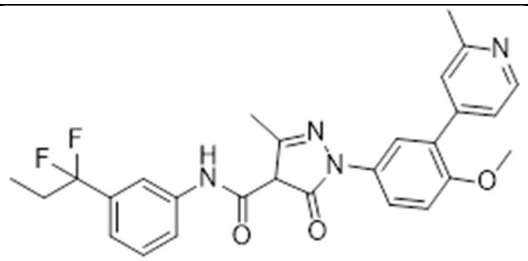
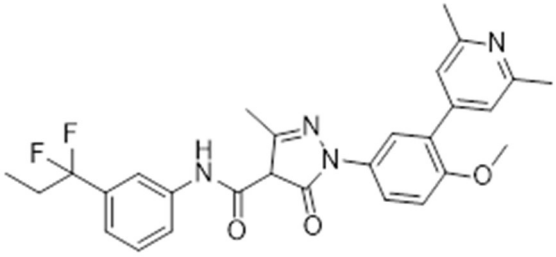
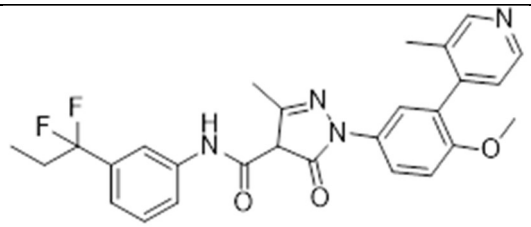
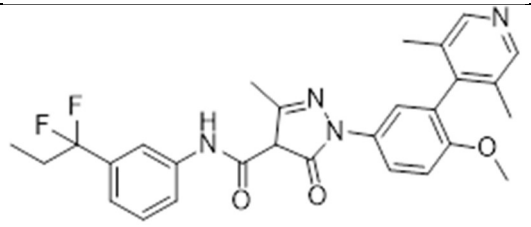
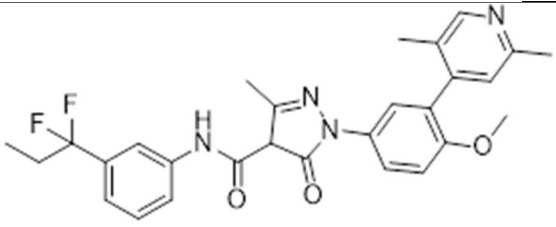
501	
502	
503	
504	

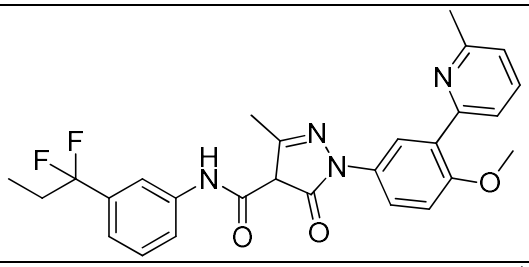
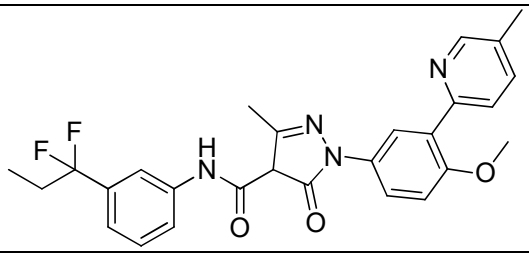
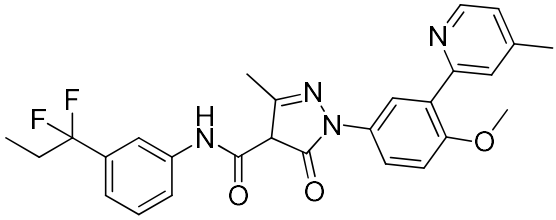
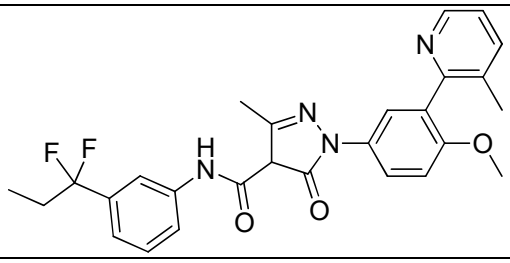
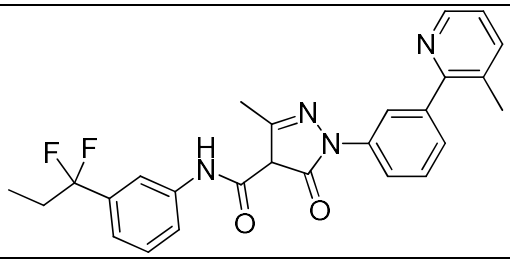
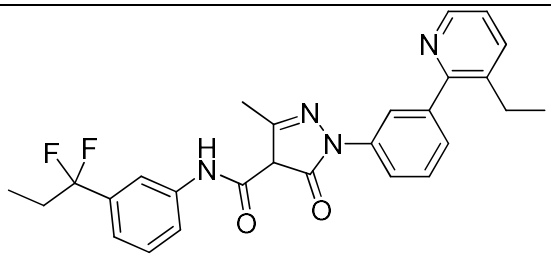
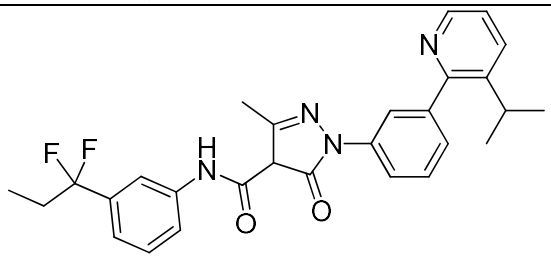
505	
506	
507	
508	

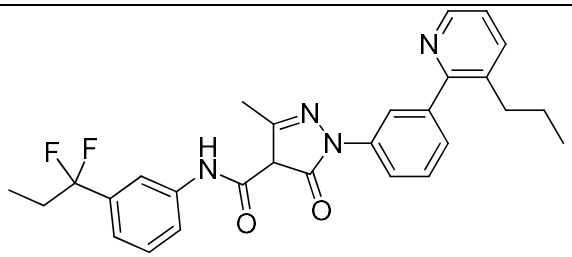
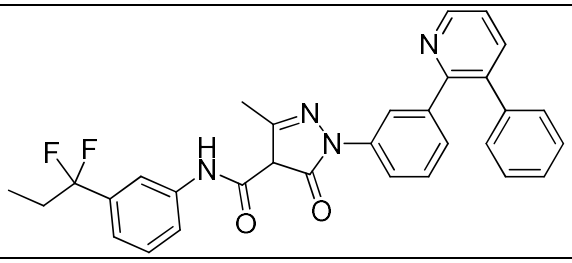
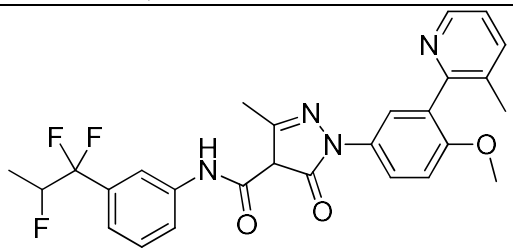
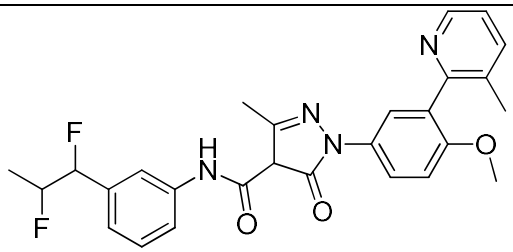
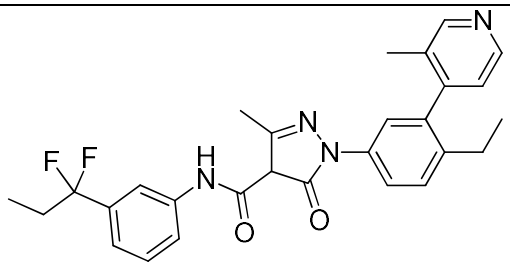
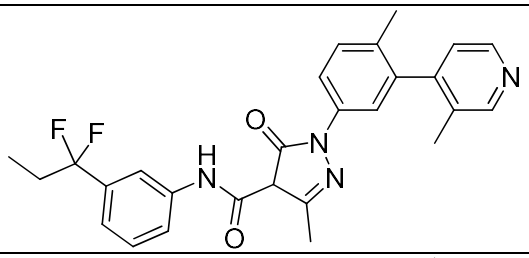
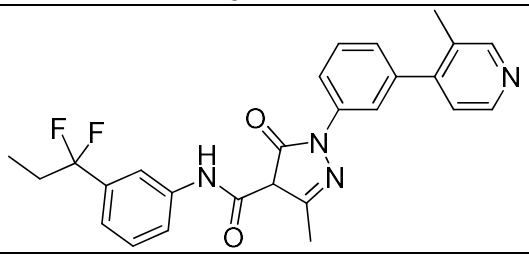
509	
510	
511	
512	

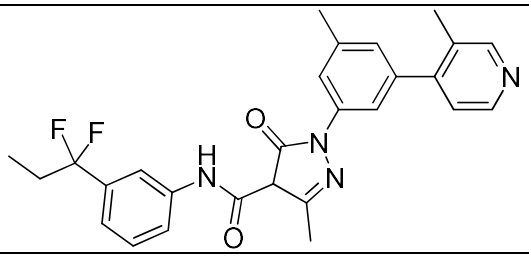
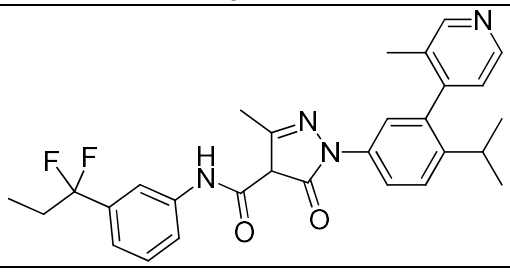
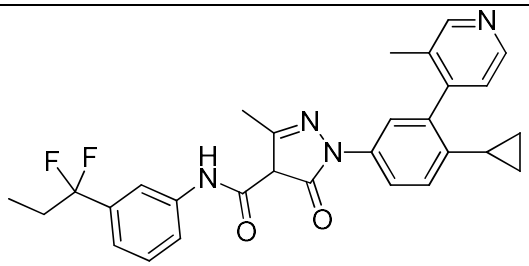
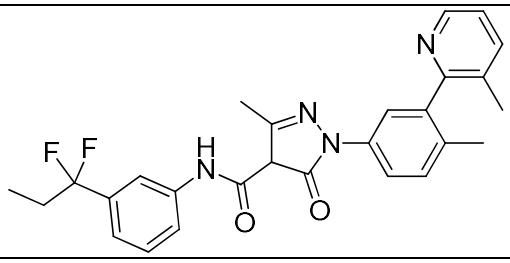
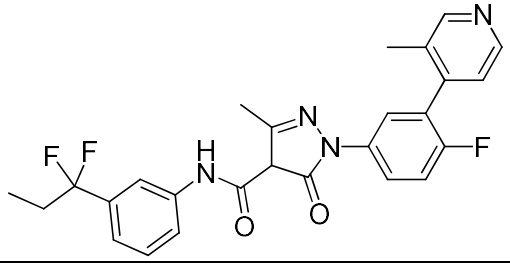
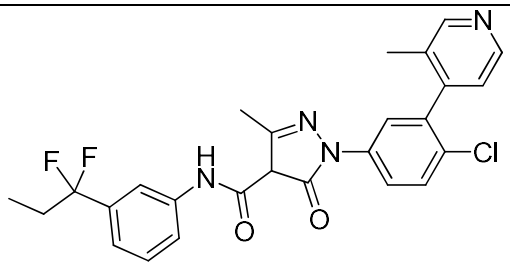
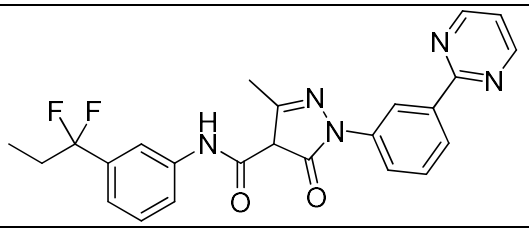
516	
524	
529	
530	
531	

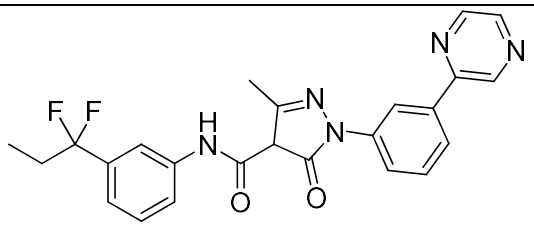
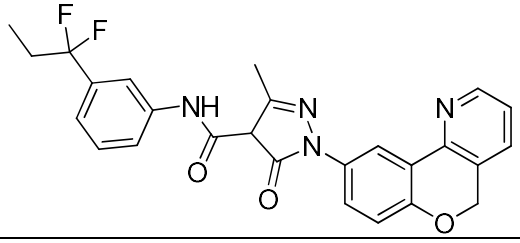
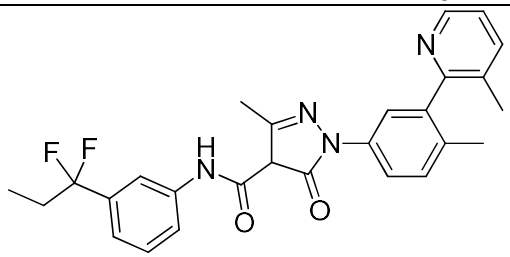
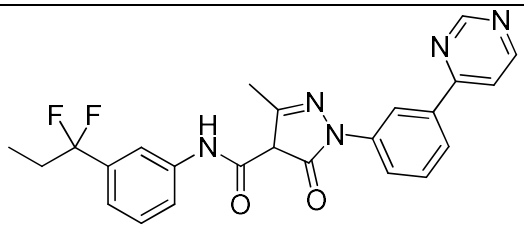
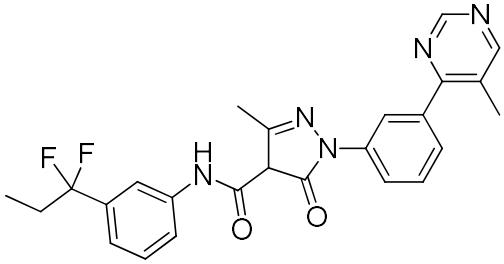
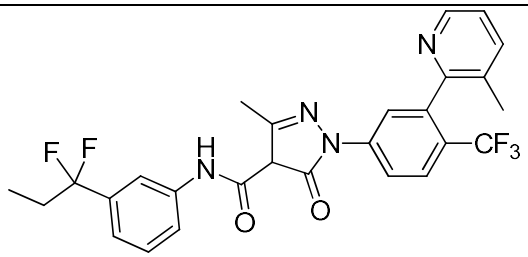
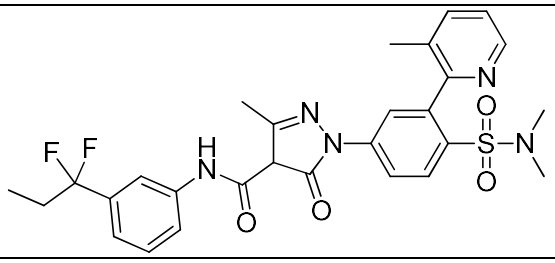
532	
534	
535	
536	
537	
538	
539	
540	

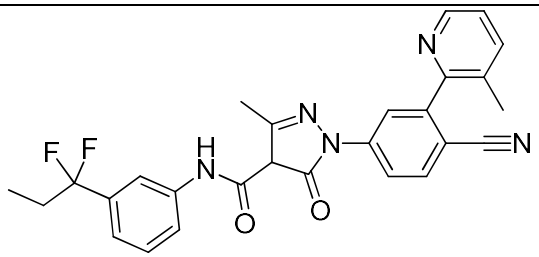
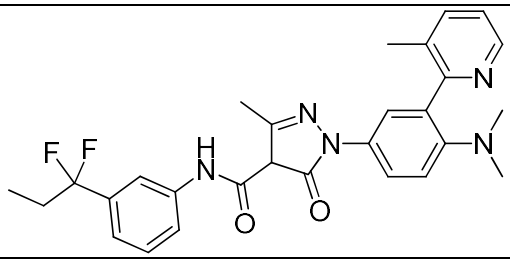
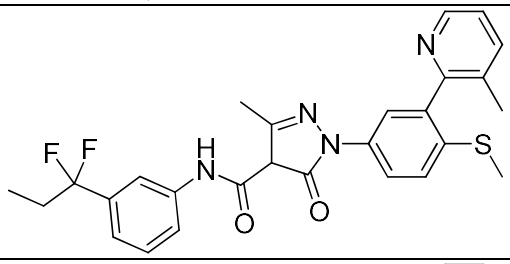
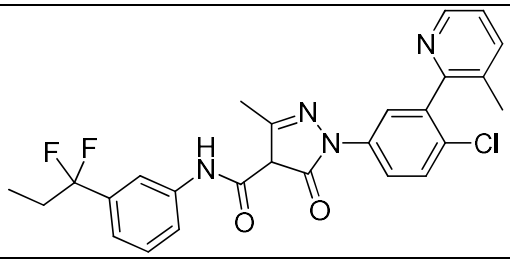
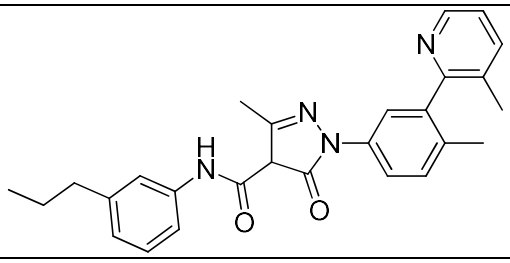
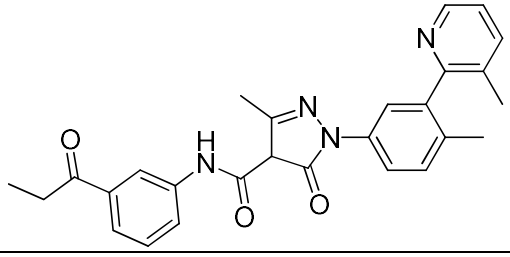
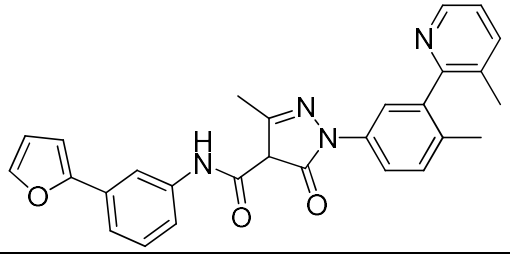
541	
542	
543	
544	
545	
546	
547	
548	

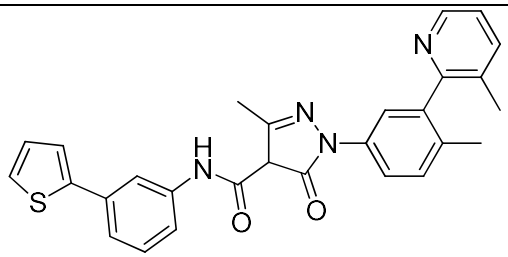
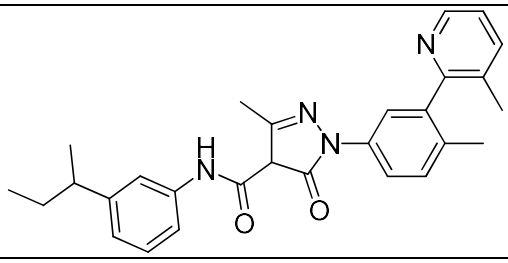
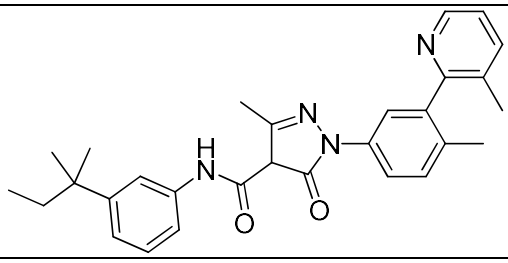
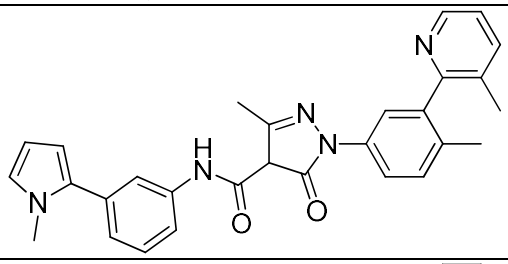
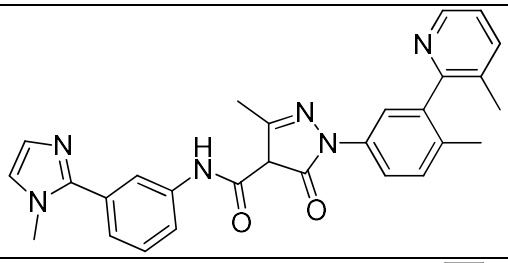
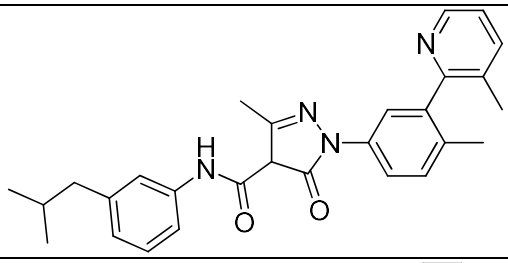
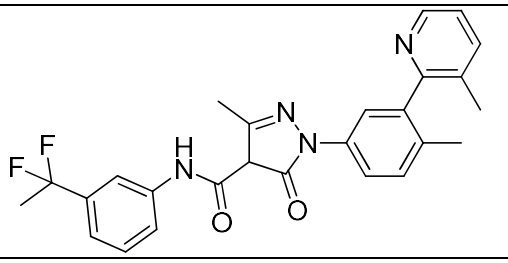
549	
550	
551	
552	
553	
554	
555	

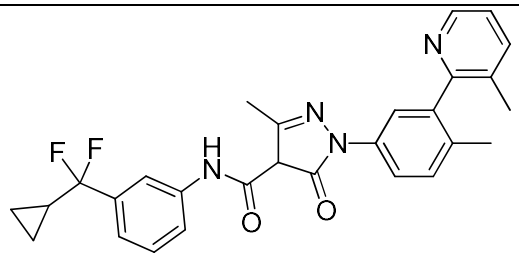
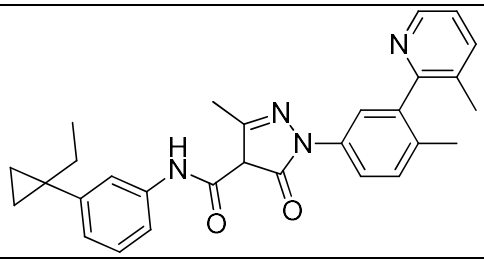
556	
557	
558	
559	
560	
561	
562	

563	
564	
565	
566	
567	
568	
569	

570	
571	
572	
573	
574	
575	
576	

577	
578	
579	
580	
581	
582	
583	

584	
585	
586	
587	
588	
589	
590	

591	
592	

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

2. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

3. The compound of claim 1, wherein the compound is an Acyl-CoA Synthetase Short-Chain Family Member 2 (ACSS2) inhibitor.

4. Use of a compound according to claim 1 or 3, or the pharmaceutical composition of claim 2, in the manufacture of a medicament for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a disease or condition selected from: cancer, human alcoholism, a viral infection, an alcoholic steatohepatitis (ASH), a non alcoholic fatty liver disease (NAFLD), a non-alcoholic steatohepatitis (NASH), a metabolic disorder, a neuropsychiatric disease or disorder, an inflammatory condition and an autoimmune disease or disorder in a subject.

5. The use of claim 4, wherein the cancer is selected from the list of: 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;

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

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

wherein the compound is to be administered in combination with an anti-cancer therapy, preferably wherein the anti-cancer therapy is chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof;

wherein the viral infection is human cytomegalovirus (HCMV) infection;

wherein the metabolic disorder is selected from: obesity, weight gain, hepatic steatosis and fatty liver disease; and/or

wherein the neuropsychiatric disease or disorder is selected from: anxiety, depression, schizophrenia, autism and post-traumatic stress disorder.

6. Use of a compound according to claim 1 or 3, or the pharmaceutical composition of claim 2, in the manufacture of a medicament in suppressing, reducing or inhibiting tumor growth in a subject.

7. The use of claim 6, wherein the tumor growth is enhanced by increased acetate uptake by cancer cells of said cancer; wherein the cancer cells are under hypoxic stress; 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; or any combination thereof.

8. The use of claim 7, wherein the increased acetate uptake is mediated by ACSS2.

9. Use of a compound according to claim 1 or 3, in the manufacture of a medicament for suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and function in a cell.

10. The use of claim 9, wherein the cell is a cancer cell.

11. 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 claim 1 or 3, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme.

12. Use of a compound according to claim 1 or 3, in the manufacture of a medicament for suppressing, reducing or inhibiting acetyl-CoA synthesis from acetate in a cell.

13. The use of claim 12, wherein the cell is a cancer cell; wherein the synthesis is mediated by ACSS2; or combination thereof.

14. Use of a compound according to claim 1 or 3, in the manufacture of a medicament for suppressing, reducing or inhibiting acetate metabolism in a cancer cell.

15. The use of claim 14, wherein the acetate metabolism is mediated by ACSS2; wherein the cancer cell is under hypoxic stress; or combination thereof.