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(54) Title: THERAPEUTICALLY ACTIVE COMPOUNDS AND THEIR METHODS OF USE

(57) **Abstract**: Provided are compounds useful for treating cancer and methods of treating cancer comprising administering to a subject in need thereof a compound described herein.

THERAPEUTICALLY ACTIVE COMPOUNDS AND THEIR METHODS OF USE

BACKGROUND OF INVENTION

Isocitrate dehydrogenases (IDHs) catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate (*i.e.*, α-ketoglutarate). These enzymes belong to two distinct subclasses, one of which utilizes NAD(+) as the electron acceptor and the other NADP(+). Five isocitrate dehydrogenases have been reported: three NAD(+)-dependent isocitrate dehydrogenases, which localize to the mitochondrial matrix, and two NADP(+)-dependent isocitrate dehydrogenases, one of which is mitochondrial and the other predominantly cytosolic. Each NADP(+)-dependent isozyme is a homodimer.

IDH1 (isocitrate dehydrogenase 1 (NADP+), cytosolic) is also known as IDH; IDP; IDCD; IDPC or PICD. The protein encoded by this gene is the NADP(+)-dependent isocitrate dehydrogenase found in the cytoplasm and peroxisomes. It contains the PTS-1 peroxisomal targeting signal sequence. The presence of this enzyme in peroxisomes suggests roles in the regeneration of NADPH for intraperoxisomal reductions, such as the conversion of 2, 4-dienoyl-CoAs to 3-enoyl-CoAs, as well as in peroxisomal reactions that consume 2-oxoglutarate, namely the alpha-hydroxylation of phytanic acid. The cytoplasmic enzyme serves a significant role in cytoplasmic NADPH production.

The human IDH1 gene encodes a protein of 414 amino acids. The nucleotide and amino acid sequences for human IDH1 can be found as GenBank entries NM_005896.2 and NP_005887.2 respectively. The nucleotide and amino acid sequences for IDH1 are also described in, *e.g.,* Nekrutenko *et al.*, Mol. Biol. Evol. 15:1674-1684(1998); Geisbrecht *et al.*, J. Biol. Chem. 274:30527-30533(1999); Wiemann *et al.*, Genome Res. 11:422-435(2001); The MGC Project Team, Genome Res. 14:2121-2127(2004); Lubec *et al.*, Submitted (DEC-2008) to UniProtKB; Kullmann *et al.*, Submitted (JUN-1996) to the EMBL/GenBank/DDBJ databases; and Sjoeblom *et al.*, Science 314:268-274(2006).

Non-mutant, *e.g.,* wild type, IDH1 catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate thereby reducing NAD^+ ($NADP^+$) to NADH (NADPH), *e.g.,* in the forward reaction:

$$\text{Isocitrate} + \text{NAD}^{+} (\text{NADP}^{+}) \rightarrow \alpha\text{-KG} + \text{CO}_2 + \text{NADH (NADPH)} + \text{H}^{+}.$$

It has been discovered that mutations of IDH1 present in certain cancer cells result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate (2HG). The production of 2HG is believed to contribute to the formation and progression of cancer (Dang, L et al., Nature 2009, 462:739-44).

IDH2 (isocitrate dehydrogenase 2 (NADP+), mitochondrial) is also known as IDH; IDP; IDHM; IDPM; ICD-M; or mNADP-IDH. The protein encoded by this gene is the NADP(+)-dependent isocitrate dehydrogenase found in the mitochondria. It plays a role in intermediary metabolism and energy production. This protein may tightly associate or interact with the pyruvate dehydrogenase complex. Human IDH2 gene encodes a protein of 452 amino acids. The nucleotide and amino acid sequences for IDH2 can be found as GenBank entries NM_002168.2 and NP_002159.2 respectively. The nucleotide and amino acid sequence for human IDH2 are also described in, *e.g.,* Huh *et al*., Submitted (NOV-1992) to the EMBL/GenBank/DDBJ databases; and The MGC Project Team, Genome Res. 14:2121-2127(2004).

Non-mutant, *e.g.,* wild type, IDH2 catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) thereby reducing NAD^{+} (NADP^{+}) to NADH (NADPH), *e.g.,* in the forward reaction:

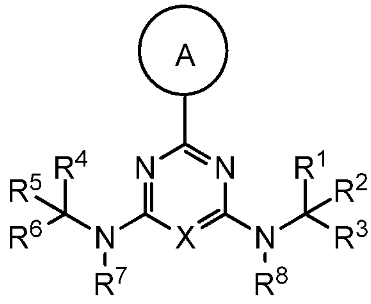
$$\text{Isocitrate} + \text{NAD}^{+} (\text{NADP}^{+}) \rightarrow \alpha\text{-KG} + \text{CO}_2 + \text{NADH (NADPH)} + \text{H}^{+}.$$

It has been discovered that mutations of IDH2 present in certain cancer cells result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate (2HG). 2HG is not formed by wild-type IDH2. The production of 2HG is believed to contribute to the formation and progression of cancer (Dang, L et al, Nature 2009, 462:739-44).

The inhibition of mutant IDH1 and/or mutant IDH2 and their neoactivity is therefore a potential therapeutic treatment for cancer. Accordingly, there is an ongoing need for inhibitors of IDH1 and/or IDH2 mutants having alpha hydroxyl neoactivity.

SUMMARY OF INVENTION

Described herein are compounds of Formula I, or a pharmaceutically acceptable salt or hydrate thereof:



(I), wherein:

ring A is an optionally substituted 5-6 member monocyclic aryl or monocyclic heteroaryl;

X is N, CH or C-halo;

R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, and CN, wherein any alkyl portion of R^1, R^3, R^4, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$;

R^2 and R^5 are each independently selected from: -(C_1-C_6 alkyl), -(C_1-C_6 alkyl)-C(O)-NH_2, -(C_1-C_6 alkyl)-CO_2H, -(C_2-C_6 alkenyl or alkynyl), -(C_1-C_6 alkylene)-N(R^6)-(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)(R^6), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1\text{-}2}$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1\text{-}2}$-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-S(O)$_{1\text{-}2}$-N(R^6)(R^6), -(C_1-C_4 alkylene)-S(O)$_{1\text{-}2}$-N(R^6)-(C_1-C_6 alkylene)-Q, -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)- (C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-S(O)$_{0\text{-}2}$-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-S(O)$_{0\text{-}2}$-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)-C(O)-N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6

alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-Q, wherein:

any alkyl or alkylene moiety present in R^2 and R^5 is optionally substituted with one or more -OH, -O(C_1-C_4 alkyl), -CO_2H, or halo;

any terminal methyl moiety present in R^2 and R^5 is optionally replaced with -CH_2OH, CF_3, -CH_2F, -CH_2Cl, C(O)CH_3, C(O)CF_3, CN, or CO_2H;

R^7 and R^8 are each independently selected from hydrogen and C_1-C_6 alkyl; and

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, any of which is optionally substituted; wherein

R^1 and R^3 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^4 and R^6 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^1 and R^2 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl; or

R^4 and R^5 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

wherein:

(i) when X is N and A is optionally substituted phenyl, then (a) neither N(R^7)C(R^4)(R^5)(R^6) nor N(R^8)C(R^1)(R^2)(R^3) is 4-[[2-[2-(2-aminoethoxy)ethoxy]ethyl]amino] and (b) N(R^7)C(R^4)(R^5)(R^6) and N(R^8)C(R^1)(R^2)(R^3) are not both NHEt, NH(n-propyl), NH(n-butyl), NH(n-docecyl), NH-[(4- methoxyphenyl)methyl], $NHCH_2CH_2CHO$, $NHCH_2CH_2OCH_3$, $NHCH_2CH_2OH$, $NHCH_2CH(OH)CH_3$, $NHCH_2CH_2OC(O)$phenyl, $NHCH_2CH_2CH_2OH$, $NHCH_2CH_2CH_2N(CH_3)$phenyl, $NHCH_2C(O)OCH_3$, $NHCH_2C(O)OCH_2CH_3$, $NHCH_2$phenyl, $NHCH(CH_3)CH_2CH_3$, or $NHCH_2CH_2OC(O)CH_3$;

(ii) when X is CH or C-Cl and A is phenyl optionally substituted with F, Cl or SO_2CH_3, then neither N(R^7)C(R^4)(R^5)(R^6) nor N(R^8)C(R^1)(R^2)(R^3) is $N(CH_3)CH_2C(O)NH$-i-propyl, $NHCH(CH_3)(CH_2)_3N(CH_2CH_3)_2$, $NHCH_2CH_2OH$, $NHCH_2CH_2OCH_3$, $NHCH_2CH_2OSO_3H$, $NHCH_2CH_2CH_2OCH_2CH_2O$-phenyl, $NHCH_2CH_2CH_2OH$, $NHCH_2CH_2CH_2OCH_3$, $NHCH_2CH(OH)CH_3$, $N(CH_2CH_3)_2$, NH-i-propyl, $NHCH_2CH_2NHC(O)OCH_3$,

$NHCH_2CH_2NHC(O)CH_3$, $NHCH_2CH_2NH_2$, or $NHCH_2$-phenyl;

(iii) when X is CH and A is optionally substituted pyridyl, then neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is $NHCH_2$-phenyl, $NHCH_2$-(2,4-difluorophenyl), $N(CH_3)CH_2CH_2C(O)OH$, $NHCH_2CH_2C(O)OH$, $NHCH_2CH_2C(O)OCH_2CH_3$, $NHCH_2CH_2C(O)O$-t-butyl, $NHCH_2CH_2C(O)NH_2$, $NHCH_2CH_2$-phenyl, $NHCH_2CH_2OH$, $NHCH_2CH_2NH_2$, $NHCH_2CH_2N(CH_3)_2$, or $NHCH_2CH_2CH_3$;

(iv) when X is CH and A is optionally substituted l-imidazolyl, optionally substituted 1-pyrrolyl or optionally substituted 1-pyrazolyl, then neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is $NH(CH_2)_7CH_3$, $NHCH_2$-(o-chloro-phenyl), or $NHCH_2CH_2OH$;

(v) when X is N and A is an optionally substituted pyridyl, then (A) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is NHC(O)-[2-chloro-4-(methylsulfonyl)], (B) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $NHC(O)C(CH_3)_3$, $NHC(O)CH=CH_2$, $NHC(O)C(CH_3)=CH_2$, $NHCH_2CH_2OH$, NH-cyclohexyl, $NHCH_2$-phenyl, NHC(O)phenyl, $NHC(O)(CH_2)_5NH_2$, $NHC(O)OCH_3$, $NHC(O)CH_3$, and NHC(O)NH-optionally substituted phenyl, and (C) when $N(R^7)C(R^4)(R^5)(R^6)$ is $NHC(CH_3)_3$, then $N(R^8)C(R^1)(R^2)(R^3)$ is not $NHCH_2$-phenyl or $NH-CH_2CH_3$;

(vi) when X is N and A is an optionally substituted heteroaryl, then $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $N(CH_2CH_3)_2$, $NHCH_2CH_2$-i-propyl, $NHCH_2CH(CH_3)_2$, and $NHC(O)CH_3$;

(vii) the compound is not selected from the group:

(1) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(2) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(3) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(3-nitrophenyl)-1,3,5-triazine-2,4-diamine,

(4) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine,

(5) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-trifluoromethoxy-phenyl)-1,3,5-triazine-2,4-diamine,

(6) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-t-butyl-phenyl)-1,3,5-triazine-2,4-diamine,

(7) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(2-thienyl)-1,3,5-triazine-2,4-diamine,

(8) N-(2-aminophenyl)-4-[[[4-[(2,3-dihydro-1H-inden-2-yl)amino]-6-phenyl-1,3,5-triazin-2-yl]amino]methyl]-benzamide,

(9) 2-chloro-N-[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-4-(methylsulfonyl)-benzamide,

(10) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(11) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]-acetamide,

(12) N^2-cyclopropyl-N^4-ethyl-6-[3-[(phenylmethyl)thio]-1H-1,2,4-triazol-1-yl]-1,3,5-triazine-2,4-diamine,

(13) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]- acetic acid methyl ester,

(14) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(2,4,6-trimethylphenyl)-1,3,5-triazine-2,4-diamine,

(15) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(16) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methylphenyl)-1,3,5-triazine-2,4-diamine,

(17) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-chlorophenyl)-1,3,5-triazine-2,4-diamine,

(18) N-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl] methyl]-4-fluoro-benzenesulfonamide,

(19) N^2-cyclopropyl-6-(3,5-dimethyl-1H-pyrazol-1-yl)-N^4-phenyl-1,3,5-triazine-2,4-diamine,

(20) N^2,N^4-dicyclohexyl-6-[3-(4-methoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-

1,3,5-triazine-2,4-diamine,

(21) N^2,N^4-dicyclohexyl-6-[3-(3,4-dimethoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(22) N^2,N^4-dicyclohexyl-6-[5-(methylthio)-3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(23) N^2,N^4-dicyclohexyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(24) 1,1'-[(6-phenyl-s-triazine-2,4-diyl)diimino]bis[dodecahydro-anthraquinone],

(25) 4,4'-[(6-phenyl-1,3,5-triazine-2,4- diyl)bis(iminomethylene)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(26) N-[4-[(4-aminobutyl)amino]-6-[5-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl] amino]-2-methylphenyl]-1,3,5-triazin-2-yl]-glycine,

(27) 4-[2-[[4-[(5-aminopentyl)amino]-6-(3- fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]- phenol,

(28) 4-[2-[[4-[(5-aminopentyl)amino]-6-(4- fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]- phenol,

(29) 6-(4-aminopyridin-3-yl)-N^2-benzyl-N^4-(tert-butyl)-1,3,5-triazine-2,4-diamine,

(30) N^2,N^4-bis(cyclohexylmethyl)-6-phenyl-1,3,5-triazine-2,4-diamine,

(31) 4,4'-[[6-[3,5-bis(1,1-dimethylethyl)-4- hydroxyphenyl]-1,3,5-triazine-2,4-diyl]bis(imino- 3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(32) 4,4'-[(6-phenyl-1,3,5-triazine-2,4- diyl)bis(imino-3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(33) N-[6-[(2,3-dihydro-1H-inden-2-yl)amino]-2-(2-pyridinyl)-4-pyrimidinyl]-β alanine,

(34) N^4-cyclopentyl-2-phenyl-N^6-(phenylmethyl)-4,6-pyrimidinediamine,

(35) 2-[[6-(bicyclo[2.2.1]hept-2-ylamino)-2-phenyl-4-pyrimidinyl]amino]-ethanol,

(36) N^2-isopropyl-6-phenyl-N4-(tetrahydro-2H-pyran-4-yl)-1,3,5-triazine-2,4-diamine,

(37) 2-chloro-4-(methylsulfonyl)-*N*-[4-[(phenylmethyl)amino]-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-benzamide,

(38) *N*-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl]methyl]-4-fluoro-benzenesulfonamide,

(39) [[4-[[[[[4-amino-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl]amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

(40) [[4-[[[[[4-[bis(hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl](hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

(41) 5-[4,6-bis(diethylamino)-1,3,5-triazin-2-yl]- 2*H*-tetrazole-2-acetic acid ethyl ester,

(42) N^2,N^2,N^4,N^4-tetraethyl-6-(2*H*-tetrazol-5-yl)-1,3,5-triazine-2,4-diamine, and

(43) *N*,*N*'-[6-[4-(acetylamino)-1,2,5-oxadiazol-3-yl]-1,3,5-triazine-2,4-diyl]bis-acetamide.

The compound of Formula I or as described in any one of the embodiments herein inhibits mutant IDH1or mutant IDH2. Also described herein are pharmaceutical compositions comprising a compound of Formula I, and methods of using such compositions to treat cancers characterized by the presence of a mutant IDH1 or mutant IDH2.

DETAILED DESCRIPTION

The details of construction and the arrangement of components set forth in the following description or illustrated in the drawings are not meant to be limiting. Other embodiments and different ways to practice the invention are expressly included. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of “including,” “comprising,” or “having,” “containing”, “involving”, and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

Definitions:

The term “halo” or “halogen” refers to any radical of fluorine, chlorine, bromine or iodine.

The term “alkyl” refers to a fully saturated or unsaturated hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_1-C_{12} alkyl indicates that the group may have from 1 to 12 (inclusive) carbon atoms in it. The term “haloalkyl” refers to an alkyl in which one or more hydrogen atoms are replaced by halo, and includes alkyl moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkyl). The terms “arylalkyl” or “aralkyl” refer to an alkyl moiety in which an alkyl hydrogen atom is replaced by an aryl group. Aralkyl includes groups in which more than one hydrogen atom has been replaced by an aryl group. Examples of “arylalkyl” or “aralkyl” include benzyl, 2-phenylethyl, 3-phenylpropyl, 9-fluorenyl, benzhydryl, and trityl groups. The term “alkyl” includes “alkenyl” and “alkynyl”.

The term “alkylene” refers to a divalent alkyl, e.g., $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and $-CH_2CH(CH_3)CH_2-$.

The term “alkenyl” refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms and having one or more double bonds. Examples of alkenyl groups include, but are not limited to, allyl, propenyl, 2-butenyl, 3-hexenyl and 3-octenyl groups. One of the double bond carbons may optionally be the point of attachment of the alkenyl substituent.

The term “alkynyl” refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms and characterized in having one or more triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, propargyl, and 3-hexynyl. One of the triple bond carbons may optionally be the point of attachment of the alkynyl substituent.

The term “alkoxy” refers to an -O-alkyl radical. The term “haloalkoxy” refers to an alkoxy in which one or more hydrogen atoms are replaced by halo, and includes alkoxy moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkoxy).

Unless otherwise specified, the term “aryl” refers to a fully aromatic monocyclic, bicyclic, or tricyclic hydrocarbon ring system. Examples of aryl moieties are phenyl, naphthyl, and anthracenyl. Unless otherwise specified, any ring atom in an aryl can be substituted by one or more substituents. The term “monocyclic aryl” means a monocyclic fully romatic hydrocarbon ring system, optionally substituted by one or more substituents which can not form a fused bicyclic or tricyclic ring.

The term “carbocyclyl” refers to a non-aromatic, monocyclic, bicyclic, or tricyclic hydrocarbon ring system. Carbocyclyl groups include fully saturated ring systems (e.g., cycloalkyls), and partially saturated ring systems. Carbocyclyl groups also include spirocyclic moieties. Examples of spirocyclic moieties include, but are not limited to, bicyclo[3.1.0]hexanyl, spiro[2.2]pentanyl, spiro[3.3]heptanyl, spiro[2.5]octanyl, spiro[3.5]nonanyl, spiro[4.5]decanyl, and spiro[3.6]decanyl. Unless otherwise specified, any ring atom in a carbocyclyl can be substituted by one or more substituents.

Bicyclic or tricyclic ring systems where an aryl is fused to a carbocyclyl and the point of attachment from the ring system to the rest of the molecule is through the non-aromatic ring are considered to be carbocyclyl (e.g., cycloalkyl). Examples of such carbocyclyl moieties include, but are not limited to, 2,3-dihydro-1H-indene and 1,2,3,4-tetrahydronaphthalene.

The term "cycloalkyl" as employed herein includes saturated cyclic, bicyclic, tricyclic, or polycyclic hydrocarbon groups having 3 to 12 carbons. Any ring atom can be substituted (e.g., by one or more substituents). Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclohexyl, methylcyclohexyl, adamantyl, and norbornyl.

Unless otherwise specified, the term "heteroaryl" refers to a fully aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (or the oxidized forms such as N^+-O^-, S(O) and $S(O)_2$). The term "monocyclic heteroaryl" means a monocyclic fully romatic ring system having 1-3 heteroatoms, optionally substituted by one or more substituents which can not form a fused bicyclic or tricyclic ring.

The term "heterocyclyl" refers to a nonaromatic, 3-10 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (or the oxidized forms such as N^+-O^-, S(O) and $S(O)_2$). The heteroatom may optionally be the point of attachment of the heterocyclyl substituent. Examples of heterocyclyl include, but are not limited to, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino, pyrrolinyl, pyrimidinyl, and pyrrolidinyl. Heterocyclyl groups include fully saturated ring systems, and partially saturated ring systems.

Bicyclic and tricyclic ring systems containing one or more heteroatoms and both aromatic and non-aromatic rings are considered to be heterocyclyl or heteroaryl groups. Bicyclic or tricyclic ring systems where an aryl or a heteroaryl is fused to a carbocyclyl or heterocyclyl and the point of attachment from the ring system to the rest of the molecule is through an aromatic ring are considered to be aryl or heteroaryl groups, respectively. Bicyclic or tricyclic ring systems where an aryl or a heteroaryl is fused to a carbocyclyl or heterocyclyl and the point of attachment from the ring system to the rest of the molecule is through the non-aromatic ring are considered to be carbocyclyl (e.g., cycloalkyl) or heterocyclyl groups, respectively.

Aryl, heteroaryl, carbocyclyl (including cycloalkyl), and heterocyclyl groups, either alone or a part of a group (e.g., the aryl portion of an aralkyl group), are optionally substituted at one or more substitutable atoms with, unless specified otherwise, substituents independently selected from: halo, -C≡N, C_1-C_4 alkyl, =O, -OR^b, -$OR^{b'}$, -SR^b, -$SR^{b'}$, -(C_1-C_4 alkyl)-N(R^b)(R^b), -(C_1-C_4 alkyl)-N(R^b)($R^{b'}$), -N(R^b)(R^b), -N(R^b)($R^{b'}$), -O-(C_1-C_4 alkyl)-N(R^b)(R^b), -O-(C_1-C_4 alkyl)-N(R^b)($R^{b'}$), -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl)-N(R^b)(R^b), -(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl)-N(R^b)($R^{b'}$), -C(O)-N(R^b)(R^b), -(C_1-C_4 alkyl)-C(O)-N(R^b)(R^b), -(C_1-C_4 alkyl)-C(O)-N(R^b)($R^{b'}$), -$OR^{b'}$, $R^{b'}$, -C(O)(C_1-C_4 alkyl), -C(O)$R^{b'}$, -C(O)N($R^{b'}$)(R^b), -N(R^b)C(O)(R^b), -N(R^b)C(O)($R^{b'}$), -N(R^b)SO_2(R^b), -SO_2N(R^b)(R^b), -N(R^b)SO_2($R^{b'}$), and -SO_2N(R^b)($R^{b'}$), wherein any alkyl substituent is optionally further substituted with one or more of -OH, -O-(C_1-C_4 alkyl), halo, -NH_2, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$;

each R^b is independently selected from hydrogen, and -C_1-C_4 alkyl; or

two R^bs are taken together with the nitrogen atom to which they are bound to form a 4- to 8-membered heterocyclyl optionally comprising one additional heteroatom selected from N, S, and O; and

each $R^{b'}$ is independently selected from C_3-C_7 carbocyclyl, phenyl, heteroaryl, and heterocyclyl, wherein one or more substitutable positions on said phenyl, cycloalkyl, heteroaryl or heterocycle substituent is optionally further substituted with one or more of -(C_1-C_4 alkyl), -(C_1-C_4 fluoroalkyl), -OH, -O-(C_1-C_4 alkyl), -O-(C_1-C_4 fluoroalkyl), halo, -NH_2, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$.

Heterocyclyl groups, either alone or as part of a group, are optionally substituted on one or more any substitutable nitrogen atom with oxo, -C_1-C_4 alkyl, or fluoro-substituted C_1-C_4 alkyl.

The term “substituted” refers to the replacement of a hydrogen atom by another group.

The term “bodily fluid” includes one or more of amniotic fluid surrounding a fetus, aqueous humour, blood (*e.g.,* blood plasma), serum, Cerebrospinal fluid, cerumen, chyme, Cowper's fluid, female ejaculate, interstitial fluid, lymph, breast milk, mucus (*e.g.,* nasal drainage or phlegm), pleural fluid, pus, saliva, sebum, semen, serum, sweat, tears, urine, vaginal secretion, or vomit.

As used herein, the terms “inhibit” or “prevent” include both complete and partial inhibition and prevention. An inhibitor may completely or partially inhibit the intended target.

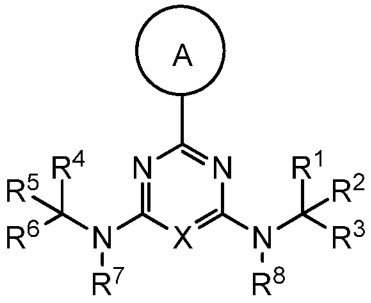
The term “treat” means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease/disorder (e.g., a cancer), lessen the severity of the disease/disorder (e.g., a cancer) or improve the symptoms associated with the disease/disorder (e.g., a cancer).

As used herein, an amount of a compound effective to treat a disorder, or a “therapeutically effective amount” refers to an amount of the compound which is effective, upon single or multiple dose administration to a subject, in treating a cell, or in curing, alleviating, relieving or improving a subject with a disorder beyond that expected in the absence of such treatment.

As used herein, the term “subject” is intended to include human and non-human animals. Exemplary human subjects include a human patient (referred to as a patient) having a disorder, e.g., a disorder described herein or a normal subject. The term “non-human animals” of one aspect of the invention includes all vertebrates, e.g., non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, e.g., sheep, dog, cat, cow, pig, etc.

Compounds

Provided is a compound of Formula I, or a pharmaceutically acceptable salt or hydrate thereof:



(I), wherein:

ring A is an optionally substituted 5-6 member monocyclic aryl or monocyclic heteroaryl;

X is N or CH;

R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, and CN, wherein any alkyl portion of R^1, R^3, R^4, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$;

R^2 and R^5 are each independently selected from: -(C_1-C_6 alkyl), -(C_1-C_6 alkyl)-C(O)-NH_2, -(C_1-C_6 alkyl)-CO_2H, -(C_2-C_6 alkenyl or alkynyl), -(C_1-C_6 alkylene)-N(R^6)-(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)(R^6), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1\text{-}2}$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1\text{-}2}$-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-S(O)$_{1\text{-}2}$-N(R^6)(R^6), -(C_1-C_4 alkylene)-S(O)$_{1\text{-}2}$-N(R^6)-(C_1-C_6 alkylene)-Q, -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)- (C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-S(O)$_{0\text{-}2}$-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-S(O)$_{0\text{-}2}$-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)-C(O)-N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-Q, wherein:

any alkyl or alkylene moiety present in R^2 and R^5 is optionally substituted with one or more -OH, -O(C_1-C_4 alkyl), -CO_2H, or halo;

any terminal methyl moiety present in R^2 and R^5 is optionally replaced with -CH_2OH, CF_3, -CH_2F, -CH_2Cl, C(O)CH_3, C(O)CF_3, CN, or CO_2H;

R^7 and R^8 are each independently selected from hydrogen and C_1-C_6 alkyl; and

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, any of which is optionally substituted; wherein

R^1 and R^3 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^4 and R^6 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^1 and R^2 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl; or

R^4 and R^5 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

wherein:

(i) when X is N and A is optionally substituted phenyl, then (a) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is 4-[[2-[2-(2-aminoethoxy)ethoxy]ethyl]amino] and (b) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both NHEt, NH(n-propyl), NH(n-butyl), NH(n-docecyl), NH-[(4- methoxyphenyl)methyl], $NHCH_2CH_2CHO$, $NHCH_2CH_2OCH_3$, $NHCH_2CH_2OH$, $NHCH_2CH(OH)CH_3$, $NHCH_2CH_2OC(O)$phenyl, $NHCH_2CH_2CH_2OH$, $NHCH_2CH_2CH_2N(CH_3)$phenyl, $NHCH_2C(O)OCH_3$, $NHCH_2C(O)OCH_2CH_3$, $NHCH_2$phenyl, $NHCH(CH_3)CH_2CH_3$, or $NHCH_2CH_2OC(O)CH_3$;

(ii) when X is CH or C-Cl and A is phenyl optionally substituted with F, Cl or SO_2CH_3, then neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is $N(CH_3)CH_2C(O)NH$-i-propyl, $NHCH(CH_3)(CH_2)_3N(CH_2CH_3)_2$, $NHCH_2CH_2OH$, $NHCH_2CH_2OCH_3$, $NHCH_2CH_2OSO_3H$, $NHCH_2CH_2CH_2OCH_2CH_2O$-phenyl, $NHCH_2CH_2CH_2OH$, $NHCH_2CH_2CH_2OCH_3$, $NHCH_2CH(OH)CH_3$, $N(CH_2CH_3)_2$, NH-i-propyl, $NHCH_2CH_2NHC(O)OCH_3$, $NHCH_2CH_2NHC(O)CH_3$, $NHCH_2CH_2NH_2$, or $NHCH_2$-phenyl;

(iii) when X is CH and A is optionally substituted pyridyl, then neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is $NHCH_2$-phenyl, $NHCH_2$-(2,4-difluorophenyl), $N(CH_3)CH_2CH_2C(O)OH$, $NHCH_2CH_2C(O)OH$, $NHCH_2CH_2C(O)OCH_2CH_3$, $NHCH_2CH_2C(O)O$-t-butyl, $NHCH_2CH_2C(O)NH_2$, $NHCH_2CH_2$-phenyl, $NHCH_2CH_2OH$, $NHCH_2CH_2NH_2$, $NHCH_2CH_2N(CH_3)_2$, or $NHCH_2CH_2CH_3$;

(iv) when X is CH and A is optionally substituted l-imidazolyl, optionally substituted 1-pyrrolyl or optionally substituted 1-pyrazolyl, then neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is $NH(CH_2)_7CH_3$, $NHCH_2$-(o-chloro-phenyl), or $NHCH_2CH_2OH$;

(v) when X is N and A is an optionally substituted pyridyl, then (A) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is NHC(O)-[2-chloro-4-(methylsulfonyl)], (B) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $NHC(O)C(CH_3)_3$, $NHC(O)CH{=}CH_2$, $NHC(O)C(CH_3){=}CH_2$, $NHCH_2CH_2OH$, NH-cyclohexyl, $NHCH_2$-phenyl, NHC(O)phenyl, $NHC(O)(CH_2)_5NH_2$, $NHC(O)OCH_3$, $NHC(O)CH_3$, and NHC(O)NH-optionally substituted phenyl, and (C) when $N(R^7)C(R^4)(R^5)(R^6)$ is $NHC(CH_3)_3$, then $N(R^8)C(R^1)(R^2)(R^3)$ is not $NHCH_2$-phenyl or $NH\text{-}CH_2CH_3$;

(vi) when X is N and A is an optionally substituted heteroaryl, then $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $N(CH_2CH_3)_2$, $NHCH_2CH_2$-i-propyl, $NHCH_2CH(CH_3)_2$, and $NHC(O)CH_3$;

(vii) the compound is not selected from the group:

(1) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(2) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(3) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(3-nitrophenyl)-1,3,5-triazine-2,4-diamine,

(4) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine,

(5) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-trifluoromethoxy-phenyl)-1,3,5-triazine-2,4-diamine,

(6) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-t-butyl-phenyl)-1,3,5-triazine-2,4-diamine,

(7) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(2-thienyl)-1,3,5-triazine-2,4-diamine,

(8) N-(2-aminophenyl)-4-[[[4-[(2,3-dihydro-1H-inden-2-yl)amino]-6-phenyl-1,3,5-triazin-2-yl]amino]methyl]-benzamide,

(9) 2-chloro-N-[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-4-(methylsulfonyl)-benzamide,

(10) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(11) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]-acetamide,

(12) N^2-cyclopropyl-N^4-ethyl-6-[3-[(phenylmethyl)thio]-1H-1,2,4-triazol-1-yl]-1,3,5-triazine-2,4-diamine,

(13) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]- acetic acid methyl ester,

(14) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(2,4,6-trimethylphenyl)-1,3,5-triazine-2,4-diamine,

(15) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(16) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methylphenyl)-1,3,5-triazine-2,4-diamine,

(17) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-chlorophenyl)-1,3,5-triazine-2,4-diamine,

(18) N-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl] methyl]-4-fluoro-benzenesulfonamide,

(19) N^2-cyclopropyl-6-(3,5-dimethyl-1H-pyrazol-1-yl)-N^4-phenyl-1,3,5-triazine-2,4-diamine,

(20) N^2,N^4-dicyclohexyl-6-[3-(4-methoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(21) N^2,N^4-dicyclohexyl-6-[3-(3,4-dimethoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(22) N^2,N^4-dicyclohexyl-6-[5-(methylthio)-3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(23) N^2,N^4-dicyclohexyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(24) 1,1'-[(6-phenyl-s-triazine-2,4-diyl)diimino]bis[dodecahydro-anthraquinone],

(25) 4,4'-[(6-phenyl-1,3,5-triazine-2,4- diyl)bis(iminomethylene)]bis[2,6-bis(1,1-

dimethylethyl)-phenol,

(26) N-[4-[(4-aminobutyl)amino]-6-[5-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl] amino]-2-methylphenyl]-1,3,5-triazin-2-yl]-glycine,

(27) 4-[2-[[4-[(5-aminopentyl)amino]-6-(3- fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]- phenol,

(28) 4-[2-[[4-[(5-aminopentyl)amino]-6-(4- fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]- phenol,

(29) 6-(4-aminopyridin-3-yl)-N^{2}-benzyl-N^{4}-(tert-butyl)-1,3,5-triazine-2,4-diamine,

(30) N^{2},N^{4}-bis(cyclohexylmethyl)-6-phenyl-1,3,5-triazine-2,4-diamine,

(31) 4,4'-[[6-[3,5-bis(1,1-dimethylethyl)-4- hydroxyphenyl]-1,3,5-triazine-2,4-diyl]bis(imino- 3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(32) 4,4'-[(6-phenyl-1,3,5-triazine-2,4- diyl)bis(imino-3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(33) N-[6-[(2,3-dihydro-1H-inden-2-yl)amino]-2-(2-pyridinyl)-4-pyrimidinyl]-βalanine,

(34) N^{4}-cyclopentyl-2-phenyl-N^{6}-(phenylmethyl)-4,6-pyrimidinediamine,

(35) 2-[[6-(bicyclo[2.2.1]hept-2-ylamino)-2-phenyl-4-pyrimidinyl]amino]-ethanol,

(36) N^{2}-isopropyl-6-phenyl-N4-(tetrahydro-2H-pyran-4-yl)-1,3,5-triazine-2,4-diamine,

(37) 2-chloro-4-(methylsulfonyl)-*N*-[4-[(phenylmethyl)amino]-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-benzamide,

(38) *N*-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl]methyl]-4-fluoro-benzenesulfonamide,

(39) [[4-[[[[[4-amino-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl]amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

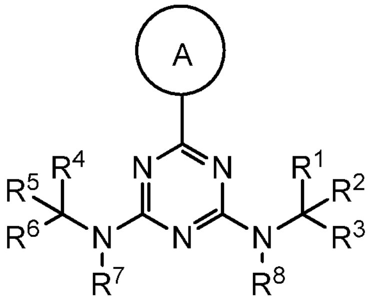
(40) [[4-[[[[[4-[bis(hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl](hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

(41) 5-[4,6-bis(diethylamino)-1,3,5-triazin-2-yl]- 2*H*-tetrazole-2-acetic acid ethyl ester,

(42) N^{2},N^{2},N^{4},N^{4}-tetraethyl-6-(2*H*-tetrazol-5-yl)-1,3,5-triazine-2,4-diamine, and

(43) *N*,*N*'-[6-[4-(acetylamino)-1,2,5-oxadiazol-3-yl]-1,3,5-triazine-2,4-diyl]bis-acetamide.

Also provided is a compound of Formula Ia, or a pharmaceutically acceptable salt or hydrate thereof:



(Ia), wherein:

ring A is an optionally substituted 5-6 member monocyclic aryl or monocyclic heteroaryl;

R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, and CN, wherein any alkyl portion of R^1, R^3, R^4, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$;

R^2 and R^5 are each independently selected from: -(C_1-C_6 alkyl), -(C_1-C_6 alkyl)-C(O)-NH_2, -(C_1-C_6 alkyl)-CO_2H, -(C_2-C_6 alkenyl or alkynyl), -(C_1-C_6 alkylene)-N(R^6)-(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)(R^6), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1-2}$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1-2}$-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-S(O)$_{1-2}$-N(R^6)(R^6), -(C_1-C_4 alkylene)-S(O)$_{1-2}$-N(R^6)-(C_1-C_6 alkylene)-Q, -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)- (C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-S(O)$_{0-2}$-(C_1-C_6

alkyl), -(C_0-C_6 alkylene)-S(O)$_{0\text{-}2}$-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)-C(O)-N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-Q, wherein:

any alkyl or alkylene moiety present in R^2 and R^5 is optionally substituted with one or more -OH, -O(C_1-C_4 alkyl), -CO_2H, or halo;

any terminal methyl moiety present in R^2 and R^5 is optionally replaced with -CH_2OH, CF_3, -CH_2F, -CH_2Cl, $C(O)CH_3$, $C(O)CF_3$, CN, or CO_2H;

R^7 and R^8 are each independently selected from hydrogen and C_1-C_6 alkyl; and

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, any of which is optionally substituted; wherein

R^1 and R^3 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^4 and R^6 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^1 and R^2 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl; or

R^4 and R^5 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

wherein:

(i) when A is optionally substituted phenyl, then (a) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is 4-[[2-[2-(2-aminoethoxy)ethoxy]ethyl]amino] and (b) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both NHEt, NH(n-propyl), NH(n-butyl), NH(n-dodecyl), NH-[(4- methoxyphenyl)methyl], $NHCH_2CH_2CHO$, $NHCH_2CH_2OCH_3$, $NHCH_2CH_2OH$, $NHCH_2CH(OH)CH_3$, $NHCH_2CH_2OC(O)$phenyl, $NHCH_2CH_2CH_2OH$, $NHCH_2CH_2CH_2N(CH_3)$phenyl, $NHCH_2C(O)OCH_3$, $NHCH_2C(O)OCH_2CH_3$, $NHCH_2$phenyl, $NHCH(CH_3)CH_2CH_3$, or $NHCH_2CH_2OC(O)CH_3$;

(ii) when X is N and A is an optionally substituted pyridyl, then (A) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is NHC(O)-[2-chloro-4-(methylsulfonyl)], (B) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $NHC(O)C(CH_3)_3$, $NHC(O)CH{=}CH_2$, $NHC(O)C(CH_3){=}CH_2$, $NHCH_2CH_2OH$, NH-cyclohexyl, $NHCH_2$-phenyl, NHC(O)phenyl,

$NHC(O)(CH_2)_5NH_2$, $NHC(O)OCH_3$, $NHC(O)CH_3$, and NHC(O)NH-optionally substituted phenyl, and (C) when $N(R^7)C(R^4)(R^5)(R^6)$ is $NHC(CH_3)_3$, then $N(R^8)C(R^1)(R^2)(R^3)$ is not $NHCH_2$-phenyl or $NH\text{-}CH_2CH_3$;

(iii) when X is N and A is an optionally substituted heteroaryl, then $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $N(CH_2CH_3)_2$, $NHCH_2CH_2$-i-propyl, $NHCH_2CH(CH_3)_2$, and $NHC(O)CH_3$;

(iv) the compound is not selected from the group:

(1) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(2) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(3) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(3-nitrophenyl)-1,3,5-triazine-2,4-diamine,

(4) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine,

(5) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-trifluoromethoxy-phenyl)-1,3,5-triazine-2,4-diamine,

(6) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-t-butyl-phenyl)-1,3,5-triazine-2,4-diamine,

(7) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(2-thienyl)-1,3,5-triazine-2,4-diamine,

(8) N-(2-aminophenyl)-4-[[[4-[(2,3-dihydro-1H-inden-2-yl)amino]-6-phenyl-1,3,5-triazin-2-yl]amino]methyl]-benzamide,

(9) 2-chloro-N-[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-4-(methylsulfonyl)-benzamide,

(10) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(11) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]-acetamide,

(12) N^2-cyclopropyl-N^4-ethyl-6-[3-[(phenylmethyl)thio]-1H-1,2,4-triazol-1-yl]-1,3,5-triazine-2,4-diamine,

(13) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]- acetic acid methyl ester,

(14) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(2,4,6-trimethylphenyl)-1,3,5-triazine-2,4-diamine,

(15) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(16) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methylphenyl)-1,3,5-triazine-2,4-diamine,

(17) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-chlorophenyl)-1,3,5-triazine-2,4-diamine,

(18) N-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl] methyl]-4-fluoro-benzenesulfonamide,

(19) N^2-cyclopropyl-6-(3,5-dimethyl-1H-pyrazol-1-yl)-N^4-phenyl-1,3,5-triazine-2,4-diamine,

(20) N^2,N^4-dicyclohexyl-6-[3-(4-methoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(21) N^2,N^4-dicyclohexyl-6-[3-(3,4-dimethoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(22) N^2,N^4-dicyclohexyl-6-[5-(methylthio)-3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(23) N^2,N^4-dicyclohexyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(24) 1,1'-[(6-phenyl-s-triazine-2,4-diyl)diimino]bis[dodecahydro-anthraquinone],

(25) 4,4'-[(6-phenyl-1,3,5-triazine-2,4- diyl)bis(iminomethylene)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(26) N-[4-[(4-aminobutyl)amino]-6-[5-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl] amino]-2-methylphenyl]-1,3,5-triazin-2-yl]-glycine,

(27) 4-[2-[[4-[(5-aminopentyl)amino]-6-(3-fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]-

phenol,

(28) 4-[2-[[4-[(5-aminopentyl)amino]-6-(4-fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]-phenol,

(29) 6-(4-aminopyridin-3-yl)-N^2-benzyl-N^4-(tert-butyl)-1,3,5-triazine-2,4-diamine,

(30) N^2,N^4-bis(cyclohexylmethyl)-6-phenyl-1,3,5-triazine-2,4-diamine,

(31) 4,4'-[[6-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,5-triazine-2,4-diyl]bis(imino-3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(32) 4,4'-[(6-phenyl-1,3,5-triazine-2,4-diyl)bis(imino-3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(33) N^2-isopropyl-6-phenyl-N4-(tetrahydro-2H-pyran-4-yl)-1,3,5-triazine-2,4-diamine,

(34) 2-chloro-4-(methylsulfonyl)-*N*-[4-[(phenylmethyl)amino]-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-benzamide,

(35) *N*-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl]methyl]-4-fluoro-benzenesulfonamide,

(36) [[4-[[[[[4-amino-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl]amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

(37) [[4-[[[[[4-[bis(hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl](hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

(38) 5-[4,6-bis(diethylamino)-1,3,5-triazin-2-yl]- 2*H*-tetrazole-2-acetic acid ethyl ester,

(39) N^2,N^2,N^4,N^4-tetraethyl-6-(2*H*-tetrazol-5-yl)-1,3,5-triazine-2,4-diamine, and

(40) *N*,*N*'-[6-[4-(acetylamino)-1,2,5-oxadiazol-3-yl]-1,3,5-triazine-2,4-diyl]bis-acetamide.

In some embodiments, R^1 and R^4 are each independently selected from hydrogen, $-CH_3$, $-CH_2CH_3$,$-CH_2OH$, CN, or R^1 and R^3 are taken together to form =O; or R^4 and R^6 are optionally taken together with the carbon atom to which they are attached to form C(=O).

In some embodiments, R^1 and R^2 are taken together to form carbocyclyl or heterocyclyl, either of which is optionally substituted with up to 3 substituents independently selected from halo, e.g., fluoro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -CN, =O, -OH, and -C(O)C_1-C_4 alkyl.

In some embodiments, R^4 and R^5 are taken together to form carbocyclyl or heterocyclyl, either of which is optionally substituted with up to 3 substituents independently selected from halo, e.g., fluoro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, -CN, =O, -OH, and -C(O)C_1-C_4 alkyl.

In some embodiments, R^2 and R^5 are each independently selected from: -(C_1-C_4 alkyl) optionally substituted with halo, e.g., fluoro or -OH; -(C_0-C_4 alkylene)-O-(C_1-C_4 alkyl), -(C_0-C_2 alkylene)-N(R^6)-(C_1-C_6 alkyl), -(C_0-C_2 alkylene)-Q, and -O-(C_0-C_2 alkylene)-Q, wherein Q is optionally substituted with up to 3 substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, =O, -C(O)-C_1-C_4 alkyl, -CN, and halo. In one aspect of these embodiments, Q is selected from pyridinyl, tetrahydrofuranyl, cyclobutyl, cyclopropyl, phenyl, pyrazolyl, morpholinyl and oxetanyl, wherein Q is optionally substituted with up to 2 substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, =O, fluoro, chloro, and bromo. In another aspect of these embodiments, Q is selected from pyridinyl, tetrahydrofuranyl, cyclobutyl, cyclopropyl, phenyl, pyrazolyl, morpholinyl and oxetanyl, wherein Q is optionally substituted with up to 2 substituents independently selected from -CH_3 and =O.

In some embodiments, R^1 and R^2 are taken together to form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, oxetanyl, bicyclo[2.2.1]heptanyl, oxobicyclo[3.1.0]hexanyl, azetidinyl, any of which is optionally substituted with up to 2 substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, -OH, -C(O)CH_3, fluoro, and chloro.

In some embodiments, R^4 and R^5 are taken together to form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, oxetanyl, bicyclo[2.2.1]heptanyl, oxobicyclo[3.1.0]hexanyl, azetidinyl, any of which is optionally substituted with up to 2 substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, -OH, -C(O)CH_3, fluoro, and chloro.

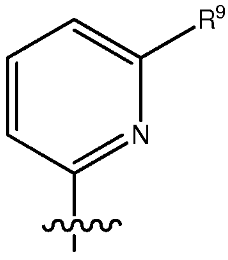
In some embodiments, ring A is an optionally substituted 6-membered monocyclic aryl. In some embodiments, ring A is an optionally substituted 5-6 membered heteroaryl. In some embodiments, ring A is an optionally substituted 6-membered heteroaryl.

In some embodiments, ring A is selected from phenyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and thiazolyl, wherein ring A is optionally substituted with up to two substituents independently selected from halo, -C_1-C_4 alkyl, -C_1-C_4 haloalkyl, -C_1-C_4 hydroxyalkyl, -NH-$S(O)_2$-(C_1-C_4 alkyl), -$S(O)_2$NH(C_1-C_4 alkyl), -CN, -$S(O)_2$-(C_1-C_4 alkyl), C_1-C_4 alkoxy, -NH(C_1-C_4 alkyl), -OH, -OCF_3, -CN, -NH_2, -C(O)NH_2, -C(O)NH(C_1-C_4 alkyl), -C(O)-N(C_1-C_4 alkyl)$_2$, and cyclopropyl optionally substituted with OH.

In some embodiments, ring A is selected from phenyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and thiazolyl, wherein ring A is optionally substituted with up to two substituents independently selected from halo, -C_1-C_4 alkyl, -C_1-C_4 haloalkyl, -C_1-C_4 hydroxyalkyl, -NH-$S(O)_2$-(C_1-C_4 alkyl), -$S(O)_2$NH(C_1-C_4 alkyl), -CN, -$S(O)_2$-(C_1-C_4 alkyl), C_1-C_4 alkoxy, -NH(C_1-C_4 alkyl), -OH, -CN, and -NH_2.

In some embodiments, ring A is monocyclic heteroaryl optionally substituted with halo, -C_1-C_4 alkyl, -C_1-C_4 haloalkyl, -O-C_1-C_4 haloalkyl, -OH, -CN, and -NH_2; R^1, R^3, R^4, and R^6 are each independently selected from hydrogen and C_1-C_4 alkyl; and R^2 and R^5 are each independently -(C_0-C_6 alkylene)-Q; or R^1 and R^2 are optionally taken together to form an optionally substituted carbocyclyl, an optionally substituted heterocyclyl or an optionally substituted heteroaryl; or R^4 and R^5 are optionally taken together to form an optionally substituted carbocyclyl, an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

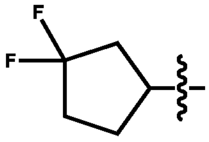
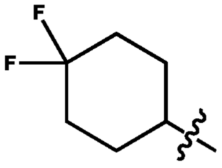
In some embodiments, ring A is pyridinyl optionally substituted with halo or -C_1-C_4 haloalkyl. In some embodiments, ring A is pyridinyl optionally substituted with halo, e.g., chloro or fluoro. In some embodiments, ring A is pyridin-2-yl substituted with -C_1-C_4 haloalkyl, e.g., -CHF_2 and CF_3. In some embodiments, ring A is:

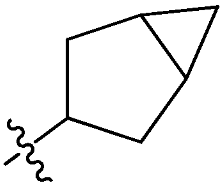


, wherein R^9 is selected from hydrogen, halo, and -C_1-C_4 haloalkyl. In some embodiments, R^9 is chloro or fluoro. In some embodiments, R^9 is -CHF_2 or CF_3. In some embodiments, R^9 is CF_3 or chloro. In some embodiments, R^9 is CF_3.

In some embodiments, ring A is pyridinyl optionally substituted with halo or -C_1-C_4 haloalkyl. In some embodiments, ring A is pyridinyl substituted with halo, e.g., chloro or fluoro.

In some embodiments, ring A is pyridinyl substituted with -C_1-C_4 haloalkyl, e.g., -CHF_2 and CF_3. In some embodiments, R^1, R^3, R^4, and R^6 are each independently selected from hydrogen and C_1-C_4 alkyl; and R^2 and R^5 are each independently -(C_0-C_6 alkylene)-Q. In some embodiments, R^1 and R^4 are each hydrogen. In some embodiments, R^3 and R^6 are each C_1-C_4 alkyl. In some embodiments, Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, any of which is optionally substituted. In some embodiments, Q is optionally substituted carbocyclyl. In some embodiments, Q is optionally substituted cyclopropyl. In some embodiments, Q is unsubstituted cyclopropyl. In some embodiments, R^2 and R^5 are each independently unsubstituted cyclopropyl. In some embodiments, R^1 and R^4 are each hydrogen, R^3 and R^6 are each -CH_3, and R^2 and R^5 are each unsubstituted cyclopropyl. In some embodiments, R^2 is -(C_0-C_6 alkylene)-cyclopropyl and R^5 is -(C_0-C_6 alkylene)-aryl, *e.g.*, optionally substituted phenyl. In some embodiments, R^2 is cyclopropyl and R^5 is phenyl substituted with halo, *e.g.*, fluoro.

In some embodiments, ring A is pyridinyl optionally substituted with halo or -C_1-C_4 haloalkyl. In some embodiments, ring A is pyridinyl substituted with halo, e.g., chloro or fluoro. In some embodiments, ring A is pyridinyl substituted with -C_1-C_4 haloalkyl, e.g., -CHF_2 and CF_3. In some embodiments, R^3 and R^6 are each independently selected from hydrogen and C_1-C_4 alkyl; R^1 and R^2 are taken together to form an optionally substituted carbocyclyl; and R^4 and R^5 are taken together to form an optionally substituted carbocyclyl. In some embodiments, R^1 and R^2 are taken together to form a cyclopentyl or cyclohexyl, each optionally substituted. In some embodiments, R^4 and R^5 are taken together to form a cyclopentyl or cyclohexyl, each optionally substituted. In some embodiments, R^1 and R^2 are taken together to form a cyclopentyl or cyclohexyl, each substituted by one or more halo, e.g., fluoro; and R^4 and R^5 are taken together to form a cyclobutyl, cyclopentyl or cyclohexyl, each substituted by one or more halo, e.g., fluoro. In some embodiments, R^1 and R^2 are taken together to form a bicyclo[3.1.0]hexanyl; and R^4 and R^5 are taken together to form a bicyclo[3.1.0]hexanyl. In some embodiments, R^1 and R^2 taken together, and R^4 and R^5 taken together form:  or . In some embodiments, R^1 and R^2 taken together, and R^4 and R^5 taken together form:



.

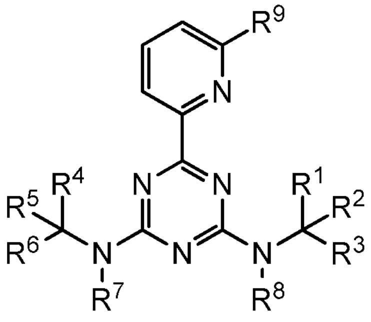
In som embodiments, ring A is pyridinyl optionally substituted with halo or -C_1-C_4 haloalkyl. In some embodiments, ring A is pyridinyl substituted with halo, e.g., chloro or fluoro. In some embodiments, ring A is pyridinyl substituted with -C_1-C_4 haloalkyl, e.g., -CHF_2 and CF_3. In some embodiments, R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, and -CN, wherein any alkyl portion of R^1, R^3, R^4, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl; and R^2 and R^5 are each independently selected from -(C_1-C_6 alkyl) and -(C_0-C_6 alkylene)-Q. In some embodiments, R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, and -CN; and R^2 and R^5 are each independently -(C_1-C_6 alkyl) and -(C_0-C_6 alkylene)-Q. In some embodiments, R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, and -CN; R^2 is -(C_1-C_6 alkyl); and R^5 is -(C_0-C_6 alkylene)-Q, wherein Q is optionally substituted carbocyclyl. In some embodiments, Q is unsubstituted carbocyclyl. In some embodiments, Q is cyclopropyl.

In some embodiments, ring A is pyridinyl optionally substituted with halo or -C_1-C_4 haloalkyl. In some embodiments, ring A is pyridinyl substituted with -C_1-C_4 haloalkyl, e.g., -CHF_2 and CF_3. In some embodiments, R^1, R^3, and R^6 are each independently selected from hydrogen and C_1-C_4 alkyl, wherein any alkyl portion of R^1, R^3, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$; R^2 is -(C_0-C_6 alkylene)-Q; and R^4 and R^5 taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl or optionally substituted heteroaryl. In some embodiments, R^4 and R^5 taken together form an optionally substituted carbocyclyl. In some embodiments, the carbocyclyl is selected from cyclopentyl and cyclohexyl optionally substituted with -OH, -O(C_1-C_4 alkyl), -CO_2H, or halo. In some embodiments, R^4 and R^5 taken together form an optionally substituted heterocyclyl optionally substituted with -OH, -O(C_1-C_4 alkyl), -CO_2H, or halo. In some embodiments, R^4 and R^5 taken together form an optionally substituted tetrahydrofuran. In some embodiments, R^1, R^3, and R^6 are each independently selected from hydrogen and C_1-C_4 alkyl, wherein any alkyl portion of R^1, R^3, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl; R^2 is -(C_0-C_6 alkylene)-Q; and R^5 is C_1-C_4 alkyl.

In some embodiments, R^7 is H. In some embodiments, R^8 is H. In some embodiments, both R^7 and R^8 are H.

In some embodiments, ring A, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 are selected from any one of the preceding embodiments.

Also provided is a compound of Formula Ib, or pharmaceutically acceptable salt or hydrate thereof:



(Ib), wherein:

R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, and CN, wherein any alkyl portion of R^1, R^3, R^4, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$;

R^2 and R^5 are each independently selected from: -(C_1-C_6 alkyl), -(C_1-C_6 alkyl)-C(O)-NH_2, -(C_1-C_6 alkyl)-CO_2H, -(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-Q, wherein:

any alkyl or alkylene moiety present in R^2 and R^5 is optionally substituted with one or more -OH, -O(C_1-C_4 alkyl), -CO_2H, or halo;

any terminal methyl moiety present in R^2 and R^5 is optionally replaced with -CH_2OH, CF_3, -CH_2F, -CH_2Cl, C(O)CH_3, C(O)CF_3, CN, or CO_2H;

R^7 and R^8 are each independently selected from hydrogen and C_1-C_6 alkyl;

R^9 is selected from hydrogen, halo, and -C_1-C_4 haloalkyl; and

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, any of which is optionally substituted; wherein

R^1 and R^3 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^4 and R^6 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^1 and R^2 are optionally taken together to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl; or

R^4 and R^5 are optionally taken together to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl;

wherein

when X is N and A is an optionally substituted pyridyl, then (A) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is NHC(O)-[2-chloro-4-(methylsulfonyl)], (B) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $NHC(O)C(CH_3)_3$, $NHC(O)CH=CH_2$, $NHC(O)C(CH_3)=CH_2$, $NHCH_2CH_2OH$, NH-cyclohexyl, $NHCH_2$-phenyl, NHC(O)phenyl, $NHC(O)(CH_2)_5NH_2$, $NHC(O)OCH_3$, $NHC(O)CH_3$, and NHC(O)NH-optionally substituted phenyl, and (C) when $N(R^7)C(R^4)(R^5)(R^6)$ is $NHC(CH_3)_3$, then $N(R^8)C(R^1)(R^2)(R^3)$ is not $NHCH_2$-phenyl or NH-CH_2CH_3; and

wherein the compound is not:

(1) 2-chloro-N-[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-4-(methylsulfonyl)-benzamide,

(2) N-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl] methyl]-4-fluoro-benzenesulfonamide,

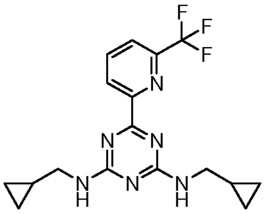
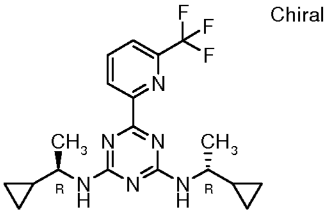
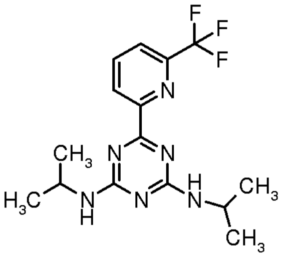
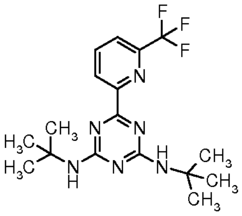
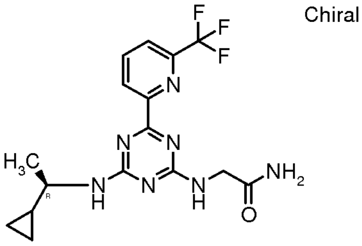
(3) 2-chloro-4-(methylsulfonyl)-*N*-[4-[(phenylmethyl)amino]-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-benzamide, or

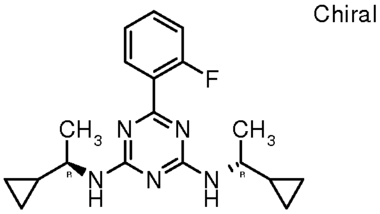
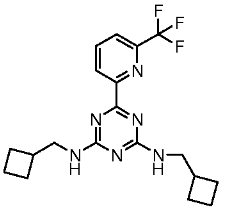
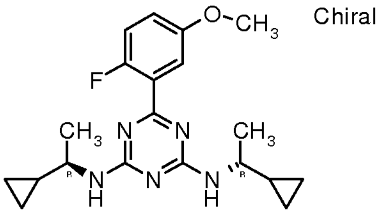
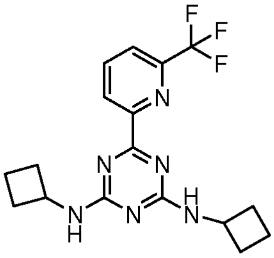
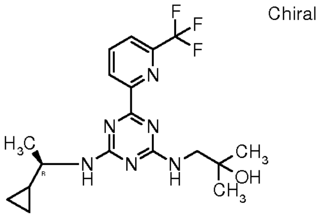
(4) *N*-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl]methyl]-4-fluoro-benzenesulfonamide.

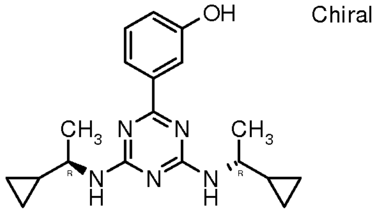
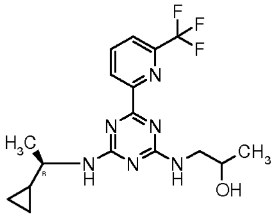
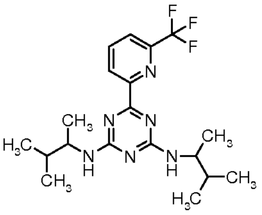
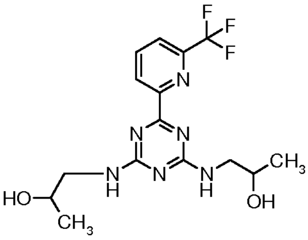
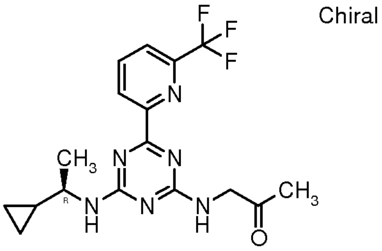
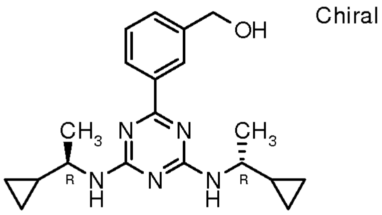
Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

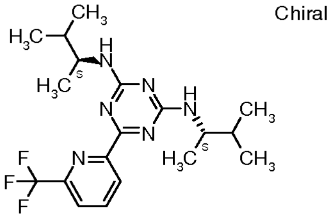
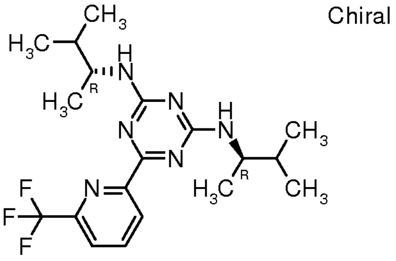
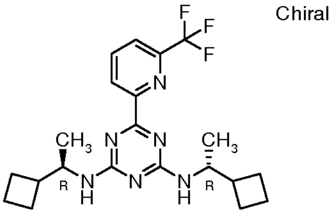
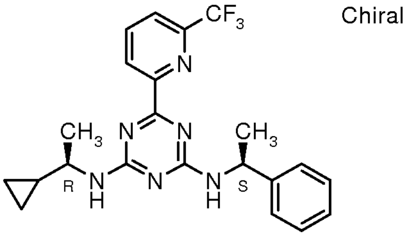
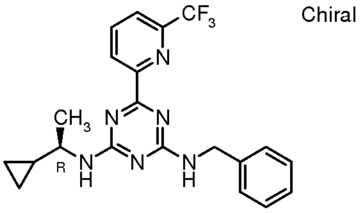
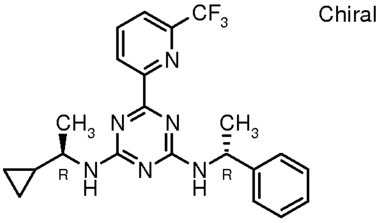
In another embodiment, the compound is selected from any one of the compounds set forth in Table 1, below.

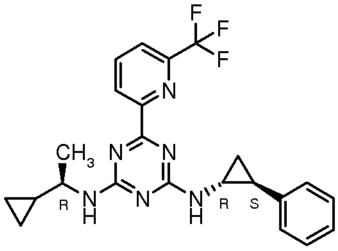
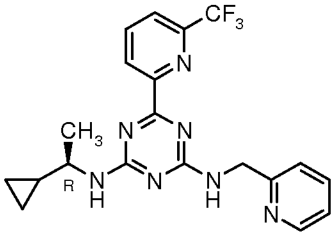
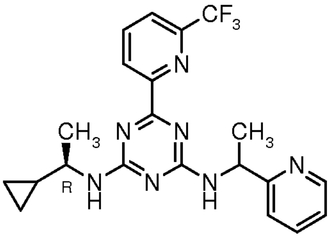
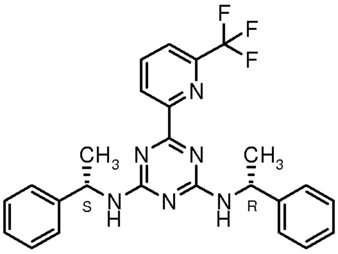
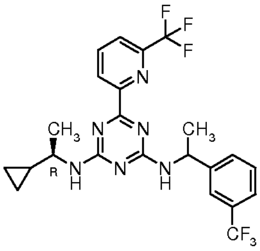
Table 1. Representative Compounds

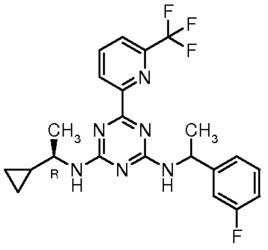
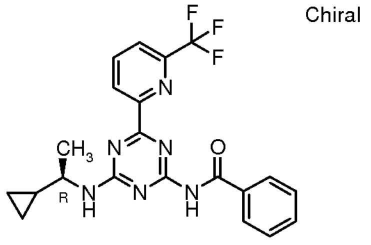
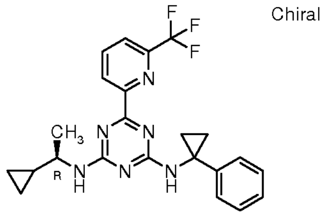
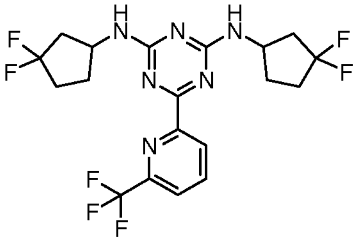
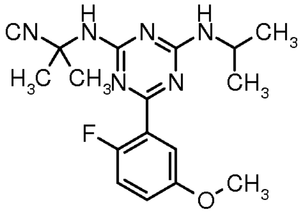
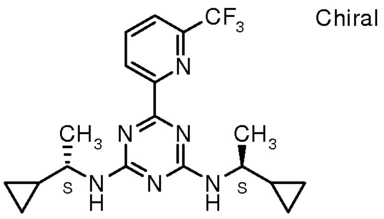
Compound Number	Structure
1	
2	
3	
4	
5	

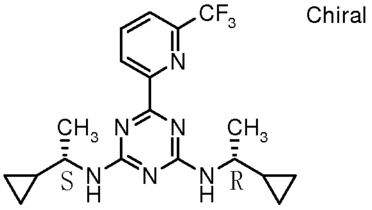
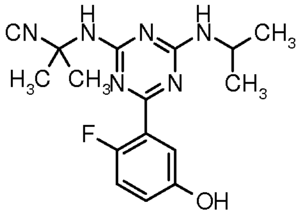
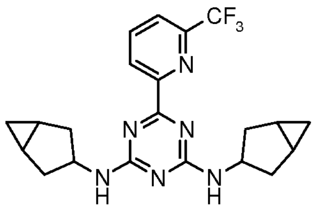
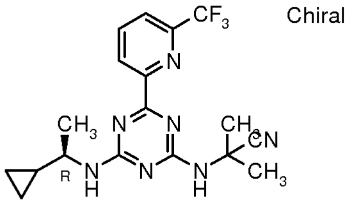
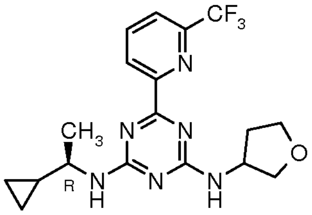
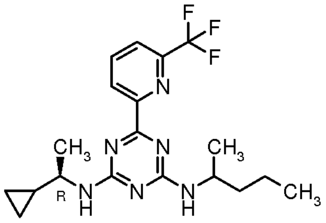
6	
7	
8	
9	
10	

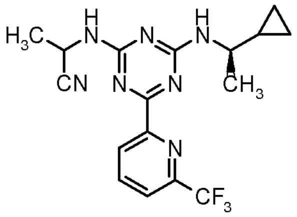
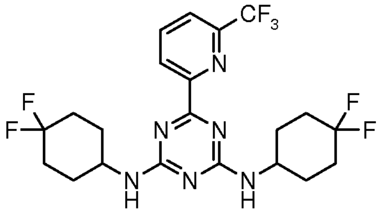
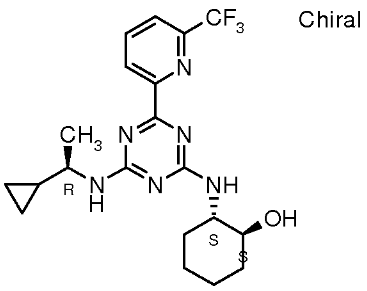
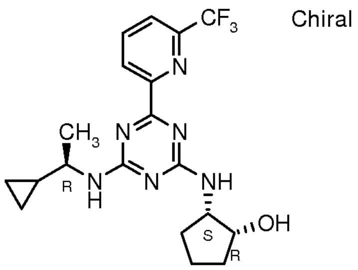
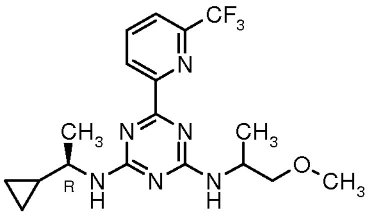
11	
12	
13	
14	
15	
16	

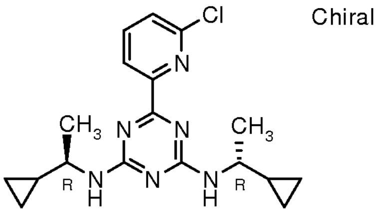
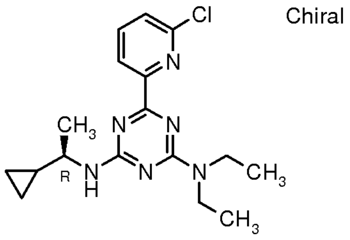
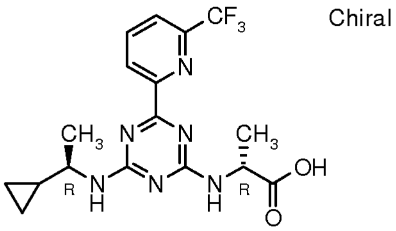
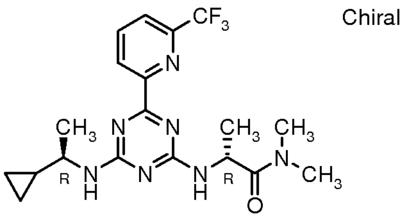
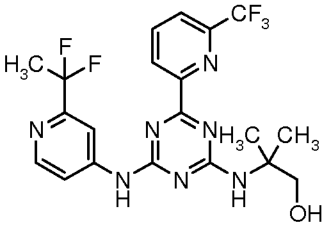
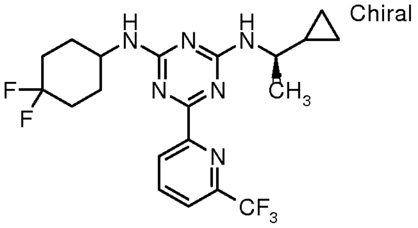
17	
18	
19	
20	
21	
22	

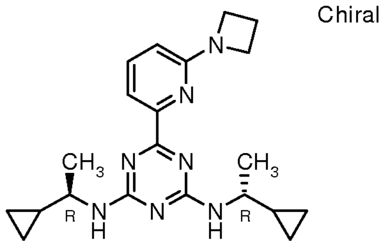
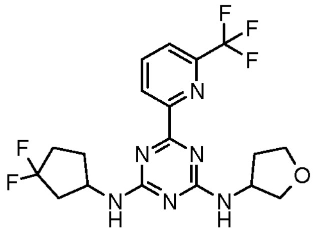
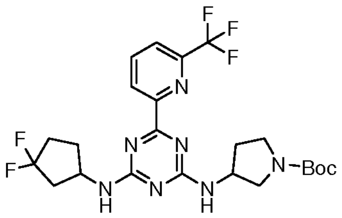
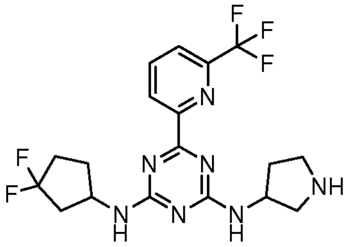
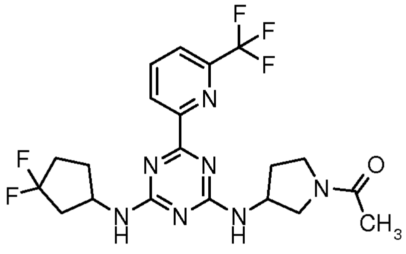
23	 Chiral
24	 Chiral
25	
26	 Chiral
27	

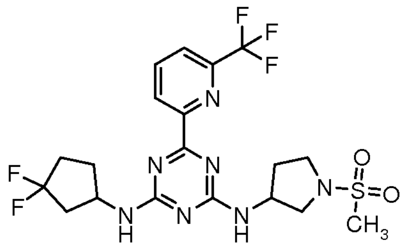
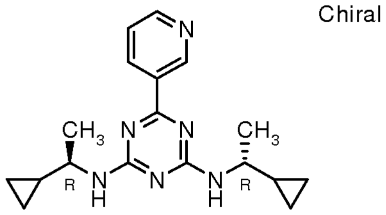
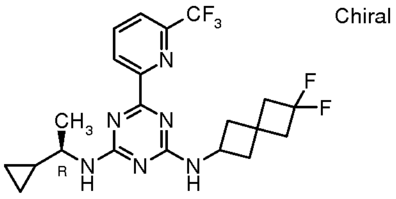
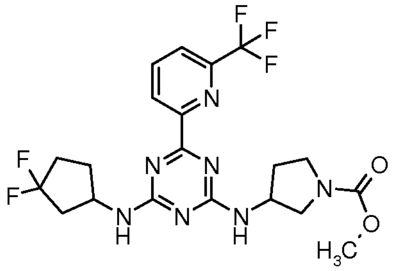
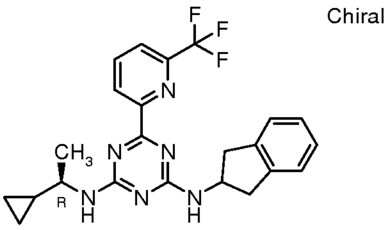
28	
29	
30	
31	
32	
33	

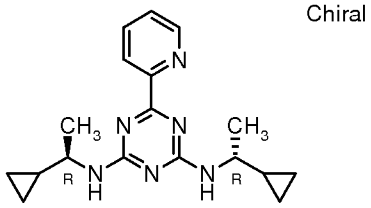
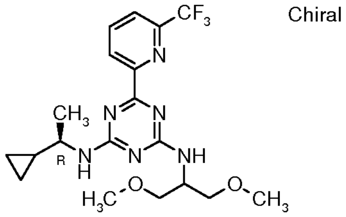
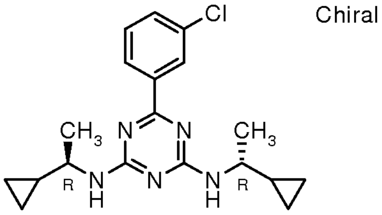
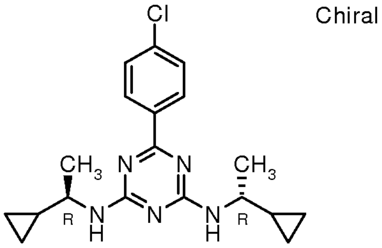
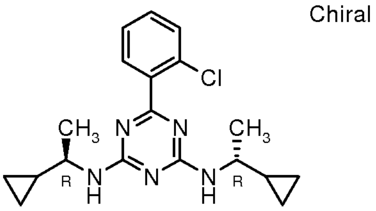
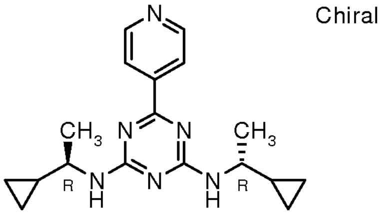
34	
35	
36	
37	
38	
39	

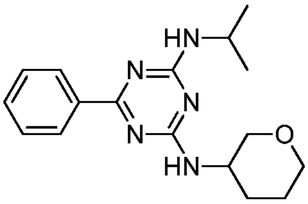
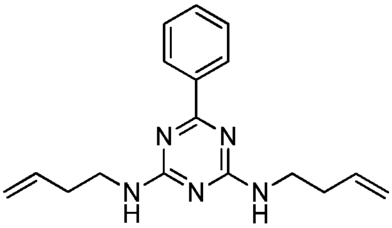
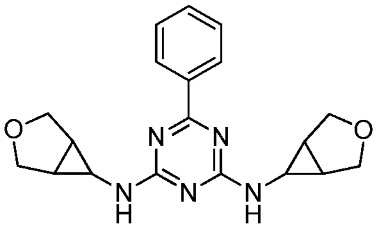
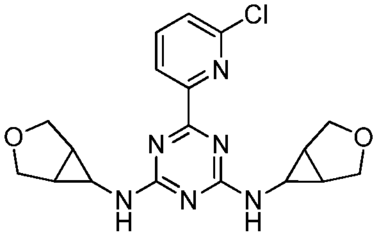
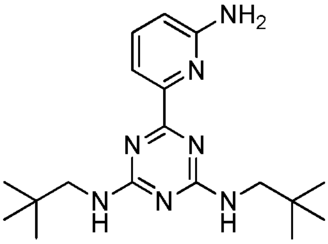
40	
41	
42	
43	
44	

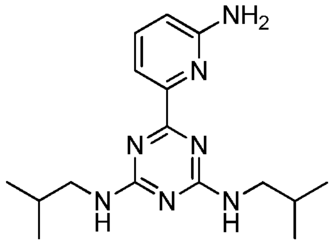
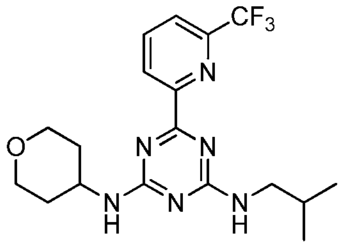
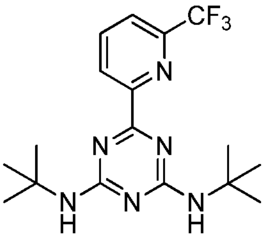
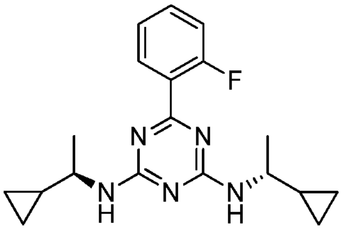
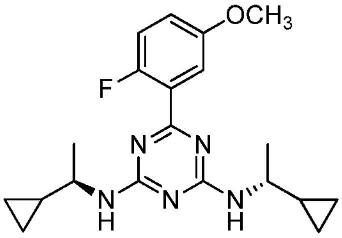
45	
46	
47	
48	
49	
50	

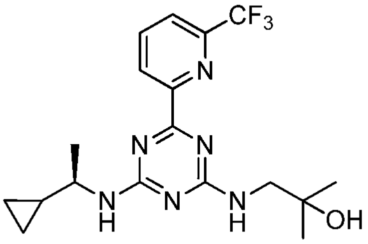
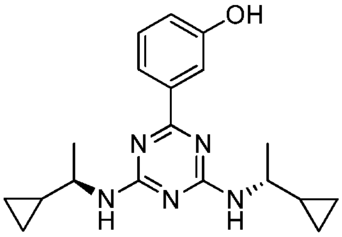
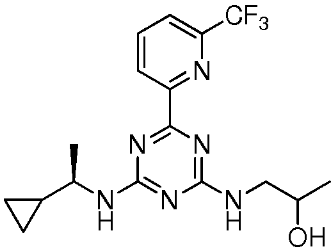
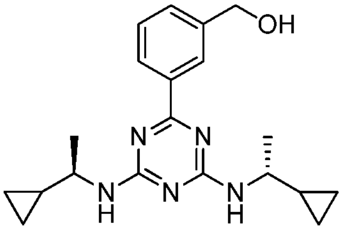
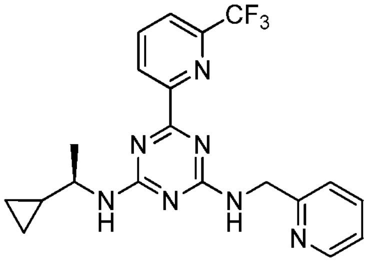
51	
52	
53	
54	
55	

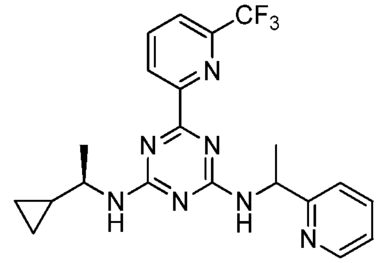
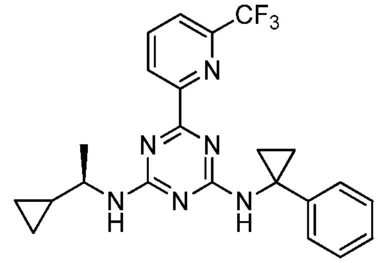
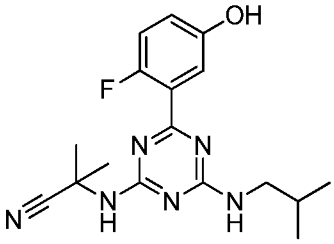
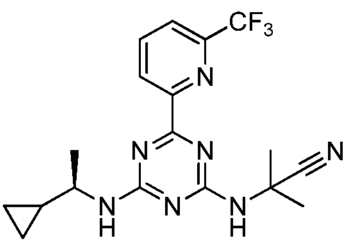
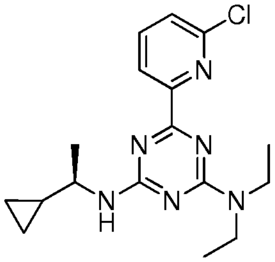
56	
57	
58	
59	
60	

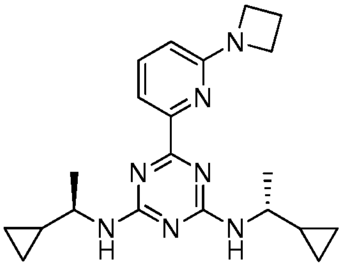
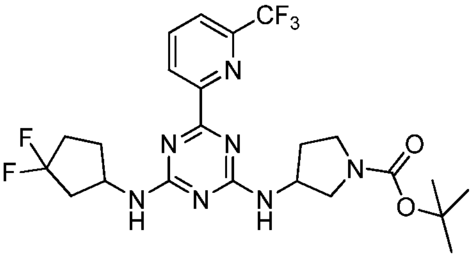
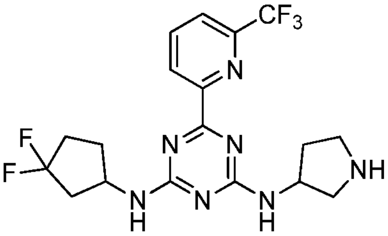
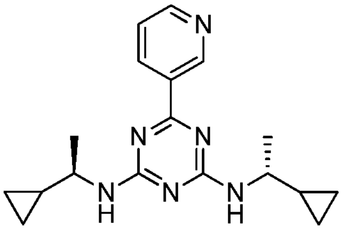
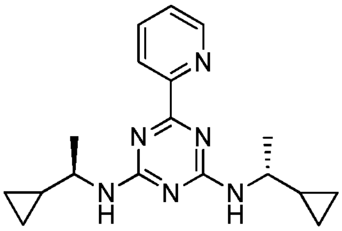
61	
63	
64	
65	
66	
67	

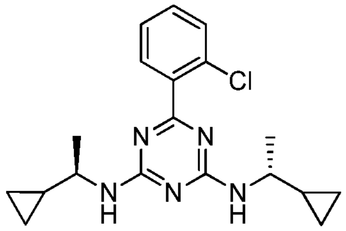
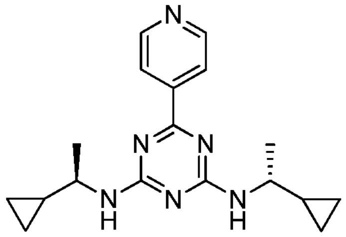
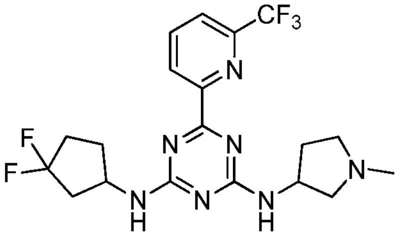
69	
70	
71	
72	
73	

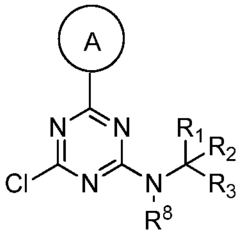
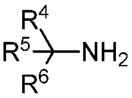
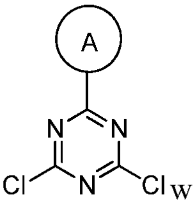
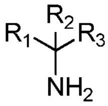
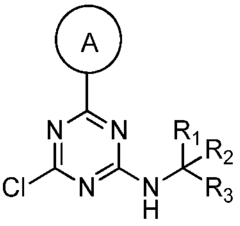
74	NH2 N N N N N H N H
75	CF3 N O N N N N H N H
76	CF3 N N N N N H N H
77	F N N N N H N H
78	OCH3 F N N N N H N H

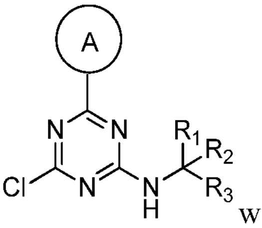
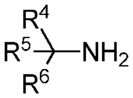
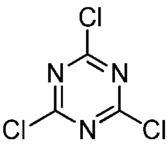
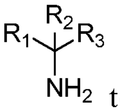
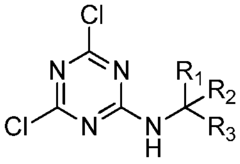
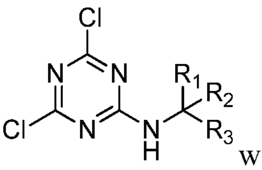
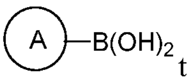
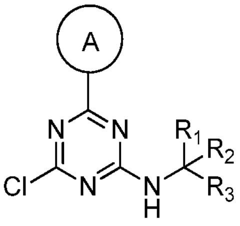
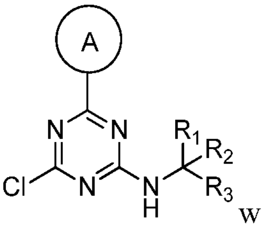
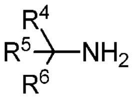
79	
80	
81	
82	
83	

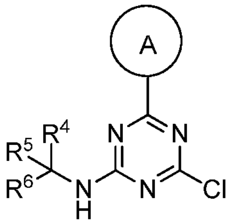
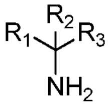
84	
85	
86	
87	
88	

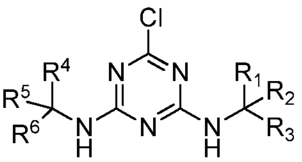
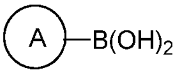
89	
90	
91	
92	
93	

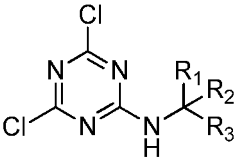
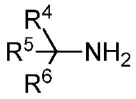
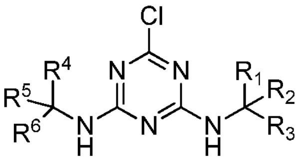
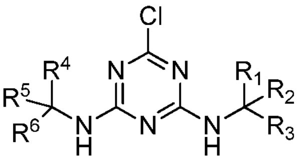
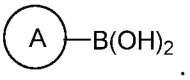
94	
95	
96	

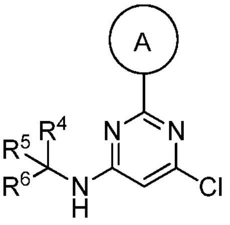
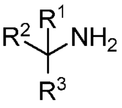
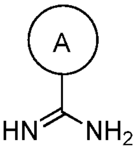
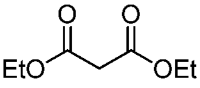
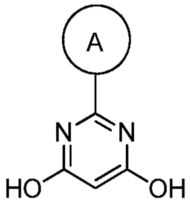
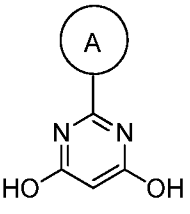
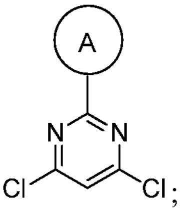
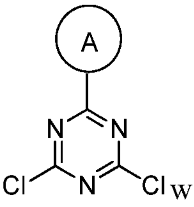
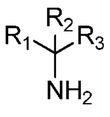
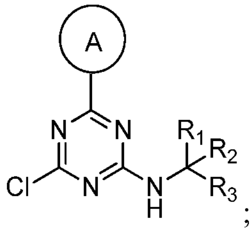
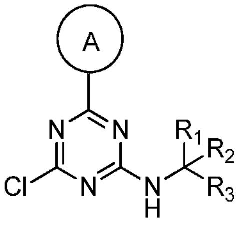
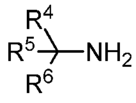
Included herein are also methods for making compounds of Formula I or a compound of any one of the embodiments described herein comprising reacting  with . In some embodiments, the preceding methods comprise step (1) reacting  with  to give ; and step (2) reacting

 with . In other embodiments, the preceding methods comprise step (1) reacting  with  to give ; step (2) reacting  with  to give ; and step (3) reacting  with .

Also included are methods for making compounds of Formula I or a compound of any one of the embodiments described herein comprising reacting  with .

Also included are methods for making compounds of Formula I or a compound of any one of the embodiments described herein comprising reacting  with . In some embodiments, the preceding methods comprise step (1) reacting

 with  to give  ; and step (2) reacting  with  .

Also included are methods for making compounds of Formula I or a compound of any one of the embodiments described herein comprising reacting  with  . In other embodiments, the preceding methods comprise step (1) converting  with  under basic conditions to give  ; step (2) reacting  with PCl$_5$, POCl$_3$ to give  ; step (3) reacting  with  to give  ; and step (4) reacting  with  .

The compounds of one aspect of this invention may contain one or more asymmetric centers and thus occur as racemates, racemic mixtures, scalemic mixtures, and diastereomeric mixtures, as well as single enantiomers or individual stereoisomers that are substantially free from another possible enantiomer or stereoisomer. The term "substantially free of other stereoisomers" as used herein means a preparation enriched in a compound having a selected stereochemistry at one or more selected stereocenters by at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%. The term "enriched" means that at least the designated percentage of a preparation is the compound having a selected stereochemistry at one or more selected stereocenters. Methods of obtaining or synthesizing an individual enantiomer or stereoisomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

In certain embodiments, the compound of Formula I, Ia, or Ib is enriched for a structure or structures having a selected stereochemistry at one or more carbon atoms. For example, the compound is enriched in the specific stereoisomer by at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%.

The compounds of Formula I, Ia, or Ib may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D or deuterium), and ^{3}H (T or tritium); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like. For example, the compound is enriched in a specific isotopic form of H, C and/or O by at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%.

Unless otherwise indicated when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

The compounds of one aspect of this invention may also be represented in multiple tautomeric forms, in such instances, one aspect of the invention expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented (e.g., alkylation of a ring system may result in alkylation at multiple sites, one aspect of the invention expressly includes all such reaction products; and keto-enol tautomers). All such isomeric forms of such compounds are expressly included herein.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts." J. Pharm. Sci. Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (*e.g.,* -COOH may be $-COO^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (*i.e.*, NH_4^+) and substituted ammonium ions (*e.g.,* NH_3R^+, NH_2R^{2+}, NHR^{3+}, NR^{4+}). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group that may be cationic (*e.g.,* $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Mesylates of each compound in Table 1 are explicitly included herein. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

The compounds provided herein therefore include the compounds themselves, as well as their salts, hydrates and their prodrugs, if applicable. The compounds provided herein may be modified and converted to prodrugs by appending appropriate functionalities to enhance selected biological properties, e.g., targeting to a particular tissue. Such modifications (i.e., prodrugs) are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. Examples of prodrugs include esters (e.g., phosphates, amino acid (e.g.,valine) esters), carbamates and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active compounds. Calcium and sodium phosphates of each compound in Table 1, if applicable, are explicitly included herein. Amino acid (e.g., valine) esters of each compound in Table 1, if applicable, are explicitly included herein.

Compositions and routes of administration

The compounds utilized in the methods described herein may be formulated together with a pharmaceutically acceptable carrier or adjuvant into pharmaceutically acceptable compositions prior to be administered to a subject. In another embodiment, such pharmaceutically acceptable compositions further comprise additional therapeutic agents in amounts effective for achieving a modulation of disease or disease symptoms, including those described herein.

The term “pharmaceutically acceptable carrier or adjuvant” refers to a carrier or adjuvant that may be administered to a subject, together with a compound of one aspect of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of one aspect of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

The pharmaceutical compositions of one aspect of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of one aspect of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer’s solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of one aspect of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of one aspect of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of one aspect of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of one aspect of this invention is useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of one aspect of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of one aspect of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation.

Topically-transdermal patches are also included in one aspect of this invention.

The pharmaceutical compositions of one aspect of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

When the compositions of one aspect of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of one aspect of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of one aspect of this invention in a single composition.

The compounds described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of one aspect of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular subject will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the subject's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a subject's condition, a maintenance dose of a compound, composition or combination of one aspect of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Subjects may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

The pharmaceutical compositions described above comprising a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments herein, may further comprise another therapeutic agent useful for treating cancer.

Methods of Use

Provided is a method for inhibiting mutant IDH1 activity comprising contacting a subject in need thereof with a compound (including its tautomers and/or isotopologues) of Formula I, Ia, or Ib, or a compound described in any one of the embodiments herein, or a pharmaceutically acceptable salt thereof. In one embodiment, the cancer to be treated is characterized by a mutant allele of IDH1 wherein the IDH1 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a subject. In one aspect of this embodiment, the mutant IDH1 has an R132X mutation. In one aspect of this embodiment, the R132X mutation is selected from R132H, R132C, R132L, R132V, R132S and R132G. In another aspect, the R132X mutation is R132H or R132C. In yet another aspect, the R132X mutation is R132H.

Also provided are methods of treating a cancer characterized by the presence of a mutant allele of IDH1 comprising the step of administering to subject in need thereof (a) a compound of

Formula I, Ia, or Ib, or a compound described in any one of the embodiments herein, or a pharmaceutically acceptable salt thereof, or (b) a pharmaceutical composition comprising (a) and a pharmaceutically acceptable carrier.

In one embodiment, the cancer to be treated is characterized by a mutant allele of IDH1 wherein the IDH1 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a patient. In one aspect of this embodiment, the IDH1 mutation is an R132X mutation. In another aspect of this embodiment, the R132X mutation is selected from R132H, R132C, R132L, R132V, R132S and R132G. In another aspect, the R132X mutation is R132 H or R132C. A cancer can be analyzed by sequencing cell samples to determine the presence and specific nature of (e.g., the changed amino acid present at) a mutation at amino acid 132 of IDH1.

Without being bound by theory, applicants believe that mutant alleles of IDH1 wherein the IDH1 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate, and in particular R132H mutations of IDH1, characterize a subset of all types of cancers, without regard to their cellular nature or location in the body. Thus, the compounds and methods of this invention are useful to treat any type of cancer that is characterized by the presence of a mutant allele of IDH1 imparting such acitivity and in particular an IDH1 R132H or R132C mutation.

In one aspect of this embodiment, the efficacy of cancer treatment is monitored by measuring the levels of 2HG in the subject. Typically levels of 2HG are measured prior to treatment, wherein an elevated level is indicated for the use of the compound of Formula I, Ia, or Ib, or a compound described in any one of the embodiments described herein to treat the cancer. Once the elevated levels are established, the level of 2HG is determined during the course of and/or following termination of treatment to establish efficacy. In certain embodiments, the level of 2HG is only determined during the course of and/or following termination of treatment. A reduction of 2HG levels during the course of treatment and following treatment is indicative of efficacy. Similarly, a determination that 2HG levels are not elevated during the course of or following treatment is also indicative of efficacy. Typically, the these 2HG measurements will be utilized together with other well-known determinations of efficacy of cancer treatment, such as reduction in number and size of tumors and/or other cancer-associated lesions, improvement in the general health of the subject, and alterations in other biomarkers that are associated with cancer treatment efficacy.

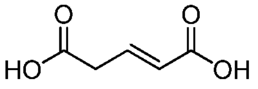
2HG can be detected in a sample by LC/MS. The sample is mixed 80:20 with methanol, and centrifuged at 3,000 rpm for 20 minutes at 4 degrees Celsius. The resulting supernatant can be collected and stored at -80 degrees Celsius prior to LC-MS/MS to assess 2-hydroxyglutarate levels. A variety of different liquid chromatography (LC) separation methods can be used. Each method can be coupled by negative electrospray ionization (ESI, -3.0 kV) to triple-quadrupole mass spectrometers operating in multiple reaction monitoring (MRM) mode, with MS parameters optimized on infused metabolite standard solutions. Metabolites can be separated by reversed phase chromatography using 10 mM tributyl-amine as an ion pairing agent in the aqueous mobile phase, according to a variant of a previously reported method (Luo *et al. J Chromatogr A* 1147, 153-64, 2007). One method allows resolution of TCA metabolites: t = 0, 50% B; t = 5, 95% B; t= 7, 95% B; t= 8, 0% B, where B refers to an organic mobile phase of 100% methanol. Another method is specific for 2-hydroxyglutarate, running a fast linear gradient from 50% -95% B (buffers as defined above) over 5 minutes. A Synergi Hydro-RP, 100mm × 2 mm, 2.1 μm particle size (Phenomonex) can be used as the column, as described above. Metabolites can be quantified by comparison of peak areas with pure metabolite standards at known concentration. Metabolite flux studies from ^{13}C-glutamine can be performed as described, *e.g.,* in Munger *et al.* Nat Biotechnol 26, 1179-86, 2008.

In one embodiment 2HG is directly evaluated.

In another embodiment a derivative of 2HG formed in process of performing the analytic method is evaluated. By way of example such a derivative can be a derivative formed in MS analysis. Derivatives can include a salt adduct, *e.g.,* a Na adduct, a hydration variant, or a hydration variant which is also a salt adduct, *e.g.*, a Na adduct, *e.g.*, as formed in MS analysis.

In another embodiment a metabolic derivative of 2HG is evaluated. Examples include species that build up or are elevated, or reduced, as a result of the presence of 2HG, such as glutarate or glutamate that will be correlated to 2HG, *e.g.,* R-2HG.

Exemplary 2HG derivatives include dehydrated derivatives such as the compounds provided below or a salt adduct thereof:



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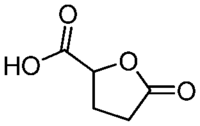

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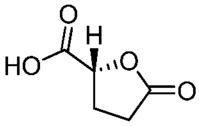

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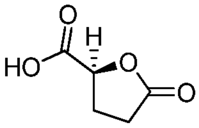

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In one embodiment the cancer is a tumor wherein at least 30, 40, 50, 60, 70, 80 or 90% of the tumor cells carry an IDH1 mutation, and in particular an IDH1 R132H or R132C mutation, at the time of diagnosis or treatment.

IDH1 R132X mutations are known to occur in certain types of cancers as indicated in Table 2, below.

Table 2. IDH mutations associated with certain cancers

Cancer Type	**IDH1 R132X Mutation**	**Tumor Type**
brain tumors	R132H	primary tumor
	R132C	primary tumor
	R132S	primary tumor
	R132G	primary tumor
	R132L	primary tumor
	R132V	primary tumor
fibrosarcoma	R132C	HT1080 fibrosarcoma cell line
Acute Myeloid Leukemia (AML)	R132H	primary tumor
	R132G	primary tumor
	R132C	primary tumor
Prostate cancer	R132H	primary tumor
	R132C	primary tumor
Acute lymphoblastic leukemia (ALL)	R132C	primary tumor
paragangliomas	R132C	primary tumor

IDH1 R132H mutations have been identified in glioblastoma, acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer, cholangiocarcinomas, chondrosarcoma, myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN), colon cancer, and angio-immunoblastic non-Hodgkin's lymphoma (NHL). Accordingly, in one embodiment, the methods described herein are used to treat glioma (glioblastoma), acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer (NSCLC) or cholangiocarcinomas, chondrosarcoma, myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN), colon cancer, or angio-immunoblastic non-Hodgkin's lymphoma (NHL) in a patient.

Accordingly in one embodiment, the cancer is a cancer selected from any one of the cancer types listed in Table 2, and the IDH R132X mutation is one or more of the IDH1 R132X mutations listed in Table 2 for that particular cancer type.

Treatment methods described herein can additionally comprise various evaluation steps prior to and/or following treatment with a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments described herein.

In one embodiment, prior to and/or after treatment with a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments described herein, the method further comprises the step of evaluating the growth, size, weight, invasiveness, stage and/or other phenotype of the cancer.

In one embodiment, prior to and/or after treatment with a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments described herein, the method further comprises the step of evaluating the IDH1 genotype of the cancer. This may be achieved by ordinary methods in the art, such as DNA sequencing, immuno analysis, and/or evaluation of the presence, distribution or level of 2HG.

In one embodiment, prior to and/or after treatment with a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments described herein, the method further comprises the step of determining the 2HG level in the subject. This may be achieved by spectroscopic analysis, *e.g.,* magnetic resonance-based analysis, *e.g.,* MRI and/or MRS measurement, sample analysis of bodily fluid, such as serum or spinal cord fluid analysis, or by analysis of surgical material, *e.g.,* by mass-spectroscopy.

Also provided is a method for inhibiting a mutant IDH2 activity comprising contacting a subject in need thereof with a compound of Formula I, Ia, or Ib, a compound described in any one of the embodiments herein, or a pharmaceutically acceptable salt thereof. In one embodiment, the cancer to be treated is characterized by a mutant allele of IDH2 wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a subject. In one aspect of this embodiment, the mutant IDH2 has an R140X mutation. In another aspect of this embodiment, the R140X mutation is a R140Q mutation. In another aspect of this embodiment, the R140X mutation is a R140W mutation. In another aspect of this embodiment, the R140X mutation is a R140L mutation. In another aspect of this embodiment, the mutant IDH2 has an R172X mutation. In another aspect of this embodiment, the R172X mutation is a R172K mutation. In another aspect of this embodiment, the R172X mutation is a R172G mutation.

Also provided are methods of treating a cancer characterized by the presence of a mutant allele of IDH2 comprising the step of administering to subject in need thereof (a) a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments herein, or a pharmaceutically acceptable salt thereof, or (b) a pharmaceutical composition comprising (a) and a pharmaceutically acceptable carrier.

In one embodiment, the cancer to be treated is characterized by a mutant allele of IDH2 wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a patient. In one aspect of this embodiment, the mutant IDH2 has an R140X mutation. In another aspect of this embodiment, the R140X mutation is a R140Q mutation. In another aspect of this embodiment, the R140X mutation is a R140W mutation. In another aspect of this embodiment, the R140X mutation is a R140L mutation. In another aspect of this embodiment, the mutant IDH2 has an R172X mutation. In another aspect of this embodiment, the R172X mutation is a R172K mutation. In another aspect of this embodiment, the R172X mutation is a R172G mutation. A cancer can be analyzed by sequencing cell samples to determine the presence and specific nature of (e.g., the changed amino acid present at) a mutation at amino acid 140 and/or 172 of IDH2.

Without being bound by theory, applicants believe that mutant alleles of IDH2 wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate, and in particular R140Q and/or R172K mutations of IDH2, characterize a subset of all types of cancers, without regard to their cellular nature or location in the body. Thus, the compounds and methods of one aspect of this invention are useful to treat any type of cancer that is characterized by the presence of a mutant allele of IDH2 imparting such acitivity and in particular an IDH2 R140Q and/or R172K mutation.

In one aspect of this embodiment, the efficacy of cancer treatment is monitored by measuring the levels of 2HG as described herein.

In one embodiment the cancer is a tumor wherein at least 30, 40, 50, 60, 70, 80 or 90% of the tumor cells carry an IDH2 mutation, and in particular an IDH2 R140Q, R140W, or R140L and/or R172K or R172G mutation, at the time of diagnosis or treatment.

In another embodiment, one aspect of the invention provides a method of treating a cancer selected from glioblastoma (glioma), myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), acute myelogenous leukemia (AML), sarcoma, melanoma, non-small cell lung cancer, chondrosarcoma, cholangiocarcinomas or angioimmunoblastic lymphoma in a patient by administering to the patient a compound of Formula I, Ia, or Ib in an amount effective to treat the cancer. In a more specific embodiment the cancer to be treated is glioma, myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), acute myelogenous leukemia (AML), melanoma, chondrosarcoma, or angioimmunoblastic non-Hodgkin's lymphoma (NHL).

2HG is known to accumulate in the inherited metabolic disorder 2-hydroxyglutaric aciduria. This disease is caused by deficiency in the enzyme 2-hydroxyglutarate dehydrogenase, which converts 2HG to α-KG (Struys, E. A. et al. Am J Hum Genet 76, 358-60 (2005)). Patients with 2-hydroxyglutarate dehydrogenase deficiencies accumulate 2HG in the brain as assessed by MRI and CSF analysis, develop leukoencephalopathy, and have an increased risk of developing brain tumors (Aghili, M., Zahedi, F. & Rafiee, J Neurooncol 91, 233-6 (2009); Kolker, S., Mayatepek, E. & Hoffmann, G. F. Neuropediatrics 33, 225-31 (2002); Wajner, M., Latini, A., Wyse, A. T. & Dutra-Filho, C. S. J Inherit Metab Dis 27, 427-48 (2004)). Furthermore, elevated brain levels of 2HG result in increased ROS levels (Kolker, S. et al. Eur J Neurosci 16, 21-8 (2002); Latini, A. et al. Eur J Neurosci 17, 2017-22 (2003)), potentially contributing to an increased risk of cancer. The ability of 2HG to act as an NMDA receptor agonist may contribute to this effect (Kolker, S. et al. Eur J Neurosci 16, 21-8 (2002)). 2HG may also be toxic to cells by competitively inhibiting glutamate and/or αKG utilizing enzymes. These include transaminases which allow utilization of glutamate nitrogen for amino and nucleic acid biosynthesis, and αKG-dependent prolyl hydroxylases such as those which regulate HIF1-alpha levels.

Thus, according to another embodiment, one aspect of the invention provides a method of treating 2-hydroxyglutaric aciduria, particularly D-2-hydroxyglutaric aciduria, in a patient by administering to the patient a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments described herein.

Treatment methods described herein can additionally comprise various evaluation steps prior to and/or following treatment with a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments described herein.

In one embodiment, prior to and/or after treatment with a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments described herein, the method further comprises the step of evaluating the growth, size, weight, invasiveness, stage and/or other phenotype of the cancer.

In one embodiment, prior to and/or after treatment with a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments described herein, the method further comprises the step of evaluating the IDH2 genotype of the cancer. This may be achieved by ordinary methods in the art, such as DNA sequencing, immuno analysis, and/or evaluation of the presence, distribution or level of 2HG.

In one embodiment, prior to and/or after treatment with a compound of Formula I, Ia, or Ib or a compound described in any one of the embodiments described herein, the method further comprises the step of determining the 2HG level in the subject. This may be achieved by spectroscopic analysis, *e.g.,* magnetic resonance-based analysis, *e.g.,* MRI and/or MRS measurement, sample analysis of bodily fluid, such as serum or spinal cord fluid analysis, or by analysis of surgical material, *e.g.,* by mass-spectroscopy.

Combination therapies

In some embodiments, the methods described herein comprise the additional step of co-administering to a subject in need thereof a second therapy *e.g.,* an additional cancer therapeutic agent or an additional cancer treatment. Exemplary additional cancer therapeutic agents include for example, chemotherapy, targeted therapy, antibody therapies, immunotherapy, and hormonal therapy. Additional cancer treatments include, for example: surgery, and radiation therapy. Examples of each of these treatments are provided below.

The term "co-administering" as used herein with respect to an additional cancer therapeutic agents means that the additional cancer therapeutic agent may be administered together with a compound of one aspect of this invention as part of a single dosage form (such as a composition of one aspect of this invention comprising a compound of one aspect of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional cancer therapeutic agent may be administered prior to, consecutively with, or following the administration of a compound of one aspect of this invention. In such combination therapy treatment, both the compounds of one aspect of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of one aspect of this invention, comprising both a compound of one aspect of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of one aspect of this invention to said subject at another time during a course of treatment. The term "co-administering" as used herein with respect to an additional cancer treatment means that the additional cancer treatment may occur prior to, consecutively with, concurrently with or following the administration of a compound of one aspect of this invention.

In some embodiments, the additional cancer therapeutic agent is a chemotherapy agent. Examples of chemotherapeutic agents used in cancer therapy include, for example, antimetabolites (*e.g.,* folic acid, purine, and pyrimidine derivatives), alkylating agents (*e.g.,* nitrogen mustards, nitrosoureas, platinum, alkyl sulfonates, hydrazines, triazenes, aziridines, spindle poison, cytotoxic agents, topoisomerase inhibitors and others), and hypomethylating agents (*e.g.*, decitabine (5-aza-deoxycytidine), zebularine, isothiocyanates, azacitidine (5-azacytidine), 5-flouro-2'-deoxycytidine, 5,6-dihydro-5-azacytidine and others). Exemplary agents include Aclarubicin, Actinomycin, Alitretinoin, Altretamine, Aminopterin, Aminolevulinic acid, Amrubicin, Amsacrine, Anagrelide, Arsenic trioxide, Asparaginase, Atrasentan, Belotecan, Bexarotene, bendamustine, Bleomycin, Bortezomib, Busulfan, Camptothecin, Capecitabine, Carboplatin, Carboquone, Carmofur, Carmustine, Celecoxib, Chlorambucil, Chlormethine, Cisplatin, Cladribine, Clofarabine, Crisantaspase, Cyclophosphamide, Cytarabine, Dacarbazine, Dactinomycin, Daunorubicin, Decitabine, Demecolcine, Docetaxel, Doxorubicin, Efaproxiral, Elesclomol, Elsamitrucin, Enocitabine, Epirubicin, Estramustine, Etoglucid, Etoposide, Floxuridine, Fludarabine, Fluorouracil (5FU), Fotemustine, Gemcitabine, Gliadel implants, Hydroxycarbamide, Hydroxyurea, Idarubicin, Ifosfamide, Irinotecan, Irofulven, Ixabepilone, Larotaxel, Leucovorin, Liposomal doxorubicin, Liposomal daunorubicin, Lonidamine, Lomustine, Lucanthone, Mannosulfan, Masoprocol, Melphalan, Mercaptopurine, Mesna, Methotrexate, Methyl aminolevulinate, Mitobronitol, Mitoguazone, Mitotane, Mitomycin, Mitoxantrone, Nedaplatin, Nimustine, Oblimersen, Omacetaxine, Ortataxel, Oxaliplatin, Paclitaxel, Pegaspargase, Pemetrexed, Pentostatin, Pirarubicin, Pixantrone, Plicamycin, Porfimer sodium, Prednimustine, Procarbazine, Raltitrexed, Ranimustine, Rubitecan, Sapacitabine, Semustine, Sitimagene ceradenovec, Strataplatin, Streptozocin, Talaporfin, Tegafur-uracil, Temoporfin, Temozolomide, Teniposide, Tesetaxel, Testolactone, Tetranitrate, Thiotepa, Tiazofurine, Tioguanine, Tipifarnib, Topotecan, Trabectedin, Triaziquone, Triethylenemelamine, Triplatin, Tretinoin, Treosulfan, Trofosfamide, Uramustine, Valrubicin, Verteporfin, Vinblastine, Vincristine, Vindesine, Vinflunine, Vinorelbine, Vorinostat, Zorubicin, and other cytostatic or cytotoxic agents described herein.

Because some drugs work better together than alone, two or more drugs are often given at the same time. Often, two or more chemotherapy agents are used as combination chemotherapy.

In some embodiments, the additional cancer therapeutic agent is a differentiation agent. Such differentiation agent includes retinoids (such as all-trans-retinoic acid (ATRA), 9-cis retinoic acid, 13-*cis*-retinoic acid (13-cRA) and 4-hydroxy-phenretinamide (4-HPR)); arsenic trioxide; histone deacetylase inhibitors HDACs (such as azacytidine (Vidaza) and butyrates (e.g., sodium phenylbutyrate)); hybrid polar compounds (such as hexamethylene bisacetamide ((HMBA)); vitamin D; and cytokines (such as colony-stimulating factors including G-CSF and GM-CSF, and interferons).

In some embodiments the additional cancer therapeutic agent is a targeted therapy agent. Targeted therapy constitutes the use of agents specific for the deregulated proteins of cancer cells. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within the cancer cell. Prominent examples are the tyrosine kinase inhibitors such as Axitinib, Bosutinib, Cediranib, dasatinib, erlotinib, imatinib, gefitinib, lapatinib, Lestaurtinib, Nilotinib, Semaxanib, Sorafenib, Sunitinib, and Vandetanib, and also cyclin-dependent kinase inhibitors such as Alvocidib and Seliciclib. Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells. Examples include the anti-HER2/neu antibody trastuzumab (HERCEPTIN®) typically used in breast cancer, and the anti-CD20 antibody rituximab and Tositumomab typically used in a variety of B-cell malignancies. Other exemplary antibodies include Cetuximab, Panitumumab, Trastuzumab, Alemtuzumab, Bevacizumab, Edrecolomab, and Gemtuzumab. Exemplary fusion proteins include Aflibercept and Denileukin diftitox. In some embodiments, the targeted therapy can be used in combination with a compound described herein, *e.g.,* a biguanide such as metformin or phenformin, preferably phenformin.

Targeted therapy can also involve small peptides as “homing devices” which can bind to cell surface receptors or affected extracellular matrix surrounding the tumor. Radionuclides which are attached to these peptides (*e.g.,* RGDs) eventually kill the cancer cell if the nuclide decays in the vicinity of the cell. An example of such therapy includes BEXXAR®.

In some embodiments, the additional cancer therapeutic agent is an immunotherapy agent. Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the subject's own immune system to fight the tumor. Contemporary methods for generating an immune response against tumors include intravesicular BCG immunotherapy for superficial bladder cancer, and use of interferons and other cytokines to induce an immune response in renal cell carcinoma and melanoma subjects.

Allogeneic hematopoietic stem cell transplantation can be considered a form of immunotherapy, since the donor’s immune cells will often attack the tumor in a graft-versus-tumor effect. In some embodiments, the immunotherapy agents can be used in combination with a compound or composition described herein.

In some embodiments, the additional cancer therapeutic agent is a hormonal therapy agent. The growth of some cancers can be inhibited by providing or blocking certain hormones. Common examples of hormone-sensitive tumors include certain types of breast and prostate cancers. Removing or blocking estrogen or testosterone is often an important additional treatment. In certain cancers, administration of hormone agonists, such as progestogens may be therapeutically beneficial. In some embodiments, the hormonal therapy agents can be used in combination with a compound or a composition described herein.

Other possible additional therapeutic modalities include imatinib, gene therapy, peptide and dendritic cell vaccines, synthetic chlorotoxins, and radiolabeled drugs and antibodies.

EXAMPLES

ABBREVIATIONS

anhy. - anhydrous
aq. - aqueous
min - minute(s)
mL - milliliter
mmol - millimole(s)
mol - mole(s)
MS - mass spectrometry
NMR - nuclear magnetic resonance
TLC - thin layer chromatography
HPLC - high-performance liquid chromatography
Hz - hertz
δ - chemical shift
J - coupling constant
s - singlet
d - doublet
t - triplet
q - quartet
m - multiplet
br - broad
qd - quartet of doublets
dquin - doublet of quintets
dd - doublet of doublets
dt - doublet of triplets
$CHCl_3$ - chloroform
DCM - dichloromethane
DMF - dimethylformamide
Et_2O - diethyl ether
EtOH - ethyl alcohol
EtOAc - ethyl acetate
MeOH - methyl alcohol
MeCN - acetonitrile
PE - petroleum ether
THF - tetrahydrofuran
AcOH - acetic acid
HCl - hydrochloric acid

H_2SO_4 - sulfuric acid
NH_4Cl - ammonium chloride
KOH - potassium hydroxide
NaOH - sodium hydroxide
K_2CO_3 - potassium carbonate
Na_2CO_3 - sodium carbonate
TFA - trifluoroacetic acid
Na_2SO_4 - sodium sulfate
$NaBH_4$ - sodium borohydride
$NaHCO_3$ - sodium bicarbonate
LiHMDS - lithium hexamethyldisilylamide
NaHMDS - sodium hexamethyldisilylamide
LAH - lithium aluminum hydride
$NaBH_4$ - sodium borohydride
LDA - lithium diisopropylamide
Et_3N - triethylamine
DMAP - 4-(dimethylamino)pyridine
DIPEA - *N,N*-diisopropylethylamine
NH_4OH - ammonium hydroxide
EDCI - 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBt - 1-hydroxybenzotriazole
HATU - *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetra-methyluronium
BINAP - 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl

In the following examples, reagents were purchased from commercial sources (including Alfa, Acros, Sigma Aldrich, TCI and Shanghai Chemical Reagent Company), and used without further purification. Nuclear magnetic resonance (NMR) spectra were obtained on a Brucker AMX-400 NMR (Brucker, Switzerland). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Mass spectra were run with electrospray ionization (ESI) from a Waters LCT TOF Mass Spectrometer (Waters, USA).

For exemplary compounds disclosed in this section, the specification of a stereoisomer (e.g., an (R) or (S) stereoisomer) indicates a preparation of that compound such that the compound is enriched at the specified stereocenter by at least about 90%, 95%, 96%, 97%, 98%, or 99%. The chemical name of each of the exemplary compound described below is generated by ChemDraw software.

Abbreviations list:

General

anhy.	anhydrous
aq.	aqueous
min	minute(s)
hrs	hours
mL	milliliter
mmol	millimole(s)
mol	mole(s)
MS	mass spectrometry
NMR	nuclear magnetic resonance
TLC	thin layer chromatography
HPLC	high-performance liquid chromatography

Spectrum

Hz	hertz
δ	chemical shift
J	coupling constant
s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
br	broad
qd	quartet of doublets
dquin	doublet of quintets
dd	doublet of doublets
dt	doublet of triplets

Solvents and Reagents

DAST	diethylaminosulfurtrifluoride
$CHCl_3$	chloroform

DCM	dichloromethane
DMF	dimethylformamide
Et_2O	diethyl ether
EtOH	ethyl alcohol
EtOAc	ethyl acetate
MeOH	methyl alcohol
MeCN	acetonitrile
PE	petroleum ether
THF	tetrahydrofuran
DMSO	dimethyl sulfoxide
AcOH	acetic acid
HCl	hydrochloric acid
H_2SO_4	sulfuric acid
NH_4Cl	ammonium chloride
KOH	potassium hydroxide
NaOH	sodium hydroxide
K_2CO_3	potassium carbonate
Na_2CO_3	sodium carbonate
TFA	trifluoroacetic acid
Na_2SO_4	sodium sulfate
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
LiHMDS	lithium hexamethyldisilylamide
LAH	lithium aluminum hydride
$NaBH_4$	sodium borohydride
LDA	lithium diisopropylamide
Et_3N	triethylamine
Py	pyridine
DMAP	4-(dimethylamino)pyridine
DIPEA	*N,N*-diisopropylethylamine

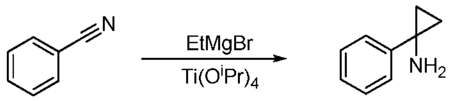
Xphos	2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl
BINAP	2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl
dppf	1,1'-bis(diphenylphosphino)ferrocene
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
DPPA	diphenylphosphoryl azide

General experimental notes:

In the following examples, the reagents (chemicals) were purchased from commercial sources (such as Alfa, Acros, Sigma Aldrich, TCI and Shanghai Chemical Reagent Company), and used without further purification. Analytical and preparative thin layer chromatography (TLC) plates were HSGF 254 (0.15-0.2 mm thickness, Shanghai Anbang Company, China). Nuclear magnetic resonance (NMR) spectra were obtained on a Brucker AMX-400 NMR (Brucker, Switzerland). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Mass spectra were given with electrospray ionization (ESI) from a Shimadzu LCMS-2020 Mass Spectrometer (Shimadzu, Japan). Microwave reactions were run on an Initiator 2.5 Microwave Synthesizer (Biotage, Sweden).

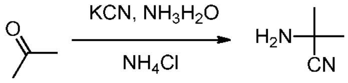
Preparation of Intermediates

Preparation of 1-phenylcyclopropanamine.



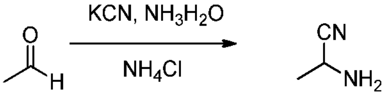
Ethylmagnesium bromide (48.5 mL, 146 mmol) was added dropwise over 30 min to a solution of benzonitrile (5 g, 48 mmol, 3 eq) and titanium tetraisopropanolate (21.5 mL, 73 mmol, 1.5 eq) in dry THF (140 mL) at -70°C. The solution was stirred at r.t. for 1.5 hr, followed by dropwise addition of boron trifluorideetherate (15 mL, 121 mmol, 2.5 eq) over 15 min. The mixture was stirred at r.t. for another 1.5 hr followed by addition of 1N aq. HCl and Et_2O. The resulting mixture was poured into 10% aq. NaOH, and extracted with Et_2O. Combined organic layers were dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography using PE/EtOAc/$NH_3.H_2O$ (4:1:0.1%) to afford the desired product. LC-MS: m/z 134.1 $(M+H)^+$.

Preparation of 2-amino-2-methylpropanenitrile



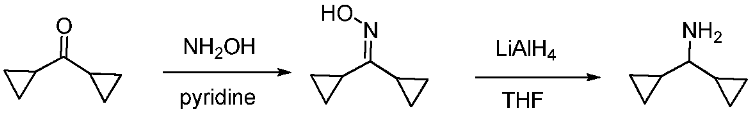
To a mixture of NH_4Cl (4.9 g, 92.3 mmol) and acetone (7 mL, 92.3 mmol) in ammonium hydroxide (40 mL, 230.7 mmol) was added KCN (5 g, 76.9 mmol) at r.t. The reaction mixture was stirred at r.t for 3 days. The mixture was extracted with DCM (2 x 30 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the desired product which was used directly in the next step without any further purification.

Preparation of 2-aminopropanenitrile



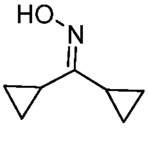
To a mixture of NH_4Cl (981 mg, 18.5mmol), acetaldehyde (1 mL, 18.5mmol) in ammonium hydroxide (3 mL) was added KCN (1 g, 15.4mmol) at room temperature. The reaction mixture was stirred at r.t for 2 days. The mixture was extracted with DCM (2 x 30 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford the desired product which was used directly in the next step without any further purification.

Preparation of dicyclopropylmethanamine



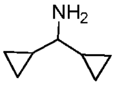
Step1. Preparation of dicyclopropylmethanoneoxime. To a mixture of dicyclopropylmethanone (500 mg, 4.5 mmol) in pyridine (5 mL) was added hydroxylamine hydrochloride (469 mg, 6.75 mmol). The reaction mixture was stirred at 100°C for 4 hr and cooled to r.t followed by addition of EtOAc. The resulting mixture was washed with 1 N aq. HCl and brine, dried over anhydrous

Na_2SO_4, and concentrated under reduced pressure to give the desired product which was used directly in the next step without any further purification.



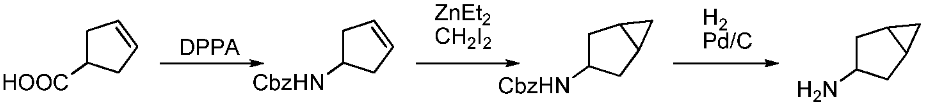
LC-MS : m/z 124.1 $(M-H)^-$.

Step 2. Preparation of dicyclopropylmethanamine. To a cooled solution of dicyclopropylmethanoneoxime (550 mg, 4.4 mmol) in THF (5 mL) was added $LiAlH_4$ (200 mg, 5.3 mmol). The mixture was then stirred at 80°C for 6 hr and cooled to room temperature. The mixture was quenched by 1N aq.NaOH until gas evolution ceased and then filtered. The filtrate was extracted with EtOAc. Combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the desired product which was used directly in the next step without any further purification.

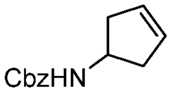


LC-MS : m/z 112.1 $(M+H)^+$.

Preparation of bicyclo[3.1.0]hexan-3-amine

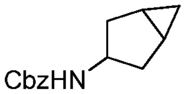


Step 1: Preparation of benzyl cyclopent-3-enylcarbamate. To a solution of cyclopent-3-enecarboxylic acid (5 g, 44.6 mmol, 1eq) and DPPA (13.5 g, 49 mmol, 1.1 eq) in toluene (80 mL) was added Et_3N (7.4 mL, 53.5 mmol, 1.2 eq) at r.t.. The mixture was then stirred at reflux for 2hr during which period a larger amount of nitrogen evolved. After BnOH (7 mL, 66.9 mmol, 1.5 eq) was added, the resulting mixture was stirred at 100°C overnight and cooled to room temperature. After quenched with saturated aqueous $NaHCO_3$. The resulting mixture was extracted with EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography using PE/EtOAc (5:1) as eluent to give the desired product.



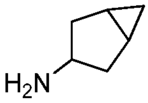
LC-MS: m/z 218.0 $(M+H)^+$.

Step 2: Preparation of benzyl bicyclo[3.1.0]hexan-3-ylcarbamate. To a solution of benzyl cyclopent-3-enylcarbamate (1 g, 4.6 mmol, 1 eq) in anhydrous DCM at 0°C under an atmosphere of nitrogen was added $ZnEt_2$ (9.7 mL, 9.7 mmol, 2.1 eq), followed by dropwise addition of CH_2I_2 (0.78 mL, 9.7 mmol, 2.1 eq). The reaction mixture was warmed to room temperature and stirred for 4 hr. The resulting reaction mixture was quenched with brine and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography using PE/EtOAc (5:1) as eluent to give the desired product.



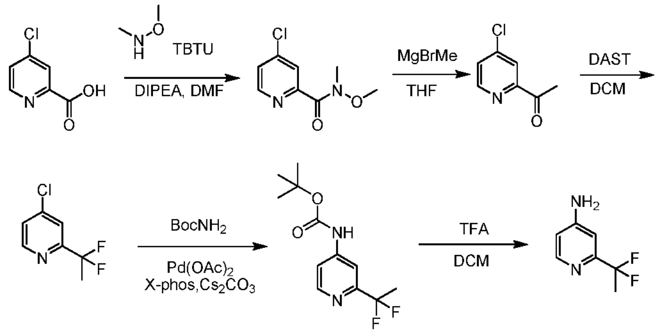
LC-MS: m/z 232.1 $(M+H)^+$.

Step 3: Preparation of bicyclo[3.1.0]hexan-3-amine. To a solution of benzyl bicyclo[3.1.0]hexan-3-ylcarbamate (2 g) in MeOH (20 mL) at r.t. under an atmosphere of nitrogen was added Pd/C (0.2 g)in one portion. The resulting mixture was then stirred under a hydrogen balloon overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the desired product which was used directly in the next step without any further purification.

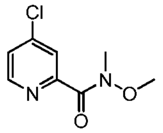


LC-MS: m/z 98.1 $(M+H)^+$.

Preparation of 2-(1,1-difluoroethyl)pyridin-4-amine

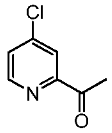


Step 1: Preparation of 4-chloro-N-methoxy-N-methylpicolinamide. To a solution of 4-chloropicolinic acid (10 g, 63.5 mmol) in DMF (150 mL) was added TBTU (30.6 g, 95.2 mmol), N,O-dimethylhydroxylamine(9.3 g, 95.2 mmol) and DIPEA (24.6 g, 190.4 mmol) at 0°C.The mixture was stirred at room temperature overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give the desired product.



LC-MS: m/z 201.0 $(M+H)^+$.

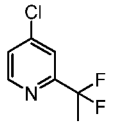
Step 2: Preparation of 1-(4-chloropyridin-2-yl)ethanone. To a solution of 4-chloro-N-methoxy-N-methylpicolinamide (11.25 g, 56.08 mmol) in THF (50 mL) at 0°C was added MeMgBr (28.04mL, 84.12 mmol). The mixture was then stirred at r.t. overnight and quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give the desired product.



^1H NMR (400 MHz, $CDCl_3$): δ8.52(d, J = 5.2 Hz, 1H), 7.96 (s, 1H), 7.40 (d, J = 5.2 Hz, 1H), 2.64 (s, 3H).LC-MS: m/z 156.0 $(M+H)^+$.

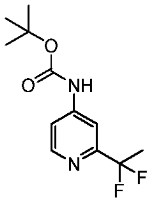
Step 3: 4-chloro-2-(1,1-difluoroethyl)pyridine. To a solution of 1-(4-chloropyridin-2-yl)ethanone (6.3 g, 40.5 mmol) in DCM (30 mL)was added DAST (65.2 g, 405 mmol) at 0°C. The mixture was then stirred at r.t. overnight and quenched with saturated aqueous $NaHCO_3$.

The resulting mixture was extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give the desired product.



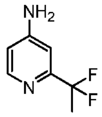
^1H NMR (400 MHz, $CDCl_3$):δ8.48 (d, *J* = 5.2 Hz, 1H), 7.60 (s, 1H), 7.31 (d, *J* = 5.2 Hz, 1H) , 1.90-1.99 (m, 3H).LC-MS: m/z 178.0 $(M+H)^+$.

Step 4:Preparation of tert-butyl (2-(1,1-difluoroethyl)pyridin-4-yl)carbamate. To a solution of 4-chloro-2-(1,1-difluoroethyl)pyridine (6.0 g, 33.8 mmol) in dioxane(20 mL)was added $BocNH_2$(4.74 g, 40.5 mmol), X-phos (1.14 g, 1.7 mmol), $CsCO_3$ (16.5 g, 50.7 mmol) and $Pd(OAc)_2$ (1.32 g, 2.7 mmol) at room temperature. The mixture was then stirred at 80 °C overnight and then cooled to room temperature. The reaction mixture was diluted with Sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4andconcentrated. The residue was purified by flash chromatography to give the desired product.



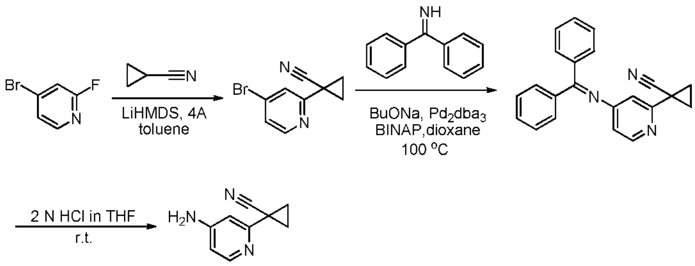
LC-MS: m/z 259.1$(M+H)^+$.

Step 5:Preparation of 2-(1,1-difluoroethyl)pyridin-4-amine. A solution of tert-butyl (2-(1,1-difluoroethyl)pyridin-4-yl)carbamate (7.97 g, 30.86 mmol) in DCM (30 mL) was cooled under ice-water bath. TFA (10 mL) was then added dropwise. The reaction mixture was stirred at room temperature for 4 hrs and monitored by TLC. Once the reaction completed, the mixture was diluted with water and adjusted pH>7 by saturated aqueous $NaHCO_3$. The resulting mixture was extracted with DCM. Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give the desired product which was used in the next step without further purification.

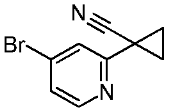


LC-MS: m/z 159.1 $(M+H)^+$.

Preparation of1-(4-aminopyridin-2-yl)cyclopropanecarbonitrile

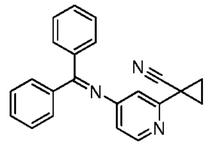


Step 1: Preparation of1-(4-bromopyridin-2-yl)cyclopropanecarbonitrile. LiHMDS (1M in toluene, 17.6 mL, 17.6 mmol, 3.1 eq) was added dropwise to a cold (-5°C) mixture of 4-bromo-2-fluoropyridine (1 g, 5.7 mmol), cyclopanecarbonitrile (1.25 mL, 17 mmol, 3 eq) and 4A MS in toluene (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for 16 hr. After it was poured into water, the mixture was filtered. The filtrate was diluted with EtOAc and H_2O, and extracted with EtOAc. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography using PE/EtOAc (9:1) as eluent to give the desired product.



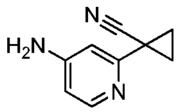
LC-MS: m/z 223.0 $(M+H)^+$.

Step 2: Preparation of1-(4-(diphenylmethyleneamino)pyridin-2-yl) cyclopropanecarbonitrile. To a mixture of 1-(4-bromopyridin-2-yl)cyclopropanecarbonitrile (0.45g, 2.1 mmol), BINAP (0.04 g, 0.063 mmol), $Pd_2(dba)_3$ (0.019g, 0.021 mmol) and NaO^tBu (0.282 g, 2.94 mmol) in toluene (6 mL) at r.t. under an atmosphere of nitrogen was added diphenylmethanimine (0.45 g, 2.51 mmol). The reaction mixture was stirred at reflux for 2 hr and then cooled to room temperature. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography to give the desired product.



LC-MS: m/z 324.1 $(M+H)^+$.

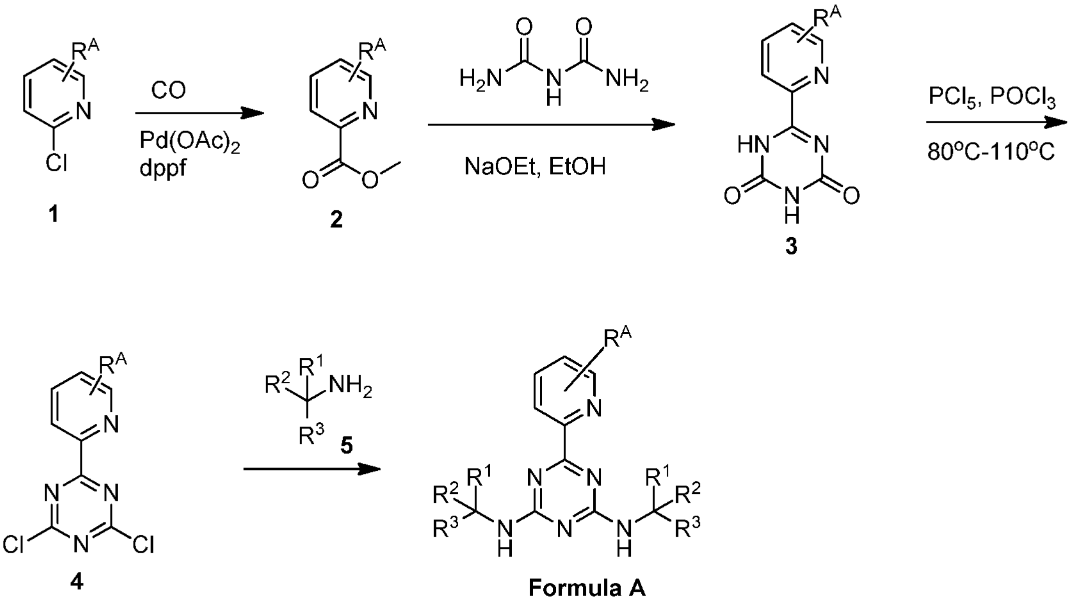
Step 3: Preparation of1-(4-aminopyridin-2-yl)cyclopropanecarbonitrile.A mixture of 1-(4-(diphenylmethyleneamino)pyridin-2-yl)cyclopropanecarbonitrile (0.48 g, 1.49 mmol), THF (10 mL) and aq. HCl (2N, 2.0 mL)was stirred at room temperature for 1 hour. The mixture was then partitioned between EtOAc (15 mL) and water (15 mL). The aqueous phase was extracted with EtOAc (2 x 25 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to give the desired product.



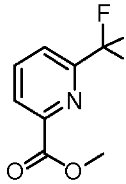
LC-MS: m/z 160.1 $(M+H)^+$.

Example 1 Preparation of Di-aliphatic Triazine Compounds of Formula A Wherein Ring A is substituted Pyridin-2-yl or Phenyl. The compounds of this Example are prepared by general **Scheme 1**, set forth below.

Scheme 1

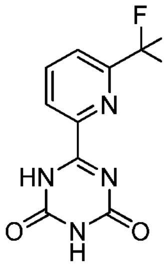


Step 1: Preparation of 6-trifluomethyl-pyridine-2-carboxylic acid methyl ester (2). To a solution of 2-chloro-6-trifluoromethyl-pyridine (2 g, 11.1 mmol, 1.0 eq) in MeOH (20 mL) was add Pd(OAc)$_2$ (124 mg, 0.05eq) and dppf (600 mg, 0.1eq) under an atmosphere of nitrogen. Et$_3$N (2.3 mL, 1.5eq) was then added to the resulting orange solution. The reaction solution was then stirred under an atmosphere of carbon monoxide (40 psi) at 60°C for 22 hr. Once the reaction completed, the mixture was filtered and the filtrate was concentrated in high vacuum. The residue was purified by column chromatography to afford the desired product.



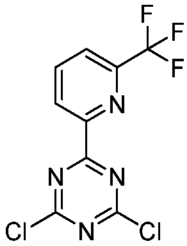
^{1}HNMR (400 MHz, CDCl$_3$): δ 8.32 (d, J = 8 Hz, 1H), 8.06 (t, J = 8 Hz, 1H), 8.88 (d, J = 8 Hz, 1H), 4.04 (s, 3H).LC-MS: m/z 206 (M+H)$^+$.

Step 2: Preparation of 6-(6- trifluomethylpyridin-2-yl)-1,3,5-triazine-2,4-dione. To a solution of freshly prepared NaOEt from Na (3.84 g, 0.16 mol, 3 eq) in ethanol (500 mL) was added methyl 6-trifluoromethylpicolinate (33 g, 0.16 mol, 3eq) and biuret (5.3 g, 0.052 mol). The resulting mixture was heated to reflux for 1 hr and then concentrated. The residue was poured into water and treated with Sat. aq. NaHCO$_3$ to adjust pH to 7. The precipitated solid was collected by filtration and dried under air to give the desired compound.



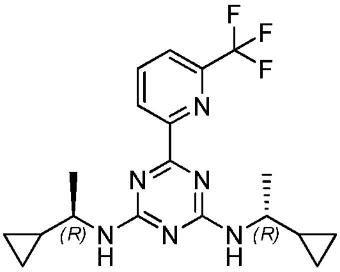
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.88 (s, 1H), 8.46 (d, J = 7.4 Hz, 1H), 8.28 (t, J = 7.3 Hz, 1H), 8.11 (d, J = 7.4 Hz, 1H).LC-MS: m/z 259 (M+H)$^+$.

Step 3: Preparation of 2,4-dichloro-6-(6-trifluomethyl-pyridin-2-yl)-1,3,5-triazine. To a solution of 6-(6-trifluomethyl-pyridin-2-yl)-1,3,5-triazine-2,4(1H,3H)-dione (3.37 g, 0.013mol) in $POCl_3$ (48 mL) was added PCl_5 (23 g, 0.1 mol). The mixture was stirred at 100°C for 2 hr and then concentrated. The residue was dissolved inEtOAc and then washed with Sat. aq. $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated to give the desired product.



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 7.9 Hz, 1H), 8.19 (t, J = 7.9 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H).LC-MS: m/z 294.9 $(M+H)^+$.

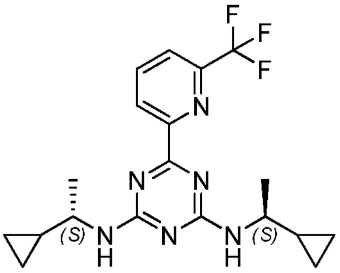
Step 4: Preparation of N^2,N^4-bis((R)-1-cyclopropylethyl)-6-(6-(trifluoromethyl) -pyridin-2-yl)-1,3,5-triazine-2,4-diamine. To a mixture of 2,4-dichloro-6-(6-(trifluoromethyl)pyridine-2-yl)-1,3,5-triazine (600 mg, 2.0mmol, 1.0 eq) and (R)-1-cyclopropylethanamine hydrochloride salt (536 mg, 4.4mmol, 2.2eq) in THF (12 mL) were added CsF (1.2 g, 8.0mmol, 2eq) and DIPEA (1.4 mL, 8.0mmol, 4eq) at room temperature. The mixture was stirred at 60°C overnight and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by a standard method to give the desired product.



^{1}H NMR (400 MHz, CD_3OD): δ 8.70-8.68 (m, 1 H), 8.34-8.32 (m, 1 H), 8.16-8.14 (m, 1 H), 3.61-3.57 (m, 2 H), 1.36-1.32 (m, 6 H), 1.06-1.01 (m, 2 H), 0.61-0.39 (m, 8 H).LC-MS: m/z 393.2 $(M+H)^+$.

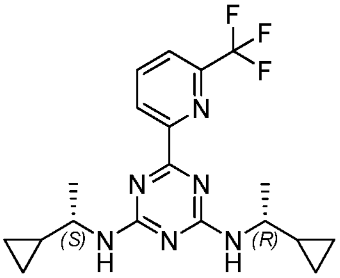
The procedure set forth above was used to produce the following compounds using the appropriate starting materials.

Compound N^2,N^4-bis((S)-1-cyclopropylethyl)-6-(6-(trifluoromethyl)pyridin-2-yl)- 1,3,5-triazine-2,4-diamine



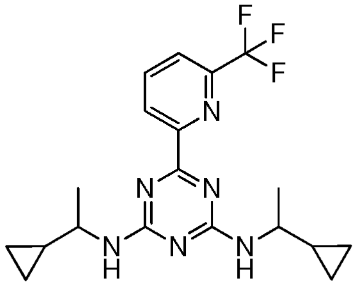
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.50 (s, 1H), 7.99 (t, J = 7.9 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 5.44 – 5.18 (m, 2H), 3.66 – 3.57 (m, 2H), 1.27 (d, J = 5.4 Hz, 6H), 0.93 – 0.88 (m, 2H), 0.52 – 0.27 (m, 8H).LC-MS: m/z 393.2 (M+H)$^+$.

Compound N^2-((R)-1-cyclopropylethyl)-N^4-((S)-1-cyclopropylethyl)-6-(6-(trifluoro methyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



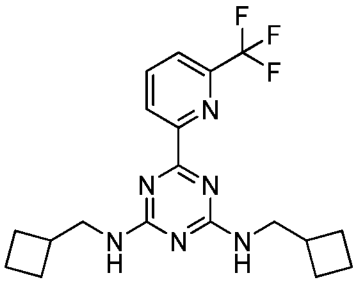
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.51 (s, 1H), 7.99 (t, J = 7.9 Hz, 1H), 7.77 (d, J = 7.3 Hz, 1H), 5.46 – 5.19 (m, 2H), 3.67 – 3.54 (m, 2H), 1.32 – 1.22 (m, 6H), 0.95 – 0.83 (m, 2H), 0.59 – 0.23 (m, 8H).LC-MS: m/z 393.2(M+H)$^+$.

Compound N^2,N^4-bis(1-cyclopropylethyl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5 -triazine-2,4-diamine



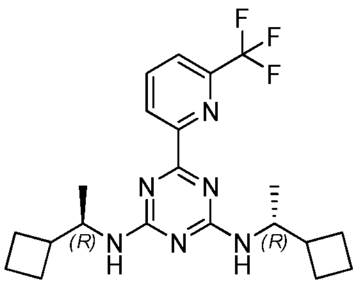
^{1}HNMR (400 MHz, CD_3OD): δ8.6 (m, 1H), 8.2-8.1 (m, 1H), 8.0-7.9 (m, 1H), 4.0-3.52 (m, 2H), 1.4-1.2 (m, 6H), 1.0 (m, 2H), 0.6-0.35 (m, 6H), 0.35-0.2 (m, 2H).LC-MS: m/z 393.2 $(M+H)^+$.

Compound N^2,N^4-bis(cyclobutylmethyl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5 -triazine-2,4-diamine



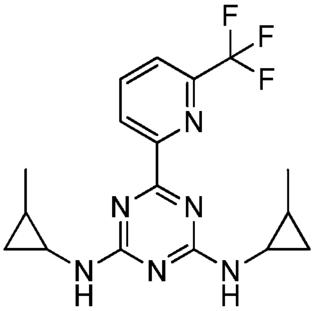
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (m, 1H), 8.00 (m, 1H), 7.78 (d, J = 5.9 Hz, 1H), 5.27 (m, 2H), 3.69 – 3.32 (m, 4H), 2.59 (m, 2H), 2.10 (m, 4H), 1.92 (m, 4H), 1.84 – 1.62 (m, 4H).LC-MS: m/z 393.2 $(M+H)^+$.

Compound N^2,N^4-bis((R)-1-cyclobutylethyl)-6-(6-(trifluoromethyl)pyridin-2-yl)- 1,3,5-triazine-2,4-diamine



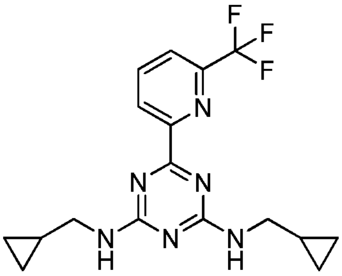
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 – 8.41 (m, 1H), 7.99 (d, J = 7.4 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 5.34 – 4.84 (m, 2H), 4.30 – 3.96 (m, 2H), 2.44 – 2.28 (m, 2H), 2.09 – 1.96 (m, 4H), 1.93 – 1.78 (m, 8H), 1.14 (d, J = 5.9 Hz, 6H).LC-MS: m/z 421.2 $(M+H)^+$.

Compound N^2,N^4-bis(2-methylcyclopropyl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



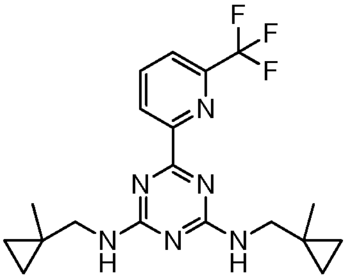
^{1}HNMR (400 MHz, CD_3OD): δ8.65-8.4 (m, 1H), 8.1-7.75 (m, 2H), 2.55-2.25 (m, 2H), 1.2-1.0 (m, 6H), 0.9-0.8 (m, 2H), 0.7-0.6 (m, 2H), 0.5-0.38 (m, 2H).LC-MS: m/z 365.3 $(M+H)^+$.

Compound N^2,N^4-bis(cyclopropylmethyl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



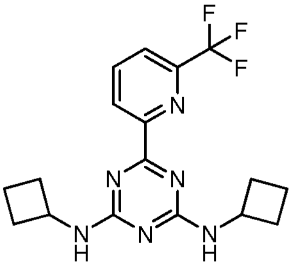
^{1}H NMR (400 MHz, CD_3OD): δ 8.60-8.68 (m, 1H), 8.21 (t, J = 8.0 Hz, 1H), 7.93-8.00 (m, 1H), 3.26-3.42 (m, 4H), 1.08-1.19 (m, 2H), 0.51-0.58 (m, 4H), 0.25-0.34 (m, 4H).LC-MS: m/z 365.2 $(M+H)^+$.

Compound N^2,N^4-bis((1-methylcyclopropyl)methyl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



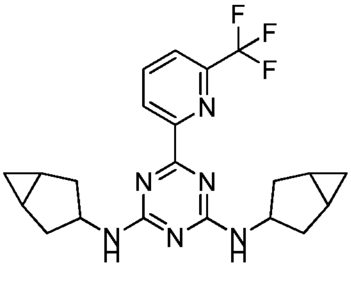
^{1}HNMR (400 MHz, CD_3OD): δ 8.61-8.59 (m, 1 H), 8.17-8.15 (m, 1H), 7.94-7.92 (m, 1H), 3.43-3.33 (m, 4H), 1.14 (s, 6H), 0.55-0.53 (m, 4H), 0.34-0.32 (m, 4H).LC-MS: m/z 393.2 $(M+H)^+$.

Compound N^2,N^4-dicyclobutyl-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine- 2,4-diamine



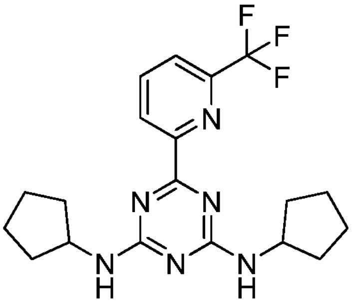
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 – 8.38 (m, 1H), 7.99 (d, J = 6.8 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 5.52 (m 2H), 4.80 – 4.32 (m, 2H), 2.41 (s, 4H), 2.20 (s, 1H), 2.06 – 1.62 (m, 8H).LC-MS: m/z 365.2 $(M+H)^+$.

Compound N^2,N^4-di(bicyclo[3.1.0]hexan-3-yl)-6-(6-(trifluoromethyl)pyridin-2-yl) -1,3,5-triazine-2,4-diamine



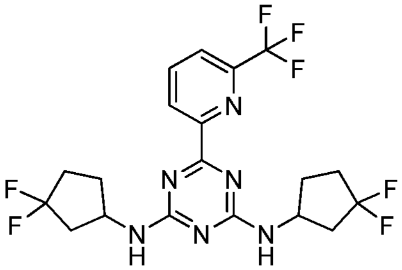
^{1}H NMR (400 MHz, CD_3OD): δ 8.66 – 8.57 (m, 1H), 8.14 (t, J = 8.0 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 4.60 -4.44 (m, 2H), 2.44 – 2.21 (m, 4H), 1.80 – 1.69 (m, 4H), 1.35 (d, J = 3.4 Hz, 4H), 0.69 – 0.53 (m, 2H), 0.32 (d, J = 4.3 Hz, 2H).LC-MS: m/z 417.2 $(M+H)^+$.

Compound N,N'-dicyclopentyl-6-(6-trifluoromethyl-pyridin-2-yl)-[1,3,5]triazine- 2,4-diamine



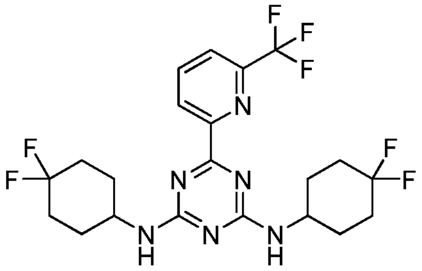
^{1}HNMR (400 MHz, CD_3OD): δ 8.60-8.68 (m, 1H), 8.20 (t, J = 7.6 Hz, 1H), 7.95-8.01 (m, 1H), 4.29-4.55 (m, 2H), 2.00-2.15 (m, 4H), 1.75-1.84 (m, 4H), 1.51-1.74 (m, 8H).LC-MS : m/z 393.5 $(M+H)^+$.

Compound N^2,N^4-bis(3,3-difluorocyclopentyl)-6-(6-(trifluoromethyl)pyridin-2-yl)- 1,3,5-triazine-2,4-diamine



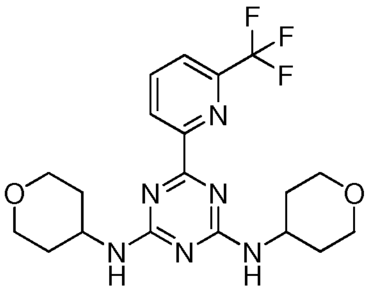
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (m, 1H), 8.08 – 8.02 (m, 1H), 7.85 – 7.80 (m, 1H), 5.78 – 5.18 (m, 2H), 4.82 – 4.38 (m, 2H), 2.82 – 2.50 (m, 2H), 2.31 – 2.05 (m, 8H), 1.93 - 1.80 (m, 2H).LC-MS: m/z 465.2 $(M+H)^+$.

Compound N^2,N^4-bis(4,4-difluorocyclohexyl)-6-(6-(trifluoromethyl)pyridin-2-yl)- 1,3,5-triazine-2,4-diamine



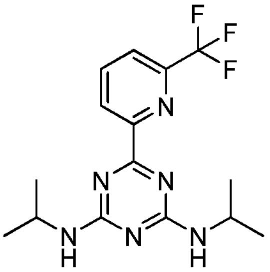
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.64 – 8.42 (m, 1H), 8.05 (t, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 6.6 Hz, 1H), 6.24 – 5.25 (m, 2H), 4.18 – 4.01 (m, 2H), 2.43 – 1.48 (m, 16H).LC-MS: m/z 493.2 (M+H)$^+$.

Compound N,N'-bis-(tetrahydro-pyran-4-yl)-6-(6-trifluoromethyl-pyridin- 2-yl)-[1,3,5]triazine-2,4-diamine



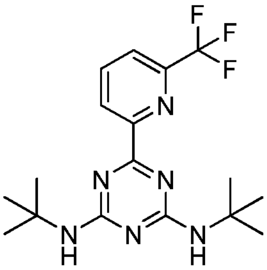
^{1}HNMR (400 MHz, DMSO-d$_6$): δ 7.43-8.55 (m, 5H), 3.82-4.15 (m, 6H), 3.48-3.50 (m, 4H), 1.75-1.87 (m, 4H), 1.46-1.60 (m, 4H).LC-MS : m/z 425.1 (M+H)$^+$.

Compound N^2,N^4-diisopropyl-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine -2,4-diamine



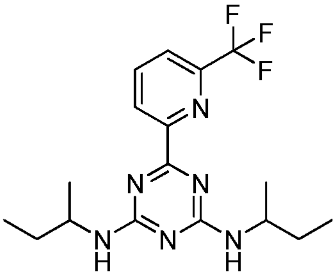
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.67 – 8.41 (m, 1H), 7.99 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 5.18 (m, 2H), 4.45 – 4.03 (m, 2H), 2.15 (m, 1H), 1.26 (d, *J* = 4.5 Hz, 12H).LC-MS: m/z 341.2 (M+H)$^+$.

Compound N^2,N^4-di-tert-butyl-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine -2,4-diamine



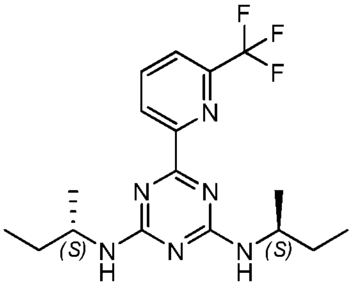
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 – 8.31 (m, 1H), 8.19 – 8.12 (m, 1H), 7.93 (d, *J* = 7.3 Hz, 1H), 7.16 – 6.77 (m, 2H), 1.35 (s, 18H).LC-MS: m/z 369.2 (M+H)$^+$.

Compound N,N'-di-sec-butyl-6-(6-trifluoromethyl-pyridin-2-yl)-[1,3,5]triazine- 2,4-diamine



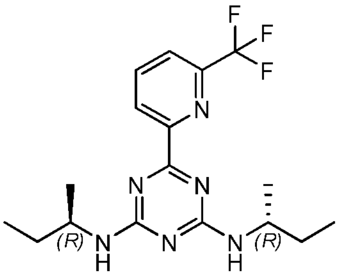
^{1}HNMR (400 MHz, CD_3OD): δ 8.42-8.68 (m, 1H), 8.15-8.21 (m, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 4.01-4.29 (m, 2H), 1.55-1.69 (m, 4H), 1.19-1.30 (m, 6H), 0.95-1.05 (m, 6H).LC-MS : m/z 369.5 (M+H)$^+$.

Compound N,N'-Di-sec-butyl-6-(6-trifluoromethyl-pyridin-2-yl)-[1,3,5]triazine-2,4 –diamine



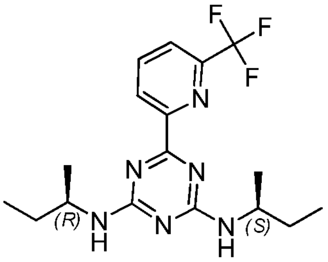
^{1}HNMR (400 MHz, CD_3OD): δ 8.72-8.79 (m, 1H), 8.38-8.43 (m, 1 H), 8.20-8.23 (m, 1H), 4.13-4.45 (m, 2H), 1.67-1.74 (m, 4H), 1.29-1.33 (m, 6H), 1.01-1.05 (m, 6H).LC-MS: m/z 369.2 (M+H)$^+$.

Compound N^2,N^4-di-sec-butyl-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4- diamine



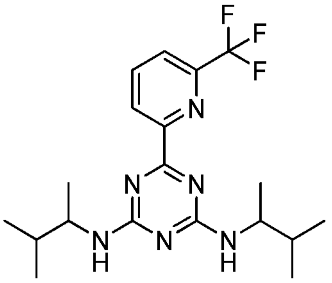
^{1}HNMR (400 MHz, CD_3OD): δ 8.72-8.79 (m, 1H), 8.38-8.43 (m, 1 H), 8.20-8.23 (m, 1H), 4.13-4.45 (m, 2H), 1.67-1.74 (m, 4H), 1.29-1.33 (m, 6H), 1.01-1.05 (m, 6H).LC-MS: m/z 369.2 $(M+H)^+$.

Compound N^2-((R)-sec-butyl)-N^4-((S)-sec-butyl)-6-(6-(trifluoromethyl)pyridin- 2-yl)-1,3,5-triazine-2,4-diamine



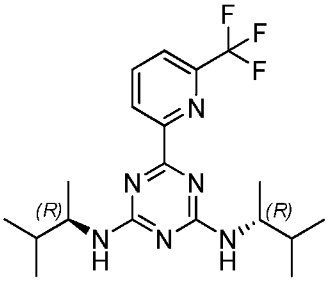
^{1}H NMR (400 MHz, CD_3OD): δ 8.59-8.65 (m, 1H), 8.15-8.19 (m, 1 H), 7.94-7.95 (m, 1H), 4.06-4.24 (m, 2H), 1.58-1.65 (m, 4H), 1.21-1.26 (m, 6H), 0.98-1.01 (m, 6H).LC-MS: m/z 369.2 $(M+H)^+$.

Compound N^2,N^4-bis(3-methylbutan-2-yl)-6-(6-(trifluoromethyl)pyridin-2-yl)- 1,3,5-triazine-2,4-diamine



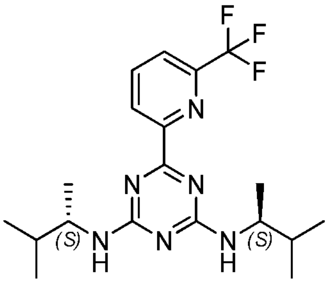
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.58 – 8.47 (m, 1H), 7.99 (t, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 5.30 – 5.03 (m, 2H), 4.16 – 3.97 (m, 2H), 1.93 – 1.75 (m, 2H), 1.16 (d, *J* = 6.6 Hz, 6H), 0.97 – 0.93 (m, 12H).LC-MS: m/z 397.2 (M+H)$^+$.

Compound N^2,N^4-bis((R)-3-methylbutan-2-yl)-6-(6-(trifluoromethyl)pyridin-2-yl)- 1,3,5-triazine-2,4-diamine



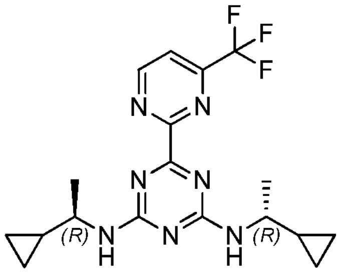
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.46 (m, 1H), 8.21 (m, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.36 (m, 2H), 3.90 (m 2H), 1.79 (m, 2H), 1.05 (t, *J* = 7.6 Hz, 6H), 0.87 (t, *J* = 7.6 Hz, 12H).LC-MS: m/z 397.2 (M+H)$^+$.

Compound N^2,N^4-bis((S)-3-methylbutan-2-yl)-6-(6-(trifluoromethyl)pyridin-2-yl)- 1,3,5-triazine-2,4-diamine



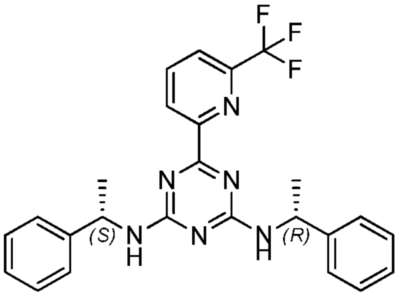
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.46 (d, *J* = 7.9 Hz, 1H), 8.24 (d, *J* = 6.9 Hz, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.55 (m, 2H), 4.25 – 3.78 (m, 1H), 1.93 – 1.65 (m, 1H), 1.15 – 1.00 (m, 6H), 0.89 (t, *J* = 7.8 Hz, 12H).LC-MS: m/z 397.2 (M+H)$^+$.

Compound N^2,N^4-bis((R)-1-cyclopropylethyl)-6-(4-(trifluoromethyl)pyrimidin -2-yl)-1,3,5-triazine-2,4-diamine



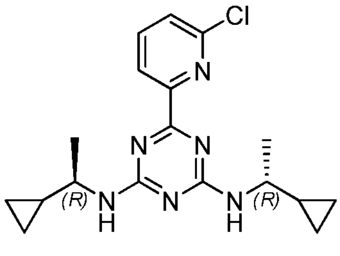
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H), 7.74 (s, 1H), 5.46 (m, 2H), 3.59 (m, 2H), 1.26 (m, 8H), 0.91 (s, 2H), 0.65 – -0.27 (m, 8H).LC-MS: m/z 394.2 $(M+H)^+$.

Compound N^2-((R)-1-phenylethyl)-N^4-((S)-1-phenylethyl)-6-(6-(trifluoromethyl) pyridin-2-yl)-1,3,5-triazine-2,4-diamine



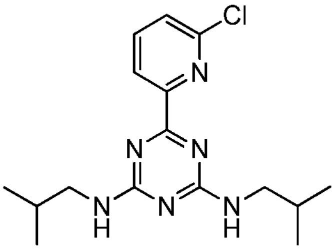
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 – 8.33 (m, 1H), 8.05 – 7.86 (m, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.52 – 7.18 (m, 10H), 5.82 – 5.40 (m, 2H), 5.37 – 4.92 (m, 2H), 1.65 – 1.39 (m, 6H).LC-MS: m/z 465.2 $(M+H)^+$.

Compound 6-(6-chloropyridin-2-yl)-N^2,N^4-bis((R)-1-cyclopropylethyl)-1,3,5-tria -zine-2,4-diamine



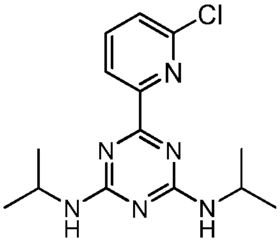
^{1}H NMR (400 MHz, CD_3OD): δ 8.37 (t, *J* = 7.8 Hz, 1H), 8.02 (t, *J* = 7.8 Hz, 1H), 7.71 – 7.65 (m, 1H), 3.74 – 3.54 (m, 2H), 1.32 (d, *J* = 6.6 Hz, 6H), 1.08 – 0.94 (m, 2H), 0.63 – 0.21 (m, 8H).LC-MS: m/z 359.2 $(M+H)^+$.

Compound 6-(6-chloropyridin-2-yl)-N^2,N^4-diisobutyl-1,3,5-triazine-2,4-diamine



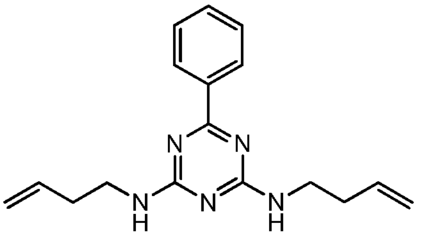
^{1}HNMR (400 MHz, CD3OD): δ8.5-8.38 (m, 1H), 8.0-7.9 (m, 1H), 7.6-7.5 (m, 1H), 3.35-3.16 (m, 4H), 2.0-1.9 (m, 2H), 1.0-0.9 (m, 12H).LC-MS: m/z 335.1 $(M+H)^+$.

Compound 6-(6-chloropyridin-2-yl)-N^2,N^4-diisopropyl-1,3,5-triazine-2,4-diamine



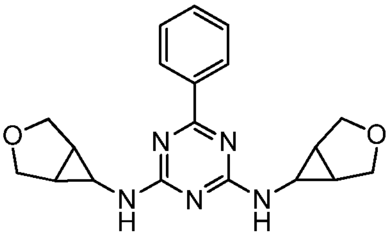
^{1}HNMR (400 MHz, CD_3OD): δ 8.25-8.19 (m, 1H), 7.81 (brs, 1 H), 7.46 (d, J = 7.6 Hz, 1H), 4.26-4.11 (m, 2H), 1.15 (d, J = 6.0 Hz, 12H).LC-MS: m/z 307.1 $(M+H)^+$.

Compound N^2,N^4-di(but-3-en-1-yl)-6-phenyl-1,3,5-triazine-2,4-diamine



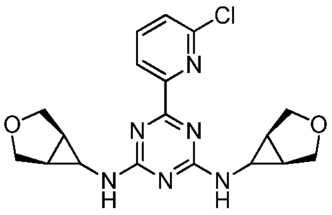
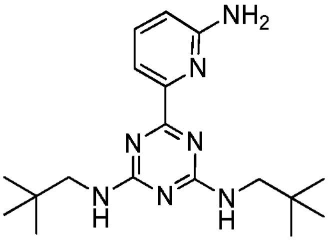
^{1}HNMR (400 MHz, CD_3OD): δ8.19-8.13 (m, 2H), 7.77-7.61 (m, 3H), 5.95-5.85 (m, 2H), 5.20-5.11 (m, 4H), 3.72-3.59 (m, 4H), 2.49-2.44 (m, 4H).LC-MS: m/z 296.3 $(M+H)^+$.

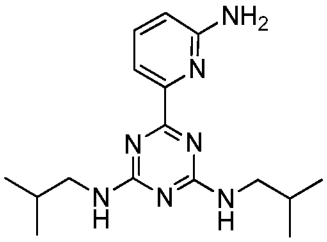
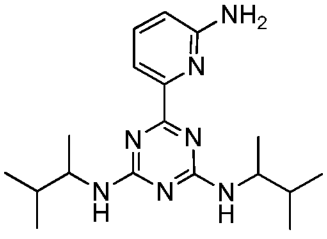
Compound N^2,N^4-di(3-oxabicyclo[3.1.0]hexan-6-yl)-6-phenyl-1,3,5-triazine-2,4- diamine



^{1}HNMR (400 MHz, CD_3OD): δ 8.35-8.1 (m, 2H), 8.3-8.2 (m, 1H), 7.7-7.6 (m, 2H), 4.1-4.0 (m, 4H), 3.85-3.7 (m, 4H), 2.9-2.55 (m, 2H), 2.1-2.0 (m, 2H).LC-MS: m/z 352.2 $(M+H)^+$.

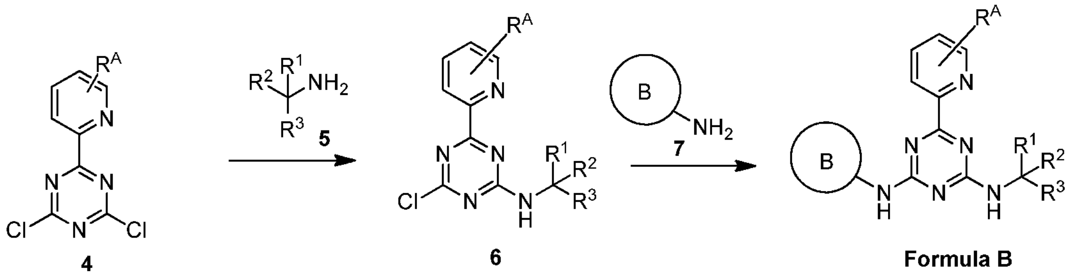
Table 1: The following compounds were prepared by following the procedure described in Scheme 1 above.

Compound No.	**Name**	**Structure**	**LCMS**	
			Expected MW	**Found $(M+1)^+$**
72	***N*²,*N*⁴-di((1R,5S)-3-oxabicyclo[3.1.0]hexan-6-yl)-6-(6-chloropyridin- 2-yl)-1,3,5-triazine-2,4-diamine**		386.1	387.1
73	***6-(6-aminopyridin-2-yl)-N²,N⁴-dineopentyl-1,3,5-triazine-2,4-diamine***		343.2	344.2

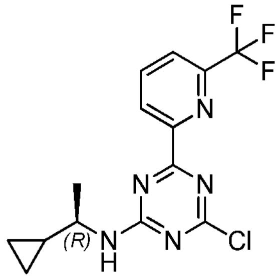
74	***6-(6-aminopyridin-2-yl)-N^2,N^4-diisobutyl-1,3,5-triazine-2,4-diamine***		315.2	316.2
	6-(6-aminopyridin-2-yl)-N^2,N^4-bis(3-methylbutan-2-yl)-1,3,5-triazine- 2,4-diamine		343.2	344.2

Example 2 Preparation of Di-aliphatic Triazine Compounds of Formula B Wherein Ring A is substituted Pyridin-2-yl or Phenyl. The compounds of this Example are prepared by general **Scheme 2**, set forth below.

Scheme 2

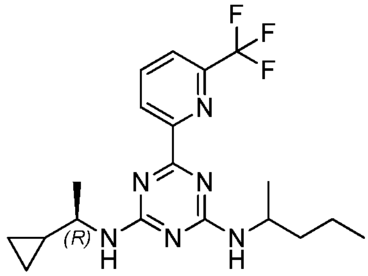


Step 1:Preparation of(R)-4-chloro-N-(1-cyclopropylethyl)-6- (6-(trifluoromethyl) pyridin-2-yl)-1,3,5-triazin-2-amine. To a mixture of 2,4-dichloro-6-(6-(trifluoromethyl)pyridine -2-yl)-1,3,5-triazine (600 mg, 2.0mmol, 1.0 eq) and (R)-1-cyclopropylethanamine hydrochloride salt (268 mg, 2.2mmol, 1.1 eq) in THF (6 mL) were added CsF (608 mg, 4.0mmol, 2eq) and DIPEA (0.7 mL, 4.0mmol, 2 eq) at room temperature. The mixture was stirred at 40°C overnight and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by a standard method to give the desired product.



LC-MS: m/z 344.1 $(M+H)^+$.

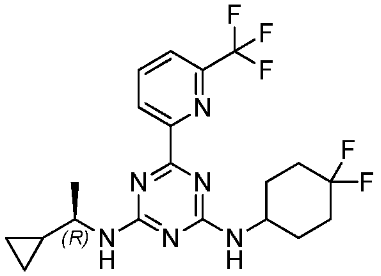
Step2: Preparation of N^2-((R)-1-cyclopropylethyl)-N4-(pentan-2-yl)-6- (6-(trifluoromethyl)pyridin-2-yl) -1,3,5-triazine-2,4-diamine. To a mixture of (R)-4-chloro-N-(1-cyclopropylethyl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazin-2-amine (80 mg, 0.23mmol, 1.0 eq) and pentan-2-amine (25 mg,0.28mmol, 1.2eq) in THF (2 mL) were added CsF (70 mg, 0.46mmol, 2eq) and DIPEA (0.08 mL, 0.46 mmol, 2 eq) at room temperature. The mixture was stirred at 60°C overnight and filtered. The filtrate was concentrated under reduced pressure and then purified by a standard method to give the desired product.



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 – 8.42 (m, 1H), 8.23 (t, J = 7.8 Hz, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 9.5 Hz, 1H), 4.27 – 3.96 (m, 1H), 3.65 – 3.47 (m, 1H), 1.60 – 1.46 (m, 1H), 1.41 – 1.29 (m, 3H), 1.22 (d, 6.5 Hz, 3H), 1.12 (d, J = 6.1 Hz, 3H), 1.01 – 0.96 (m, 1H), 0.88 (t, J = 7.1 Hz, 3H), 0.50 – 0.29 (m, 3H), 0.26 – 0.07 (m, 1H).LC-MS: m/z 395.2 $(M+H)^+$.

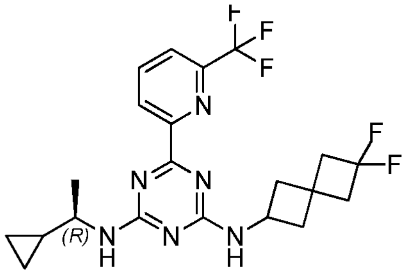
The procedure set forth above was used to produce the following compounds using the appropriate starting materials.

Compound (R)-N^2-(1-cyclopropylethyl)-N^4-(4,4-difluorocyclohexyl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



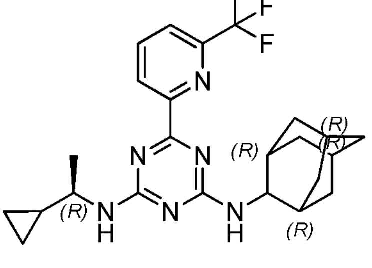
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.66 – 8.39 (m, 1H), 8.02 (t, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 5.34 (m, 2H), 4.11 (m, 1H), 3.63 (m, 1H), 2.32 – 1.54 (m, 9H), 1.29 (m, 3H), 0.95 (s, 1H), 0.70 – 0.16 (m, 4H).LC-MS: m/z 443.2 (M+H)$^+$.

Compound N^2-((R)-1-cyclopropylethyl)-N^4-(6,6-difluorospiro[3.3]heptan-2-yl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



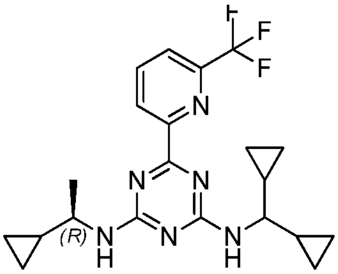
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.54 – 8.49 (m, 1H), 8.01 (t, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 5.60 – 5.27 (m, 2H), 4.57 – 4.37 (m, 1H), 3.67 – 3.57 (m, 1H), 2.70 – 2.65 (m, 2H), 2.57 (m, 3H), 2.22 – 1.92 (m, 4H), 1.30 (d, *J* = 5.8 Hz, 2H), 0.93 (s, 1H), 0.54 – 0.29 (m, 4H).LC-MS: m/z 455.2 (M+H)$^+$.

Compound N^2-((1R,3R,5R,7R)-adamantan-2-yl)-N^4-((R)-1-cyclopropylethyl) -6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



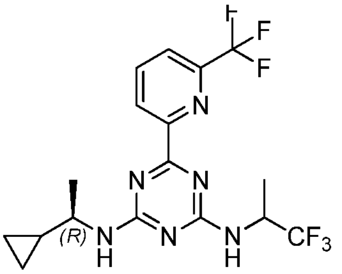
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.63 – 8.34 (m, 1H), 8.00 (t, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 5.57 (m, 2H), 4.21 (m, 1H), 3.85 – 3.32 (m, 1H), 2.22 – 1.57 (m, 15H), 1.25 (m, 4H), 0.90 (m, 1H), 0.66 –0.24 (m, 4H).LC-MS: m/z 459.2 (M+H)$^+$.

Compound (R)-N^2-(1-cyclopropylethyl)-N^4-(dicyclopropylmethyl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



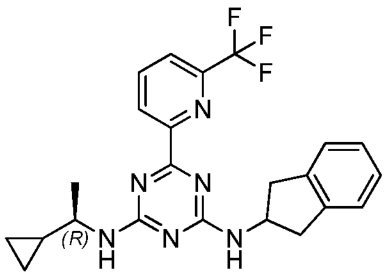
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.49 (d, *J* = 7.5 Hz, 1H), 7.99 (t, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 5.71 – 5.05 (m, 2H), 3.59 (m, 2H), 1.25 (m, 3H), 1.07 – 0.80 (m, 3H), 0.64 – 0.19 (m, 12H).LC-MS: m/z 419.2 (M+H)$^+$.

Compound N^2-((R)-1-cyclopropylethyl)-6-(6-(trifluoromethyl)pyridin-2-yl)-N^4-(1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine



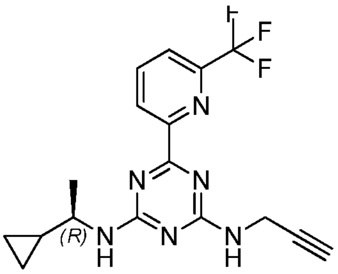
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.53 (s, 1H), 8.01 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 5.91 – 4.65 (m, 3H), 3.67 (m, 1H), 1.51 – 1.15 (m, 6H), 0.93 (s, 1H), 0.74 – 0.10 (m, 4H).LC-MS: m/z 421.1 (M+H)$^+$.

Compound (R)-N^2-(1-cyclopropylethyl)-N^4-(2,3-dihydro-1H-inden-2-yl)-6-(6 - (trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



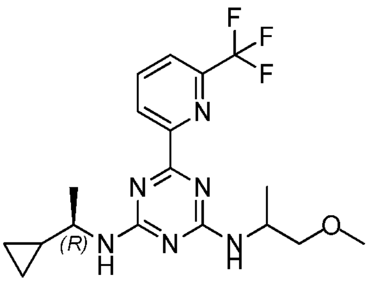
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.61 - 8.46 (m, 1H), 7.99 (t, J = 8.1 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.26 – 7.17 (m, 4H), 5.75 – 5.30 (m, 2H), 5.11 – 4.75 (m, 1H), 3.78 – 3.54 (m, 1H), 3.46 – 3.31 (m, 2H), 2.94 – 2.88 (m, 2H), 1.32 (d, J = 6.4 Hz, 3H), 1.24 – 1.19 (m, 1H), 0.98 – 0.86 (m, 1H), 0.52 – 043(m, 3H), 0.29 (s, 1H).LC-MS: m/z 441.2 (M+H)$^+$.

Compound (R)-N^2-(1-cyclopropylethyl)-N^4-(prop-2-yn-1-yl)-6-(6-(trifluoromethyl) pyridin-2-yl)-1,3,5-triazine-2,4-diamine



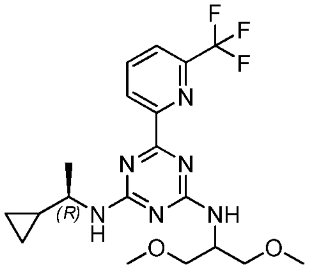
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.55 (m, 1H), 8.01 (t, J = 7.8 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 5.94 – 5.12 (m, 2H), 4.30 (m 2H), 3.59 (m, 1H), 2.23 (s, 1H), 2.01 (s, 3H), 0.90 (m, 1H), 0.59 – 0.16 (m, 4H).LC-MS: m/z 363.1 (M+H)$^+$.

Compound N^2-((R)-1-cyclopropylethyl)-N^4-(1-methoxypropan-2-yl)-6-(6-(trifluoro methyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



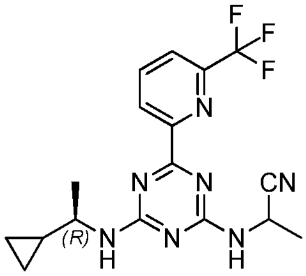
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.51 (m, 1H), 7.99 (t, J = 7.9 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 5.55 – 5.33 (m, 2H), 4.45 – 4.29 (m, 2H), 3.68 – 3.39 (m, 4H), 1.85 (s, 3H), 1.28 – 0.93 (m, 6H), 0.60 – 0.27 (m, 3H).LC-MS: m/z 397.2 (M+H)$^+$.

Compound (R)-N^2-(1-cyclopropylethyl)-N^4-(1,3-dimethoxypropan-2-yl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



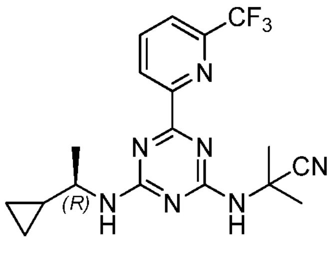
^{1}H NMR (400 MHz, CDCl$_3$): 8.47 (m, 1H), 8.05 – 7.80 (m, 1H), 7.71 (d, J = 7.7 Hz, 1H), 5.90 – 5.06 (m, 2H), 4.57 – 4.05 (m, 1H), 3.65 – 3.38 (m, 4H), 3.33 (m, 6H), 1.23 (m, 4H), 0.84 (m, 1H), 0.61 – 0.05 (m, 4H).LC-MS: m/z 427.2 (M+H)$^+$.

Compound 2-((4-(((R)-1-cyclopropylethyl)amino)-6-(6-(trifluoromethyl)pyridine -2-yl)-1,3,5-triazin-2-yl)amino)propanenitrile



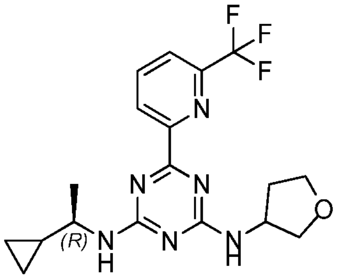
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.56 (m, 1H), 8.03 (t, J = 7.8 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 5.52 (m, 2H), 5.16 – 4.85 (m, 1H), 3.76 – 3.44 (m, 1H), 1.72 – 1.55 (m, 3H), 1.39 – 1.21 (m, 3H), 0.95 (s, 1H), 0.65 – 0.16 (m, 4H).LC-MS: m/z 378.2 (M+H)$^+$.

Compound (R)-2-(4-(1-cyclopropylethylamino)-6-(6-(trifluoromethyl)pyridin-2-yl)- 1,3,5-triazin-2-ylamino)-2-methylpropanenitrile



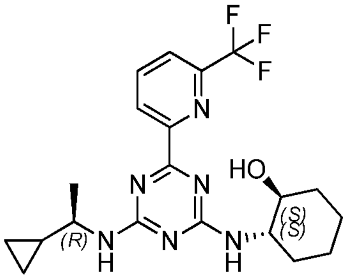
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.56 (d, J = 8.2 Hz, 1H), 8.03 (t, J = 7.7 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 5.71 – 5.54 (m, 2H), 3.70 (m, 1H), 1.82 (s, 6H), 1.36 – 1.25 (m, 4H), 0.97 (d, J = 7.7 Hz, 1H), 0.62 – 0.26 (m, 4H).LC-MS: m/z 392 (M+H)$^+$.

Compound N^2-((R)-1-cyclopropylethyl)-N^4-(tetrahydrofuran-3-yl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



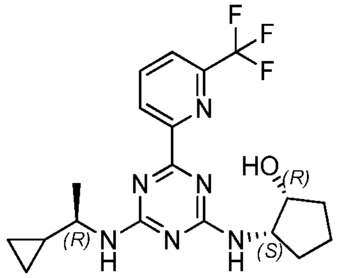
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.57 – 8.47 (m, 1H), 7.99 (t, J = 7.2 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 5.73 – 5.32 (m, 2H), 4.79 – 4.60 (m, 1H), 3.99 – 3.49 (m, 5H), 2.29 (m, 2H), 1.91 (m, 1H), 1.30 (m, 3H), 0.56 – 0.23 (m, 4H).LC-MS: m/z 395.2 (M+H)$^+$.

Compound (1S,2S)-2-(4-((R)-1-cyclopropylethylamino)-6-(6-(trifluoro-methyl)pyridin-2-yl)-1,3,5-triazin-2-ylamino)cyclohexanol



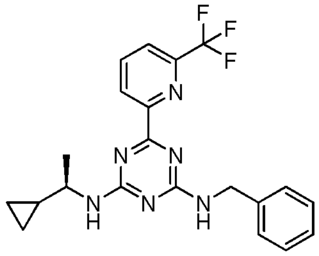
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.48 (d, J = 7.4 Hz, 1H), 8.01 (t, J = 7.8 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 5.67 – 5.28 (m, 2H), 3.65 (m, 4H), 2.09 (s, 3H), 1.47 – 1.23 (m, 8H), 0.92 (s, 1H), 0.62 – 0.40 (m, 3H), 0.30 (s, 1H).LC-MS: m/z 423.2 (M+H)$^+$.

Compound (1R,2S)-2-(4-((R)-1-cyclopropylethylamino)-6-(6-(trifluoromethyl) -pyridin-2-yl)-1,3,5-triazin-2-ylamino)cyclopentanol



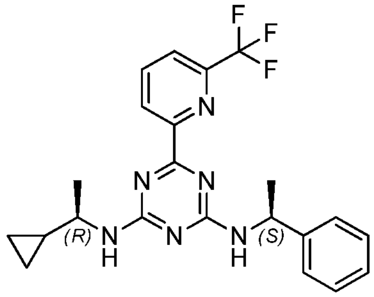
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.51 (m, 1H), 8.01 (t, J = 7.6 Hz, 1H), 7.80 (t, J = 6.4 Hz, 1H), 5.40 – 5.31 (m, 1H), 4.10 – 3.97 (m, 2H), 3.69 – 3.52 (m, 1H), 2.25 – 2.09 (m, 2H), 1.95 – 1.55 (m, 7H), 1.29 (d, J = 6.0 Hz, 2H), 0.93 (d, J = 7.5 Hz, 1H), 0.66 – 0.16 (m, 4H).LC-MS: m/z 409.2 (M+H)$^+$.

Compound (R)-N²-benzyl-N⁴-(1-cyclopropylethyl)-6-(6-(trifluoromethyl)pyridin- 2-yl)-1,3,5-triazine-2,4-diamine



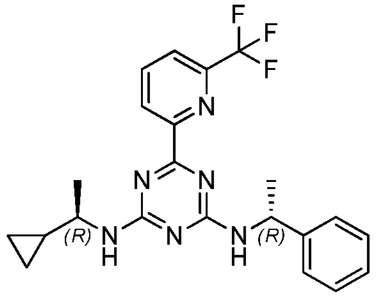
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.49 (d, J = 7.2 Hz, 1H), 7.98 (t, J = 7.7 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.31 (m, 5H), 5.51 (m, 2H), 4.67 (m, 2H), 3.63 (m, 1H), 1.27 (m, 3H), 0.91 (s, 1H), 0.38 (m, 4H).LC-MS: m/z 415.2 (M+H)$^+$.

Compound N²-((R)-1-cyclopropylethyl)-N⁴-((S)-1-phenylethyl)-6-(6-(trifluoromethyl) pyridin-2-yl)-1,3,5-triazine-2,4-diamine



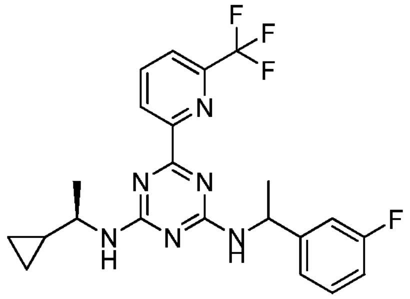
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.45 (t, *J* = 10.4 Hz, 1H), 7.98 (t, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.54 – 7.03 (m, 5H), 5.70 (d, *J* = 6.9 Hz, 1H), 5.45 (m, 1H), 5.15 (m, 1H), 3.50 (m, 1H), 1.55 (m, 3H), 1.28 (m, 1H), 0.96 (m, 3H), 0.64 – 0.18 (m, 4H).LC-MS: m/z 429.2 (M+H)$^+$.

Compound N^2-((R)-1-cyclopropylethyl)-N^4-((R)-1-phenylethyl)-6-(6-(trifluoro methyl) pyridin-2-yl)-1,3,5-triazine-2,4-diamine



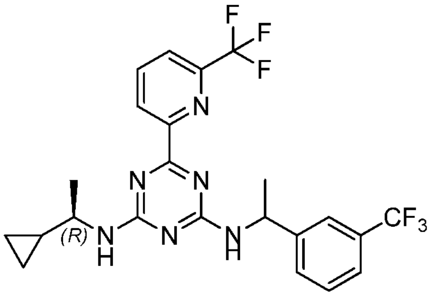
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.47 (d, *J* = 8.3 Hz, 1H), 7.98 (t, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.50 – 7.02 (m, 5H), 5.78 – 5.07 (m, 3H), 3.55 (m, 1H), 1.72 (m, 1H), 1.56 (d, *J* = 6.7 Hz, 3H), 0.97 (m, 3H), 0.58 – 0.15 (m, 4H).LC-MS: m/z 429.2 (M+H)$^+$.

Compound N^2-((R)-1-cyclopropylethyl)-N^4-(1-(3-fluorophenyl)ethyl)-6-(6 - (trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



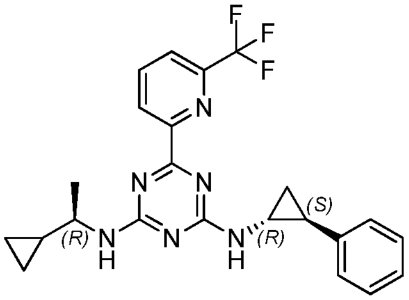
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.55 – 8.36 (m, 1H), 8.00 (t, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.18 – 6.90 (m, 3H), 5.71 – 5.06 (m, 3H), 3.78 – 3.32 (m, 1H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.34 – 1.22 (m, 3H), 1.00 (d, *J* = 6.3 Hz, 1H), 0.94 – 0.72 (m, 1H), 0.54 – 0.37 (m, 2H), 0.31 – 0.20 (m, 1H).LC-MS: m/z 447.2 (M+H)$^+$.

Compound N^2-((R)-1-cyclopropylethyl)-N^4-(1-(3-(trifluoromethyl)phenyl)ethyl) -6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



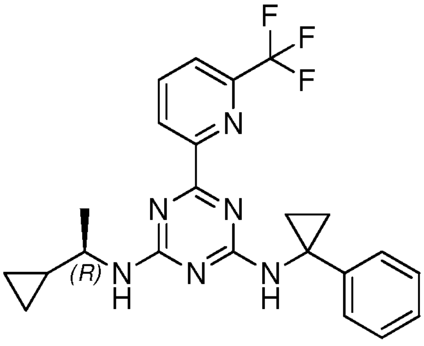
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.42 (m, 1H), 8.08 – 7.93 (m, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.67 – 7.38 (m, 4H), 5.84 – 5.49 (m, 1H), 5.49 – 5.03 (m, 2H), 3.72 – 3.16 (m, 1H), 1.57 (d, *J* = 6.9 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 1H), 0.73 (m, 1H), 0.53 – 0.41 (m, 1H), 0.37 (m, 1H), 0.25 (m, 1H).LC-MS: m/z 497.2 (M+H)$^+$.

Compound N^2-((R)-1-cyclopropylethyl)-N^4-((1R,2S)-2-phenylcyclopropyl)-6-(6 -(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



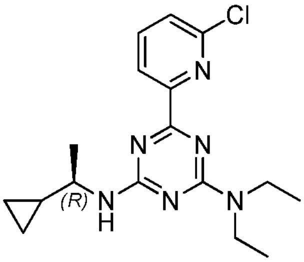
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.47 (d, *J* = 8.3 Hz, 1H), 7.98 (t, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.37 (m, 4H), 7.23 (m, 1H), 5.81 – 5.05 (m, 3H), 3.55 (m 1H), 1.72 (s, 1H), 1.56 (d, *J* = 6.7 Hz, 3H), 0.97 (m 3H), 0.63 – 0.18 (m, 4H).LC-MS: m/z 441.2 (M+H)$^+$.

Compound (R)-N^2-(1-cyclopropylethyl)-N^4-(1-phenylcyclopropyl)-6-(6-(trifluoro methyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



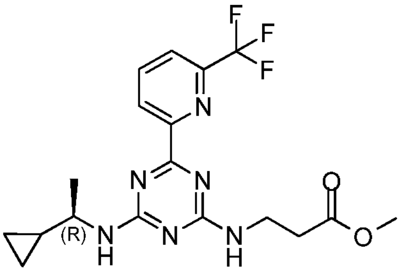
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.53 – 8.13 (m, 3H), 7.99 (m, 1H), 7.70 (m, 1H), 7.45 – 7.04 (m, 5H), 3.30 – 3.19 (m, 1H), 1.38 – 1.09 (m, 5H), 1.07 – 0.75 (m, 3H), 0.43 – -0.09 (m, 4H).LC-MS: m/z 441.2 (M+H)$^+$.

Compound (R)-6-(6-chloropyridin-2-yl)-N^2-(1-cyclopropylethyl)-N^4,N^4-diethyl- 1,3,5-triazine-2,4-diamine



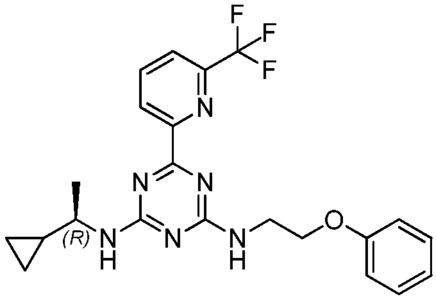
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 6.6 Hz, 1H), 7.75 (s, 1H), 7.42 (s, 1H), 5.51 (s, 1H), 3.62 (m, 5H), 1.42 – 1.03 (m, 9H), 0.92 (d, *J* = 7.7 Hz, 1H), 0.63 – 0.17 (m, 4H). LC-MS: m/z 347.2 (M+H)$^+$.

Compound (R)-methyl 3-((4-((1-cyclopropylethyl)amino)-6-(6-(trifluoromethyl)pyri -din-2-yl)-1,3,5-triazin-2-yl)amino)propanoate



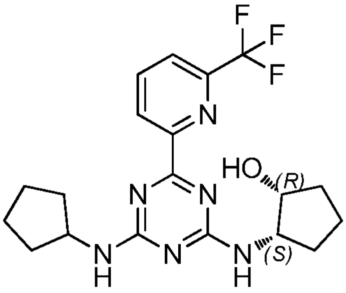
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.52 (m, 1H), 8.00 (t, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 5.63 (m, 2H), 3.73 (m, 9H), 2.66 (d, *J* = 5.9 Hz, 2H), 1.29 (m, 3H), 1.01 – 0.79 (m, 1H), 0.60 – 0.17 (m, 4H).LC-MS: m/z 411.2 (M+H)$^+$.

Compound (R)-N^2-(1-cyclopropylethyl)-N^4-(2-phenoxyethyl)-6-(6-(trifluoromethyl) pyridin-2-yl)-1,3,5-triazine-2,4-diamine



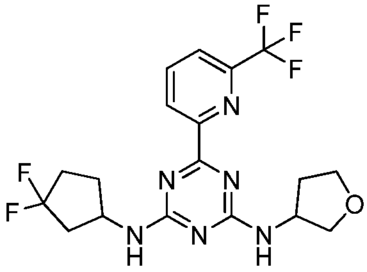
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.43 (d, *J* = 8.0 Hz, 1H), 7.93 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.34 – 7.18 (m, 2H), 7.00 – 6.69 (m, 3H), 6.03 – 5.08 (m, 2H), 4.07 (s, 2H), 3.94 – 3.71 (m, 2H), 3.53 (d, *J* = 6.8 Hz, 1H), 1.34 – 1.04 (m, 4H), 0.35 (m, 4H).LC-MS: m/z 445.2 (M+H)$^+$.

Compound (1R,2S)-2-((4-(cyclopentylamino)-6-(6-(trifluoromethyl)pyridin-2 -yl)-1,3,5-triazin-2-yl)amino)cyclopentanol



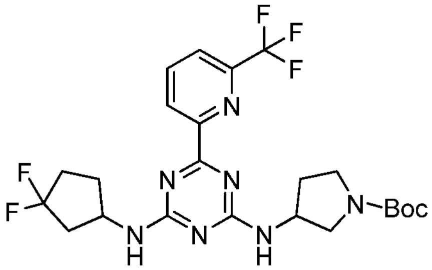
^{1}HNMR (400 MHz, CD$_3$OD): δ8.63-8.57 (m, 1H), 8.17-8.14 (m, 1 H), 7.94-7.92 (m, 1H), 4.48-4.23 (m, 3H), 2.05-1.91 (m, 5H), 1.78-1.59 (m, 9H).LC-MS: m/z 409.3 (M+H).

Compound N^2-(3,3-difluorocyclopentyl)-N^4-(tetrahydrofuran-3-yl)-6-(6-(trifluoro methyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine



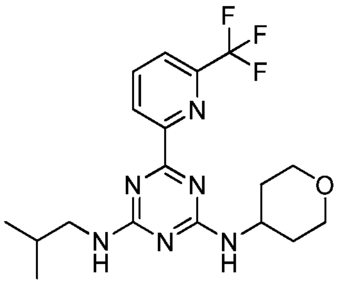
^{1}H NMR (400 MHz, CD$_3$OD): δ 8.68-8.56 (m, 1H), 8.15 (t, *J* = 8.3 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 4.81 – 4.43 (m, 2H), 4.11 – 3.92 (m, 2H), 3.86 (m, 1H), 3.78 – 3.66 (m, 1H), 2.74 - 2.50 (m, 1H), 2.38 – 1.75 (m, 7H).LC-MS: m/z 431.2 (M+H)$^+$.

Compound tert-butyl 3-((4-((3,3-difluorocyclopentyl)amino)-6-(6-(trifluoromethyl) pyridin-2-yl)-1,3,5-triazin-2-yl)amino)pyrrolidine-1-carboxylate



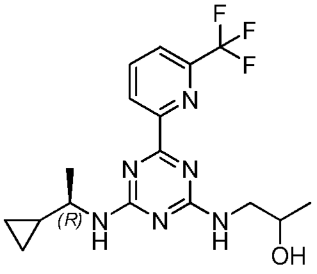
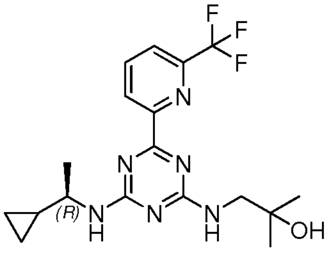
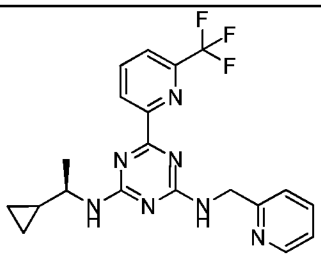
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.62 – 8.46 (m, 1H), 8.03 (d, *J* = 6.9 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 5.91 – 5.19 (m, 2H), 4.61 (m, 2H), 3.82 – 3.59 (m, 1H), 3.50 (s, 1H), 3.29 (m, 1H), 2.65 (m, 1H), 2.43 – 2.06 (m, 5H), 1.97 (s, 1H), 1.47 (s, 9H). LC-MS: m/z 530.2 (M+H)$^+$.

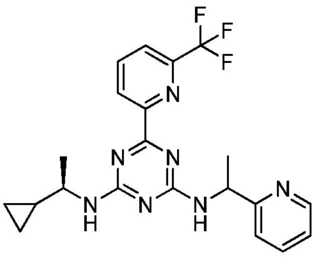
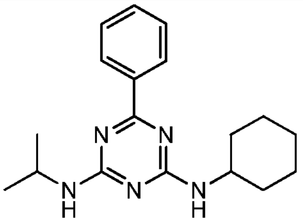
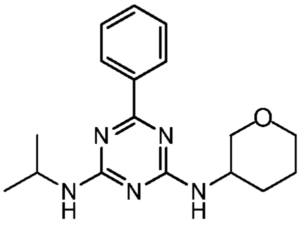
Compound N^2-isobutyl-N^4-(tetrahydro-2H-pyran-4-yl)-6-(6-(trifluoromethyl) -pyridin-2-yl)-1,3,5-triazine-2,4-diamine



^{1}HNMR (400 MHz, CD_3OD): δ8.7-8.6 (m, 1H), 8.25-8.15 (m, 1H), 8.0-7.9 (m, 1H), 4.4-4.1 (m, 1H), 4.05-3.96 (m, 2H), 3.3-3.2 (m, 2H), 2.1-1.9 (m, 3H), 1.63-1.5 (m, 2H), 1.05-0.9 (m, 6H). LC-MS: m/z 397.3 $(M+H)^+$.

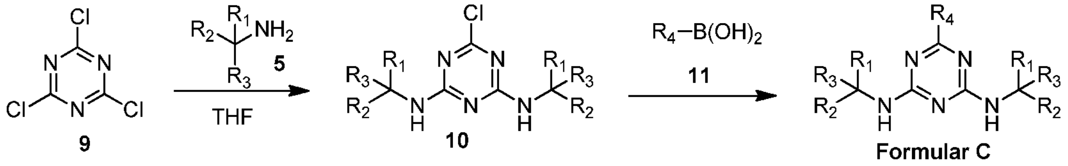
Table 2: The following targets were prepared by the procedure described in Scheme 2 above.

Compound ID	Name	Structure	LCMS	
			Expected MW	Found $(M+1)^+$
12	***1-(4-((R)-1-cyclopropylethylamino)-6-(6-(trifluoromethyl)pyridin-2-yl) -1,3,5-triazin-2-ylamino)propan-2-ol***		382.2	383.2
10	***1-(4-(1-cyclopropylethylamino)-6-(6-(trifluoromethyl)pyridin-2-yl) -1,3,5-triazin-2-ylamino)-2-methylpropan-2-ol***		396.2	397.2
24	***(R)-N^2-(1-cyclopropylethyl)-N^4-(pyridin-2-ylmethyl)-6-(6-(trifluoro methyl)pyridin-2-yl)-***		415.2	416.2

	1,3,5-triazine-2,4-diamine			
25	***N^2-((R)-1-cyclopropylethyl)-N^4-(1-(pyridin-2-yl)ethyl)-6-(6-(trifluoro methyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine***		429.2	430.2
	N^2-cyclohexyl-N^4-isopropyl-6-phenyl-1,3,5-triazine-2,4-diamine		311.2	312.2
69	***N^2-isopropyl-6-phenyl-N^4-(tetrahydro-2H-pyran-3-yl)-1,3,5-triazine-2,4 -diamine***		313.2	314.2

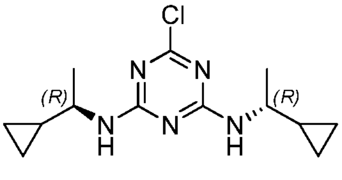
Example 3 Preparation of Di-aliphatic Triazine Compounds of Formula C. The compounds of this Example are prepared by general **Scheme 3**, set forth below.

Scheme 3



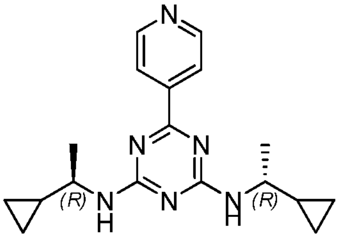
Step 1: Preparation of 6-chloro-N^2,N^4-bis((R)-1-cyclopropylethyl) -1,3,5-triazine-2,4-diamine. To a mixture of 2,4,6-trichloro-1,3,5-triazine (2g, 10.9 mmol, 1 eq) and (R)-1-

cyclopropylethanamine hydrochloride (2.7 g, 22.8 mmol, 2.1 eq)in acetone (50 mL) was added DIPEA (4.5 mL, 27.3 mmol, 2.5 eq) and CsF (3.3 g, 21.8 mmol, 2.0 eq). The mixture was stirred at 40°C for 3 hr and then at 50°C for another 3 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by a standard method to afford the desired product.



LC-MS: m/z 282.1 $(M+H)^+$.

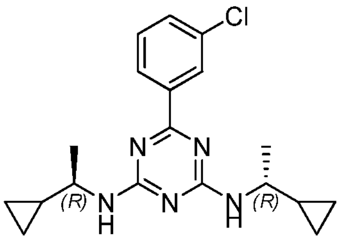
Step 2: Preparation of N^2,N^4-bis((R)-1-cyclopropylethyl)-6-(pyridin-4-yl)- 1,3,5-triazine-2,4-diamine.To a mixture of 6-chloro-N^2,N^4-bis((R)-1-cyclo -propylethyl)-1,3,5-triazine-2,4-diamine (100 mg, 0.36 mmol), pyridin-4-ylboronic acid (66 mg, 0.52 mmol), and K_2CO_3 (99 mg, 0.72 mmol) in 1,4-dioxane (3 mL) and water (1 mL) stirred at r.t. under the atmosphere of nitrogenwas added $Pd(PPh_3)_4$ (42 mg, 0.036 mmol) in one portion. The reaction mixture was stirred at 80°C overnight. The mixture was partitioned between water and EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by a standard method to give the desired product.



^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61 – 7.28 (m, 6H), 3.58 – 3.39 (m, 2H), 1.23 – 1.10 (m, 3H), 1.02 – 0.89 (m, 2H), 0.48 – 0.26 (m, 6H), 0.20 – 0.10 (m, 2H). LC-MS: m/z 325.2 $(M+H)^+$.

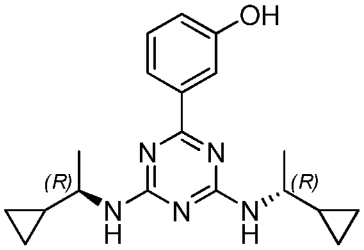
The procedure set forth above was used to produce the following compounds using the appropriate starting materials.

Compound 6-(3-chlorophenyl)-N^2,N^4-bis((R)-1-cyclopropylethyl)-1,3,5-triazine -2,4-diamine



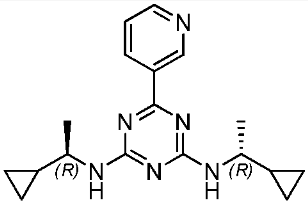
^{1}H NMR (400 MHz, DMSO-d_6):δ 8.30 – 8.14 (m, 2H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.26 (m, 1H), 3.70 – 3.43 (m, 2H), 1.26 – 1.15 (m, 6H), 1.02 – 0.92 (m, 2H), 0.49 – 0.30 (m, 6H), 0.26 – 0.11 (m, 2H).LC-MS: m/z 358.2 (M+H)$^+$.

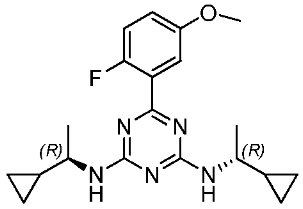
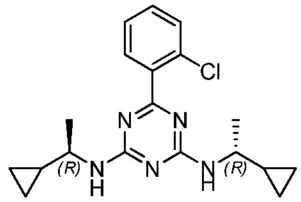
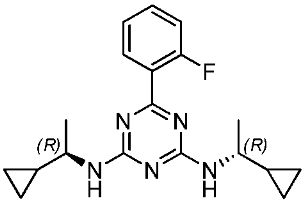
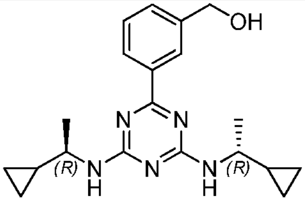
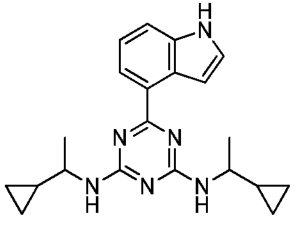
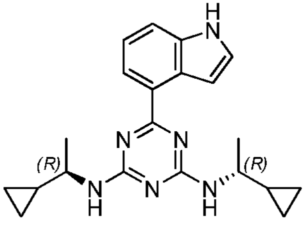
Compound 3-(4,6-bis((R)-1-cyclopropylethylamino)-1,3,5-triazin-2-yl)phenol



^{1}H NMR (400 MHz, CDCl$_3$): δ 7.99 – 7.64 (m, 2H), 7.29 (d, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 5.78 – 5.04 (m, 2H), 4.07 (s, 1H), 3.60 (m, 2H), 1.27 (d, *J* = 4.3 Hz, 6H), 0.89 (d, *J* = 3.6 Hz, 2H), 0.43 (m, 8H). LC-MS: m/z 340.2 (M+H)$^+$.

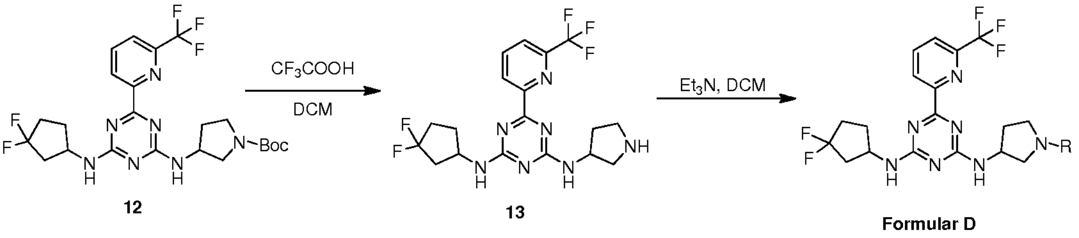
Table 3: The following targets were prepared by the procedure described in Scheme 3 above.

Compound ID	Name	Structure	LCMS	
			Expected MW	Found (M+1)$^+$
92	***N^2,N^4-bis((R)-1-cyclopropylethyl)-6-(pyridin-3-yl)-1,3,5-triazine-2,4- diamine***		324.2	325.2

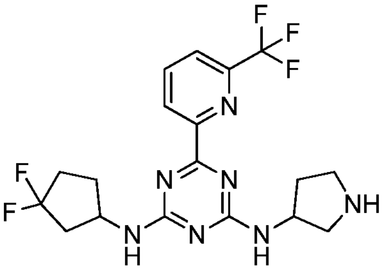
78	***N^2,N^4-bis((R)-1-cyclopropylethyl)-6-(2-fluoro-5-methoxyphenyl)-1,3,5-triazine-2,4-diamine***		371.2	372.2
66	***6-(2-chlorophenyl)-N^2,N^4-bis((R)-1-cyclopropylethyl)-1,3,5-triazine -2,4-diamine***		357.2	358.2
77	***6-(2-fluorophenyl)-N^2,N^4-bis((R)-1-cyclopropylethyl)-1,3,5-triazine -2,4-diamine***		341.2	342.2
82	***(3-(4,6-bis((R)-1-cyclopropylethylamino)-1,3,5-triazin-2-yl)phenyl) methanol***		353.2	354.2
	N^2,N^4-bis(1-cyclopropylethyl)-6-(1H-indol-4-yl)-1,3,5-triazine-2,4- diamine		362.2	363.2
	N^2,N^4-bis((R)-1-cyclopropylethyl)-6-(1H-indol-4-yl)-1,3,5-triazine-2,4- diamine		362.2	363.2

Example 4 Preparation of Di-aliphatic Triazine Compounds of Formula D. The compounds of this Example are prepared by general **Scheme 4**, set forth below.

Scheme 4

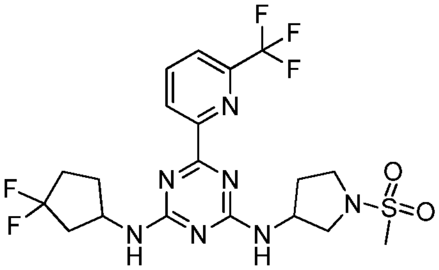


Step 1. Preparation of N^2-(3,3-difluorocyclopentyl)-N^4-(pyrrolidin-3-yl)-6-(6- (trifluoro methyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine. To a solution of tert-butyl 3-(4-(3,3-difluorocyclopentylamino)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazin-2-ylamino)pyrrolidine-1-carboxylate (160 mg, 0.3 mmol) in DCM (3 mL) at 0°C was added TFA (1 mL). The mixture was stirred at room temperature for 2 hrs and then concentrated. The residue was extracted with EtOAc. Combined organic layerswere washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and then concentrated to afford the desired product which was used in the next step without any further purification.



LC-MS: m/z 430.2 $(M+H)^+$.

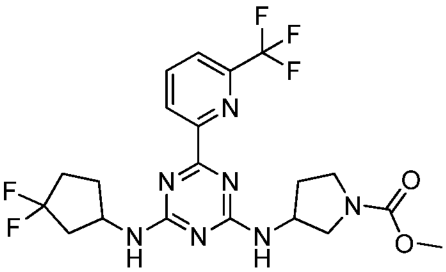
Step 2. Preparation of N^2-(3,3-difluorocyclopentyl)-N^4-(1-(methylsulfonyl)pyrroli -din-3-yl)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine. A mixture of N^2-(3,3-difluorocyclopentyl)-N^4-(pyrrolidin-3-yl)-6-(6-(trifluoromethyl) pyridin-2-yl)-1,3,5-triazine-2,4-diamine (20 mg, 0.05 mmol), Et_3N (9.4 mg, 0.09 mmol), MsCl (6 mg, 0.06 mmol) in DCM (2 mL) was stirred at room temperature overnight. The mixture was concentrated and the residue was purified by a standard method to afford the desired product.



^{1}H NMR (400 MHz, CDCl$_3$): δ 8.62 – 8.46 (m, 1H), 8.04 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 5.79 – 5.38 (m, 2H), 4.80 – 4.53 (m, 2H), 3.76 – 3.52 (m, 2H), 3.39 – 3.23 (m,1H), 2.91 (s, 3H), 2.69 – 2.57 (m, 1H), 2.45 – 2.25 (m, 3H), 2.20 – 1.98 (m, 3H), 1.95 – 1.81 (m, 1H), 1.22 – 1.18 (m, 1H).LC-MS: m/z 508.1 (M+H)$^+$.

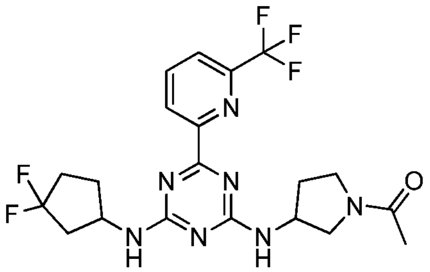
The procedure set forth above was used to produce the following compounds using the appropriate starting material.

Coumpound methyl 3-((4-((3,3-difluorocyclopentyl)amino)-6-(6-(trifluoro methyl)pyridin-2-yl)-1,3,5-triazin-2-yl)amino)pyrrolidine-1-carboxylate.



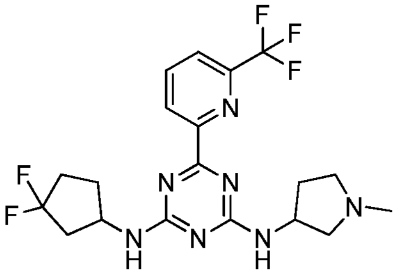
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.58-8.48 (m, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 5.94 – 5.18 (m, 2H), 4.72 - 4.47 (m, 2H), 3.83 - 3.74 (m, 1H), 3.72 (s, 3H), 3.65 - 3.51 (m, 2H), 3.44 - 3.28 (m, 1H), 2.45 – 1.80 (m, 7H).LC-MS: m/z 488.2 (M+H)$^+$.

Compound 1-(3-((4-((3,3-difluorocyclopentyl)amino)-6-(6-(trifluoromethyl)pyridin -2-yl)-1,3,5-triazin-2-yl)amino)pyrrolidin-1-yl)ethanone



^{1}H NMR (400 MHz, CDCl$_3$): δ 8.55 (m, 1H), 8.07 (d, J = 6.8 Hz, 1H), 7.85 (t, J = 6.7 Hz, 1H), 4.84 – 4.30 (m, 2H), 3.97 – 3.52 (m, 4H), 2.62 (m, 1H), 2.50 – 2.22 (m, 3H), 2.22 – 1.98 (m, 3H), 1.25 (s, 3H).LC-MS: m/z 472.2 (M+H)$^+$.

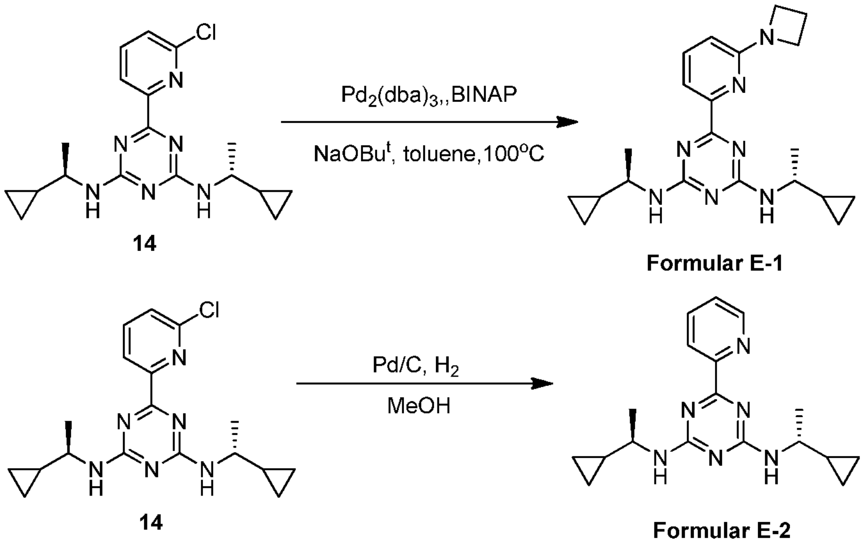
Compound N^2-(3,3-difluorocyclopentyl)-N^4-(1-methylpyrrolidin-3-yl) -6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazine-2,4-diamine. To a solution of tert-butyl 3-(4-(3,3-difluorocyclopentylamino)-6-(6-(trifluoromethyl)pyridin-2-yl)-1,3,5-triazin-2-ylamino)pyrrolidine-1-carboxylate (25 mg, 0.05mmol) in THF (3 mL) at 0°C was added LiAlH$_4$(5 mg, 0.14 mmol). The mixture was stirred at 0°Cfor 2hr, then at r.t for 30 min, and finally at 60 °C for 2hr. The reaction mixture was quenched with water and extracted by EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated. The residue was purified by a standard method to give the desired product.



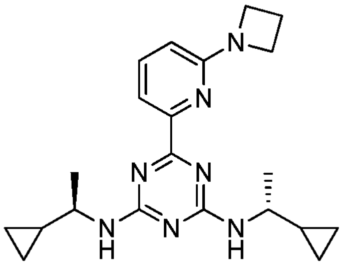
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.55 (m, 1H), 8.08 – 7.93 (m, 1H), 7.80 (t, J = 7.4 Hz, 1H), 4.63 (m, 2H), 3.47 – 2.87 (m, 3H), 2.69 (m, 6H), 2.28 (m, 4H), 1.84 (m, 4H).LC-MS: m/z 444.2 (M+H)$^+$.

Example 5 Preparation of Di-aliphatic Triazine Compounds of Formula E-1 to E-2. The compounds of this Example are prepared by general **Scheme 5**, set forth below.

Scheme 5

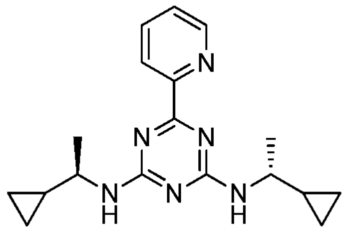


Step 1: Preparation of 6-(6-(azetidin-1-yl)pyridin-2-yl)-N^2,N^4-bis((R)-1-cyclopropyl -ethyl) -1,3,5-triazine-2,4-diamine. A mixture of 6-(6-chloropyridin-2-yl)-N^2,N^4-bis((R)-1-cyclopropylethyl) -1,3,5-triazine-2,4-diamine (40 mg, 0.11 mmol), azetidine (7.6 mg, 0.13 mmol), 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl (6.9 mg, 0.01 mmol), sodium tert-butoxide (15 mg, 0.16 mmol) and tris(dibenzylideneacetone) -dipalladium (10.2 mg, 0.01 mmol) in toluene (3 mL) was stirred at 100°C under an atmosphere of nitrogen overnight. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by a standard method to afford the desired product.



^{1}H NMR (400 MHz, CD_3OD): δ 8.49 (s, 1H), 7.72 – 7.53 (m, 2H), 6.56 (d, *J*=7.4, 1H), 4.11 (t, *J*=7.4, 4H), 3.59 (m, 2H), 2.42 (p, *J*=7.4, 2H), 1.30 (d, *J*=6.5, 6H), 0.98 (s, 2H), 0.67 – 0.13 (m, 8H). LC-MS: m/z 380.2 $(M+H)^+$.

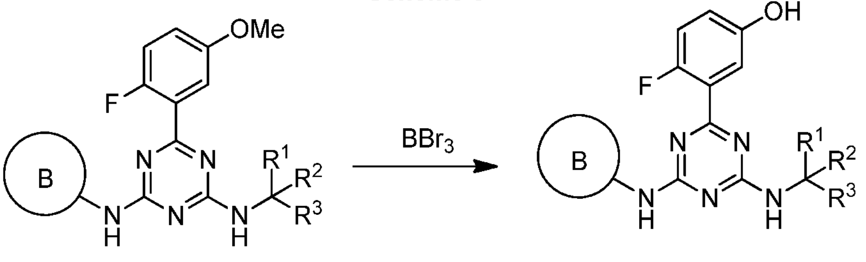
Step 2: Preparation of N^2,N^4-bis((R)-1-cyclopropylethyl)-6-(pyridin-2-yl)- 1,3,5-triazine-2,4-diamine. To a solution of 6-(6-chloropyridin-2-yl)-N^2,N^4-bis((R)-1-cyclopropylethyl)-1,3,5-triazine-2,4-diamine (20 mg, 0.05 mmol) in methanol (2 mL) was added Pd/C (2 mg) under an atmosphere of nitrogen. The mixture was then stirred at room temperature under a hydrogen balloon overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified by a standard method to afford the desired product.



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 – 8.03 (m, 4H), 7.75 (m, 2H), 3.79 – 3.45 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 6H), 1.07 – 0.84 (m, 2H), 0.55 – 0.05 (m, 8H). LC-MS: m/z 325.2 $(M+H)^+$.

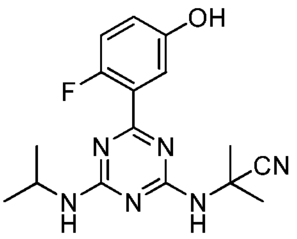
Example 6 Preparation of Di-aliphatic Triazine Compounds of Formula F. The compounds of this Example are prepared by general **Scheme 6**, set forth below.

Scheme 6



18 **Formula F**

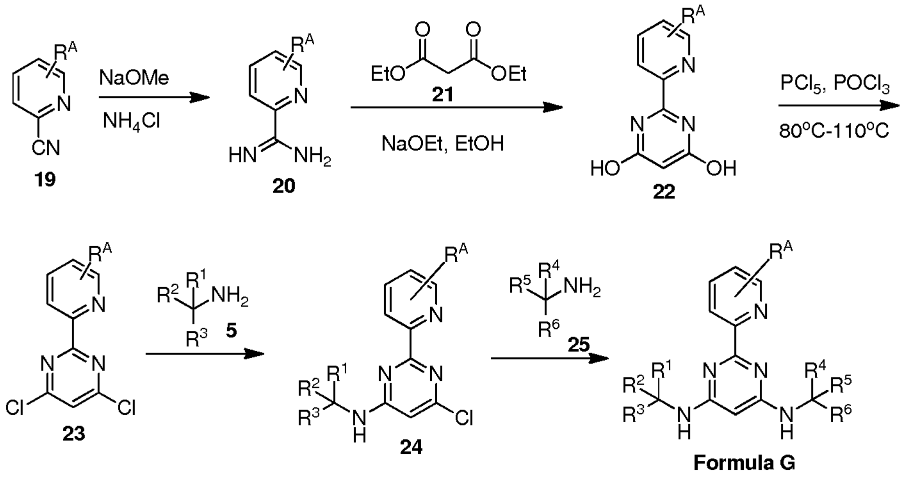
Step 1: Preparation of 2-((4-(2-fluoro-5-hydroxyphenyl)-6-(isopropylamino)-1, 3,5-triazin-2-yl)amino)-2-methylpropanenitrile. To a solution of 2-((4-(2-fluoro-5-methoxyphenyl)-6-(isopropylamino)-1,3,5-triazin-2-yl)amino)-2-methylpropanenitrile (200 mg, 0.6 mmol) in anhydrous DCM (3 mL) at -65°C was added dropwise BBr_3 (0.6 mL) and the reaction mixture was stirred at this temperature for 20 min. The mixture was slowly warmed up to 0°C and stirred for 10 min. and then stirred at room temperature for 1 hr. The reaction was quenched with icy Sat. aq. $NaHCO_3$ till pH = 8. The resulting mixture was extracted with EtOAc(2 x 10 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by a standard method to afford the desired product.



^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H), 6.96 (t, J = 9.6 Hz, 1H), 6.83 (d, J = 8.6 Hz, 1H), 5.72 (m, 2H), 4.26 (s, 1H), 1.79 (s, 6H), 1.26 (d, J = 6.1 Hz, 6H). LC-MS: m/z 331.2 $(M+H)^+$.

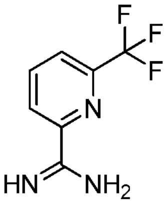
Example 7 Preparation of Di-aliphatic Pyrimidine Compounds of Formula G. The compounds of this Example are prepared by general **Scheme 7**, set forth below.

Scheme 7



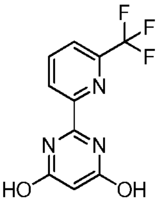
Step 1: Preparation of6-(trifluoromethyl)picolinimidamide. To a solution of6-(trifluoromethyl)picolinonitrile (50 mg, 0.3 mmol, 1 eq) in EtOH (3 mL) was added NaOMe (1.6 mg, 0.03 mmol, 0.1 eq) at 0°C. The mixture was stirred at r.t. for 1 hr, followed by addition of NH_4Cl (21 mg, 0.39 mmol, 13 eq). The resulting mixture was stirred at 90°C for 1 hr and cooled

to room temperature. The mixture was adjusted pH to 9 with saturated aqueous $NaHCO_3$ and then extracted with EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by a standard method to afford the desired product.



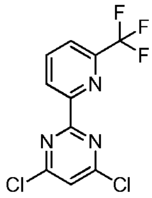
LC-MS: m/z 190.1 $(M+H)^+$.

Step 2: Preparation of2-(6-(trifluoromethyl)pyridin-2-yl)pyrimidine-4,6-diol. To a solution of sodium (366 mg, 15.9 mmol, 5.0 eq) in anhydrous EtOH (6 mL) was added dropwise a solution of 6-(trifluoromethyl)picolinimidamide (600 mg, 3.2 mmol) in EtOH. The reaction mixture was stirred at r.t. for 1 hr, followed by addition of diethyl malonate (1 mL, 6.4 mmol, 2.0 eq). The mixture was stirred at reflux overnight and then cooled to room temperature. The resulting mixture was adjusted pH to 7 by 1 N aq. HCl solution. The suspension was filtered and the filter cake was washed with water. The solid was suspended in MeOH and filtered. The filtrate was concentrated under reduced pressure to give the desired product which was used directly in the next step without any further purification.



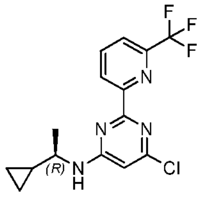
LC-MS: m/z 256.0 $(M-H)^-$.

Step 3: Preparation of4,6-dichloro-2-(6-(trifluoromethyl)pyridin-2-yl)pyrimidine. A solution of 2-(6-(trifluoromethyl)pyridin-2-yl)pyrimidine-4,6-diol (1 g, 3.9 mmol) in $POCl_3$ (6 mL) was stirred at 90°C overnight and then concentrated to remove the volatile. The residue was purified by a standard method to afford the desired product.



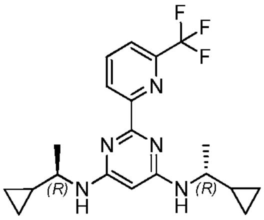
LC-MS: m/z 294.0 $(M+H)^+$.

Step 4: ***Preparation of (R)-6-chloro-N-(1-cyclopropylethyl)-2-(6-(trifluoromethyl) -pyridin-2-yl)pyrimidin-4-amine.*** To a solution of 4,6-dichloro-2-(6-(trifluoromethyl) pyridin-2-yl)pyrimidine (80 mg, 0.27 mmol, 1 eq) in THF (3 mL) was added (R)-1- -cyclopropylethanamine (0.06 mL, 0.6 mmol, 2.2 eq) and Et_3N (0.07 mL, 0.54 mmol, 2 eq). The reaction mixture was stirred at room temperature overnight and concentrated. The residue was purified by a standard method to give the desired product.



LC-MS: m/z 343.1 $(M+H)^+$.

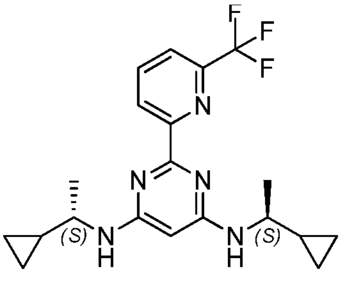
Step 5 : Preparation ofN4,N6-bis((R)-1-cyclopropylethyl)-2-(6-(trifluoromethyl)pyri din-2-yl)pyrimidine-4,6-diamine. To a solution of (R)-6-chloro-N-(1-cyclopro pylethyl)-2-(6-(trifluoromethyl) -pyridin-2-yl)pyrimidin-4-amine (50 mg, 0.15 mmol, 1 eq) in DMSO (2 mL) was added (R)-1-cyclopropylethanamine hydrochloride (22 mg, 0.18 mmol, 1.2 eq) and DIPEA (0.08 mL, 0.45 mmol, 3 eq). The mixture was irradiated under microwave at 160 °C for 1.5 hr. After addition of (R)-1-cyclopropylethanamine (0.18 mmol, 1.2 eq),the resulting mixture was stirred and irradiated under microwave at 160 °C for another 2 hr. The mixture was cooled to r.t. and then partitioned between EtOAc and water. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by a standard method to give the desired product.



^{1}H NMR (400 MHz, CDCl$_3$): δ 8.40 (d, J = 7.9 Hz, 1H), 7.87 (t, J = 7.9 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 5.19 (m, 3H), 3.13 (d, J = 6.3 Hz, 2H), 1.19 (d, J = 6.4 Hz, 6H), 0.96 – 0.72 (m, 2H), 0.52 – 0.33 (m, 4H), 0.33 – 0.10 (m, 4H).LC-MS: m/z 392.2 (M+H)$^+$.

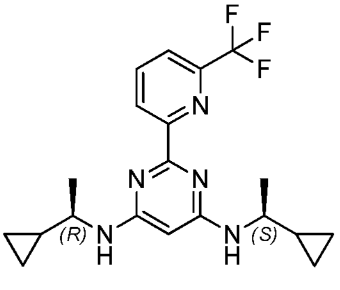
The procedure set forth above was used to produce the following compounds using the appropriate starting materials.

Compound N^4,N^6-bis((S)-1-cyclopropylethyl)-2-(6-(trifluoromethyl)pyridin-2-yl) pyrimidine-4,6-diamine



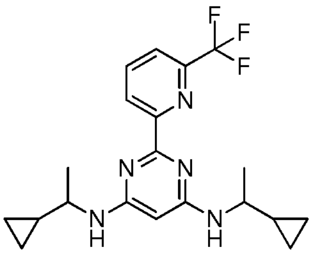
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.49 (d, J = 7.8 Hz, 1H), 7.95 (t, J = 7.9 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 5.22 (m, 3H), 3.22 (d, J = 6.5 Hz, 2H), 1.40 – 1.15 (m, 6H), 0.95 (m, 2H), 0.61 – 0.44 (m, 4H), 0.31 (m, 4H).LC-MS: m/z 392.2 (M+H)$^+$.

Compound N^4-((R)-1-cyclopropylethyl)-N^6-((S)-1-cyclopropylethyl)-2-(6-(trifluoro methyl)pyridin-2-yl)pyrimidine-4,6-diamine



^{1}H NMR (400 MHz, CDCl$_3$): δ 8.49 (d, J = 7.8 Hz, 1H), 7.97 (t, J = 7.9 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 5.22 (m, 3H), 3.22 (d, J = 6.5 Hz, 2H), 1.68 – 1.25 (m, 6H), 0.97 (m 2H), 0.61 – 0.44 (m, 4H), 0.31 (m, 4H).LC-MS: m/z 392.2 (M+H)$^+$.

Table 7: The following compounds were prepared by the procedure described in Scheme 7 above.

Compound ID	**Name**	**Structure**	**LCMS**	
			Expected MW	**Found (M+1)$^+$**
	N^4,N^6-bis(-1-cyclopropylethyl)-2-(6-(trifluoromethyl)pyridin-2-yl) pyrimidine-4,6-diamine		391.2	392.2

Example 8. Enzymatic and Cell Assays

In Vitro Assays for IDH1m (R132H or R132C) Inhibitors

The following describes the experimental procedures that can be used to obtain data on columns 2 and 4 of Table 2.

In the primary reaction, the reduction of α-KG acid to 2-HG is accompanied by a concomitant oxidation of NADPH to NADP. The amount of NADPH remaining at the end of the reaction time is measured in a secondary diaphorase/resazurin reaction in which the NADPH is consumed in a 1:1 molar ratio with the conversion of resazurin to the highly fluorescent resorufin. Uninhibited reactions exhibit a low fluorescence at the end of the assay, while reactions in which the consumption of NADPH by R132H IDH1 has been inhibited by a small molecule show a high fluorescence. The primary reaction was performed in a volume of 50 mL 1X Buffer (150 mM NaCl, 20 mM Tris 7.5, 10 mM $MgCl_2$, 0.05% (w/v) bovine serum albumin), contained 8.5 nM IDH1 wt / IDH1 R132H heterodimer, 0.1 mM alpha-ketoglutarate, 4 mM NADPH, and 30 mM NADP, and was conducted for sixty minutes at 25°C. To perform the secondary reaction, 25 mL of 1X buffer containing 36 mg/ml diaphorase and 30 mM resazurin was added to the primary reaction and incubated for a further 10 minutes at 25°C. Florescence was read on a Spectramax platereader at Ex 544 Em 590. Compounds or compound dilutions were prepared in 100% DMSO concentration and diluted 1:100 into the final reaction. IDH1 wt / IDH1 R132C was assayed under similar conditions except that 1X Buffer was 50 mM K_2HP0_4, pH 6.5; 40 mM $NaHCO_3$; 5 mM $MgCl_2$; 10% glycerol; 0.03% (w/v) bovine serum albumin and final concentrations were 1.5 nM IDH1 wt / IDH1 R132C heterodimer, 0.02 mM alpha-ketoglutarate, 4 mM NADPH, and 30 mM NADP. IC50s are determined.

IDH1 or IDH2 widetype (wt) and mutant heterodimers are expressed and purified by methods known in the art. For example, IDH1wt/R132m heterodimer is expressed and purified as follows. Co-expression of IDH1wt-his and IDH1R132C-flag is carried out in sf9 insect cells.

Cells (25g) are resuspended in 250 ml of 50mM Tirs, 500mM NaCl, pH7.4, at 4°C with stirring.

Cells are disrupted with 4 passes through an M-Y110 Micro fluidizer (Microfluidics) set to 500

psi, and then centrifuged at 22,000 rcf for 20min at 4°C. The supernatant is harvested and loaded

at 15cm/h on a Histrap FF 5*1ml column (GE) which is equilibrated with 50mM Tirs, 500mM NaCl, pH7.4. Host cell contaminants are removed by washing the column with equilibration buffer followed by equilibration buffer containing 20mM imidazole and 60mM imidazole to baseline. IDH1wt-his homodimer and IDH1wt-his / IDH1R132C-flag are eluted by equilibration buffer containing 250mM imidazole. Fractions eluted by 250mM imidazole are pooled together and loaded at 15cm/h onto a column pre-packed with 10ml ANTI-FLAG® M2 Affinity Gel (Sigma), the column is equilibrated with 50mM Tris, 500mM NaCl, pH7.4. After washing with equilibration buffer, IDH1wt-his/IDH1R132C-flag heterodimer is eluted by equilibration buffer containing flag peptide (0.2mg/ml). Aliquots of IDH1wt-his/IDH1R132C-flag are flash frozen in liquid N_2 and stored at -80°C. Same conditions are used for the purification of IDH1wt-his/IDH1R132H-flag.

In Vitro Assays for IDH1m (R132H or R132C) Inhibitors

The following describes the experimental procedures that can be used to obtain data on columns 3 and 6 of Table 2.

A test compound is prepared as 10 mM stock in DMSO and diluted to 50X final concentration in DMSO, for a 50 µl reaction mixture. IDH enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutaric acid is measured using a NADPH depletion assay. In the assay the remaining cofactor is measured at the end of the reaction with the addition of a catalytic excess of diaphorase and resazurin, to generate a fluorescent signal in proportion to the amount of NADPH remaining. IDH1-R132 homodimer enzyme is diluted to 0.125 µg/ml in 40 µl of Assay Buffer(150 mM NaCl, 20 mM Tris-Cl pH 7.5, 10 mM $MgCl_2$, 0.05% BSA, 2 mM b-mercaptoethanol); 1 µl of test compound dilution in DMSO is added and the mixture is incubated for 60 minutes at room temperature. The reaction is started with the addition of 10 µl of Substrate Mix (20 µl NADPH, 5 mM alpha-ketoglutarate, in Assay Buffer) and the mixture is incubated for 90 minutes at room temperature. The reaction is terminated with the addition of 25 µl of Detection Buffer (36 µg/ml diaphorase, 30 mM resazurin, in 1X Assay Buffer), and is incubated for 1 minute before reading on a SpectraMax platereader at Ex544/Em590.

Compounds are assayed for their activity against IDH1 R132C following the same assay as above with the following modifications: Assay Buffer is (50 mM potassium phosphate, pH 6.5;

40 mM sodium carbonate, 5 mM $MgCl_2$, 10% glycerol, 2 mM b-mercaptoethanol, and0.03% BSA). The concentration of NADPH and alpha-ketoglutarate in the Substrate Buffer is 20 µM and 1 mM, respectively.

In Vitro Assays for IDH2m R140Q Inhibitors

The following describes the experimental procedures used to obtain data on column 7 of Table 2.

Compounds are assayed for IDH2 R140Q inhibitory activity through a cofactor depletion assay. Compounds are preincubated with enzyme, then the reaction is started by the addition of NADPH and α-KG, and allowed to proceed for 60 minutes under conditions previously demonstrated to be linear with respect for time for consumption of both cofactor and substrate. The reaction is terminated by the addition of a second enzyme, diaphorase, and a corresponding substrate, resazurin. Diaphorase reduces resazurin to the highly fluorescent resorufin with the concomitant oxidation of NADPH to NADP, both halting the IDH2 reaction by depleting the available cofactor pool and facilitating quantitation of the amount of cofactor remaining after a specific time period through quantitative production of an easily detected fluorophore.

Specifically, into each of 12 wells of a 384-well plate, 1 µl of 100x compound dilution series is placed, followed by the addition of 40 µl of buffer (50 mM potassium phosphate (K_2HPO_4), pH 7.5; 150 mM NaCl; 10 mM $MgCl_2$, 10% glycerol, 0.05% bovine serum albumin, 2 mM beta-mercaptoethanol) containing 0.25 µg/ml IDH2 R140Q protein. The test compound is then incubated for one hour at room temperature with the enzyme; before starting the IDH2 reaction with the addition of 10 µl of substrate mix containing 4 µM NADPH and 1.6 mM α-KG in the buffer described above. After a further 16 hours of incubation at room temperature, the reaction is halted and the remaining NADPH measured through conversion of resazurin to resorufin by the addition of 25 µl Stop Mix (36 µg/ml diaphorase enzyme and 60 µM resazurin; in buffer). After one minute of incubation the plate is read on a plate reader at Ex544/Em590.

For determination of the inhibitory potency of compounds against IDH2 R140Q in an assay format similar to the above, a similar procedure is performed, except that the final testing concentration is 0.25 µg/ml IDH2 R140Q protein, 4 µM NADPH and 1.6 mM α-KG.

For determination of the inhibitory potency of compounds against IDH2 R140Q in a high throughput screening format, a similar procedure is performed, except that 0.25 μg/ml IDH2 R140Q protein was utilized in the preincubation step, and the reaction is started with the addition of 4 μM NADPH and 8 μM α-KG.

Cellular Assays for IDH1m (R132H or R132C) Inhibitors.

The following describes the experimental procedures that can be used to obtain data on column 5 of Table 2.

Cells (HT1080 or U87MG) are grown in T125 flasks in DMEM containing 10% FBS, 1x penicillin/streptomycin and 500ug/mL G418 (present in U87MG cells only). They are harvested by trypsin and seeded into 96 well white bottom plates at a density of 5000 cell/well in 100 ul/well in DMEM with 10% FBS. No cells are placed in columns 1 and 12. Cells are incubated overnight at 37℃ in 5% CO_2. The next day test compounds are made up at 2x the final concentration and 100ul are added to each cell well. The final concentration of DMSO is 0.2% and the DMSO control wells are plated in row G. The plates are then placed in the incubator for 48 hours. At 48 hours, 100ul of media is removed from each well and analyzed by LC-MS for 2-HG concentrations. The cell plate is placed back in the incubator for another 24 hours. At 72 hours post compound addition, 10 mL/plate of Promega Cell Titer Glo reagent is thawed and mixed. The cell plate is removed from the incubator and allowed to equilibrate to room temperature. Then 100ul of Promega Cell Titer Glo reagent is added to each well of media. The cell plate is then placed on an orbital shaker for 10 minutes and then allowed to sit at room temperature for 20 minutes. The plate is then read for luminescence with an integration time of 500ms.

U87MG pLVX-IDH2 R140Q-neo and HT1080 Cell Based Assays

The following describes the experimental procedures that are used to obtain data on column 8 of Table 2.

U87MG pLVX-IDH1 R132H-neo cells are maintained in DMEM containing 10% FBS, 1x penicillin/streptomycin and 500 μg/uL G418. HT1080 cells aremaintained in RPMI containing 10% FBS, 1x penicillin/streptomycin. Cells are seeded at a density of 5,000

(U87MG R140Q) or 2,500 (HT1080) cells/well into 96-well microtiter plates and incubated overnight at 37°C and 5% CO_2. The next day compounds are prepared in 100% DMSO and then diluted in media for a final concentration of 0.2% DMSO. Media is removed from the cell plates and 200 µL of the compound dilutions are added to each well. After 48 hours of incubation with compound at 37°C, 100 µL of media are removed from each well and analyzed by LC-MS for 2-HG concentrations as described in Dang, L. *et al. Nature,* **2009**, *462*, 739-744. The cell plates are then allowed to incubate another 24 hours. At 72 hours post compound addition, Promega Cell Titer Glo reagent is added to each well and the plates are read for luminescence to determine any compound effects on growth inhibition (GI_{50}).

The data for various compounds of one aspect of the invention in the R132H enzymatic assay, R132C enzymatic assay, R140Q enzymatic assay, R132C cell-based assay, and R140Q cell-based assay as described above or similar thereto are presented below in Table 2. For each assay, values indicated as “A” represent an IC50 of less than 50 nM; values indicated as “B” represent an IC50 of between 50 nM and 100 nM; values indicated as “C” represent an IC50 of greater than 100 nM and less than 1 µM; values indicated as “D” represent an IC50 of greater than or equal to 1 µM; values indicated as “no fit” are inactives and blank values represent that the compound was either inactive or not tested in that particular assay.

Table 2. Inhibitory Activities of Representative Compounds of formula I

Compound No.	IDH1 wt/R132H_NADPH_NADP IC50	IDH1 R132H IC50	IDH1 wtR132C_NADPH_NADP IC50	HT1080 IC50	IDH1 R132C IC50	IDH2 R140Q IC50	U87MG IC50
1		D			D	A	A
2		A		A	A	A	A
3		C			B		
4		B		B	B	A	
5		D			No Fit		
6		D			C		
7		C			D	A	
8		No Fit			D	B	
9		B			C	A	
10		D			D	B	
11		C		B	B	A	

12		D			D	B	
13		A		A	B		
14		D			D	D	
15		D			D		
16		D			D	A	
17		B		A	B		
18		A		B	B		
19		B		B	B		
20	A	B			B	A	
21		D			D	A	
22		B			C	A	
23		B			B		
24		D			D		
25		D			D		
26		C			D	A	
27		B			C		
28	A	B		B	B		
29		C			D		
30		B			C	B	
31		A		A	A	A	
32		D			D		
33		A		A	B		
34		A		A	B		
35		D			D		
36	A	A			B		
37		B			D		
38		B			C		
39		A		B	B		
40		B			B		
41		B			D		
42		B			C		
43		C			D		
44		C			D		
45		A			B		
46		D			D		
47		D			No Fit		
48		D			No Fit		
49		D			D		
50	A	A			B		
51		D			D		

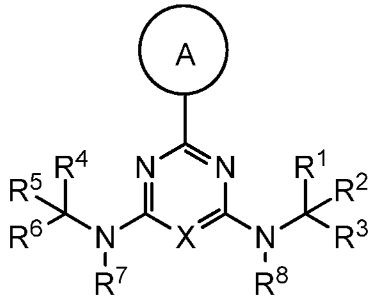
52	B		A				
53	C		B				
54	D		D				
55	C		B				
56	B		A				
57	D		D				
58	A		A				
59	A						
60	A						
61	D						
62	B						
63	B						
64	B						
65	No Fit						
66	D						
67	D						
69							C
70							B
71							B
72						D	B
73						A	B
74						A	B
75						B	A
76		B		B	B	A	
77		D			C		
78		No Fit			D	B	
79		D			D	B	
80		C		B	B	A	
81		D			D	B	
82		D			D	A	
83		D			D		
84		D			D		
85		B			C	B	
86	B	D			D		
87		B			D		
88		D			D		
89		D			D		
90	C		B				
91	D		D				
92	D		D				

93	D						
94	D						
95	D						
96	D						

Having thus described several aspects of several embodiments, it is to be appreciated various alterations, modifications, and improvements will readily occur to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of this disclosure, and are intended to be within the spirit and scope of the invention. Accordingly, the foregoing description and drawings are by way of example only.

Claims

1. A compound having Formula I or a pharmaceutically acceptable salt or hydrate thereof:



(I), wherein:

ring A is an optionally substituted 5-6 member monocyclic aryl or monocyclic heteroaryl;

X is N, CH or C-halo;

R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, and CN, wherein any alkyl portion of R^1, R^3, R^4, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$;

R^2 and R^5 are each independently selected from: -(C_1-C_6 alkyl), -(C_1-C_6 alkyl)-C(O)-NH_2, -(C_1-C_6 alkyl)-CO_2H, -(C_2-C_6 alkenyl or alkynyl), -(C_1-C_6 alkylene)-N(R^6)-(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)(R^6), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1\text{-}2}$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1\text{-}2}$-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-S(O)$_{1\text{-}2}$-N(R^6)(R^6), -(C_1-C_4 alkylene)-S(O)$_{1\text{-}2}$-N(R^6)-(C_1-C_6 alkylene)-Q, -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)- (C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6

alkylene)-C(O)N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-S(O)$_{0-2}$-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-S(O)$_{0-2}$-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)-C(O)-N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-Q, wherein:

any alkyl or alkylene moiety present in R^2 and R^5 is optionally substituted with one or more -OH, -O(C_1-C_4 alkyl), -CO_2H, or halo;

any terminal methyl moiety present in R^2 and R^5 is optionally replaced with -CH_2OH, CF_3, -CH_2F, -CH_2Cl, C(O)CH_3, C(O)CF_3, CN, or CO_2H;

R^7 and R^8 are each independently selected from hydrogen and C_1-C_6 alkyl; and

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, any of which is optionally substituted; wherein

R^1 and R^3 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^4 and R^6 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^1 and R^2 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl; or

R^4 and R^5 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

wherein:

(i) when X is N and A is optionally substituted phenyl, then (a) neither N(R^7)C(R^4)(R^5)(R^6) nor N(R^8)C(R^1)(R^2)(R^3) is 4-[[2-[2-(2- aminoethoxy)ethoxy]ethyl]amino] and (b) N(R^7)C(R^4)(R^5)(R^6) and N(R^8)C(R^1)(R^2)(R^3) are not both NHEt, NH(n-propyl), NH(n-butyl), NH(n-docecyl), NH-[(4- methoxyphenyl)methyl], $NHCH_2CH_2CHO$, $NHCH_2CH_2OCH_3$, $NHCH_2CH_2OH$, $NHCH_2CH(OH)CH_3$, $NHCH_2CH_2OC(O)$phenyl, $NHCH_2CH_2CH_2OH$, $NHCH_2CH_2CH_2N(CH_3)$phenyl, $NHCH_2C(O)OCH_3$, $NHCH_2C(O)OCH_2CH_3$, $NHCH_2$phenyl, $NHCH(CH_3)CH_2CH_3$, or $NHCH_2CH_2OC(O)CH_3$;

(ii) when X is CH or C-Cl and A is phenyl optionally substituted with F, Cl or SO_2CH_3, then neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is $N(CH_3)CH_2C(O)NH$-i-propyl, $NHCH(CH_3)(CH_2)_3N(CH_2CH_3)_2$, $NHCH_2CH_2OH$, $NHCH_2CH_2OCH_3$, $NHCH_2CH_2OSO_3H$, $NHCH_2CH_2CH_2OCH_2CH_2O$-phenyl, $NHCH_2CH_2CH_2OH$, $NHCH_2CH_2CH_2OCH_3$, $NHCH_2CH(OH)CH_3$, $N(CH_2CH_3)_2$, NH-i-propyl, $NHCH_2CH_2NHC(O)OCH_3$, $NHCH_2CH_2NHC(O)CH_3$, $NHCH_2CH_2NH_2$, or $NHCH_2$-phenyl;

(iii) when X is CH and A is optionally substituted pyridyl, then neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is $NHCH_2$-phenyl, $NHCH_2$-(2,4-difluorophenyl), $N(CH_3)CH_2CH_2C(O)OH$, $NHCH_2CH_2C(O)OH$, $NHCH_2CH_2C(O)OCH_2CH_3$, $NHCH_2CH_2C(O)O$-t-butyl, $NHCH_2CH_2C(O)NH_2$, $NHCH_2CH_2$-phenyl, $NHCH_2CH_2OH$, $NHCH_2CH_2NH_2$, $NHCH_2CH_2N(CH_3)_2$, or $NHCH_2CH_2CH_3$;

(iv) when X is CH and A is optionally substituted l-imidazolyl, optionally substituted 1-pyrrolyl or optionally substituted 1-pyrazolyl, then neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is $NH(CH_2)_7CH_3$, $NHCH_2$-(o-chloro-phenyl), or $NHCH_2CH_2OH$;

(v) when X is N and A is an optionally substituted pyridyl, then (A) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is NHC(O)-[2-chloro-4-(methylsulfonyl)], (B) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $NHC(O)C(CH_3)_3$, $NHC(O)CH=CH_2$, $NHC(O)C(CH_3)=CH_2$, $NHCH_2CH_2OH$, NH-cyclohexyl, $NHCH_2$-phenyl, NHC(O)phenyl, $NHC(O)(CH_2)_5NH_2$, $NHC(O)OCH_3$, $NHC(O)CH_3$, and NHC(O)NH-optionally substituted phenyl, and (C) when $N(R^7)C(R^4)(R^5)(R^6)$ is $NHC(CH_3)_3$, then $N(R^8)C(R^1)(R^2)(R^3)$ is not $NHCH_2$-phenyl or $NH-CH_2CH_3$;

(vi) when X is N and A is an optionally substituted heteroaryl, then $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $N(CH_2CH_3)_2$, $NHCH_2CH_2$-i-propyl, $NHCH_2CH(CH_3)_2$, and $NHC(O)CH_3$;

(vii) the compound is not selected from the group:

(1) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(2) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(3) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(3-nitrophenyl)-1,3,5-triazine-2,4-diamine,

(4) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine,

(5) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-trifluoromethoxy-phenyl)-1,3,5-triazine-2,4-diamine,

(6) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-t-butyl-phenyl)-1,3,5-triazine-2,4-diamine,

(7) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(2-thienyl)-1,3,5-triazine-2,4-diamine,

(8) N-(2-aminophenyl)-4-[[[4-[(2,3-dihydro-1H-inden-2-yl)amino]-6-phenyl-1,3,5-triazin-2-yl]amino]methyl]-benzamide,

(9) 2-chloro-N-[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-4-(methylsulfonyl)-benzamide,

(10) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(11) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]-acetamide,

(12) N^2-cyclopropyl-N^4-ethyl-6-[3-[(phenylmethyl)thio]-1H-1,2,4-triazol-1-yl]-1,3,5-triazine-2,4-diamine,

(13) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]- acetic acid methyl ester,

(14) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(2,4,6-trimethylphenyl)-1,3,5-triazine-2,4-diamine,

(15) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(16) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methylphenyl)-1,3,5-triazine-2,4-diamine,

(17) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-chlorophenyl)-1,3,5-triazine-2,4-diamine,

(18) N-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-

yl]amino]methyl]cyclohexyl] methyl]-4-fluoro-benzenesulfonamide,

(19) N^2-cyclopropyl-6-(3,5-dimethyl-1H-pyrazol-1-yl)-N^4-phenyl-1,3,5-triazine-2,4-diamine,

(20) N^2,N^4-dicyclohexyl-6-[3-(4-methoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(21) N^2,N^4-dicyclohexyl-6-[3-(3,4-dimethoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(22) N^2,N^4-dicyclohexyl-6-[5-(methylthio)-3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(23) N^2,N^4-dicyclohexyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(24) 1,1'-[(6-phenyl-s-triazine-2,4-diyl)diimino]bis[dodecahydro-anthraquinone],

(25) 4,4'-[(6-phenyl-1,3,5-triazine-2,4- diyl)bis(iminomethylene)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(26) N-[4-[(4-aminobutyl)amino]-6-[5-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl] amino]-2-methylphenyl]-1,3,5-triazin-2-yl]-glycine,

(27) 4-[2-[[4-[(5-aminopentyl)amino]-6-(3- fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]- phenol,

(28) 4-[2-[[4-[(5-aminopentyl)amino]-6-(4- fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]- phenol,

(29) 6-(4-aminopyridin-3-yl)-N^2-benzyl-N^4-(tert-butyl)-1,3,5-triazine-2,4-diamine,

(30) N^2,N^4-bis(cyclohexylmethyl)-6-phenyl-1,3,5-triazine-2,4-diamine,

(31) 4,4'-[[6-[3,5-bis(1,1-dimethylethyl)-4- hydroxyphenyl]-1,3,5-triazine-2,4-diyl]bis(imino- 3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(32) 4,4'-[(6-phenyl-1,3,5-triazine-2,4- diyl)bis(imino-3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(33) N-[6-[(2,3-dihydro-1H-inden-2-yl)amino]-2-(2-pyridinyl)-4-pyrimidinyl]-βalanine,

(34) N^4-cyclopentyl-2-phenyl-N^6-(phenylmethyl)-4,6-pyrimidinediamine,

(35) 2-[[6-(bicyclo[2.2.1]hept-2-ylamino)-2-phenyl-4-pyrimidinyl]amino]-ethanol,

(36) N^2-isopropyl-6-phenyl-N4-(tetrahydro-2H-pyran-4-yl)-1,3,5-triazine-2,4-diamine,

(37) 2-chloro-4-(methylsulfonyl)-*N*-[4-[(phenylmethyl)amino]-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-benzamide,

(38) *N*-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl]methyl]-4-fluoro-benzenesulfonamide,

(39) [[4-[[[[[4-amino-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl]amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

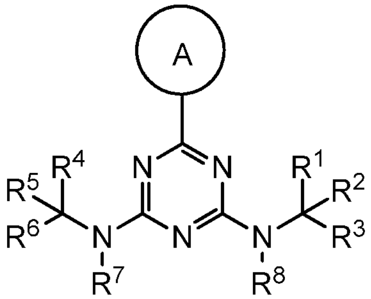
(40) [[4-[[[[[4-[bis(hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl](hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

(41) 5-[4,6-bis(diethylamino)-1,3,5-triazin-2-yl]- 2*H*-tetrazole-2-acetic acid ethyl ester,

(42) N^2,N^2,N^4,N^4-tetraethyl-6-(2*H*-tetrazol-5-yl)-1,3,5-triazine-2,4-diamine, and

(43) *N,N'*-[6-[4-(acetylamino)-1,2,5-oxadiazol-3-yl]-1,3,5-triazine-2,4-diyl]bis-acetamide.

2. A compound having Formula Ia or a pharmaceutically acceptable salt or hydrate thereof:



(Ia), wherein:

ring A is an optionally substituted 5-6 member monocyclic aryl or monocyclic heteroaryl;

R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, and CN, wherein any alkyl portion of R^1, R^3, R^4, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$;

R^2 and R^5 are each independently selected from: -(C_1-C_6 alkyl), -(C_1-C_6 alkyl)-C(O)-NH_2, -(C_1-C_6 alkyl)-CO_2H, -(C_2-C_6 alkenyl or alkynyl), -(C_1-C_6 alkylene)-N(R^6)-(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-(C_0-C_6

alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)(R^6), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1-2}$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)-S(O)$_{1-2}$-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-S(O)$_{1-2}$-N(R^6)(R^6), -(C_1-C_4 alkylene)-S(O)$_{1-2}$-N(R^6)-(C_1-C_6 alkylene)-Q, -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)- (C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -C(O)N(R^6)-(C_1-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkyl)-Q, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-O-(C_1-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-O-C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)N(R^6)-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-N(R^6)C(O)-(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-S(O)$_{0-2}$-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-S(O)$_{0-2}$-(C_0-C_6 alkylene)-Q, -(C_1-C_6 alkylene)-N(R^6)-C(O)-N(R^6)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-Q, wherein:

any alkyl or alkylene moiety present in R^2 and R^5 is optionally substituted with one or more -OH, -O(C_1-C_4 alkyl), -CO_2H, or halo;

any terminal methyl moiety present in R^2 and R^5 is optionally replaced with -CH_2OH, CF_3, -CH_2F, -CH_2Cl, C(O)CH_3, C(O)CF_3, CN, or CO_2H;

R^7 and R^8 are each independently selected from hydrogen and C_1-C_6 alkyl; and

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, any of which is optionally substituted; wherein

R^1 and R^3 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^4 and R^6 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^1 and R^2 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl; or

R^4 and R^5 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

wherein:

(i) when A is optionally substituted phenyl, then (a) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is 4-[[2-[2-(2-aminoethoxy)ethoxy]ethyl]amino] and (b) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both NHEt, NH(n-propyl), NH(n-butyl), NH(n-dodecyl), NH-[(4- methoxyphenyl)methyl], $NHCH_2CH_2CHO$, $NHCH_2CH_2OCH_3$, $NHCH_2CH_2OH$, $NHCH_2CH(OH)CH_3$, $NHCH_2CH_2OC(O)$phenyl, $NHCH_2CH_2CH_2OH$, $NHCH_2CH_2CH_2N(CH_3)$phenyl, $NHCH_2C(O)OCH_3$, $NHCH_2C(O)OCH_2CH_3$, $NHCH_2$phenyl, $NHCH(CH_3)CH_2CH_3$, or $NHCH_2CH_2OC(O)CH_3$;

(ii) when X is N and A is an optionally substituted pyridyl, then (A) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is NHC(O)-[2-chloro-4-(methylsulfonyl)], (B) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $NHC(O)C(CH_3)_3$, $NHC(O)CH{=}CH_2$, $NHC(O)C(CH_3){=}CH_2$, $NHCH_2CH_2OH$, NH-cyclohexyl, $NHCH_2$-phenyl, NHC(O)phenyl, $NHC(O)(CH_2)_5NH_2$, $NHC(O)OCH_3$, $NHC(O)CH_3$, and NHC(O)NH-optionally substituted phenyl, and (C) when $N(R^7)C(R^4)(R^5)(R^6)$ is $NHC(CH_3)_3$, then $N(R^8)C(R^1)(R^2)(R^3)$ is not $NHCH_2$-phenyl or NH-CH_2CH_3;

(iii) when X is N and A is an optionally substituted heteroaryl, then $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $N(CH_2CH_3)_2$, $NHCH_2CH_2$-i-propyl, $NHCH_2CH(CH_3)_2$, and $NHC(O)CH_3$;

(iv) the compound is not selected from the group:

(1) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(2) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(3) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(3-nitrophenyl)-1,3,5-triazine-2,4-diamine,

(4) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine,

(5) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-trifluoromethoxyphenyl)-1,3,5-triazine-2,4-diamine,

(6) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(4-t-butyl-phenyl)-1,3,5-triazine-2,4-diamine,

(7) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopentyl-6-(2-thienyl)-1,3,5-triazine-2,4-diamine,

(8) N-(2-aminophenyl)-4-[[[4-[(2,3-dihydro-1H-inden-2-yl)amino]-6-phenyl-1,3,5-triazin-2-yl]amino]methyl]-benzamide,

(9) 2-chloro-N-[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-4-(methylsulfonyl)-benzamide,

(10) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine,

(11) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]-acetamide,

(12) N^2-cyclopropyl-N^4-ethyl-6-[3-[(phenylmethyl)thio]-1H-1,2,4-triazol-1-yl]-1,3,5-triazine-2,4-diamine,

(13) 2-[[1-[4-(cyclopropylamino)-6-(ethylamino)-1,3,5-triazin-2-yl]-1H-1,2,4-triazol-3-yl]thio]- acetic acid methyl ester,

(14) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(2,4,6-trimethylphenyl)-1,3,5-triazine-2,4-diamine,

(15) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(16) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-methylphenyl)-1,3,5-triazine-2,4-diamine,

(17) N^2-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-N^4-cyclopropyl-6-(4-chlorophenyl)-1,3,5-triazine-2,4-diamine,

(18) N-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl] methyl]-4-fluoro-benzenesulfonamide,

(19) N^2-cyclopropyl-6-(3,5-dimethyl-1H-pyrazol-1-yl)-N^4-phenyl-1,3,5-triazine-2,4-

diamine,

(20) N^2,N^4-dicyclohexyl-6-[3-(4-methoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(21) N^2,N^4-dicyclohexyl-6-[3-(3,4-dimethoxyphenyl)-5-(methylthio)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(22) N^2,N^4-dicyclohexyl-6-[5-(methylthio)-3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-1-yl]-1,3,5-triazine-2,4-diamine,

(23) N^2,N^4-dicyclohexyl-6-phenyl-1,3,5-triazine-2,4-diamine,

(24) 1,1'-[(6-phenyl-s-triazine-2,4-diyl)diimino]bis[dodecahydro-anthraquinone],

(25) 4,4'-[(6-phenyl-1,3,5-triazine-2,4- diyl)bis(iminomethylene)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(26) N-[4-[(4-aminobutyl)amino]-6-[5-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl] amino]-2-methylphenyl]-1,3,5-triazin-2-yl]-glycine,

(27) 4-[2-[[4-[(5-aminopentyl)amino]-6-(3-fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]-phenol,

(28) 4-[2-[[4-[(5-aminopentyl)amino]-6-(4-fluorophenyl)-1,3,5-triazin-2-yl]amino]ethyl]-phenol,

(29) 6-(4-aminopyridin-3-yl)-N^2-benzyl-N^4-(tert-butyl)-1,3,5-triazine-2,4-diamine,

(30) N^2,N^4-bis(cyclohexylmethyl)-6-phenyl-1,3,5-triazine-2,4-diamine,

(31) 4,4'-[[6-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,5-triazine-2,4-diyl]bis(imino-3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(32) 4,4'-[(6-phenyl-1,3,5-triazine-2,4-diyl)bis(imino-3,1-propanediyl)]bis[2,6-bis(1,1-dimethylethyl)-phenol,

(33) N^2-isopropyl-6-phenyl-N4-(tetrahydro-2H-pyran-4-yl)-1,3,5-triazine-2,4-diamine,

(34) 2-chloro-4-(methylsulfonyl)-*N*-[4-[(phenylmethyl)amino]-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-benzamide,

(35) *N*-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl]methyl]-4-fluoro-benzenesulfonamide,

(36) [[4-[[[[[4-amino-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl]amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

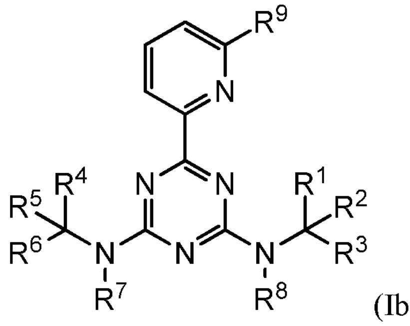
(37) [[4-[[[[[4-[bis(hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]amino]methoxy]methyl](hydroxymethyl)amino]-6-(4-pyridinyl)-1,3,5-triazin-2-yl]imino]bis-methanol,

(38) 5-[4,6-bis(diethylamino)-1,3,5-triazin-2-yl]- 2*H*-tetrazole-2-acetic acid ethyl ester,

(39) N^2,N^2,N^4,N^4-tetraethyl-6-(2*H*-tetrazol-5-yl)-1,3,5-triazine-2,4-diamine, and

(40) *N*,*N*'-[6-[4-(acetylamino)-1,2,5-oxadiazol-3-yl]-1,3,5-triazine-2,4-diyl]bis-acetamide.

3. A compound having Formula Ib, or pharmaceutically acceptable salt or hydrate thereof:



(Ib), wherein:

R^1, R^3, R^4, and R^6 are each independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, and CN, wherein any alkyl portion of R^1, R^3, R^4, and R^6 are each independently optionally substituted with -OH, -NH_2, -CN, -O-C_1-C_4 alkyl, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$;

R^2 and R^5 are each independently selected from: -(C_1-C_6 alkyl), -(C_1-C_6 alkyl)-C(O)-NH_2, -(C_1-C_6 alkyl)-CO_2H, -(C_0-C_6 alkylene)-Q, -(C_0-C_6 alkylene)-C(O)-(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-C(O)-(C_0-C_6 alkylene)-Q, wherein:

any alkyl or alkylene moiety present in R^2 and R^5 is optionally substituted with one or more -OH, -O(C_1-C_4 alkyl), -CO_2H, or halo;

any terminal methyl moiety present in R^2 and R^5 is optionally replaced with -CH_2OH, CF_3, -CH_2F, -CH_2Cl, C(O)CH_3, C(O)CF_3, CN, or CO_2H;

R^7 and R^8 are each independently selected from hydrogen and C_1-C_6 alkyl;

R^9 is selected from hydrogen, halo, and -C_1-C_4 haloalkyl; and

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, any of which is optionally substituted; wherein

R^1 and R^3 are optionally taken together with the carbon atom to which they are attached to form C(=O); or

R^4 and R^6 are optionally taken together with the carbon atom to which they are attached to form C(=O);

R^1 and R^2 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl; or

R^4 and R^5 are optionally taken together to form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

wherein

when X is N and A is an optionally substituted pyridyl, then (A) neither $N(R^7)C(R^4)(R^5)(R^6)$ nor $N(R^8)C(R^1)(R^2)(R^3)$ is NHC(O)-[2-chloro-4-(methylsulfonyl)], (B) $N(R^7)C(R^4)(R^5)(R^6)$ and $N(R^8)C(R^1)(R^2)(R^3)$ are not both $NHC(O)C(CH_3)_3$, $NHC(O)CH=CH_2$, $NHC(O)C(CH_3)=CH_2$, $NHCH_2CH_2OH$, NH-cyclohexyl, $NHCH_2$-phenyl, NHC(O)phenyl, $NHC(O)(CH_2)_5NH_2$, $NHC(O)OCH_3$, $NHC(O)CH_3$, and NHC(O)NH-optionally substituted phenyl, and (C) when $N(R^7)C(R^4)(R^5)(R^6)$ is $NHC(CH_3)_3$, then $N(R^8)C(R^1)(R^2)(R^3)$ is not $NHCH_2$-phenyl or NH-CH_2CH_3; and

wherein the compound is not:

(1) 2-chloro-N-[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-4-(methylsulfonyl)-benzamide,

(2) N-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl] methyl]-4-fluoro-benzenesulfonamide,

(3) 2-chloro-4-(methylsulfonyl)-*N*-[4-[(phenylmethyl)amino]-6-(2-pyridinyl)-1,3,5-triazin-2-yl]-benzamide, or

(4) *N*-[[4-[[[4-(cyclopropylamino)-6-(2-pyridinyl)-1,3,5-triazin-2-yl]amino]methyl]cyclohexyl]methyl]-4-fluoro-benzenesulfonamide.