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).

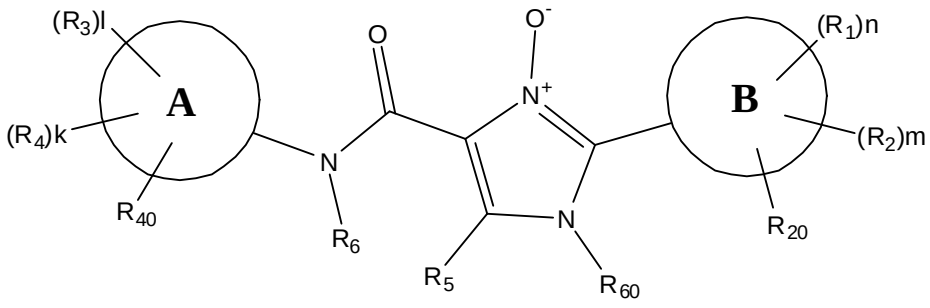
[0012] ACSS2 is also shown to enter the nucleus under certain condition (hypoxia, high fat etc.) and to affect histone acetylation and crotonylation by making available acetyl-CoA and crotonyl-CoA and thereby regulate gene expression. For example, ACSS2 decrease is shown to lower levels of nuclear acetyl-CoA 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, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula **I-IX**, 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

A and **B** rings are each independently a single or fused aromatic or heteroaromatic ring system (e.g., phenyl, indole, benzofuran, 2-, 3- or 4-pyridine, naphthalene, thiazole, thiophene, imidazole, 1-methylimidazole, benzimidazole), a single or fused C_3-C_{10} cycloalkyl (e.g. cyclohexyl), or a single or fused C_3-C_{10} heterocyclic ring (e.g., benzofuran-2(3H)-one, benzo[d][1,3]dioxole, tetrahydrothiophene 1,1-dioxide, piperidine, 1-methylpiperidine, isoquinoline, 1,3-dihydroisobenzofuran);

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-morpholine, CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR (e.g., NH-CH_3), N(R)$_2$ (e.g., N(CH_3)$_2$), R_8-N(R_{10})(R_{11}) (e.g., CH_2-CH_2-N(CH_3)$_2$, CH_2-NH_2, CH_2-N(CH_3)$_2$), R_9-R_8-N(R_{10})(R_{11}) (e.g., C≡C-CH_2-NH_2), B(OH)$_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R_{10} (e.g., NHC(O)CH_3), NHCO-N(R_{10})(R_{11}) (e.g., NHC(O)N(CH_3)$_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH(CH_3)$_2$, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., CH_2C(O)CH_3), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -C(O)NH_2, C(O)NHR, C(O)N(R_{10})(R_{11}) (e.g., C(O)N(CH_3)$_2$), SO_2R, SO_2N(R_{10})(R_{11}) (e.g., SO_2N(CH_3)$_2$, SO_2NHC(O)CH_3), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH_3, methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)$_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, 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_1-C_5 linear or branched or C_3-C_8 cyclic alkoxy (e.g. methoxy, O-(CH_2)$_2$-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluoroxylyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), or 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 (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

R_3 is I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, -CH_2CN, -R_8CN, NH_2, NHR, N(R)$_2$, R_8-N(R_{10})(R_{11}) (e.g., CH_2-NH_2, CH_2-N(CH_3)$_2$) R_9-R_8-N(R_{10})(R_{11}), B(OH)$_2$, -OC(O)CF_3, -OCH_2Ph, -NHCO-R_{10} (e.g., NHC(O)CH_3), NHCO-N(R_{10})(R_{11}) (e.g.,

$NHC(O)N(CH_3)_2$), -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), $R_8\text{-}C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), $\text{-}C(O)NH_2$, C(O)NHR (e.g., $C(O)NH(CH_3)$), $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$, $C(O)N(CH_3)(CH_2CH_3)$, $C(O)N(CH_3)(CH_2CH_2\text{-}O\text{-}CH_3)$, $C(S)N(R_{10})(R_{11})$ (e.g., $C(S)NH(CH_3)$), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2NH(CH_3)$, $SO_2N(CH_3)_2$), C_2-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C_2-C_5 linear or branched or C_3-C_8 cyclic haloalkyl (e.g., CF_2CH_3, CF_2-cyclobutyl, CF_2-cyclopropyl, CF_2-methylcyclopropyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$, $C(OH)_2CF_3$, cyclopropyl-CF_3), C_2-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), 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 (e.g., CF_3-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $CH(CF_3)(NH\text{-}R_{10})$;

R_4 and **R_{40}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, $\text{-}R_8\text{-}O\text{-}R_{10}$, (e.g., $CH_2\text{-}O\text{-}CH_3$) CF_3, CD_3, OCD_3, CN, NO_2, $\text{-}CH_2CN$, $\text{-}R_8CN$, NH_2, NHR, $N(R)_2$, $R_8\text{-}N(R_{10})(R_{11})$ (e.g., $CH_2\text{-}NH_2$, $CH_2\text{-}N(CH_3)_2$) $R_9\text{-}R_8\text{-}N(R_{10})(R_{11})$, $B(OH)_2$, $\text{-}OC(O)CF_3$, $\text{-}OCH_2Ph$, $\text{-}NHCO\text{-}R_{10}$ (e.g., $NHC(O)CH_3$), $NHCO\text{-}N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), $R_8\text{-}C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), $\text{-}C(O)NH_2$, C(O)NHR (e.g., $C(O)NH(CH_3)$), $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$, $C(O)N(CH_3)(CH_2CH_3)$, $C(O)N(CH_3)(CH_2CH_2\text{-}O\text{-}CH_3)$, $C(S)N(R_{10})(R_{11})$ (e.g., $C(S)NH(CH_3)$), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2NH(CH_3)$, $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C_1-C_5 linear or branched or C_3-C_8 cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CF_2-cyclopropyl, CF_2-methylcyclopropyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$, $C(OH)_2CF_3$, cyclopropyl-CF_3), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), 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 (e.g., CF_3-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole,

methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $CH(CF_3)(NH\text{-}R_{10})$;

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 (e.g., imidazole, [1,3]dioxole, furan-2(3H)-one, benzene, cyclopentane, imidazole);

$\mathbf{R_5}$ is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, iso-propyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), $C(=CH_2)\text{-}R_{10}$ (e.g., $C(=CH_2)\text{-}C(O)\text{-}OCH_3$, $C(=CH_2)\text{-}CN$) substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

$\mathbf{R_6}$ is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

$\mathbf{R_{60}}$ is H, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, $CH_2\text{-}OC(O)CH_3$, $CH_2\text{-}PO_4H_2$, $CH_2\text{-}PO_4H\text{-}tBu$, $CH_2\text{-}OP(O)(OCH_3)_2$), C(O)R, or $S(O)_2R$;

$\mathbf{R_8}$ 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, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), $R_8\text{-}O\text{-}R_{10}$ (e.g., $CH_2CH_2\text{-}O\text{-}CH_3$), C(O)R (e.g., $C(O)(OCH_3)$), or $S(O)_2R$;

or $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl, propyl), C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2\text{-}OH$, $CH_2CH_2\text{-}OH$), C_2-C_5 linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., $CH{\equiv}C\text{-}CH_3$), alkoxy, ester (e.g., $OC(O)\text{-}CH_3$), $N(R)_2$, CF_3, aryl, phenyl, R_8-aryl (e.g., CH_2CH_2-Ph), heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), C_3-C_8 heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., $tBu\text{-}PO_4H$), dihydrogen-phosphate (i.e., $OP(O)(OH)_2$), dialkylphosphate (e.g., $OP(O)(OCH_3)_2$), CN and NO_2;

R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl,

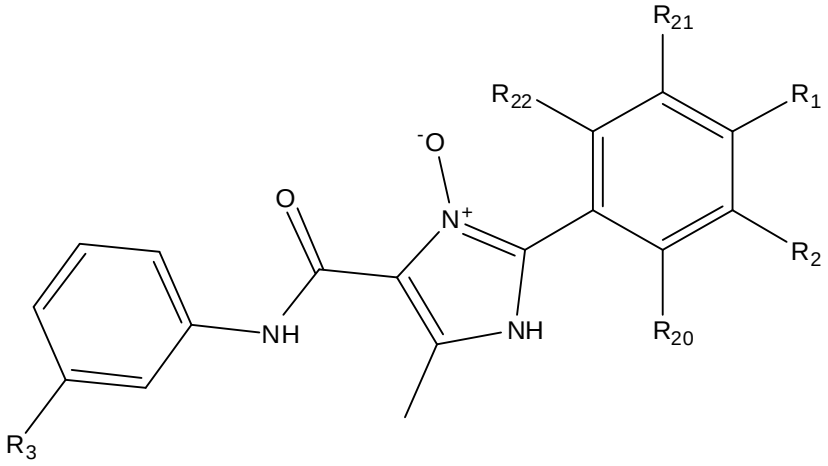
or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

m, **n** and **k** are each independently an integer between 0 and 4 (e.g., 0, 1 or 2);

l is an integer between 1 and 4 (e.g., 1 or 2);

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

[0014b] In one aspect, the present disclosure refers to a compound represented by the structure of formula **VIII**:



VIII

wherein

R_1 is H, methoxy, OCD_3, F, Cl, or $OCHF_2$;

R_2 is xylyl, 2,6-difluorophenyl, 4-fluoroxylyl or isopropyl;

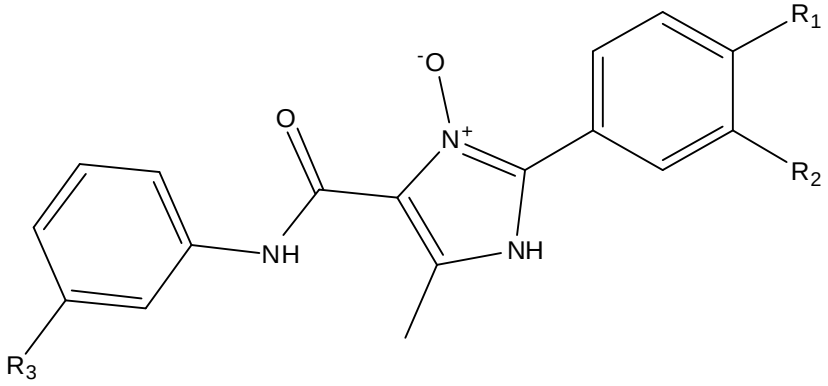
R_{22} is F, OH, or NH_2;

R_{20} and **R_{21}** are both H;

R_3 is oxadiazole, oxazole, isoxazole, or tetrazole;

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

[0014c] In one aspect, the present disclosure refers to a compound represented by the structure of formula **VI**:



VI

wherein

R_3 is I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g.,

$CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -$C(O)NH_2$, C(O)NHR (e.g., $C(O)NH(CH_3)$), $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$, $C(O)N(CH_3)(CH_2CH_3)$, $C(O)N(CH_3)(CH_2CH_2\text{-}O\text{-}CH_3)$, $C(S)N(R_{10})(R_{11})$ (e.g., $C(S)NH(CH_3)$), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2NH(CH_3)$, $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)$(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C_1-C_5 linear or branched or C_3-C_8 cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CF_2-cyclopropyl, CF_2-methylcyclopropyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$, $C(OH)_2CF_3$, cyclopropyl-CF_3), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), 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 (e.g., CF_3-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $CH(CF_3)(NH\text{-}R_{10})$.

[0015] This disclosure further provides a pharmaceutical composition comprising a compound or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula **I-IX**, 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 disclosed herein and a pharmaceutically acceptable carrier.

[0016] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer comprising administering a compound represented by the structure of formula **I- IX**, 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 one aspect, the present disclosure refers to use of a compound as disclosed herein, in the preparation of a medicament for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer in a subject. 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] 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-IX**, 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 functionin a cell, comprising contacting a compound represented by the structure of formula **I-IX**, 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, comprising contacting a compound as disclosed herein, with a cell under conditions effective to suppress, reduce or inhibit lipid synthesis and/or regulating histones acetylation and function in said cell.

[0019] This disclosure further provides a method of binding an ACSS2 inhibitor compound to an ACSS2 enzyme, comprising the step of contacting an ACSS2 enzyme with an ACSS2 inhibitor compound represented by the structure of formula **I-IX**, 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 disclosed herein, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme.

[0020] This disclosure further provides a method of suppressing, reducing or inhibiting acetyl-CoA synthesis from acetate in a cell, comprising contacting a compound represented by the structure of formula **I-IX**, 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 one aspect, the present disclosure refers to an *in vitro* method of suppressing, reducing or inhibiting acetyl-CoA synthesis from acetate in a cell, comprising contacting a compound as disclosed herein 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-IX**, 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 one aspect, the present disclosure refers to an *in vitro* method of suppressing, reducing or inhibiting acetate metabolism in a cancer cell, comprising contacting a compound as disclosed herein 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.

[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-IX**, 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-IX**, 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-IX**, 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-IX**, 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-IX**, 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-IX**, 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.

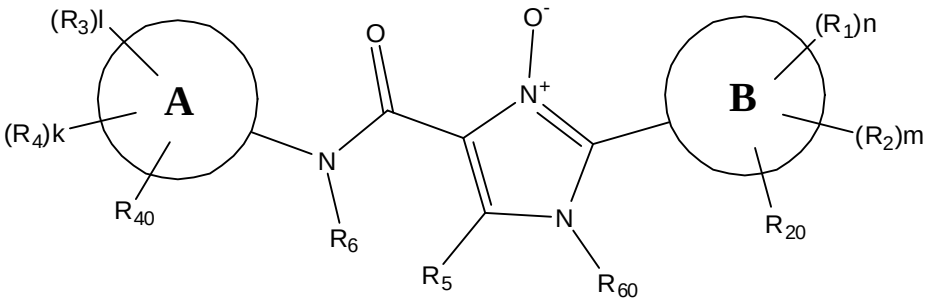
[0028] This disclosure further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting inflammatory condition in a subject, comprising administering a compound represented by the structure of formula **I-IX**, and by the structures listed in Table 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 a method 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-IX**, 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.

[0029a] In one aspect, the present disclosure refers to use of a compound as disclosed herein, for preparation of a medicament for: suppressing, reducing or inhibiting tumour growth in a subject suffering from cancer; treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject; treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a viral infection in a subject; treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting alcoholic steatohepatitis (ASH) in a subject; treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non alcoholic fatty liver disease (NAFLD) in a subject; treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non-alcoholic steatohepatitis (NASH) in a subject; treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a metabolic disorder in a subject; in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting inflammatory condition in a subject; treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject; treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a neuropsychiatric disease or disorder in a subject; or any combination thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0030] In various embodiments, this invention is directed to a compound represented by the structure of formula **I**:



I

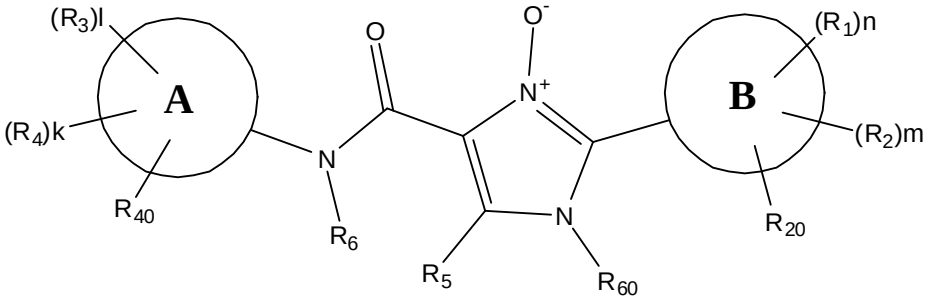
wherein

A and **B** rings are each independently a single or fused aromatic or heteroaromatic ring system (e.g., phenyl, indole, benzofuran, 2-, 3- or 4-pyridine, naphthalene, thiazole, thiophene, imidazole, 1-methylimidazole, benzimidazole,), or a single or fused C_3-C_{10} cycloalkyl (e.g. cyclohexyl) or a single or fused C_3-C_{10} heterocyclic ring (e.g., benzofuran-2(3H)-one, benzo[d][1,3]dioxole, tetrahydrothiophene 1,1-dioxide, piperidine, 1-methylpiperidine, isoquinoline, and 1,3-dihydroisobenzofuran);

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-morpholine, CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR (e.g., NH-CH_3), N(R)$_2$ (e.g., N(CH_3)$_2$), R_8-N(R_{10})(R_{11}) (e.g., CH_2-CH_2-N(CH_3)$_2$, CH_2-NH_2,

WHAT IS CLAIMED:

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



I

A and **B** rings are each independently a single or fused aromatic or heteroaromatic ring system (e.g., phenyl, indole, benzofuran, 2-, 3- or 4-pyridine, naphthalene, thiazole, thiophene, imidazole, 1-methylimidazole, benzimidazole), a single or fused C_3-C_{10} cycloalkyl (e.g. cyclohexyl), or a single or fused C_3-C_{10} heterocyclic ring (e.g., benzofuran-2(3H)-one, benzo[d][1,3]dioxole, tetrahydrothiophene 1,1-dioxide, piperidine, 1-methylpiperidine, isoquinoline, 1,3-dihydroisobenzofuran);

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-morpholine, CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR (e.g., NH-CH_3), N(R)$_2$ (e.g., N(CH_3)$_2$), R_8-N(R_{10})(R_{11}) (e.g., CH_2-CH_2-N(CH_3)$_2$, CH_2-NH_2, CH_2-N(CH_3)$_2$), R_9-R_8-N(R_{10})(R_{11}) (e.g., C≡C-CH_2-NH_2), B(OH)$_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R_{10} (e.g., NHC(O)CH_3), NHCO-N(R_{10})(R_{11}) (e.g., NHC(O)N(CH_3)$_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH(CH_3)$_2$, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., CH_2C(O)CH_3), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -C(O)NH_2, C(O)NHR, C(O)N(R_{10})(R_{11}) (e.g., C(O)N(CH_3)$_2$), SO_2R, SO_2N(R_{10})(R_{11}) (e.g., SO_2N(CH_3)$_2$, SO_2NHC(O)CH_3), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH_3, methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)$_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, 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_1-C_5 linear or branched or C_3-C_8 cyclic alkoxy (e.g. methoxy, O-(CH_2)$_2$-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl),

substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluoroxylyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), or $CH(CF_3)(NH\text{-}R_{10})$;

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 (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

$\mathbf{R_3}$ is I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -OC(O)CF_3, -OCH_2Ph, -NHCO-R_{10} (e.g., NHC(O)CH_3), NHCO-$N(R_{10})(R_{11})$ (e.g., NHC(O)$N(CH_3)_2$), -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., CH_2C(O)CH_3), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -C(O)NH_2, C(O)NHR (e.g., C(O)NH(CH_3)), C(O)$N(R_{10})(R_{11})$ (e.g., C(O)$N(CH_3)_2$, C(O)N(CH_3)(CH_2CH_3), C(O)N(CH_3)(CH_2CH_2-O-CH_3), C(S)$N(R_{10})(R_{11})$ (e.g., C(S)NH(CH_3)), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., SO_2NH(CH_3), $SO_2N(CH_3)_2$), C_2-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH_3)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C_2-C_5 linear or branched or C_3-C_8 cyclic haloalkyl (e.g., CF_2CH_3, CF_2-cyclobutyl, CF_2-cyclopropyl, CF_2-methylcyclopropyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$, $C(OH)_2CF_3$, cyclopropyl-CF_3), C_2-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), 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 (e.g., CF_3-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $CH(CF_3)(NH\text{-}R_{10})$;

$\mathbf{R_4}$ and $\mathbf{R_{40}}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -OC(O)CF_3, -OCH_2Ph, -NHCO-R_{10} (e.g., NHC(O)CH_3), NHCO-$N(R_{10})(R_{11})$ (e.g., NHC(O)$N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g.,

$CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -$C(O)NH_2$, C(O)NHR (e.g., $C(O)NH(CH_3)$), $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$, $C(O)N(CH_3)(CH_2CH_3)$, $C(O)N(CH_3)(CH_2CH_2\text{-}O\text{-}CH_3)$, $C(S)N(R_{10})(R_{11})$ (e.g., $C(S)NH(CH_3)$), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2NH(CH_3)$, $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)$(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C_1-C_5 linear or branched or C_3-C_8 cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CF_2-cyclopropyl, CF_2-methylcyclopropyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$, $C(OH)_2CF_3$, cyclopropyl-CF_3), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), 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 (e.g., CF_3-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $CH(CF_3)(NH\text{-}R_{10})$;

or **R_3** and **R_4** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., imidazole, [1,3]dioxole, furan-2(3H)-one, benzene, cyclopentane, imidazole);

R_5 is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, iso-propyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), $C(=CH_2)$-R_{10} (e.g., $C(=CH_2)\text{-}C(O)\text{-}OCH_3$, $C(=CH_2)$-CN) substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R_6 is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

R_{60} is H, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, $CH_2\text{-}OC(O)CH_3$, $CH_2\text{-}PO_4H_2$, $CH_2\text{-}PO_4H\text{-}tBu$, $CH_2\text{-}OP(O)(OCH_3)_2$), C(O)R, or $S(O)_2R$;

R_8 is $[CH_2]_p$

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

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

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

R_{10} and **R_{11}** are each independently H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), $R_8\text{-}O\text{-}R_{10}$ (e.g., $CH_2CH_2\text{-}O\text{-}CH_3$), C(O)R (e.g., $C(O)(OCH_3)$), or $S(O)_2R$;

or **R_{10}** and **R_{11}** are joined to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl, propyl), C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_2-C_5 linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., $CH{\equiv}C$-CH_3), alkoxy, ester (e.g., $OC(O)$-CH_3), $N(R)_2$, CF_3, aryl, phenyl, R_8-aryl (e.g., CH_2CH_2-Ph), heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), C_3-C_8 heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO_4H), dihydrogen-phosphate (i.e., $OP(O)(OH)_2$), dialkylphosphate (e.g., $OP(O)(OCH_3)_2$), CN and NO_2;

R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl,

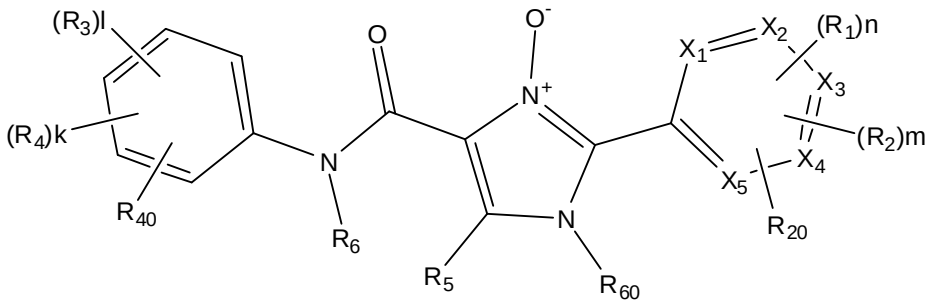
or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

m, **n** and **k** are each independently an integer between 0 and 4 (e.g., 0, 1 or 2);

l is an integer between 1 and 4 (e.g., 1 or 2);

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

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

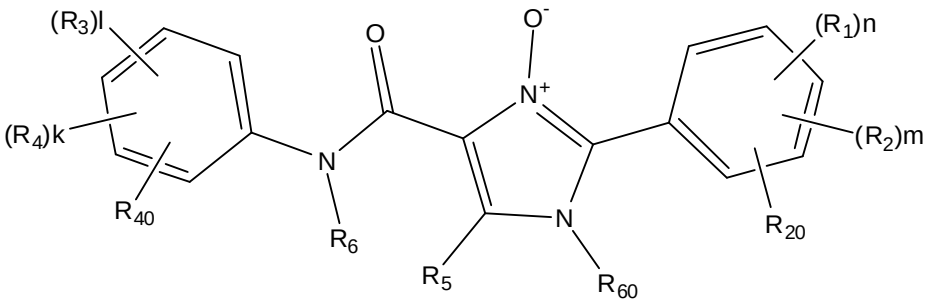


II

wherein

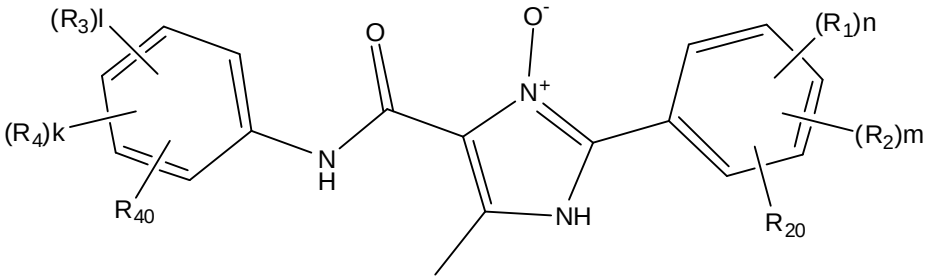
X_1, **X_2**, **X_3**, **X_4** and **X_5** are each independently C or N;

by the structure of formula **III**:



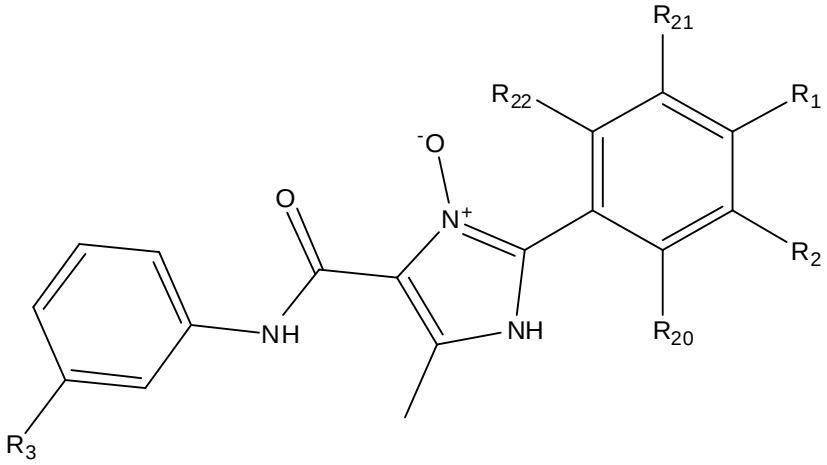
III;

by the structure of formula **IV**:



IV;

by the structure of formula **VIII**:



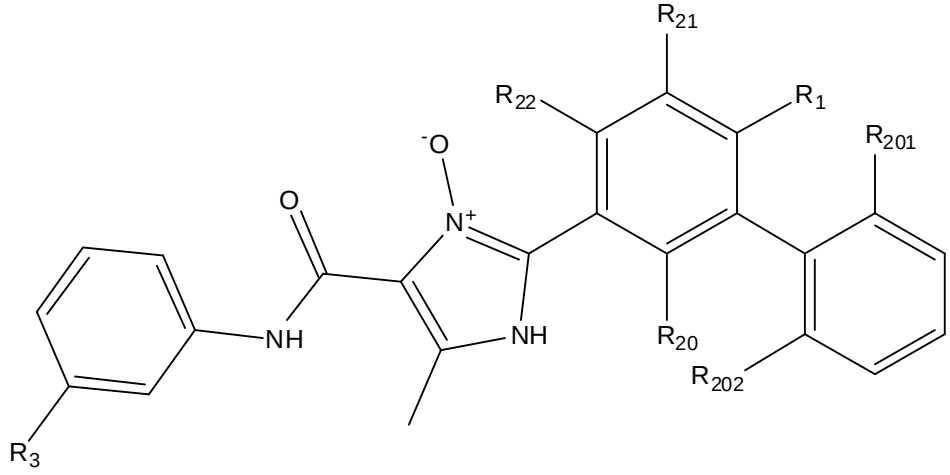
VIII

wherein

R_{21} and **R_{22}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-morpholine, CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR (e.g., NH-CH_3), N(R)$_2$ (e.g., N(CH_3)$_2$), R_8-N(R_{10})(R_{11}) (e.g., CH_2-CH_2-N(CH_3)$_2$, CH_2-NH_2, CH_2-N(CH_3)$_2$), R_9-R_8-N(R_{10})(R_{11}) (e.g., C≡C-CH_2-NH_2), B(OH)$_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R_{10} (e.g., NHC(O)CH_3), NHCO-N(R_{10})(R_{11}) (e.g., NHC(O)N(CH_3)$_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH(CH_3)$_2$, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., CH_2C(O)CH_3), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3,

$C(O)$-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH_3, methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, 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_1-C_5 linear or branched or C_3-C_8 cyclic alkoxy (e.g. methoxy, O-$(CH_2)_2$-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluoroxylyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), or $CH(CF_3)(NH$-$R_{10})$; or

by the structure of formula **IX**:



IX

wherein

R_1, R_{20}, R_{21} and **R_{22}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-morpholine, CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR (e.g., NH-CH_3), $N(R)_2$ (e.g., $N(CH_3)_2$), R_8-$N(R_{10})(R_{11})$

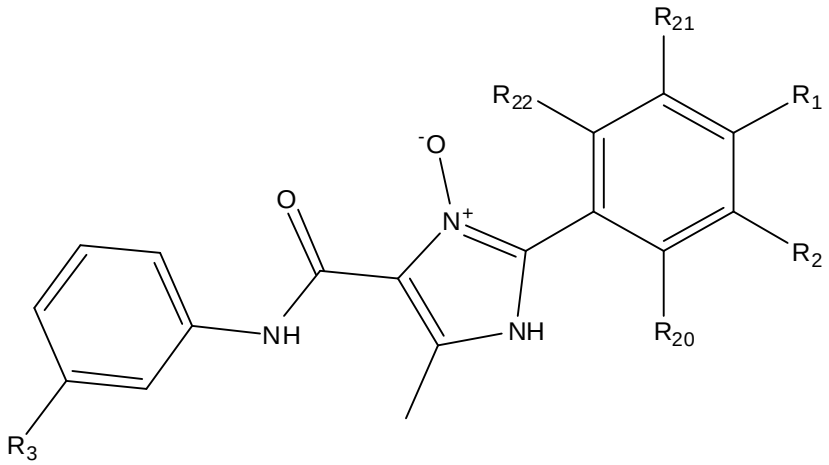
(e.g., CH_2-CH_2-$N(CH_3)_2$, CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, $NHC(O)$-R_{10} (e.g., $NHC(O)CH_3$), $NHCO$-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O$-R_{10} (e.g. $C(O)O$-CH_3, $C(O)O$-$CH(CH_3)_2$, $C(O)O$-CH_2CH_3), R_8-$C(O)$-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)$-R_{10} (e.g., $C(O)$-CH_3, $C(O)$-CH_2CH_3, $C(O)$-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)$-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., $C(H)(OH)$-CH_3, methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, 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_1-C_5 linear or branched or C_3-C_8 cyclic alkoxy (e.g. methoxy, O-$(CH_2)_2$-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluoroxylyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), $CH(CF_3)(NH$-$R_{10})$;

or $\mathbf{R_{21}}$ and $\mathbf{R_1}$ are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

or $\mathbf{R_{21}}$ and $\mathbf{R_{22}}$ are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine); and

$\mathbf{R_{201}}$ and $\mathbf{R_{202}}$ are each independently H, F, Cl, Br, I, CF_3, or C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl).

3. A compound represented by the structure of formula **VIII**:



VIII

wherein

R_1 is H, methoxy, OCD_3, F, Cl, or $OCHF_2$;

R_2 is xylyl, 2,6-difluorophenyl, 4-fluoroxylyl or isopropyl;

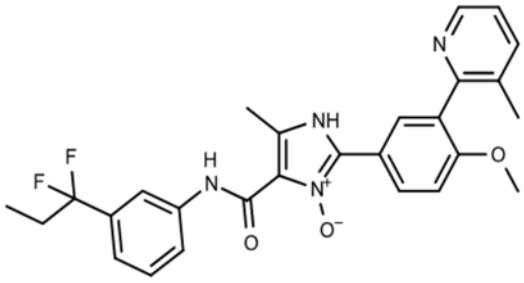
R_{22} is F, OH, or NH_2;

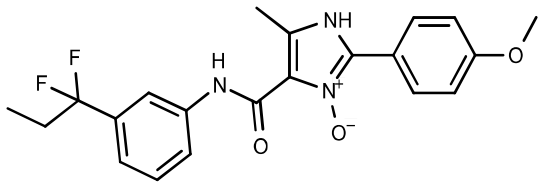
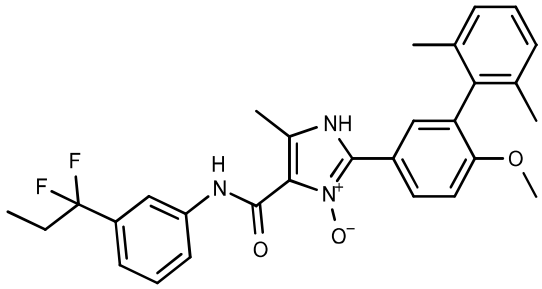
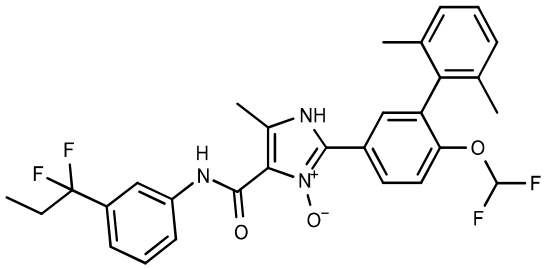
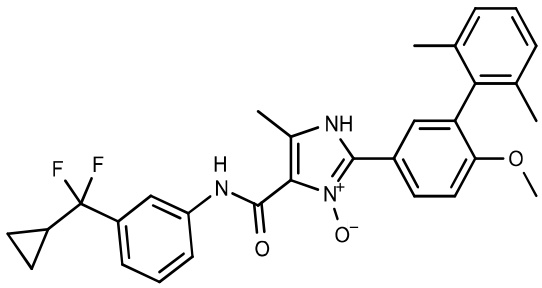
R_{20} and **R_{21}** are both H;

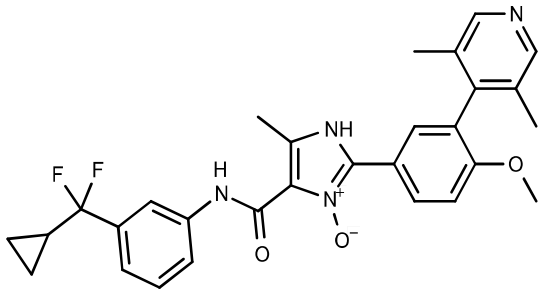
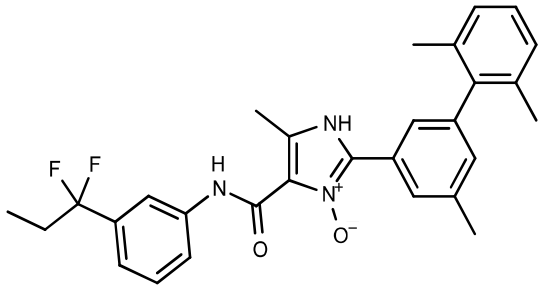
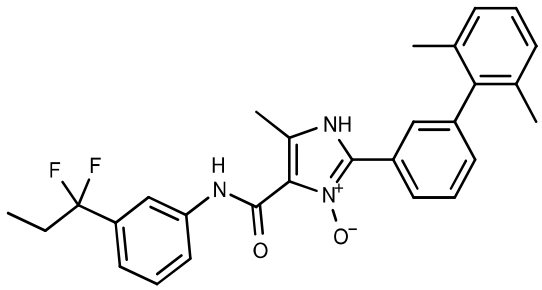
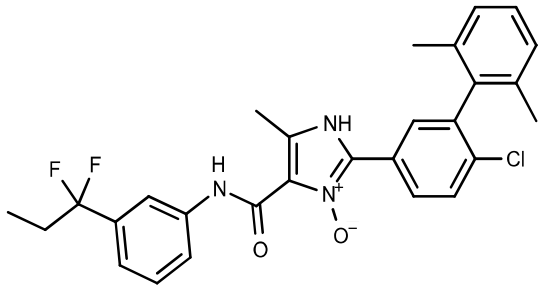
R_3 is oxadiazole, oxazole, isoxazole, or tetrazole;

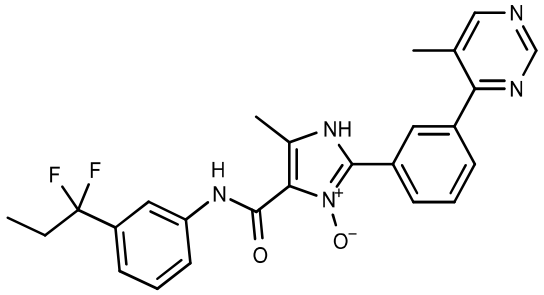
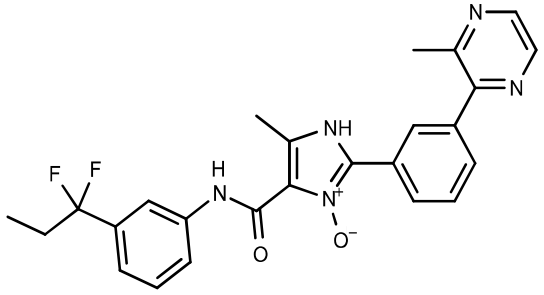
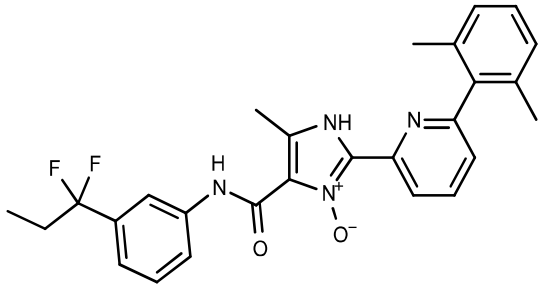
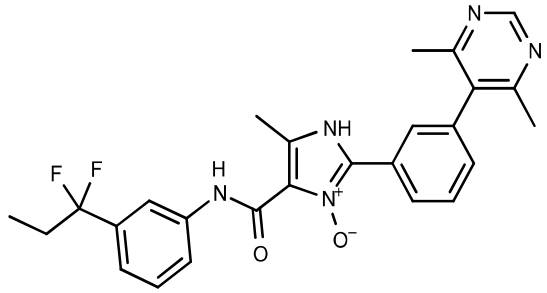
or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

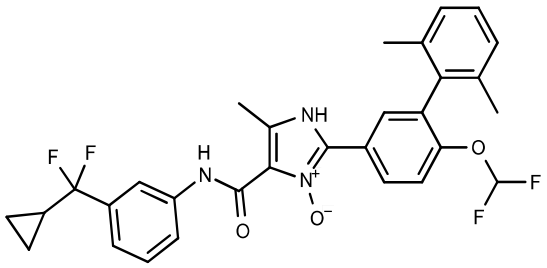
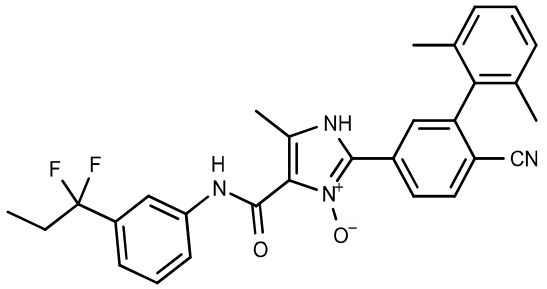
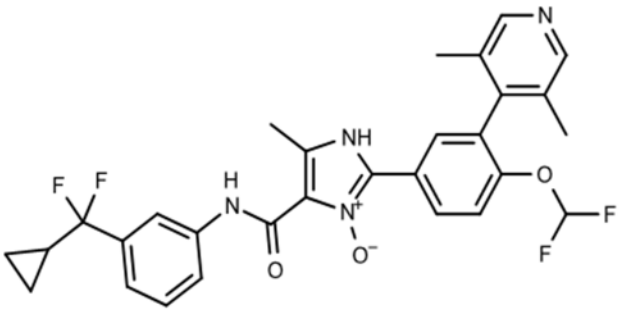
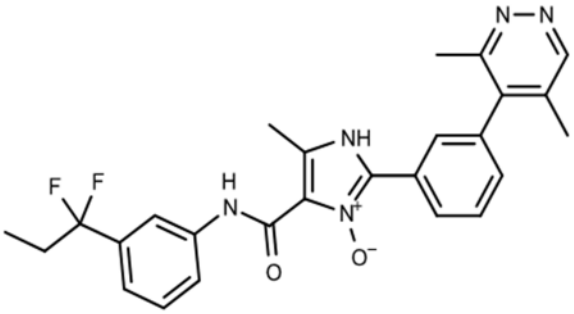
4. The compound of any one of the preceding claims, selected from the following:

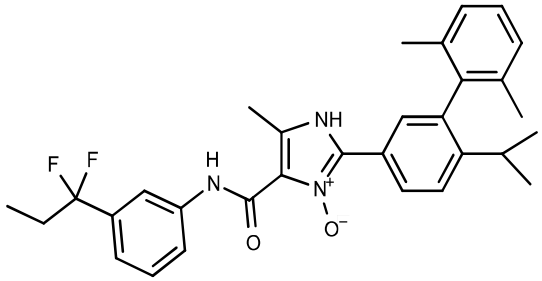
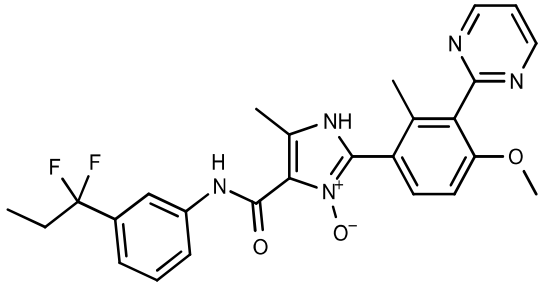
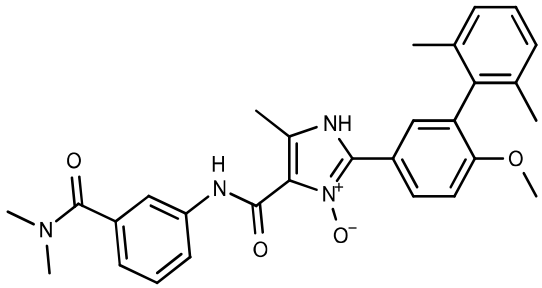
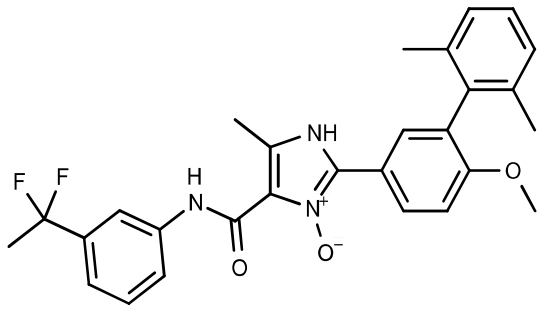
Compound Number	**Compound Structure**
100	

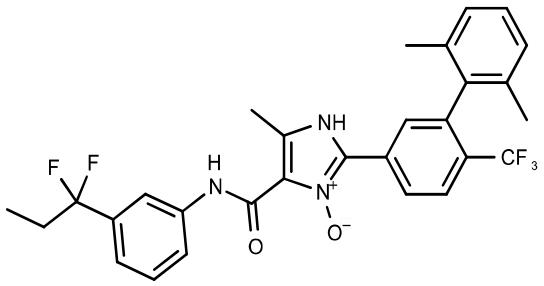
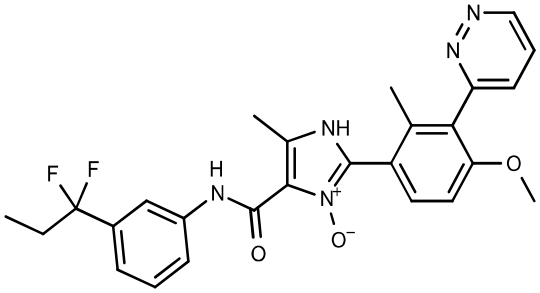
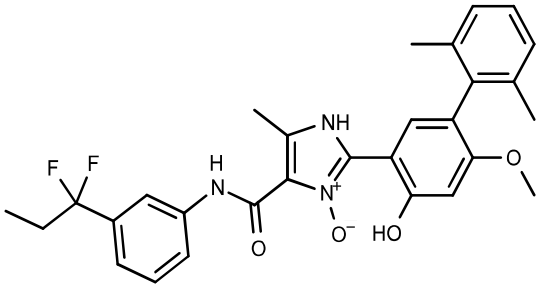
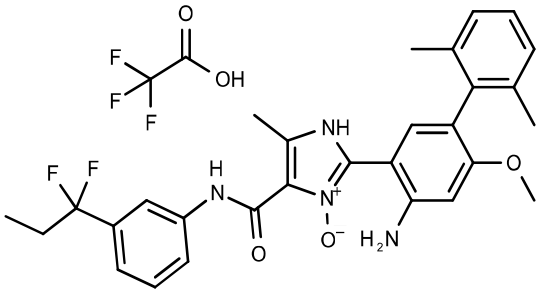
101	
102	
103	
104	

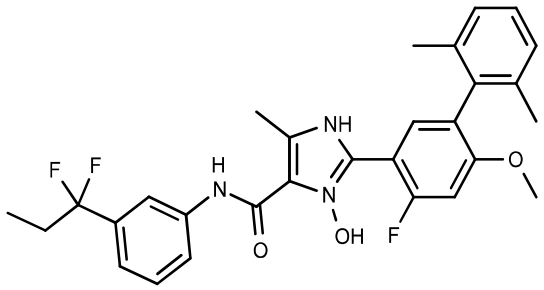
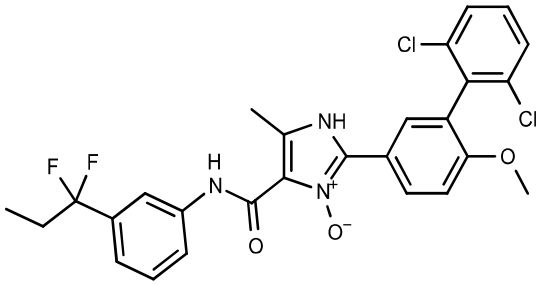
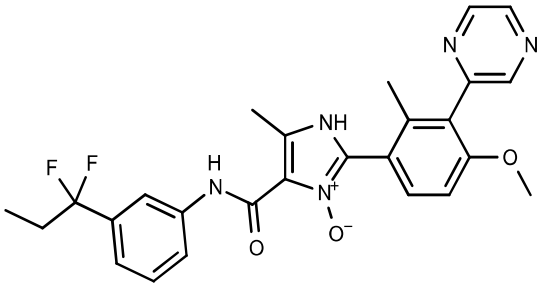
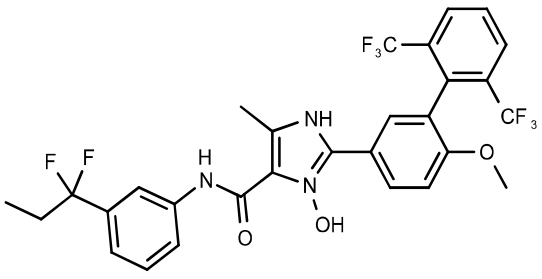
105	
106	
107	
108	

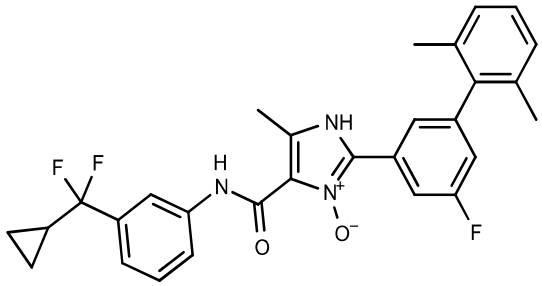
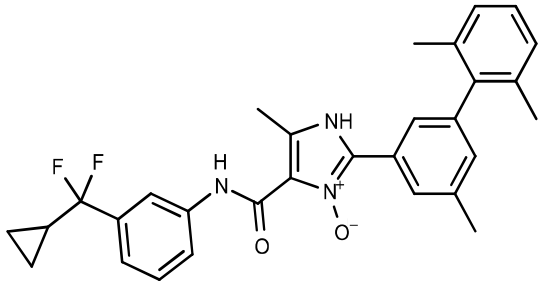
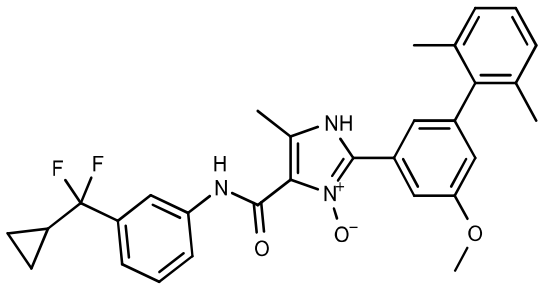
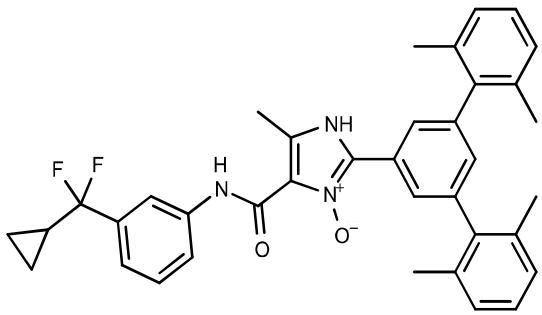
109	
110	
111	
112	

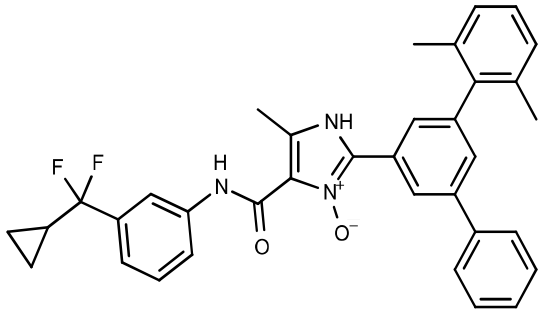
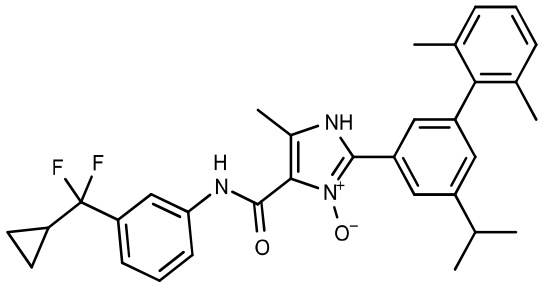
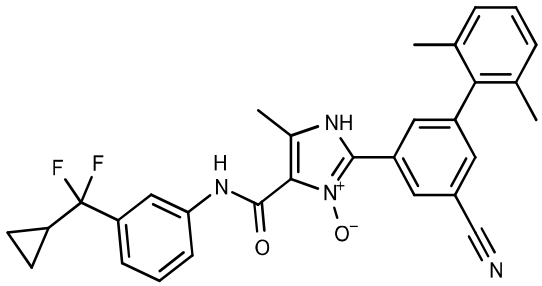
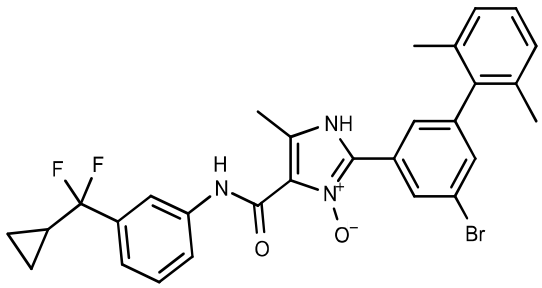
113	
114	
115	
116	

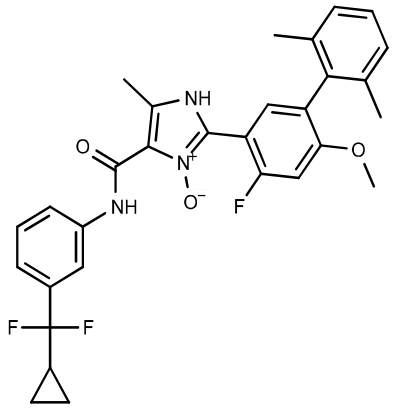
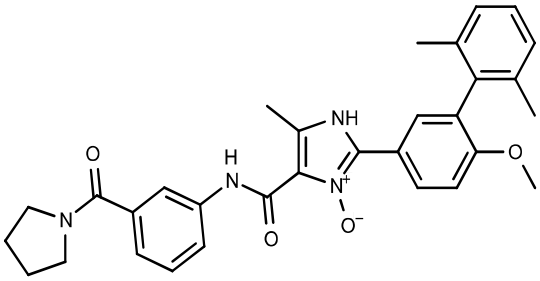
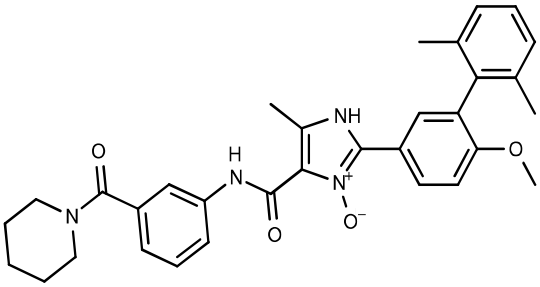
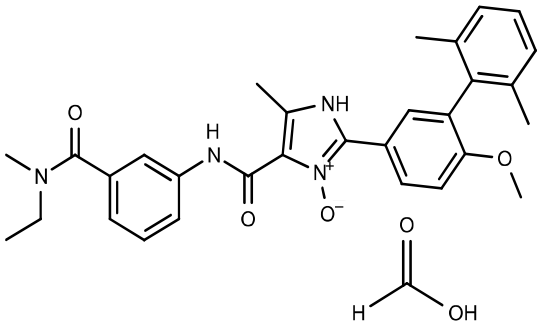
117	
118	
119	
120	

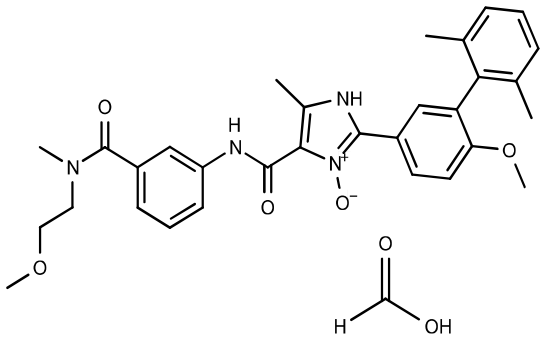
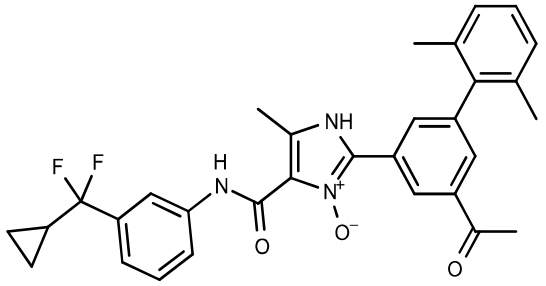
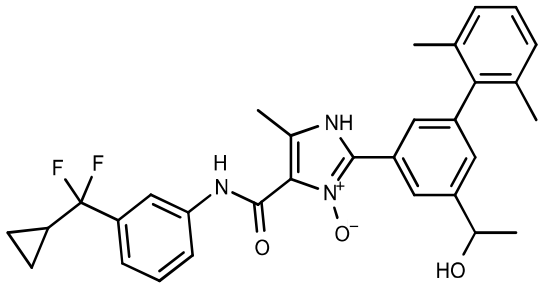
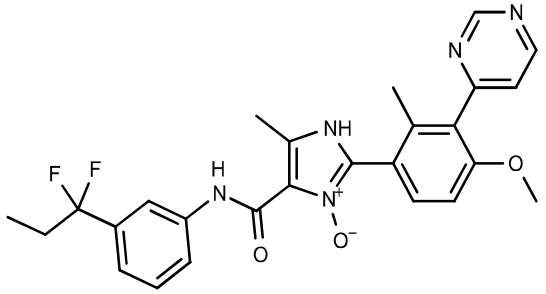
121	
122	
123	
124	

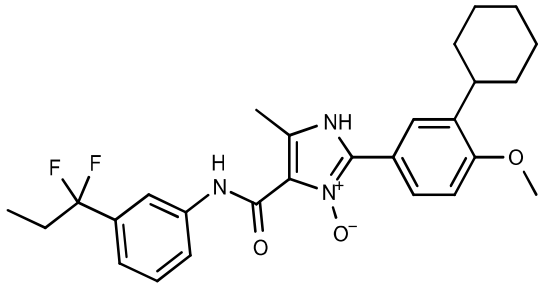
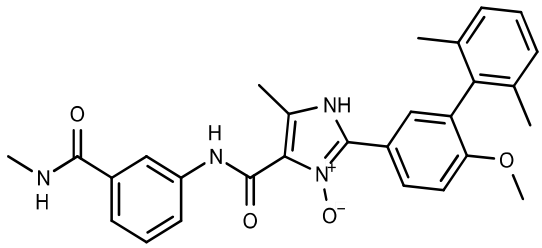
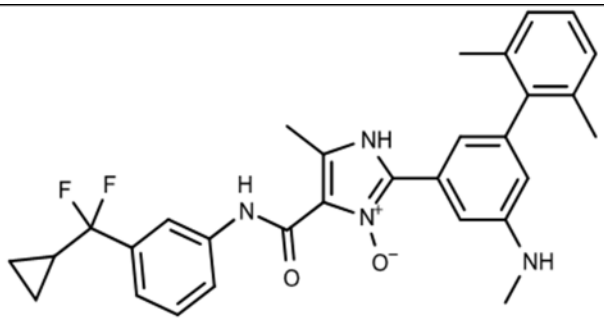
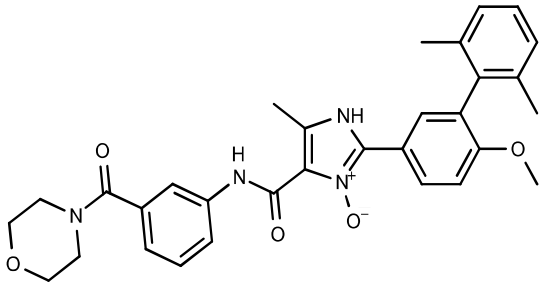
125	
126	
127	
128	

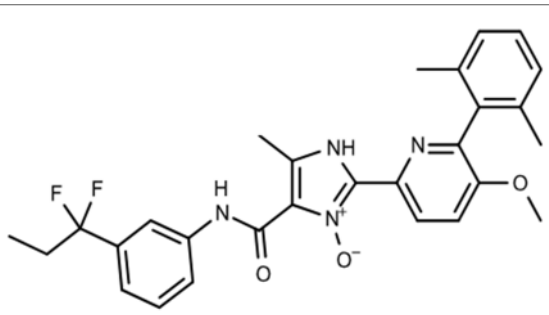
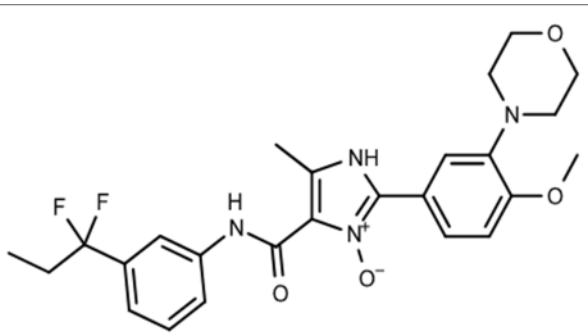
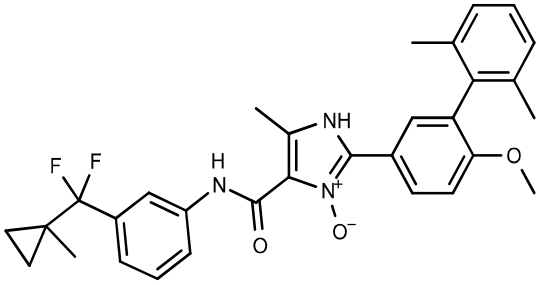
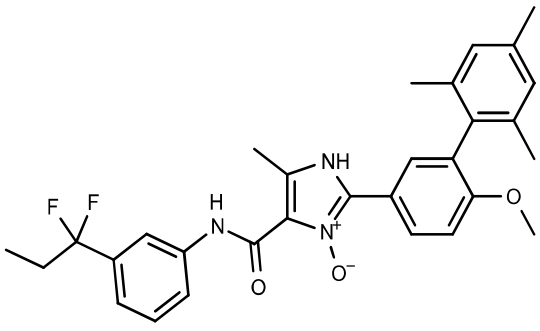
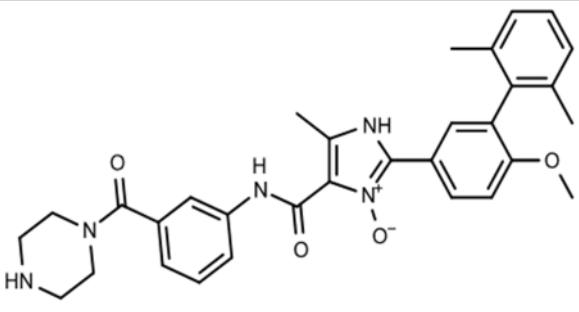
129	
130	
131	
132	

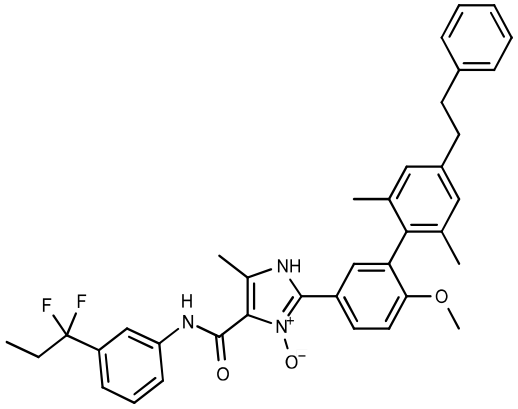
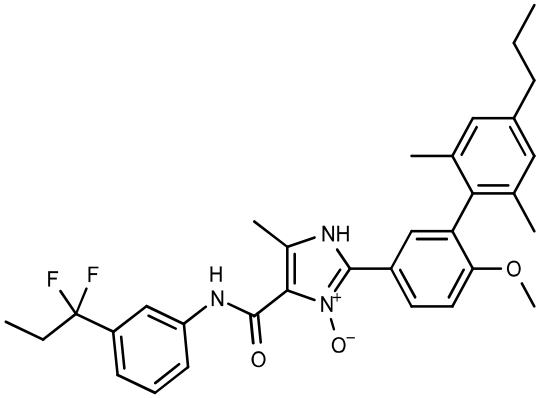
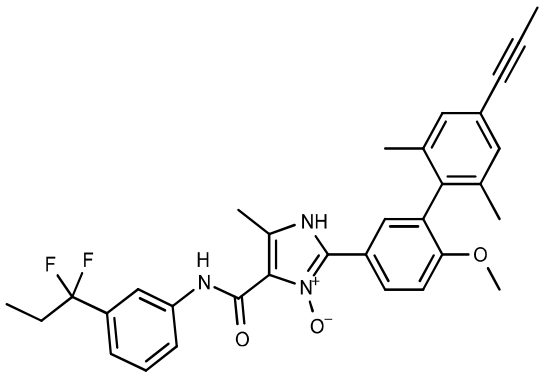
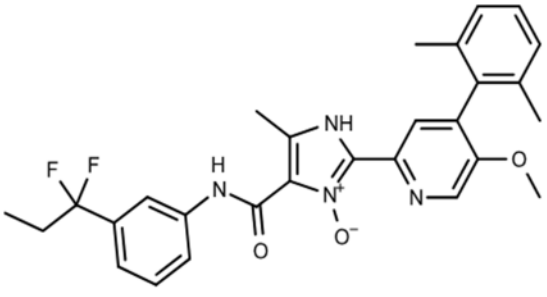
133	
134	
135	
136	

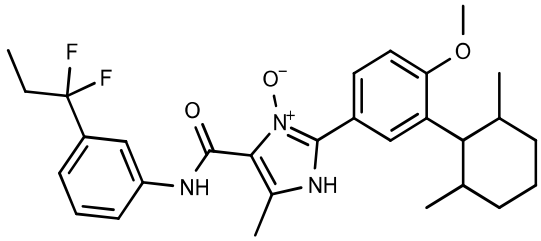
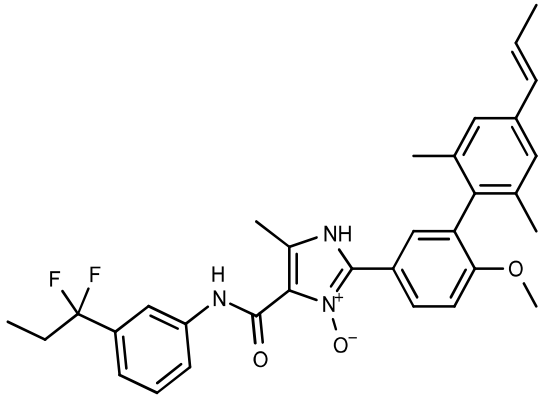
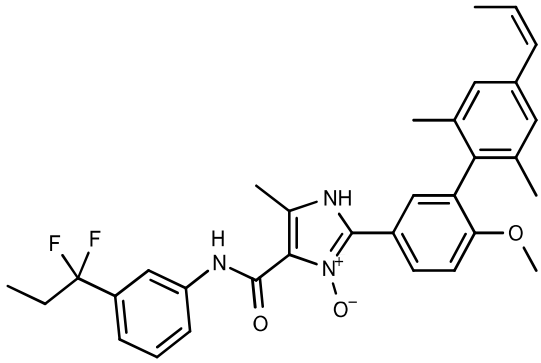
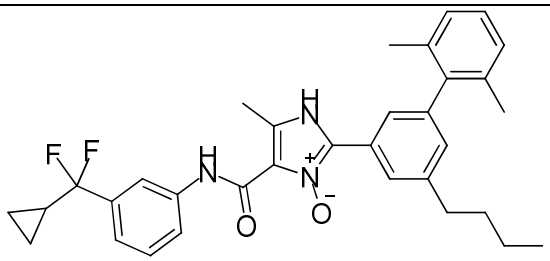
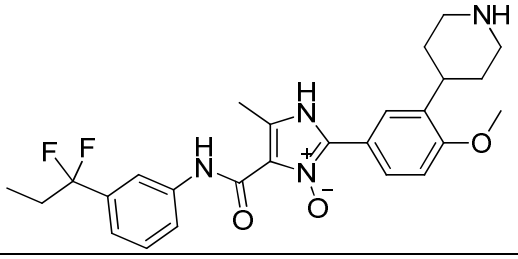
137	
138	
139	
140	

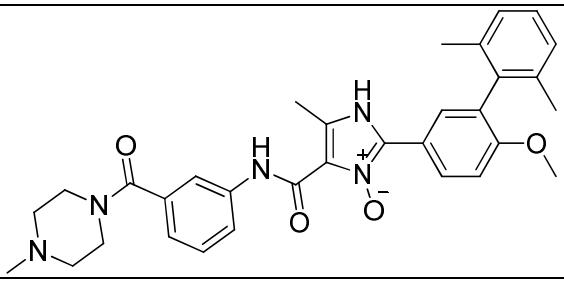
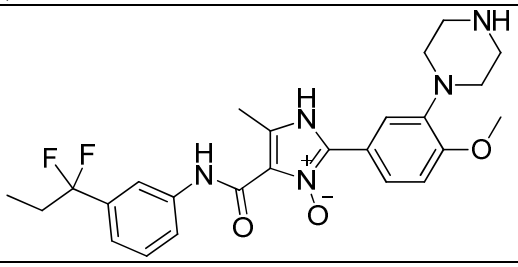
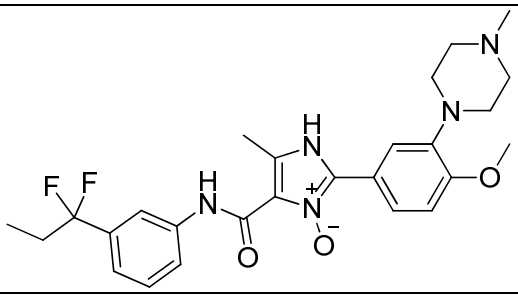
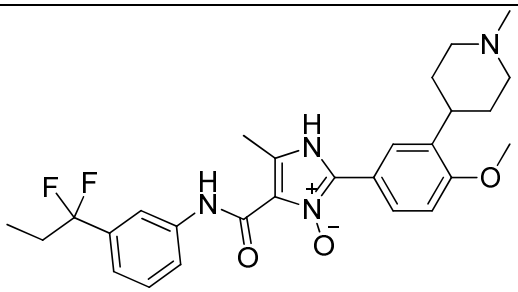
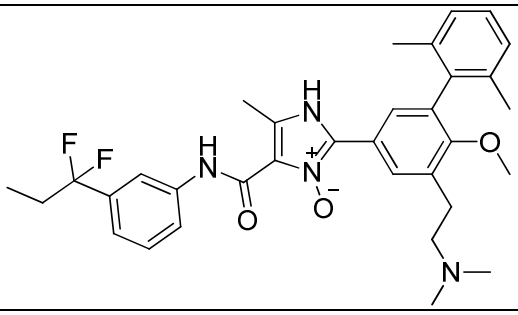
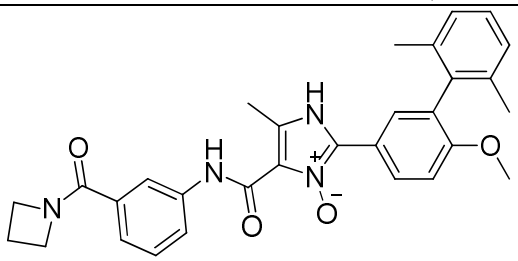
141	
142	
143	
144	

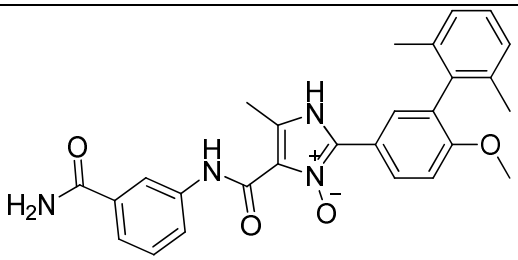
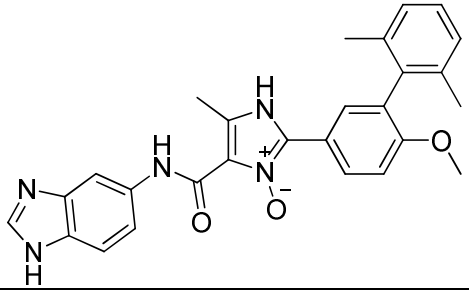
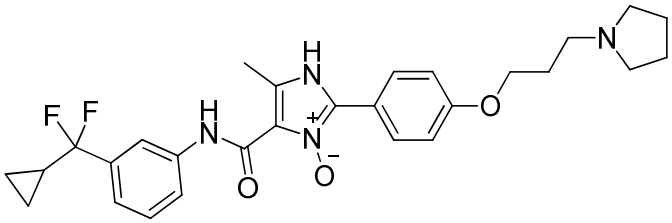
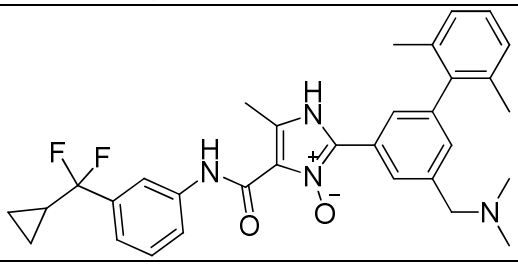
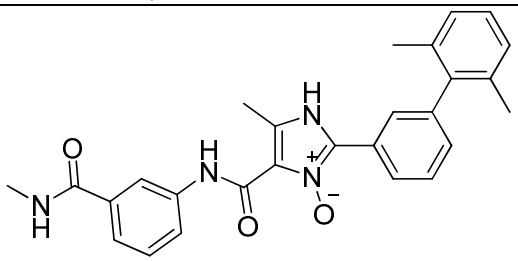
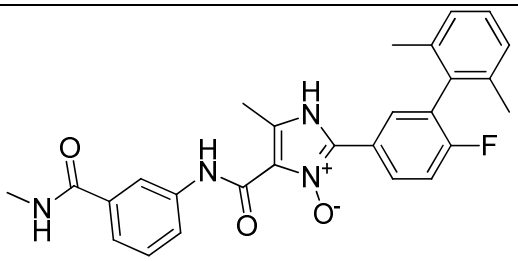
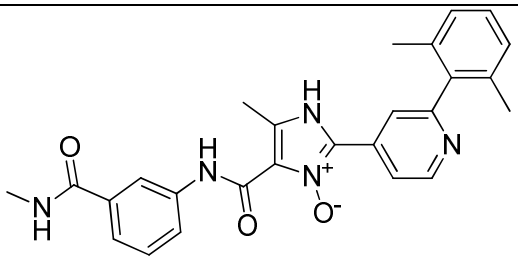
145	
146	
147	
148	

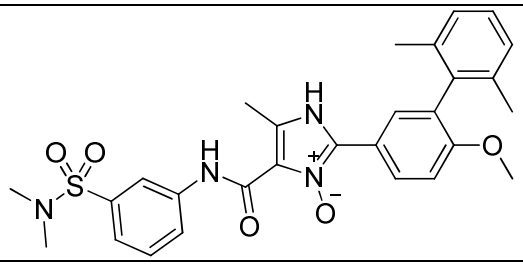
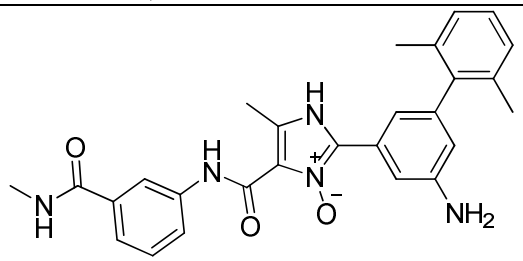
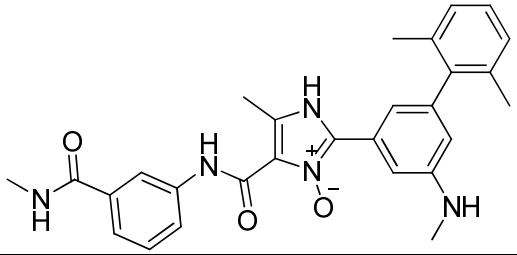
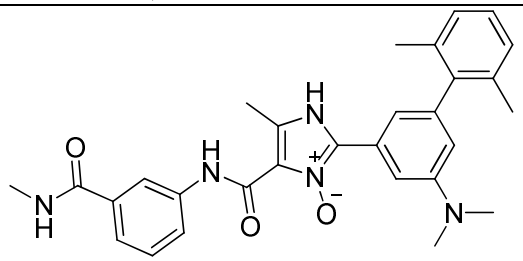
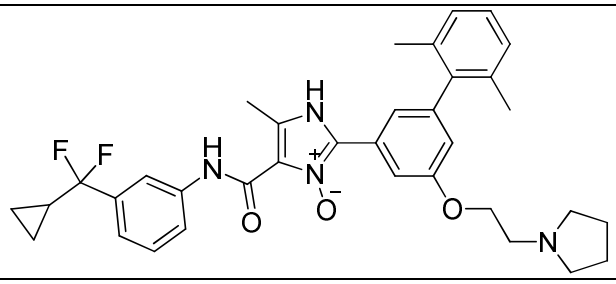
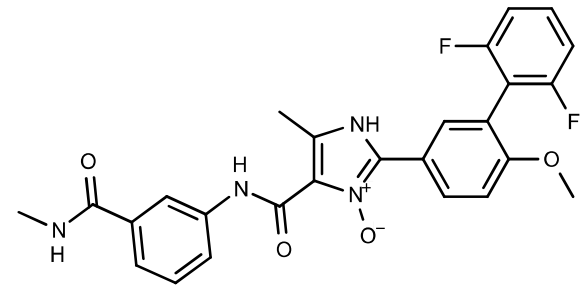
149	
150	
151	
152	
153	

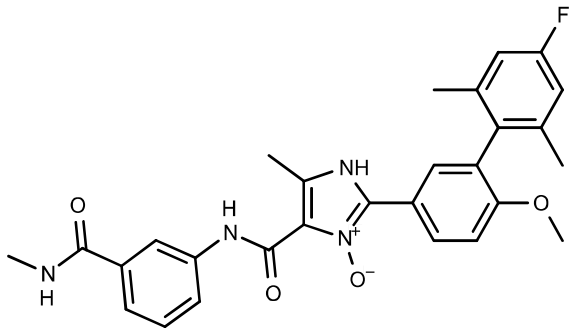
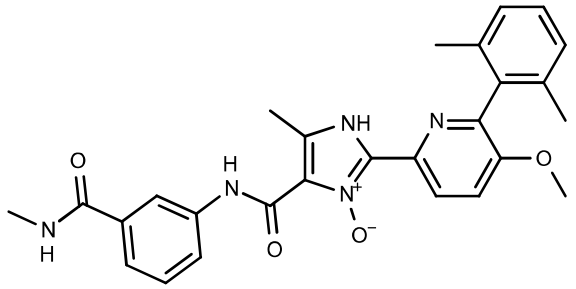
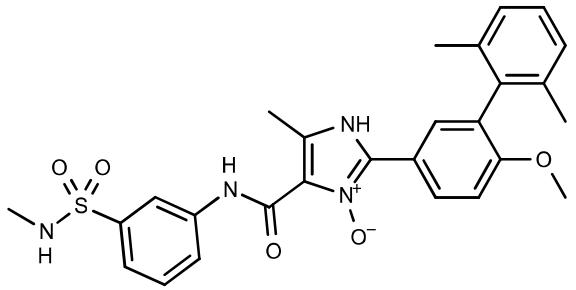
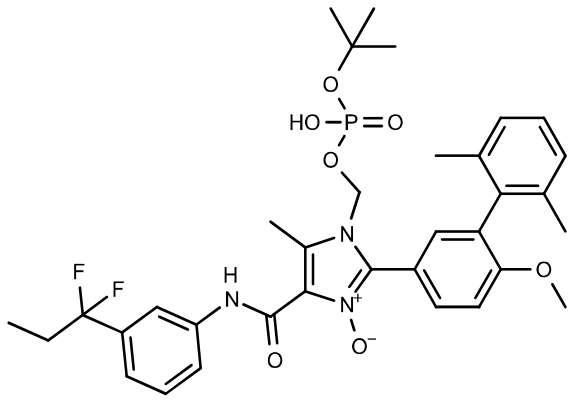
154	
155	
156	
157	

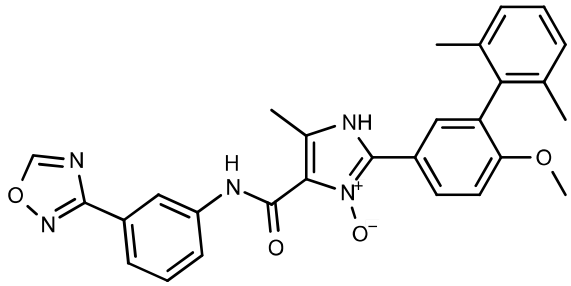
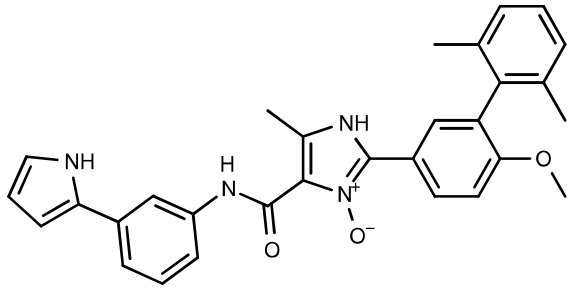
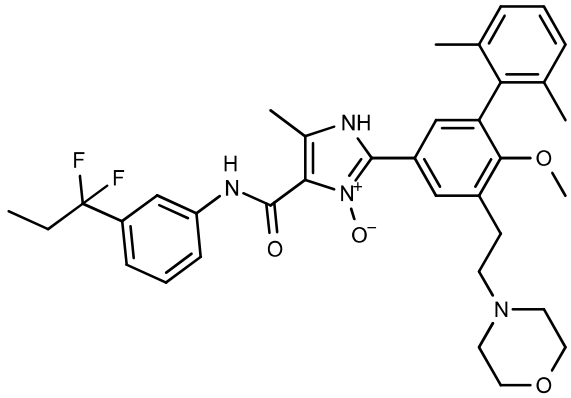
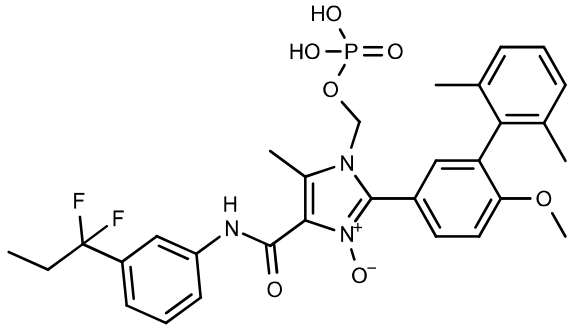
158	
159	
160	
161	
162	

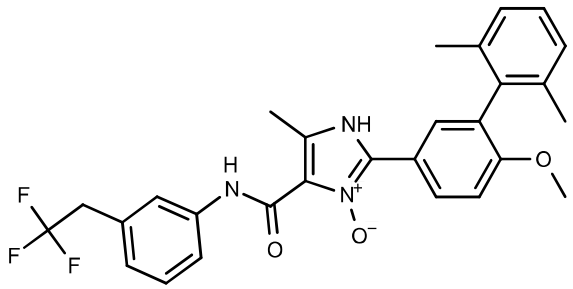
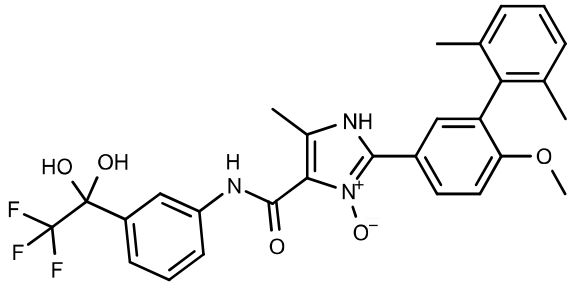
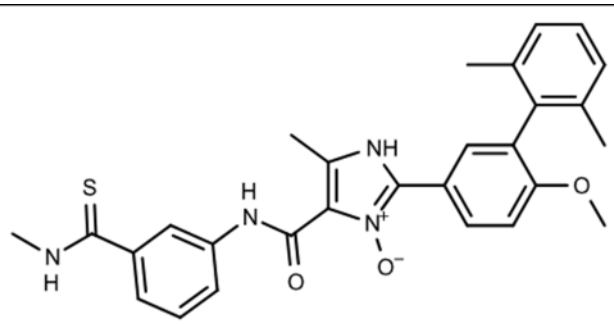
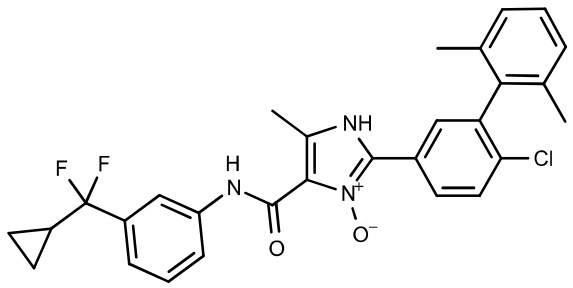
163	
164	
165	
166	
169	
170	

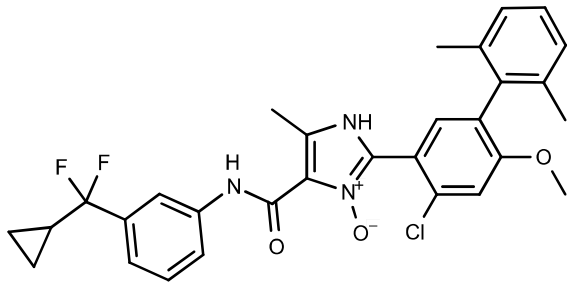
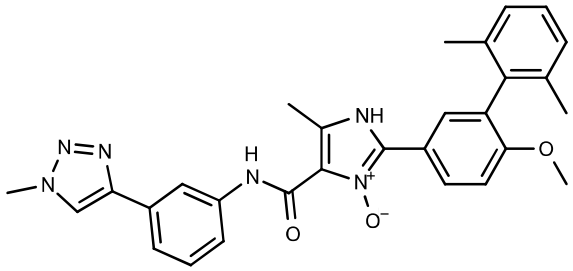
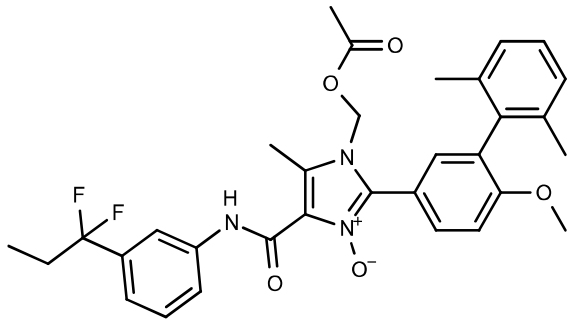
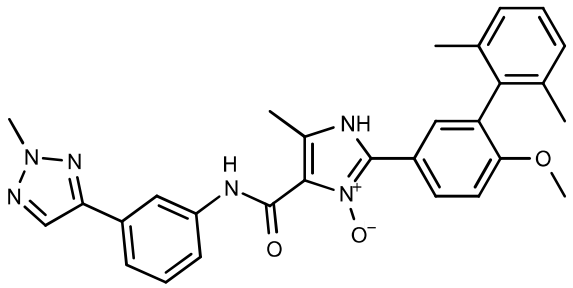
172	
173	
174	
175	
176	
177	
178	

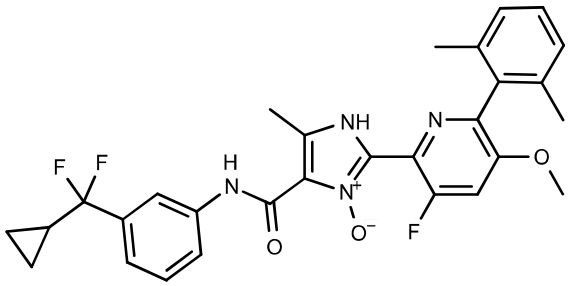
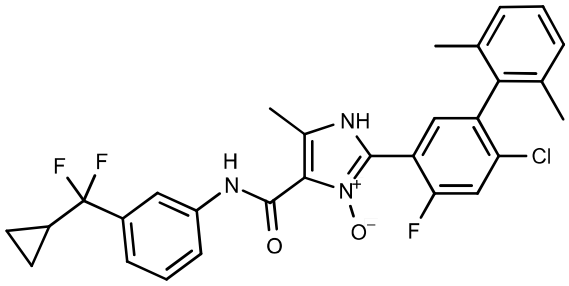
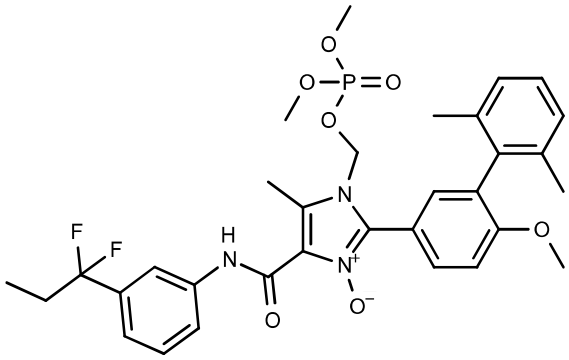
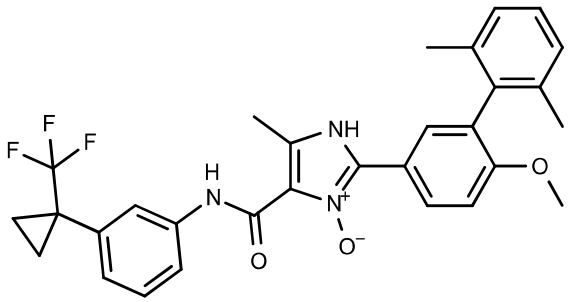
179	
180	
181	
182	
183	
184	

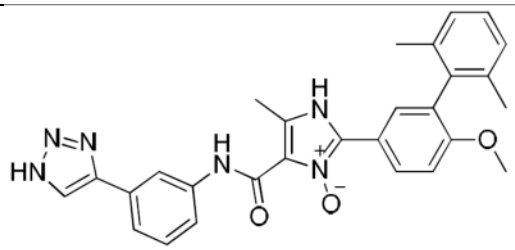
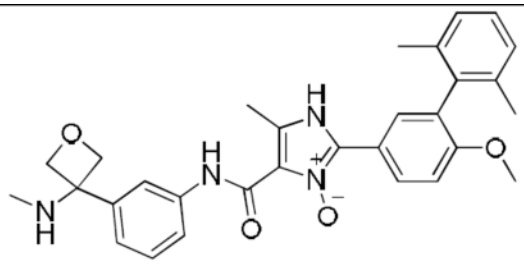
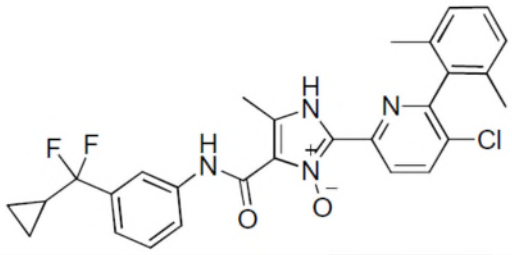
185	
186	
187	
188	

190	
191	
192	
193	

194	
195	
196	
197	

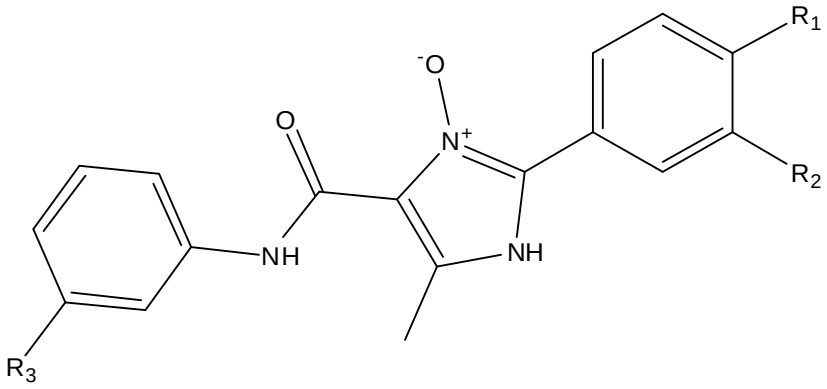
198	
199	
200	
201	

202	
204	
205	
206	

210	
211	
213	

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

5. A compound represented by the structure of formula **VI**:



VI

wherein

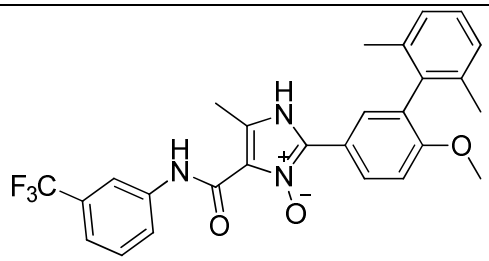
R_3 is I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -$C(O)NH_2$, C(O)NHR (e.g., $C(O)NH(CH_3)$), $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$,

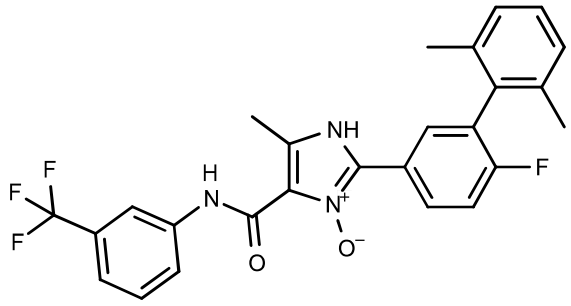
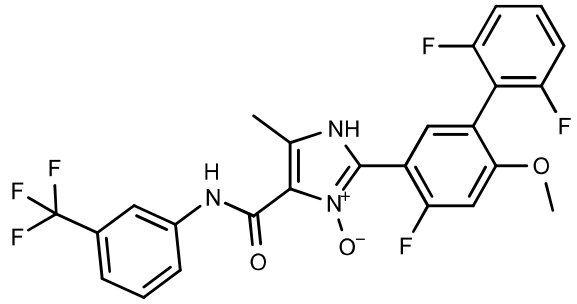
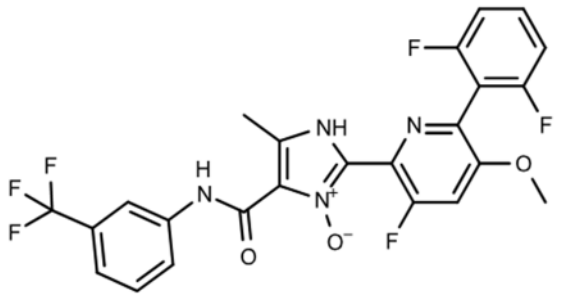
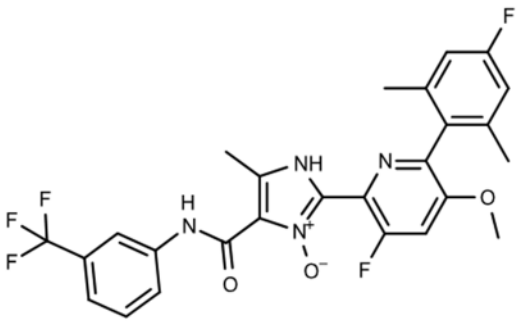
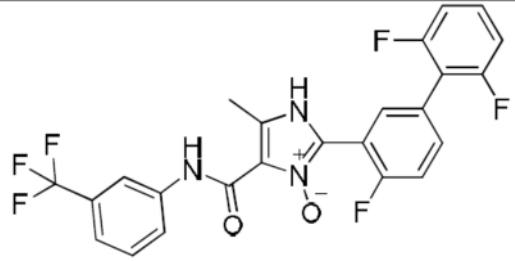
$C(O)N(CH_3)(CH_2CH_3)$, $C(O)N(CH_3)(CH_2CH_2\text{-}O\text{-}CH_3)$, $C(S)N(R_{10})(R_{11})$ (e.g., $C(S)NH(CH_3)$), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2NH(CH_3)$, $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C_1-C_5 linear or branched or C_3-C_8 cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CF_2-cyclopropyl, CF_2-methylcyclopropyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$, $C(OH)_2CF_3$, cyclopropyl-CF_3), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), 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 (e.g., CF_3-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $CH(CF_3)(NH\text{-}R_{10})$.

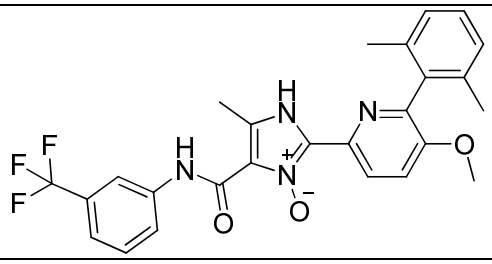
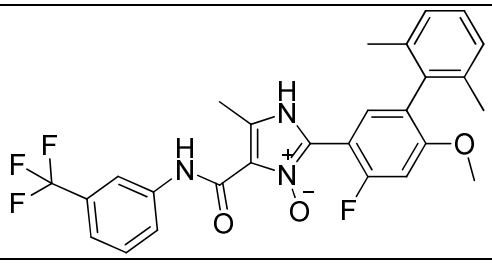
6. The compound of claim 5, wherein:

R_3 is $C(O)NH_2$, C(O)NHR (e.g., $C(O)NH(CH_3)$), $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$, $C(O)N(CH_3)(CH_2CH_3)$, $C(O)N(CH_3)(CH_2CH_2\text{-}O\text{-}CH_3)$, $C(S)N(R_{10})(R_{11})$ (e.g., $C(S)NH(CH_3)$), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2NH(CH_3)$, $SO_2N(CH_3)_2$), or substituted or unsubstituted C_1-C_5 linear or branched or C_3-C_8 cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CF_2-cyclopropyl, CF_2-methylcyclopropyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)\text{-}CH(CH_3)_2$, $C(OH)_2CF_3$, cyclopropyl-CF_3).

7. The compound of claim 5 or 6, selected from the following:

Compound Number	Compound Structure
171	

203	
207	
208	
209	
212	

214	
215	

8. A pharmaceutical composition comprising a compound according to any one of the preceding claims and a pharmaceutically acceptable carrier.
9. Use of a compound according to any one of claims 1 to 7, in the preparation of a medicament for treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer in a subject.
10. The use of claim 9,

wherein the cancer is selected from the list of: hepatocellular carcinoma, melanoma (e.g., BRAF mutant melanoma), glioblastoma, breast cancer (e.g., invasive ductal carcinomas of the breast, triple-negative breast cancer), prostate cancer, liver cancer, brain cancer, ovarian cancer, lung cancer, Lewis lung carcinoma (LLC), colon carcinoma, pancreatic cancer, renal cell carcinoma and mammary carcinoma;

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

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

wherein the compound is to be administered in combination with an anti-cancer therapy;

or any combination thereof.

11. The use of claim 9, wherein the anti-cancer therapy is chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof.
12. Use of a compound according to any one of claims 1 to 7, for preparation of a medicament for:

suppressing, reducing or inhibiting tumour growth in a subject suffering from cancer;

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

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

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

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

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

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

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

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

treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a neuropsychiatric disease or disorder in a subject;

or any combination thereof.

13. The use of claim 12,

wherein the tumor growth is enhanced by increased acetate uptake by cancer cells of said cancer,

wherein the cancer cells are under hypoxic stress;

wherein the tumor growth is suppressed due to suppression of lipid (e.g., fatty acid) synthesis and/or regulating histones acetylation and function induced by ACSS2 mediated acetate metabolism to acetyl-CoA;

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

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

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

or any combination thereof.

14. The use of claim 13, wherein the increased acetate uptake is mediated by ACSS2.
15. An *in vitro* method of suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and function in a cell, comprising contacting a compound according to any one of claims 1 to 7, with a cell under conditions effective to suppress, reduce or inhibit lipid synthesis and/or regulating histones acetylation and function in said cell.
16. The method of claim 15, wherein the cell is a cancer cell.
17. 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 7, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme.

18. An *in vitro* method of suppressing, reducing or inhibiting acetyl-CoA synthesis from acetate in a cell, comprising contacting a compound according to any one of claims 1 to 7 with a cell, under conditions effective to suppress, reduce or inhibit acetyl-CoA synthesis from acetate in said cell.

19. The method of claim 18,

    wherein the cell is a cancer cell;

    wherein the synthesis is mediated by ACSS2;

    or combination thereof.

20. An *in vitro* method of suppressing, reducing or inhibiting acetate metabolism in a cancer cell, comprising contacting a compound according to any one of claims 1 to 7 with a cancer cell, under conditions effective to suppress, reduce or inhibit acetate metabolism in said cells.

21. The method of claim 20,

    wherein the acetate metabolism is mediated by ACSS2;

    wherein the cancer cell is under hypoxic stress.