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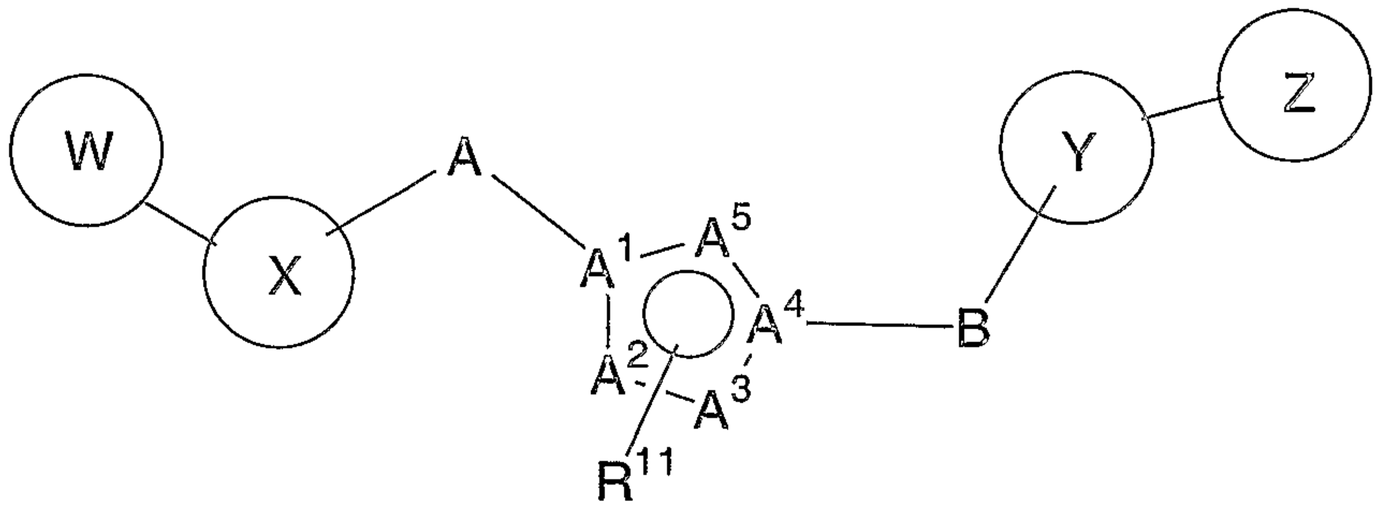
(54) Titre : MODULATEURS AU TRIAZOLE A SUBSTITUTION DIARYLE DU RECEPTEUR-5 DE GLUTAMATE METABOTROPIQUE

(54) Title: DI-ARYL SUBSTITUTED TRIAZOLE MODULATORS OF METABOTROPIC GLUTAMATE RECEPTOR-5



(I)

(57) Abrégé/Abstract:
Novel triazole compounds represented by Formula (I): (where A, A^1, A^2, A^3, A^4, A^5, B, R^{11}, W, X, Y and Z are as defined herein) in which the triazole is substituted directly, or by a bridge, with i) a heteroaryl moiety containing N adjacent to the point of connection of the heteroaryl and ii) another heteroaryl or aryl ring, with at least one of the rings being further substituted with another ring, are mGluR5 modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, panic, and bipolar disorder, as well as in the treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, circadian rhythm disorders, drug addiction, drug abuse, drug withdrawal, obesity and other diseases.

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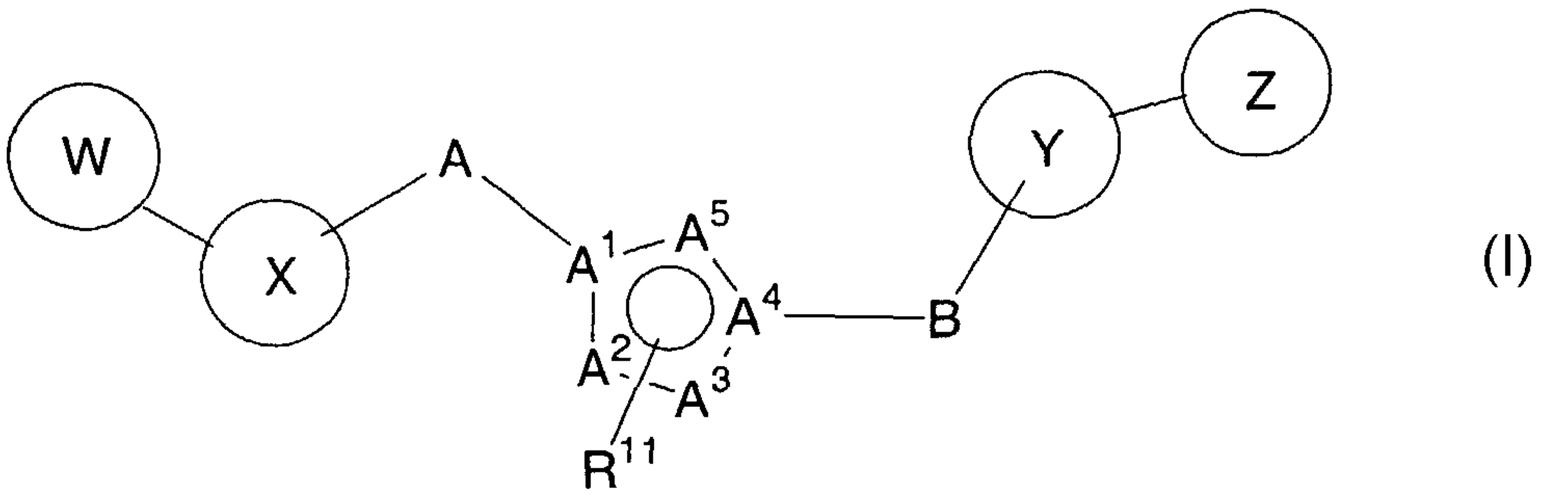
(54) Title: DI-ARYL SUBSTITUTED TRIAZOLE MODULATORS OF METABOTROPIC GLUTAMATE RECEPTOR-5



(I)

(57) Abstract: Novel triazole compounds represented by Formula (I): (where A, A^1, A^2, A^3, A^4, A^5, B, R^{11}, W, X, Y and Z are as defined herein) in which the triazole is substituted directly, or by a bridge, with i) a heteroaryl moiety containing N adjacent to the point of connection of the heteroaryl and ii) another heteroaryl or aryl ring, with at least one of the rings being further substituted with another ring, are mGluR5 modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, panic, and bipolar disorder, as well as in the treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, circadian rhythm disorders, drug addiction, drug abuse, drug withdrawal, obesity and other diseases.

WO 2004/089306 A3

TITLE OF THE INVENTION

DI-ARYL SUBSTITUTED TRIAZOLE MODULATORS OF METABOTROPIC GLUTAMATE RECEPTOR-5

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention is directed to triazole compounds substituted with i) a heteroaryl ring and ii) another heteroaryl or aryl ring with at least one of the rings being further substituted with another ring. In particular, this invention is directed to triazole compounds substituted directly, or by a bridge, with i) a heteroaryl moiety containing N adjacent to the point of connection of the heteroaryl and ii) another heteroaryl or aryl ring, with at least one of the rings being further substituted with another ring, which are metabotropic glutamate receptor – subtype 5 ("mGluR5") modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, panic, bipolar disorder, and circadian rhythm disorders, as well as in the treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, drug addiction, drug abuse, drug withdrawal, obesity and other diseases.

RELATED BACKGROUND

A major excitatory neurotransmitter in the mammalian nervous system is the glutamate molecule, which binds to neurons, thereby activating cell surface receptors. Such surface receptors are characterized as either ionotropic or metabotropic glutamate receptors. The metabotropic glutamate receptors ("mGluR") are G protein-coupled receptors that activate intracellular second messenger systems when bound to glutamate. Activation of mGluR results in a variety of cellular responses. In particular, mGluR1 and mGluR5 activate phospholipase C, which is followed by mobilizing intracellular calcium.

Modulation of metabotropic glutamate receptor subtype 5 (mGluR5) is useful in the treatment of diseases that affect the nervous system (see for example W.P.J.M Spooren et al., *Trends Pharmacol. Sci.*, 22:331-337 (2001) and references cited therein). For example, recent evidence demonstrates the involvement of mGluR5 in nociceptive processes and that modulation of mGluR5 using mGluR5-selective compounds is useful in the treatment of various pain states, including acute, persistent and chronic pain [K Walker et al., *Neuropharmacology*, 40:1-9 (2001); F. Bordi, A. Ugolini *Brain Res.*, 871:223-233 (2001)], inflammatory pain [K Walker et al., *Neuropharmacology*, 40:10-19 (2001); Bhave et al. *Nature Neurosci.* 4:417-423 (2001)] and neuropathic pain [Dogrul et al. *Neurosci. Lett.* 292:115-118 (2000)].

Further evidence supports the use of modulators of mGluR5 in the treatment of psychiatric and neurological disorders. For example, mGluR5-selective compounds such as 2-methyl-6-(phenylethynyl)-pyridine ("MPEP") are effective in animal models of mood disorders, including anxiety and depression [W.P.J.M Spooren et al., *J. Pharmacol. Exp. Ther.*, 295:1267-1275 (2000); E. Tatarczynska et al, *Brit. J. Pharmacol.*, 132:1423-1430 (2001); A. Klodzynska et al, *Pol. J. Pharmacol.*, 132:1423-1430 (2001)]. Gene expression data from humans indicate that modulation of mGluR5 may be useful for the treatment of schizophrenia [T. Ohnuma et al, *Mol. Brain. Res.*, 56:207-217 (1998); *ibid*, *Mol. Brain. Res.*, 85:24-31 (2000)]. Studies have also shown a role for mGluR5, and the potential utility of mGluR5-modulatory compounds, in the treatment of movement disorders such as Parkinson's disease [W.P.J.M Spooren et al., *Europ. J. Pharmacol.* 406:403-410 (2000); H. Awad et al., *J. Neurosci.* 20:7871-7879 (2000); K. Ossawa et al. *Neuropharmacol.* 41:413-420 (2001)]. Other research supports a role for mGluR5 modulation in the treatment of cognitive dysfunction [G. Riedel et al, *Neuropharmacol.* 39:1943-1951 (2000)], epilepsy [A. Chapman et al, *Neuropharmacol.* 39:1567-1574 (2000)] and neuroprotection [V. Bruno et al, *Neuropharmacol.* 39:2223-2230 (2000)]. Studies with mGluR5 knockout mice and MPEP also suggest that modulation of these receptors may be useful in the treatment of drug addiction, drug abuse and drug withdrawal [C. Chiamulera et al. *Nature Neurosci.* 4:873-874 (2001)].

International Patent Publications WO 01/12627 and WO 99/26927 describe heteropolycyclic compounds and their use as metabotropic glutamate receptor antagonists.

S. Kamiya et al., *Chem. Pharm. Bull.*, 38(12):3226-3229(1990) describes 1-(4-methoxy phenyl)-3-pyridyl-5-hydroxy-triazole and 1-phenyl-3-pyridyl-5-hydroxy-triazole.

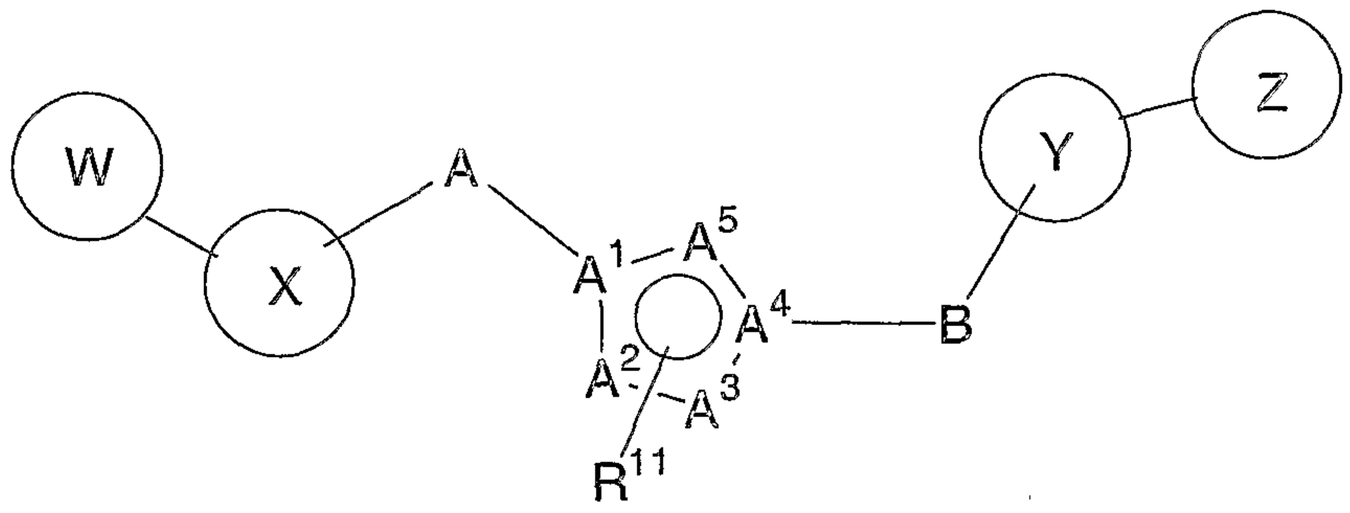
U.S. Patent No. 3,647,809 describes pyridyl-1,2,4-oxadiazole derivatives. U.S. Patent No. 4,022,901 describes 3-pyridyl-5-isothiocyanophenyl oxadiazoles. International Patent Publication WO 98/17652 describes oxadiazoles, WO 97/03967 describes various substituted aromatic compounds, and WO 94/22846 describes various heterocyclic compounds.

Compounds that include ringed systems are described by various investigators as effective for a variety of therapies and utilities. For example, International Patent Publication No. WO 98/25883 describes ketobenzamides as calpain inhibitors, European Patent Publication No. EP 811610 and U.S. Patent Nos. 5,679,712, 5,693,672 and 5,747,541describe substituted benzoylguanidine sodium channel blockers, and U.S. Patent No. 5,736,297 describes ring systems useful as a photosensitive composition.

However, there remains a need for novel compounds and compositions that therapeutically inhibit mGluR5 with minimal side effects.

SUMMARY OF THE INVENTION

The present invention is directed to novel triazole compounds represented by Formula (I):



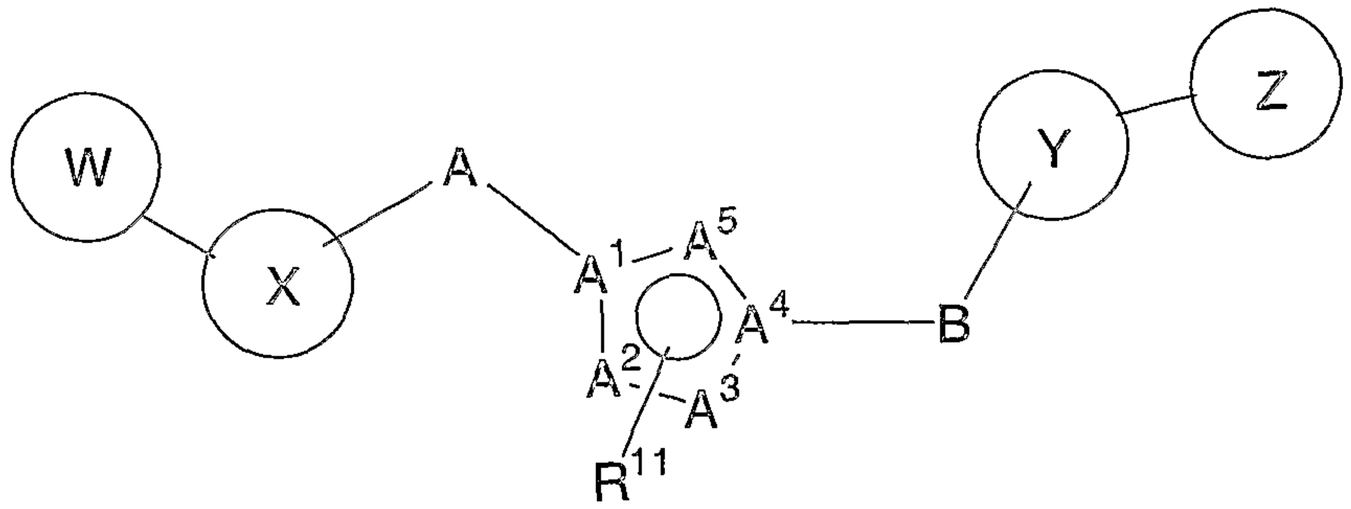
(I)

(where A, A^1, A^2, A^3, A^4, A^5, B, R^{11}, W, X, Y and Z are as defined herein) wherein the triazole is substituted directly, or by a bridge, with i) a heteroaryl moiety containing N adjacent to the point of connection of the heteroaryl and ii) another heteroaryl or aryl ring, with at least one of the rings being further substituted with another ring, which are metabotropic glutamate receptor – subtype 5 modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, bipolar disorders, and panic, as well as in the treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, circadian rhythm and sleep disorders – such as shift-work induced sleep disorder and jet-lag, drug addiction, drug abuse, drug withdrawal, obesity and other diseases. This invention also provides a pharmaceutical composition which includes an effective amount of the novel triazole compounds substituted with a heteroaryl moiety, and a pharmaceutically acceptable carrier.

This invention further provides a method of treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, panic, bipolar disorders, and circadian rhythm and sleep disorders, as well as a method of treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, obesity, drug addiction, drug abuse and drug withdrawal by the administration of an effective amount of the novel triazole compounds substituted with a heteroaryl moiety.

DETAILED DESCRIPTION OF THE INVENTION

A compound of this invention is represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X and Y each independently is aryl or heteroaryl wherein at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively;

three of A^1, A^2, A^3, A^4, and A^5 are N, the remaining are C, and one of A^1 and A^4 must be N, but not both A^1 and A^4 are N;

W is $-C_{3-7}$cycloalkyl, $-$heteroC_{3-7}cycloalkyl, $-C_{0-6}$alkylaryl, or $-C_{0-6}$alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, -C_{1-6}alkenyl, -C_{1-6}alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$, $-SR^4$, -SOR^4, $-SO_2R^4$, $-SO_2NR^1R^2$, -COR^1, -CO_2R^1, $-CONR^1R^2$, -$C(=NR^1)R^2$, or -$C(=NOR^1)R^2$ substituents;

X is optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$, $-SR^4$, -SOR^4, $-SO_2R^4$, $-SO_2NR^1R^2$, -COR^1, -CO_2R^1, $-CONR^1R^2$, -$C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the $-C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), –O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or $-N(C_{0-6}$alkyl)(aryl) groups;

R^1, R^2, and R^3 each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), –O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or $-N(C_{0-6}$alkyl)(aryl) substituents;

R^4 is $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), -O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), $-N(C_{0-6}$alkyl)(C_{3-7}cycloalkyl), or $-N(C_{0-6}$alkyl)(aryl) substituents;

A is –C_{0-4}alkyl, –C_{0-2}alkyl–SO–C_{0-2}alkyl–, –C_{0-2}alkyl–SO_2–C_{0-2}alkyl–, –C_{0-2}alkyl–CO–C_{0-2}alkyl–, –C_{0-2}alkyl–NR^9CO–C_{0-2}alkyl–, –C_{0-2}alkyl–NR^9SO_2–C_{0-2}alkyl– or –heteroC_{0-4}alkyl;

Y is optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, –C_{2-6}alkenyl, –C_{2-6}alkynyl, -OR^5, –NR^5R^6, -$C(=NR^5)NR^6R^7$, -$N(=NR^5)NR^6R^7$, –NR^5COR^6, -$NR^5CO_2R^6$, -$NR^5SO_2R^8$, –$NR^5CONR^6R^7$,–SR^8, -SOR^8, –SO_2R^8, –$SO_2NR^5R^6$, -COR^5, -CO_2R^5, –$CONR^5R^6$, -$C(=NR^5)R^6$, or –$C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the –C_{1-6}alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), –O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) groups;

R^5, R^6, and R^7 each independently is –C_{0-6}alkyl, –C_{3-7}cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), –O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) substituents;

R^8 is –C_{1-6}alkyl, –C_{3-7}cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), -O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), –N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) substituents;

B is –C_{0-4}alkyl, –C_{0-2}alkyl–SO–C_{0-2}alkyl–, –C_{0-2}alkyl–SO_2–C_{0-2}alkyl–, –C_{0-2}alkyl–CO–C_{0-2}alkyl–, –C_{0-2}alkyl–NR^{10}CO–C_{0-2}alkyl–, –C_{0-2}alkyl–$NR^{10}SO_2$–C_{0-2}alkyl–, or –heteroC_{0-4}alkyl;

R^9 and R^{10} each independently is –C_{0-6}alkyl, –C_{3-7}cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), –O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), –N(C_{0-6}alkyl)(aryl) substituents;

Z is –C_{3-7}cycloalkyl, –heteroC_{3-7}cycloalkyl, –C_{0-6}alkylaryl, or –C_{0-6}alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, -C_{1-6}alkenyl, -C_{1-6}alkynyl, -OR^1, –NR^1R^2, –$C(=NR^1)NR^2R^3$, -$N(=NR^1)NR^2R^3$, –NR^1COR^2, -$NR^1CO_2R^2$, -$NR^1SO_2R^4$, –$NR^1CONR^2R^3$,–SR^4, -SOR^4, –SO_2R^4, –$SO_2NR^1R^2$, -COR^1, -CO_2R^1, –$CONR^1R^2$, -$C(=NR^1)R^2$, or -$C(=NOR^1)R^2$ substituents;R^{11} is halogen, –C_{0-6}alkyl, –C_{0-6}alkoxyl, =O, =N(C_{0-4}alkyl),or –N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^{11} is halogen, –C_{0-6}alkyl, –C_{0-6}alkoxyl, =O, =N(C_{0-4}alkyl),or –N(C_{0-4}alkyl)(C_{0-4}alkyl);

any alkyl optionally substituted with 1-5 independent halogen substitutents;

any N may be an N-oxide; and

one of W and Z is optionally absent.

In one embodiment, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

three of A^1, A^2, A^3, A^4, and A^5 are N, the remaining are C, and one of A^1 and A^4 must be N, but not both A^1 and A^4 are N;

W is $-C_{3-7}$cycloalkyl, $-$heteroC$_{3-7}$cycloalkyl, $-C_{0-6}$alkylaryl, or $-C_{0-6}$alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, -C_{1-6}alkenyl, -C_{1-6}alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$,$-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;

X is 2-pyridyl optionally substituted with 1-4 independent halogen, -CN, NO_2, -C_{1-6}alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$,$-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the $-C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), -O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or $-N(C_{0-6}$alkyl)(aryl) groups;

R^1, R^2, and R^3 each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), –O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), $-N(C_{0-6}$alkyl)(aryl) substituents;

R^4 is $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), -O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), $-N(C_{0-6}$alkyl)(C_{3-7}cycloalkyl), $-N(C_{0-6}$alkyl)(aryl) substituents;

A is $-C_{0-4}$alkyl, $-C_{0-2}$alkyl–SO–C_{0-2}alkyl–, $-C_{0-2}$alkyl–SO_2–C_{0-2}alkyl–, $-C_{0-2}$alkyl–CO–C_{0-2}alkyl–, $-C_{0-2}$alkyl–NR^9CO–C_{0-2}alkyl–, $-C_{0-2}$alkyl–NR^1SO_2–C_{0-2}alkyl– or –heteroC$_{0-4}$alkyl;

Y is aryl or heteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-OR^5$, $-NR^5R^6$, $-C(=NR^5)NR^6R^7$, $-N(=NR^5)NR^6R^7$, $-NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^8$, $-NR^5CONR^6R^7$,$-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^5R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-C(=NR^5)R^6$, or $-C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the $-C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5

independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), –O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) groups;

R^5, R^6, and R^7 each independently is –C_{0-6}alkyl, –C_{3-7}cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), –O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), –N(C_{0-6}alkyl)(aryl) substituents;

R^8 is –C_{1-6}alkyl, –C_{3-7}cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), -O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), –N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), –N(C_{0-6}alkyl)(aryl) substituents;

B is –C_{0-4}alkyl, –C_{0-2}alkyl–SO–C_{0-2}alkyl–, –C_{0-2}alkyl–SO_2–C_{0-2}alkyl–, –C_{0-2}alkyl–CO–C_{0-2}alkyl–, –C_{0-2}alkyl–NR^{10}CO–C_{0-2}alkyl–, –C_{0-2}alkyl–NR^1SO_2–C_{0-2}alkyl– or –heteroC_{0-4}alkyl;

R^9 and R^{10} each independently is –C_{0-6}alkyl, –C_{3-7}cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), –O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), –N(C_{0-6}alkyl)(aryl) substituents;

Z is –C_{3-7}cycloalkyl, –heteroC_{3-7}cycloalkyl, –C_{0-6}alkylaryl, or –C_{0-6}alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, -C_{1-6}alkenyl, -C_{1-6}alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;R^{11} is halogen, –C_{0-6}alkyl, –C_{0-6}alkoxyl, =O, =N(C_{0-4}alkyl),or –N(C_{0-4}alkyl)(C_{0-4}alkyl);

R^{11} is halogen, –C_{0-6}alkyl, –C_{0-6}alkoxyl, =O, =N(C_{0-4}alkyl),or –N(C_{0-4}alkyl)(C_{0-4}alkyl);

any alkyl optionally substituted with 1-5 independent halogen substitutents;

any N may be an N-oxide; and

one of W and Z is optionally absent.

In another embodiment, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

three of A^1, A^2, A^3, A^4, and A^5 are N, the remaining are C, and one of A^1 and A^4 must be N, but not both A^1 and A^4 are N;

W is –C_{3-7}cycloalkyl, –heteroC_{3-7}cycloalkyl, –C_{0-6}alkylaryl, or –C_{0-6}alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, -C_{1-6}alkenyl, -C_{1-6}alkynyl,

$-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;

X is aryl or heteroaryl optionally substituted with 1-7 independent halogen, -CN, NO_2, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the $-C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, -O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $-N(C_{0-6}alkyl)$(aryl) groups;

R^1, R^2, and R^3 each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)$(aryl) substituents;

R^4 is $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, -O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)$(aryl) substituents;

A is $-C_{0-4}$alkyl, $-C_{0-2}alkyl-SO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-SO_2-C_{0-2}alkyl-$, $-C_{0-2}alkyl-CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^9CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^1SO_2-C_{0-2}alkyl-$ or –heteroC_{0-4}alkyl;

Y is phenyl optionally substituted with 1-5 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-OR^5$, $-NR^5R^6$, $-C(=NR^5)NR^6R^7$, $-N(=NR^5)NR^6R^7$, $-NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^8$, $-NR^5CONR^6R^7$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^5R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-C(=NR^5)R^6$, or $-C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the $-C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $-N(C_{0-6}alkyl)$(aryl) groups;

R^5, R^6, and R^7 each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)$(aryl) substituents;

R^8 is $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), -O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), $-N(C_{0-6}$alkyl)(C_{3-7}cycloalkyl), $-N(C_{0-6}$alkyl)(aryl) substituents;

B is $-C_{0-4}$alkyl, $-C_{0-2}$alkyl–SO–C_{0-2}alkyl–, $-C_{0-2}$alkyl–SO_2–C_{0-2}alkyl–, $-C_{0-2}$alkyl–CO–C_{0-2}alkyl–, $-C_{0-2}$alkyl–NR^{10}CO–C_{0-2}alkyl–, $-C_{0-2}$alkyl–NR^1SO_2–C_{0-2}alkyl– or –heteroC_{0-4}alkyl;

R^9 and R^{10} each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), –O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), $-N(C_{0-6}$alkyl)(C_{3-7}cycloalkyl), $-N(C_{0-6}$alkyl)(aryl) substituents;

Z is $-C_{3-7}$cycloalkyl, –heteroC_{3-7}cycloalkyl, $-C_{0-6}$alkylaryl, or $-C_{0-6}$alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $-C_{1-6}$alkenyl, $-C_{1-6}$alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$,–SR^4, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;R^{11} is halogen, $-C_{0-6}$alkyl, $-C_{0-6}$alkoxyl, =O, $=N(C_{0-4}$alkyl),or $-N(C_{0-4}$alkyl)(C_{0-4}alkyl);

R^{11} is halogen, $-C_{0-6}$alkyl, $-C_{0-6}$alkoxyl, =O, $=N(C_{0-4}$alkyl),or $-N(C_{0-4}$alkyl)(C_{0-4}alkyl);

any alkyl optionally substituted with 1-5 independent halogen substitutents;

any N may be an N-oxide, and

one of W and Z is optionally absent..

In still another embodiment, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

three of A^1, A^2, A^3, A^4, and A^5 are N, the remaining are C, and one of A^1 and A^4 must be N, but not both A^1 and A^4 are N;

W is $-C_{3-7}$cycloalkyl, –heteroC_{3-7}cycloalkyl, $-C_{0-6}$alkylaryl, or $-C_{0-6}$alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $-C_{1-6}$alkenyl, $-C_{1-6}$alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$,–SR^4, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;

X aryl or heteroaryl optionally substituted with 1-7 independent hydrogen, halogen, -CN, NO_2, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$,–SR^4, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents, wherein optionally two substituents

are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the $-C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, -O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $-N(C_{0-6}alkyl)$(aryl) groups;

R^1, R^2, and R^3 each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)$(aryl) substituents;

R^4 is $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, -O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)$(aryl) substituents;

A is $-C_{0-4}$alkyl, $-C_{0-2}alkyl-SO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-SO_2-C_{0-2}alkyl-$, $-C_{0-2}alkyl-CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^9CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^1SO_2-C_{0-2}alkyl-$ or $-heteroC_{0-4}$alkyl;

Y is aryl or heteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-OR^5$, $-NR^5R^6$, $-C(=NR^5)NR^6R^7$, $-N(=NR^5)NR^6R^7$, $-NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^8$, $-NR^5CONR^6R^7$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^5R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-C(=NR^5)R^6$, or $-C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the $-C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $-N(C_{0-6}alkyl)$(aryl) groups;

R^5, R^6, and R^7 each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)$(aryl) substituents;

R^8 is $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, -O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)$(aryl) substituents;

B is $-C_{0-4}$alkyl, $-C_{0-2}alkyl-SO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-SO_2-C_{0-2}alkyl-$, $-C_{0-2}alkyl-CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^{10}CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^1SO_2-C_{0-2}alkyl-$ or $-heteroC_{0-4}$alkyl;

R^9 and R^{10} each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, –

$O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $–N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $–N(C_{0-6}alkyl)$(aryl) substituents;

Z is $–C_{0-6}$alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $-C_{1-6}$alkenyl, $-C_{1-6}$alkynyl, $–OR^1$, $–NR^1R^2$, $–C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $–NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $–NR^1CONR^2R^3$,$–SR^4$, $-SOR^4$, $–SO_2R^4$, $–SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $–CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;R^{11} is halogen, $–C_{0-6}$alkyl, $–C_{0-6}$alkoxyl, =O, $=N(C_{0-4}alkyl)$,or $–N(C_{0-4}alkyl)(C_{0-4}alkyl)$;

R^{11} is halogen, $–C_{0-6}$alkyl, $–C_{0-6}$alkoxyl, =O, $=N(C_{0-4}alkyl)$,or $–N(C_{0-4}alkyl)(C_{0-4}alkyl)$;

any alkyl is optionally substituted with 1-5 independent halogen substitutents;

any N may be an N-oxide, and

one of W and Z is optionally absent.

In another embodiment, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is 2-pyridyl optionally substituted with 1-4 independent halogen, -CN, NO_2, $-C_{1-6}$alkyl, $–C_{2-6}$alkenyl, $–C_{2-6}$alkynyl, $–OR^1$, $–NR^1R^2$, $–C(=NR^1)NR^2R^3$, $–N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $–NR^1CONR^2R^3$,$–SR^4$, $-SOR^4$, $–SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $–CONR^1R^2$, $-C(=NR^1)R^2$, or $–C(=NOR^1)R^2$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the $–C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $–C_{1-6}$alkyl, $–O(C_{0-6}alkyl)$, $–O(C_{3-7}cycloalkyl)$, -O(aryl), –O(heteroaryl), $–N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $–N(C_{0-6}alkyl)$(aryl) groups; and

Y is aryl or heteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $–C_{2-6}$alkenyl, $–C_{2-6}$alkynyl, $-OR^5$, $–NR^5R^6$, $-C(=NR^5)NR^6R^7$, $-N(=NR^5)NR^6R^7$, $–NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^8$, $–NR^5CONR^6R^7$,$–SR^8$, $-SOR^8$, $–SO_2R^8$, $–SO_2NR^5R^6$, $-COR^5$, $-CO_2R^5$, $–CONR^5R^6$, $-C(=NR^5)R^6$, or $–C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the $–C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $–C_{1-6}$alkyl, $–O(C_{0-6}alkyl)$, $–O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $–N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $–N(C_{0-6}alkyl)$(aryl) groups.

In an embodiment of the invention, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is aryl or heteroaryl optionally substituted with 1-7 independent halogen, -CN, NO_2, -C_{1-6}alkyl, –C_{2-6}alkenyl, –C_{2-6}alkynyl, –OR^1, –NR^1R^2, –$C(=NR^1)NR^2R^3$, –$N(=NR^1)NR^2R^3$, -NR^1COR^2, -$NR^1CO_2R^2$, -$NR^1SO_2R^4$, –$NR^1CONR^2R^3$,–SR^4, -SOR^4, –SO_2R^4, -$SO_2NR^1R^2$, -COR^1, -CO_2R^1, –$CONR^1R^2$, -$C(=NR^1)R^2$, or –$C(=NOR^1)R^2$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the –C_{1-6}alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), -O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) groups; and

Y is phenyl optionally substituted with 1-5 independent halogen, –CN, NO_2, -C_{1-6}alkyl, –C_{2-6}alkenyl, –C_{2-6}alkynyl, -OR^5, –NR^5R^6, -$C(=NR^5)NR^6R^7$, -$N(=NR^5)NR^6R^7$, –NR^5COR^6, -$NR^5CO_2R^6$, -$NR^5SO_2R^8$, –$NR^5CONR^6R^7$,–SR^8, -SOR^8, –SO_2R^8, –$SO_2NR^5R^6$, -COR^5, -CO_2R^5, –$CONR^5R^6$, -$C(=NR^5)R^6$, or –$C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the –C_{1-6}alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), –O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) groups.

In another embodiment, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is aryl or heteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, –C_{2-6}alkenyl, –C_{2-6}alkynyl, –OR^1, –NR^1R^2, –$C(=NR^1)NR^2R^3$, –$N(=NR^1)NR^2R^3$, -NR^1COR^2, -$NR^1CO_2R^2$, -$NR^1SO_2R^4$, –$NR^1CONR^2R^3$,–SR^4, -SOR^4, –SO_2R^4, -$SO_2NR^1R^2$, -COR^1, -CO_2R^1, –$CONR^1R^2$, -$C(=NR^1)R^2$, or –$C(=NOR^1)R^2$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the –C_{1-6}alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), -O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) groups; Y is aryl or heteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, –C_{2-6}alkenyl, –C_{2-6}alkynyl, -OR^5, –NR^5R^6, -$C(=NR^5)NR^6R^7$, -$N(=NR^5)NR^6R^7$, –NR^5COR^6, -$NR^5CO_2R^6$, -$NR^5SO_2R^8$, –$NR^5CONR^6R^7$,–SR^8, -SOR^8, –SO_2R^8, –$SO_2NR^5R^6$, -COR^5, -CO_2R^5, –$CONR^5R^6$, -$C(=NR^5)R^6$, or –$C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the –C_{1-6}alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent

halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), –O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) groups; and

Z is –C_{0-6}alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, -C_{1-6}alkenyl, -C_{1-6}alkynyl, –OR^1, –NR^1R^2, –$C(=NR^1)NR^2R^3$, -$N(=NR^1)NR^2R^3$, –NR^1COR^2, -$NR^1CO_2R^2$, -$NR^1SO_2R^4$, –$NR^1CONR^2R^3$,–SR^4, -SOR^4, –SO_2R^4, –$SO_2NR^1R^2$, -COR^1, -CO_2R^1, –$CONR^1R^2$, -$C(=NR^1)R^2$, or -$C(=NOR^1)R^2$ substituents;R^{11} is halogen, –C_{0-6}alkyl, –C_{0-6}alkoxyl, =O, =N(C_{0-4}alkyl),or –N(C_{0-4}alkyl)(C_{0-4}alkyl).

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The terms “group” and “groups,” “substituent” and “substituents” are used within this application interchangeably.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term “aryl” means an aromatic substituent which is a single ring or multiple rings fused together. When formed of multiple rings, at least one of the constituent rings is aromatic. The preferred aryl substituents are phenyl and naphthyl groups.

The term “cycloalkyloxy” unless specifically stated otherwise includes a cycloalkyl group connected by a short C_{1-2}alkyl length to the oxy connecting atom.

The term “C_{0-6}alkyl” includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminal group and is a direct bond when the alkyl is a bridging group.

The term "hetero" unless specifically stated otherwise includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a heterocycloC5alkyl is a five-member ring containing from 4 to no carbon atoms. Examples of heteroaryls include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl. Examples of heterocycloalkyls include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "heteroC$_{0-4}$alkyl" means a heteroalkyl containing 3, 2, 1, or no carbon atoms. However, at least one heteroatom must be present. Thus, as an example, a heteroC$_{0-4}$alkyl having no carbon atoms but one N atom would be a -NH– if a bridging group and a –NH$_2$ if a terminal group. Analogous bridging or terminal groups are clear for an O or S heteroatom.

The term "amine" unless specifically stated otherwise includes primary, secondary and tertiary amines substituted with C$_{0-6}$alkyl.

The term "carbonyl" unless specifically stated otherwise includes a C$_{0-6}$alkyl substituent group when the carbonyl is terminal.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. Further, optionally substituted multiple moieties such as, for example, alkylaryl are intended to mean that the aryl and the aryl groups are optionally substituted. If only one of the multiple moieties is optionally substituted then it will be specifically recited such as "an alkylaryl, the aryl optionally substituted with halogen or hydroxyl."

Compounds described herein contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers.

Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization

procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Such additional therapeutic ingredients include, for example, i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) GABA-A receptor modulators, x) dopamine agonists or antagonists, xi) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), xii) tricyclic antidepressant drugs, xiv) norepinephrine modulators, xv) L-DOPA, xvi) buspirone, xvii) lithium, xviii) valproate, ixx) neurontin (gabapentin), xx) olanzapine, xxi) nicotinic agonists or antagonists including nicotine, xxii) muscarinic agonists or antagonists, xxiii) heroin substituting drugs such as methadone, levo-alpha-acetylmethadol,

buprenorphine and naltrexone, and xxiv) disulfiram and acamprosate. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

Creams, ointments, jellies, solutions, or suspensions containing the compound of Formula I can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, panic, bipolar disorders, and circadian disorders, as well as being useful in the treatment of pain which are responsive to mGluR5 inhibition, or alternatively about 0.5mg to about 7g per patient per day. For example, schizophrenia, anxiety, depression, and panic may be effectively treated by the administration of from about 0.01mg to 75mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Pain may be effectively treated by the administration of from about 0.01mg to 125mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 5.5g per patient per day. Further, it is understood that the mGluR5 inhibiting compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 1000mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g.,

oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1mg,

1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as mGluR5 inhibitors. Accordingly, another aspect of the invention is the treatment in mammals of, for example, schizophrenia, anxiety, depression, panic, bipolar disorders, circadian rhythm and sleep disorders, pain, Parkinson's disease, cognitive dysfunction, epilepsy, drug addiction, drug abuse and drug withdrawal – maladies that are amenable to amelioration through inhibition of mGluR5 – by the administration of an effective amount of the compounds of this invention. The term "mammals" includes humans, as well as other animals such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than humans is the treatment of clinical correlating afflictions to those above recited examples that are human afflictions.

Further, as described above, the compound of this invention can be utilized in combination with other therapeutic compounds. In particular, the combinations of the mGluR5 inhibiting compound of this invention can be advantageously used in combination with i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) GABA-A receptor modulators, x) dopamine agonists or antagonists, xi) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), xii) tricyclic antidepressant drugs, xiii) norepinephrine modulators, xiv) L-DOPA, xv) buspirone, xvi) lithium, xvii) valproate, xviii) neurontin (gabapentin), xix) olanzapine, xx) nicotinic agonists or antagonists including nicotine, xxi) muscarinic agonists or antagonists, xxii) heroin substituting drugs such as methadone, levo-alpha-acetylmethadol, buprenorphine and naltrexone, and xxiii) disulfiram and acamprosate.

The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
BINAP	1,1'-bi-2-naphthol
Bn	benzyl
CAMP	cyclic adenosine-3',5'-monophosphate
DAST	(diethylamino)sulfur trifluoride
DEAD	diethyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide

dppf	1,1'-bis(diphenylphosphino)-ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_3N	triethylamine
GST	glutathione transferase
HMDS	hexamethyldisilazide
LDA	lithium diisopropylamide
m-CPBA	metachloroperbenzoic acid
MMPP	monoperoxyphthalic acid
MPPM	monoperoxyphthalic acid, magnesium salt $6H_2O$
Ms	methanesulfonyl = mesyl = SO_2Me
Ms0	methanesulfonate = mesylate
NBS	N-bromo succinimide
NSAID	non-steroidal anti-inflammatory drug
o-Tol	ortho-tolyl
OXONE®	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
PCC	pyridinium chlorochromate
$Pd_2(dba)_3$	Bis(dibenzylideneacetone) palladium(0)
PDC	pyridinium dichromate
PDE	Phosphodiesterase
Ph	Phenyl
Phe	Benzenediyl
PMB	para-methoxybenzyl
Pye	Pyridinediyl
r.t.	room temperature
Rac.	Racemic
SAM	aminosulfonyl or sulfonamide or SO_2NH_2
SEM	2-(trimethylsilyl)ethoxymethoxy
SPA	scintillation proximity assay
TBAF	tetra-n-butylammonium fluoride
Th	2- or 3-thienyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	Tetrahydrofuran

Thi	Thiophenediyl
TLC	thin layer chromatography
TMS-CN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
Tz	1H (or 2H)-tetrazol-5-yl
XANTPHOS	4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene
C_3H_5	Allyl

ALKYL GROUP ABBREVIATIONS

Me	=	Methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

ASSAYS DEMONSTRATING BIOLOGICAL ACTIVITY

The compounds of this invention were tested against the hmGluR5a receptor stably expressed in mouse fibroblast Ltk$^-$ cells (the hmGluR5a/L38-20 cell line) and activity was detected by changes in $[Ca^{++}]_i$, measured using the fluorescent Ca^{++}-sensitive dye, fura-2. InsP assays were performed in mouse fibroblast Ltk$^-$ cells (LM5a cell line) stably expressing hmGluR5a. The assays described in International Patent Publication WO 0116121 can be used.

Calcium Flux Assay

The activity of compounds was examined against the hmGluR5a receptor stably expressed in mouse fibroblast Ltk- cells (the hmGluR5a/L38 cell line). See generally Daggett et al., *Neuropharmacology* 34:871-886 (1995). Receptor activity was detected by changes in intracellular calcium ($[Ca^{2+}]_i$) measured using the fluorescent calcium-sensitive dye, fura-2. The hmGluR5a/L38-20 cells were plated onto 96-well plates, and loaded with 3 μM fura-2 for 1h. Unincorporated dye was washed from the cells, and the cell plate was transferred to a 96-channel fluorimeter (SIBIA-SAIC, La Jolla, CA) which is integrated into a fully automated plate handling and liquid delivery system. Cells were excited at 350 and 385nm with a xenon source combined with optical filters. Emitted light was collected from the sample through a dichroic mirror and a 510nm interference filter and directed into a cooled CCD camera (Princeton Instruments). Image pairs were captured approximately every 1s, and ratio images were generated after background subtraction. After a basal reading of 20s, an EC_{80} concentration of glutamate (10μM) was added to the well, and the response evaluated for another 60s. The glutamate-evoked increase in $[Ca']_i$ in the presence of the screening compound was compared to the response of glutamate alone (the positive control).

Phosphatidylinositol hydrolysis (PI) assays

Inositolphosphate assays were performed as described by Berridge et al. [Berridge et al, *Biochem. J.* 206: 587-5950 (1982); and Nakajima et al., *J. Biol. Chem.* 267:2437-2442 (1992)] with slight modifications. Mouse fibroblast Ltk cells expressing hmGluR5 (hmGluR5/L38- 20 cells) were seeded in 24-well plates at a density of 8x105cells/well. One μCi of [^{3}H]-inositol (Amersham PT6-271; Arlington Heights, Ill.; specific activity = 17.7 Ci/mmol) was added to each well and incubated for 16h at 37°C. Cells were washed twice and incubated for 45min in 0.5mL of standard Hepes buffered saline buffer (HBS; 125mM NaCl, 5mM KCl, 0.62mM $MgSO_4$, 1.8mM $CaCl_2$, 20mM HEPES, 6mM glucose, pH to 7.4). The cells were washed with HBS containing 10mM LiCl, and 400μL buffer added to each well. Cells were incubated at 37°C for 20min. For testing, 50μL of 10X compounds used in the practice of the invention (made in HBS/LiCl (100mM)) was added and incubated for 10 minutes. Cells were activated by the addition of 10μM glutamate, and the plates left for 1 hour at 37°C. The incubations were terminated by the addition of 1mL ice-cold methanol to each well. In order to isolate inositol phosphates (IPs), the cells were scraped from wells, and placed in numbered glass test tubes. One mL of chloroform was added to each tube, the tubes were mixed, and the phases separated by centrifugation. IPs were separated on Dowex anion exchange columns (AG 1-X8 100-200 mesh formate form). The upper aqueous layer (750μL) was added to the Dowex columns, and the columns eluted with 3mL of distilled water. The eluents were discarded, and the columns were washed with 10mLs of 60mM ammonium formate/5mM Borax, which was also discarded as waste. Finally, the columns were eluted with 4mL of 800mM ammonium formate/0.1M formic acid, and the samples collected in scintillation

vials. Scintillant was added to each vial, and the vials shaken, and counted in a scintillation counter after 2 hours. Phosphatidylinositol hydrolysis in cells treated with certain exemplary compounds was compared to phosphatidylinositol hydrolysis in cells treated with the agonist alone in the absence of compound.

The compounds of this application have mGluR5 inhibitory activity as shown by IC_{50} values of less than 10 μM in the calcium flux assay or inhibition of >50% at a concentration of 100 μM in the PI assay. Preferably, the compounds should have IC_{50} values of less than 1 μM in the calcium flux assay and IC_{50} values of less than 10 μM in the PI assay. Even more preferably, the compounds should have IC_{50} values of less than 100 nM in the calcium flux assay and IC_{50} values of less than 1 μM in the PI assay.

Examples 1-10 have mGluR5 inhibitory activity as shown by IC_{50} values of 10 μM or better in the calcium flux assay and/or inhibition of >50% at 100 μM concentration in the PI assay.

The examples that follow are intended as an illustration of certain preferred embodiments of the invention and no limitation of the invention is implied.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room or ambient temperature - that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. When given, yields are for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300MHz, 400MHz or 500MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations are used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)),mL (milliliters), g (gram(s)),mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

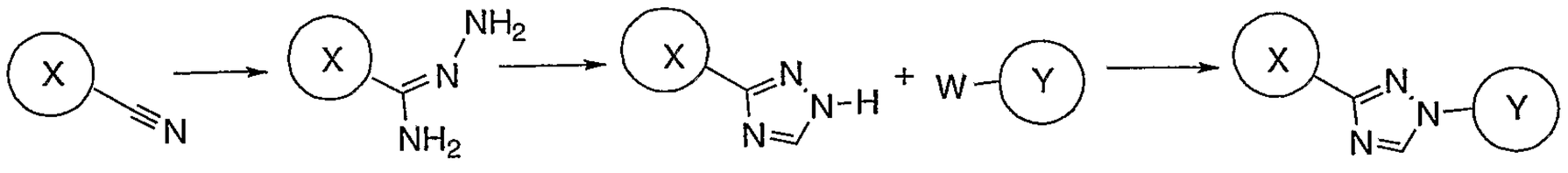
Methods of Synthesis

Compounds of the present invention can be prepared according to the following methods shown in the reaction schemes below. Accordingly, the present invention provides methods for the preparation of the novel heteroaryl-substituted triazole compounds. Some of the novel heterocyclic

compounds of this invention can be prepared using synthetic chemistry techniques well known in the art (see *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R. and Rees, C. W. eds., Pergamon Press, Oxford, 1984) starting from a heteroaryl-substituted triazole of the present invention (Formula (I)).

In Schemes 1 to 10 the substituents are the same as in Formula I except where defined otherwise. Thus, in **Scheme 1** below, X and Y are as defined above. Substituents such as R_1 and R_2 are clear from context to correspond to, or to yield, the substituents described in Formula (**I**).

Scheme 1



Thus in **Scheme 1**, ring system X containing a nitrile moiety (prepared using synthetic chemistry techniques well known in the art) is reacted with hydrazine hydrate in a suitable solvent (*e.g.* EtOH, MeOH, iPrOH, H_2O *etc.*) at a temperature from 0°C to 100°C, with 25°C being presently preferred, for a sufficient period of time (typically about 12 to 18h) to form a substituted amidrazone derivative (see for example Hage, R. *et al. .J. Chem. Soc. Dalton Trans.* **1987**, 1389-1395). The resulting amidrazone is then cyclized under the appropriate conditions (*e.g.* hot HCO_2H, or trialkylorthoformate with a catalytic amount of acid) to provide a monosubstituted 1,2,4-triazole derivative as shown (see Sugiyarto, J. H. *et al. Aust. J. Chem.* **1995**, *48*, 35-54 and Beck, J. R.; Babbitt, G. E.; Lynch, M. P. .*J. Heterocyclic Chem.* **1988**, *25*, 1467-1470).

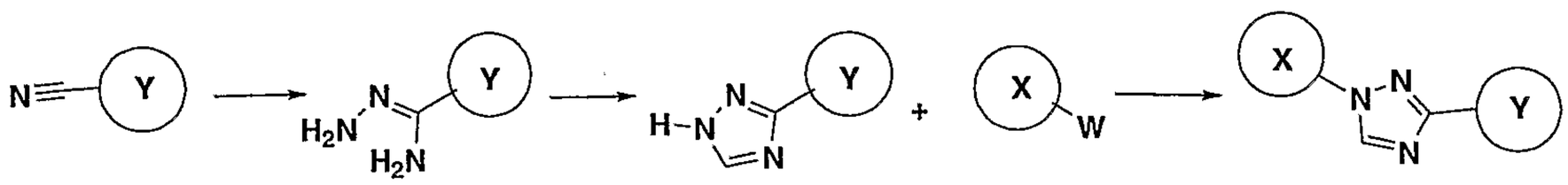
As shown in **Scheme 1**, the 1,2,4-triazole may then be coupled with a species **Y** substituted with a group **W**. **W** maybe a metalloid species such as $B(OR)_2$, BiLn and the like and the reaction maybe promoted with stoichiometric or catalytic amounts of metal salts such as $Cu(OAc)_2$, CuI or CuOTf and the like. Typically, a base (*e.g.* pyridine, NEt_3, Cs_2CO_3, K_2CO_3 *etc.*) will also be present and the reaction carried out in a suitable solvent (*e.g.* DCM, THF, DME, toluene, MeCN, DMF, H_2O *etc.*). Additionally, molecular sieves may be used as a cocatalyst (see for example Fedorov, A. Y.; Finet, J-P. *Tetrahedron Lett.* **1999**, *40*, 2747-2748). Alternatively, **W** maybe a halogen or other functional group capable of undergoing a metal catalyzed *N*-arylation cross-coupling reaction. In which case, additional promoters such as 1,10-phenanthroline and dibenzylideneacetone may also be added to the reaction mixture. The cross-coupling reaction may be carried out at ambient temperature or heated to a temperature anywhere between about 30°C to 150°C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to 72 hours, with 18 hours typically being sufficient. The product from the reaction can be isolated and purified employing standard techniques,

such as solvent extraction, chromatography, crystallization, distillation and the like (see for example Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Cham, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944 and Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657-2660).

In another embodiment of the present invention when W is a good aryl leaving group such as F, and Y is electron deficient or has one or more electron withdrawing substituents (*e.g.* NO_2, CN *etc.*), the coupling reaction may be effected thermally in a temperature range of about 60°C up to about 250°C. Typically, this reaction is carried out in the presence of base (*e.g.* pyridine, NEt_3, Cs_2CO_3, K_2CO_3 *etc.*) in a suitable solvent, such as DMSO, DMF, DMA H_2O and the like, and takes from 1h up to about 72h with 18 hours typically being sufficient (see for example Russell, S. S.; Jahangir; *Synth.Commun.* **1994**, *24*, 123-130).

In another embodiment of the invention, the compounds of the present invention can be made as shown in **Scheme 2** below.

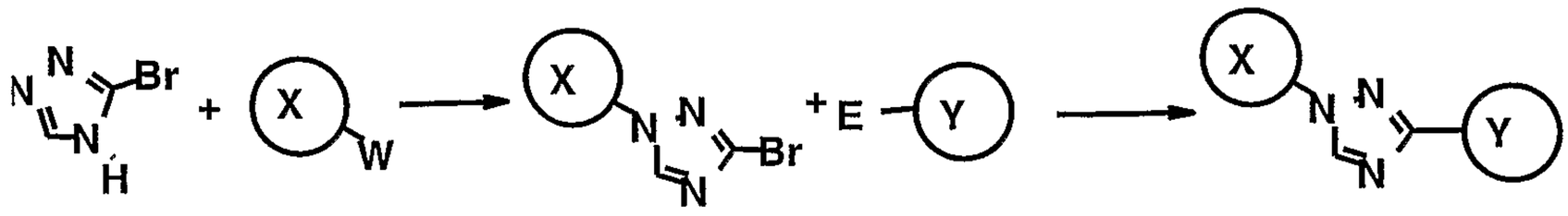
Scheme 2



In **Scheme 2** the same synthetic chemistry is employed as for **Scheme 1** but the nitrile functional group is now attached to **Y,** and **W** is bonded to ring system **X**. The product disubstituted 1,2,4-triazoles from **Schemes 1** and **2** can be isolated and purified employing standard techniques, such as solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like.

In another embodiment of the present invention, the compounds of the invention can be made as illustrated in **Scheme 3** below.

Scheme 3



Thus, 3-bromo-1,2,4-triazole, prepared using synthetic chemistry well known to those skilled in the art (see for example Bagal, L. I. et al. *Khim. Geterotsikl. Soedin.* **1970**, *6*, 1701-1703), may be coupled with a species X substituted with a group **W** to provide a halogenated 1,2,4-triazole derivative. **W** maybe a metalloid species such as $B(OR)_2$, BiLn and the like and the reaction maybe promoted with stoichiometric or catalytic amounts of metal salts such as $Cu(OAc)_2$, CuI or CuOTf and the like. Typically, a base (*e.g.* pyridine, NEt_3, Cs_2CO_3, K_2CO_3 *etc.*) will also be present and the reaction

carried out in a suitable solvent (*e.g.* DCM, THF, DME, toluene, MeCN, DMF, H_2O *etc.*). Additionally, molecular sieves may be used as a cocatalyst (see for example Fedorov, A. Y.; Finet, J-P. *Tetrahedron Lett.* **1999**, *40*, 2747-2748).

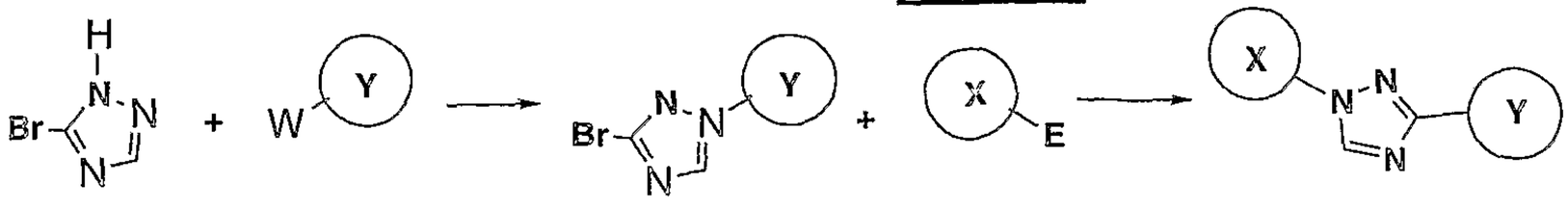
Alternatively, W may be a halogen or other functional group capable of undergoing a metal catalyzed *N*-arylation cross-coupling reaction in which case additional promoters such as 1,10-phenanthroline and dibenzylideneacetone may also be added to the reaction mixture. The cross-coupling reaction maybe carried out at ambient temperature or heated to a temperature anywhere between about 30°C to 150°C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to 72 hours, with 18 hours typically being sufficient (see for example Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Cham, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944 and Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657-2660).

In another embodiment of the present invention, when **W** is a good aryl leaving group such as F, and **Y** is electron deficient or has one or more electron withdrawing substituents (*e.g.* NO_2, CN *etc.*), the coupling reaction may be effected thermally in a temperature range of about 60°C up to about 250°C. Typically, this reaction is carried out in the presence of base (*e.g.* pyridine, NEt_3, Cs_2CO_3, K_2CO_3 *etc.*) in a suitable solvent, such as DMSO, DMF, DMA H_2O and the like, and takes from 1h up to about 72h with 18 hours typically being sufficient (see for example Russell, S. S.; Jahangir; *Synth.Commun.* **1994**, *24*, 123-130). The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like.

In turn, the halogenated 1,2,4-triazole derivative prepared in **Scheme 3** is reacted with a species **Y** under metal-catalyzed cross-coupling conditions where **E** is a metallic or metalloid species such as $B(OR)_2$, Li, MgHal, SnR_3, ZnHal, SiR_3 and the like which is capable of undergoing a metal-catalyzed cross-coupling reaction. The coupling may be promoted by a homogeneous catalyst such as $Pd(PPh_3)_4$, or by a heterogeneous catalyst such as Pd on carbon in a suitable solvent (*e.g.* THF, DME, toluene, MeCN, DMF, H_2O *etc.*). Typically a base, such as K_2CO_3, NEt_3, and the like, will also be present in the reaction mixture. Other promoters may also be used such as CsF. The coupling reaction is typically allowed to proceed by allowing the reaction temperature to warm slowly from about 0°C up to ambient temperature over a period of several hours. The reaction mixture is then maintained at ambient temperature, or heated to a temperature anywhere between about 30°C to150°C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to 48 hours, with about 18 hours typically being sufficient (see for example Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483). The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like.

In another embodiment of the present invention, the compounds of the invention are made as illustrated in **Scheme 4** below.

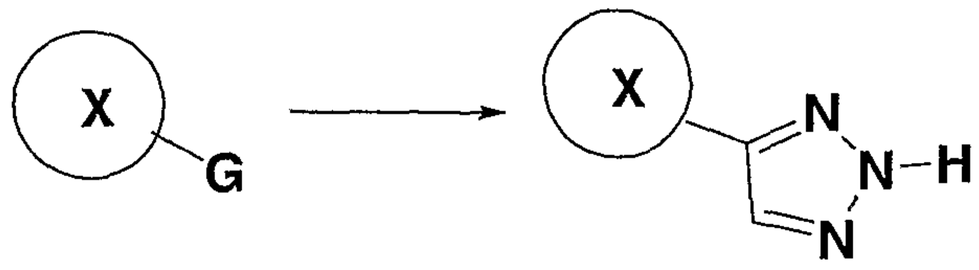
Scheme 4



In **Scheme 4**, the same synthetic chemistry is employed as in **Scheme 3**, but the **W** functional group is now attached to the species **Y**, and **E** is bonded to ring system **X**. The product disubstituted 1,2,4-triazole from **Scheme 4** can be isolated and purified employing standard techniques, such as solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like.

Another embodiment of the present invention is illustrated in **Scheme 5** below.

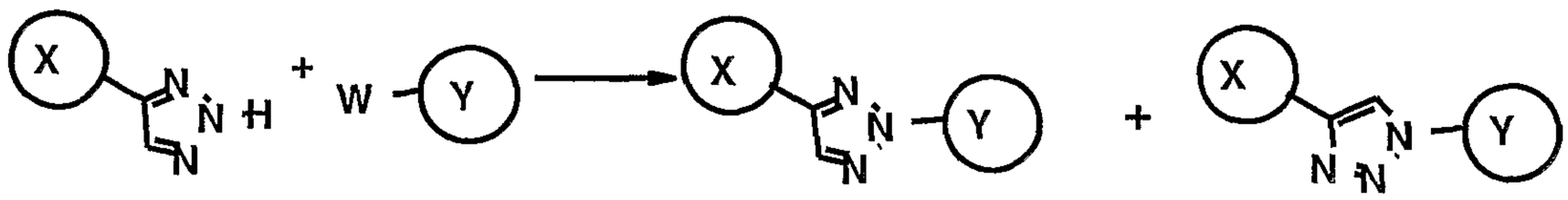
Scheme 5



Thus, in **Scheme 5** species **X** (prepared using methods well known in the art) contains a functional group **G** which may be an alkynyl or a 2-nitroethenyl moiety. Species **X** is reacted with an azide moiety, such as LiN_3, NaN_3 or $TMSN_3$, in a suitable solvent (*e.g.* toluene, benzene, xylenes *etc.*) at a temperature in the range of about 25°C up to about 180°C to form a monosubstituted triazole. This reaction is often performed in the presence of added catalyst such as tetrabutylammonium fluoride or dibutyltin oxide (see for example Moltzen, E. K.; Pedersen, H.; Boegesoe, K. P.; Meier, E.; Frederiksen, K. *J.Med.Chem.* **1994**, 37, 4085-4099).

In an embodiment, the compounds of this invention can be made according to **Scheme 6** below:

Scheme 6



The resulting 1,2,3-triazole from **Scheme 5** may then be coupled with a species **Y** substituted with a group **W**. **W** maybe a metalloid species such as $B(OR)_2$, BiLn and the like; the reaction may be promoted with stoichiometric or catalytic amounts of metal salts such as $Cu(OAc)_2$, CuI or CuOTf and the like. Typically, a base (*e.g.* pyridine, NEt_3, Cs_2CO_3, K_2CO_3 *etc.*) will also be present

and the reaction is carried out in a suitable solvent (*e.g.* DCM, THF, DME toluene, MeCN, DMF, H_2O *etc.*). Additionally, molecular sieves maybe used as a cocatalyst (see for example Fedorov, A. Y.; Finet, J-P. *Tetrahedron Lett.* **1999**, *40*, 2747-2748).

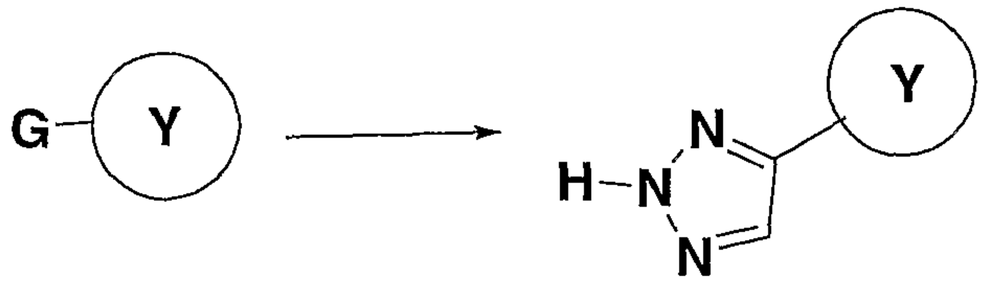
Alternatively, W may be a halogen or other functional group capable of undergoing a metal catalyzed *N*-arylation cross-coupling reaction. In which case, additional promoters such as 1,10-phenanthroline and dibenzylideneacetone may also be added to the reaction mixture. The cross-coupling reaction maybe carried out at ambient temperature or heated to a temperature anywhere between about 30°C to 150°C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to 72 hours, with 18 hours typically being sufficient (see for example Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Cham, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944 and Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657-2660).

In another embodiment of the present invention, when **W** is a good aryl leaving group such as F, and **Y** is electron deficient or has one or more electron withdrawing substituents (*e.g.* NO_2, CN *etc.*), the coupling reaction may be effected thermally in a temperature range of about 60°C up to about 250°C. Typically, this reaction is carried out in the presence of base (*e.g.* pyridine, NEt_3, Cs_2CO_3, K_2CO_3 *etc.*) in a suitable solvent, such as DMSO, DMF, DMA H_2O and the like, and takes from 1h up to about 72h with 18 hours typically being sufficient (see for example Russell, S. S.; Jahangir; *Synth.Commun.* **1994**, *24*, 123-130).

The products from **Scheme 6**, two isomeric disubstituted 1,2,3-triazoles, can be separated and purified employing standard techniques, such as solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like.

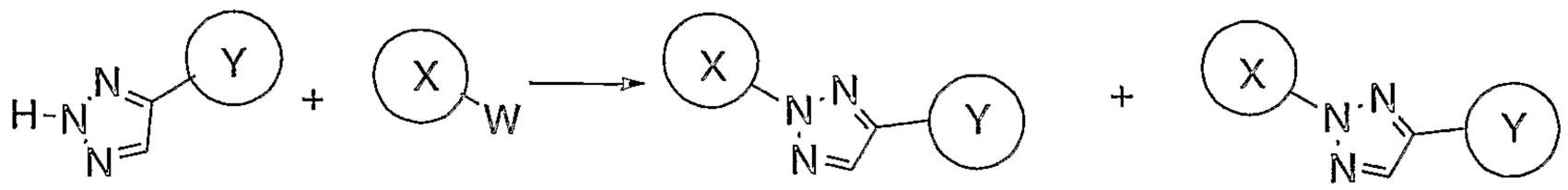
Another embodiment of the present invention is illustrated in **Scheme 7** and **8** below.

Scheme 7



Thus, in **Scheme** 7 species **Y** (prepared using methods well known in the art) contains a functional group **G** which may be an alkynyl or a 2-nitroethenyl moiety. Species **Y** is reacted with an azide moiety, such as LiN_3, NaN_3 or $TMSN_3$, in a suitable solvent (*e.g.* toluene, benzene, xylenes *etc.*) at a temperature in the range of about 25°C up to about 180°C to form a monosubstituted triazole. This reaction is often performed in the presence of added catalyst such as tetrabutylammonium fluoride or dibutyltin oxide (see for example Moltzen, E. K.; Pedersen, H.; Boegesoe, K. P.; Meier, E.; Frederiksen, K. *J.Med.Chem.* **1994**, 37, 4085-4099).

Scheme 8



The resulting 1,2,3-triazole from **Scheme 7** may then be coupled with a species X substituted with a group **W** (**Scheme 8**). **W** may be a metalloid species such as $B(OR)_2$, BiLn and the like and the reaction may be promoted with stoichiometric or catalytic amounts of metal salts such as $Cu(OAc)_2$, CuI or CuOTf and the like. Typically a base (*e.g.* pyridine, NEt_3, Cs_2CO_3, K_2CO_3 *etc.*) will also be present and the reaction is carried out in a suitable solvent (*e.g.* DCM, THF, DME toluene, MeCN, DMF, H_2O *etc.*). Additionally, molecular sieves maybe used as a cocatalyst (see for example Fedorov, A. Y.; Finet, J-P. *Tetrahedron Lett.* **1999**, *40*, 2747-2748).

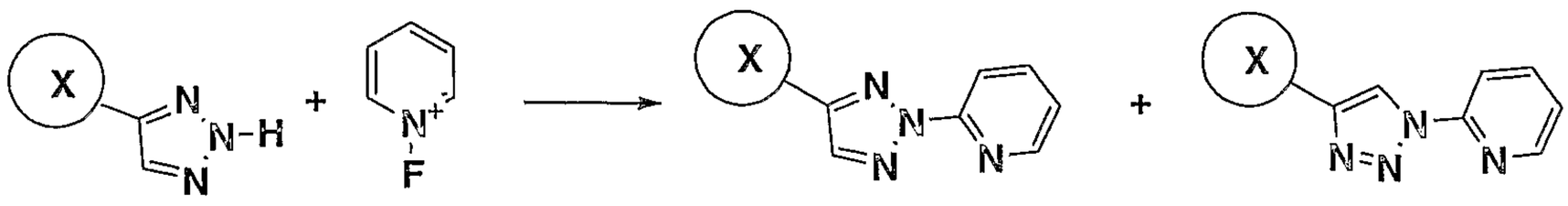
Alternatively, **W** may be a halogen or other functional group capable of undergoing a metal catalyzed *N*-arylation cross-coupling reaction in which case additional promoters such as 1,10-phenanthroline and dibenzylideneacetone may also be added to the reaction mixture. The cross-coupling reaction maybe carried out at ambient temperature or heated to a temperature anywhere between about 30°C to 150°C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to 72 hours, with 18 hours typically being sufficient (see for example Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Cham, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944 and Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657-2660).

In another embodiment of the present invention, when **W** is a good aryl leaving group such as F, and **Y** is electron deficient or has one or more electron withdrawing substituents (*e.g.* NO_2, CN *etc.*), the coupling reaction may be effected thermally in a temperature range of about 60°C up to about 250° C. Typically this reaction is carried out in the presence of base (*e.g.* pyridine, NEt_3, Cs_2CO_3, K_2CO_3 *etc.*) in a suitable solvent, such as DMSO, DMF, DMA H_2O and the like, and takes from 1h up to about 72h with 18 hours typically being sufficient (see for example Russell, S. S.; Jahangir; *Synth.Commun.* **1994**, *24*, 123-130).

The products from **Scheme 8**, two isomeric disubstituted 1,2,3-triazoles, can be separated and purified employing standard techniques, such as solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like.

Yet another embodiment of the present invention is illustrated in **Scheme 9** below.

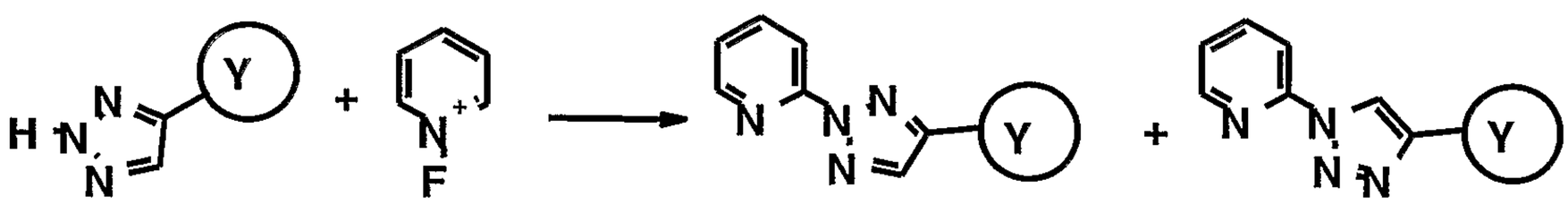
Scheme 9



In **Scheme 9**, the monosubstituted triazole is prepared as in **Scheme 5**. The triazole is then reacted with an *N*-fluoropyridinium salt, which may be optionally substituted, in the presence of a suitable base (*e.g.* MeONa, EtONa, *t*BuOK and the like) for period of about 1 to 12h at a temperature in the range of –100° C to 50° C, with –78° C to 23° C being presently preferred (see for example Kiselyov, A. S. and Strekowski, L. .*J. Heterocyclic Chem.* **1993**, *30*, 1361-1364). The products from **Scheme 9**, isomeric 2-pyridyltriazole derivatives, can be separated and purified employing standard techniques, such as solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like.

A further embodiment of the present invention is illustrated in **Scheme 10** below.

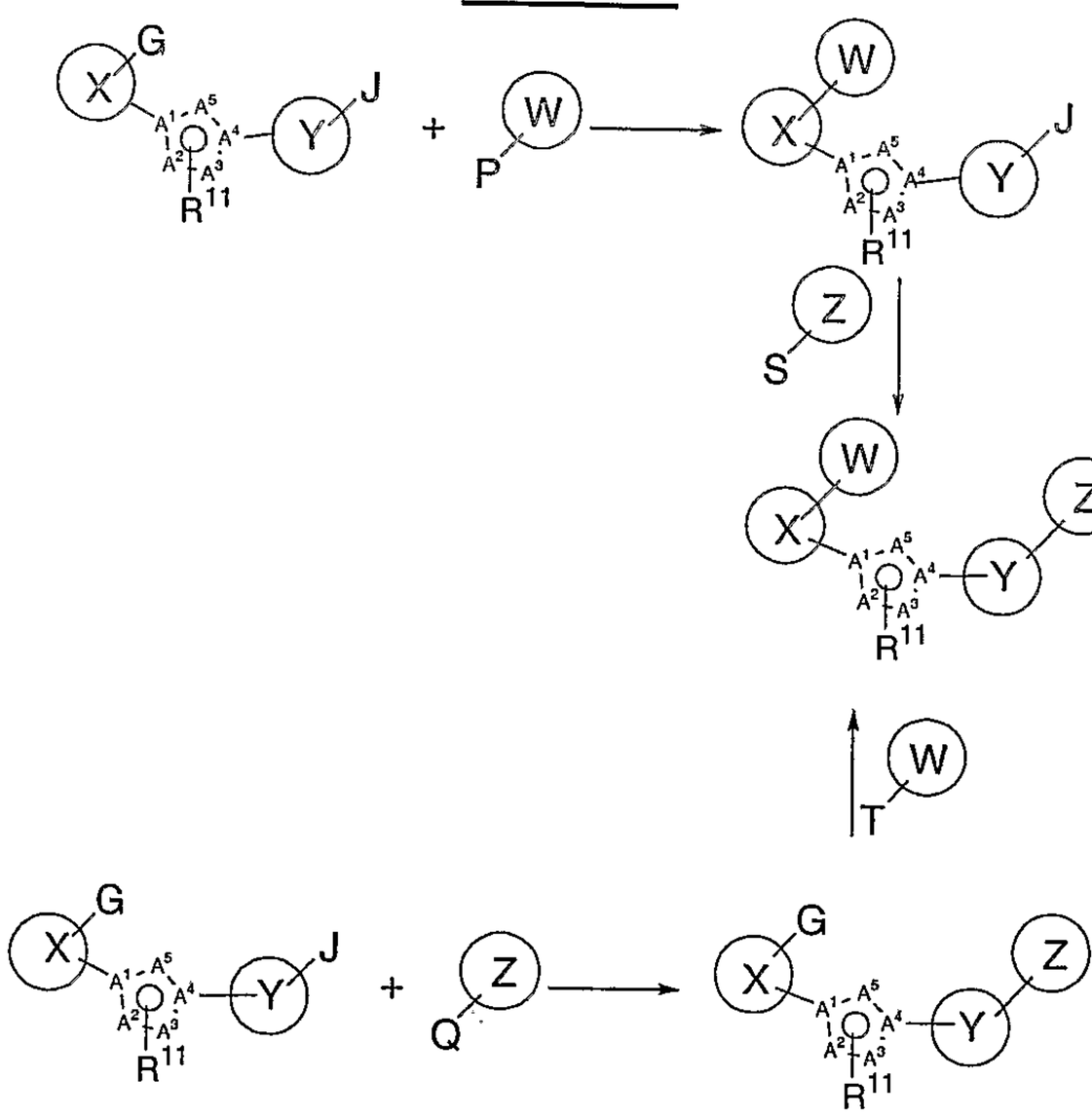
Scheme 10



In **Scheme 10**, the monosubstituted triazole is prepared as in **Scheme 7**. The triazole is then reacted with an *N*-fluoropyridinium salt, which may be optionally substituted, in the presence of a suitable base (*e.g.* MeONa, EtONa, *t*BuOK and the like) for period of about 1 to 12h at a temperature in the range of –100° C to 50° C, with –78° C to 23° C being presently preferred (see for example Kiselyov, A. S. and Strekowski, L. .*J. Heterocyclic Chem.* **1993**, *30*, 1361-1364). The products from Scheme 10, isomeric 2-pyridyltriazole derivatives, can be separated and purified employing standard techniques, such as solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like.

In the schemes above, ring systems X and/or Y may already contain a pendant ring W and/or Z. However, if required, ring systems W and/or Z may be appended to X and/or Y respectively where G and/or J are functional groups capable of undergoing a metal catalyzed-cross coupling (such as halogen, trifluoromethane-sulfonate, $B(OR)_2$, ZnX, SnR_3, and the like -**Scheme 11** below). Ring systems W and Z are substituted with groups P, Q, S and T which may be for example, halogen, trifluoromethanesulfonate, $B(OR)_2$, ZnX, SnR_3, and the like. Typically, a transition metal catalyst such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$, $NiCl_2(dppe)$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $Cu(OAc)_2$, CuI or the like may be employed, typically along with a suitable base such as K_2CO_3, K_3PO_4, Cs_2CO_3, Et_3N, pyridine or the like. Additionally, ligands such as BINAP, di-*tert*-butyl phosphinobiphenyl, di-cyclohexylphosphino biphenyl, tri *tert*-butylphosphine, XANTPHOS, triphenylarsine and the like may be added. The reaction is carried out in a suitable solvent such as toluene, DME, dioxane, THF, water or a combination of the above and is typically heated at 50°C – 150°C for between 1 and 48 hrs. The reaction may be homogeneous or heterogeneous (see for example Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483 and Dai, C.; Fu, G.C *J. Am. Chem. Soc.,* **2001**, *123*, 2719-2724 and Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* **1999**, *38*, 6, 2411-2413 and Dai, C; Fu, G.C. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2724).

Scheme 11



Alternatively ring systems W or Z may be a nitrogen containing heterocycle wherein the nitrogen is directly attached to the ring system X or Y respectively. In this case G and/or J are groups capable of undergoing a metal catalyzed N-aryl cross-coupling (such as halogen, trifluoromethane-sulfonate, $B(OR)_2$, ZnX, SnR_3, and the like – **Scheme 6**). Typically a transition metal such as CuI, $Cu(OAc)_2$, $Cu(OTf)_2$, $Pd(PPh_3)_4$, Pd(PPh3)2Cl2, Pd(OAc)2, $Pd_2(dba)_3$, $NiCl_2(dppe)$ is used along with a suitable base such as as K_2CO_3, K_3PO_4, Cs_2CO_3, NaO*t*Bu or the like. Additionally, phosphine containing ligands such as BINAP, di-*tert*-butyl phosphinobiphenyl, di-cyclohexylphosphino biphenyl, tri *tert*-butylphosphine, XANTPHOS and the like may be added. Further, additives such as 1,10-phenanthroline, 1,2-diaminocyclohexane, dibenzylideneacetone may be used. The reaction is typically carried out in a solvent such as toluene, DME, dioxane, THF, water or a combination of the above and is typically heated at 50°C – 150°C for between 1 and 48 hrs. The reaction may be homogeneous or heterogeneous. The product from **Scheme 11**, can be isolated and purified employing standard techniques, such as solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like (see for example Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Cham, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944 and Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657-2660 and Wolfe, J.P.; Tomori, H.; Sadighi, J.P.; Yin, J.; Buchwald, S.L *J. Org. Chem.*, **2000**, *65*, 1158-1174 and Yin, J.; Buchwald, S.L.; *Org. Lett.*, **2000**, *2*, 1101-1104).

In addition, many of the heterocyclic compounds described above can be prepared using other synthetic chemistry techniques well known in the art (see *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R. and Rees, C. W. eds., Pergamon Press, Oxford, 1984) and references cited there within.

COMPOUND 1

1-(3-Methoxy-4-pyridin-2-ylphenyl)-2-nitroethanol

A THF solution of 3-methoxy-4-pyridin-2-ylbenzaldehyde (0.3 g, 1.4 mmol), nitromethane (0.23 mL, 4.2 mmol) and TEA (0.2 mL, 1.4 mmol) was stirred at 55 °C over night, concentrated and purified on silica gel (2:1 hexane-ethyl acetate) to afford a yellow foam.

COMPOUND 2

2-{2-Methoxy-4-[(*Z*)-2-nitroethenyl]phenyl}pyridine

A solution of 1-(3-methoxy-4-pyridin-2-ylphenyl)-2-nitroethanol (290 mg, 1.06 mmol) in anhydrous dichloromethane (5 mL) was treated with triethylamine (0.24 mL, 1.69 mmol), followed by methanesulfonyl chloride (0.10 mL, 1.27 mmol), 1 hr later, the mixture was partitioned between sat. $NaHCO_3$ (10 mL) and dichloromethane (20 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford a yellow solid.

COMPOUND 3

2-[2-Methoxy-4-(1*H*-1,2,3-triazol-4-yl)phenyl]pyridine

A solution of 2-{2-methoxy-4-[(*Z*)-2-nitroethenyl]phenyl}pyridine (0.23 g, 0.89 mmol) and $TMSN_3$ (0.18 mL, 1.34 mmol) in DMF (1 mL) was heated to slowly to 50 °C while TBAF (0.98 mL, 1.0 M in THF, 0.98 mmol) was added dropwise over 20 min. The resulting reaction mixture was continued to stir at 50 °C for 30 min. The mixture was partitioned between sat. $NaHCO_3$ (20 mL) and EtOAc (60 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified on silica gel (20:1 hexane-ethyl acetate) to afford a yellow solid.

EXAMPLE 1

2-[4-(3-Methoxy-4-pyridin-2-ylphenyl)-2*H*-1,2,3-triazol-2-yl]pyridine

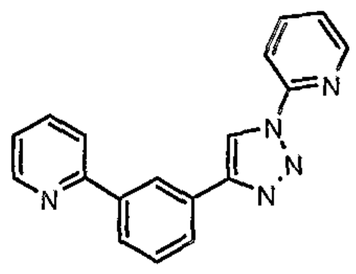
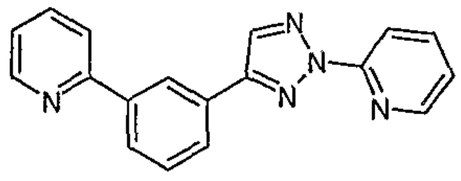
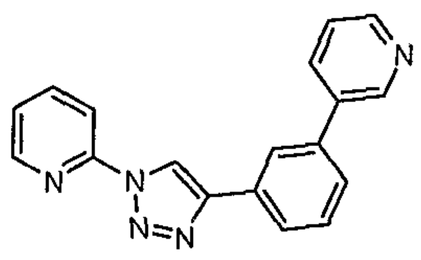
To a solution of 2-[2-methoxy-4-(1*H*-1,2,3-triazol-4-yl)phenyl]pyridine (180 mg, 0.71 mmol) in anhydrous MeOH was added Cs_2CO_3 (462 mg, 1.42 mmol) and 1-fluoropyridinium triflate (350 mg, 1.42 mmol). The resulting reaction mixture was stirred overnight. The mixture was partitioned between 10 % aqueous NaOH (10 ml) and EtOAc (60 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified on silica gel (1:2 hexane-ethyl acetate) to afford 2-[4-(3-methoxy-4-pyridin-2-ylphenyl)-2*H*-1,2,3-triazol-2-yl]pyridine which was dissolved in ether and HCl (1N in ether) was added. The solution was filtered to give a HCl salt as white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.86-8.47 (m, 1H), 8.72-8.68 (m, 1H), 8.64-8.62 (m, 2H), 8.39-8.37 (m, 1H), 8.26-8.25 (m, 1H), 8.15-8.11 (m, 1H), 8.07-8.04 (m, 1H), 8.02 (m, 1H), 7.91-7.80 (m, 2H), 7.60 (m, 1H). MS (ESI) 330 ($M+H^+$).

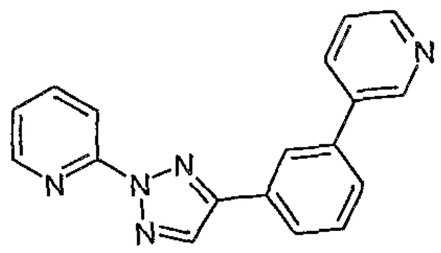
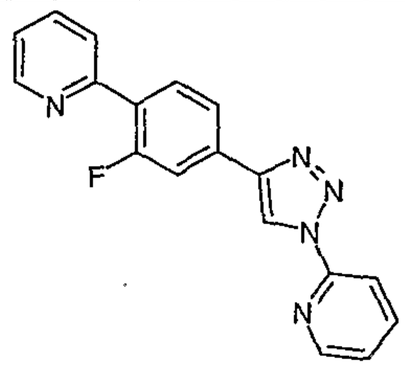
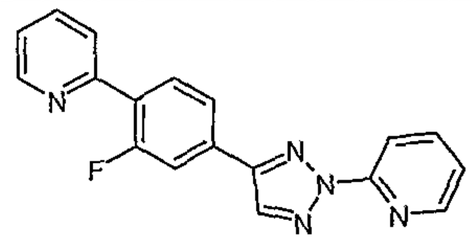
EXAMPLE 2

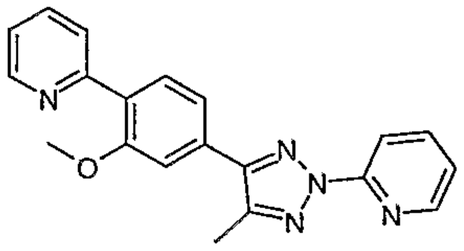
2-[4-(3-methoxy-4-pyridin-2-ylphenyl)-1*H*-1,2,3-triazol-1-yl]pyridine

The title compound was isolated from the reaction described above for 2-[2-methoxy-4-(2-phenyl-2*H*-1,2,3-triazol-4-yl)phenyl]pyridine (**EXAMPLE 1**) to afford the isomer 2-[4-(3-methoxy-4-pyridin-2-ylphenyl)-1*H*-1,2,3-triazol-1-yl]pyridinewhich was dissolved in ether and HCl (1N in ether) was added. The solution was filtered to give a HCl salt as white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 9.41 (s, 1H), 8.85-8.83 (m, 1H), 8.69-8.68 (m, 1H), 8.38-8.37 (m, 2H), 8.24 (m, 1H), 8.12-8.11 (m, 1H), 8.04 (m, 1H), 7.94 (m, 1H), 7.86-7.85 (m, 2H), 7.54 (m, 1H). MS (ESI) 330 ($M+H^+$).

EXAMPLE 3 to **EXAMPLE 10** shown below were prepared similarly to the schemes and procedures described above (ND = not determined).

EXAMPLE	Structure	^{1}H NMR	MS (ESI)	NAME
3		δ 9.34 (s, 1H), 8.90-8.88 (m, 1H), 8.73-8.72 (m, 1H), 8.62-8.61 (m, 1H), 8.60-8.59 (m, 1H), 8.51-8.49 (m, 1H), 8.32-8.30 (m, 1H), 8.26-8.24 (m, 1H), 8.13-8.07 (m, 2H), 7.98-7.97 (m, 1H), 7.84-7.81 (m, 1H), 7.54-7.53 (m, 1H).	300.1 ($M+H^+$)	2-[4-(3-pyridin-2-ylphenyl)-1*H*-1,2,3-triazol-1-yl]pyridine
4		δ 8.82-8.81 (m, 1H), 8.68-8.64 (m, 1H), 8.56 (m, 1H), 8.56-8.52 (m, 2H), 8.45-8.43 (m, 1H), 8.28-8.26 (m, 1H), 8.17 (m, 1H), 8.07-8.00 (m, 2H), 7.94-7.92 (m, 1H), 7.77-7.74 (m, 1H), 7.48-7.43 (m, 1H).	300.1 ($M+H^+$)	2-[4-(3-pyridin-2-ylphenyl)-2*H*-1,2,3-triazol-2-yl]pyridine
5		δ 9.13-9.12 (m, 2H), 8.87-8.84 (m, 1H), 8.71-8.70 (d, 1H), 8.44-8.43 (d, 1H), 8.28-8.27 (m, 1H), 8.07-8.02 (m, 2H), 8.00-7.96 (m, 1H), 7.94-7.91 (m, 1H),	300.1 ($M+H^+$)	2-[4-(3-pyridin-3-ylphenyl)-1*H*-1,2,3-triazol-1-yl]pyridine

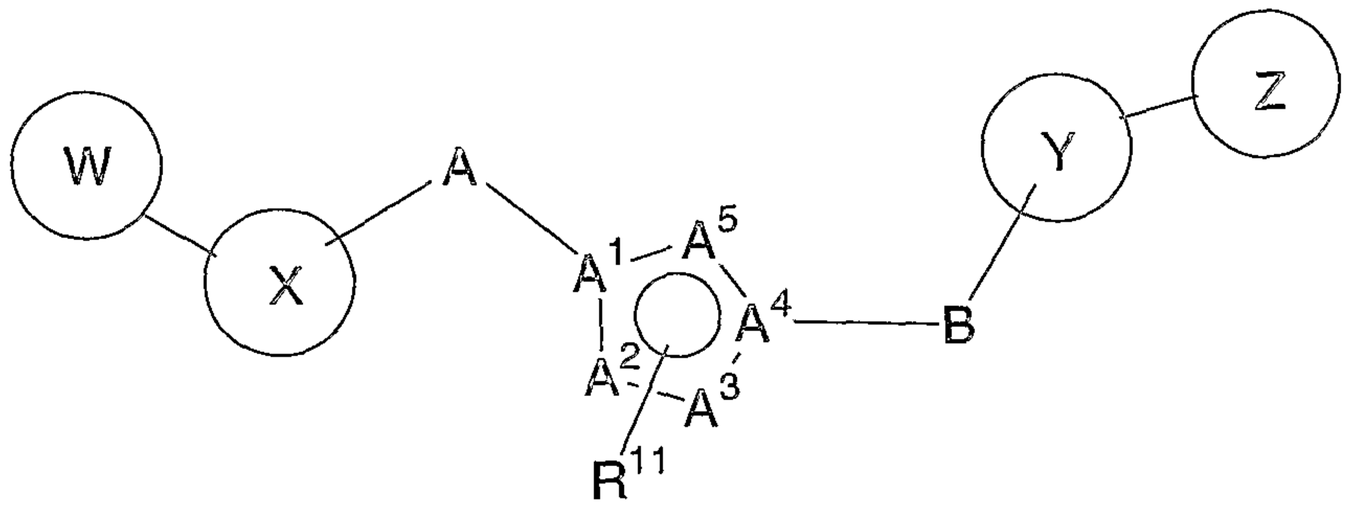
		7.70-7.68 (m, 1H), 7.57-7.54 (m, 1H), 7.36-7.34 (m, 1H).		
6		δ 9.24 (m, 1H), 9.00-8.98 (m, 1H), 8.84-8.8.72 (m, 1H), 8.50-8.46 (m, 3H), 8.18-8.14 (m, 3H), 8.04-8.03 (m, 1H), 7.84-7.83 (m, 1H), 7.69-7.65 (m, 1H), 7.44 (m, 1H).	300.1 ($M+H^+$)	2-[4-(3-pyridin-3-ylphenyl)-2*H*-1,2,3-triazol-2-yl]pyridine
7		δ 9.28-9.27 (m, 1H), 8.69-8.68 (m, 1H), 8.62-8.61 (m, 1H), 8.24-8.22 (m, 1H), 8.12-8.10 (m, 1H), 7.96-7.87(m, 5H), 7.54-7.52 (m, 1H), 7.45-7.42 (m, 1H).	318.1 ($M+H^+$)	2-[4-(3-fluoro-4-pyridin-2-ylphenyl)-1*H*-1,2,3-triazol-1-yl]pyridine
8		δ 8.98-8.97 (m, 1H), 8.80-8.76 (m, 1H), 8.67 (s, 1H), 8.63-8.62 (m, 1H), 8.44-8.41 (m, 1H), 8.31-8.30 (m, 1H), 8.22-8.15 (m, 4H), 8.02-7.98 (m, 1H), 7.61-7.59 (m, 1H).	318.1 ($M+H^+$)	2-[4-(3-fluoro-4-pyridin-2-ylphenyl)-2*H*-1,2,3-triazol-2-yl]pyridine
9		δ 8.62-8.61(m, 1H), 8.55-8.54 (m, 1H), 8.16-8.15 (m, 1H), 8.07-8.04 (m, 1H), 7.87-7.86 (m, 2H), 7.31-7.32 (m, 1H),	344.2 ($M+H^+$)	2-[2-methoxy-4-(5-methyl-1-pyridin-2-yl-1*H*-1,2,3-triazol-4-yl)phenyl]pyridine

		7.69 (m, 1H), 7.57-7.55 (m, 1H), 4.47-7.44 (m, 1H), 7.38-7.36 (m, 1H), 3.97 (s, 3H), 2.68 (s, 3H).		
10		δ 8.63-8.58 (m, 2H), 8.28-8.25 (m, 1H), 8.18-8.17 (m, 1H), 8.09-8.06 (m, 1H), 7.90-7.85 (m, 1H), 7.75-7.67 (m, 2H), 7.56-7.54 (m, 1H), 7.44 (m, 1H), 7.40-7.36 (m, 1H), 3.97 (s, 3H), 2.78 (s, 3H).	344.2 ($M+H^+$)	2-[2-methoxy-4-(5-methyl-2-pyridin-2-yl-2*H*-1,2,3-triazol-4-yl)phenyl]pyridine

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X and Y each independently is aryl or heteroaryl wherein at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively;

three of A^1, A^2, A^3, A^4, and A^5 are N, the remaining are C, and one of A^1 and A^4 must be N, but not both A^1 and A^4 are N;

W is $-C_{3-7}$cycloalkyl, $-$heteroC_{3-7}cycloalkyl, $-C_{0-6}$alkylaryl, or $-C_{0-6}$alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $-C_{1-6}$alkenyl, $-C_{1-6}$alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$,–SR^4, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;

X is optionally substituted with 1-7 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$,–SR^4, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the $-C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), –O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), $-N(C_{0-6}$alkyl)(C_{3-7}cycloalkyl), or $-N(C_{0-6}$alkyl)(aryl) groups;

R^1, R^2, and R^3 each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}$alkyl), $-O(C_{3-7}$cycloalkyl), –O(aryl), –O(heteroaryl), $-N(C_{0-6}$alkyl)(C_{0-6}alkyl), $-N(C_{0-6}$alkyl)(C_{3-7}cycloalkyl), or $-N(C_{0-6}$alkyl)(aryl) substituents;

R^4 is $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, -O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $-N(C_{0-6}alkyl)$(aryl) substituents;

A is $-C_{0-4}$alkyl, $-C_{0-2}alkyl-SO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-SO_2-C_{0-2}alkyl-$, $-C_{0-2}alkyl-CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^9CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^9SO_2-C_{0-2}alkyl-$ or $-heteroC_{0-4}$alkyl;

Y is optionally substituted with 1-7 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-OR^5$, $-NR^5R^6$, $-C(=NR^5)NR^6R^7$, $-N(=NR^5)NR^6R^7$, $-NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^8$, $-NR^5CONR^6R^7$,$-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^5R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-C(=NR^5)R^6$, or $-C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the $-C_{1-6}$alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $-N(C_{0-6}alkyl)$(aryl) groups;

R^5, R^6, and R^7 each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $-N(C_{0-6}alkyl)$(aryl) substituents;

R^8 is $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, -O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $-N(C_{0-6}alkyl)$(aryl) substituents;

B is $-C_{0-4}$alkyl, $-C_{0-2}alkyl-SO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-SO_2-C_{0-2}alkyl-$, $-C_{0-2}alkyl-CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^{10}CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^{10}SO_2-C_{0-2}alkyl-$, or $-heteroC_{0-4}$alkyl;

R^9 and R^{10} each independently is $-C_{0-6}$alkyl, $-C_{3-7}$cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, $-C_{1-6}$alkyl, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, –O(aryl), –O(heteroaryl), $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)$(aryl) substituents;

Z is $-C_{3-7}$cycloalkyl, $-heteroC_{3-7}$cycloalkyl, $-C_{0-6}$alkylaryl, or $-C_{0-6}$alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, $-C_{1-6}$alkyl, $-C_{1-6}$alkenyl, $-C_{1-6}$alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$,$-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;

R^{11} is halogen, $-C_{0-6}$alkyl, $-C_{0-6}$alkoxyl, =O, $=N(C_{0-4}alkyl)$,or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$;

any alkyl optionally substituted with 1-5 independent halogen substitutents;
any N may be an N-oxide;
and one of W and Z is optionally absent.

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is 2-pyridyl optionally substituted with 1-4 independent halogen, -CN, NO_2, -C_{1-6}alkyl, –C_{2-6}alkenyl, –C_{2-6}alkynyl, –OR^1, –NR^1R^2, –$C(=NR^1)NR^2R^3$, –$N(=NR^1)NR^2R^3$, -NR^1COR^2, -$NR^1CO_2R^2$, -$NR^1SO_2R^4$, –$NR^1CONR^2R^3$,–SR^4, -SOR^4, –SO_2R^4, -$SO_2NR^1R^2$, -COR^1, -CO_2R^1, –$CONR^1R^2$, -$C(=NR^1)R^2$, or –$C(=NOR^1)R^2$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the –C_{1-6}alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), -O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) groups.

3. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Y is phenyl optionally substituted with 1-5 independent halogen, –CN, NO_2, -C_{1-6}alkyl, –C_{2-6}alkenyl, –C_{2-6}alkynyl, -OR^5, –NR^5R^6, -$C(=NR^5)NR^6R^7$, -$N(=NR^5)NR^6R^7$, –NR^5COR^6, -$NR^5CO_2R^6$, -$NR^5SO_2R^8$, –$NR^5CONR^6R^7$,–SR^8, -SOR^8, –SO_2R^8, –$SO_2NR^5R^6$, -COR^5, -CO_2R^5, –$CONR^5R^6$, -$C(=NR^5)R^6$, or –$C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the –C_{1-6}alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, –C_{1-6}alkyl, –O(C_{0-6}alkyl), –O(C_{3-7}cycloalkyl), –O(aryl), –O(heteroaryl), –N(C_{0-6}alkyl)(C_{0-6}alkyl), -N(C_{0-6}alkyl)(C_{3-7}cycloalkyl), or –N(C_{0-6}alkyl)(aryl) groups.

4. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Z is –C_{0-6}alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO_2, -C_{1-6}alkyl, -C_{1-6}alkenyl, -C_{1-6}alkynyl, –OR^1, –NR^1R^2, –$C(=NR^1)NR^2R^3$, -$N(=NR^1)NR^2R^3$, –NR^1COR^2, -$NR^1CO_2R^2$, -$NR^1SO_2R^4$, –$NR^1CONR^2R^3$,–SR^4, -SOR^4, –SO_2R^4, –$SO_2NR^1R^2$, -COR^1, -CO_2R^1, –$CONR^1R^2$, -$C(=NR^1)R^2$, or -$C(=NOR^1)R^2$ substituents;R^{11} is halogen, –C_{0-6}alkyl, –C_{0-6}alkoxyl, =O, =N(C_{0-4}alkyl),or –N(C_{0-4}alkyl)(C_{0-4}alkyl).;

5. The compound according to Claim 1, consisting of

2-[4-(3-Methoxy-4-pyridin-2-ylphenyl)-2*H*-1,2,3-triazol-2-yl]pyridine;

2-[4-(3-methoxy-4-pyridin-2-ylphenyl)-1*H*-1,2,3-triazol-1-yl]pyridine;

2-[4-(3-pyridin-2-ylphenyl)-1*H*-1,2,3-triazol-1-yl]pyridine;

2-[4-(3-pyridin-2-ylphenyl)-2*H*-1,2,3-triazol-2-yl]pyridine;

2-[4-(3-pyridin-3-ylphenyl)-1*H*-1,2,3-triazol-1-yl]pyridine;

2-[4-(3-pyridin-3-ylphenyl)-2*H*-1,2,3-triazol-2-yl]pyridine;

2-[4-(3-fluoro-4-pyridin-2-ylphenyl)-1*H*-1,2,3-triazol-1-yl]pyridine;

2-[4-(3-fluoro-4-pyridin-2-ylphenyl)-2*H*-1,2,3-triazol-2-yl]pyridine;

2-[2-methoxy-4-(5-methyl-1-pyridin-2-yl-1*H*-1,2,3-triazol-4-yl)phenyl]pyridine;

2-[2-methoxy-4-(5-methyl-2-pyridin-2-yl-2*H*-1,2,3-triazol-4-yl)phenyl]pyridine.

or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising: a therapeutically effective amount of the compound according to claim 1, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

7. The pharmaceutical composition according to claim 6, further comprising i) an opiate agonist, ii) an opiate antagonist, iii) a calcium channel antagonist, iv) a 5HT receptor agonist, v) a 5HT receptor antagonist, vi) a sodium channel antagonist, vii) an NMDA receptor agonist, viii) an NMDA receptor antagonist, ix) a COX-2 selective inhibitor, x) an NK1 antagonist, xi) a non-steroidal anti-inflammatory drug, xii) a GABA-A receptor modulator, xiii) a dopamine agonist, xiv) a dopamine antagonist, xv) a selective serotonin reuptake inhibitor, xvi) a tricyclic antidepressant drug, xvii) a norepinephrine modulator, xviii) L-DOPA, xix) buspirone, xx) a lithium salt, xxi) valproate, xxii) neurontin, xxiii) olanzapine, xxiv) a nicotinic agonist, xxv) a nicotinic antagonist, xxvi) a muscarinic agonist, xxvii) a muscarinic antagonist, xxviii) a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), xxix) a heroin substituting drug, xxx) disulfiram, or xxxi) acamprosate.

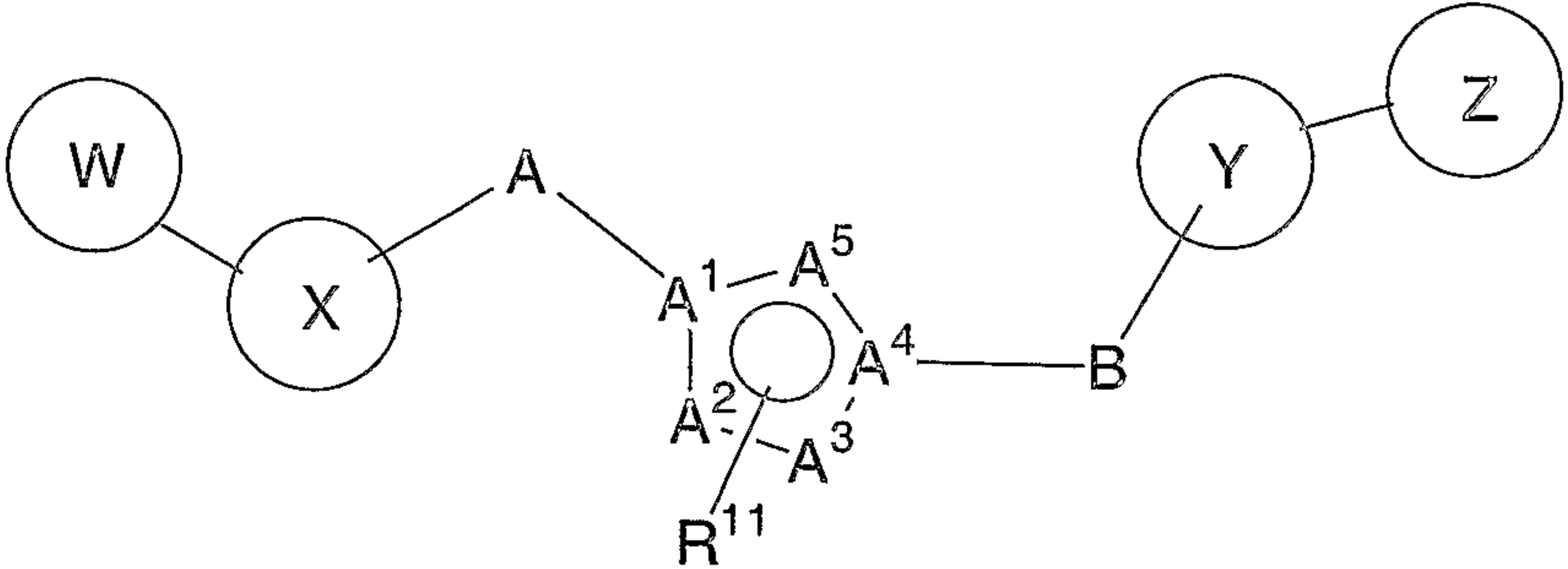
8. The pharmaceutical composition according to claim 7, wherein said heroin substituting drug is methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone.

9. The use of the compound of Claim 1 for the preparation of a medicament useful in the treatment of pain disorders, extrapyramidal motor function disorders, anxiety disorders, Parkinson's disease, depression, epilepsy, cognitive disfunction, drug addiction, circadian rhythm and sleep disorders, and obesity.

10. The use according to claim 9 wherein said pain disorder is acute pain, persistent pain, chronic pain, inflammatory pain, or neuropathic pain.

11. The use of the compound of Claim 1 for the preparation of a medicament useful in the treatment of anxiety, depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia or panic.

12. The use according to claim 9 wherein said disorder of extrapyramidal motor function is Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, or tardive dyskinesia.



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