

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
30 October 2008 (30.10.2008)

PCT

(10) International Publication Number  
**WO 2008/130951 A1**

## (51) International Patent Classification:

C07D 487/04 (2006.01) A61P 3/06 (2006.01)  
 C07D 495/14 (2006.01) A61P 3/08 (2006.01)  
 A61K 31/5025 (2006.01) A61P 3/10 (2006.01)  
 A61K 31/519 (2006.01) A61P 9/12 (2006.01)  
 A61K 31/4985 (2006.01) A61P 27/06 (2006.01)  
 A61P 3/04 (2006.01)

08534 (US). **ROBL, Jeffrey, A.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **HAMANN, Lawrence, G.** [US/US]; 7 Whitney Street, North Grafton, MA 01536 (US).

## (21) International Application Number:

PCT/US2008/060395

(22) International Filing Date: 16 April 2008 (16.04.2008)

(25) Filing Language: English

(26) Publication Language: English

## (30) Priority Data:

60/912,186 17 April 2007 (17.04.2007) US  
 61/044,951 15 April 2008 (15.04.2008) US

(71) Applicant (for all designated States except US): **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, NJ 08543-4000 (US).

## (72) Inventors; and

(75) Inventors/Applicants (for US only): **LI, Jun** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **LI, James, J.** [US/US]; 76 Stanford Road East, Pennington, NJ 08534 (US). **O'CONNOR, Stephen, P.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **WANG, Haixia** [CN/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **KENNEDY, Lawrence, J.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ

(74) Agents: **BOGIE, Terence, J.** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

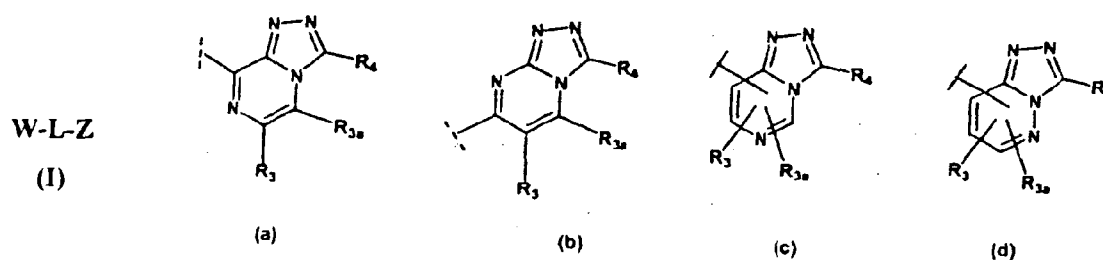
## Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

## Published:

- with international search report

(54) Title: FUSED HETEROCYCLIC 11-BETA-HYDROXYSTEROID DEHYDROGENASE TYPE I INHIBITORS



(57) Abstract: Novel compounds are provided which are 11-beta-hydroxysteroid dehydrogenase type I inhibitors. 11-beta-hydroxysteroid dehydrogenase type I inhibitors are useful in treating, preventing, or slowing the progression of diseases requiring 11-beta-hydroxysteroid dehydrogenase type I inhibitor therapy. These novel compounds have the structure: W-L-Z or stereoisomers or prodrugs or pharmaceutically acceptable salts thereof, wherein W, L are defined herein and Z is selected from the following bicyclic heteroaryl groups: (a), (b), (c), (d).

WO 2008/130951 A1

**FUSED HETEROCYCLIC 11-BETA-HYDROXYSTEROID  
DEHYDROGENASE TYPE I INHIBITORS**

**BACKGROUND OF THE INVENTION**

- 5    **[0001]**     The steroid hormone cortisol is a key regulator of many physiological processes. However, an excess of cortisol, as occurs in Cushing's Disease, provokes severe metabolic abnormalities including: type 2 diabetes, cardiovascular disease, obesity, and osteoporosis. Many patients with these diseases, however, do not show significant increases in plasma cortisol levels. In addition to plasma cortisol,
- 10 individual tissues can regulate their glucocorticoid tone via the in situ conversion of inactive cortisone to the active hormone cortisol. Indeed, the normally high plasma concentration of cortisone provides a ready supply of precursor for conversion to cortisol via the intracellular enzyme 11-beta-hydroxysteroid dehydrogenase type I (11-beta-HSD1).
- 15    **[0002]**     11-beta-HSD1 is a member of the short chain dehydrogenase superfamily of enzymes. By catalyzing the conversion of biologically inactive cortisone to cortisol, 11-beta-HSD1 controls the intracellular glucocorticoid tone according to its expression and activity levels. In this manner, 11-beta-HSD1 can determine the overall metabolic status of the organ. 11-beta-HSD1 is expressed at high levels in the
- 20 liver and at lower levels in many metabolically active tissues including the adipose, the CNS, the pancreas, and the pituitary. Taking the example of the liver, it is predicted that high levels of 11-beta-HSD1 activity will stimulate gluconeogenesis and overall glucose output. Conversely, reduction of 11-beta-HSD1 activity will downregulate gluconeogenesis resulting in lower plasma glucose levels.
- 25    **[0003]**     Various studies have been conducted that support this hypothesis. For example, transgenic mice expressing 2X the normal level of 11-beta-HSD1 in only the adipose tissue show abdominal obesity, hyperglycemia, and insulin resistance. (Masuzaki, H. et al., "A Transgenic Model of Visceral Obesity and the Metabolic Syndrome", *Science*, 294:2166-2170 (2001). Conversely, when the 11-beta-HSD1
- 30 gene is ablated by homologous recombination, the resulting mice are resistant to diet induced obesity and the accompanying dysregulation of glucose metabolism (Morton, N.M. et al., "Novel Adipose Tissue-Mediated Resistance to Diet-induced Visceral

Obesity in 11 $\beta$ -Hydroxysteroid Dehydrogenase Type 1-Deficient Mice”, *Diabetes*, 53:931-938 (2004). In addition, treatment of genetic mouse models of obesity and diabetes (ob/ob, db/db and KKAY mice) with a specific inhibitor of 11-beta-HSD1 causes a decrease in glucose output from the liver and an overall increase in insulin sensitivity (Alberts, P. et al., “Selective Inhibition of 11 $\beta$ -Hydroxysteroid Dehydrogenase Type I Improves Hepatic Insuling Sensitivity in Hyperglycemic Mice Strains”, *Endocrinology*, 144:4755-4762 (2003)). Based in part on these studies, it is believed that local control of cortisol levels is important in metabolic diseases in these model systems. In addition, the results of these studies also suggest that inhibition of 11-beta-HSD1 will be a viable strategy for treating metabolic diseases such as type 2 diabetes, obesity, and the metabolic syndrome.

[0004] Lending further support to this idea are the results of a series of preliminary clinical studies. For example, several reports have shown that adipose tissue from obese individuals has elevated levels of 11-beta-HSD1 activity. In addition, studies with carbenoxolone, a natural product derived from licorice that inhibits both 11-beta-HSD1 and 11-beta-HSD2 (converts cortisol to cortisone in kidney) have shown promising results. A seven day, double blind, placebo controlled, cross over study with carbenoxolone in mildly overweight individuals with type 2 diabetes showed that patients treated with the inhibitor, but not the placebo group, displayed a decrease in hepatic glucose production (Andrews, R.C. et al., *J. Clin. Endocrinol. Metab.*, 88:285-291 (2003)). This observation is consistent with the inhibition of 11-beta-HSD1 in the liver. Furthermore, another clinical study reported that the inhibition of 11-beta-HSD1 may provide a novel treatment option for patients with glaucoma (Rauz et al., *IOVS*, 42(9):2037-2042 (August 2001)). The results of these preclinical and early clinical studies strongly support the concept that treatment with a potent and selective inhibitor of 11-beta-HSD1 will be an efficacious therapy in patients afflicted with various disorders.

#### SUMMARY OF THE INVENTION

[0005] In accordance with the present invention, aryl and heterocyclyl and related compounds are provided that have the general structure of formula I:

**W-L-Z****(I)**

wherein W, L and Z are defined below.

**[0006]** Compounds of the present invention inhibit the activity of the enzyme 11-  
5 beta-hydroxysteroid dehydrogenase type I. Consequently, the compounds of the  
present invention may be used in the treatment of multiple diseases or disorders  
associated with 11-beta-hydroxysteroid dehydrogenase type I, such as diabetes and  
related conditions, microvascular complications associated with diabetes, the  
macrovascular complications associated with diabetes, cardiovascular diseases,  
10 glaucoma, Metabolic Syndrome and its component conditions, and other maladies.  
Examples of diseases or disorders associated with the activity of the enzyme 11-beta-  
hydroxysteroid dehydrogenase type I that can be prevented, inhibited, or treated  
according to the present invention include, but are not limited to, diabetes,  
hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia,  
15 retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its  
sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome,  
hypertension, obesity, dislipidemia, dyslipidemia, hyperlipidemia,  
hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac  
ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative  
20 disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV  
protease associated lipodystrophy and glaucoma.

**[0007]** The present invention provides for compounds of formula I,  
pharmaceutical compositions employing such compounds, and for methods of using  
such compounds. In particular, the present invention provides a pharmaceutical  
25 composition comprising a therapeutically effective amount of a compound of formula  
I, alone or in combination with a pharmaceutically acceptable carrier.

**[0008]** Further, in accordance with the present invention, a method is provided for  
preventing, inhibiting, or treating the progression or onset of diseases or disorders  
associated with the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase  
30 type I, such as defined above and hereinafter, wherein a therapeutically effective  
amount of a compound of formula I is administered to a mammalian, i.e., human,  
patient in need of treatment.

[0009] The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

[0010] Further, the present invention provides a method for preventing, 5 inhibiting, or treating the diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of formula I and another compound of formula I and/or at least one other type of therapeutic agent, is administered to a mammalian, i.e., human, patient in need of treatment.

10

### DESCRIPTION OF THE INVENTION

[0011] In accordance with the present invention, compounds of formula I are provided

#### W-L-Z

#### (I)

15 enantiomers, diastereomers, solvates, salts or prodrugs thereof wherein:

W is  $-C(=O)R_6$ ,  $-C(OH)R_6(R_6)$ ,  $-C(=O)OR_6$ ,  $-C(=O)NR_6R_6$ , halogen,  $-OH$ , alkyl, alkenyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, wherein the alkyl, alkenyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$ ;

20  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$  are independently hydrogen, halogen,  $-OH$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R_6$ ,  $-CONR_6R_6$ ,  $-SO_2NR_6R_6$ ,  $-SOR_6$ ,  $-SO_2R_6$ ,  $-NR_6SO_2R_6$ ,  $-NR_6CO_2R_6$ ,  $-OCONR_6R_6$ , tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, 25 cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ;

or alternatively any two  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$  can be taken together to form a fused cycloalkyl, aryl, heteroaryl, heterocyclyl ring or spiro heterocyclyl ring;

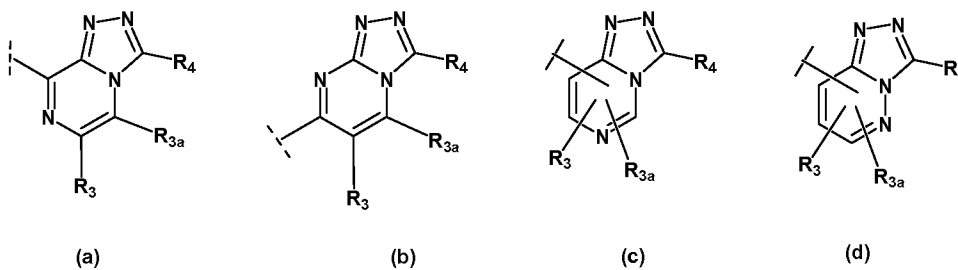
L is a bond, O, S, SO,  $SO_2$ ,  $C(=O)$ , alkenyl, cycloalkyl,  $NR_5$ ,  $CR_2R_{2a}$ ,  $CR_2R_6$ , 30  $CR_2R_{2a}CR_{2b}R_{2c}$ ,  $SO_2NR_6$ ,  $OCR_2R_{2a}$ ,  $OCR_2R_{2a}CR_{2b}R_{2c}$ ,  $CR_2R_{2a}O$ ,  $CR_{2b}R_{2c}CR_2R_{2a}O$ ,  $N(R_5)CR_2R_{2a}$ ,  $CR_2R_{2a}N(R_5)$ ,  $SCR_2R_{2a}$ ,  $CR_2R_{2a}S$ ,  $CR_2R_{2a}SO$ ,  $CR_2R_{2a}SO_2$ ,  $SOCR_2R_{2a}$ ,  $SO_2CR_2R_{2a}$ ,  $CR_2R_{2a}OCR_{2b}R_{2c}$ ,  $CR_2R_{2a}SCR_{2b}R_{2c}$ ,  $CR_2R_{2a}SO_2CR_{2b}R_{2c}$ ,

SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub>, COCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>CO, CONR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub>, CR<sub>2</sub>R<sub>2a</sub>CR<sub>2b</sub>R<sub>2c</sub>S,  
 CR<sub>2</sub>R<sub>2a</sub>CR<sub>2b</sub>R<sub>2c</sub>SO, CR<sub>2</sub>R<sub>2a</sub>CR<sub>2b</sub>R<sub>2c</sub>SO<sub>2</sub>, provided that W is not halogen or -OH when  
 L is O, S, SO, SO<sub>2</sub>, C(=O) or NR<sub>5</sub>;

R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl,  
 5 cycloalkyl, aryl, or haloalkyl;

or alternatively any two R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub>, and R<sub>2c</sub> can be taken together to which  
 the atom they are attached to form a cycloalkyl, halogen substituted cycloalkyl or  
 heterocyclyl ring;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>,  
 -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl,  
 cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl,  
 alkylamino, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl, wherein the  
 15 tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally  
 substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>,  
 -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl,  
 cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl,  
 20 alkylamino, aminoalkyl, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl,  
 wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be  
 optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

or alternatively any R<sub>3</sub> and R<sub>3a</sub> can be taken together to form a fused  
 cycloalkyl, aryl, heteroaryl or heterocyclyl ring, which may be optionally substituted  
 25 with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

or alternatively one of R<sub>3</sub> or R<sub>3a</sub> can be taken together with W-L to form a fused cycloalkyl, aryl, heteroaryl or heterocyclyl ring, which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more  
 5 substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>,  
 -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>,  
 -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino,  
 heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl,  
 spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted  
 10 with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl,  
 cycloalkyl, heteroaryl or heterocyclyl and (ii) Z is formula (d); or

R<sub>4</sub> is heterocyclyl, which may be optionally substituted with one or more  
 substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>,  
 -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>,  
 15 -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino,  
 heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl,  
 spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted  
 with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents  
 20 selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>,  
 -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl,  
 cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or  
 heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro  
 heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  
 25 R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>5</sub>, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, haloalkyl, COR<sub>6</sub>, CO<sub>2</sub>R<sub>6</sub>, SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, or SO<sub>2</sub>R<sub>6</sub>;

R<sub>6</sub>, at each occurrence, is independently H, alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; or

30 two R<sub>6</sub>'s may be taken together with the atom to which they are attached to form a 3- to 7-membered cycloalkyl or heterocyclyl ring, which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub> and R<sub>7c</sub>;

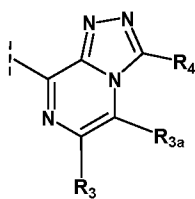
$R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ , at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with  $R_8$ ,  $R_{8a}$ ,  $R_{8b}$ , and  $R_{8c}$ ; and

$R_8$ ,  $R_{8a}$ ,  $R_{8b}$ , and  $R_{8c}$ , at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

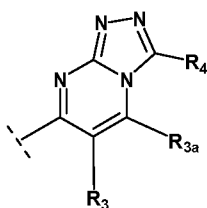
**[0012]** In one embodiment, compounds of formula I are provided wherein W is alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, all of which may be optionally substituted with  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$ .

**[0013]** In another embodiment, compounds of formula I are provided wherein W is phenyl or cyclopropyl, both of which are optionally substituted with  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$ .

**[0014]** In still another embodiment, compounds of formula I are provided wherein Z is selected from the following bicyclic heteroaryl groups:

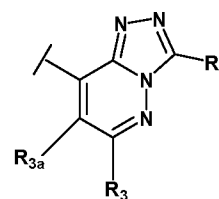


(a)



(b)

or



(d-1)

[0015] In still another embodiment, compounds of formula I are provided wherein:

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>,  
 5 -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>,  
 -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl,  
 10 cycloalkyl, heteroaryl or heterocyclyl and (ii) Z is formula (d); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>,  
 -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or  
 15 heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>5</sub>, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, haloalkyl, COR<sub>6</sub>, CO<sub>2</sub>R<sub>6</sub>, SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, or SO<sub>2</sub>R<sub>6</sub>;

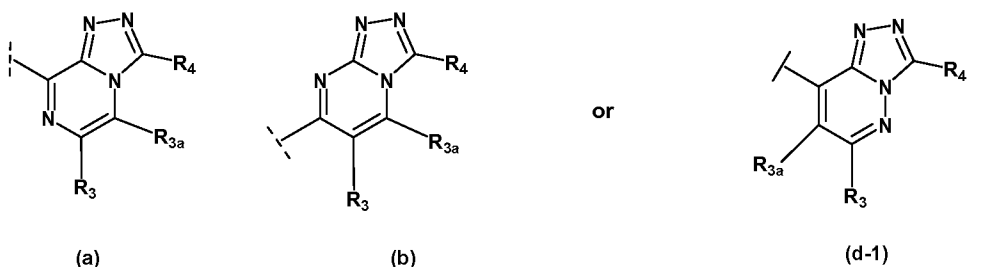
20 R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl,  
 25 heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio,  
 30 arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

$R_8$ ,  $R_{8a}$ ,  $R_{8b}$ , and  $R_{8c}$ , at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

**[0016]** In yet still another embodiment, compounds of formula I are provided wherein:

10 Z is selected from the following bicyclic heteroaryl groups:



$R_4$  is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, alkoxy, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ; provided that  $R_4$  is not cycloalkyl when (i) W is aryl, cycloalkyl, heteroaryl or heterocyclyl and (ii) Z is formula (d-1);

20  $R_5$ , at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, haloalkyl, COR<sub>6</sub>, CO<sub>2</sub>R<sub>6</sub>, SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, or SO<sub>2</sub>R<sub>6</sub>;

$R_6$ , at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ;

25  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ , at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio,

arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, 5 arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, 10 heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

**[0017]** In one embodiment, compounds of formula I are provided wherein:

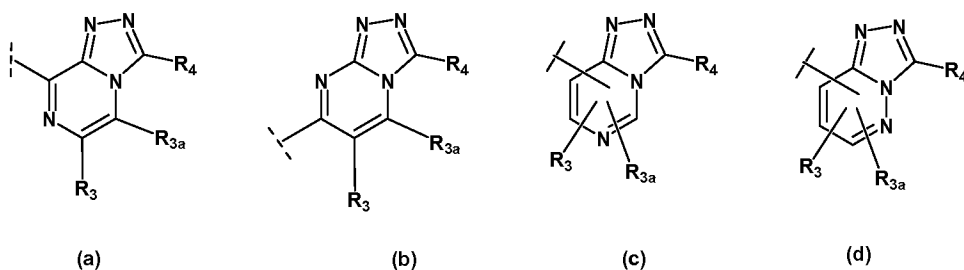
15 W is alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, all of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl, 20 haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

L is a bond, O, S, SO<sub>2</sub>, C(=O), CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, SO<sub>2</sub>NR<sub>6</sub>, OCR<sub>2</sub>R<sub>2a</sub>, 25 OCR<sub>2</sub>R<sub>2a</sub>CR<sub>2b</sub>R<sub>2c</sub>, CR<sub>2</sub>R<sub>2a</sub>O, CR<sub>2b</sub>R<sub>2c</sub>CR<sub>2</sub>R<sub>2a</sub>O, SCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>S, CR<sub>2</sub>R<sub>2a</sub>SO, CR<sub>2</sub>R<sub>2a</sub>SO<sub>2</sub>, SO<sub>2</sub>CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>, CR<sub>2</sub>R<sub>2a</sub>SCR<sub>2b</sub>R<sub>2c</sub>, CR<sub>2</sub>R<sub>2a</sub>SO<sub>2</sub>CR<sub>2b</sub>R<sub>2c</sub>, SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub>, COCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>CO, CONR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub>, CR<sub>2</sub>R<sub>2a</sub>CR<sub>2b</sub>R<sub>2c</sub>S, CR<sub>2</sub>R<sub>2a</sub>CR<sub>2b</sub>R<sub>2c</sub>SO, or CR<sub>2</sub>R<sub>2a</sub>CR<sub>2b</sub>R<sub>2c</sub>SO<sub>2</sub>;

R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl, 30 cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroaryl, heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroaryl, heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl, cycloalkyl, heteroaryl or heterocyclyl and (ii) Z is formula (d); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro

heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>5</sub>, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, haloalkyl, COR<sub>6</sub> or CO<sub>2</sub>R<sub>6</sub>;

5 R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

**[0018]** In another embodiment, compounds of formula I are provided wherein:

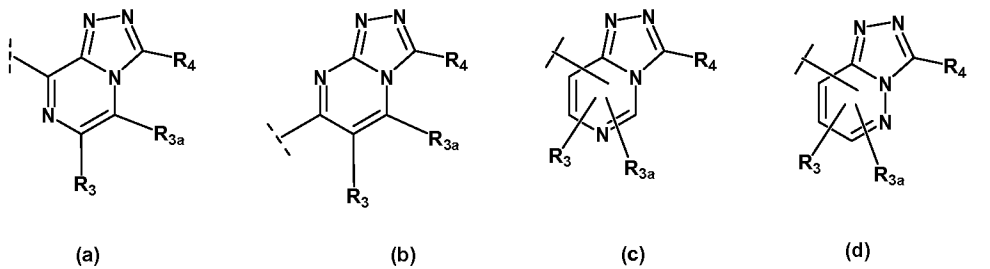
25 W is alkyl, aryl, cycloalkyl or heteroaryl, all of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

L is a bond, O, S, SO, SO<sub>2</sub>, C(=O), NR<sub>2</sub>, CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, CR<sub>2</sub>R<sub>2a</sub>CR<sub>2b</sub>R<sub>2c</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O, SCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>S, CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>, CR<sub>2</sub>R<sub>2a</sub>SCR<sub>2b</sub>R<sub>2c</sub>, CR<sub>2</sub>R<sub>2a</sub>SO<sub>2</sub>CR<sub>2b</sub>R<sub>2c</sub> or SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub>;

R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl, 5 cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, 10 haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, 15 haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more 20 substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not 25 cycloalkyl when (i) W is aryl, cycloalkyl or heteroaryl and (ii) Z is formula (d); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H,

-OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

5 R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

**[0019]** In still another embodiment, compounds of formula I are provided  
25 wherein:

W is alkyl, aryl or cycloalkyl, all of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

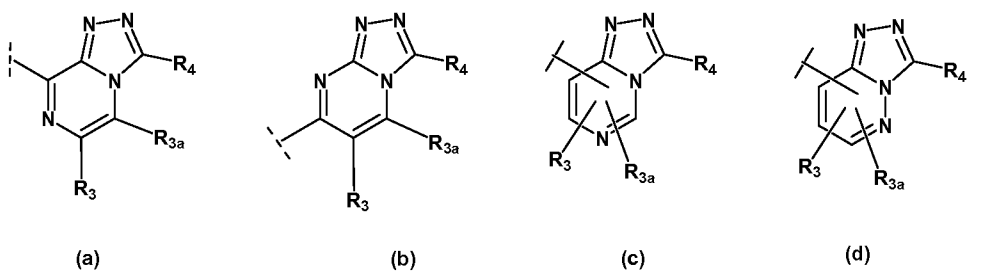
R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the  
30

tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ;

L is a bond, O, S, SO,  $SO_2$ ,  $C(=O)$ ,  $CR_2R_{2a}$ ,  $CR_2R_6$ ,  $OCR_2R_{2a}$ ,  $CR_2R_{2a}O$ ,  $SO_2NR_6CR_{2a}R_{2b}$  or  $CR_2R_{2a}OCR_{2b}R_{2c}$ ;

5  $R_2$ ,  $R_{2a}$ ,  $R_{2b}$  and  $R_{2c}$  are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



$R_3$  is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>,  
 10 -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ;

$R_{3a}$  is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>,  
 15 -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ;

$R_4$  is cycloalkyl, which may be optionally substituted with one or more  
 20 substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ; provided that  $R_4$  is not  
 25 cycloalkyl when (i) W is aryl or cycloalkyl and (ii) Z is formula (d); or

$R_4$  is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H,

-OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

5 R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

[0020] In yet still another embodiment, compounds of formula I are provided  
25 wherein:

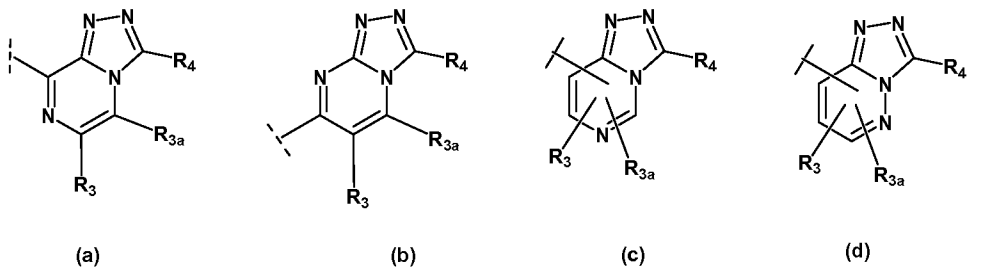
W is alkyl, aryl or cycloalkyl, all of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

L is a bond, O, S, SO, SO<sub>2</sub>, C(=O), CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O, SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub> or CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>;

R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl or haloalkyl;

5 Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl or cycloalkyl and (ii) Z is formula (d); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro

cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

5 R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -  
 10 CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

15 R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -  
 20 CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

**[0021]** In one embodiment, compounds of formula I are provided wherein:

W is alkyl, aryl or cycloalkyl, all of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

25 R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

30 L is a bond, O, S, SO, SO<sub>2</sub>, C(=O), CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O, SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub> or CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>;



arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

**[0022]** In another embodiment, compounds of formula I are provided wherein:

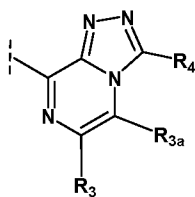
W is alkyl, aryl or cycloalkyl, all of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

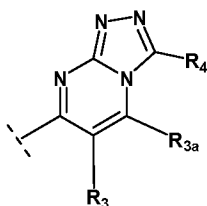
L is a bond, O, S, SO, SO<sub>2</sub>, C(=O), CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O, SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub> or CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>;

R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:

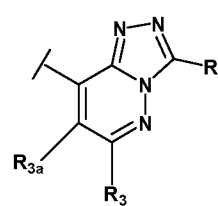


(a)



(b)

or



(d-1)

;

R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  
5 R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally  
10 substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro  
15 cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl,  
20 haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl,  
25 arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl,  
30 haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio,

arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

[0023] In still another embodiment, compounds of formula I are provided

5 wherein:

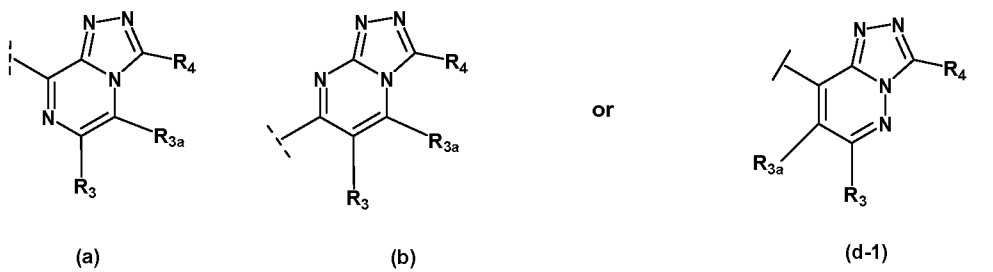
W is aryl or cycloalkyl, both of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, 10 arylsulfonyl, alkylamino, aminoalkyl, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

L is a bond, O, S, C(=O), CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O or CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>;

15 R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, 20 cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, 25 cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when Z is formula (d-1); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl; R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

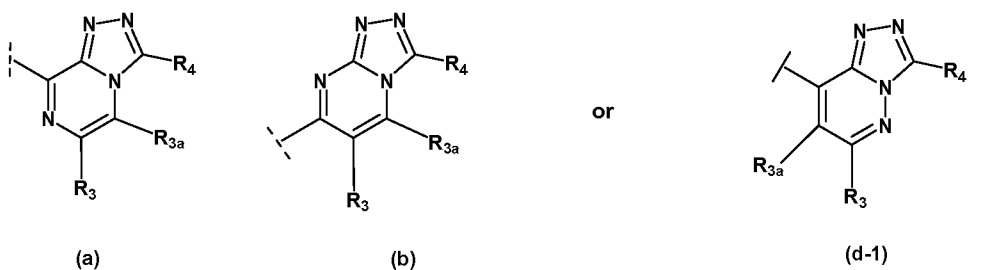
**[0024]** In another embodiment, compounds of formula I are provided wherein:

W is phenyl or cyclopropyl, both of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, aryl, heteroaryl or heterocyclyl;

L is a bond, O, S, C(=O), CHR<sub>6</sub>, SCH<sub>2</sub>, OCH<sub>2</sub>, CH<sub>2</sub>O or CH<sub>2</sub>OCH<sub>2</sub>;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aryl, heteroaryl or heterocyclyl;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, aryl, heteroaryl or heterocyclyl;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

provided that R<sub>4</sub> is not cycloalkyl when Z is formula (d-1); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylalkyl, cycloalkyl, amino, -OH, hydroxyalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, alkylthio, arylalkylthio, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H or tetrazolyl; wherein the alkyl, alkoxy, aryl, aryloxy, arylalkyl, cycloalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, alkylthio, arylalkylthio or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

**[0025]** In one embodiment, compounds of formula I are provided wherein L is a bond or O.

**[0026]** In another embodiment, compounds of the present invention are selected from the compounds exemplified in the examples.

**[0027]** In another embodiment, the present invention relates to pharmaceutical compositions comprised of a therapeutically effective amount of a compound of the present invention, alone or, optionally, in combination with a pharmaceutically acceptable carrier and/or one or more other agent(s).

**[0028]** In another embodiment, the present invention relates to methods of inhibiting the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I comprising administering to a mammalian patient, for example, a human patient, in need thereof a therapeutically effective amount of a compound of the present invention, alone, or optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

**[0029]** In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective

amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

**[0030]** Examples of diseases or disorders associated with the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I that can be prevented, inhibited, or treated according to the present invention include, but are not limited to, diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dislipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy and glaucoma.

**[0031]** In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of diabetes, hyperglycemia, obesity, dyslipidemia, hypertension and cognitive impairment comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

**[0032]** In still another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of diabetes, comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

**[0033]** In yet still another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of hyperglycemia comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a

compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

5 [0034] In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of obesity comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

10 [0035] In one embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of dyslipidemia comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

15 [0036] In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of hypertension comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

20 [0037] In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of cognitive impairment comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

25 [0038] In another embodiment, the present invention relates to the use of a compound of the present invention in the preparation of a medicament that may be used for inhibiting the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I comprising administering to a mammalian patient, for example, a human patient, in need thereof a therapeutically effective amount of a compound of the

30

present invention, alone, or optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

**[0039]** In another embodiment, the present invention relates to the use of a compound of the present invention in the preparation of a medicament that may be used for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

**[0040]** In another embodiment, the present invention relates to the use of a compound of the present invention in the preparation of a medicament that may be used for preventing, inhibiting, or treating the progression or onset of diabetes, hyperglycemia, obesity, dyslipidemia, hypertension and cognitive impairment comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

**[0041]** In still another embodiment, the present invention relates to the use of a compound of the present invention in the preparation of a medicament that may be used for preventing, inhibiting, or treating the progression or onset of diabetes, comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

**[0042]** In yet still another embodiment, the present invention relates to the use of a compound of the present invention in the preparation of a medicament that may be used for preventing, inhibiting, or treating the progression or onset of hyperglycemia comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a

compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

5 [0043] In another embodiment, the present invention relates to the use of a compound of the present invention in the preparation of a medicament that may be used for preventing, inhibiting, or treating the progression or onset of obesity comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

10 [0044] In one embodiment, the present invention relates to the use of a compound of the present invention in the preparation of a medicament that may be used for preventing, inhibiting, or treating the progression or onset of dyslipidemia comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

15 [0045] In another embodiment, the present invention relates to the use of a compound of the present invention in the preparation of a medicament that may be used for preventing, inhibiting, or treating the progression or onset of hypertension comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

20 [0046] In another embodiment, the present invention relates to the use of a compound of the present invention in the preparation of a medicament that may be used for preventing, inhibiting, or treating the progression or onset of cognitive impairment comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

25  
30

[0047] In another embodiment, the present invention provides a compound of the present invention for use in therapy.

[0048] In another embodiment, the present invention provides a compound of the present invention for use in therapy for treating a metabolic disorder.

5 [0049] In another embodiment, the present invention also provides the use of a compound of the present invention for the manufacture of a medicament for the treatment of a metabolic disorder.

[0050] In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic  
10 agent(s) for simultaneous, separate or sequential use in therapy.

[0051] In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in treatment of a metabolic disorder.

15 [0052] In another embodiment, the present invention provides a novel article of manufacture, comprising: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention; and (c) a package insert stating that the pharmaceutical composition can be used for the  
20 treatment of a metabolic disorder.

[0053] In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising: (d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

25

[0054] In another embodiment, the present invention provides a novel article of manufacture, comprising: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention; and (c) a  
30 package insert stating that the pharmaceutical composition can be used in combination with a second therapeutic agent to treat a metabolic disorder.

[0055] In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising: (d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

5

[0056] The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment may be combined with any and all other elements from any of the embodiments to describe additional embodiments.

10

15

#### DEFINITIONS

[0057] The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

20

25

30

[0058] One enantiomer of a compound of Formula I may display superior activity compared with the other. Thus, all of the stereochemistries are considered to be a part of the present invention. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent

such as camphonic chloride as in Young, S.D. et al., *Antimicrobial Agents and Chemotherapy*, 2602-2605 (1995).

**[0059]** To the extent that compounds of the formula I, and salts thereof, may exist in their tautomeric form, all such tautomeric forms are contemplated herein as part of  
5 the present invention.

**[0060]** The term "substituted," as used herein, means that any one or more hydrogens on the designated atom or ring is replaced with a selection from the indicated group, provided that the designated atom's or ring atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a  
10 substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

**[0061]** When any variable (e.g.,  $R_4$ ) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with  $(R_4)_m$  and  $m$  is 0-3, then said group may optionally be substituted  
15 with up to three  $R_4$  groups and  $R_4$  at each occurrence is selected independently from the definition of  $R_4$ . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

**[0062]** When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When  
20 a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

**[0063]** As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups containing 1 to 20 carbons, preferably 1  
25 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethyl-pentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups may  
30 optionally include 1 to 4 substituents such as halo, for example F, Br, Cl, or I, or  $CF_3$ , alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl,

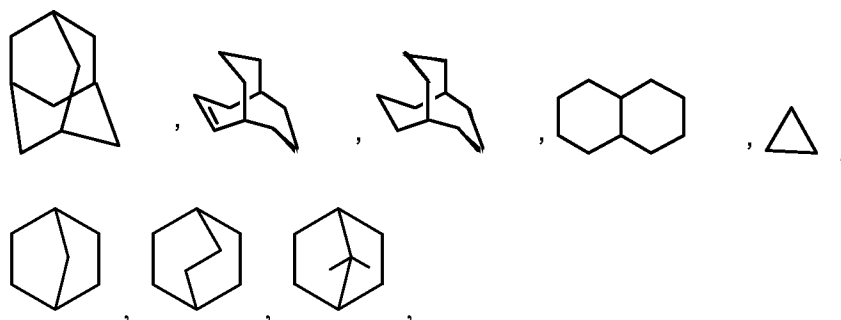
heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl, and/or alkylthio.

**[0064]** Unless otherwise indicated, the term “alkenyl” as used herein by itself or  
5 as part of another group refers to straight or branched chain radicals of 2 to 20  
carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal  
chain, which include one to six double bonds in the normal chain, such as vinyl, 2-  
propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-  
heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-  
10 dodecenyl, 4,8,12-tetradecatienyl, and the like, and which may be optionally  
substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy,  
alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl,  
cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonyl-amino, nitro, cyano, thiol,  
alkylthio, and/or any of the alkyl substituents set out herein.

**[0065]** Unless otherwise indicated, the term “alkynyl” as used herein by itself or  
15 as part of another group refers to straight or branched chain radicals of 2 to 20  
carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal  
chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-  
butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-  
20 heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl, 3-undecynyl, 4-dodecynyl, and  
the like, and which may be optionally substituted with 1 to 4 substituents, namely,  
halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino,  
heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido,  
arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the alkyl  
25 substituents set out herein.

**[0066]** Unless otherwise indicated, the term “cycloalkyl” as employed herein  
alone or as part of another group includes saturated or partially unsaturated  
(containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 10 rings,  
preferably 1 to 3 rings, including monocyclic alkyl, bicyclic alkyl (or bicycloalkyl)  
30 and tricyclic alkyl, containing a total of 3 to 20 carbons forming the ring, preferably 3  
to 15 carbons, more preferably 3 to 10 carbons, forming the ring and which may be  
fused to 1 or 2 aromatic rings as described for aryl, which includes cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl,  
cyclododecyl, cyclohexenyl,



- 5 any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol, and/or alkylthio, and/or any of the substituents for alkyl.

**[0067]** Where alkyl groups as defined above have single bonds for attachment to  
10 other groups at two different carbon atoms, they are termed “alkylene” groups and may optionally be substituted as defined above for “alkyl”.

**[0068]** Where alkenyl groups as defined above and alkynyl groups as defined  
above, respectively, have single bonds for attachment at two different carbon atoms,  
they are termed “alkenylene groups” and “alkynylene groups”, respectively, and may  
15 optionally be substituted as defined above for “alkenyl” and “alkynyl”.

**[0069]** “Halo” or “halogen” as used herein refers to fluoro, chloro, bromo, and  
iodo; and “haloalkyl” is intended to include both branched and straight-chain  
saturated aliphatic hydrocarbon groups, for example  $CF_3$ , having the specified  
number of carbon atoms, substituted with 1 or more halogen (for example  $-C_vF_w$   
20 where  $v = 1$  to  $3$  and  $w = 1$  to  $(2v+1)$ ).

**[0070]** Unless otherwise indicated, the term “aryl” as employed herein alone or as  
part of another group refers to monocyclic and bicyclic aromatic groups containing 6  
to 10 carbons in the ring portion (such as phenyl or naphthyl, including 1-naphthyl  
and 2-naphthyl) and may optionally include 1 to 3 additional rings fused to a  
25 carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl, or  
cycloheteroalkyl rings  
for example



and may be optionally substituted through available carbon atoms with 1, 2, or 3  
 5 substituents, for example, hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy,  
 haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl,  
 cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy,  
 aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl,  
 heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino  
 10 wherein the amino includes 1 or 2 substituents (which are alkyl, aryl, or any of the  
 other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio,  
 heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkyl-  
 aminocarbonyl, arylaminocarbonyl, alkoxy carbonyl, aminocarbonyl,  
 alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino,  
 15 arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino, or arylsulfon-aminocarbonyl,  
 and/or any of the alkyl substituents set out herein.

**[0071]** Unless otherwise indicated, the term “lower alkoxy”, “alkoxy”, “aryloxy”  
 or “aralkoxy” as employed herein alone or as part of another group includes any of  
 the above alkyl, aralkyl, or aryl groups linked to an oxygen atom.

20 **[0072]** Unless otherwise indicated, the term “amino” as employed herein alone or  
 as part of another group refers to amino that may be substituted with one or two  
 substituents, which may be the same or different, such as alkyl, aryl, arylalkyl,  
 heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl,  
 cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, or thioalkyl. These  
 25 substituents may be further substituted with a carboxylic acid and/or any of the R<sup>1</sup>  
 groups or substituents for R<sup>1</sup> as set out above. In addition, the amino substituents

may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl or 4-diarylalkyl-1-piperazinyl, all of which may be optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl, or hydroxy.

**[0073]** Unless otherwise indicated, the term “lower alkylthio,” “alkylthio,” “arylthio,” or “aralkylthio” as employed herein alone or as part of another group includes any of the above alkyl, aralkyl, or aryl groups linked to a sulfur atom.

**[0074]** Unless otherwise indicated, the term “lower alkylamino,” “alkylamino,” “arylamino,” or “arylalkylamino” as employed herein alone or as part of another group includes any of the above alkyl, aryl, or arylalkyl groups linked to a nitrogen atom.

**[0075]** As used herein, the term “heterocyclyl” or “heterocyclic system” is intended to mean a stable 4- to 14-membered monocyclic, bicyclic or tricyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom, which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. As used herein, the term “aromatic heterocyclic system” or “heteroaryl” is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and is aromatic in nature.

**[0076]** Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 1H-indolyl, 4-piperidonyl, 4aH-

carbazole, 4H-quinoliziny, 6H-1,2,5-thiadiaziny, acridiny, azociny,  
 benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl,  
 benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl,  
 benzimidazalonyl, carbazolyl, 4aH-carbazolyl,  $\beta$ -carboliny, chromanyl, chromenyl,  
 5 cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiaziny, dihydrofuro[2,3-  
*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidiny, imidazoliny, imidazolyl,  
 indazolyl, indolenyl, indoliny, indoliziny, indolyl, isobenzofuranyl, isochromanyl,  
 isoindazolyl, isoindoliny, isoindolyl, isoquinoliny (benzimidazolyl), isothiazolyl,  
 isoxazolyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-  
 10 oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny,  
 oxazolyl, oxazolidinylperimidiny, phenanthridiny, phenanthroliny, phenarsaziny,  
 phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperaziny,  
 piperidiny, pteridiny, piperidonyl, 4-piperidonyl, pteridiny, puriny, pyranly,  
 pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole,  
 15 pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidiny, pyrrolidiny,  
 pyrroliny, pyrrolyl, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny,  
 quinuclidiny, carboliny, tetrahydrofuranyl, tetrahydroisoquinoliny,  
 tetrahydroquinoliny, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,  
 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl,  
 20 thienooxazolyl, thienoimidazolyl, thiophenyl, triaziny, 1,2,3-triazolyl, 1,2,4-triazolyl,  
 1,2,5-triazolyl, 1,3,4-triazolyl, tetrazolyl, and xanthenyl. In another aspect of the  
 invention, the heterocycles include, but are not limited to, pyridiny, thiophenyl,  
 furanyl, indazolyl, benzothiazolyl, benzimidazolyl, benzothiaphenyl, benzofuranyl,  
 benzoxazolyl, benzisoxazolyl, quinoliny, isoquinoliny, imidazolyl, indolyl,  
 25 isoidolyl, piperidiny, piperidonyl, 4-piperidonyl, piperonyl, pyrrazolyl, 1,2,4-  
 triazolyl, 1,2,3-triazolyl, tetrazolyl, thiazolyl, oxazolyl, pyraziny, and pyrimidiny.  
 Also included are fused ring and spiro compounds containing, for example, the above  
 heterocycles.

**[0077]** Examples of heteroaryls are 1H-indazole, 2H,6H-1,5,2-dithiaziny,  
 30 indolyl, 4aH-carbazole, 4H-quinoliziny, 6H-1,2,5-thiadiaziny, acridiny, azociny,  
 benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl,  
 benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl,

benzimidazolonyl, carbazolyl, 4*aH*-carbazolyl,  $\beta$ -carboliny, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, indazolyl, indolenyl, indolinyl, indoliziny, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyrazolotriazinyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazoliny, quinolinyl, 4*H*-quinoliziny, quinoxaliny, quinuclidinyl, carboliny, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, tetrazolyl, and xanthenyl. In another aspect of the invention, examples of heteroaryls are indolyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolonyl, cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl, isoquinolinyl isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyrazolotriazinyl, pyridazinyl, pyridyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazoliny, quinolinyl, thiazolyl, thienyl, and tetrazolyl.

**[0078]** The term “heterocyclylalkyl” or “heterocyclyl” as used herein alone or as part of another group refers to heterocyclyl groups as defined above linked through a C atom or heteroatom to an alkyl chain.

**[0079]** The term “heteroarylalkyl” or “heteroarylalkenyl” as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to an alkyl chain, alkylene, or alkenylene as defined above.

**[0080]** The term “cyano” as used herein, refers to a -CN group.

**[0081]** The term “nitro” as used herein, refers to an -NO<sub>2</sub> group.

[0082] The term “hydroxy” as used herein, refers to an OH group.

[0083] The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of  
5 human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0084] As used herein, “pharmaceutically acceptable salts” refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not  
10 limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts  
15 include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane  
20 disulfonic, oxalic, isethionic, and the like.

[0085] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the  
25 appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985), the disclosure of which is hereby incorporated by reference.

[0086] Any compound that can be converted *in vivo* to provide the bioactive agent (i.e., the compound of formula I) is a prodrug within the scope and spirit of the  
30 invention.

[0087] The term “prodrugs” as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula I with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, and the like.

[0088] Various forms of prodrugs are well known in the art and are described in:

- a) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch. 31 (Academic Press, 1996);
  - b) *Design of Prodrugs*, edited by H. Bundgaard (Elsevier, 1985);
  - 10 c) *A Textbook of Drug Design and Development*, P. Krogsgaard-Larson and H. Bundgaard, eds., Ch. 5, pp. 113-191 (Harwood Academic Publishers, 1991); and
  - d) *Hydrolysis in Drug and Prodrug Metabolism*, Bernard Testa and Joachim M. Mayer (Wiley-VCH, 2003).
- 15 Said references are incorporated herein by reference.

[0089] In addition, compounds of the formula I are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% formula I compound (“substantially pure” compound I), which is then used or formulated as described herein. Such “substantially pure” compounds of the formula I are also contemplated herein as part of the present invention.

[0090] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents and/or exhibit polymorphism. Consequently, compounds of formula I can exist in enantiomeric, or diastereomeric forms, or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers, or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

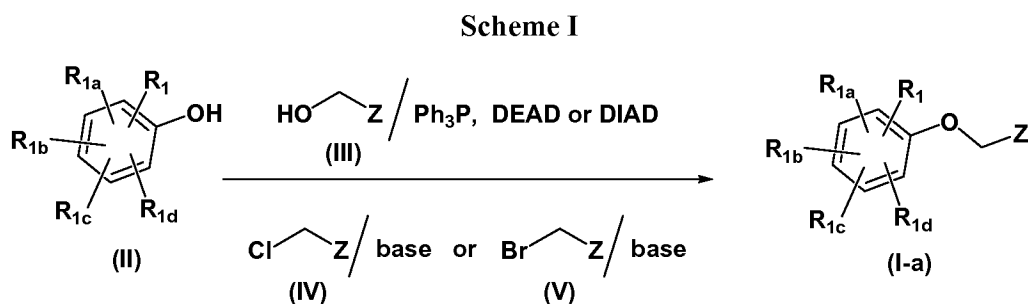
[0091] “Stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

5 [0092] “Therapeutically effective amount” is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to inhibit 11-beta-HSD1 or effective to treat or prevent metabolic disorders.

10 [0093] As used herein, “treating” or “treatment” cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e.,  
 15 causing regression of the disease state.

### SYNTHESIS

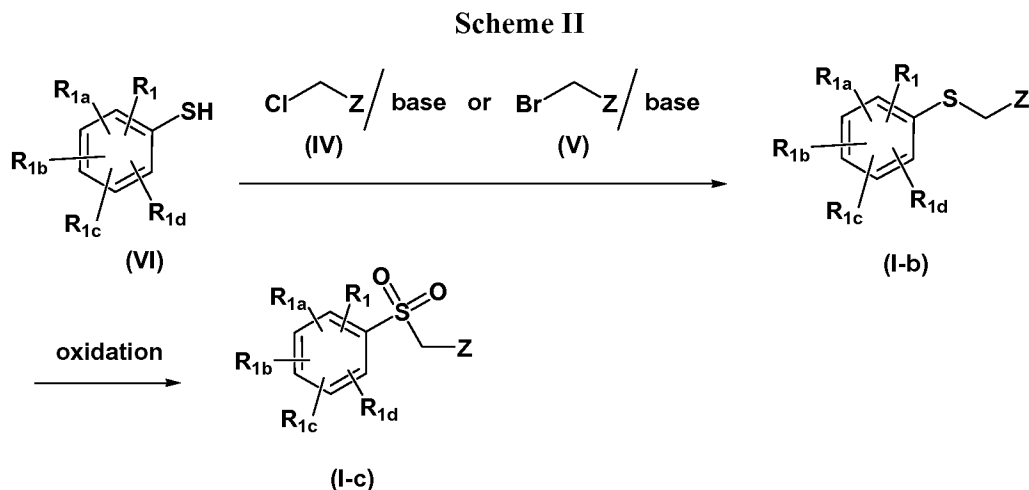
[0094] Compounds of formula I may be prepared as shown in the following reaction schemes and description thereof, as well as relevant literature procedures that  
 20 may be used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working examples set forth below.



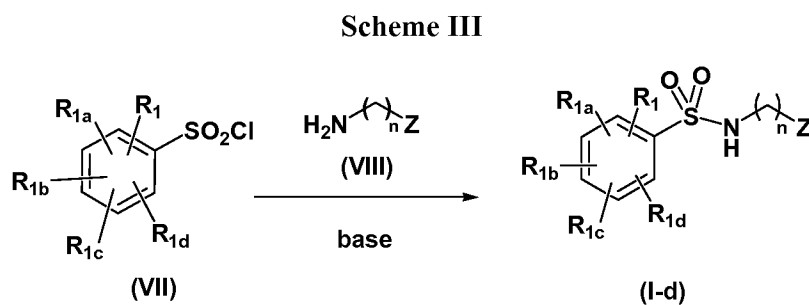
25 [0095] Scheme I describes a method for preparing compounds of formula I-a (a subset of compounds of formula I). A phenol intermediate II can be obtained commercially, prepared by methods known in the literature or by other methods known to one skilled in the art. Formation of a compound I-a can be carried out from

a phenol **II** and an alcohol **III** using triphenylphosphine and DEAD or DIAD, commonly known as the Mitsunobu Reaction. Alternatively, a compound **I-a** can be obtained from alkylation of a phenol **II** with a chloride **IV** or a bromide **V** in the presence of an appropriate base, such as sodium carbonate or DIEA.

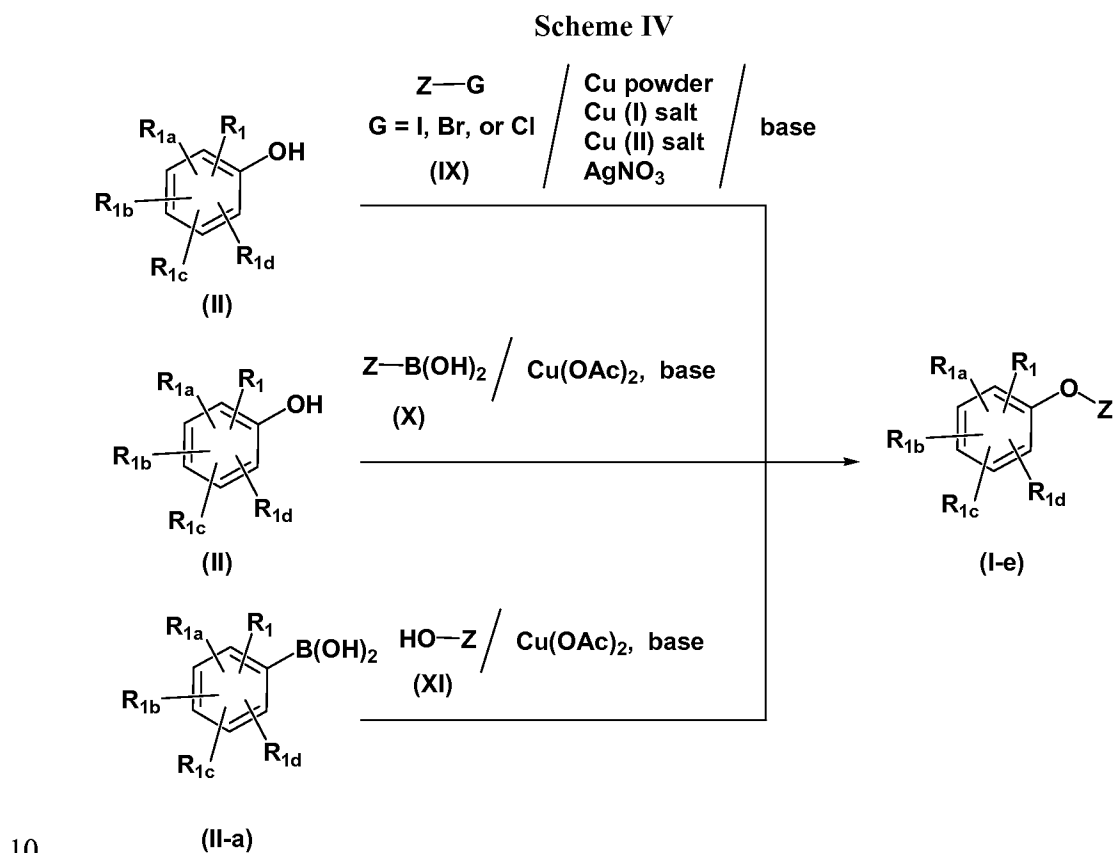
5



[0096] Scheme II describes a method for preparing compounds of formula **I-b** and formula **I-c** (subsets of compounds of formula **I**). A thiophenol intermediate **VI** can be obtained commercially, prepared by methods known in the literature or by other methods known to one skilled in the art. Formation of a compound **I-b** can be obtained from alkylation of a thiophenol **VI** with a chloride **IV** or a bromide **V** in the presence of an appropriate base, such as sodium carbonate or DIEA. Subsequent oxidation of a compound **I-b** with an appropriate oxidizing reagent such as *m*CPBA, Oxone<sup>®</sup>, *p*-toluenesulfonic peracid generated in situ (*Tetrahedron*, 52:5773-5787 (1996)) or by other reagents known to one skilled in the art provides a compound **I-c**.



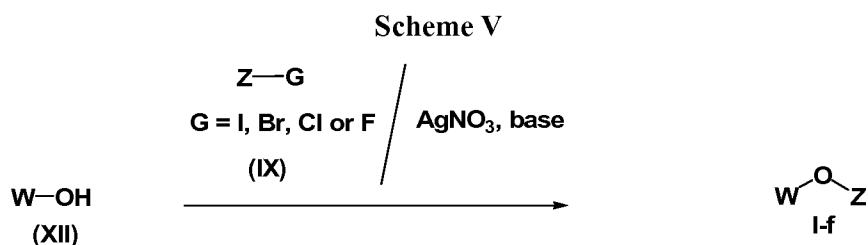
[0097] Scheme III describes a method for preparing compounds of formula **I-d** (a subset of compounds of formula **I**). An arylsulfonyl chloride intermediate **VII** can be obtained commercially, prepared by methods known in the literature or by other methods known to one skilled in the art. Formation of a compound **I-d** can be achieved from the reaction of a compound of formula **VII** with an amine **VIII** in the presence of an appropriate base such as pyridine, DIEA or other reagents known to one skilled in the art to provide a compound **I-d**.



[0098] Scheme IV describes a method for preparing compounds of formula **I-e** (a subset of compounds of formula **I**). A phenol intermediate **II** can be obtained commercially, prepared by methods known in the literature or by other methods known to one skilled in the art. Formation of a compound **I-e** can be achieved from treatment of a potassium salt of a phenol **II** and a chloro, bromo- or iodo-substituted intermediate **IX** ( $G$  is  $Cl$ ,  $Br$  or  $I$ ) in the presence of copper powder, copper (I) salt or copper (II) salt at elevated temperature, commonly known as Ullmann ether synthesis

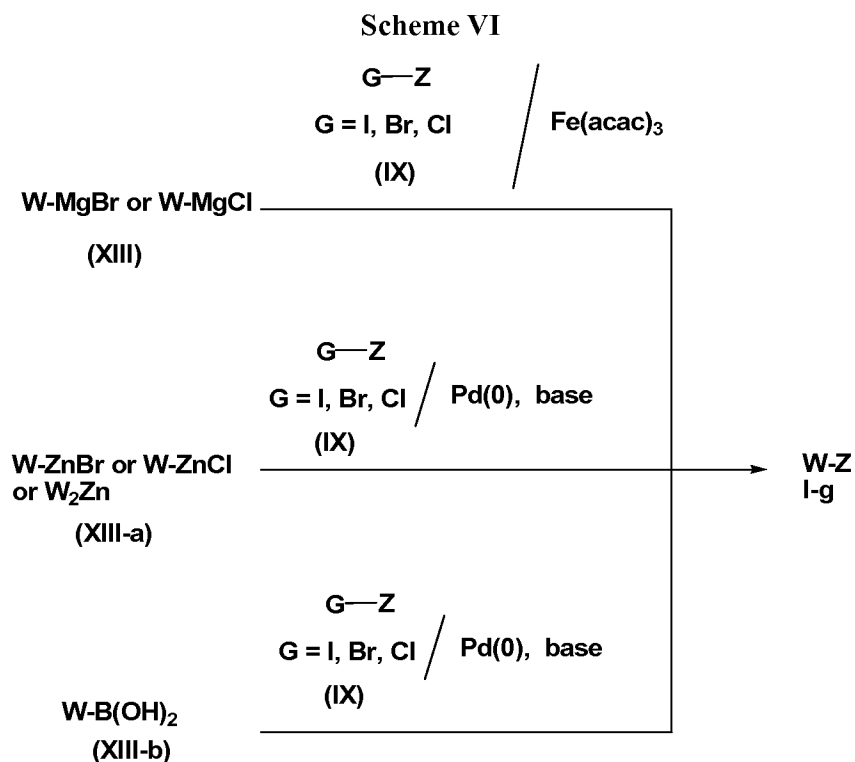
(*Tetrahedron*, 40:1433-1456 (1984)). The reactions can be carried out under a conventional procedure or done in a microwave reactor. Alternatively, a compound **I-e** can be obtained via coupling reaction of a phenol **II** and a bromo-, chloro- and iodo-substituted intermediate **IX** (G is Br, Cl or I) in the presence of silver nitrate and a base such as potassium hydroxide at elevated temperature (*Syn. Comm.*, 32:813-817 (2002)). Furthermore, a compound **I-e** can be obtained from a copper acetate-mediated aryl ether synthesis using a phenol **II** and an arylboronic acid **X** or a phenol **XI** and an arylboronic acid **II-a** (*Tetrahedron Lett.*, 39:2937-2940 (1998)).

10



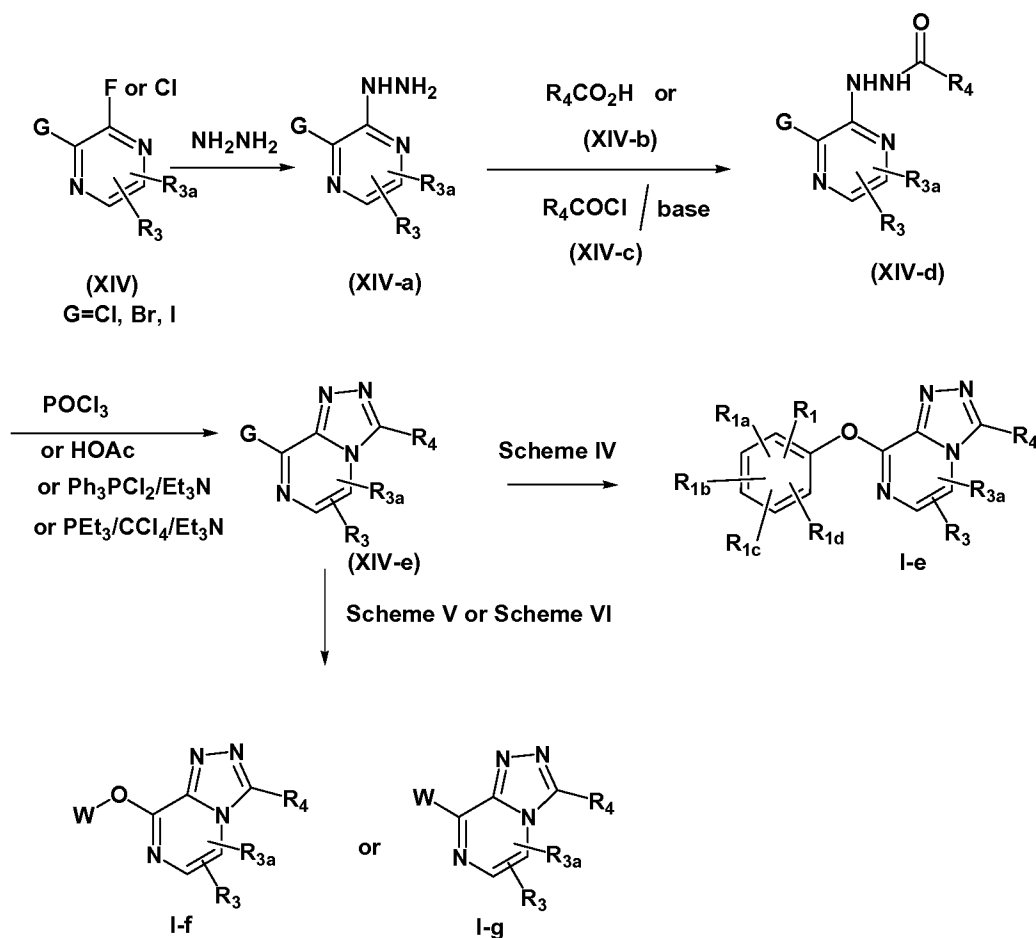
[0099] Scheme V describes a method for preparing compounds of formula **I-f** (a subset of compounds of formula **I**). A hydroxyl intermediate **XII** can be obtained commercially, prepared by methods known in the literature or by other methods known to one skilled in the art. Compound **I-f** can be obtained via coupling reaction of a hydroxyl **XII** and a bromo-, and chloro- or iodo-substituted intermediate **IX** (G is Br, Cl, I) in the presence of silver nitrate and a base such as potassium hydroxide at elevated temperature. The reactions can be carried out under a conventional procedure or done in a microwave reactor.

20



[00100] Scheme VI describes a method for preparing compounds of formula **I-g** (a subset of compounds of formula **I**). An intermediate **XIII**, or **XIII-a**, or **XIII-b** can be obtained commercially, prepared by methods known in the literature or by other methods known to one skilled in the art. Formation of a compound **I-g** can be achieved from treatment of a Grignard reagent **XIII** and a chloro, bromo- or iodo-substituted intermediate **IX** (G is Cl, Br or I) in the presence of iron acetylacetonate (*Organic Lett.*, 7(11):2169 (2005)). Alternatively, a compound **I-g** can be obtained via coupling reaction of an organo zinc halide or organo zinc **XIII-a** with a bromo-, chloro- or iodo-substituted intermediate **IX** (G is Br, Cl, I) in the presence of a palladium catalyst and a base such as potassium carbonate at elevated temperature. The reactions can be carried out under a conventional procedure or done in a microwave reactor. Furthermore, a compound **I-g** can be obtained from a palladium-mediated C-C coupling reaction using a non-aryl boronic acid **XIII-b** and a bromo-, chloro- or iodo-substituted intermediate **IX** (G is Br, Cl, I) in the presence of palladium catalyst and a base such as potassium carbonate at elevated temperature, commonly known as the Suzuki or modified Suzuki reaction (*J. Organomet. Chem.*, 576:147-168 (1999)).

## Scheme VII



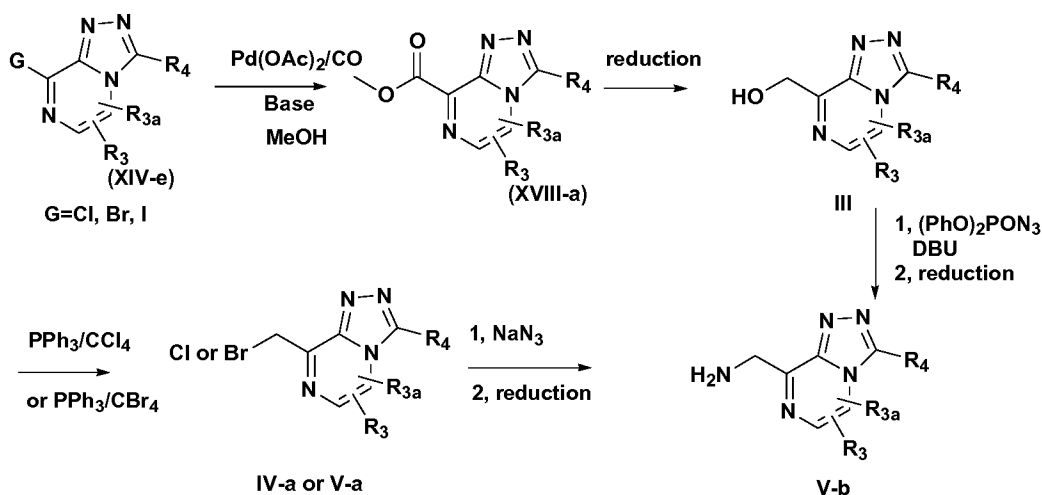
- [00101] Scheme VII describes a method for preparing compounds of formula I-e, I-f and I-g (subsets of compounds of formula I where Z is a triazolopyrazine group). A chloro- or fluoropyrazine intermediate XIV can be obtained commercially, prepared by methods known in the literature or by other methods known to one skilled in the art. Reaction of a compound of formula XIV with hydrazine can be carried out at elevated temperature to provide an intermediate XIV-a. Acylation of an intermediate XIV-a with an acid XIV-b using an appropriate set of amide coupling reagents such as NMM/isobutylchloroformate, EDAC/HOBT or other reagents described in *The Practice of Peptide Synthesis*, 2<sup>nd</sup> Ed., Spring-Verlag, Bodanszy, Miklos (1993) provides a hydrazide intermediate XIV-d. Alternatively, an acyl hydrazide XIV-d can be prepared from the reaction of a compound of formula XIV-a and an acid chloride XIV-c in the presence of an appropriate base such as DIEA or TEA.

Formation of triazolopyrazine **XIV-e** can be achieved from the reaction of **XIV-d** with  $\text{POCl}_3$  at an elevated temperature. Formation of triazolopyrazine **XIV-e** can also be achieved from **XIV-d** in the presence of acetic acid at an elevated temperature, either under a conventional procedure or a microwave reactor. Alternatively,

5 formation of triazolopyrazine **XIV-e** can be achieved from the reaction of **XIV-d** with  $\text{Ph}_3\text{PCl}_2$  in the presence of a base such as TEA or by  $\text{P}(\text{alkyl})_3/\text{CCl}_4$  in the presence of a base such as TEA or DIPEA, or other methods known to one skilled in the art. Formation of a compound of formula **1-e**, **1-f** and **1-g** can be achieved using reactions described in Schemes IV to VI or by other methods known to one skilled in the art.

10

Scheme VIII



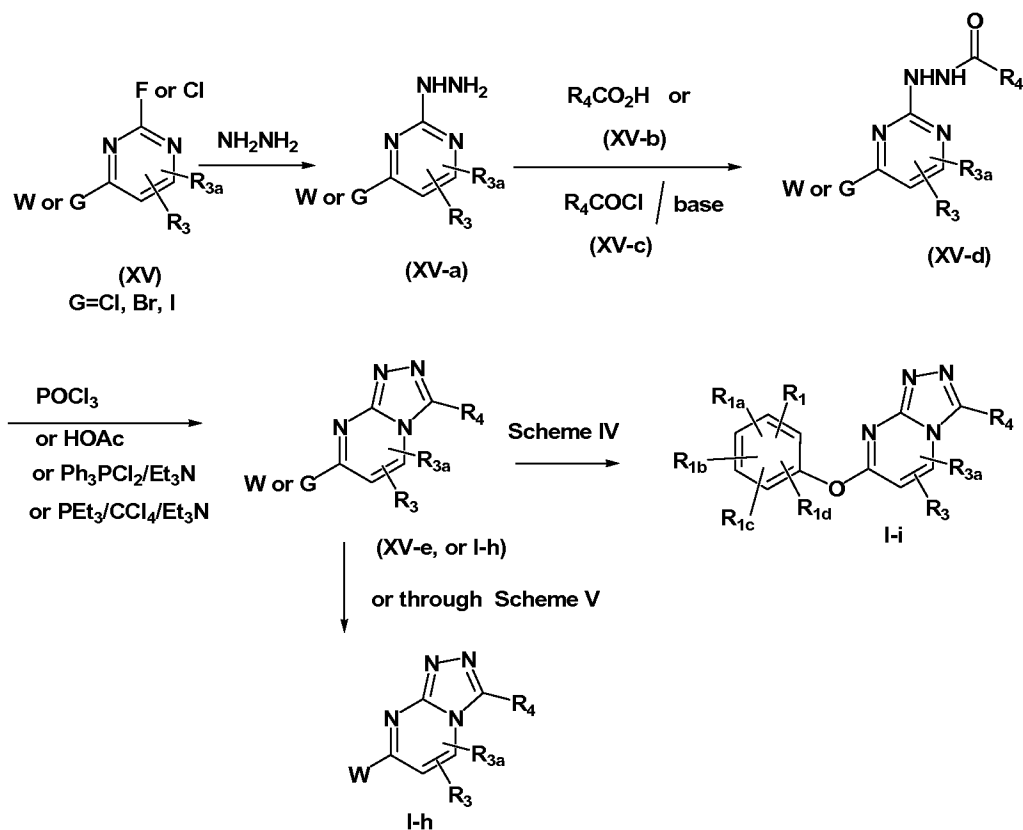
[00102] Scheme VIII describes a method for preparing compounds of formula **XVIII-a**, **III**, **IV-a**, **V-a** or **V-b**. An intermediate **XVIII-a** can be obtained by

15 carboxylation of **XIV-e** in the presence of a palladium catalyst and carbon monoxide, or prepared by methods known in the literature or by other methods known to one skilled in the art. Reduction of the carbonyl group to an alcohol to generate compound **III** can be performed by a reducing reagent such as  $\text{NaBH}_4$ , or other reducing reagent such as DIBAL or by methods known in the literature or by

20 other methods known to one skilled in the art. Formation of a compound **IV-a** or **V-a** can be achieved by reaction of a compound **III** with  $\text{PPh}_3/\text{CCl}_4$  or  $\text{PPh}_3/\text{CBr}_4$  in the presence of a base such as TEA, or prepared by methods known in the literature or by other methods known to one skilled in the art. Formation of amine **V-b** can be

achieved by a transformation of **III** or **IV-a** or **V-a**, both methods known in the literature or by other methods known to one skilled in the art.

Scheme IX



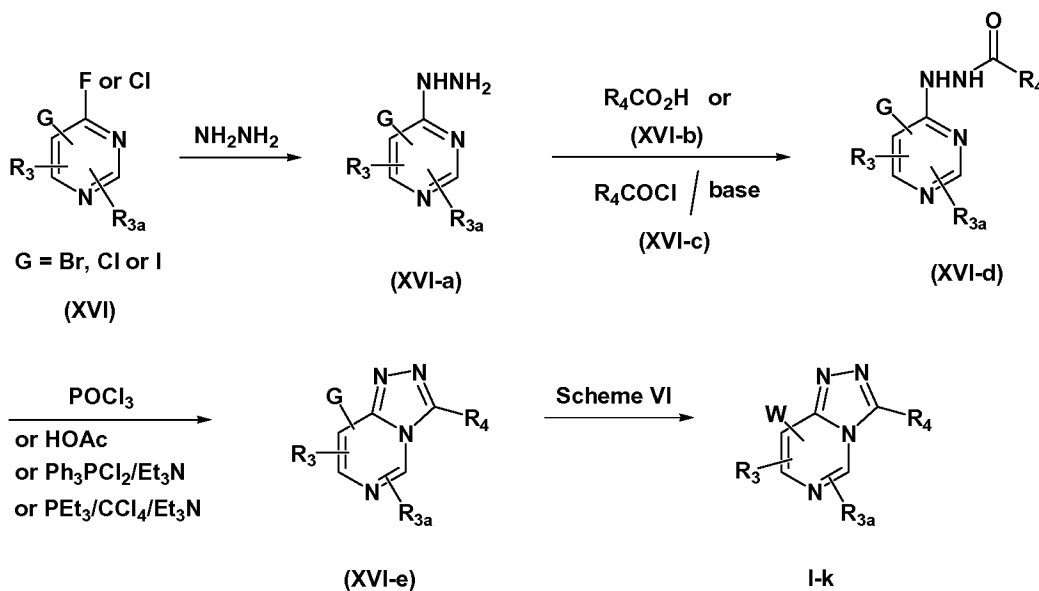
5

[00103] Scheme IX describes a method for preparing compounds of formula **I-i** and **I-h** (subsets of compounds of formula **I** where **Z** is a triazolopyrimidine group). A chloro- or fluopyrimidine intermediate **XV** can be obtained commercially, prepared by methods known in the literature or by other methods known to one skilled in the art. Reaction of a compound of formula **XV** with hydrazine was carried out at elevated temperature to provide an intermediate **XV-a**. Acylation of intermediate **XV-a** with acid **XV-b** using an appropriate set of amide coupling reagents such as NMM/isobutylchloroformate, EDAC/HOBT or other reagents described in *The Practice of Peptide Synthesis*, 2<sup>nd</sup> Ed., Spring-Verlag, Bodanszy, Miklos (1993) provides a hydrazide intermediate **XV-d**. Alternatively, the acyl hydrazide **XV-d** can be prepared from the reaction of a compound of formula **XV-a** and an acid chloride **XV-c** in the presence of an appropriate base such as DIEA or TEA.

Formation of triazolopyrimidine **XV-e** (or **I-h**) can be achieved from the reaction of **XV-d** with  $\text{POCl}_3$  at an elevated temperature. Formation of triazolopyrimidine **XV-e** (or **I-h**) can also be achieved from **XV-d** in the presence of acetic acid at an elevated temperature, either under a conventional procedure or a microwave reactor.

- 5 Alternatively, formation of triazolopyrimidine **XV-e** (or **I-h**) can be achieved from the reaction of **XV-d** with  $\text{Ph}_3\text{PCl}_2$  in the presence of a base such as TEA or by  $\text{P}(\text{alkyl})_3/\text{CCl}_4$  in the presence of a base such as TEA or DIPEA, or other methods known to one skilled in the art. Formation of a compound of formula **I-i** and **I-h** can be achieved using reactions described in Schemes IV to VI or by other methods
- 10 known to one skilled in the art.

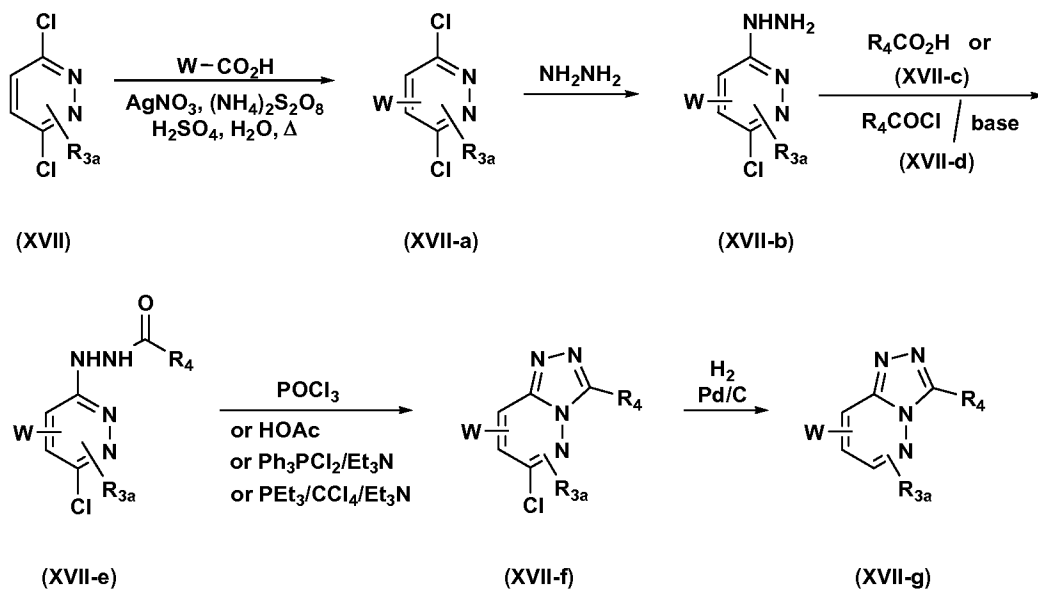
Scheme X



- [00104] Scheme X describes a method for preparing compounds of formula **I-k** (a subset of compounds of formula **I** where **Z** is a triazolopyrimidine group). A chloro- or fluoropyrimidine intermediate **XVI** can be obtained commercially, prepared by methods known in the literature or by other methods known to one skilled in the art. Reaction of a compound of formula **XVI** with hydrazine was carried out at elevated temperature to provide an intermediate **XVI-a**. Acylation of intermediate **XVI-a** with
- 15 an acid **XVI-b** using an appropriate set of amide coupling reagents such as NMM/isobutylchloroformate, EDAC/HOBT or other reagents described in *The Practice of Peptide Synthesis*, 2<sup>nd</sup> Ed., Springer-Verlag, Bodanszky, Miklos (1993) provides an
- 20

acyl hydrazide intermediate **XVI-d**. Alternatively, hydrazide **XVI-d** can be prepared from the reaction of a compound of formula **XVI-a** and an acid chloride **XVI-c** in the presence of an appropriate base such as DIEA or TEA. Formation of triazolopyrimidine **XVI-e** can be achieved from the reaction of **XVI-d** with  $\text{POCl}_3$  at an elevated temperature. Formation of triazolopyrimidine **XVI-e** can also be achieved from **XVI-d** in the presence of acetic acid at an elevated temperature, either under a conventional procedure or a microwave reactor. Alternatively, formation of triazolopyrazine **XVI-e** can be achieved from the reaction of **XVI-d** with  $\text{Ph}_3\text{PCl}_2$  in the presence of a base such as TEA or by  $\text{P}(\text{alkyl})_3/\text{CCl}_4$  in the presence of a base such as TEA or DIPEA, or other methods known to one skilled in the art. Formation of a compound of formula **I-k** can be achieved using reactions described in Scheme VI or by other methods known to one skilled in the art.

Scheme XI



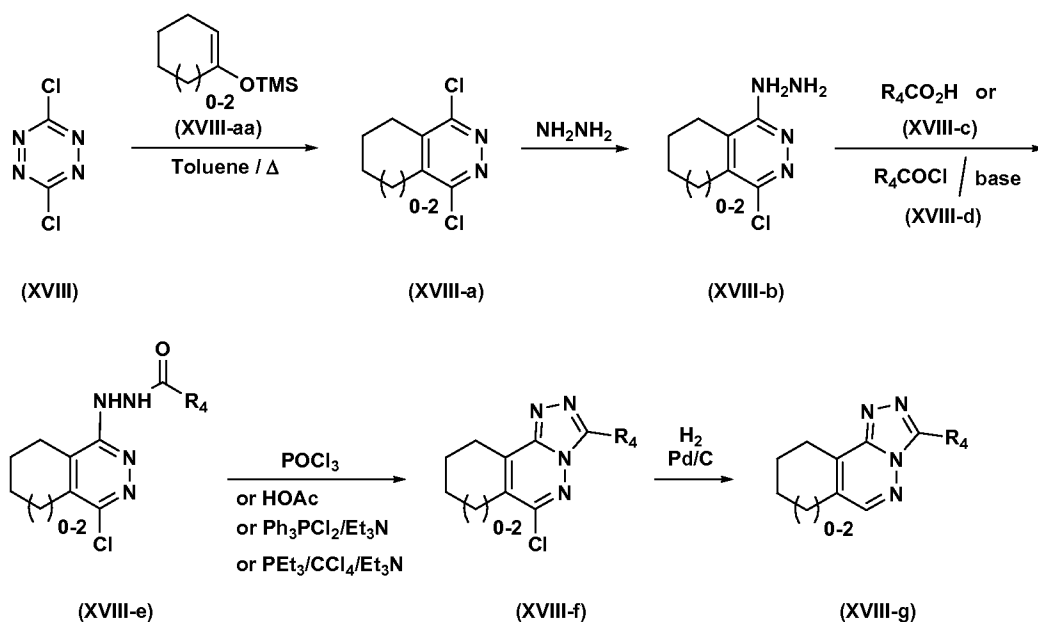
[00105] Scheme XI describes a method for preparing compounds of formula **XVII-g** (a subset of compounds of formula **I** where **Z** is a triazolopyridazine group). A dichloropyridazine intermediate **XVII**, obtained commercially or prepared by methods known in the literature or by other methods known to one skilled in the art, can be converted to the substituted analog **XVII-a** under Minisci reaction conditions as described by Samaritoni and Babbitt (*J. Het. Chem.*, 28:583 (1991)). Reaction of a compound of formula **XVII-a** with hydrazine can be carried out at elevated

temperature to provide an intermediate **XVII-b**. Acylation of an intermediate **XVII-b** with an acid **XVII-c** using an appropriate set of amide coupling reagents such as NMM/isobutylchloroformate, EDAC/HOBT or other reagents described in *The Practice of Peptide Synthesis*, 2<sup>nd</sup> Ed., Spring-Verlag, Bodanszy, Miklos (1993) provides a hydrazide intermediate **XVII-e**. Alternatively, an acyl hydrazide **XVII-e** can be prepared from the reaction of a compound of formula **XVII-b** and an acid chloride **XVII-d** in the presence of an appropriate base such as DIEA or TEA. Formation of triazolopyridazine **XVII-f** can be achieved from the reaction of **XVII-e** with POCl<sub>3</sub> at an elevated temperature. Formation of triazolopyridazine **XVII-f** can also be achieved from **XVII-e** in the presence of acetic acid at an elevated temperature, either under a conventional procedure or a microwave reactor. Alternatively, formation of triazolopyridazine **XVII-f** can be achieved from the reaction of **XVII-e** with Ph<sub>3</sub>PCl<sub>2</sub> in the presence of a base such as TEA or by P(alkyl)<sub>3</sub>/CCl<sub>4</sub> in the presence of a base such as TEA or DIPEA, or other methods known to one skilled in the art.

Dechlorination of **XVII-e** to yield **XVII-g** can be accomplished under hydrogenolytic conditions in the presence of catalytic palladium on carbon in solvents such as methanol, ethyl acetate, tetrahydrofuran, methylene chloride, or by other methods known to one skilled in the art.

20

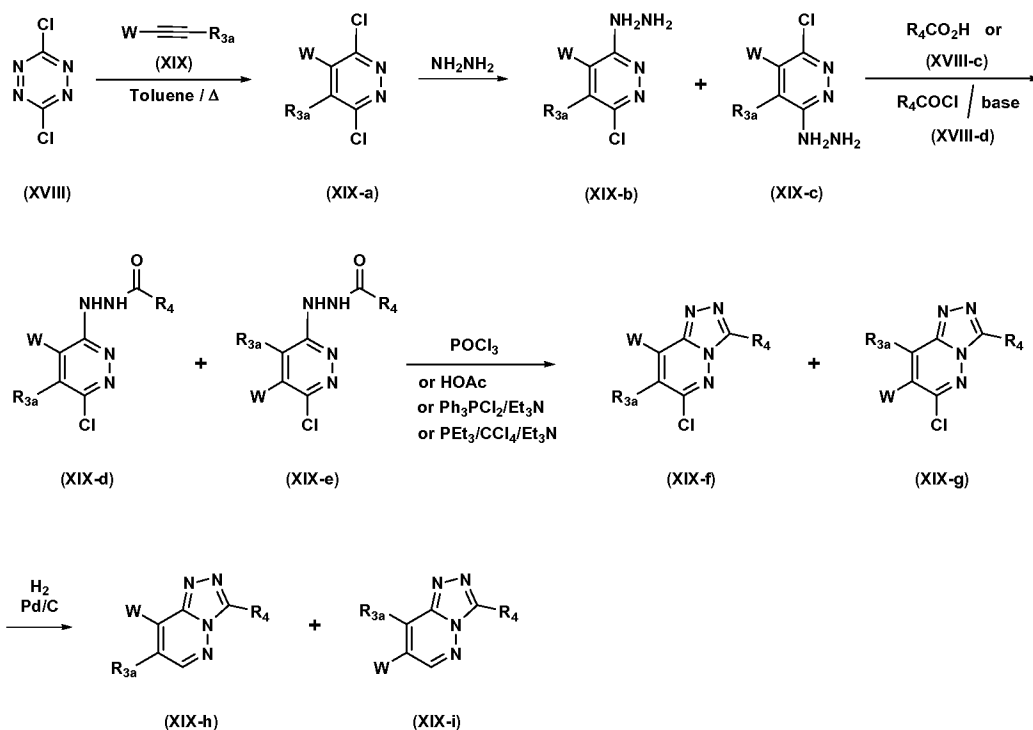
Scheme XII



[00106] Scheme XII describes a method for preparing compounds of formula XVIII-g (a subset of compounds of formula I where Z is a triazolopyridazine group). Dichlorotetrazine XVIII can be converted to dichloropyridazines such as XVIII-a by reaction with cyclic trimethylsilyl enol ethers such as XVIII-aa in toluene at reflux  
5 using the procedure described by Sparey and Harrison (*Tet. Lett.*, 39:5873 (1998)). Reaction of a compound of formula XVIII-a with hydrazine can be carried out at elevated temperature to provide an intermediate XVIII-b. Acylation of an intermediate XVIII-b with an acid XVIII-c using an appropriate set of amide coupling reagents such as NMM/isobutylchloroformate, EDAC/HOBT or other reagents  
10 described in *The Practice of Peptide Synthesis*, 2<sup>nd</sup> Ed., Springer-Verlag, Bodanszky, Miklos (1993) provides a hydrazide intermediate XVIII-e. Alternatively, an acyl hydrazide XVIII-e can be prepared from the reaction of a compound of formula XVIII-b and an acid chloride XVIII-d in the presence of an appropriate base such as DIEA or TEA. Formation of triazolopyridazine XVIII-f can be achieved from the  
15 reaction of XVIII-e with POCl<sub>3</sub> at an elevated temperature. Formation of triazolopyridazine XVIII-f can also be achieved from XVIII-e in the presence of acetic acid at an elevated temperature, either under a conventional procedure or a microwave reactor. Alternatively, formation of triazolopyridazine XVIII-f can be achieved from the reaction of XVIII-e with Ph<sub>3</sub>PCl<sub>2</sub> in the presence of a base such as  
20 TEA or by P(alkyl)<sub>3</sub>/CCl<sub>4</sub> in the presence of a base such as TEA or DIPEA, or other methods known to one skilled in the art. Dechlorination of XVIII-f to yield XVIII-g can be accomplished under hydrogenolytic conditions in the presence of catalytic palladium on carbon in solvents such as methanol, ethyl acetate, tetrahydrofuran, methylene chloride, or by other methods known to one skilled in the art.

25

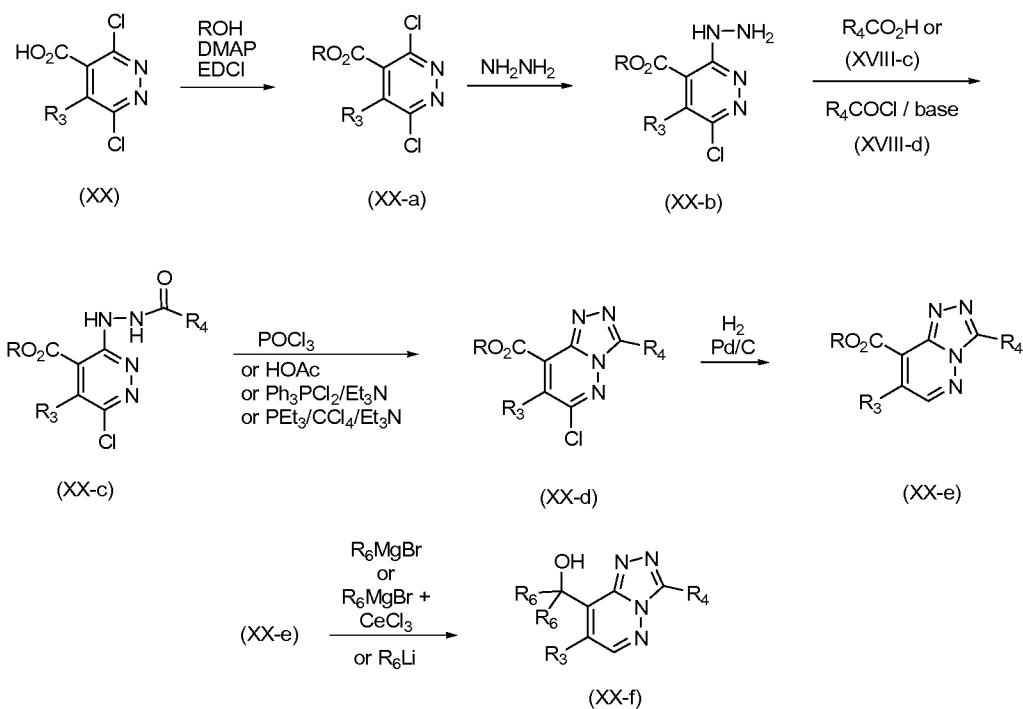
## Scheme XIII



[00107] Scheme XIII describes a method for preparing compounds of formula XIX-h and XIX-i (a subset of compounds of formula I where Z is a triazolopyridazine group). Dichlorotetrazine XVIII can be converted to dichloropyridazines such as XIX-a by reaction with alkynes such as XIX in toluene at reflux using the procedure described by Sparey and Harrison (*Tet. Lett.*, 39:5873 (1998)). Reaction of a compound of formula XIX-a with hydrazine was carried out at elevated temperature to provide a mixture of regioisomeric intermediates XIX-b and XIX-c. Acylation of intermediates XIX-b and XIX-c with an acid XVIII-c using an appropriate set of amide coupling reagents such as NMM/isobutylchloroformate, EDAC/HOBT or other reagents described in *The Practice of Peptide Synthesis*, 2<sup>nd</sup> Ed., Spring-Verlag, Bodanszky, Miklos (1993) provides hydrazide regioisomeric intermediates XIX-d and XIX-e. Alternatively, acyl hydrazide XIX-d and XIX-e can be prepared from the reaction of a compounds of formula XIX-b and XIX-c and an acid chloride XVIII-d in the presence of an appropriate base such as DIEA or TEA. Formation of triazolopyridazines of formula XIX-f and XIX-g can be achieved from the reaction of compounds of formula XIX-d and XIX-e with POCl<sub>3</sub> at an elevated temperature. Formation of triazolopyridazines XIX-f and XIX-g can also be

achieved from **XIX-d** and **XIX-e** in the presence of acetic acid at an elevated temperature, either under a conventional procedure or a microwave reactor. Alternatively, formation of triazolopyridazines **XIX-f** and **XIX-g** can be achieved from the reaction of **XIX-d** and **XIX-e** with  $\text{Ph}_3\text{PCl}_2$  in the presence of a base such as TEA or by  $\text{P}(\text{alkyl})_3/\text{CCl}_4$  in the presence of a base such as TEA or DIPEA, or other methods known to one skilled in the art. Dechlorination of **XIX-f** and **XIX-g** to yield **XIX-h** and **XIX-i** can be accomplished under hydrogenolytic conditions in the presence of catalytic palladium on carbon in solvents such as methanol, ethyl acetate, tetrahydrofuran, methylene chloride, or by other methods known to one skilled in the art. Separation of the reioisomeric intermediates or products may be carried out at any stage depending on the relative ease of chromatographic purification by methods known to one skilled in the art.

Scheme XIV

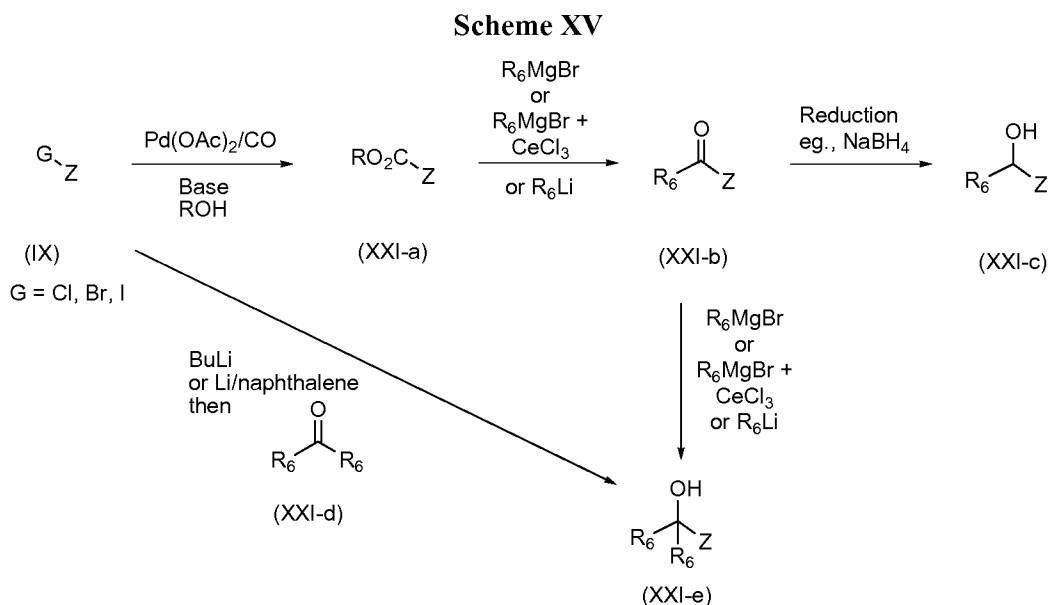


15

**[00108]** Scheme XIV describes a method for preparing compounds of formula **XX-f** (a subset of compounds of formula **I** where **Z** is a triazolopyridazine group).

Dichloropyridazine carboxylic acid **XX** may be converted to the ester **XX-a** using an alcohol, DMAP, and EDCI (EDAC), or by other acylation condition known to one

skilled in the art. Reaction of a compound of formula **XX-a** with hydrazine was carried out at room temperature or elevated temperature to provide an intermediate **XX-b**. Acylation of an intermediate **XX-b** with an acid **XVIII-c** using an appropriate set of amide coupling reagents such as NMM/isobutylchloroformate, EDAC/HOBT or  
5 other reagents described in *The Practice of Peptide Synthesis*, 2<sup>nd</sup> Ed., Spring-Verlag, Bodanszy, Miklos (1993) provides a hydrazide intermediate **XX-c**. Alternatively, an acyl hydrazide **XX-c** can be prepared from the reaction of a compound of formula **XX-b** and an acid chloride **XVIII-d** in the presence of an appropriate base such as DIEA or TEA. Formation of triazolopyridazine **XX-d** can be achieved from the  
10 reaction of **XX-c** with POCl<sub>3</sub> at an elevated temperature. Formation of triazolopyridazine **XX-d** can also be achieved from **XX-c** in the presence of acetic acid at an elevated temperature, either under a conventional procedure or a microwave reactor. Alternatively, formation of triazolopyridazine **XX-d** can be achieved from the reaction of **XX-c** with Ph<sub>3</sub>PCl<sub>2</sub> in the presence of a base such as  
15 TEA or by P(alkyl)<sub>3</sub>/CCl<sub>4</sub> in the presence of a base such as TEA or DIPEA, or other methods known to one skilled in the art. Dechlorination of **XX-d** to yield **XX-e** can be accomplished under hydrogenolytic conditions in the presence of catalytic palladium on carbon in solvents such as methanol, ethyl acetate, tetrahydrofuran, methylene chloride, or by other methods known to one skilled in the art. Compound  
20 **XX-e** can be converted to carbinol **XX-f** by the use of two equivalents of a Grignard reagent, a Grignard reagent plus cerium trichloride, or a lithium reagent using methods known to one skilled in the art.



**[00109]** Scheme XV describes a method for preparing compounds of formula **XXI-b**, **XXI-c** and **XXI-e**. A compound represented by **IX**, where Z is defined as

5 previously described in the Claims and G = Cl, Br, or I, can be carbonylated using an appropriate catalyst such as palladium acetate under an atmosphere of carbon monoxide in the presence of a suitable base such as potassium carbonate when conducted in an alcoholic solvent to provide ester **XXI-a**. Compound **XXI-a** can be converted to carbonyl compound **XXI-b** by the use of one equivalent of a Grignard reagent, a Grignard reagent plus cerium trichloride, or a lithium reagent using

10 methods known to one skilled in the art. Compound **XXI-b** can be converted to carbinol **XXI-c** by reduction with an appropriate reagent such as sodium borohydride. Compound **XXI-b** can be reacted with a second equivalent of a Grignard reagent, a Grignard reagent plus cerium trichloride, or a lithium reagent to give compound

15 **XXI-e**. Compound **XXI-e** can also be produced by the reaction of compound **IX** with butyllithium or a lithium/naphthalene mixture (to generate the intermediate organomagnesium halide or organolithium) followed by reaction with a ketone **XXI-d** as described by Wang et al. (*Tet. Lett.*, 41:4335 (2000)) or by using methods known to one skilled in the art.

20

## EXAMPLES

[00110] The following working Examples serve to better illustrate, but not limit, some of the preferred embodiments of the present invention.

### GENERAL

5 [00111] The term HPLC refers to a Shimadzu high performance liquid chromatography with one of following methods:

**Method A:** Phenomenex C18 5 micron 4.6 X 50mm column using a 4 minute gradient of 0-100% solvent B [90% MeOH:10% H<sub>2</sub>O:0.2% H<sub>3</sub>PO<sub>4</sub>] and 100-0% solvent A [10% MeOH:90% H<sub>2</sub>O:0.2% H<sub>3</sub>PO<sub>4</sub>] with 4 mL/min flow rate and a 1 min.  
10 hold, an ultra violet (UV) detector set at 220 nm.

**Method B:** Phenomenex S5 ODS 4.6 x 30 mm column, gradient elution 0-100% B/A over 2 min (solvent A = 10% MeOH/H<sub>2</sub>O containing 0.1% TFA, solvent B = 90% MeOH/H<sub>2</sub>O containing 0.1% TFA), flow rate 5 mL/min, UV detection at 220 nm.

15 **Method C:** YMC S7 ODS 3.0 x 50 mm column, gradient elution 0-100% B/A over 2 min (solvent A = 10% MeOH/H<sub>2</sub>O containing 0.1% TFA, solvent B = 90% MeOH/H<sub>2</sub>O containing 0.1% TFA), flow rate 5 mL/min, UV detection at 220 nm.

**Method D:** YMC S-5 C18 5 micron 4.6 X 50mm column using a 4 minute  
20 gradient of 0-100% solvent B [90% CH<sub>3</sub>CN:10% H<sub>2</sub>O:0.1% TFA] and 100-0% solvent A [10% CH<sub>3</sub>CN:90% H<sub>2</sub>O:0.1% TFA] with 4 mL/min flow rate and a 1 min. hold (100% B), an ultra violet (UV) detector set at 220 nm.

[00112] The term prep HPLC refers to an automated Shimadzu HPLC system  
25 using a mixture of solvent A (10% MeOH/90%H<sub>2</sub>O/0.1%TFA) and solvent B (90% MeOH/10%H<sub>2</sub>O/0.1% TFA) or a mixture of solvent A (10% CH<sub>3</sub>CN/90%H<sub>2</sub>O/0.1%TFA) and solvent B (90% CH<sub>3</sub>CN /10%H<sub>2</sub>O/0.1% TFA). The preparative columns were packed with YMC or Phenomenex ODS C18 5 micron resin or equivalent.

30

### ABBREVIATIONS

[00113] The following abbreviations are employed in the Examples and elsewhere herein:

- Ph = phenyl  
Bn = benzyl
- 5 i-Bu = iso-butyl  
Me = methyl  
Et = ethyl  
Pr = propyl  
Bu = butyl
- 10 AIBN = 2,2'-Azobisisobutyronitrile  
Boc or BOC = *tert*-butoxycarbonyl  
Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl  
DCM = dichloromethane  
DEAD = Diethyl azodicarboxylate
- 15 DIAD = Diisopropyl azodicarboxylate  
DIEA = N,N-diisopropylethylamine  
DIPEA = Diisopropylethylamine  
DMA = N,N-dimethylacetamide  
DMF = N,N-dimethylformamide
- 20 DMSO = dimethylsulfoxide  
EtOAc = ethyl acetate  
EDAC = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide hydrochloride (or 1-[(3-(dimethylamino)propyl)]-3-ethylcarbodiimide hydrochloride); EDCI  
Fmoc = fluorenylmethoxycarbonyl
- 25 HOAc or AcOH = acetic acid  
HOAT = 1-hydroxy-7-azabenzotriazole  
HOBT = 1-hydroxybenzotriazole  
LAH = lithium aluminum hydride  
mCPBA = 3-Chloroperoxybenzoic acid
- 30 NMM = N-methyl morpholine  
NBS = N-Bromosuccinimide  
n-BuLi = n-butyllithium

- Oxone<sup>®</sup> = Monopersulfate  
Pd/C = palladium on carbon  
PtO<sub>2</sub> = platinum oxide  
PyBOP reagent = benzotriazol-1-yloxy-tripyrrolidino phosphonium  
5 hexafluorophosphate  
Pd(dppf)Cl<sub>2</sub>-CH<sub>2</sub>Cl<sub>2</sub>=1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride  
dichloromethane complex  
SOCl<sub>2</sub> = Thionyl chloride  
TBAF = tetrabutylammonium fluoride  
10 TBS = *tert*-Butyldimethylsilyl  
TMS = trimethylsilyl  
TEA = triethylamine  
TFA = trifluoroacetic acid  
THF = tetrahydrofuran  
15 equiv = equivalent(s)  
min = minute(s)  
h or hr = hour(s)  
L = liter  
mL = milliliter  
20 μL = microliter  
g = gram(s)  
mg = milligram(s)  
mol = mole(s)  
mmol = millimole(s)  
25 meq = milliequivalent  
RT = room temperature  
sat or sat'd = saturated  
aq. = aqueous  
TLC = thin layer chromatography  
30 HPLC = high performance liquid chromatography  
HPLC R<sub>t</sub> = HPLC retention time  
LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

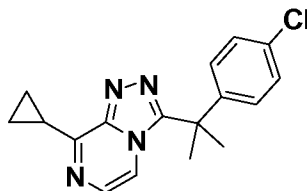
NMR = nuclear magnetic resonance

mp = melting point

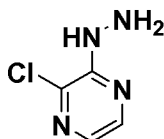
5

### EXAMPLE 1

#### 3-(2-(4-Chlorophenyl)propan-2-yl)-8-cyclopropyl-[1,2,4]triazolo[4,3-a]pyrazine



#### Compound 1A: 2-Chloro-3-hydrazinylpyrazine

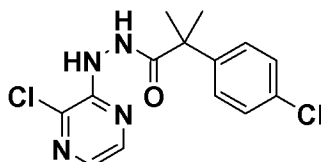


10

[00114] 2,3-Dichloropyrazine (25 g) and anhydrous hydrazine (21 ml) were dissolved in pyridine (100 mL) and heated to 60 °C. After 3h, the reaction was concentrated *in vacuo* to yield a residue. The residue was rinsed with water and the filtered. The resulting solid was collected by filtration and dried at 40 °C *in vacuo* to afford Compound 1A as a light yellow solid (20.3 g, 88%).

15

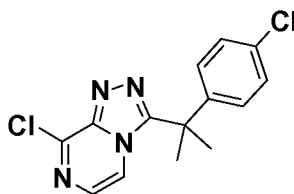
#### Compound 1B: 2-(4-Chlorophenyl)-N'-(3-chloropyrazine-2-yl)-2-methylpropanehydrazide



20 [00115] To a 0 °C solution of 2-(4-chlorophenyl)-2-methylpropanoic acid (99.3 mg, 0.50 mmol) in THF (2 mL) was added 4-methylmorpholine (60.5 μL, 0.55 mmol). After 10 minutes, isobutyl chloroformate (67.4 μL, 0.52 mmol) was added dropwise over 2 minutes. After 2.5 h, a solution of Compound 1A (72.3mg, 0.50 mmol) in THF (3 mL) was added dropwise over 2 minutes. After 10 minutes the

cooling bath was removed and the reaction mixture was warmed to room temperature. After 3 h at room temperature, water (5 mL) and ethyl acetate (10 mL) were added, and the resulting mixture was stirred for 10 minutes. At the conclusion of this period, the organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo* to yield a residue. The residue was purified by flash chromatography (SiO<sub>2</sub>, 0-100% ethyl acetate / hexanes) to provide compound **1B**, which was used directly in the preparation of compound **1C** set forth below. LC/MS (m/z) = 325 (M+H)<sup>+</sup>.

**Compound 1C: 8-Chloro-3-(2-(4-chlorophenyl)propan-2yl)-[1,2,4]triazolo[4,3-a]pyrazine**



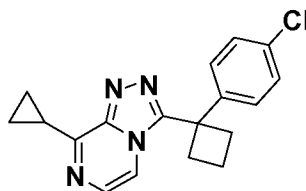
**[00116]** Compound **1B** was dissolved in THF (3 mL) and CCl<sub>4</sub> (2 mL). The resulting solution was cooled to 0 °C. Once at the prescribed temperature, DIPEA (697 μL, 4.0 mmol) was added. Triethylphosphine (221 μL, 1.5 mmol) was then added dropwise over a 3 minute period. Upon completion of addition, the reaction was allowed to slowly warm to room temperature where it stirred for 16 h. After 16 h, water (5 mL) and ethyl acetate (5 mL) were added, and the resulting mixture was stirred vigorously for 10 minutes. After this time, the organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo* to yield a residue. The residue was purified by flash chromatography (SiO<sub>2</sub>, 0-100% ethyl acetate / hexanes) to provide compound **1C** (98.7 mg, 64%). LC/MS (m/z) = 307 (M+H)<sup>+</sup>.

### Example 1

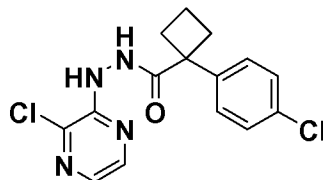
**[00117]** Compound **1C** (92.2 mg, 0.30 mmol) and Fe(acac)<sub>3</sub> (21.2 mg, 0.06 mmol) were dissolved in THF (1.5 mL) and 1-methyl-2-pyrrolidinone (188 μL) and the resulting solution was cooled to 0 °C. Once at the prescribed temperature, cyclopropylmagnesium bromide (1.20 mL, 0.60 mmol, 0.5 M solution in THF) was added over a 1 min period. The resulting mixture was stirred for an additional 1h. After the 1h, cyclopropylmagnesium bromide (1.20 mL, 0.60 mmol, 0.5 M solution in

THF) was added, and the resulting mixture was stirred for 16 h. At the conclusion of this period, additional Fe(acac)<sub>3</sub> (21.2 mg, 0.06 mmol) and cyclopropylmagnesium bromide (1.20 mL, 0.60 mmol, 0.5 M solution in THF) were added. Upon completion of addition, the reaction mixture was stirred for an hour, quenched with water and then partitioned between ethyl acetate (10 mL) and water (5 mL). The organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO<sub>2</sub>, 0-100% ethyl acetate / hexanes) to afford **Example 1** as an off-white solid (71.5 mg, 76%). HPLC t<sub>R</sub> (Method D): 2.29 min (>99% pure). LC/MS (m/z) = 313 (M+H)<sup>+</sup>.

10

**EXAMPLE 2****3-(1-(4-Chlorophenyl)cyclobutyl)-8-cyclopropyl-[1,2,4]triazolo[4,3-a]pyrazine**

15 **Compound 2A: 1-(4-Chlorophenyl)-N'-(3-chloropyrazine-2-yl)cyclobutanecarbohydrazide**

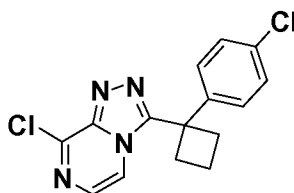


[00118] To a 0 °C solution of 1-(4-chlorophenyl)cyclobutanecarboxylic acid (105.3 mg, 0.50 mmol) in THF (2 mL) was added 4-methylmorpholine (60.5 μL, 0.55 mmol). The reaction mixture was stirred for 10 minutes, and then isobutyl chloroformate (67.4 μL, 0.52 mmol) was added dropwise over a 2 minute period. Upon completion of addition, the reaction mixture was stirred for 1 h. A solution of Compound 1A (72.3 mg, 0.50 mmol) in THF (3 mL) was then added dropwise over a 2 minute period. The resulting mixture was stirred for 10 minutes and then the cooling bath was removed. The reaction mixture was allowed to warm to room temperature where it stirred for 1 h. After this time, water (5 mL) and ethyl acetate

25

(10 mL) were added, and the resulting mixture was stirred for 10 minutes. At the conclusion of this period, the organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO<sub>2</sub>, 0-60% ethyl acetate / hexanes) to afford compound **2A**, which was used directly in the preparation of compound **2B** set forth below. LC/MS (m/z) = 337 (M+H)<sup>+</sup>.

**Compound 2B: 8-Chloro-3-(1-(4-chlorophenyl)cyclobutyl)-[1,2,4]triazolo[4,3-a]pyrazine**



10

**[00119]** Compound **2A** was dissolved in THF (3 mL) and CCl<sub>4</sub> (2 mL) and the resulting solution was cooled to 0 °C. Once at the prescribed temperature, DIPEA (697 μL, 4.0 mmol) was added. Triethylphosphine (221 μL, 1.5 mmol) was then added dropwise over a 3 minute period. The resulting mixture was stirred for 10 minutes, and then the ice-bath was removed. The mixture was stirred for an additional 1 h and then water (5 mL) and ethyl acetate (5 mL) were added. The resulting mixture was stirred vigorously for 10 minutes. After this time, the organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo* to yield a residue. The residue was purified by flash chromatography (SiO<sub>2</sub>, 0-60% ethyl acetate / hexanes) to afford compound **2B** as an off-white solid (32.6 mg, 20% yield from compound **1A**). LC/MS (m/z) = 319 (M+H)<sup>+</sup>.

15

20

**Example 2**

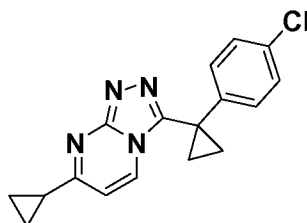
**[00120]** Compound **2B** (31.9 mg, 0.10 mmol) and Fe(acac)<sub>3</sub> (7.1 mg, 0.02 mmol) were dissolved in THF (0.5 mL) and 1-methyl-2-pyrrolidinone (62.5 μL). The resulting solution was cooled to 0 °C and then cyclopropylmagnesium bromide (400 μL, 0.20 mmol, 0.5 M solution in THF) was added over a 1 min period. Upon completion of addition, the reaction mixture was stirred for 1 h. At the conclusion of this period, the reaction mixture was quenched with a 50% saturated NH<sub>4</sub>Cl solution

25

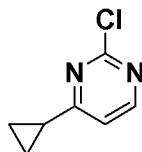
and then partitioned between ethyl acetate (10 mL) and 50% saturated NH<sub>4</sub>Cl solution (5 mL). The organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo* to yield a residue. The residue was purified by automated flash chromatography (SiO<sub>2</sub>, 0-60% ethyl acetate / hexanes) to afford **Example 2** as an off-white foam (24.9 mg, 77%). HPLC t<sub>R</sub> (Method D): 2.41 min (97% pure). LC/MS (m/z) = 325 (M+H)<sup>+</sup>.

### EXAMPLE 3

#### 3-(1-(4-Chlorophenyl)cyclopropyl)-7-cyclopropyl-[1,2,4]triazolo[4,3-a]pyrimidine



#### Compound 3A: 2-Chloro-4-cyclopropylpyrimidine

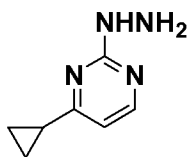


15 [00121] Argon was bubbled through a mixture of 2,4-dichloropyrimidine (298 mg, 2.0 mmol), cyclopropylboronic acid (172 mg, 2.0 mmol), and K<sub>3</sub>PO<sub>4</sub> (1.06 g, 5.0 mmol) in THF (10 mL) in a crimp-top reaction tube for 10 minutes. After this period, Pd(dppf)<sub>2</sub>Cl<sub>2</sub>-CH<sub>2</sub>Cl<sub>2</sub> (163 mg, 0.2 mmol) was added, and the vessel was capped. The resulting mixture was heated to 90 °C for 17 h. After this time, the reaction mixture

20 was partitioned between water (2 mL) and diethyl ether (6 mL). The organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO<sub>2</sub>, 0-100% ethyl acetate / hexanes) to afford compound **3A**, which was used in the preparation of compound **3B** set forth below, as a colorless oil (108 mg, 35%). LC/MS (m/z) = 155 (M+H)<sup>+</sup>.

25

#### Compound 3B: 4-Cyclopropyl-2-hydrazinylpyrimidine

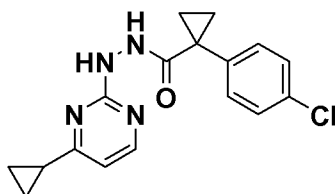


[00122] Compound **3A** and anhydrous hydrazine (204  $\mu$ L, 6.5 mmol) were dissolved in pyridine (2.6 mL). The reaction mixture was heated to 60  $^{\circ}$ C where it stirred for 4 h. At the conclusion of this period, the reaction mixture was

5 concentrated *in vacuo* to yield a residue. The residue was purified by flash chromatography ( $\text{SiO}_2$ , 0-100% ethyl acetate / hexanes) to afford compound **3B** as a white solid (85.4 mg, 88%). LC/MS ( $m/z$ ) = 151 ( $M+H$ ) $^+$ .

**Compound 3C: 1-(4-Chlorophenyl)-N'-(4-cyclopropylpyrimidine-2-yl)cyclopropanecarbohydrazide**

10



[00123] To a 0  $^{\circ}$ C solution of 1-(4-chlorophenyl)cyclopropanecarboxylic acid (98.3 mg, 0.50 mmol) in THF (2 mL) was added 4-methylmorpholine (60.5  $\mu$ L, 0.55 mmol). Upon completion of addition, the mixture was stirred for 10 minutes, and

15 then isobutyl chloroformate (67.4  $\mu$ L, 0.52 mmol) was added dropwise over a 2 minute period. Upon completion of addition, the reaction mixture was stirred for 1 h. After this time, a solution of hydrazine **3B** (75.1 mg, 0.50 mmol) in THF (3 mL) was added dropwise over a 2 minute period. The resulting mixture was stirred for 10 minutes and then the cooling bath was removed. The reaction mixture was warmed to

20 room temperature over a 1 h period. After this time, water (5 mL) and ethyl acetate (10 mL) were added, and the resulting mixture was stirred for 10 minutes. At the conclusion of this period, the organic phase was separated, dried over  $\text{Na}_2\text{SO}_4$ , and then concentrated *in vacuo*. The resulting residue was purified by flash chromatography ( $\text{SiO}_2$ , 0-60% ethyl acetate / hexanes) to afford compound **3C** as a

25 pale-yellow solid (121 mg, 74%). LC/MS ( $m/z$ ) = 329 ( $M+H$ ) $^+$ .

**Example 3**

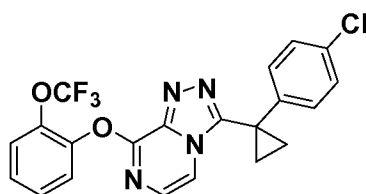
[00124] Compound **3C** (69.0 mg, 0.21 mmol) was dissolved in POCl<sub>3</sub> (2 mL) and the resulting mixture was heated to reflux where it stirred for 3 h. After this time, the reaction mixture was concentrated *in vacuo* to yield a residue. The residue was

5 partitioned between ethyl acetate and water, and the pH was adjusted to 7 with 1N NaOH. Once at the prescribed pH, the organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo* to yield a residue. This residue was purified by flash chromatography (SiO<sub>2</sub>, 0-100% ethyl acetate / hexanes) to afford **Example 3** as an off-white solid (16.0 mg, 25%) HPLC t<sub>R</sub> (Method D): 1.88 min (>99% pure).

10 LC/MS (m/z) = 311(M+H)<sup>+</sup>.

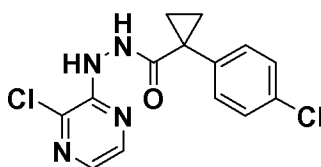
**EXAMPLE 4**

**8-(2-(Trifluoromethoxy)phenoxy)-3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyrazine**



15

**Compound 4A: 1-(4-Chlorophenyl)-N'-(3-chloropyrazine-2-yl)cyclopropanecarbohydrazide**



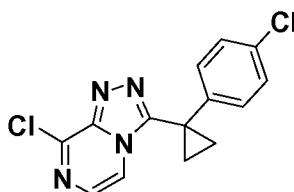
20 [00125] To a 0 °C solution of 1-(4-chlorophenyl)cyclopropanecarboxylic acid (0.77 g, 3.92 mmol) in THF (15 mL) was added 4-methylmorpholine (0.43 g, 4.3 mmol). The resulting mixture was stirred for 5 minutes, and then isobutyl chloroformate (0.56 g, 4.14 mmol) was added dropwise over 5 minutes. The resulting mixture was stirred for 1h, and then a solution of compound **1A** (0.56g, 3.92 mmol) in

25 THF/DMF/NMM (10 ml/2 ml/2 ml) was added. Upon completion of addition, the reaction mixture was warmed to room temperature where it stirred for 4 h. After this

time, brine (15 mL) and ethyl acetate (50 mL) were added. The organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO<sub>2</sub>, 0-85% ethyl acetate / hexanes) to afford compound **4A** as a solid (0.78 g, 61%). LC/MS (m/z) = 323 (M+H)<sup>+</sup>.

5

**Compound 4B: 8-Chloro-3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyrazine**



[00126] Compound **4A** (0.342 g, 1.06 mmol) was dissolved in POCl<sub>3</sub> (5 mL) and  
10 the resulting mixture was heated to 115 °C where it stirred for 12 h. At the conclusion  
of this period, the reaction mixture was concentrated *in vacuo* to yield a residue. The  
residue was partitioned between ethyl acetate and water, and the pH was adjusted to 7  
with 10N NaOH. Once at the prescribed pH, the organic layer was separated, dried  
over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated *in vacuo* to yield a residue. The residue was  
15 purified by flash chromatography (SiO<sub>2</sub>, 0-100% ethyl acetate / hexanes) to afford  
compound **4B** as an off-white solid (0.24 g, 74%). LC/MS (m/z) = 306(M+H)<sup>+</sup>.

#### Example 4

[00127] A mixture of compound **4B** (30.5 mg, 0.1 mmol), 2-(trifluoromethoxy)-  
20 phenol (36 mg, 0.2 mmol), silver nitrate (17 mg, 0.1 mmol) and KOH (8.2 mg, 0.2  
mmol) in 1 ml of DMF was heated to 80 °C in a sealed tube for 4 h. At the  
conclusion of this period, the reaction mixture was cooled to room temperature. Once  
at the prescribed temperature, 3 ml of brine was added and the resulting mixture was  
extracted with ethyl acetate (3x5 ml). The organic layer was separated and  
25 concentrated *in vacuo* to yield a residue. The residue was purified by prep HPLC to  
afford **Example 4** as an off-white solid (35 mg, 78%) HPLC R<sub>t</sub> (Method A): 3.66  
min. LC/MS (m/z) = 447(M+H)<sup>+</sup>.

#### EXAMPLES 5 TO 27

[00128] Examples 5 to 27 in Table 1 were synthesized according to the procedures described in Examples 1 to 4 above, or by other similar methods known to one skilled in the art, with other appropriate reagents.

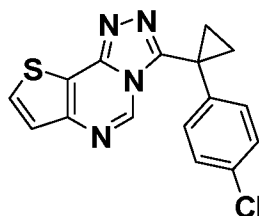
5

TABLE 1

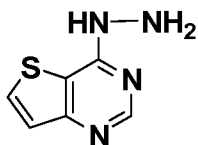
Example No.	Structure	LC/MS (ES+, M+H)	HPLC purity (%)
5		279	97
6		359	97
7		311	97
8		311	97
9		277	97
10		313	96
11		306	>95
12		311	>95

Example No.	Structure	LC/MS (ES+, M+H)	HPLC purity (%)
13		445	>95
14		324	>95
15		329	>95
16		289	>95
17		358	>95
18		339	>95
19		355	>95
20		345	>95
21		361	>95
22		431	>95

Example No.	Structure	LC/MS (ES+, M+H)	HPLC purity (%)
23		447	>95
24		359	>95
25		325	>95
26		371	>95
27		357	>95

**EXAMPLE 28****3-(1-(4-Chlorophenyl)cyclopropyl)thieno[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine**

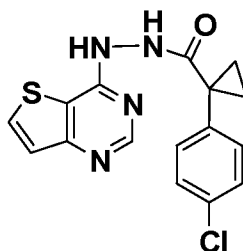
5

**Compound 28A: 4-Hydrazinylthieno[3,2-d]pyrimidine**

[00129] To a suspension of 4-chlorothieno[3,2-d]pyrimidine (1.71 g, 10 mmol) THF (10 mL) was added hydrazine (640 mg, 20 mmol) and the mixture was stirred at room temperature for 64 hours. The thick, pale tan slurry was filtered and the solid (desired product) was washed with THF (2x4 mL) and hexane (2x4 mL). This

provided 1.968 g of crude compound **28A** as a pale tan powder which was used as is in the next step. LC/MS (m/z) = 167 (M+H)<sup>+</sup>.

**Compound 28B: 1-(4-Chlorophenyl)-N'-(thieno[3,2-d]pyrimidin-4-yl)cyclopropanecarbohydrazide**



[00130] To a solution of 1-(4-chlorophenyl)cyclopropanecarboxylic acid (1.97 g, 10 mmol) in 20 mL of THF was added NMM (1.11 g, 11 mmol). The resulting mixture was cooled to 0 °C and then isobutyl chloroformate (1.37 g, 10 mmol) was added. After 20 minutes at 0 °C, compound **28A** (1.66 g, 10 mmol) was added to the resulting white suspension. Upon completion of addition, the reaction mixture was allowed to warm to rt and stirred overnight. EtOAc (300 mL) and water (100 mL) was added. The aqueous layer was removed and the EtOAc layer (which contained the desired product as a precipitate) was washed successively with 100 mL of saturated aqueous sodium bicarbonate, ammonium chloride, and brine. The EtOAc layer (containing a solid precipitate) was filtered and the solid was washed with EtOAc (2x5 mL) to provide compound **28B** as a tan powder (805 mg, 23%). LC/MS (m/z) = 345.8 (M+H)<sup>+</sup>.

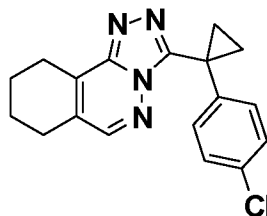
**Example 28**

[00131] To a slurry of compound **28B** (35 mg, 0.1 mmol) in 1 mL of THF and 0.5 mL of carbon tetrachloride was added diisopropylethylamine (129 mg, 1.0 mmol). Upon completion of addition, the reaction mixture was cooled to 0 °C and then triethylphosphine (59 mg, 0.5 mmol) was added. The resulting mixture was stirred at 0 °C for 30 minutes and then water (2 mL) was added. The aqueous suspension was extracted with EtOAc (2x5 mL) and the combined extracts concentrated to give 47 mg of a yellow oil. This material was purified using silica gel chromatography (1% methanol in methylene chloride) followed by further purification of mixed fractions

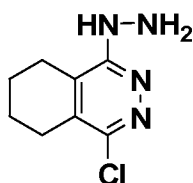
using silica gel preparative TLC (one Whatman 500 micron plate) to yield **Example 28** as a pale yellow foam (21 mg, 64%). LC/MS (m/z) = 327.8 (M+H)<sup>+</sup>.

### EXAMPLE 29

#### 5      3-(1-(4-Chlorophenyl)cyclopropyl)-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazine TFA Salt



#### Compound 29A: 1-Chloro-4-hydrazinyl-5,6,7,8-tetrahydrophthalazine

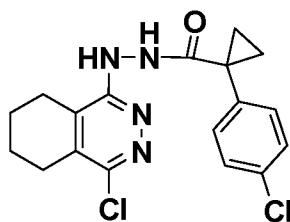


10

**[00132]** To 1,4-dichloro-5,6,7,8-tetrahydrophthalazine (406 mg, 2.0 mmol) in 2 mL THF was added hydrazine (704  $\mu$ L, 704 mmol, 12 mmol) and the mixture heated at 60 °C for 5.5 hours. To the mixture was added 3 mL of water and 10 mL EtOAc. The resulting suspension was filtered, washed with water (3x5 mL) and concentrated to provide Compound **29A** as a pale tan powder (222 mg, 56%). LC/MS (m/z) = 199.7 (M+H)<sup>+</sup>.

15

#### Compound 29B: N'-(4-Chloro-5,6,7,8-tetrahydrophthalazin-1-yl)-1-(4-chlorophenyl)cyclopropanecarbohydrazide

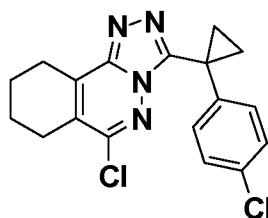


20

**[00133]** To a solution of 1-(4-chlorophenyl)cyclopropanecarboxylic acid (50 mg, 0.25 mmol) in 0.5 mL of THF was added NMM (28 mg, 0.28 mmol). The resulting

mixture was cooled to 0 °C and then isobutyl chloroformate (34 mg, 0.25 mmol) was added. After 10 minutes, compound **29A** (50 mg, 0.25 mmol) was added to the resulting white suspension. Upon completion of addition, the reaction mixture was stirred for 110 minutes and then EtOAc (3 mL) was added. Upon completion of addition, the resulting mixture was washed successively with 3 mL of saturated aqueous ammonium chloride, sodium bicarbonate, and brine; dried over magnesium sulfate, filtered, and then concentrated to provide compound **29B** as an off-white powder (44 mg, 47%). LC/MS (m/z) = 378.7 (M+H)<sup>+</sup>.

10 **Compound 29C: 6-Chloro-3-(1-(4-chlorophenyl)cyclopropyl)-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazine**

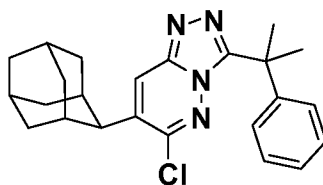


[00134] To a suspension of compound **29B** (44 mg, 0.117 mmol) in 0.5 mL of THF and 0.2 mL of carbon tetrachloride was added diisopropylethylamine (120.7 mg, 0.936 mmol). Upon completion of addition, the reaction mixture was cooled to 0 °C and then triethylphosphine (55.2 mg, 0.468 mmol) was added. The resulting mixture was stirred for 40 minutes and then EtOAc (3 mL) was added. Upon completion of addition, the mixture was washed successively with 3 mL of saturated aqueous ammonium chloride, sodium bicarbonate, and brine; dried over magnesium sulfate, filtered, and concentrated to yield a residue. The residue was taken up in methanol (2 mL) water (1 mL) and TFA (3 drops). The resulting mixture was heated to reflux briefly and then allowed to cool to room temperature. Once at room temperature, the white precipitate that formed was filtered and washed with a 2:1 mixture of methanol and water (3x1 mL) to yield compound **29C** as white crystals (24 mg, 57%, >95% HPLC purity). LC/MS (m/z) = 360.7 (M+H)<sup>+</sup>.

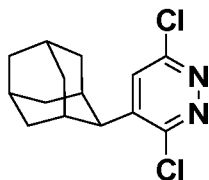
**Example 29**

[00135] To 10% Pd-C (7 mg, 6.58  $\mu\text{mol}$ ) under nitrogen in a 25 mL pear-shaped flask equipped with a stirbar was added a suspension of compound **29C** (16 mg, 0.045 mmol) in methanol (1 mL). The reaction mixture was flushed three times with vacuum then hydrogen (1 atm) and then stirred under an atmosphere of hydrogen (1 atm) for 15 h. After this time, the reaction mixture was filtered through a Celite plug (~4mm id x 10 mm, using 3x1 mL methanol rinse) and then concentrated to yield crude solids (16 mg). The crude solids were purified by prep HPLC to give **Example 29** as a pale yellow, oily solid (9 mg, 0.021 mmol, 46% yield). LC/MS ( $m/z$ ) = 325.8 ( $M+H$ )<sup>+</sup>.

10

**EXAMPLE 30****7-(Adamant-2-yl)-6-chloro-3-(2-phenyl)propan-2-yl)-[1,2,4]triazolo[4,3-b]pyridazine**

15

**Compound 30A: 4-(Adamant-2-yl)-3,6-dichloropyridazine**

[00136] To a suspension of 1-adamantane carboxylic acid (6309 mg, 35.0 mmol), 3,6-dichloropyridazine (1490 mg, 10 mmol), and sulfuric acid (800  $\mu\text{L}$ , 15 mmol) in water (15 mL) was added silver(I) nitrate (425 mg, 2.5 mmol). Upon completion of addition, the mixture was heated to 70  $^{\circ}\text{C}$ . Once at the prescribed temperature, a solution of ammonium peroxydisulfate (5705 mg, 25 mmol) in water (15 mL) was added during a 15 minute period. During addition, a slow evolution of gas was observed. Upon completion of addition, the reaction mixture was heated at 70  $^{\circ}\text{C}$  for 35 minutes. After this time, the grey-tan suspension was cooled to 0  $^{\circ}\text{C}$ , and then adjusted to a pH of 9-10 using conc. aq.  $\text{NH}_4\text{OH}$  (8-9 mL). Once at the prescribed

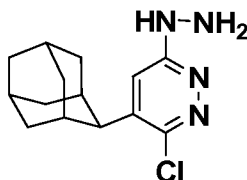
20

25

pH, the suspension was filtered and washed with water (3x15mL). The resulting solids were slurried in ether (20 mL), filtered and then rinsed with ether (3x20 mL). The filtrate and ethereal washes were combined and then concentrated to yield compound **30A** as a tan solid (923 mg, 33%). LC/MS (m/z) = 284 (M+H)<sup>+</sup>.

5

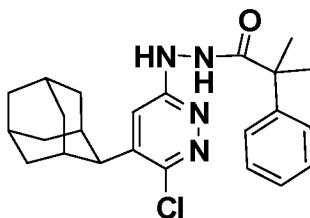
**Compound 30B: 4-(Adamant-2-yl)-3chloro-6-hydrazinopyridazine**



[00137] To **Compound 30A** (330 mg, 1.17 mmol) was added 3 mL of THF and then hydrazine (373 mg, 11.7 mmol). The resulting mixture was capped and then placed in a 60 °C oil bath for 225 minutes. After this time, the mixture was cooled to RT and then concentrated to yield a residue. The residue was suspended in methanol (2 mL) and then heated to reflux. The resulting mixture was cooled to room temperature, filtered, and then washed with methanol (2x1 mL) to yield compound **30B** as a tan solid (74 mg, 23 %). LC/MS (m/z) = 289.8 (M+H)<sup>+</sup>.

15

**Compound 30C: N'-(5-Adamant-2-yl-6-chloropyridazin-3-yl)-2-methyl-2-phenylpropanehydrazide**



[00138] To a solution of 2-methyl-2-phenylpropanoic acid (27.7 mg, 0.169 mmol) and 4-methylmorpholine (20.39 μL, 0.185 mmol) in 0.5 mL THF at 0 °C added isobutyl chloroformate (22.14 μL, 0.169 mmol). Upon completion of addition, the mixture was stirred for 10 min and then solid compound **30B** (47 mg, 0.169 mmol) was added. The reaction mixture was stirred for 75 min and then EtOAc (3 mL) was added. Upon completion of addition, the reaction mixture was washed successively with 2 mL each of saturated aqueous ammonium chloride, sodium bicarbonate, and

25

then brine. The mixture was dried over magnesium sulfate, filtered and then concentrated to give crude compound **30C** (76 mg). LC/MS (m/z) = 425.9 (M+H)<sup>+</sup>.

### Example 30

5 **[00139]** To a solution of compound **30C** (76 mg, 0.179 mmol) and DIPEA (0.250 mL, 1.431 mmol) in THF (0.7 mL) and CCl<sub>4</sub> (0.3 mL) stirred at 0 °C was added triethylphosphine (0.106 mL, 0.715 mmol). Upon completion of addition, an emulsion containing much yellow precipitate was formed. The emulsion was stirred for 30 min and then EtOAc (3 mL) was added. The resulting mixture was washed  
10 successively with 2 mL each of saturated aqueous ammonium chloride, sodium bicarbonate, and brine; dried over magnesium sulfate, filtered and then concentrated to yield a residue. The residue was purified by prep HPLC to give **Example 30** (26 mg, 28%). LC/MS (m/z) = 407.9 (M+H)<sup>+</sup>.

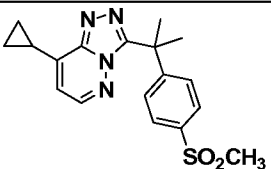
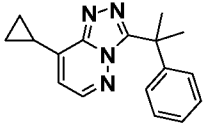
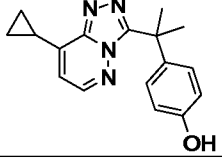
15

### EXAMPLES 31 TO 33

**[00140]** **Examples 31 to 33** in Table 2 were synthesized in a similar manner as that described in Example 34 below, or by other similar methods known to one skilled in the art, with other appropriate reagents.

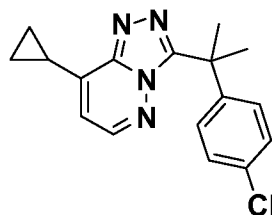
20

TABLE 2

Example No.	Structure	LC/MS (ES+, M+H)	HPLC purity (%)
31		356	100
32		279	97
33		295	95

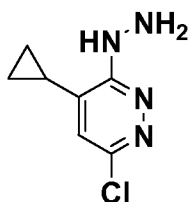
## EXAMPLE 34

## 3-(2-(4-Chlorophenyl)propan-2-yl)-8-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazine



5

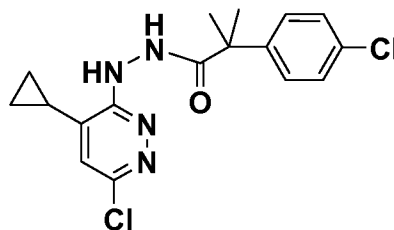
## Compound 34A: 6-Chloro-4-cyclopropyl-3-hydrazinylpyridazine



[00141] To a solution of 3,6-dichloro-4-cyclopropylpyridazine (3.2 g, 15.07 mmol) in THF (30 mL) was added hydrazine (1.893 mL, 60.3 mmol). The reaction mixture was heated at 60 °C for 9 h. After this time, the reaction mixture was cooled to rt. Once at the prescribed temperature, H<sub>2</sub>O (30 mL) was added to the mixture, and the resulting mixture was extracted with EtOAc (3x30 mL). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated by rotary evaporation to yield a crude residue. The residue was dissolved in MeOH (12 mL) and then purified via preparative HPLC to yield compound **34A** (400 mg, 14 %) as a yellow solid. LC/MS (m/z) = 185.1 (M+H)<sup>+</sup>.

15

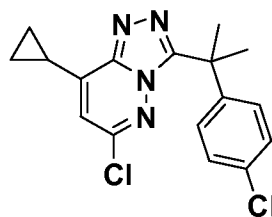
## Compound 34B: 6-Chloro-3-(2-(4-chlorophenyl)propan-2-yl)-8-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazine



20

[00142] To a solution of 2-(4-chlorophenyl)-2-methylpropanoic acid (48.9 mg, 0.246 mmol) and 4-methylmorpholine (0.030 ml, 0.271 mmol) in THF (1 mL) at 0 °C was added isobutyl chloroformate (0.032 ml, 0.246 mmol). Upon completion of addition, the resulting mixture was stirred for 15 min. After this time, a solution of  
5 compound **34A** (50 mg, 0.271 mmol) in THF (1.5 mL) was added and the reaction mixture was stirred for 10 min. At the conclusion of this period, the reaction mixture was quenched with saturated aq. NaHCO<sub>3</sub> and then diluted with EtOAc (5 mL). After stirring for 5 min., the organic layer was separated and washed with saturated aq. NH<sub>4</sub>Cl and aq. NaCl. The organic layer was dried over anhydrous sodium sulfate and  
10 then concentrated by rotary evaporation to yield compound **34B** (92 mg) as a crude yellow solid with a purity of 83%. The crude product was utilized in the next step without further purification. LC/MS (m/z) = 366 (M+H)<sup>+</sup>.

**Compound 34C: 6-Chloro-3-(2-(4-chlorophenyl)propan-2-yl)-8-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazine**  
15



[00143] To a solution of compound **34B** (82mg, 0.224 mmol) in THF (0.8 mL) and CCl<sub>4</sub> (0.6 mL) was added DIPEA (0.392 mL, 2.245 mmol). The mixture was cooled to 0 °C and then triethylphosphine (0.332 mL, 2.245 mmol) was added. Upon the  
20 completion of the addition, the reaction mixture was stirred for 20 min. After this time, the reaction mixture was quenched with saturated aq. NaHCO<sub>3</sub> and then mixed with EtOAc (6 ml). The resulting mixture was vigorously stirred for 10 min. The organic layer was collected, washed with saturated aq. NH<sub>4</sub>Cl followed by saturated aq. NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and then concentrated by rotary evaporation  
25 to yield compound **34C** (90 mg) as the crude product with a purity about 85%. The crude product was utilized in the next step without further purification. LC/MS (m/z) = 347.1 (M+H)<sup>+</sup>.

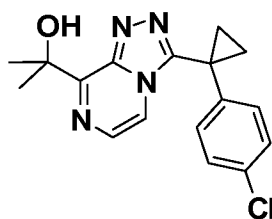
**Example 34**

[00144] To a flask flushed with N<sub>2</sub> and Pd/C (22 mg, 10% wt) in MeOH (0.5 mL) was added a solution of **Compound 34C** (90 mg, 0.220 mmol) in MeOH (0.5 mL). The reaction mixture was evacuated and filled with H<sub>2</sub> and then a H<sub>2</sub> balloon was placed on the top of the flask. The reaction mixture was stirred at rt under H<sub>2</sub> atmosphere for 5 h. Upon completion of the reaction, the reaction mixture was filtered through Celite to remove the insolubles, purified via preparative HPLC and then neutralized to yield **Example 34** (22 mg, 31% ) as a white solid. LC/MS (m/z) = 313.2 (M+H)<sup>+</sup>.

10

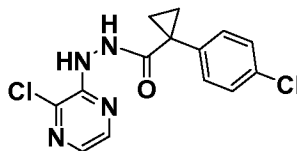
**EXAMPLE 35**

**2-(3-(1-(4-Chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyrazin-8-yl)propan-2-ol TFA salt**



15

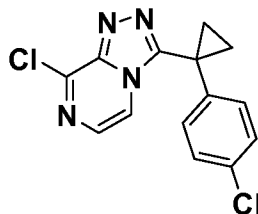
**Compound 35A: 1-(4-Chlorophenyl)-N'-(3-chloropyrazin-2-yl)cyclopropanecarbohydrazide**



[00145] To a solution of 1-(4-chlorophenyl)cyclopropanecarboxylic acid (6300 mg, 32.0 mmol) and 4-methylmorpholine (3.87 mL, 35.2 mmol) in THF (100 mL) at 0 °C was added isobutyl chloroformate (4.21 mL, 32.0 mmol). After completion of addition, the reaction mixture was stirred for 25 min, and then a solution of 2-chloro-3-hydrazinylpyrazine (5095 mg, 35.2 mmol) in THF (60 mL) was added. The resulting mixture was stirred for 45 min. After that time, the reaction mixture was quenched with saturated aq. NaHCO<sub>3</sub> and then extracted with EtOAc (25 mL). The organic layer was collected, washed with saturated aq. NH<sub>4</sub>Cl followed by aq. NaCl,

dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated by rotary evaporation to yield compound **35A** (10 g, 97 % yield) as a yellow solid. The crude product was utilized in the next step without further purification. LC/MS (m/z) = 323.1 [M+1]<sup>+</sup>.

5 **Compound 35B: 8-Chloro-3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyrazine**



**[00146]** To a solution of compound **35A** (10 g, 30.9 mmol) in THF (80 mL) and CCl<sub>4</sub> (30 mL) was added DIPEA (27.0 mL, 155 mmol). Upon completion of  
10 addition, the resulting mixture was cooled to 0 °C and triethylphosphine (22.85 mL, 155 mmol) was slowly added. The reaction mixture was stirred for 40 min and then analyzed by LC/MS, which indicated that all of the reactants had been consumed. The reaction mixture was quenched with saturated aq. NaHCO<sub>3</sub> and then diluted with EtOAc (300 ml). The organic layer was collected, washed with saturated aq. NH<sub>4</sub>Cl,  
15 followed by aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentration by rotary evaporation to yield a yellow residue. The yellow residue was purified via ISCO column chromatography to yield compound **35B** (4.7 g) as a yellow solid. LC/MS (m/z) = 305.1 (M+H)<sup>+</sup>.

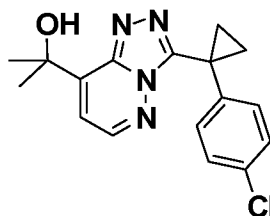
20 **Example 35**

**[00147]** To a suspension of lithium pieces (1024 mg, 147 mmol) in THF (20 mL) was slowly added a solution of compound **35B** (300 mg, 0.983 mmol) and acetone (1.08 mL, 14.75 mmol) in THF (5 mL) at -78 °C. The suspension was stirred at -78 °C for 30 minutes and then warmed to 0 °C, where it stirred for 15 minutes. After this  
25 time, the reaction mixture was re-cooled to -78 °C and the majority of the remaining lithium pieces were removed via spatula. Water was added to the cold solution, and the resulting mixture was allowed to warm to RT. Once at the prescribed temperature, the aqueous solution was extracted with ethyl acetate followed by 10%

MeOH/CHCl<sub>3</sub>. The organic extracts were combined, dried over MgSO<sub>4</sub>, and concentrated by rotary evaporation to yield a residue. The residue was purified via column chromatography (SiO<sub>2</sub>, 0-100% ethyl acetate / hexanes – 20 % methanol / ethyl acetate), followed by prep HPLC to yield **Example 35** as a colorless oil (8.3mg, 0.018 mmol, 2% yield). HPLC R<sub>t</sub> (Method B): 1.83 min. LC/MS (m/z) = 329(M+H)<sup>+</sup>.

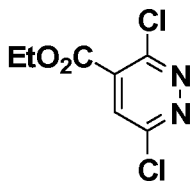
### EXAMPLE 36

#### 2-(3-(1-(4-Chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-b]pyridazin-8-yl)propan-2-ol



10

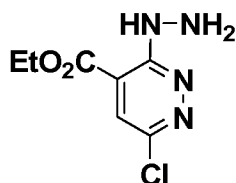
#### Compound 36A: Ethyl 3,6-dichloropyridazine-4-carboxylate



[00148] To a solution of 3,6-dichloropyridazine-4-carboxylic acid (5 g, 25.9 mmol), EtOH (4.77 g, 104 mmol), and DMAP (317 mg, 2.59 mmol) in THF (30 mL) was added EDCI (5.46 g, 28.5 mmol). The reaction mixture was stirred for 50 min. After this time, the solvent was removed *in vacuo* and EtOAc (200 mL) was added. Upon completion of addition, the resulting mixture was washed with 100 mL each of water, saturated aqueous NaHCO<sub>3</sub>, and brine, dried over MgSO<sub>4</sub>, filtered and then concentrated to give compound **36A** (4.4 g, 77%) as a pale yellow oil. LC/MS (m/z) = 222 (M+H)<sup>+</sup>.

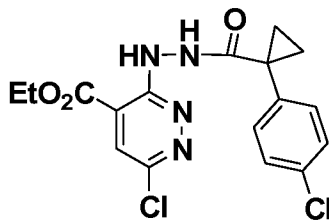
20

#### Compound 36B: Ethyl 6-chloro-3-hydrazinylpyridazine-4-carboxylate



[00149] To a solution of compound **36A** (13.8 g, 62.4 mmol) in THF (60 mL) was added hydrazine hydrate (6.68 mL, 137 mmol). Upon completion of addition, the clear, pale yellow solution immediately turned red-brown and cloudy. A tan suspension with a red-brown thick oily precipitate on the walls of the flask developed shortly thereafter. The mixture was stirred for 80 min and the THF solution and precipitate was decanted away from the dark, oily residue. The oily residue was rinsed with THF (2x10 mL) and added to the decanted THF/solid mixture. Water (60 mL) was added to the THF slurry and the resulting mixture was heated to near reflux and then allowed to cool to RT with stirring. Once at the prescribed temperature, the mixture was filtered and the collected solid was washed with water (3x 20 mL) to yield crude compound **36B** (9.93 g) as a tan-orange solid. A portion of the crude material (8.762 g) was dissolved in EtOH (100 mL). The resulting solution was heated to reflux and then allowed to cool to room temperature where it was stirred for 2 hours (after 10-20 minutes crystals began to form). After this time, the mixture was filtered and the solid was washed with EtOH (3x5 mL) followed by hexane (3x20 mL) to give compound **36B** (5.99 g) as orange crystalline needles. LC/MS (m/z) = 217.6 (M+H)<sup>+</sup>.

20 **Compound 36C: Ethyl 6-chloro-3-(2-(1-(4-chlorophenyl)cyclopropanecarbonyl)hydrazinyl)-pyridazine-4-carboxylate**

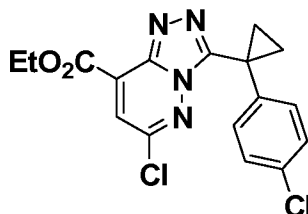


[00150] To a solution of 1-(4-chlorophenyl)cyclopropanecarboxylic acid (2.00 g, 10.16 mmol) in 40 mL THF was added 4-methylmorpholine (1.68 mL, 15.23 mmol). Upon completion of addition, the solution temperature was lowered to 0 °C, and ethyl

chloroformate (1.10 g, 10.16 mmol) was added with stirring. Upon completion of addition, the mixture was stirred at 0 °C for 30 minutes, and then compound **36B** (2.20 g, 10.16 mmol) was added. The reaction mixture was stirred at 0 °C for another hour. After this time, the reaction mixture was quenched with water (10 mL) and then extracted with ethyl acetate (60+30mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated by rotary evaporation to yield a residue. The residue was purified by column chromatography (0-50% ethyl acetate / hexanes) to provide compound **36C** (3.75 g, 93% yield) as a yellow powder. LC/MS (m/z) = 395 (M+H)<sup>+</sup>.

10

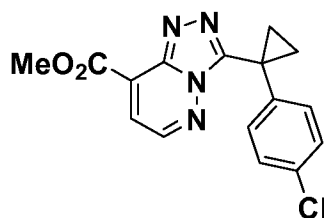
**Compound 36D: Ethyl 6-chloro-3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxylate**



[00151] Compound **36C** (3.74 g, 9.46 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and the resulting solution was cooled to -78 °C. Once at the prescribed temperature, DIPEA (8.26 mL, 47.3 mmol), triethylphosphine (2.236 g, 18.93 mmol), and carbon tetrachloride (13.73 mL, 142 mmol) were added sequentially. Upon completion of addition, the mixture was stirred at -78 °C for 20 minutes and then at 0 °C for 10 minutes. After this time, H<sub>2</sub>O was added and the organic layer was separated from the aqueous layer. The aqueous layer was extracted again with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were combined, dried over MgSO<sub>4</sub>, and concentrated by rotary evaporation to yield a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, 0-50% ethyl acetate / hexanes) to yield compound **36D** (1.59 g, 45 % yield) as a yellow powder. LC/MS (m/z) = 377 (M+H)<sup>+</sup>.

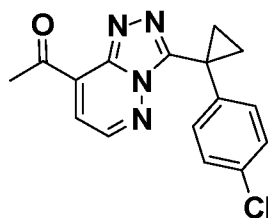
25

**Compound 36E: Methyl 3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxylate**



[00152] To a solution of compound **36D** (1.50g, 3.98 mmol) in ethyl acetate (45 mL) and methanol (15 mL) was added DIPEA (3.13 mL, 17.89 mmol) and 5% Pd/C (0.3 g). The resulting mixture was degassed and then stirred under H<sub>2</sub> balloon for 12 hours. After this time, the mixture was analyzed by LC-MS, which indicated that mono-dechlorination and transesterification had occurred. The catalyst was filtered off and the liquid portion was concentrated by rotary evaporation to yield a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, 0-100% ethyl acetate / hexanes) to provide compound **36E** (0.63 g, 48 % yield) as a yellow powder. LC/MS (m/z) = 329 (M+H)<sup>+</sup>.

**Compound 36F: 1-(3-(1-(4-Chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-b]pyridazin-8-yl)ethanone**



[00153] To a solution of compound **36E** (45 mg, 0.137 mmol) in THF (5 mL) was added fresh anhydrous cerium (III) chloride (101 mg, 0.411 mmol) under argon. Upon completion of addition, the mixture was cooled to -78 °C where it stirred for 5 minutes. After this time, a solution of methylmagnesium chloride in THF (0.091 mL, 3 M, 0.274 mmol) was added at -78 °C. The resulting mixture was stirred at -78 °C for 20 minutes and then another equivalent of a solution of methylmagnesium chloride in THF (0.046 mL, 3 M, 0.137 mmol) was added. The mixture continued to be stirred at -78 °C under argon for 5 minutes. At the conclusion of this period, the reaction was stopped by the addition of aqueous 1N HCl (2 mL) to the cold solution (-78 °C). The resulting mixture was slowly warmed to room temperature and then an aqueous 1N NaOH solution was added to adjust the pH value to about 8. Once at the

prescribed pH, the reaction mixture was extracted with 10% CH<sub>3</sub>OH / EtOAc followed by 10% CH<sub>3</sub>OH / CHCl<sub>3</sub>. The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated by rotary evaporation to yield a residue. The residue was purified by column chromatography (SiO<sub>2</sub>, 0-80% ethyl acetate / hexanes) to afford  
5 compound **36F** (19.9 mg, 47 % yield) as yellow crystals. LC/MS (m/z) = 313 (M+H)<sup>+</sup>.

### Example 36

**[00154]** To a solution of compound **36F** (19.9 mg, 0.064 mmol) in THF (5 mL)  
10 was added anhydrous cerium (III) chloride (62.7 mg, 0.255 mmol) under argon. Upon completion of addition, the resulting mixture was cooled to -78 °C where it stirred for 5 minutes. At the conclusion of this period, a solution of methylmagnesium chloride in THF (0.042 mL, 3 M, 0.127 mmol) was added at -78 °C. The resulting mixture was stirred at -78 °C for 15 minutes. An additional  
15 solution of methylmagnesium chloride in THF (0.025 mL, 3 M, 0.076 mmol) was added, and the mixture was stirred at -78 °C for 5 minutes. After this time, the reaction was stopped by the addition of aqueous 1N HCl (1 mL) to the cold solution (-78 °C). The reaction mixture was slowly warmed to room temperature and then an aqueous 1N NaOH solution was added to adjust the pH value to about 8. Once at the  
20 prescribed pH, the mixture was extracted with 10% CH<sub>3</sub>OH / EtOAc followed by 10% CH<sub>3</sub>OH / CHCl<sub>3</sub>. The combined organic extracts were dried over MgSO<sub>4</sub> and then concentrated by rotary evaporation to yield a residue. The residue was purified by prep HPLC to afford **Example 36** as a white powder (10 mg, 35 % yield). LC/MS (m/z) = 329(M+H)<sup>+</sup>.

25

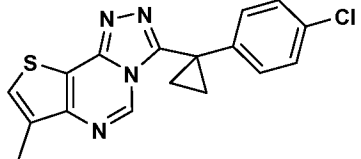
### EXAMPLES 37 TO 48

**[00155]** **Examples 37 to 48** in Table 3 were synthesized according to the procedures described above, or by other similar methods known to one skilled in the art, with other appropriate reagents.

30

### TABLE 3

Example No.	Structure	LC/MS (ES+, M+H)	HPLC purity (%)
37		295	>95
38		363	>95
39		313	>95
40		297	>95
41		291	>95
42		297	>95
43		295	>95
44		295	>95
45		295	>95
46		365	>95
47		295	>95

Example No.	Structure	LC/MS (ES+, M+H)	HPLC purity (%)
48		341	>95

**ASSAY(S) FOR 11-BETA-HYDROXYSTEROID  
DEHYDROGENASE ACTIVITY**

- [00156]** The *in vitro* inhibition of recombinant human 11beta-HSD1 was  
5 determined as follows.
- [00157]** [<sup>3</sup>H]-Cortisone with a specific radioactivity of 50 Ci/mmol (ART 743, Lot:  
050906) was from American Radiolabeled Chemicals, Inc. (St Louis, MO);  
monoclonal ab to Cortisol (P01-9294M-P, Lot: L-28) was from East Coast Bio.,  
(North Berwick, ME); Protein A-yttrium silicate, type-1, SPA bead NJ<sup>®</sup> (RPN-143)  
10 was from Amersham LifeSciences, (Piscataway, NJ); 384 well-Optiplate384<sup>®</sup>  
(#6007299) was from PerkinElmer (Boston, MA); DPBS, pH 7.4 (14040) is from  
GIBCO, (Grand Island, NY); carbenoxolone (C4790) is from Sigma, (St Louis, MO).
- [00158]** Full length recombinant human 11β-HSD1 cDNAs and the cDNA  
encoding human 11β-HSD2 were expressed stably in HEK 293 EBNA cells. Cells  
15 were grown in DMEM (high glucose) containing MEM non-essential amino acids, L-  
glutamine, hygromycin B (200 μg/ml), and G-418(200 μg/ml) in the presence of  
10% FBS.
- [00159]** Human 11β-HSD1 transfected HEK 293 EBNA cells were grown to 80%  
confluency and the cell pellet was quick frozen and stored at -80 °C before  
20 purification. Cell paste, 40 g from -80 °C storage, was thawed in water and then 100  
ml of homogenization buffer H (0.01 M sodium phosphate pH 6.5 containing 0.25 M  
sucrose and protease inhibitor cocktail (Roche #1836145 1 tablet per 50 ml) were  
added to completely thaw the paste. The cell paste suspension was homogenized  
using a Polytron for 20 seconds to create a homogeneous mixture. Additional buffer  
25 H was added to a volume of 300 ml and cells were broken open using a N2-bomb (at  
4°C) in two batches by treating at 500 psi. The extract was centrifuged at 750 X g for

30 min. The supernatant was centrifuged at 20,000 X g for 30 min. The supernatant was further centrifuged at 105,000 X g for 60 min. The 105,000 X g pellet was resuspended in buffer H and centrifuged at 105,000 X g for 60 min. The microsome pellet was scraped from the bottom of tube and resuspended in 0.01M phosphate  
5 buffer, pH 6.5 containing protease inhibitors (Roche #1836145, 1 tablet per 50 ml). Aliquots were stored at -80 °C until needed. The protein concentration was measured by the BioRad method using BSA standard.

[00160] Compounds were dissolved in DMSO to obtain 10 mM stock concentrations. From the 10 mM stock, the compounds were diluted in DMSO to  
10 achieve the concentrations.

#### **11 $\beta$ -HSD1 SPA Enzyme Assay**

[00161] 11 $\beta$ -HSD1 was assayed by Scintillation Proximity assay in a 384-well Perkin Elmer white plate. The dose response of the compounds was determined using  
15 11 half-log dilutions of compound in DMSO in duplicate. To each well, 0.5  $\mu$ l of compound dilution in DMSO were added. 15  $\mu$ l of assay buffer (for blanks) or 15  $\mu$ l of human microsomes in assay buffer were added next and the plates were incubated for 10 min at room temperature. The final microsomal protein concentration was 1.1  $\mu$ g/assay. Duplicates were in the same plate one row below the other. 10  $\mu$ l of <sup>3</sup>H-  
20 cortisone (final concentration 40 nM) was added to each well and the plate was spun down to mix and bring down the contents to the bottom of the wells. The plates were incubated at room temperature with gentle shaking for 4 hrs. The reaction was stopped with addition of 10  $\mu$ l of 10 mM carbenoxolone. Then, 0.5 mg of yttrium silicate SPA beads coupled to anti-cortisol antibody in 20  $\mu$ l were added to all the  
25 wells of plate, which were spun down once more and incubated at room temperature overnight. The plate was read in a TopCount<sup>®</sup> (1 min/well). Data were uploaded automatically to Tool Set, a Lead Evaluation informatics program for data capture and calculation. Graphs were generated with the Curve Master program.

[00162] Compounds of the present invention were tested in the assay described  
30 immediately above and the results shown in the Table 4 below were obtained.

#### **TABLE 4**

Example	h HSD1 IC <sub>50</sub> (nM)
1	1.8
3	453
4	0.5
6	0.6
16	6033
25	1.3
27	336
28	86
29	12
31	1501
35	7.9
36	1.2
38	1.8
41	5126
49	10000

[00163] The *in vivo* inhibition of recombinant human 11 $\beta$ -HSD1 was determined as follows.

[00164] Studies were conducted utilizing diet induced obese (DIO) mice obtained from Jackson Laboratory (ME, USA). These mice were fed a 60% fat diet (Research Diets D12492) soon after weaning and kept on this diet for 24 weeks. These mice were individually housed. All mice were housed under controlled temperature (23°C) and lighting (12 hours of light between 6 am to 6 pm, 12 hours of dark) with free access to water. The animals continued on this diet and were utilized for experimentation at 30 to 32 weeks of age, at which time these mice weighed 45 to 55 grams.

[00165] The basic model of 11-dehydrocorticosterone (DHC) administration to mice to produce corticosterone has been reported in the literature for clinical and preclinical evaluation of the activity of 11 $\beta$ -HSD. Essentially DHC (Steraloids INC, Newport RI), was suspended in the vehicle at a concentration of 10 mg/kg in a volume of 7.5 ml/kg of mouse body weight. For a typical study, non-fasting mice were weighed and separated into groups (n=6) where body weights are not statistically different from each other. Animals were bled via a tail nick, for a 0 time sample and then dosed orally (7.5 ml/kg) with vehicle or drug. At 60 minutes post administration of vehicle or compound, mice were bled again via the tail tip and

dosed orally (7.5 ml/kg) with DHC 10mg/kg. All animals were subsequently bled at 30, 60 and 120 minutes post DHC dosing. Thirty- five microliters of whole blood are collected per time point in microvette tubes coated with EDTA (Sarstedt Tubes Microvette CB 300/ Haematology Potassium EDTA # 16.444.300)and kept on ice.

5 Samples were centrifuged at 4°C in a Beckman Coulter centrifuge for 10 minutes at 2500 RPM. Plasma was separated and collected and immediately frozen at -20 °C until corticosterone analysis could be assessed.

[00166] Plasma Corticosterone was measured using an EIA (IDS AC-14F1). Samples were measured at (1:2) for the -30( or -60 minute) and 0 time point and  
10 (1:10) for the 30, 60 and 120 minutes time points. AUC was calculated using Graphpad and the zero timepoint was used as the baseline. One way ANOVA was calculated using Sigmastat. A p value of less that 0.05 via post hoc analysis with Dunnett's was used to determine statistical significance.

[00167] The vehicle utilized for the suspension of the compounds was 0.5%  
15 methocel; 0.1% tween 80 in water. Methocel Cellulose (M-0262) was purchased from Sigma-Aldrich, St Louis, MO 6. Tween 80 (274364) was purchased from Sigma-Aldrich, St Louis, MO. Compounds were administered in 7.5 ml/kg volumes at final dosages of 0.1 to 300 mg/kg depending on the study and compound evaluated.

## 20 UTILITIES AND COMBINATIONS

### A. Utilities

[00168] The compounds of the present invention possess activity as inhibitors of the enzyme 11-beta-hydroxysteroid dehydrogenase type I, and, therefore, may be used in the treatment of diseases associated with 11-beta-hydroxysteroid  
25 dehydrogenase type I activity. Via the inhibition of 11-beta-hydroxysteroid dehydrogenase type I, the compounds of the present invention may preferably be employed to inhibit or modulate glucocorticoid production, thereby interrupting or modulating cortisone or cortisol production.

[00169] Accordingly, the compounds of the present invention can be administered  
30 to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to, treating, preventing, or slowing the progression of diabetes and related conditions, microvascular complications

associated with diabetes, macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, inflammatory diseases and other maladies. Consequently, it is believed that the compounds of the present invention may be used in preventing, inhibiting, or treating

5 diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae (acute coronary syndrome, myocardial infarction, angina pectoris, peripheral vascular disease, intermittent claudication), abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension,

10 obesity, dislipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy, glaucoma and inflammatory diseases, such as, rheumatoid arthritis, Cushing's Disease, Alzheimer's

15 Disease and osteoarthritis.

**[00170]** Metabolic Syndrome or "Syndrome X" is described in Ford et al., *J. Am. Med. Assoc.*, 287:356-359 (2002) and Arbeeny et al., *Curr. Med. Chem. - Imm., Endoc. & Metab. Agents*, 1:1-24 (2001).

## 20 **B. Combinations**

**[00171]** The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present invention

25 can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), e.g., an antidiabetic agent or other pharmaceutically active material.

**[00172]** The compounds of the present invention may be employed in combination with other 11-beta-hydroxysteroid dehydrogenase type I inhibitors or one or more

30 other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-retinopathic agents, anti-neuropathic agents, anti-

nephropathic agents, anti-atherosclerotic agents, anti-ischemic agents, anti-hypertensive agents, anti-obesity agents, anti-dislipidemic agents, anti-dyslipidemic agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid  
5 lowering agents, appetite suppressants, memory enhancing agents, cognition promoting agents and anti-inflammatory agents.

**[00173]** Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include insulin and insulin analogs: LysPro insulin, inhaled formulations comprising insulin; glucagon-like peptides;  
10 sulfonylureas and analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glyburide, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; alpha2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linoglitride, insulinotropin, exendin-4, BTS-67582, A-4166;  
15 thiazolidinediones: ciglitazone, pioglitazone, troglitazone, rosiglitazone; PPAR-gamma agonists; PPAR-alpha agonists; PPAR alpha/gamma dual agonists; SGLT2 inhibitors; dipeptidyl peptidase-IV (DPP4) inhibitors; glucagon-like peptide-1 (GLP-1) receptor agonists; aldose reductase inhibitors; RXR agonists: JTT-501, MCC-555, MX-6054, DRF2593, GI-262570, KRP-297, LG100268; fatty acid oxidation  
20 inhibitors: clomoxir, etomoxir;  $\alpha$ -glucosidase inhibitors: precose, acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; beta-agonists: BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, TAK-667, AZ40140; phosphodiesterase inhibitors, both cAMP and cGMP type: sildenafil, L686398; L-386,398; amylin antagonists: pramlintide, AC-137; lipoxygenase inhibitors:  
25 masoprocal; somatostatin analogs: BM-23014, seglitide, octreotide; glucagon antagonists: BAY 276-9955; insulin signaling agonists, insulin mimetics, PTP1B inhibitors: L-783281, TER17411, TER17529; gluconeogenesis inhibitors: GP3034; somatostatin analogs and antagonists; antilipolytic agents: nicotinic acid, acipimox, WAG 994; glucose transport stimulating agents: BM-130795; glucose synthase  
30 kinase inhibitors: lithium chloride, CT98014, CT98023; and galanin receptor agonists.

- [00174] Other suitable thiazolidinediones include Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's GL-262570, englitazone (CP-68722, Pfizer), or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi).
- [00175] Suitable PPAR alpha/gamma dual agonists include AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck), as well as those disclosed by Murakami et al., "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation – Activated Receptor Alpha (PPAR alpha) and PPAR gamma; Effect of PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", *Diabetes*, 47:1841-1847 (1998), and WO 01/21602, the disclosure of which is incorporated herein by reference, employing dosages as set out therein, which compounds designated as preferred are preferred for use herein.
- [00176] Suitable alpha2 antagonists also include those disclosed in WO 00/59506, employing dosages as set out herein.
- [00177] Suitable SGLT2 inhibitors include T-1095, phlorizin, WAY-123783, and those described in WO 01/27128.
- [00178] Suitable DPP4 inhibitors include saxagliptan, sitagliptan, vildagliptan, and denagliptan.
- [00179] Suitable aldose reductase inhibitors include those disclosed in WO 99/26659.
- [00180] Suitable meglitinides include nateglinide (Novartis) or KAD1229 (PF/Kissei).
- [00181] Examples of glucagon-like peptide-1 (GLP-1) receptor agonists include Exenatide (Byetta<sup>TM</sup>), NN2211 (Liraglutide, Novo Nordisk), AVE0010 (Sanofi-Aventis), R1583 (Roche/Ipsen), SUN E7001 (Daiichi/Santory), GSK-716155 (GSK/Human Genome Sciences) and Exendin-4 (PC-DAC<sup>TM</sup>).
- [00182] Other anti-diabetic agents that can be used in combination with compounds of the invention include ergoset and D-chiroinositol.
- [00183] Suitable anti-ischemic agents include, but are not limited to, those described in the Physicians' Desk Reference and NHE inhibitors, including those disclosed in WO 99/43663.

[00184] Examples of suitable lipid lowering agents for use in combination with the compounds of the present invention include one or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na<sup>+</sup>/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile acid sequestrants, cholesterol ester transfer protein inhibitors (e.g., CP-529414 (Pfizer)), and/or nicotinic acid and derivatives thereof.

[00185] MTP inhibitors which may be employed as described above include those disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983, and U.S. Patent No. 5,962,440.

[00186] The HMG CoA reductase inhibitors which may be employed in combination with one or more compounds of formula I include mevastatin and related compounds, as disclosed in U.S. Patent No. 3,983,140, lovastatin, (mevinolin) and related compounds, as disclosed in U.S. Patent No. 4,231,938, pravastatin, and related compounds, such as disclosed in U.S. Patent No. 4,346,227, simvastatin, and related compounds, as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772; cerivastatin, as disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080; atorvastatin, as disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104; atavastatin (Nissan/Sankyo's nisvastatin (NK-104)), as disclosed in U.S. Patent No. 5,011,930; visastatin (Shionogi-Astra/Zeneca (ZD-4522)) as disclosed in U.S. Patent No. 5,260,440.

[00187] Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin, and ZD-4522.

[00188] The fibric acid derivatives which may be employed in combination with one or more compounds of formula I include fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate, and the like, probucol, and related compounds, as disclosed in U.S. Patent No. 3,674,836, fenofibrate and gemfibrozil being preferred, bile acid sequestrants, such as cholestyramine, colestipol and DEAE-Sephadex (Secholex<sup>®</sup>, Policexide<sup>®</sup>), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402),

tetrahydrolipstatin (THL), istigmantanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, 5 p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives, such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes, such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

**[00189]** The ACAT inhibitor which may be employed in combination with one or 10 more compounds of formula I include those disclosed in *Drugs of the Future*, 24:9-15 (1999) (Avasimibe); Nicolosi et al., "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", *Atherosclerosis* (Shannon, Irel.), 137(1):77-85 (1998); Ghiselli, G., "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by 15 selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", *Cardiovasc. Drug Rev.*, 16(1):16-30 (1998); Smith, C. et al., "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", *Bioorg. Med. Chem. Lett.*, 6(1):47-50 (1996); Krause, B.R. et al., Chapter 6: "ACAT Inhibitors: Physiologic Mechanisms for Hypolipidemic and Anti-Atherosclerotic Activities in 20 Experimental Animals", *Inflammation: Mediators and Pathways*, CRC Press, Inc., publ., Ruffolo, Jr., R.R. et al., eds., pp. 173-198 (1995); Sliskovic et al., "ACAT inhibitors: potential anti-atherosclerotic agents", *Curr. Med. Chem.*, 1(3):204-25 (1994); Stout et al., "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid- 25 regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", *Chemtracts: Org. Chem.*, 8(6):359-362 (1995), or TS-962 (Taisho Pharmaceutical Co. Ltd.).

30 **[00190]** The hypolipidemic agent may be an upregulator of LDL receptor activity, such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

- [00191] Examples of suitable cholesterol absorption inhibitors for use in combination with the compounds of the invention include ezetimibe (Zetia<sup>®</sup>).
- [00192] Examples of suitable ileal Na<sup>+</sup>/bile acid cotransporter inhibitors for use in combination with the compounds of the invention include compounds as disclosed in  
5 *Drugs of the Future*, 24:425-430 (1999).
- [00193] The lipoxygenase inhibitors which may be employed in combination with one or more compounds of formula I include 15-lipoxygenase (15-LO) inhibitors, such as benzimidazole derivatives, as disclosed in WO 97/12615, 15-LO inhibitors, as disclosed in WO 97/12613, isothiazolones, as disclosed in WO 96/38144, and 15-LO  
10 inhibitors, as disclosed by Sendobry et al., "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", *Brit. J. Pharmacology*, 120:1199-1206 (1997), and Cornicelli et al., "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", *Current Pharmaceutical Design*, 5:11-20 (1999).
- [00194] Examples of suitable anti-hypertensive agents for use in combination with  
15 the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen,  
20 chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors (e.g., aliskiren), ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan),  
25 ET receptor antagonists (e.g., sitaxsentan, atrsentan, and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.
- [00195] Examples of suitable anti-obesity agents for use in combination with the  
30 compounds of the present invention include a cannabinoid receptor 1 antagonist or

inverse agonist, a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta drug, and/or an anorectic agent.

**[00196]** Cannabinoid receptor 1 antagonists and inverse agonists which may be optionally employed in combination with compounds of the present invention include  
5 rimonabant, SLV 319, CP-945598 (Pfizer), SR-147778 (Sanofi-Aventis), MK0364 (Merck) and those discussed in Hertzog, D.L., *Expert Opin. Ther. Patents*, 14:1435-1452 (2004).

**[00197]** The beta 3 adrenergic agonists which may be optionally employed in combination with compounds of the present invention include AJ9677  
10 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer,) or other known beta 3 agonists, as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983, and 5,488,064, with AJ9677, L750,355, and CP331648 being preferred.

**[00198]** Examples of lipase inhibitors which may be optionally employed in combination with compounds of the present invention include orlistat or ATL-962  
15 (Alizyme), with orlistat being preferred.

**[00199]** The serotonin (and dopamine) reuptake inhibitor and/or modulator which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson), APD-356 (Arena) or axokine (Regeneron), with sibutramine and APD-356 being preferred.

20 **[00200]** Examples of thyroid receptor beta compounds which may be optionally employed in combination with compounds of the present invention include thyroid receptor ligands, such as those disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio), and WO 00/039077 (KaroBio), with compounds of the KaroBio applications being preferred.

25 **[00201]** The anorectic agent which may be optionally employed in combination with compounds of the present invention include dexamphetamine, phentermine, phenylpropanolamine, or mazindol, with dexamphetamine being preferred.

**[00202]** Other compounds that can be used in combination with the compounds of the present invention include CCK receptor agonists (e.g., SR-27895B); MCHR1  
30 antagonist (e.g., GSK 856464); galanin receptor antagonists; MCR-4 antagonists (e.g., HP-228); leptin or mimetics; urocortin mimetics, CRF antagonists, and CRF binding proteins (e.g., RU-486, urocortin).

[00203] Further, the compounds of the present invention may be used in combination with HIV protease inhibitors, including but not limited to Reyataz<sup>®</sup> and Kaletra<sup>®</sup>.

5 [00204] Examples of suitable memory enhancing agents, anti-dementia agents, or cognition promoting agents for use in combination with the compounds of the present invention include, but are not limited to, donepezil, rivastigmine, galantamine, memantine, tacrine, metrifonate, muscarine, xanomelline, deprenyl and physostigmine.

10 [00205] Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include, but are not limited to, prednisone, acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, interferon alpha, prednisolone, methylprednisolone, dexamethazone, flucatisone, betamethasone, hydrocortisone and beclomethasone.

15 [00206] The aforementioned patents and patent applications are incorporated herein by reference.

[00207] The above other therapeutic agents, when employed in combination with the compounds of the present invention may be used, for example, in those amounts indicated in the Physicians' Desk Reference, as in the patents set out above, or as  
20 otherwise determined by one of ordinary skill in the art.

[00208] The compounds of formula I can be administered for any of the uses described herein by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion  
25 techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents.

30 [00209] In carrying out the method of the invention for treating diabetes and related diseases, a pharmaceutical composition will be employed containing the compounds of formula I, with or without other antidiabetic agent(s) and/or

antihyperlipidemic agent(s) and/or other type therapeutic agents in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration, such as pharmaceutically acceptable carriers, excipients, binders, and the like. The compounds can be administered to a mammalian patient, including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, beads, granules or powders. The dose for adults is preferably between 1 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

**[00210]** A typical capsule for oral administration contains compounds of structure I (250 mg), lactose (75 mg), and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

**[00211]** A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

## WHAT IS CLAIMED IS:

1. A compound of formula (I)

W-L-Z

5 (I)

enantiomers, diastereomers or salts thereof wherein:

W is  $-C(=O)R_6$ ,  $-C(OH)R_6(R_6)$ ,  $-C(=O)OR_6$ ,  $-C(=O)NR_6R_6$ , halogen, -OH, alkyl, alkenyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, wherein the alkyl, alkenyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with  $R_1$ ,  $R_{1a}$ ,

10  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$ ;

$R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$  are independently hydrogen, halogen, -OH, -CN,  $-NO_2$ ,  $-CO_2R_6$ ,  $-CONR_6R_6$ ,  $-SO_2NR_6R_6$ ,  $-SOR_6$ ,  $-SO_2R_6$ ,  $-NR_6SO_2R_6$ ,  $-NR_6CO_2R_6$ ,  $-OCONR_6R_6$ , tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino,

15 heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ;

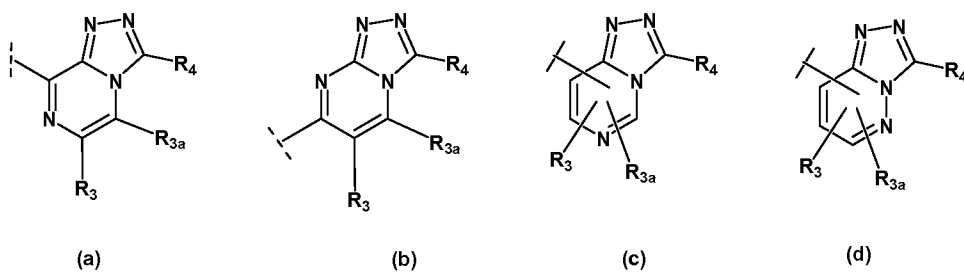
or alternatively any two  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$  can be taken together to form a fused cycloalkyl, aryl, heteroaryl, heterocyclyl ring or spiro heterocyclyl ring;

20 L is a bond, O, S, SO,  $SO_2$ ,  $C(=O)$ , alkenyl, cycloalkyl,  $NR_5$ ,  $CR_2R_{2a}$ ,  $CR_2R_6$ ,  $CR_2R_{2a}CR_{2b}R_{2c}$ ,  $SO_2NR_6$ ,  $OCR_2R_{2a}$ ,  $OCR_2R_{2a}CR_{2b}R_{2c}$ ,  $CR_2R_{2a}O$ ,  $CR_{2b}R_{2c}CR_2R_{2a}O$ ,  $N(R_5)CR_2R_{2a}$ ,  $CR_2R_{2a}N(R_5)$ ,  $SCR_2R_{2a}$ ,  $CR_2R_{2a}S$ ,  $CR_2R_{2a}SO$ ,  $CR_2R_{2a}SO_2$ ,  $SOCR_2R_{2a}$ ,  $SO_2CR_2R_{2a}$ ,  $CR_2R_{2a}OCR_{2b}R_{2c}$ ,  $CR_2R_{2a}SCR_{2b}R_{2c}$ ,  $CR_2R_{2a}SO_2CR_{2b}R_{2c}$ ,  $SO_2NR_6CR_{2a}R_{2b}$ ,  $COCR_2R_{2a}$ ,  $CR_2R_{2a}CO$ ,  $CONR_6CR_{2a}R_{2b}$ ,  $CR_2R_{2a}CR_{2b}R_{2c}S$ ,  $CR_2R_{2a}CR_{2b}R_{2c}SO$ ,  $CR_2R_{2a}CR_{2b}R_{2c}SO_2$ , provided that W is not halogen or -OH when L is O, S, SO,  $SO_2$ ,  $C(=O)$  or  $NR_5$ ;

$R_2$ ,  $R_{2a}$ ,  $R_{2b}$  and  $R_{2c}$  are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl, or haloalkyl;

30 or alternatively any two  $R_2$ ,  $R_{2a}$ ,  $R_{2b}$ , and  $R_{2c}$  can be taken together to which the atom they are attached to form a cycloalkyl, halogen substituted cycloalkyl or heterocyclyl ring;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroaryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroaryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

or alternatively any R<sub>3</sub> and R<sub>3a</sub> can be taken together to form a fused cycloalkyl, aryl, heteroaryl or heterocyclyl ring, which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

or alternatively one of R<sub>3</sub> or R<sub>3a</sub> can be taken together with W-L to form a fused cycloalkyl, aryl, heteroaryl or heterocyclyl ring, which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl, cycloalkyl, heteroaryl or heterocyclyl and (ii) Z is formula (d); or

R<sub>4</sub> is heterocyclyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>5</sub>, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, haloalkyl, COR<sub>6</sub>, CO<sub>2</sub>R<sub>6</sub>, SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, or SO<sub>2</sub>R<sub>6</sub>;

R<sub>6</sub>, at each occurrence, is independently H, alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; or two R<sub>6</sub>'s may be taken together with the atom to which they are attached to form a 3- to 7-membered cycloalkyl or heterocyclyl ring, which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub> and R<sub>7c</sub>;

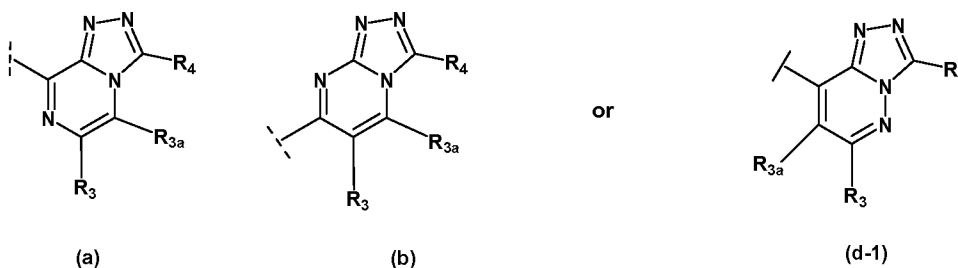
R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

$R_8$ ,  $R_{8a}$ ,  $R_{8b}$ , and  $R_{8c}$ , at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

2. The compound of claim 1, wherein W is alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, all of which may be optionally substituted with  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$ .

3. The compound of claim 1, wherein W is phenyl or cyclopropyl, both of which are optionally substituted with  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$ .

4. The compound of claim 1, wherein Z is selected from the following bicyclic heteroaryl groups:



5. The compound of claim 1, wherein:

$R_4$  is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ; provided that  $R_4$  is not cycloalkyl when (i) W is aryl, cycloalkyl, heteroaryl or heterocyclyl and (ii) Z is formula (d); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or  
 5 heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>5</sub>, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, haloalkyl, COR<sub>6</sub>, CO<sub>2</sub>R<sub>6</sub>, SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, or SO<sub>2</sub>R<sub>6</sub>;

10 R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl,  
 15 heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio,  
 20 arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl,  
 25 heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

6. The compound of claim 1, wherein:

30 Z is selected from the following bicyclic heteroaryl groups:



arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $-\text{CO}_2\text{H}$ , tetrazolyl or thiol.

7. The compound of claim 1, wherein:

5 W is alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, all of which may be optionally substituted with  $\text{R}_1$ ,  $\text{R}_{1a}$ ,  $\text{R}_{1b}$ ,  $\text{R}_{1c}$  and  $\text{R}_{1d}$ ;

$\text{R}_1$ ,  $\text{R}_{1a}$ ,  $\text{R}_{1b}$ ,  $\text{R}_{1c}$  and  $\text{R}_{1d}$  are independently hydrogen, halogen,  $-\text{OH}$ ,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{CO}_2\text{R}_6$ ,  $-\text{CONR}_6\text{R}_6$ ,  $-\text{SO}_2\text{NR}_6\text{R}_6$ ,  $-\text{SOR}_6$ ,  $-\text{SO}_2\text{R}_6$ ,  $-\text{NR}_6\text{SO}_2\text{R}_6$ ,  $-\text{NR}_6\text{CO}_2\text{R}_6$ ,  $-\text{OCONR}_6\text{R}_6$ , tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl,

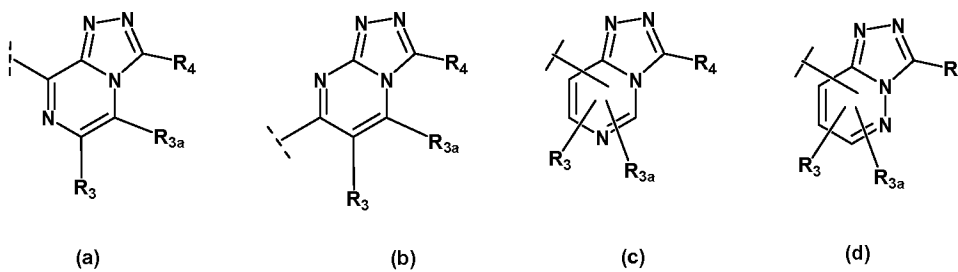
10 haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $\text{R}_7$ ,  $\text{R}_{7a}$ ,  $\text{R}_{7b}$ , and  $\text{R}_{7c}$ ;

L is a bond, O, S,  $\text{SO}_2$ ,  $\text{C}(=\text{O})$ ,  $\text{CR}_2\text{R}_{2a}$ ,  $\text{CR}_2\text{R}_6$ ,  $\text{SO}_2\text{NR}_6$ ,  $\text{OCR}_2\text{R}_{2a}$ ,

15  $\text{OCR}_2\text{R}_{2a}\text{CR}_{2b}\text{R}_{2c}$ ,  $\text{CR}_2\text{R}_{2a}\text{O}$ ,  $\text{CR}_{2b}\text{R}_{2c}\text{CR}_2\text{R}_{2a}\text{O}$ ,  $\text{SCR}_2\text{R}_{2a}$ ,  $\text{CR}_2\text{R}_{2a}\text{S}$ ,  $\text{CR}_2\text{R}_{2a}\text{SO}$ ,  $\text{CR}_2\text{R}_{2a}\text{SO}_2$ ,  $\text{SO}_2\text{CR}_2\text{R}_{2a}$ ,  $\text{CR}_2\text{R}_{2a}\text{OCR}_{2b}\text{R}_{2c}$ ,  $\text{CR}_2\text{R}_{2a}\text{SCR}_{2b}\text{R}_{2c}$ ,  $\text{CR}_2\text{R}_{2a}\text{SO}_2\text{CR}_{2b}\text{R}_{2c}$ ,  $\text{SO}_2\text{NR}_6\text{CR}_{2a}\text{R}_{2b}$ ,  $\text{COCR}_2\text{R}_{2a}$ ,  $\text{CR}_2\text{R}_{2a}\text{CO}$ ,  $\text{CONR}_6\text{CR}_{2a}\text{R}_{2b}$ ,  $\text{CR}_2\text{R}_{2a}\text{CR}_{2b}\text{R}_{2c}\text{S}$ ,  $\text{CR}_2\text{R}_{2a}\text{CR}_{2b}\text{R}_{2c}\text{SO}$ , or  $\text{CR}_2\text{R}_{2a}\text{CR}_{2b}\text{R}_{2c}\text{SO}_2$ ;

20  $\text{R}_2$ ,  $\text{R}_{2a}$ ,  $\text{R}_{2b}$  and  $\text{R}_{2c}$  are independently hydrogen, halogen,  $-\text{OH}$ , alkyl, cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



25  $\text{R}_3$  is hydrogen, halogen,  $-\text{OH}$ ,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{CO}_2\text{R}_6$ ,  $-\text{CONR}_6\text{R}_6$ ,  $-\text{SO}_2\text{NR}_6\text{R}_6$ ,  $-\text{SOR}_6$ ,  $-\text{SO}_2\text{R}_6$ ,  $-\text{NR}_6\text{SO}_2\text{R}_6$ ,  $-\text{NR}_6\text{CO}_2\text{R}_6$ ,  $-\text{OCONR}_6\text{R}_6$ , tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the

tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, alkenyl, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl, cycloalkyl, heteroaryl or heterocyclyl and (ii) Z is formula (d); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -NR<sub>6</sub>COR<sub>6</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>6</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -NR<sub>6</sub>CO<sub>2</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>5</sub>, at each occurrence, is independently hydrogen, alkyl, cycloalkyl, aryl, haloalkyl, COR<sub>6</sub> or CO<sub>2</sub>R<sub>6</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -

CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or  
 5 tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio,  
 10 arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

8. The compound of claim 1, wherein:

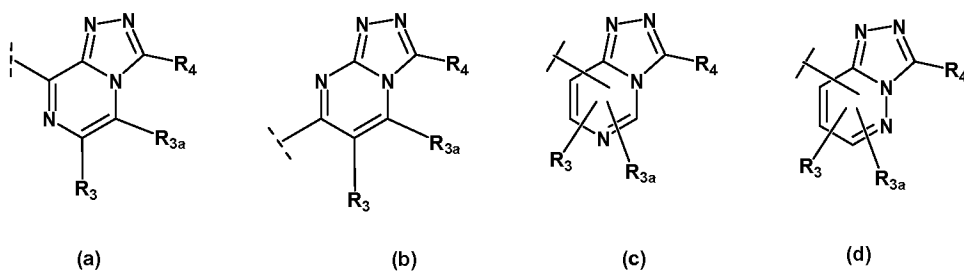
W is alkyl, aryl, cycloalkyl or heteroaryl, all of which may be optionally  
 15 substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or  
 20 heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

L is a bond, O, S, SO, SO<sub>2</sub>, C(=O), NR<sub>2</sub>, CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, CR<sub>2</sub>R<sub>2a</sub>CR<sub>2b</sub>R<sub>2c</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O, SCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>S, CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>, CR<sub>2</sub>R<sub>2a</sub>SCR<sub>2b</sub>R<sub>2c</sub>, CR<sub>2</sub>R<sub>2a</sub>SO<sub>2</sub>CR<sub>2b</sub>R<sub>2c</sub> or SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub>;

25 R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -SOR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl, cycloalkyl or heteroaryl and (ii) Z is formula (d); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

9. The compound of claim 1, wherein:

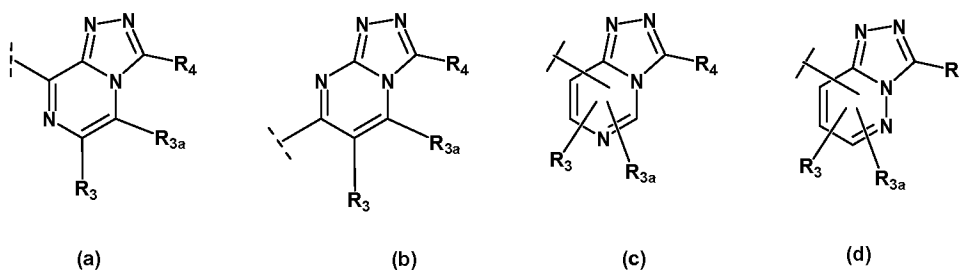
W is alkyl, aryl or cycloalkyl, all of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

L is a bond, O, S, SO, SO<sub>2</sub>, C(=O), CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O, SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub> or CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>;

R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>NR<sub>6</sub>R<sub>6</sub>, -OCONR<sub>6</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl or cycloalkyl and (ii) Z is formula (d); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -OCOR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -OCONR<sub>6</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

10. The compound of claim 1, wherein:

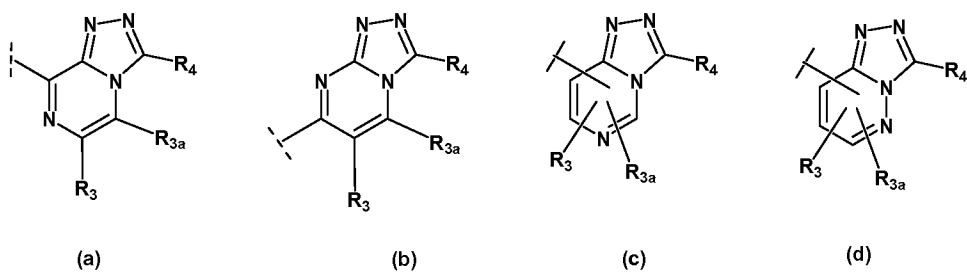
W is alkyl, aryl or cycloalkyl, all of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

L is a bond, O, S, SO, SO<sub>2</sub>, C(=O), CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O, SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub> or CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>;

R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>6</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl or cycloalkyl and (ii) Z is formula (d); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

11. The compound of claim 1, wherein:

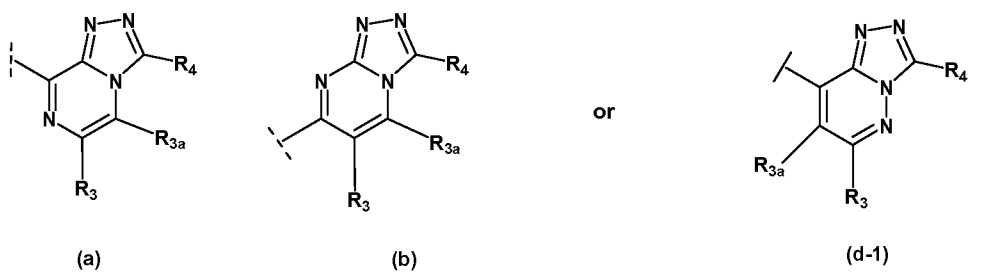
W is alkyl, aryl or cycloalkyl, all of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub> are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

L is a bond, O, S, SO, SO<sub>2</sub>, C(=O), CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O, SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub> or CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>;

R<sub>2</sub>, R<sub>2a</sub>, R<sub>2b</sub> and R<sub>2c</sub> are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



R<sub>3</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroaryl amino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when (i) W is aryl or cycloalkyl and (ii) Z is formula (d-1);

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl, all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy,

heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with  $R_8$ ,  $R_{8a}$ ,  $R_{8b}$ , and  $R_{8c}$ ; and

- 5  $R_8$ ,  $R_{8a}$ ,  $R_{8b}$ , and  $R_{8c}$ , at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

10

12. The compound of claim 1, wherein:

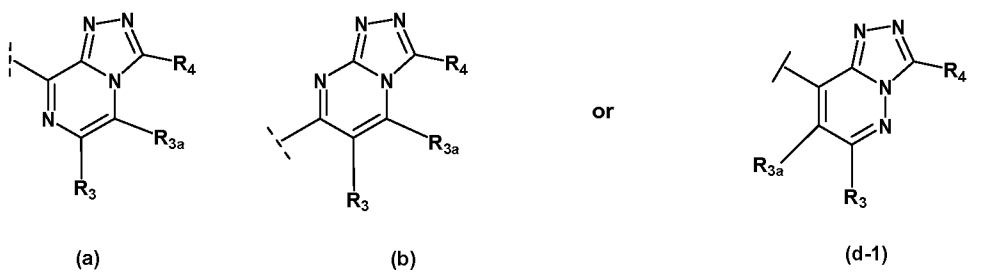
W is alkyl, aryl or cycloalkyl, all of which may be optionally substituted with  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$ ;

- 15  $R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$  are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ;

- 20 L is a bond, O, S, SO, SO<sub>2</sub>, C(=O), CR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>6</sub>, OCR<sub>2</sub>R<sub>2a</sub>, CR<sub>2</sub>R<sub>2a</sub>O, SO<sub>2</sub>NR<sub>6</sub>CR<sub>2a</sub>R<sub>2b</sub> or CR<sub>2</sub>R<sub>2a</sub>OCR<sub>2b</sub>R<sub>2c</sub>;

$R_2$ ,  $R_{2a}$ ,  $R_{2b}$  and  $R_{2c}$  are independently hydrogen, halogen, -OH, alkyl, cycloalkyl, aryl or haloalkyl;

Z is selected from the following bicyclic heteroaryl groups:



- 25  $R_3$  is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the tetrazolyl,

alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>3a</sub> is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, arylamino, heteroarylamino, aryl, heteroaryl or heterocyclyl, wherein the  
5 tetrazolyl, alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>,  
10 -SO<sub>2</sub>R<sub>6</sub>, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl,  
15 all of which may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio,  
20 arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or  
25 tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio,  
30 arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.



spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>; provided that R<sub>4</sub> is not cycloalkyl when Z is formula (d-1); or

R<sub>4</sub> is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>;

R<sub>6</sub>, at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl; R<sub>7</sub>, R<sub>7a</sub>, R<sub>7b</sub>, and R<sub>7c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol, wherein the alkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

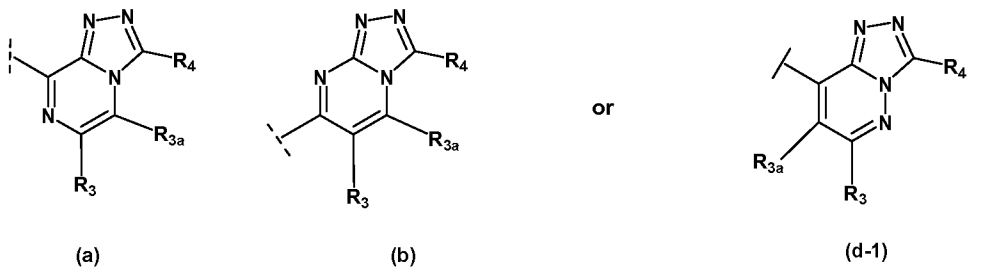
14. The compound of claim 1, wherein:

W is phenyl or cyclopropyl, both of which may be optionally substituted with R<sub>1</sub>, R<sub>1a</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1d</sub>;

$R_1$ ,  $R_{1a}$ ,  $R_{1b}$ ,  $R_{1c}$  and  $R_{1d}$  are independently hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, aryl, heteroaryl or heterocyclyl;

L is a bond, O, S, C(=O), CHR<sub>6</sub>, SCH<sub>2</sub>, OCH<sub>2</sub>, CH<sub>2</sub>O or CH<sub>2</sub>OCH<sub>2</sub>;

5 Z is selected from the following bicyclic heteroaryl groups:



$R_3$  is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aryl, heteroaryl or heterocyclyl;

10  $R_{3a}$  is hydrogen, halogen, -OH, -CN, -NO<sub>2</sub>, tetrazolyl, alkyl, haloalkyl, cycloalkyl, alkoxy, aryloxy, haloalkoxy, alkylthio, arylthio, arylsulfonyl, alkylamino, aminoalkyl, aryl, heteroaryl or heterocyclyl;

$R_4$  is cycloalkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ; provided that  $R_4$  is not cycloalkyl when Z is formula (d-1); or

$R_4$  is alkyl, which may be optionally substituted with one or more substituents selected from halogen, -OH, -OR<sub>6</sub>, -SR<sub>6</sub>, -CN, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CO<sub>2</sub>H, -CONR<sub>6</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>6</sub>, alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, amino, heterocyclyl or heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, spiro cycloalkyl, spiro heterocycloalkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with  $R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ ;

25  $R_6$ , at each occurrence, is independently alkyl, cycloalkyl, aryl or heteroaryl;

$R_7$ ,  $R_{7a}$ ,  $R_{7b}$ , and  $R_{7c}$ , at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylalkyl, cycloalkyl, amino, -OH, hydroxyalkyl,

heteroaryl, heteroaryloxy, heteroarylalkyl, alkylthio, arylalkylthio, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>H or tetrazolyl; wherein the alkyl, alkoxy, aryl, aryloxy, arylalkyl, cycloalkyl, heteroaryl, heteroaryloxy, heteroarylalkyl, alkylthio, arylalkylthio or tetrazolyl may be optionally substituted with R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>; and

5           R<sub>8</sub>, R<sub>8a</sub>, R<sub>8b</sub>, and R<sub>8c</sub>, at each occurrence, are independently halo, alkyl, haloalkyl, alkoxy, aryl, aryloxy, arylaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, -OH, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, -NO<sub>2</sub>, -  
10   CN, -CO<sub>2</sub>H, tetrazolyl or thiol.

15.       The compound of claim 1, wherein L is a bond or O.

16.       A compound selected from the compounds exemplified in the  
15   examples.

17.       A pharmaceutical composition comprising at least one compound of claim 1.

20       18.       The pharmaceutical composition of claim 17 further comprising a pharmaceutically acceptable carrier.

19.       The pharmaceutical composition of claim 17 further comprising at least one additional therapeutic agent.

25       20.       The pharmaceutical composition of claim 17, wherein the compound of Formula (I) is present in a therapeutically effective amount.

21.       A method for treating, preventing, or slowing the progression of a  
30   disease requiring 11-beta-hydroxysteroid dehydrogenase type I inhibitor therapy, which comprises administering to a mammalian patient in need of treatment a therapeutically effective amount of at least one compound of claim 1.

22. A method for treating, preventing, or slowing the progression of diabetes, hyperglycemia, obesity, dyslipidemia, hypertension, cognitive impairment Metabolic Syndrome and glaucoma, which comprises administering to a mammalian  
5 patient in need of treatment a therapeutically effective amount of at least one compound of claim 1.

23. A method of inhibiting the enzyme 11-beta-hydroxysteroid dehydrogenase type I which comprises administering to a mammalian patient in need  
10 of treatment a therapeutically effective amount of a compound of claim 1.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/060395

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 C07D495/14 A61K31/5025 A61K31/519 A61K31/4985  
 A61P3/04 A61P3/06 A61P3/08 A61P3/10 A61P9/12  
 A61P27/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/042537 A (SQUIBB BRISTOL MYERS CO [US]; DAS JAGABANDHU [US]; HYNES JOHN [US]; LE) 12 May 2005 (2005-05-12) claim 24; examples 47-52; table 5	1-5, 8, 17-20, 22
X	WO 2006/138657 A (SQUIBB BRISTOL MYERS CO [US]; SUN CHONGQING [US]; HUANG YANTING [US];) 28 December 2006 (2006-12-28) claims 9,10,13	1-3,5, 7-10,15, 20,22
X	WO 2006/138682 A (SQUIBB BRISTOL MYERS CO [US]; EWING WILLIAM R [US]; ZHU YE HENG [US]; E) 28 December 2006 (2006-12-28) claims 11,12,15	1-5, 7-15,22
	----- -/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

4 August 2008

Date of mailing of the international search report

11/08/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Schuemacher, Anne

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/060395

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/021984 A (SQUIBB BRISTOL MYERS CO [US]; YU GUIXUE [US]; LI JUN [US]; EWING WILLI) 18 March 2004 (2004-03-18) claims 9,14; examples 89,595,596 -----	1-4, 7-14,22
X	EP 1 277 754 A (YAMANOUCHI PHARMA CO LTD [JP]; LUDWIG INST CANCER RES [US]; IMP CANCER) 22 January 2003 (2003-01-22) compounds R1,68,134 -----	1
X	EP 1 050 535 A (ONO PHARMACEUTICAL CO [JP]) 8 November 2000 (2000-11-08) examples; claim 7 -----	1,22
X	EP 1 719 756 A (BANYU PHARMA CO LTD [JP]) 8 November 2006 (2006-11-08)  paragraph [0430]; claim 14 -----	1-3,5, 7-10,15, 22
X	WO 2006/135667 A (SQUIBB BRISTOL MYERS CO [US]; LI JAMES J [US]; HAMANN LAWRENCE G [US];) 21 December 2006 (2006-12-21) the whole document -----	1-23
E	WO 2008/060488 A (MERCK & CO INC [US]; COX JASON M [US]; DONG HONG [US]) 22 May 2008 (2008-05-22) claim 17; examples 5,7,50,52 -----	1-23

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/060395

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2005042537	A	12-05-2005	US 2008167304 A1 US 2005143398 A1	10-07-2008 30-06-2005
WO 2006138657	A	28-12-2006	US 2006287324 A1	21-12-2006
WO 2006138682	A	28-12-2006	EP 1891074 A1 NO 20076357 B US 2006287323 A1	27-02-2008 14-03-2008 21-12-2006
WO 2004021984	A	18-03-2004	AU 2003270065 A1 BR 0314024 A CA 2496842 A1 CN 1678372 A EP 1551511 A2 HR 20050188 A2 IS 7719 A JP 2006502162 T KR 20050040933 A MX PA05002301 A NZ 538166 A	29-03-2004 19-07-2005 18-03-2004 05-10-2005 13-07-2005 31-12-2005 28-02-2005 19-01-2006 03-05-2005 08-06-2005 26-01-2007
EP 1277754	A	22-01-2003	AT 300540 T AU 5260901 A CA 2407573 A1 CN 1426413 A CN 1600783 A DE 60112272 D1 DE 60112272 T2 DK 1277754 T3 ES 2244613 T3 WO 0183481 A1 JP 3729343 B2	15-08-2005 12-11-2001 08-11-2001 25-06-2003 30-03-2005 01-09-2005 24-05-2006 14-11-2005 16-12-2005 08-11-2001 21-12-2005
EP 1050535	A	08-11-2000	AU 9651198 A BR 9814628 A CA 2310072 A1 CN 1285834 A HU 0004359 A2 WO 9924434 A1 NO 20002451 A TR 200001728 T2 US 6451796 B1 ZA 9810271 A	31-05-1999 27-11-2001 20-05-1999 28-02-2001 28-10-2001 20-05-1999 11-07-2000 21-09-2000 17-09-2002 20-05-1999
EP 1719756	A	08-11-2006	AU 2005212096 A1 CA 2556404 A1 CN 1922183 A WO 2005077953 A1 US 2007167453 A1	25-08-2005 25-08-2005 28-02-2007 25-08-2005 19-07-2007
WO 2006135667	A	21-12-2006	AR 057357 A1 AU 2006258077 A1 EP 1912986 A1 KR 20080018942 A NO 20076054 B US 2006281750 A1	28-11-2007 21-12-2006 23-04-2008 28-02-2008 04-03-2008 14-12-2006
WO 2008060488	A	22-05-2008	NONE	