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).

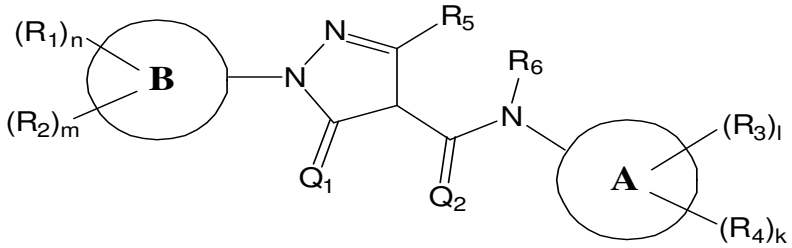
[0012] ACSS2 is also shown to enter the nucleus under certain condition (hypoxia, high fat etc.) and to affect histone acetylation and crotonylation by making available acetyl-CoA and crotonyl-CoA and thereby regulate gene expression. For example, ACSS2 decrease is shown to lower levels of nuclear acetyl-CoA 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, 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 structure of formula (I):



(**I**)

wherein

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

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

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

$\mathbf{R_3}$ is C_2-C_5 linear or branched haloalkyl, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_3-C_8 heterocyclic ring (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, CN or NO_2);

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

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

$\mathbf{R_5}$ is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl, C_1-C_5 linear or branched haloalkyl, R_8-aryl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, CN or NO_2);

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

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

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

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

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

$\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are each independently H, C_1-C_5 linear or branched alkyl, C(O)R, or $S(O)_2$R;

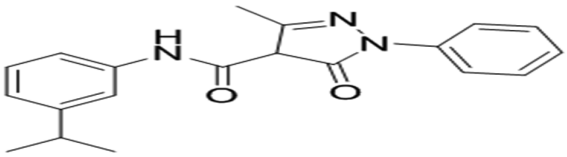
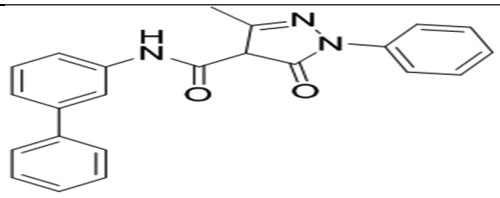
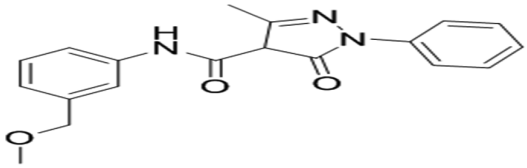
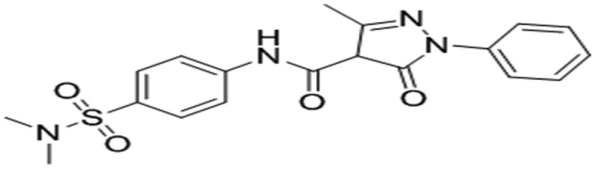
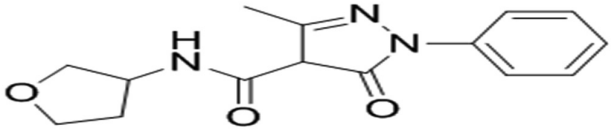
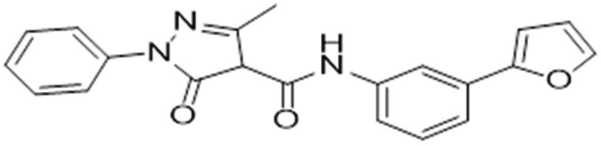
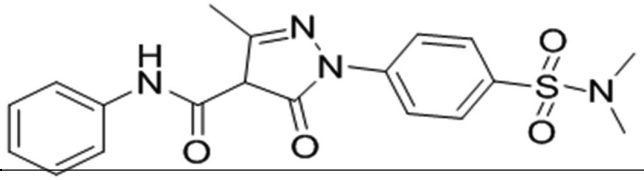
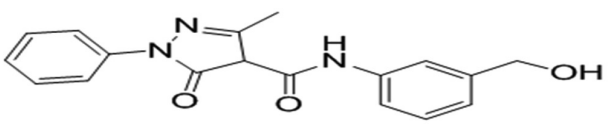
R is H, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkoxy, phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

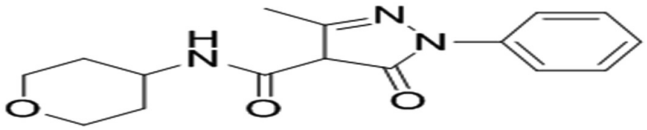
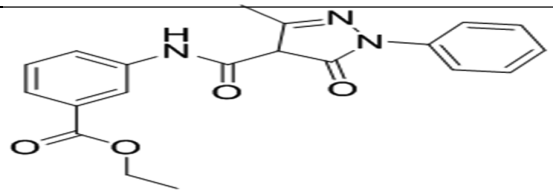
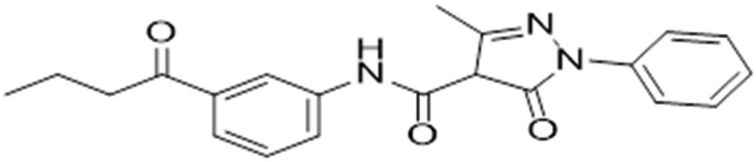
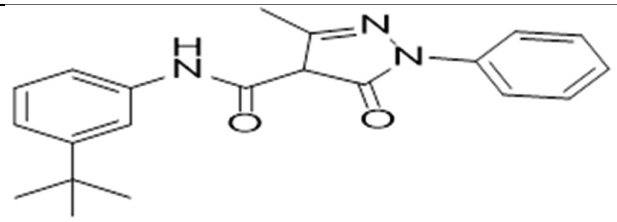
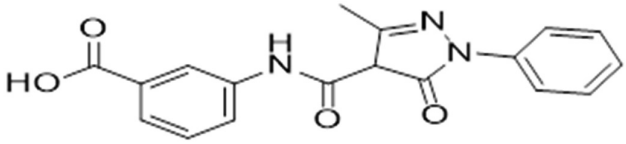
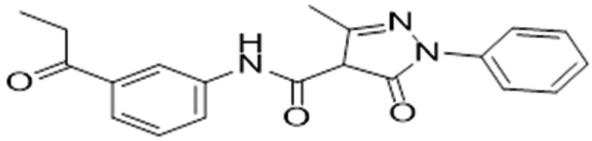
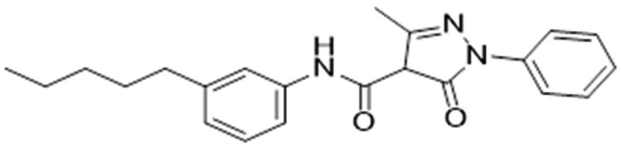
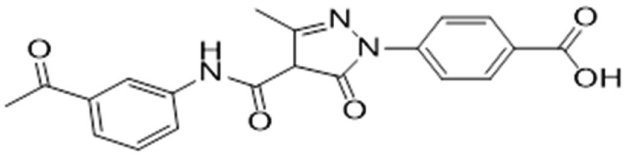
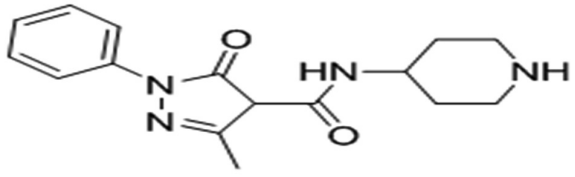
m, **n, l** and **k** are each independently an integer between 0 and 4;

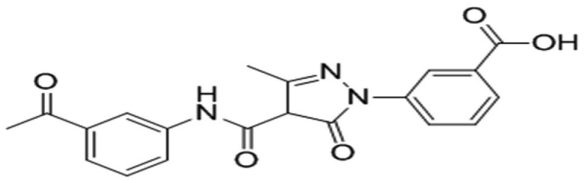
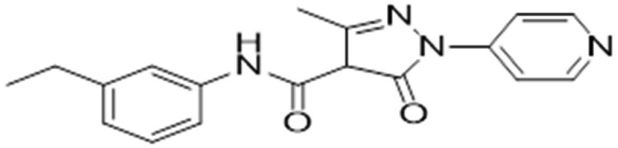
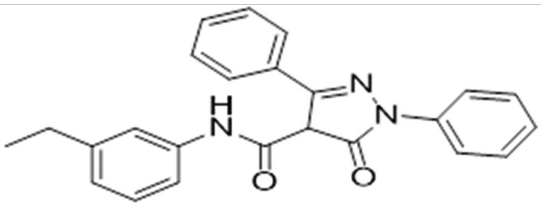
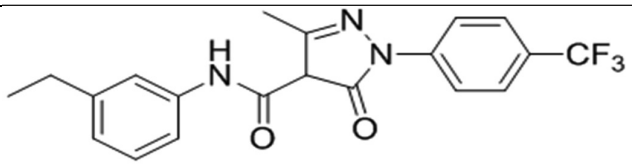
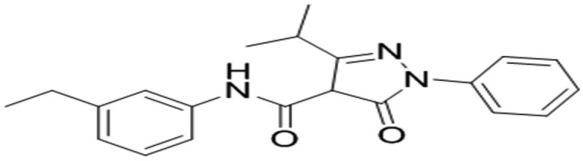
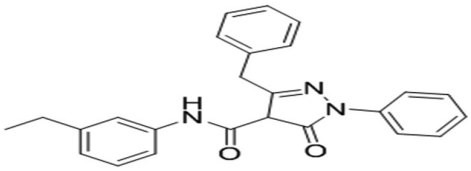
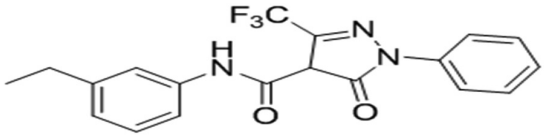
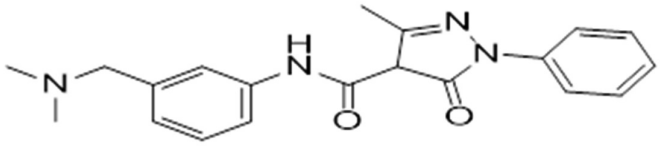
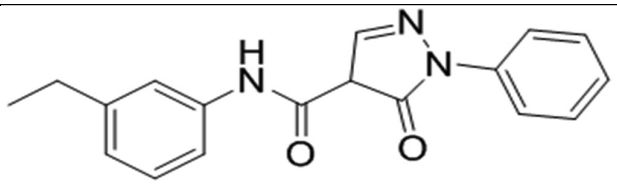
$\mathbf{Q_1}$ and $\mathbf{Q_2}$ are each independently S or O;

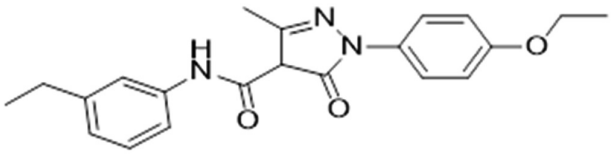
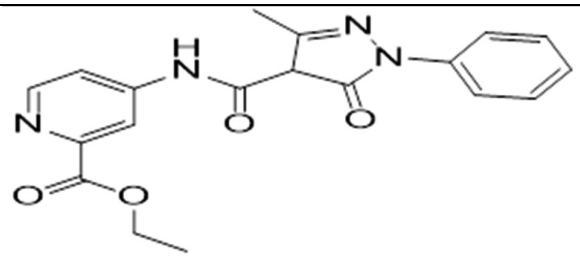
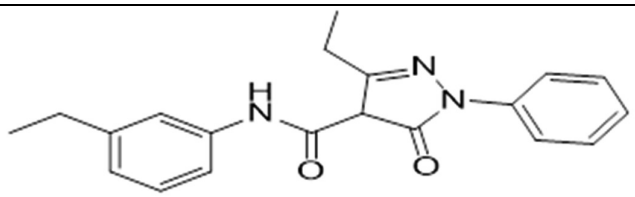
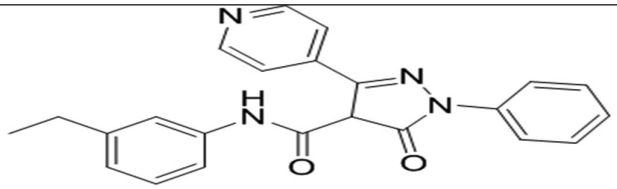
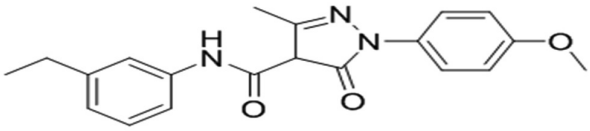
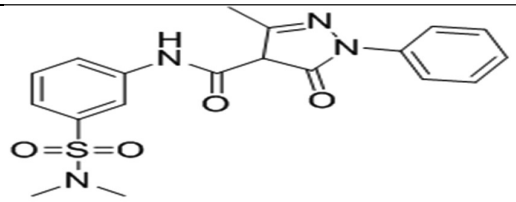
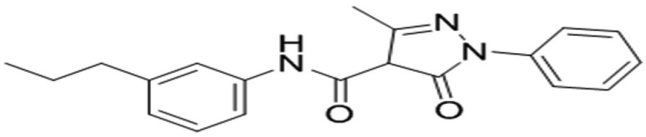
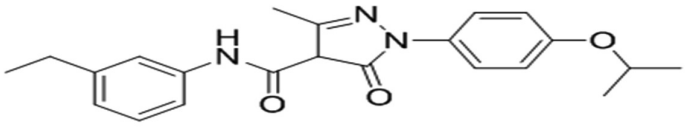
or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variant, PROTAC, pharmaceutical product or any combination thereof.

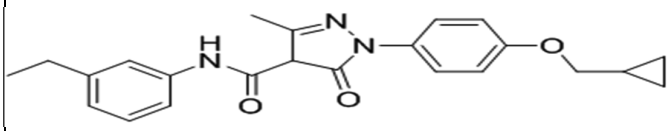
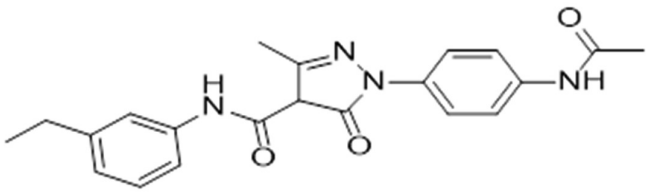
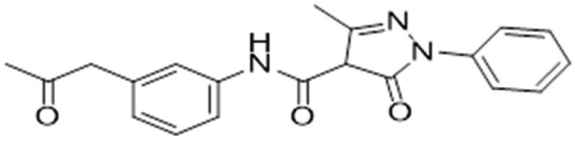
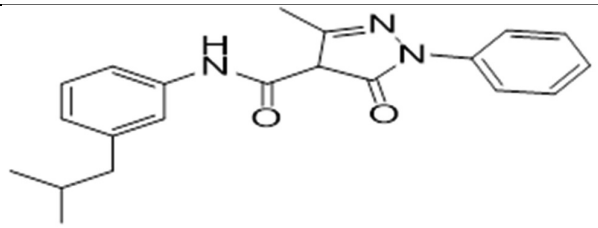
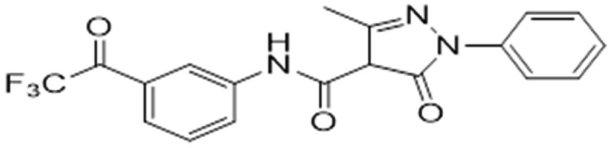
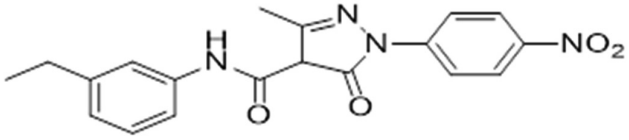
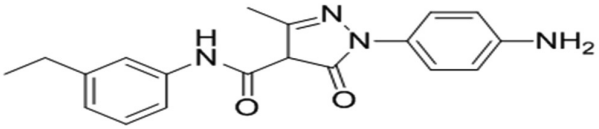
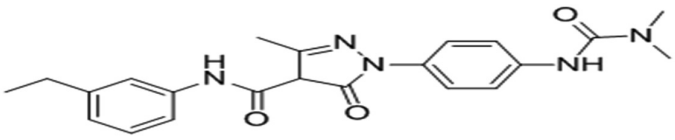
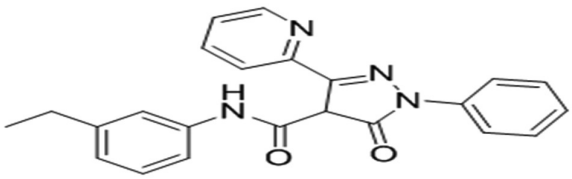
[0014b] In one aspect, the present disclosure refers to a compound represented by the following structures:

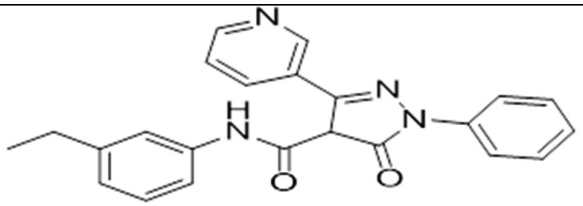
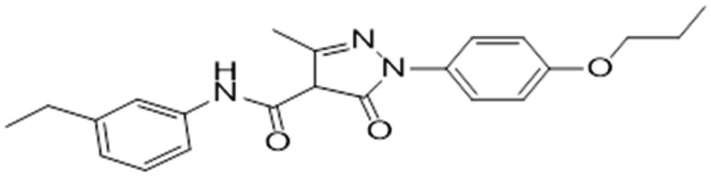
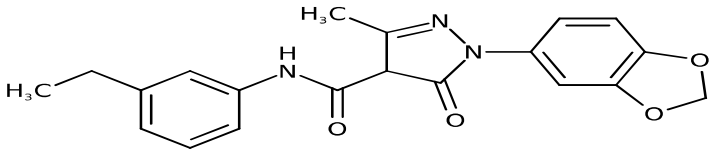
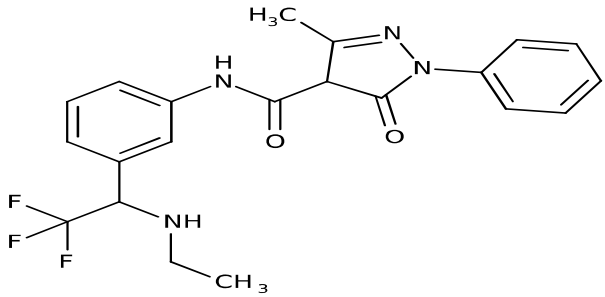
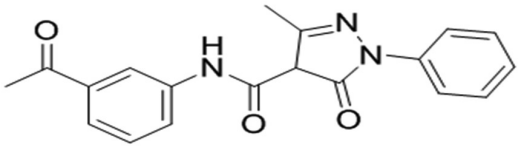
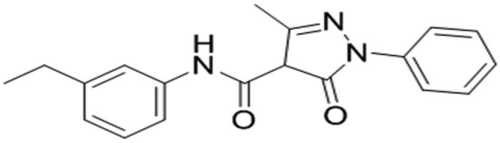
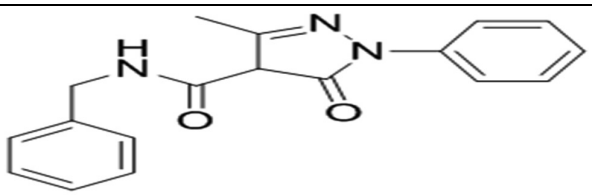
Compound name	Structure
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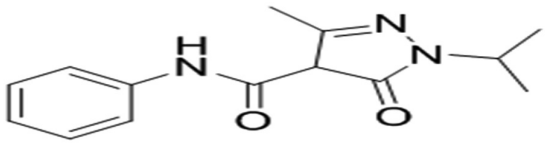
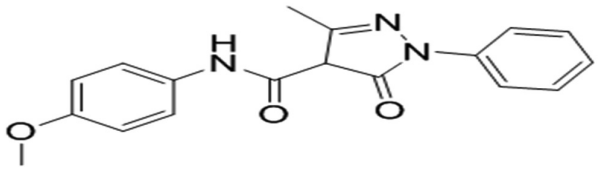
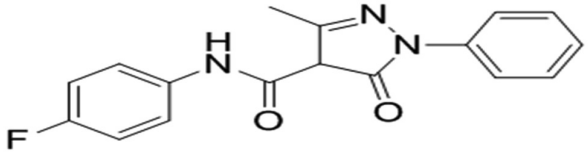
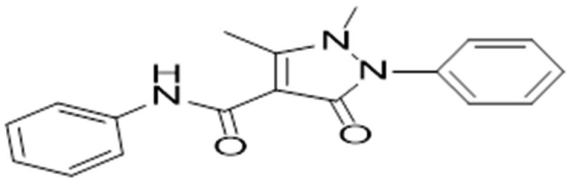
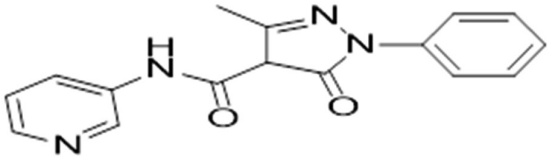
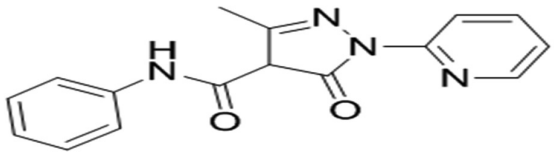
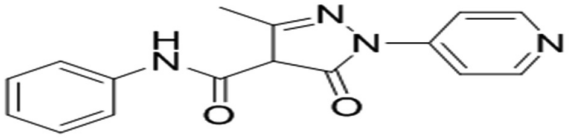
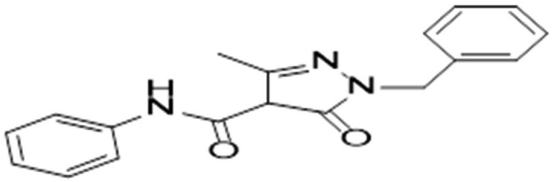
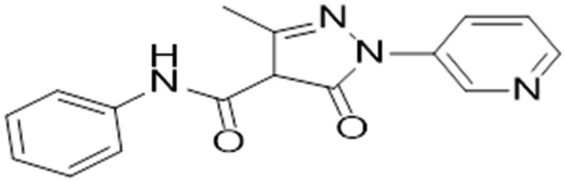
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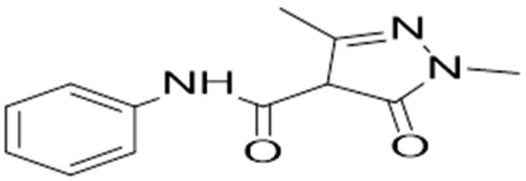
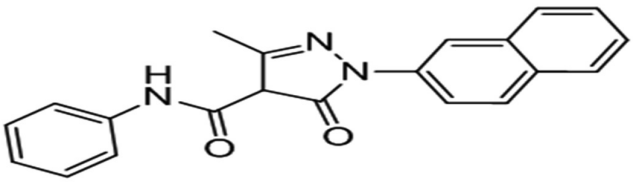
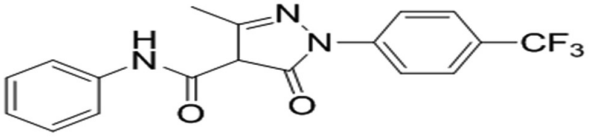
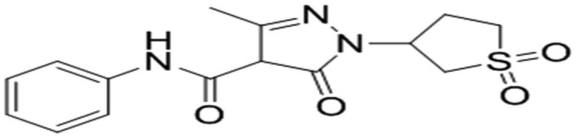
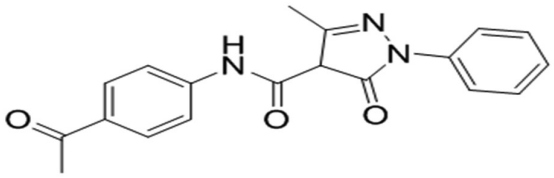
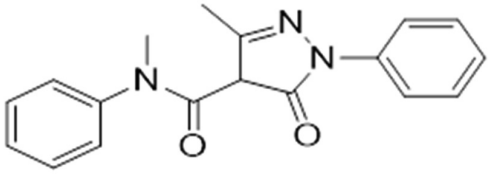
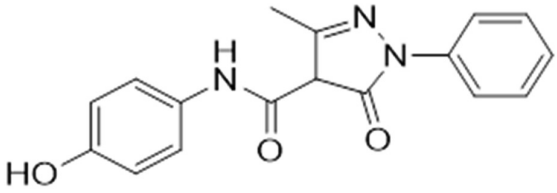
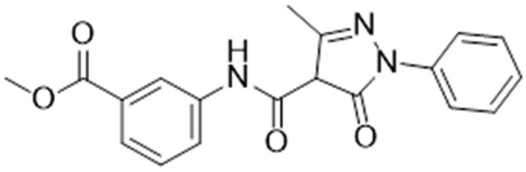
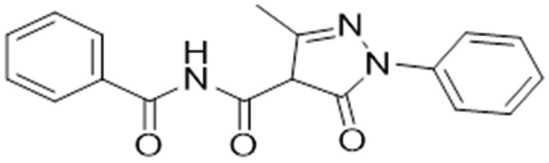
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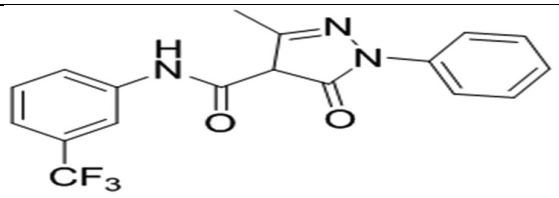
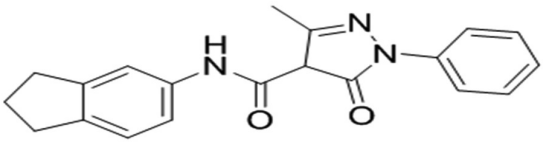
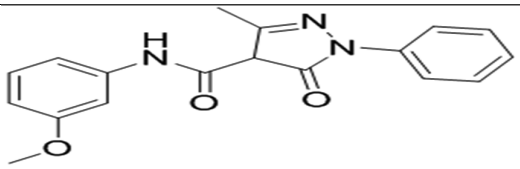
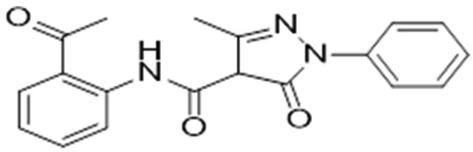
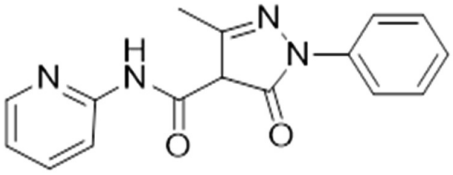
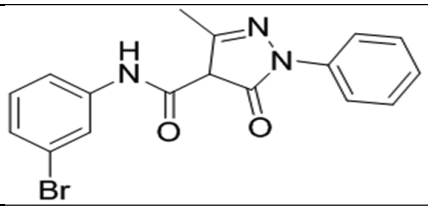
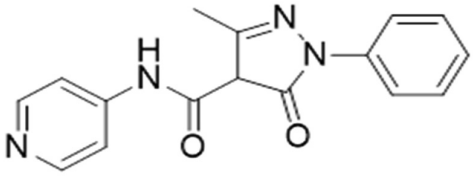
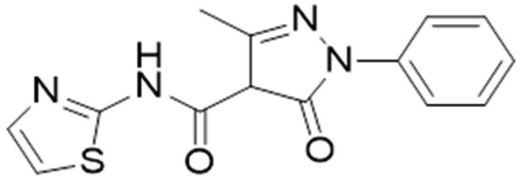
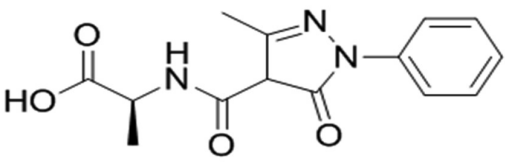
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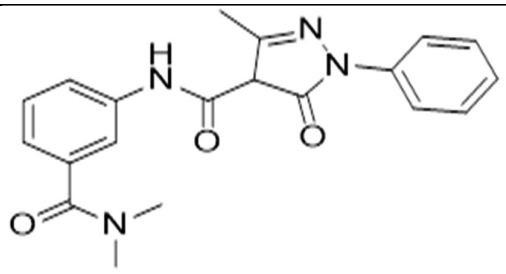
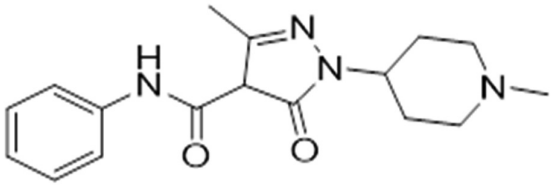
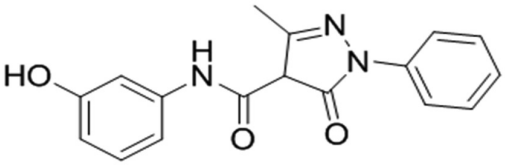
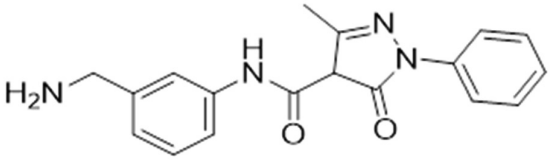
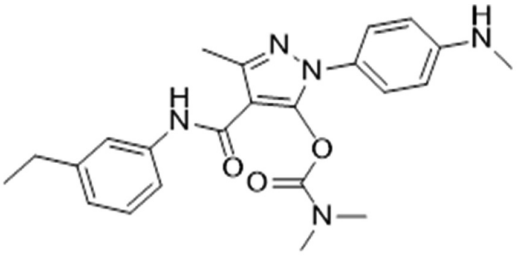
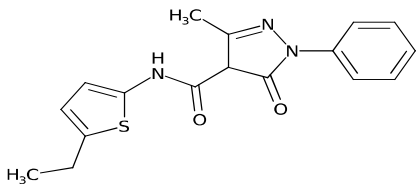
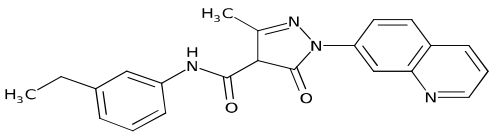
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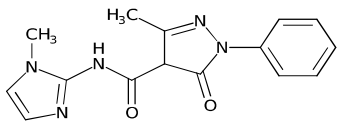
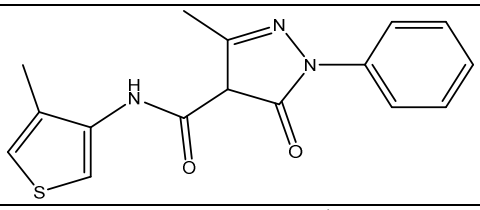
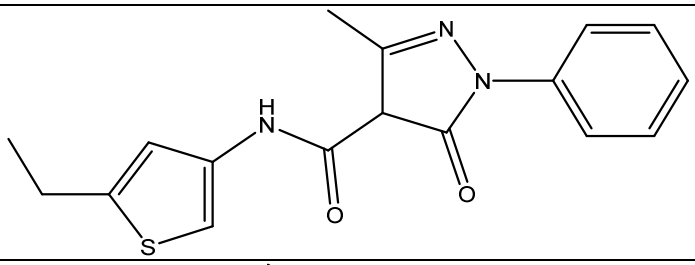
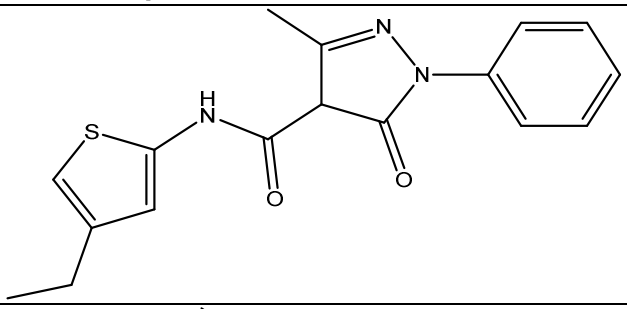
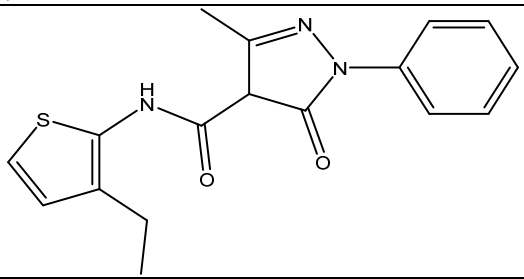
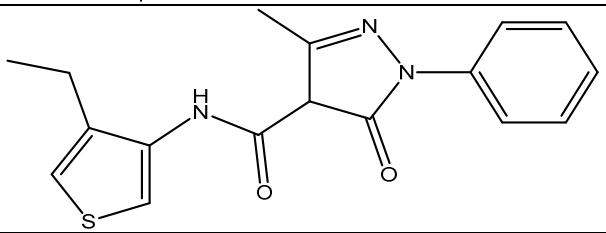
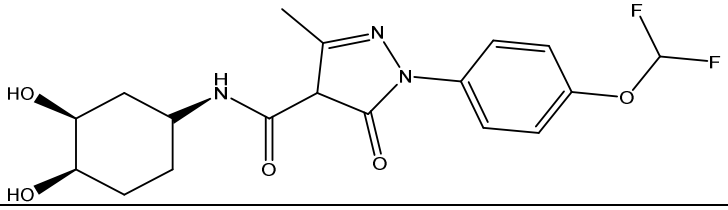
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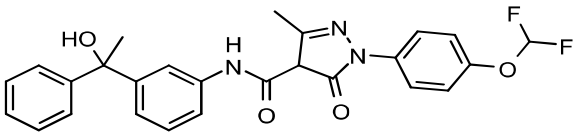
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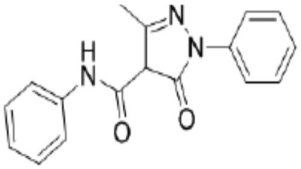
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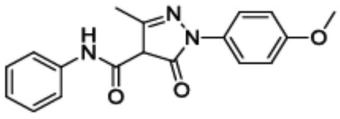
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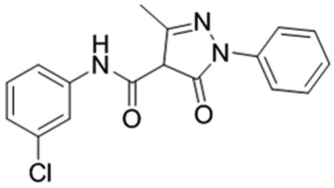
[0014c] In one aspect, the present disclosure refers to a compound represented by the following structures:



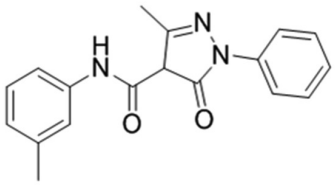
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wherein the compound is an Acyl-CoA Synthetase Short-Chain Family Member 2 (ACSS2) inhibitor.

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

[0016] In one aspect, the present disclosure refers to use of a compound as defined herein in the manufacture of a medicament for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer in a subject. 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.

[0017] In one aspect, the present disclosure refers to use of a compound as defined herein in the manufacture of a medicament for suppressing, reducing or inhibiting tumour growth in a subject. 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.

[0018] This disclosure further provides a method of suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and function 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 lipid synthesis and/or regulating histones acetylation and function in said cell. In various examples, the cell is a cancer cell. In one aspect, the present disclosure refers to an *in vitro* method of suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and function in a cell such as a cancer cell; or
of suppressing, reducing or inhibiting acetyl-CoA synthesis, such as ACSS2-mediated acetyl-CoA synthesis, from acetate in a cell such as a cancer cell; or
of suppressing, reducing or inhibiting acetate metabolism, such as ACSS2-mediated acetate metabolism, in a cancer cell, optionally wherein the cancer cell is under hypoxic stress,
the method comprising contacting the cell with a compound as defined herein.

[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. 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 as defined 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.

[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 use of a compound as defined herein in the manufacture of a medicament for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject, or

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

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

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

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

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

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

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

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

[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**.

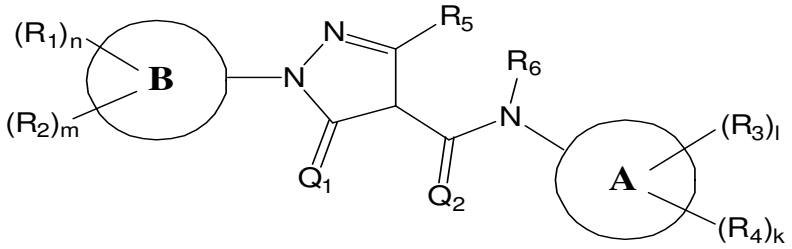
[0033] **Figure 3** depicts a synthetic scheme for compound **133**.

[0034] **Figure 4** depicts an *in-vivo* efficacy study of compound **265** in MDA-MB-468 breast cancer cells xenograft mouse model.

[0035] 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.

WHAT IS CLAIMED:

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



(**I**)

wherein

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

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

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

R_3 is C_2-C_5 linear or branched haloalkyl, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_3-C_8 heterocyclic ring (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, OH, alkoxy, N(R)$_2$, CF_3, CN or NO_2);

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

substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, CN or NO_2), $CH(CF_3)(NH\text{-}R_{10})$;

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

$\mathbf{R_5}$ is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl, C_1-C_5 linear or branched haloalkyl, R_8-aryl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, CN or NO_2);

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

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

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

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

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

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

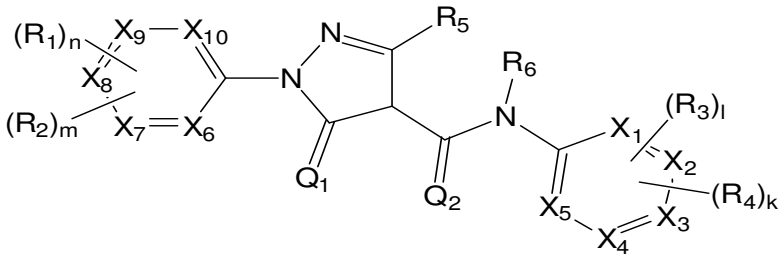
R is H, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkoxy, phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

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

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

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

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



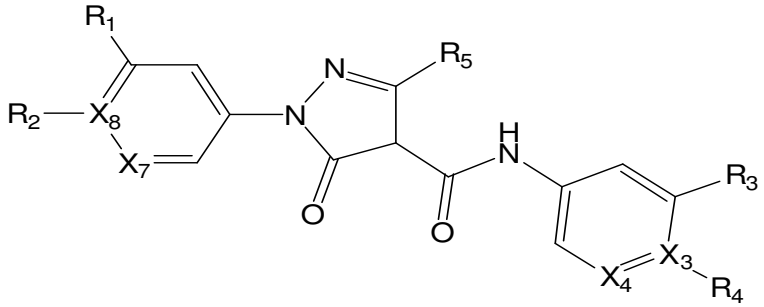
(II)

wherein

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

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

or represented by the structure of formula (IV):



(IV)

wherein

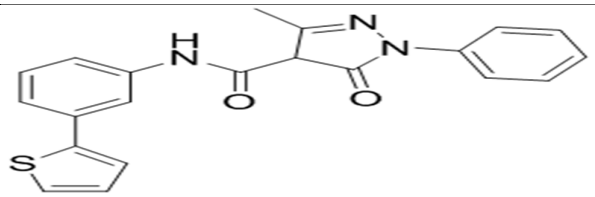
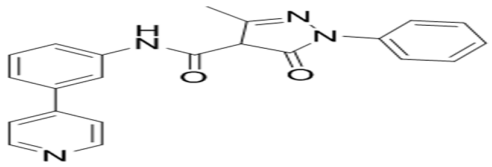
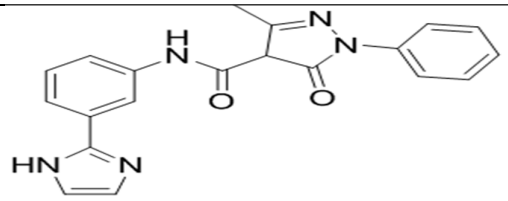
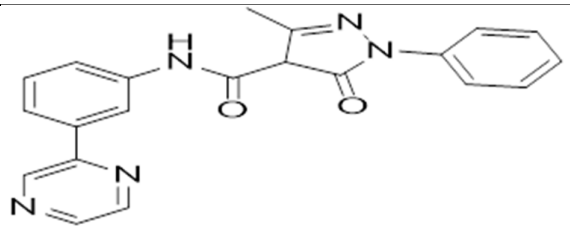
R_1, R_2, R_3, R_4, and **R_5** are as defined in claim 1; and

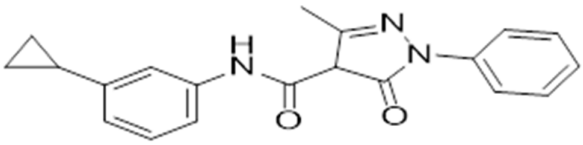
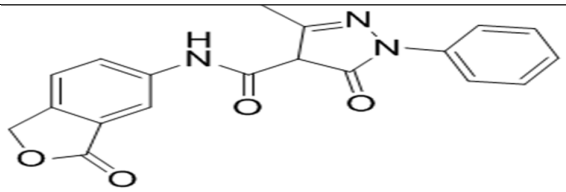
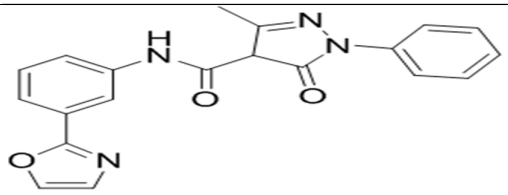
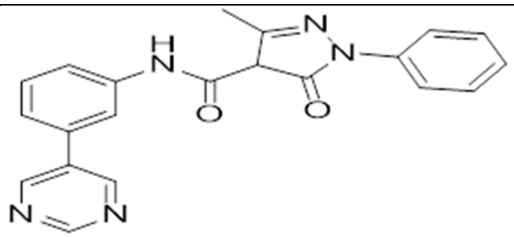
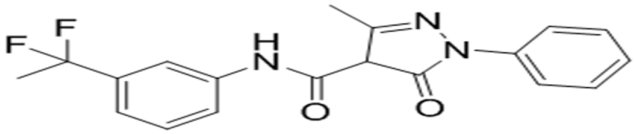
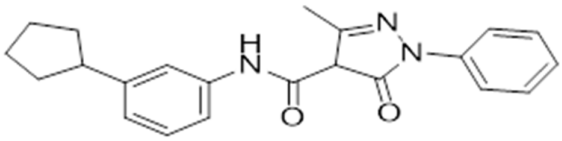
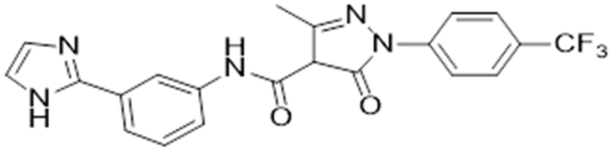
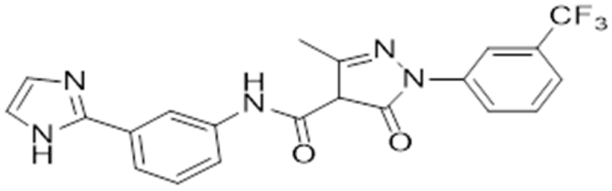
X_3, **X_4**, **X_7**, and **X_8** are each independently C or N;

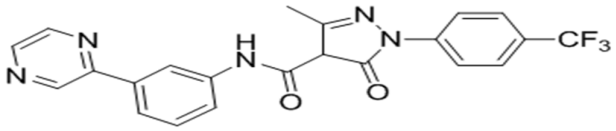
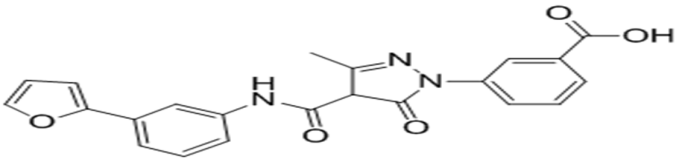
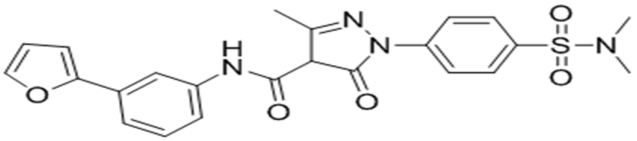
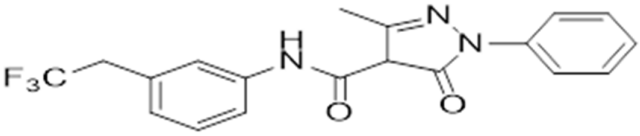
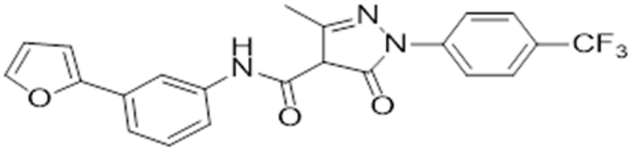
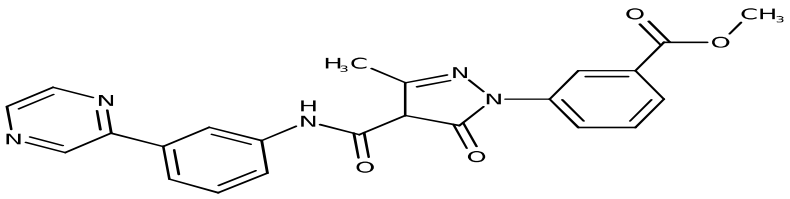
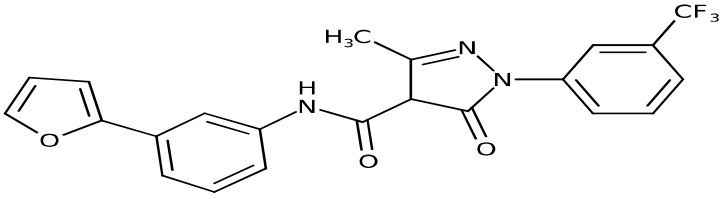
wherein if X_3 is N, then R_4 is absent; and

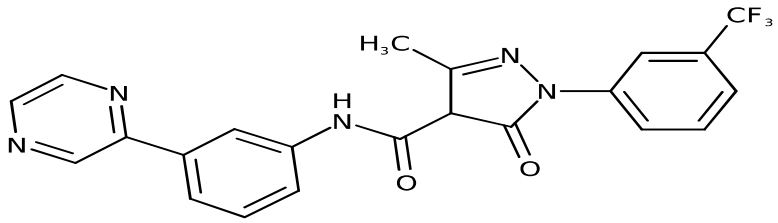
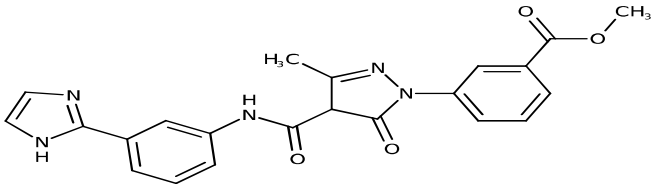
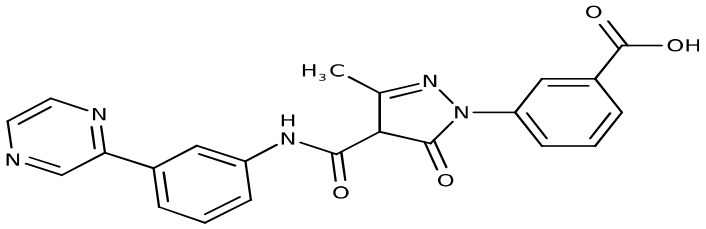
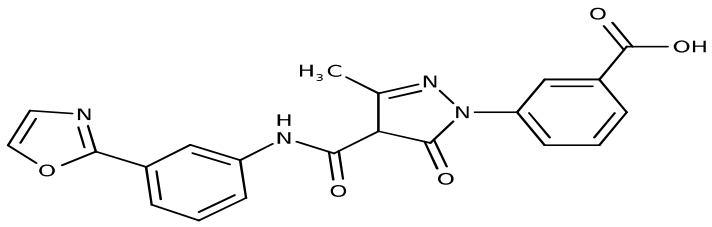
wherein if X_8 is N, then R_2 is absent.

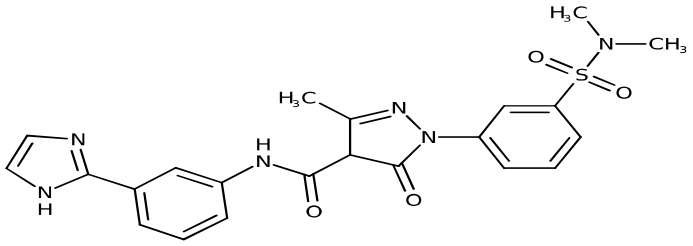
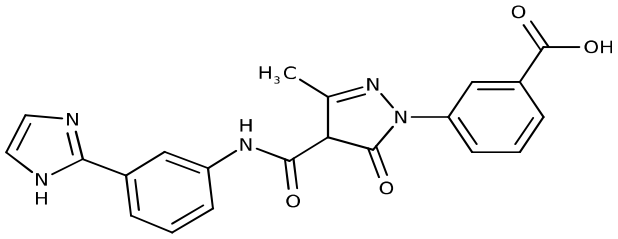
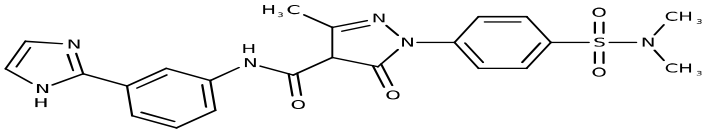
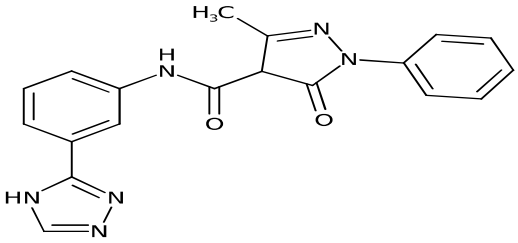
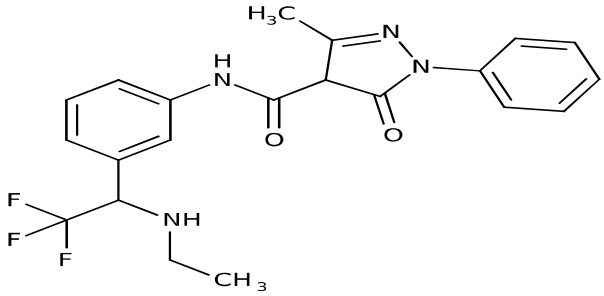
3. The compound of claim 1, selected from the following:

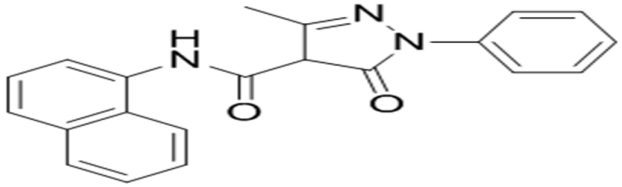
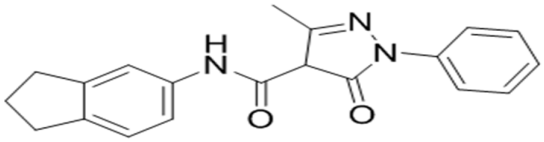
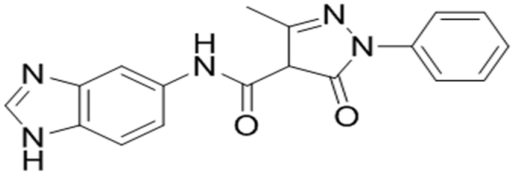
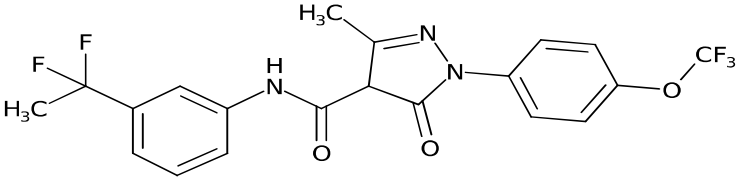
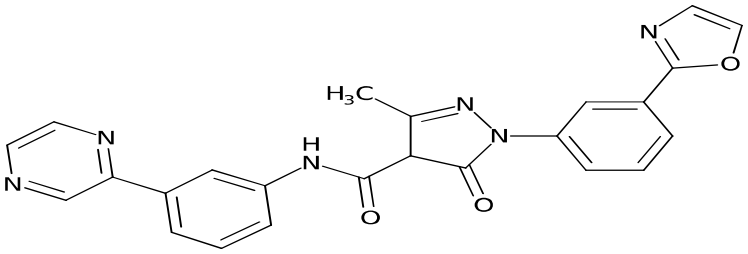
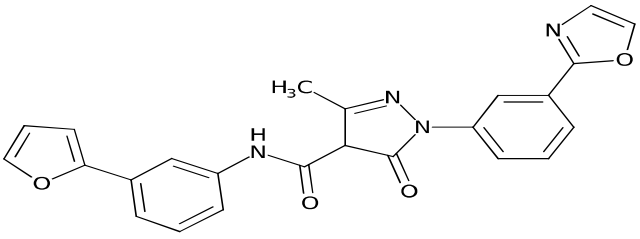
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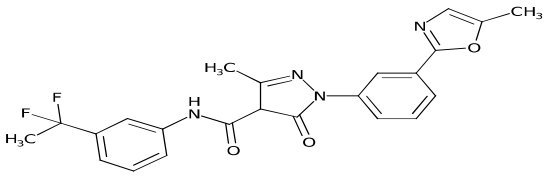
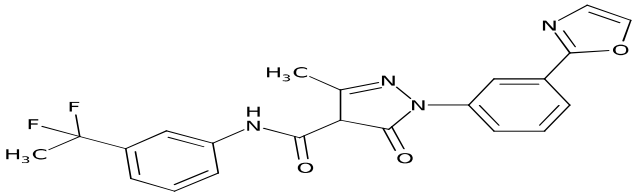
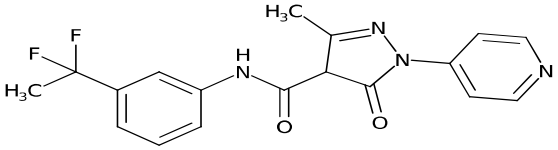
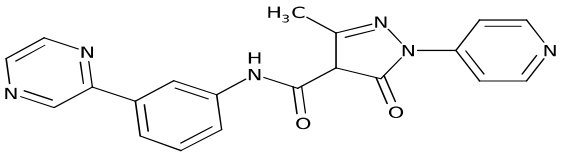
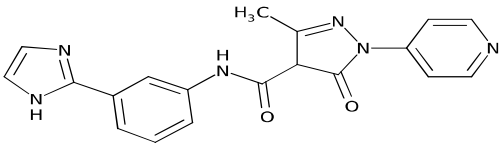
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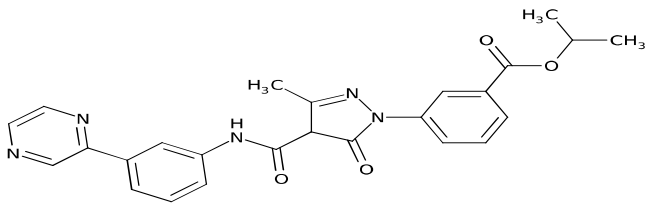
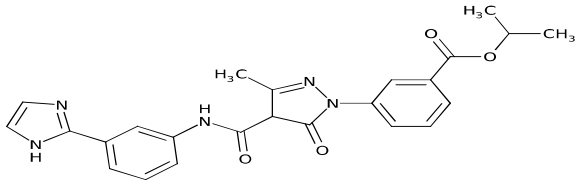
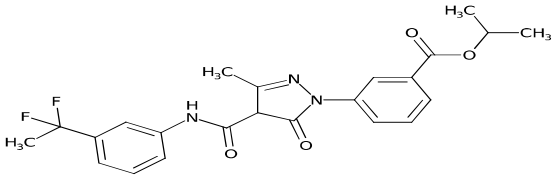
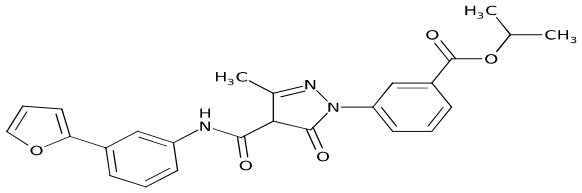
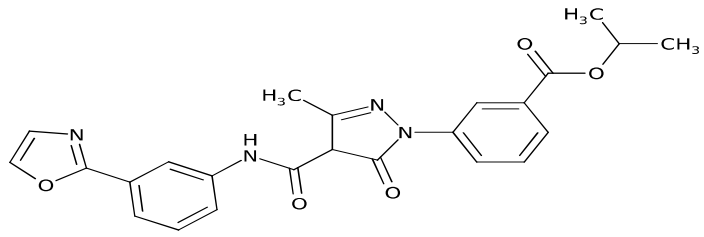
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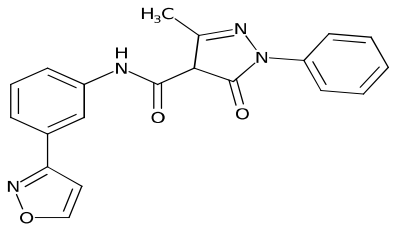
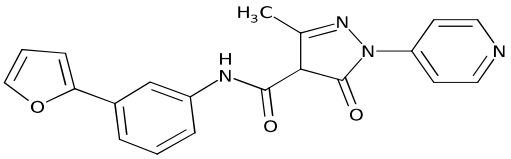
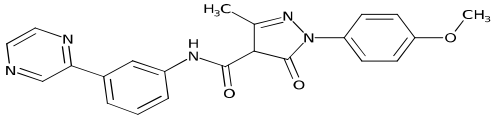
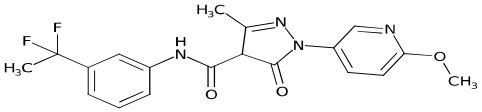
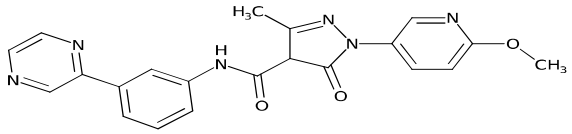
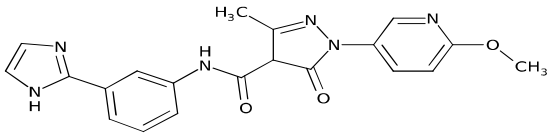
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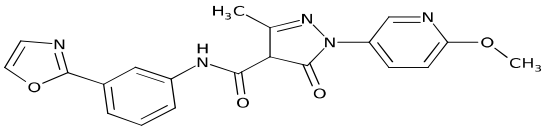
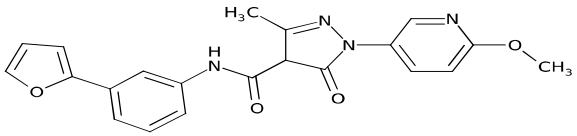
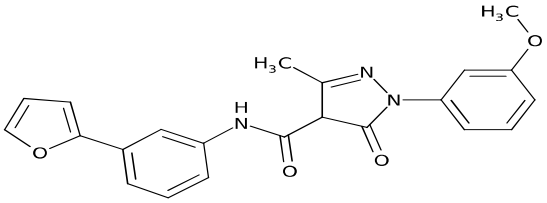
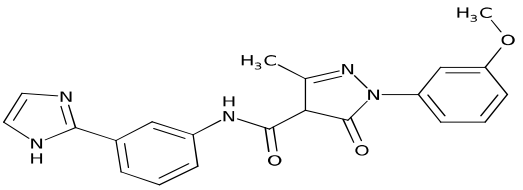
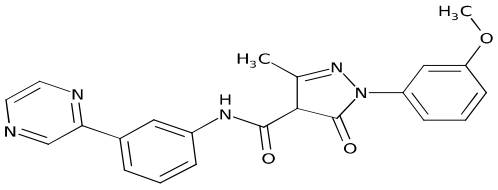
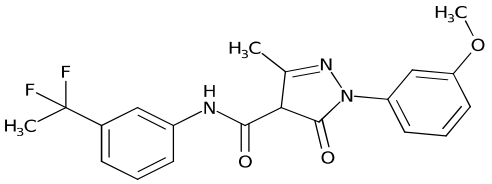
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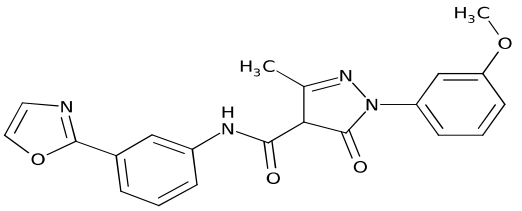
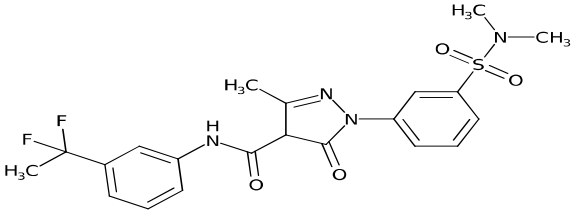
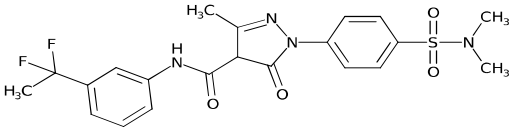
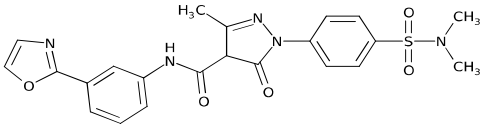
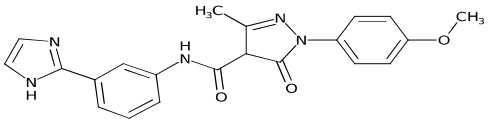
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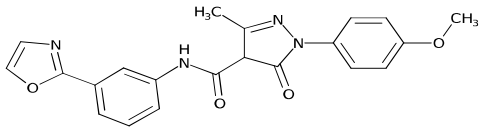
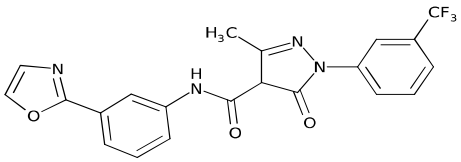
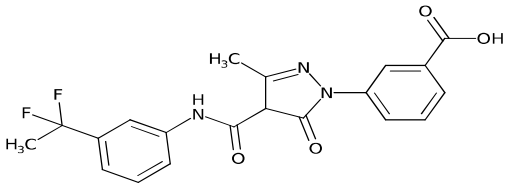
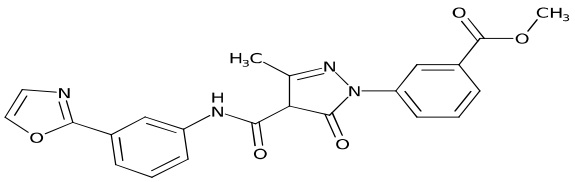
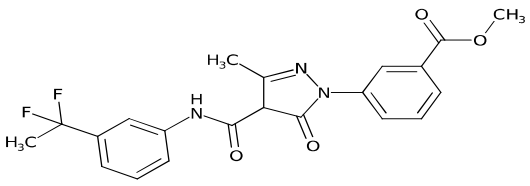
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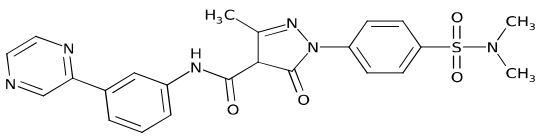
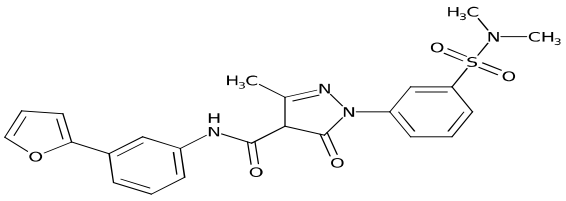
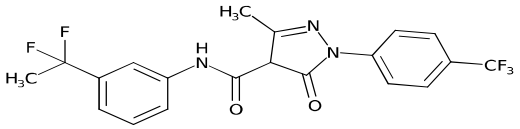
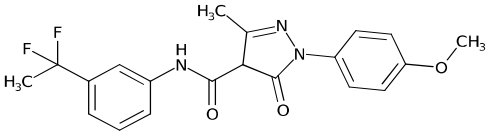
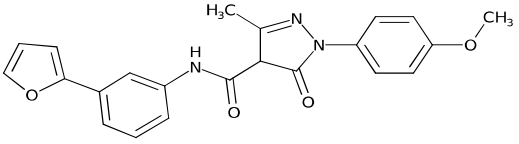
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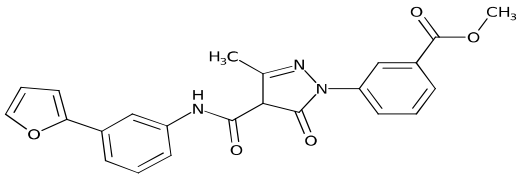
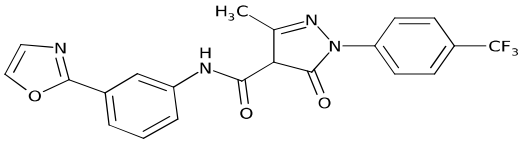
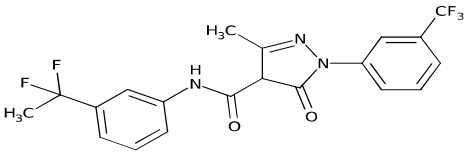
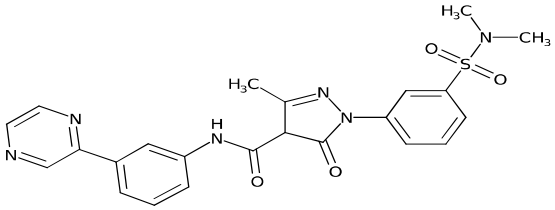
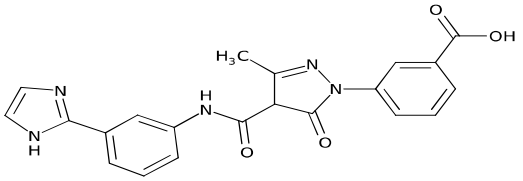
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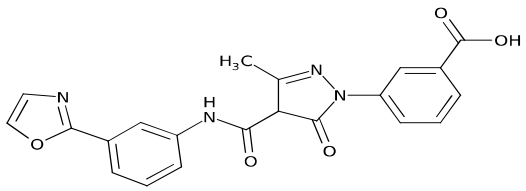
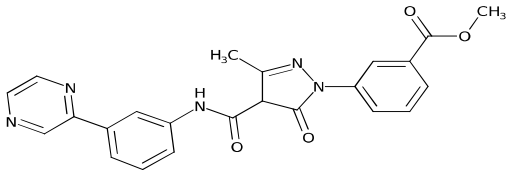
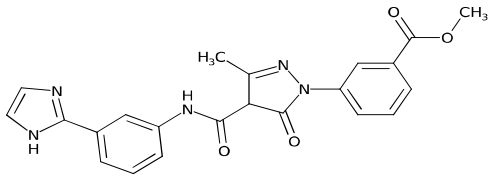
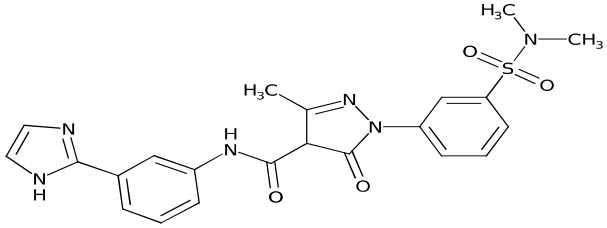
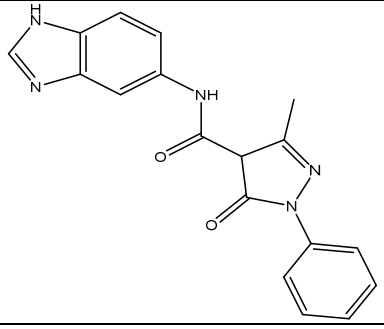
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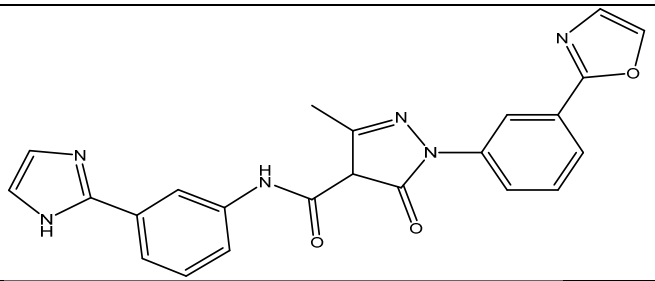
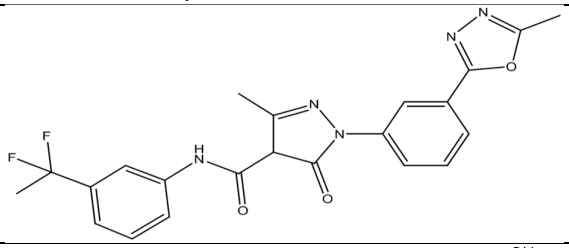
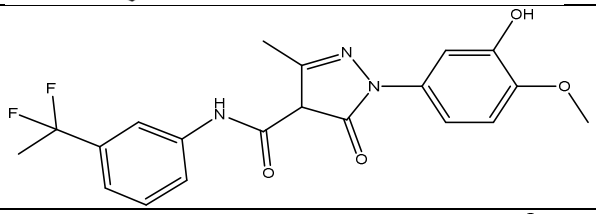
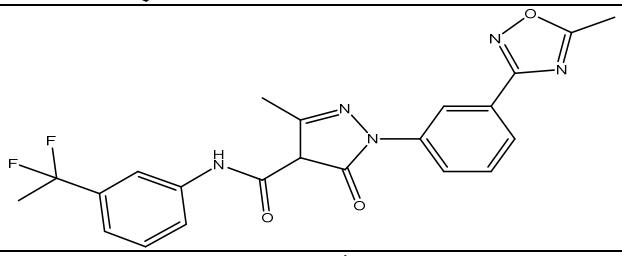
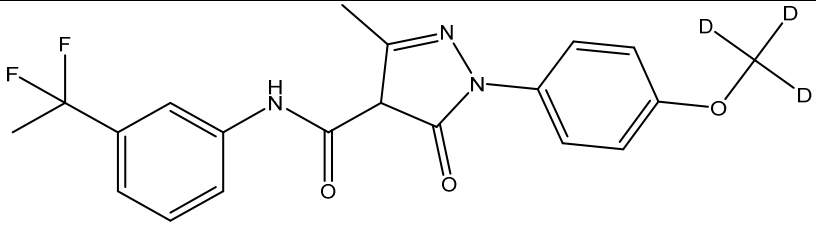
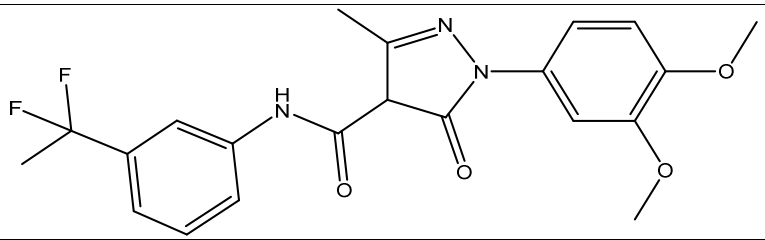
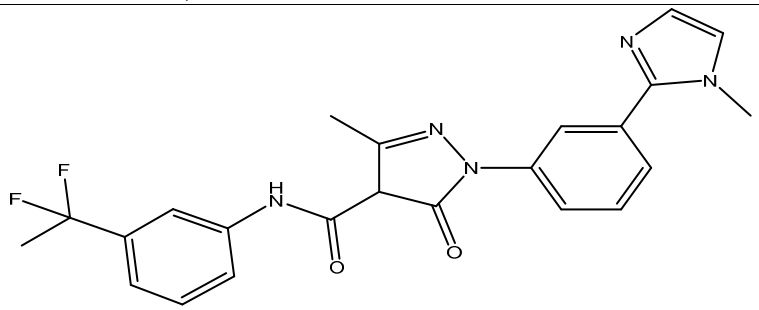
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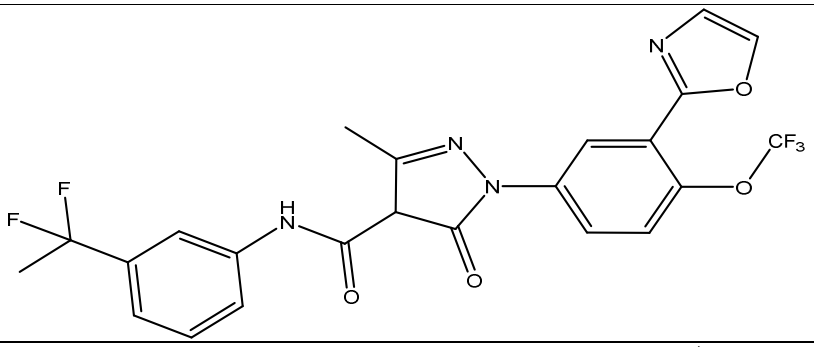
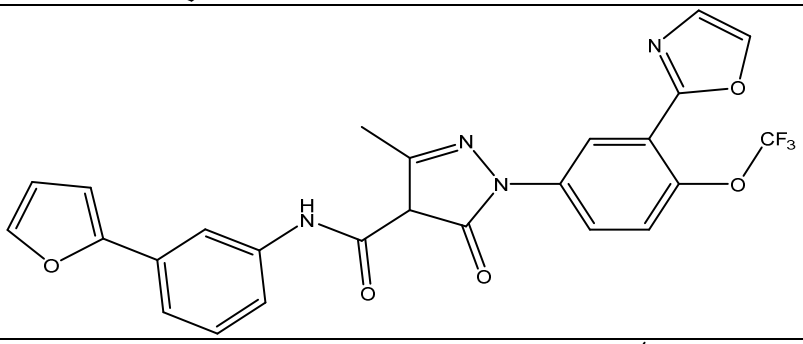
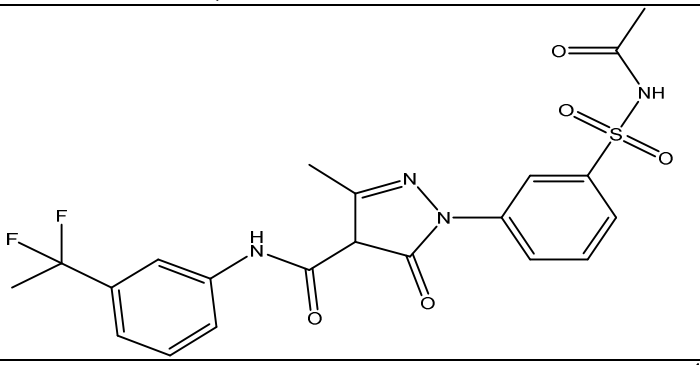
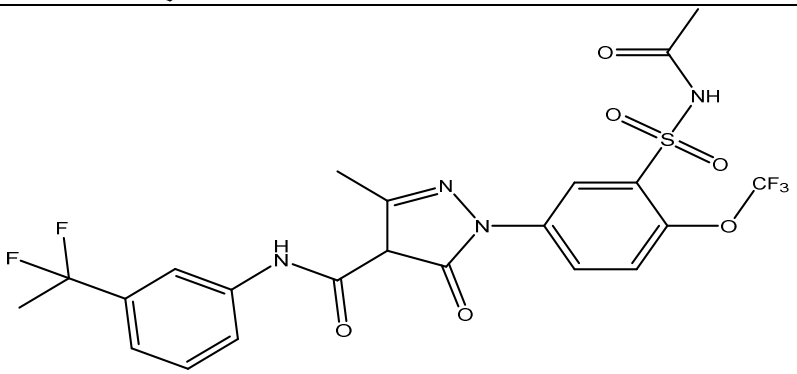
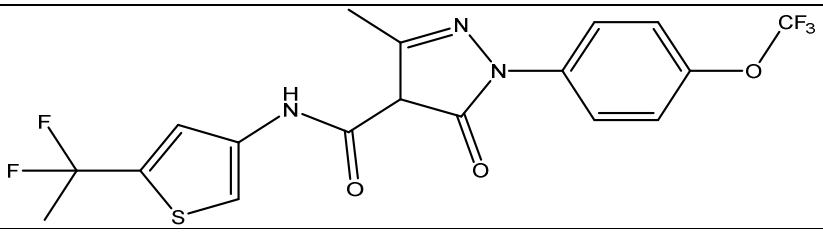
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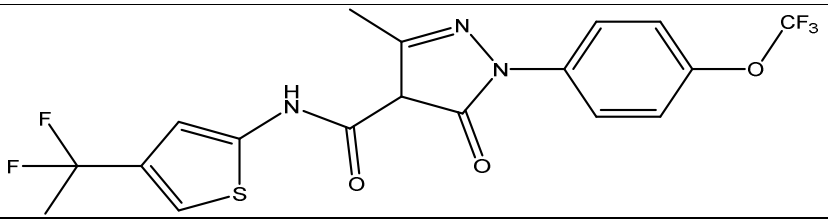
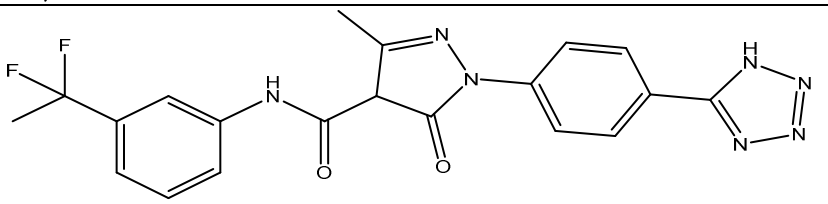
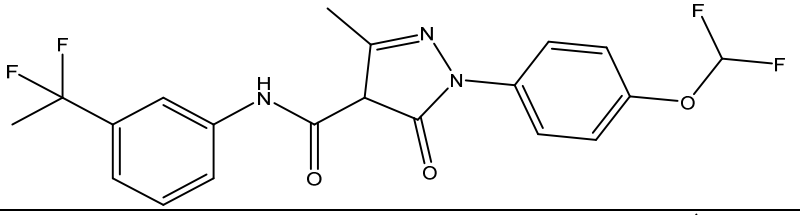
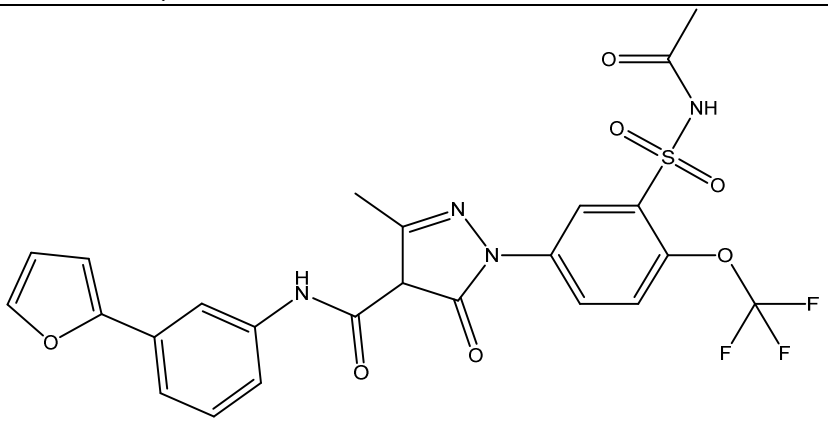
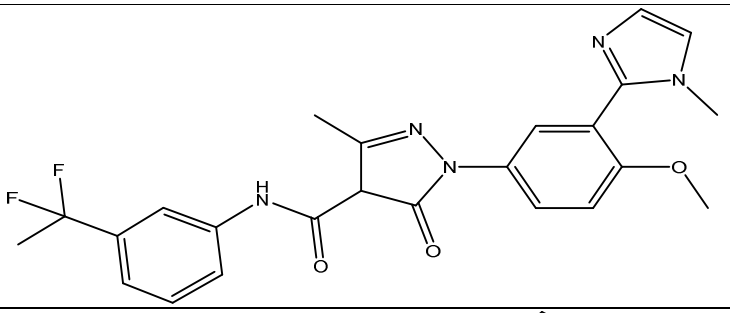
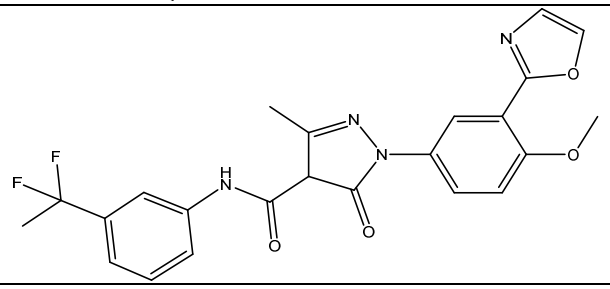
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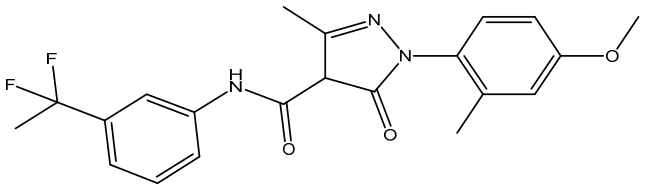
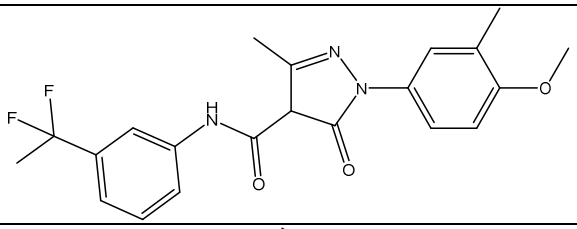
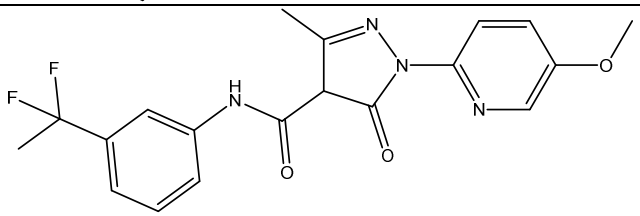
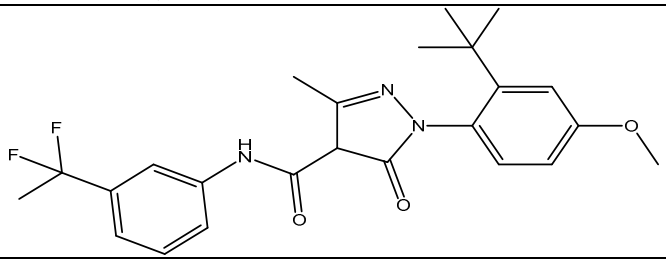
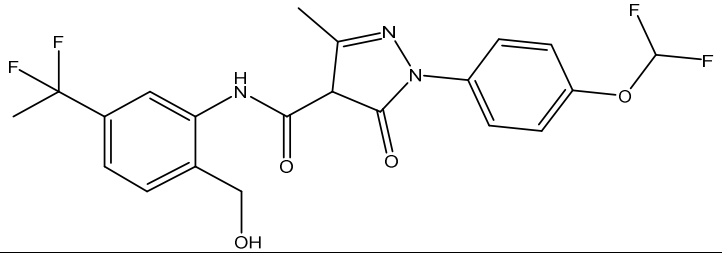
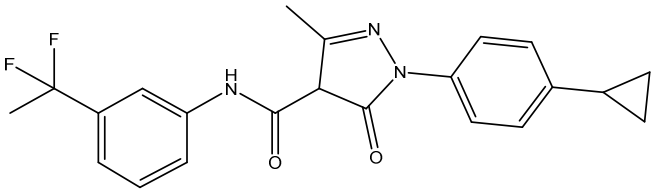
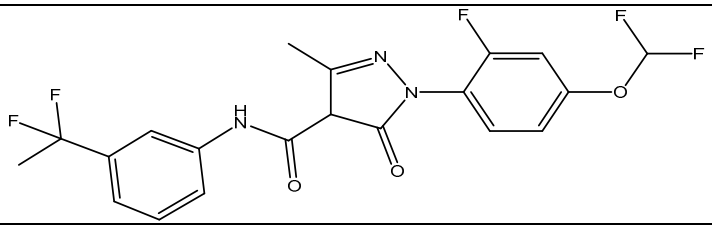
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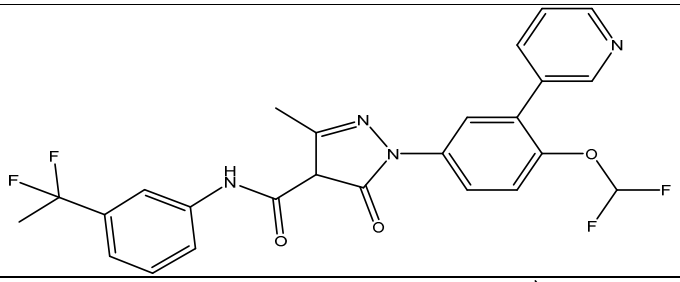
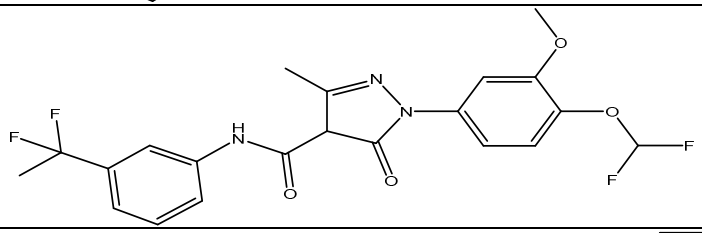
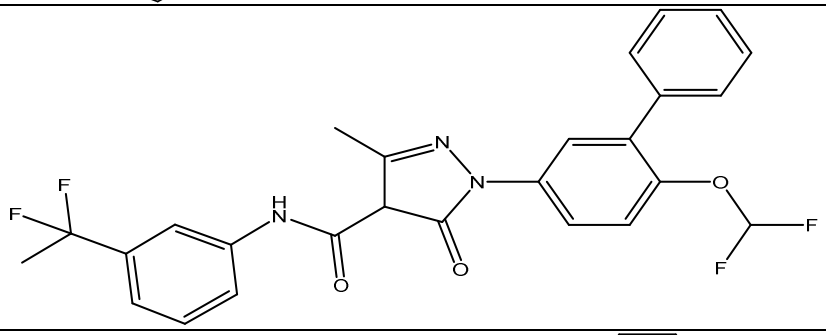
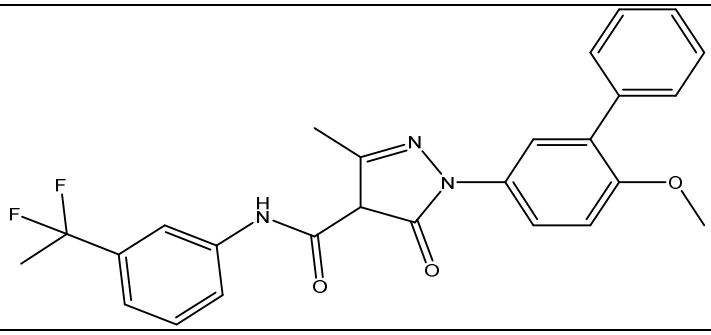
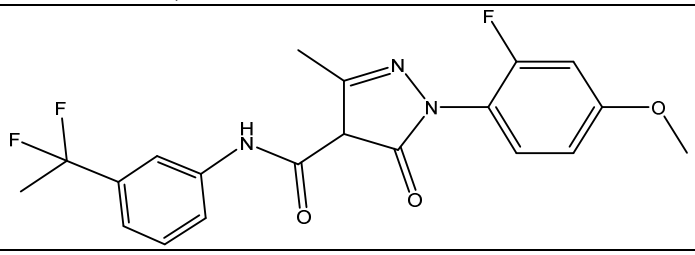
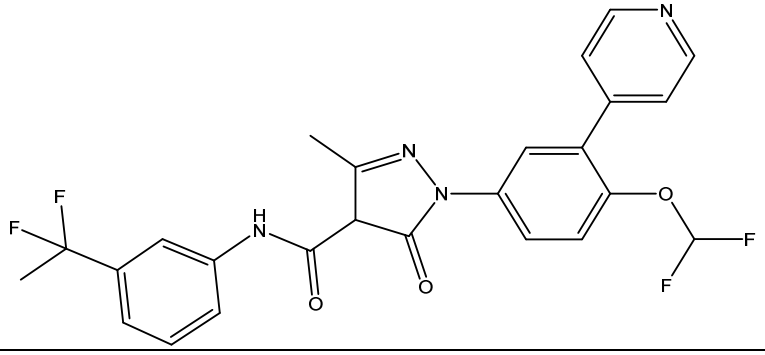
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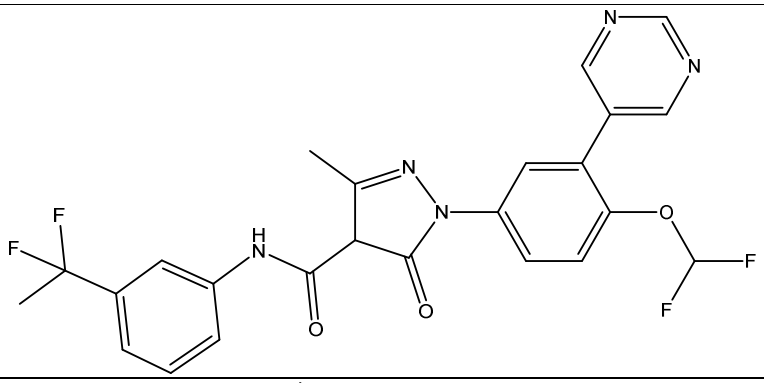
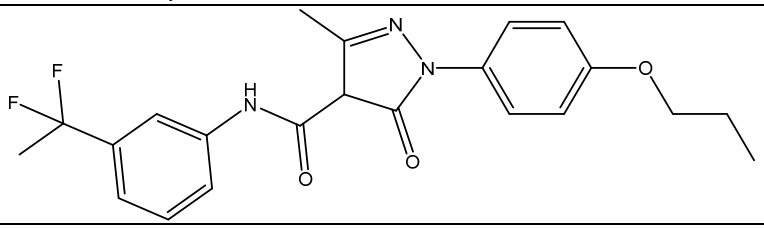
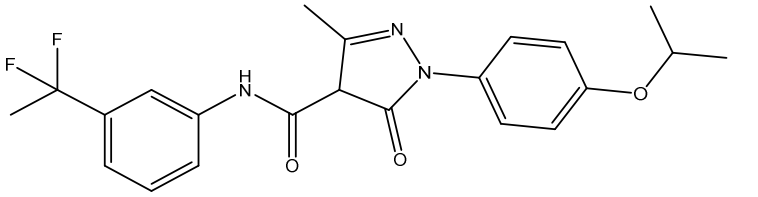
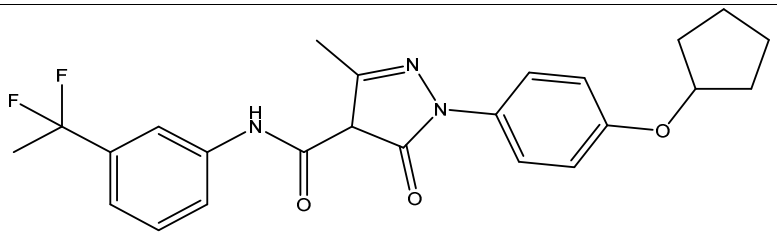
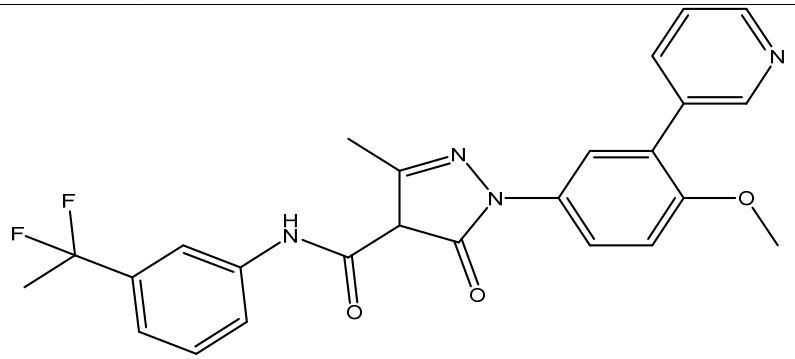
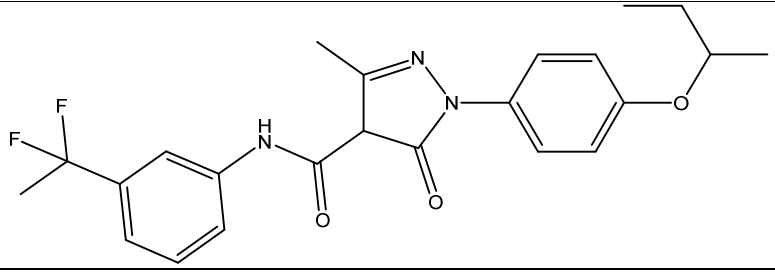
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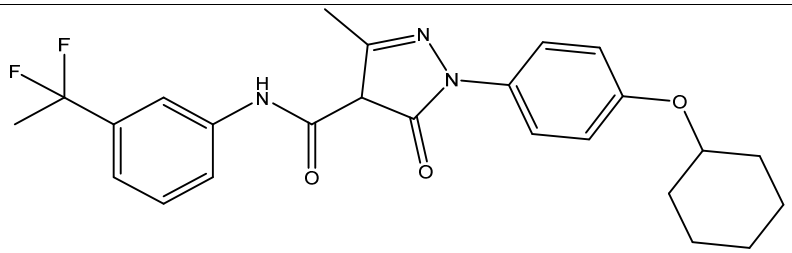
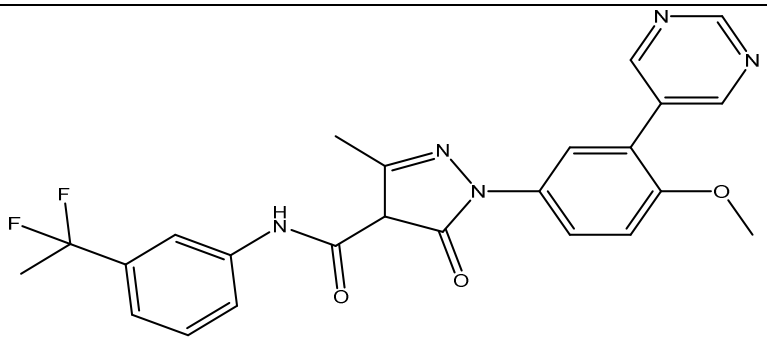
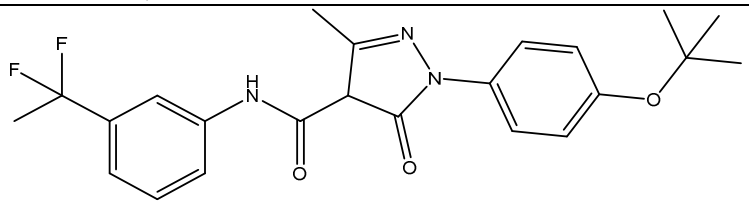
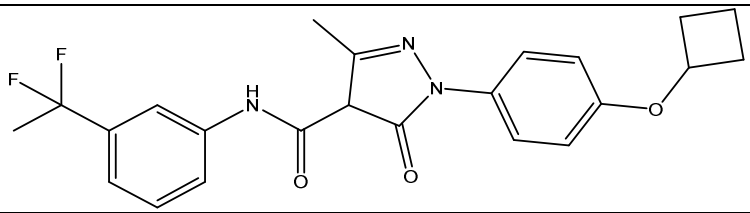
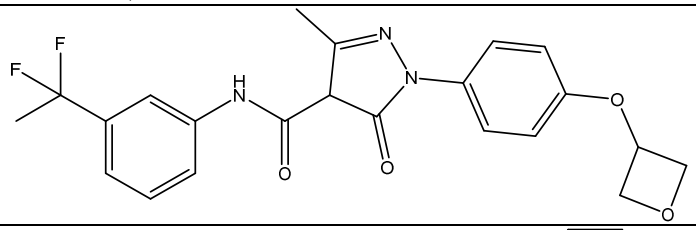
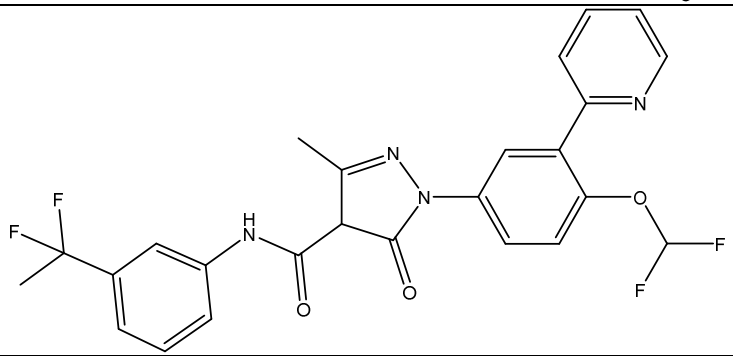
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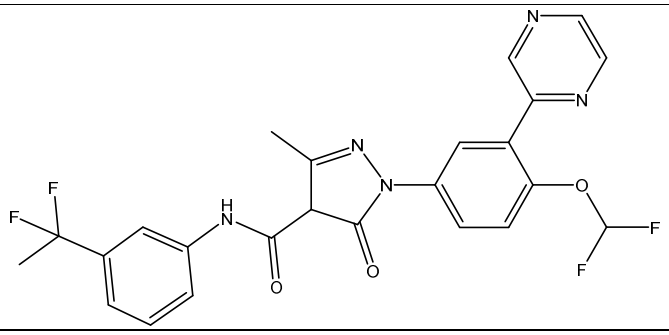
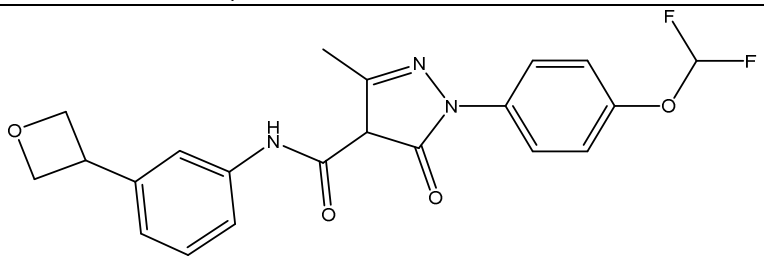
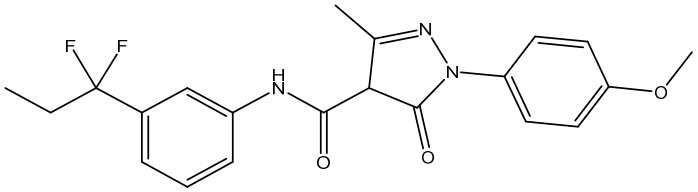
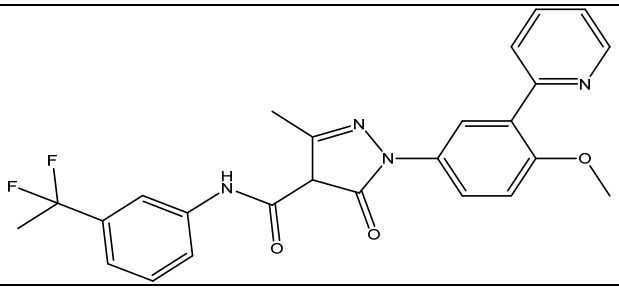
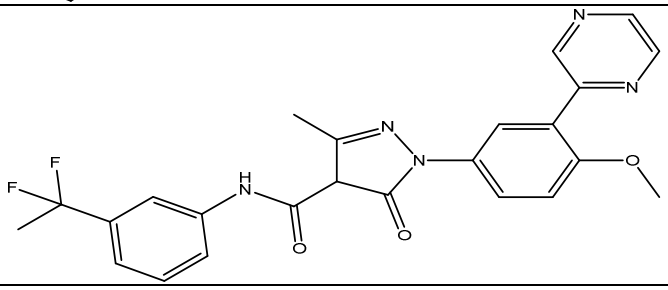
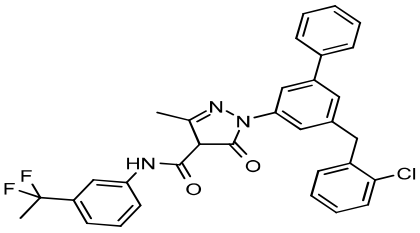
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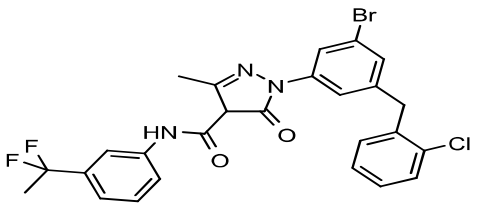
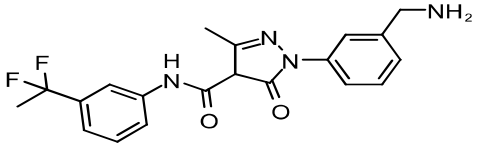
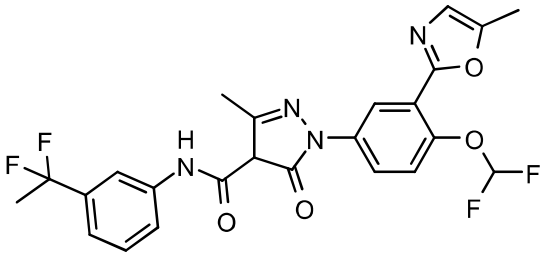
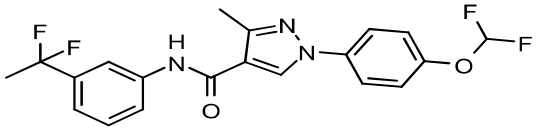
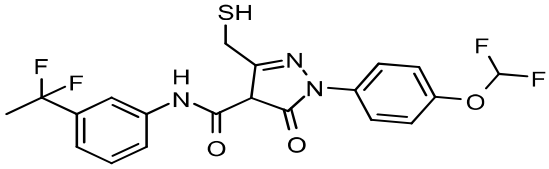
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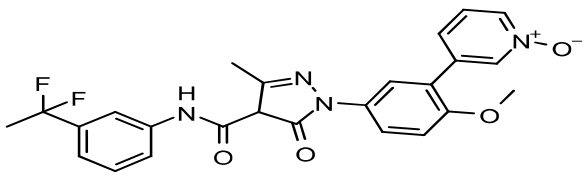
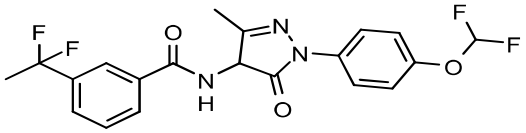
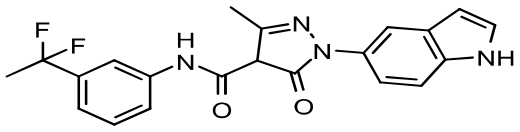
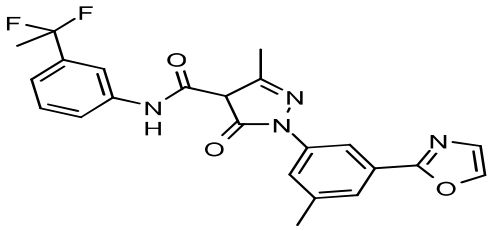
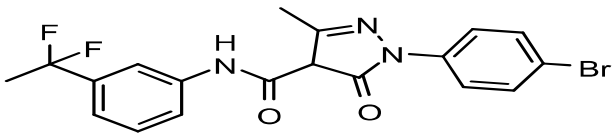
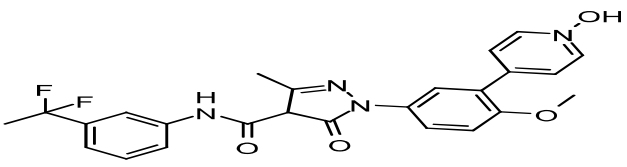
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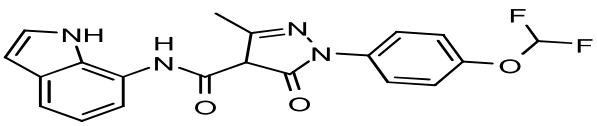
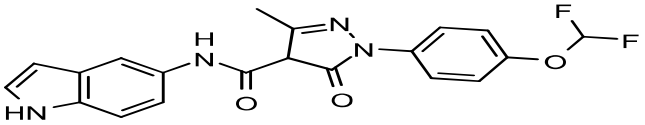
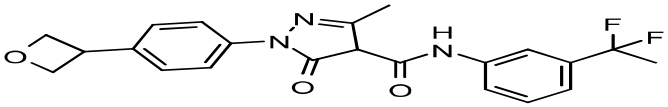
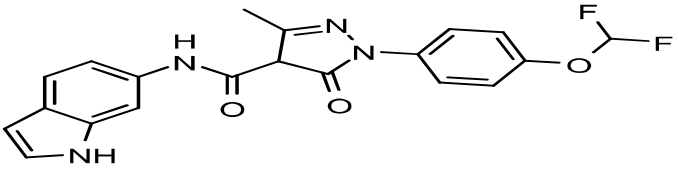
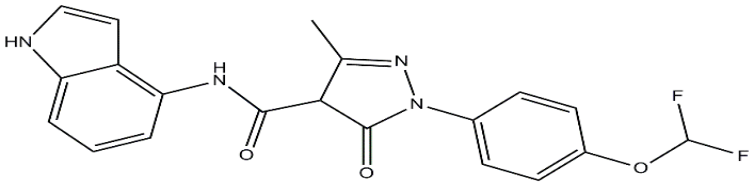
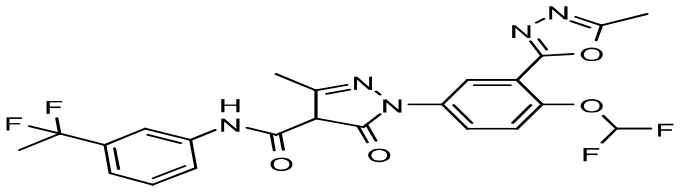
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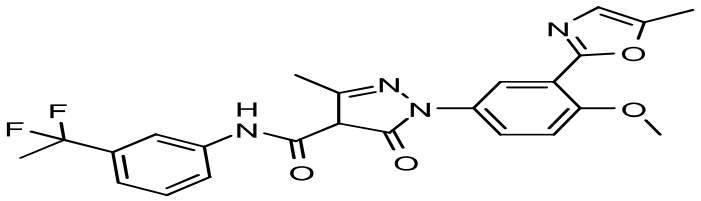
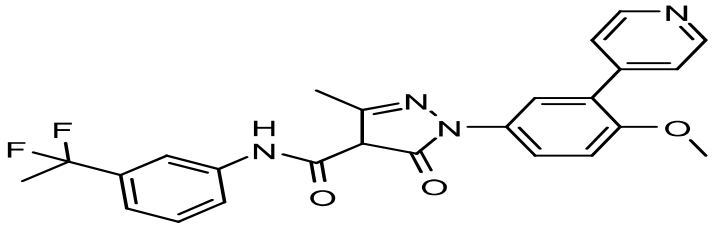
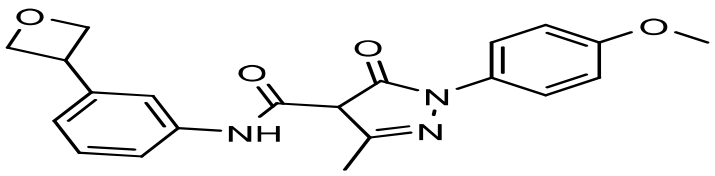
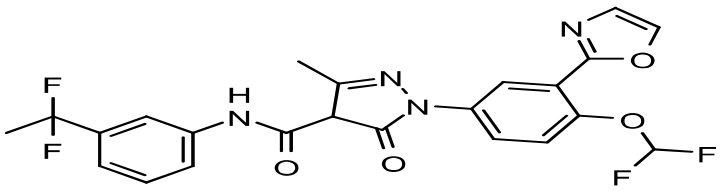
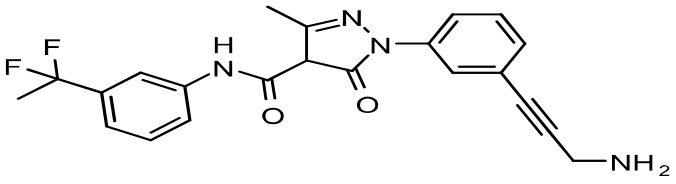
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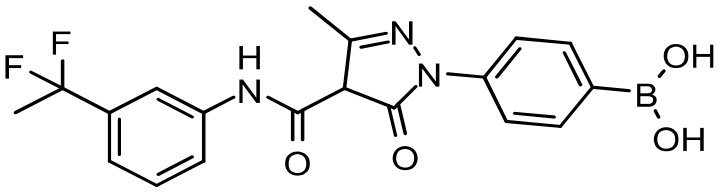
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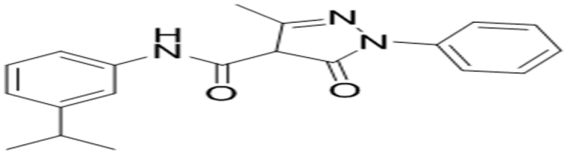
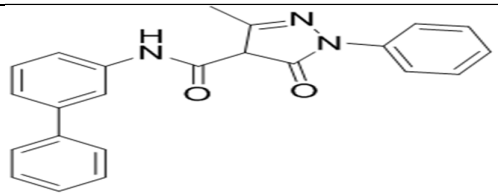
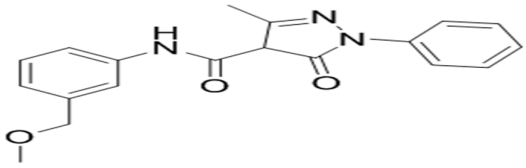
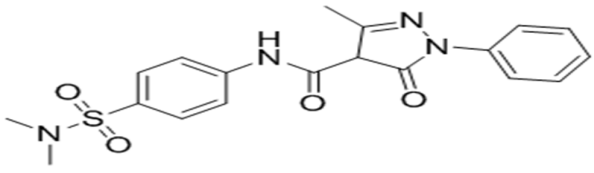
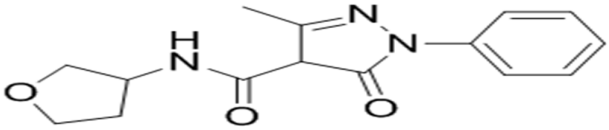
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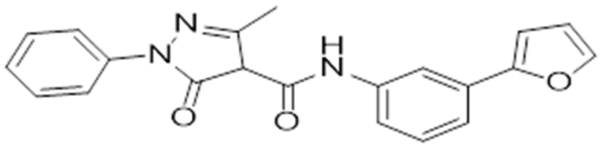
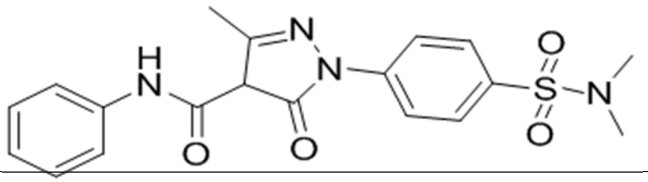
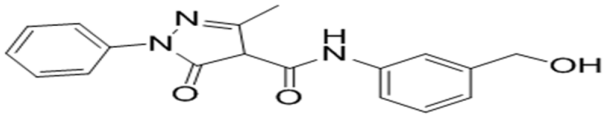
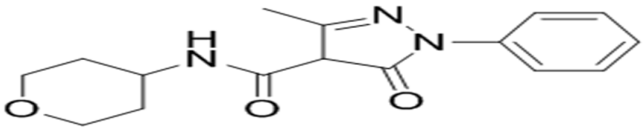
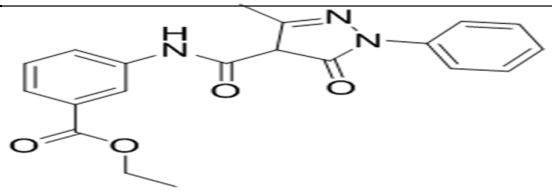
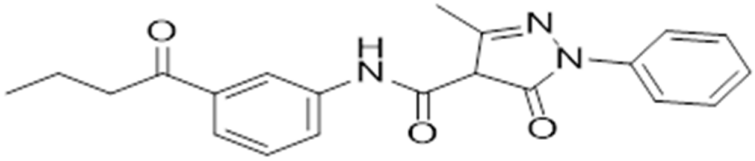
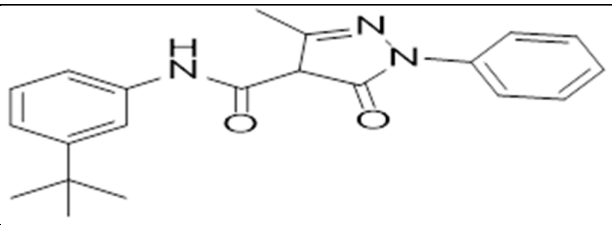
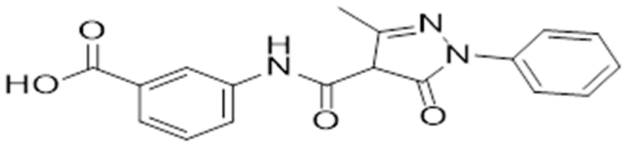
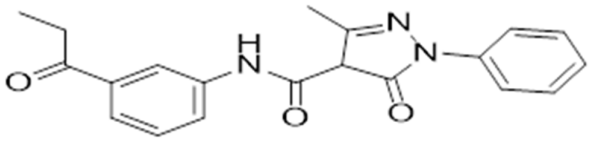
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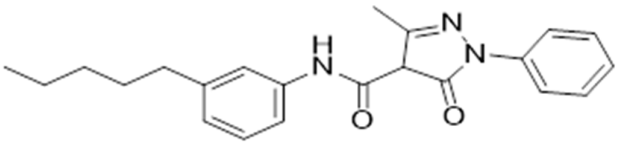
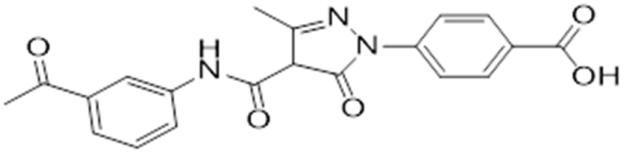
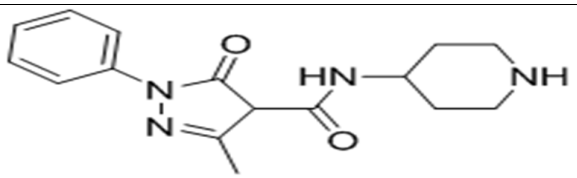
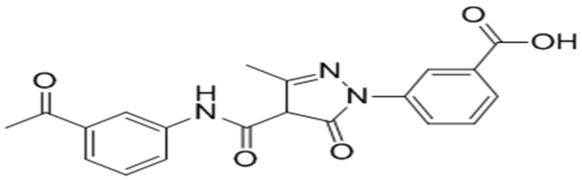
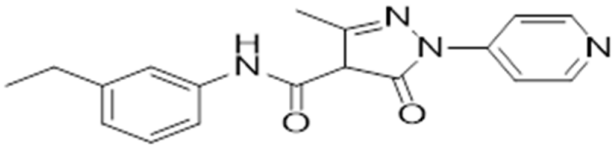
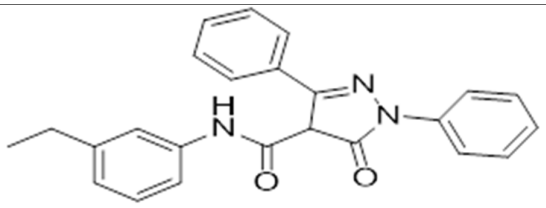
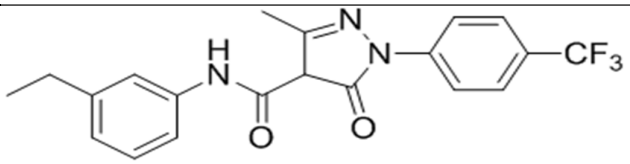
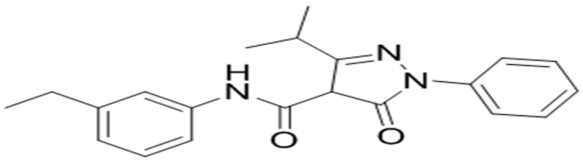
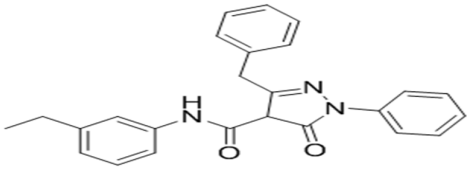
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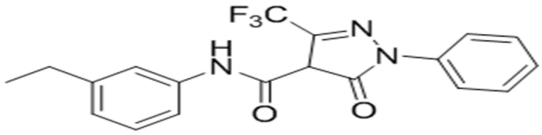
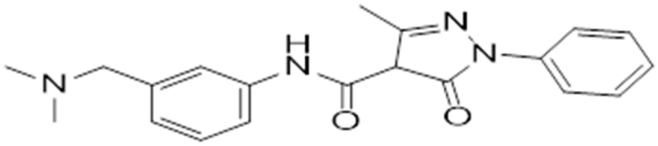
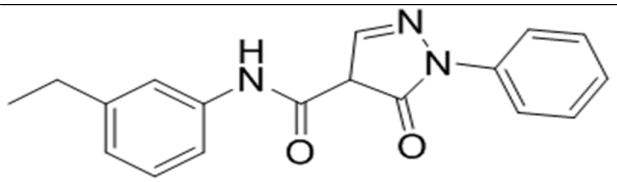
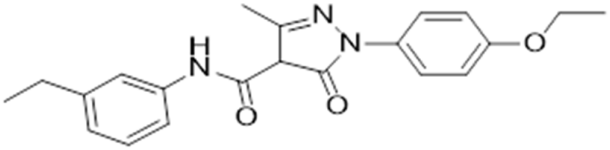
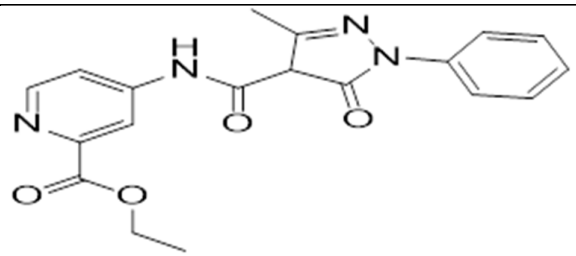
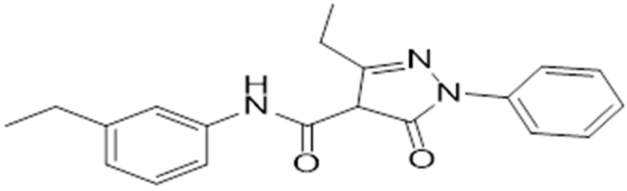
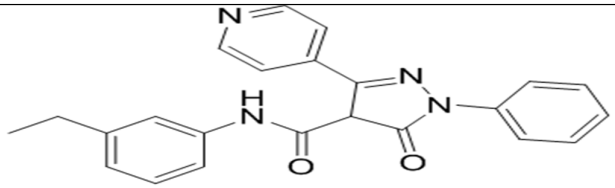
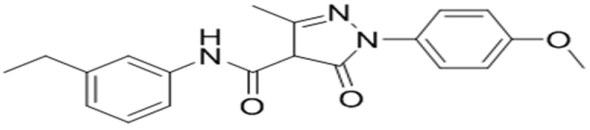
or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

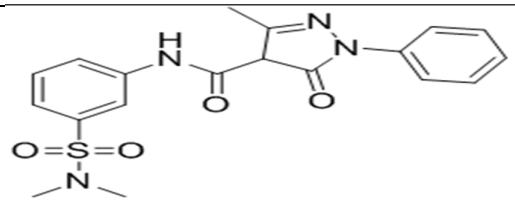
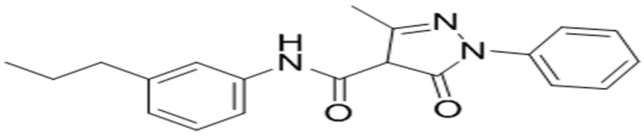
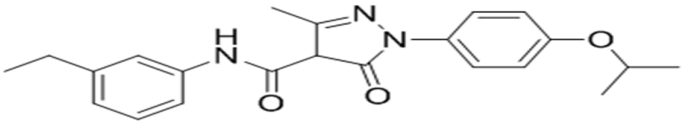
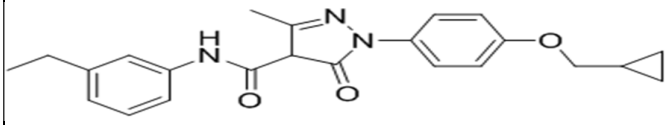
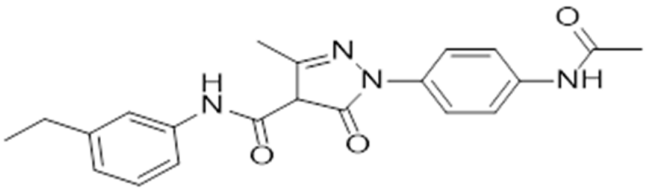
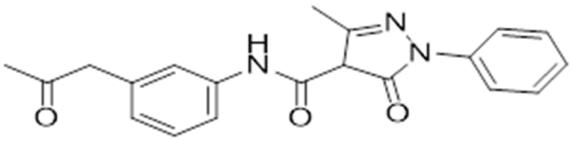
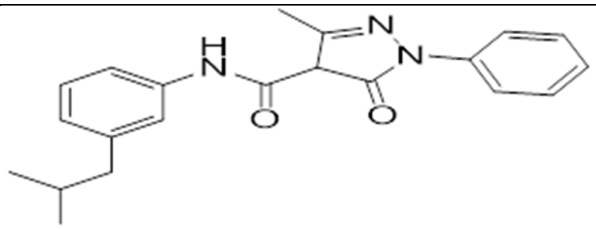
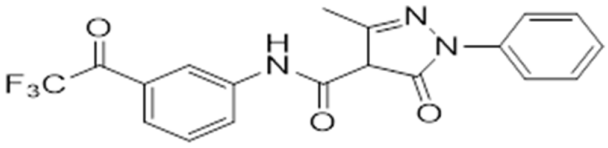
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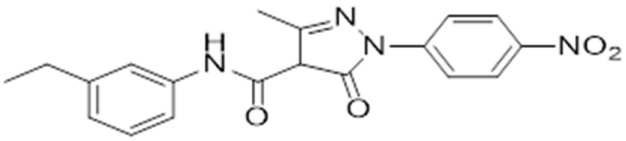
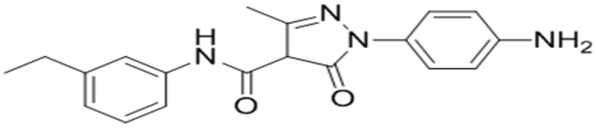
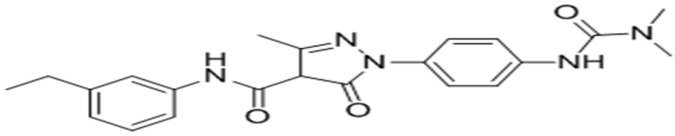
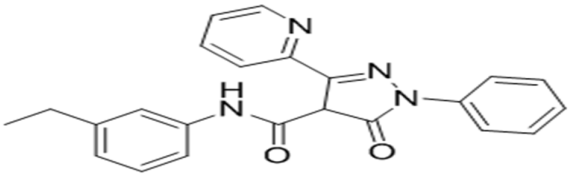
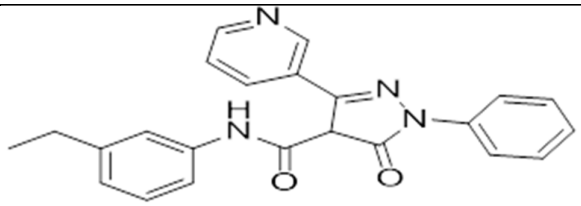
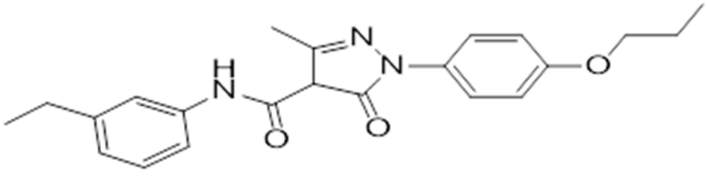
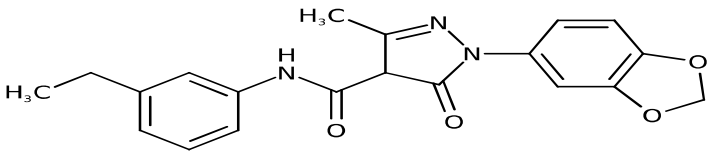
Compound name	**Structure**
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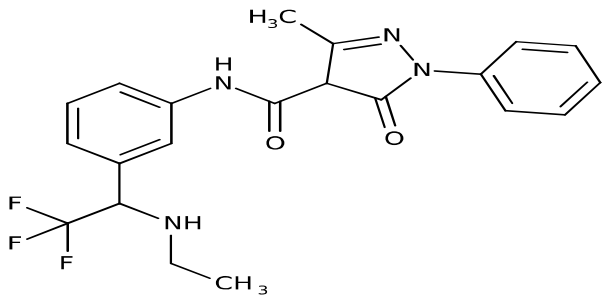
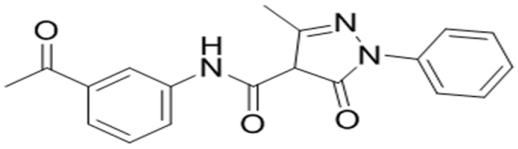
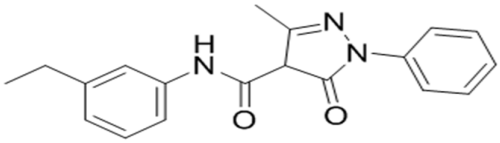
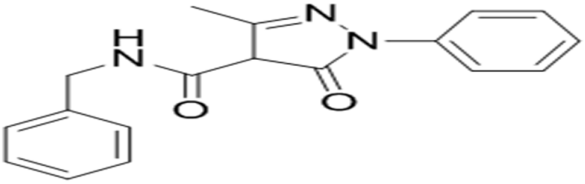
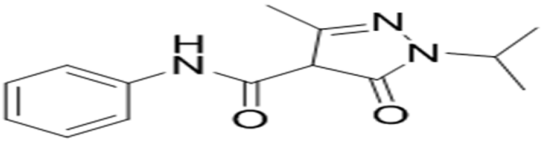
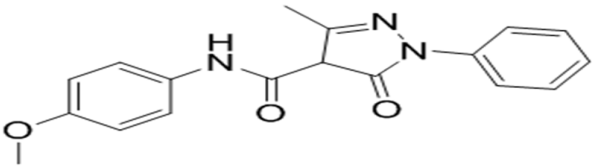
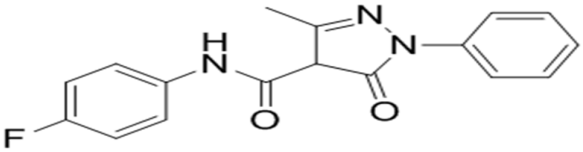
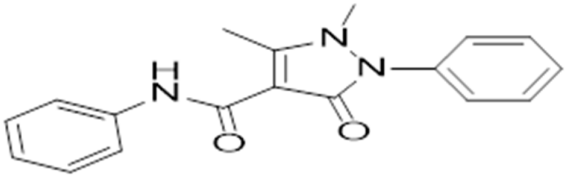
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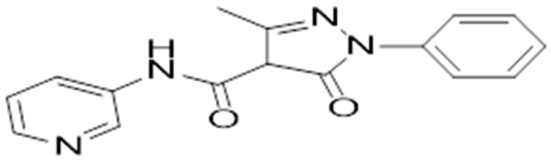
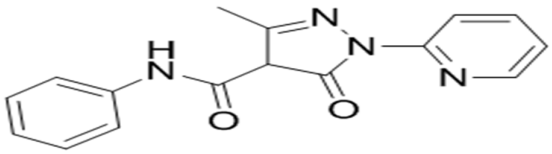
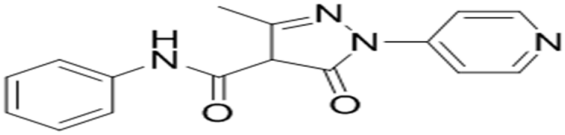
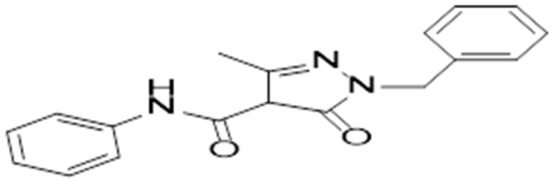
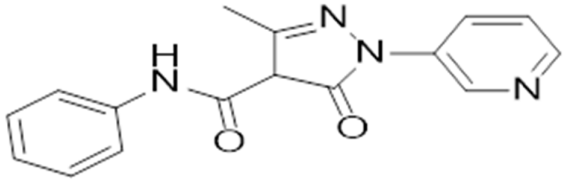
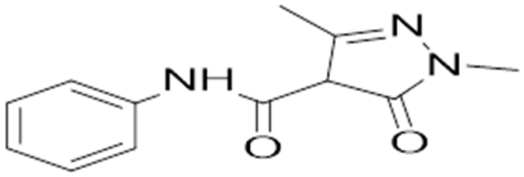
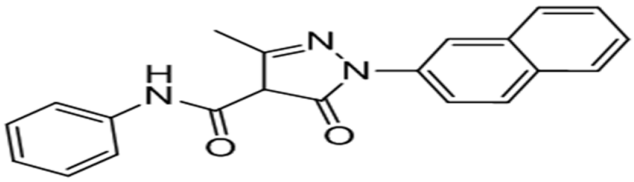
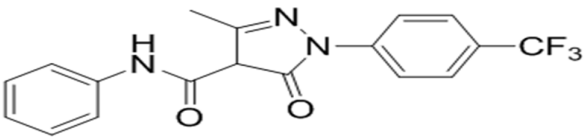
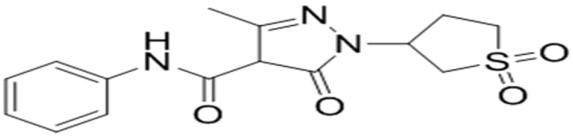
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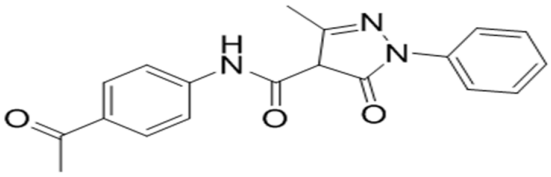
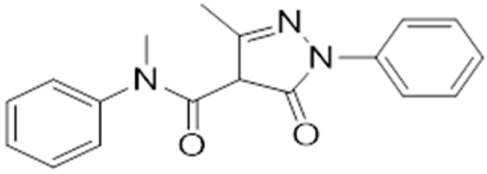
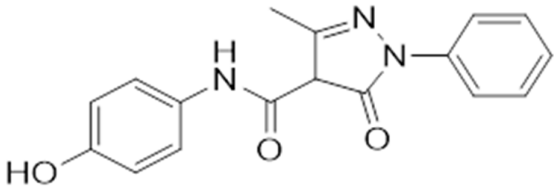
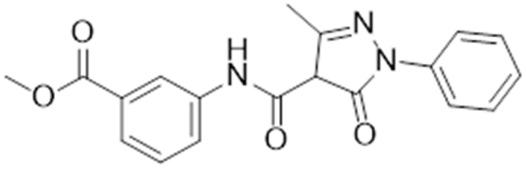
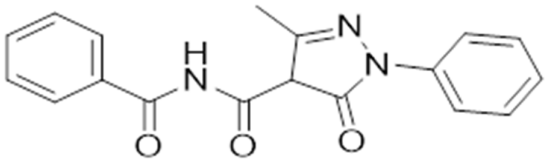
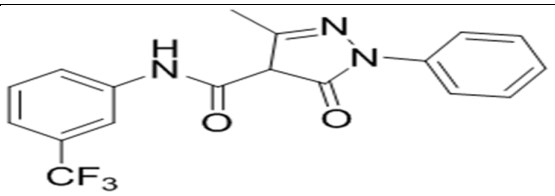
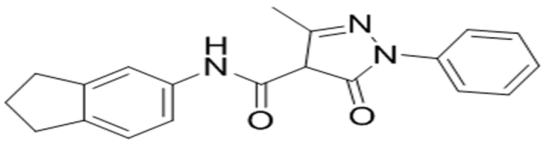
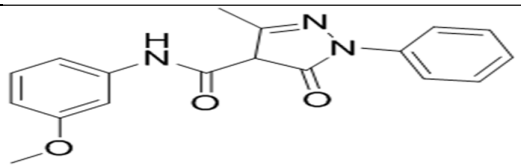
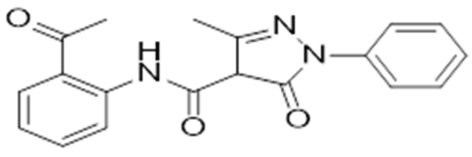
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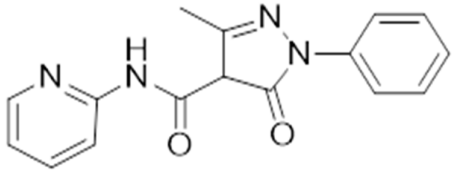
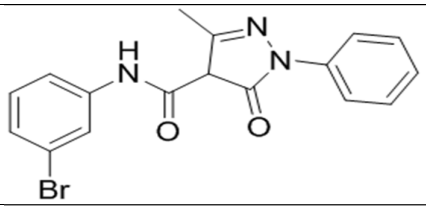
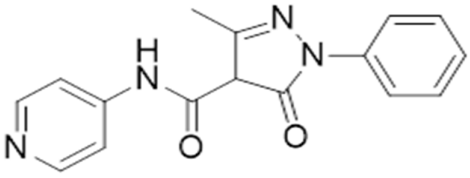
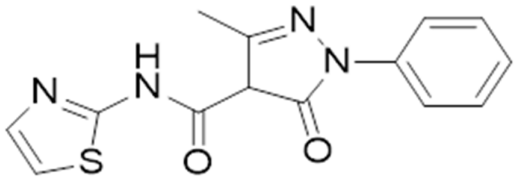
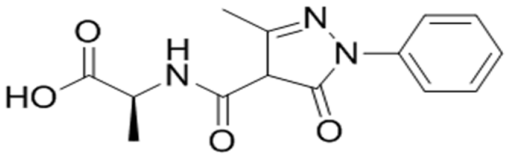
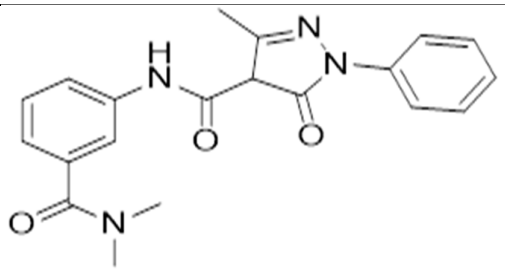
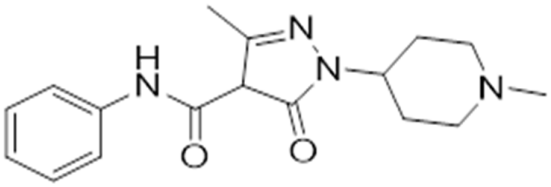
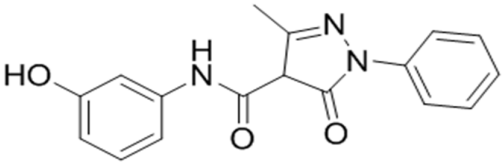
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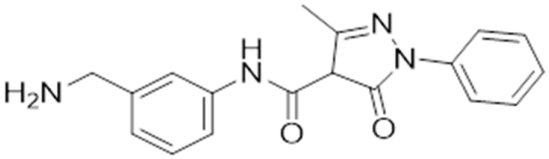
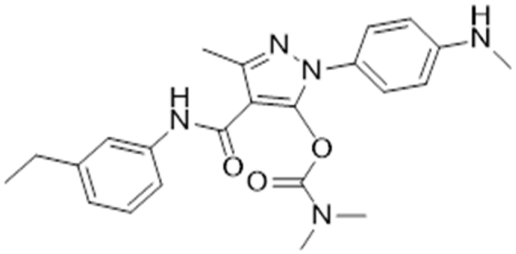
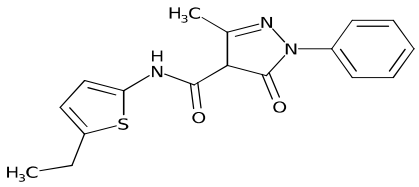
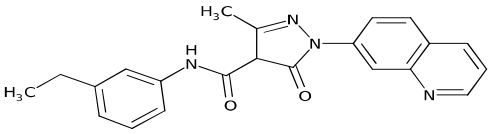
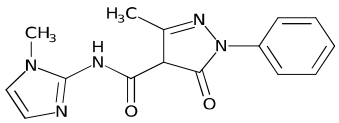
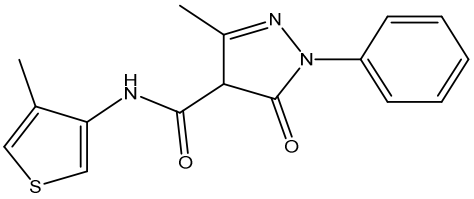
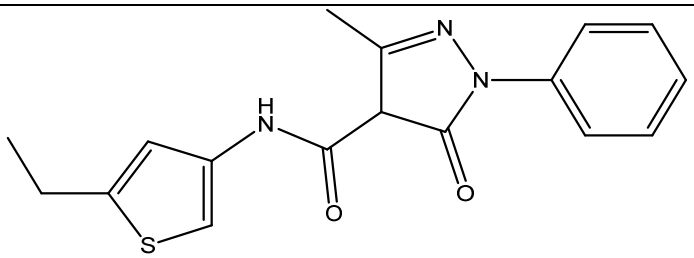
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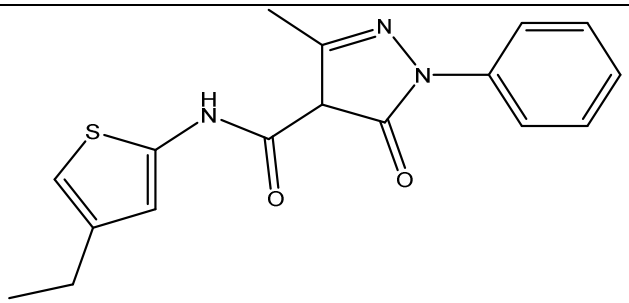
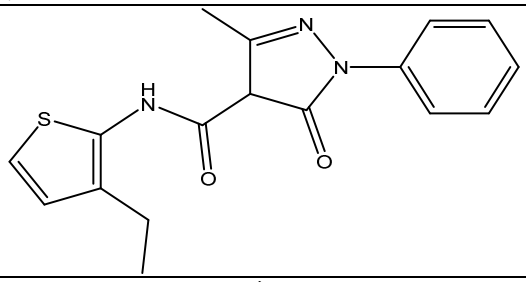
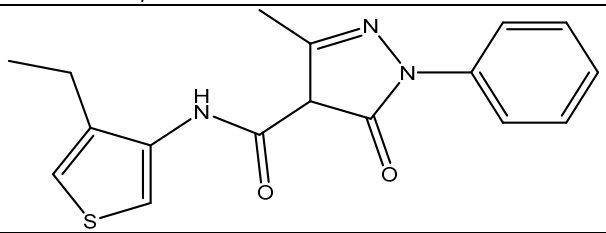
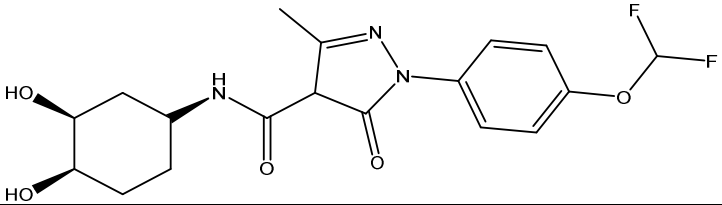
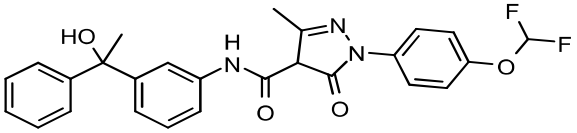
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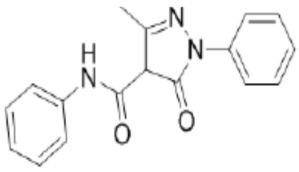
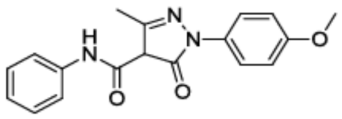
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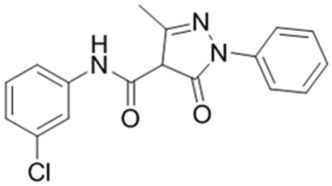
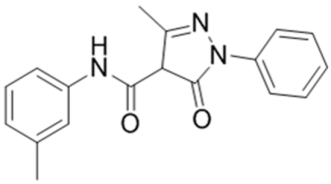
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5. The compound of any one of the preceding claims, wherein the compound is an Acyl-CoA Synthetase Short-Chain Family Member 2 (ACSS2) inhibitor.

6. A compound represented by the following structures:

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

210 ; **212** ;

wherein the compound is an Acyl-CoA Synthetase Short-Chain Family Member 2 (ACSS2) inhibitor.

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

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

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

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

11. Use of a compound according to any of claims 1-6 in the manufacture of a medicament for suppressing, reducing or inhibiting tumour growth in a subject.
12. The use according to claim 11, wherein the tumor growth is enhanced by increased acetate uptake by cancer cells of said cancer, for example:

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

    wherein the tumour cells are under hypoxic stress, or

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

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

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

    the method comprising contacting the cell with a compound according to any one of claims 1 to 6.
14. An *in vitro* method of binding an ACSS2 inhibitor compound to an ACSS2 enzyme, comprising the step of contacting an ACSS2 enzyme with an ACSS2 inhibitor compound according to any one of claims 1 to 6, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme.
15. Use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject, or

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

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

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

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

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

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

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

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