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(54) **Title**: BIARYL BENZOTRIAZOLE DERIVATIVES

(57) **Abstract**: The present invention is directed to biaryl benzotriazole derivatives which are potentiators of metabotropic glutamate receptors, particularly the mGluR2 receptor, and which are useful in the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction and diseases in which metabotropic glutamate receptors are involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which metabotropic glutamate receptors are involved.

TITLE OF THE INVENTION

BIARYL BENZOTRIAZOLE DERIVATIVES

BACKGROUND OF THE INVENTION

The excitatory amino acid L-glutamate (sometimes referred to herein simply as glutamate) through its many receptors mediates most of the excitatory neurotransmission within the mammalian central nervous system (CNS). The excitatory amino acids, including glutamate, are of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiration, cardiovascular regulation, and sensory perception.

Glutamate acts via at least two distinct classes of receptors. One class is composed of the ionotropic glutamate (iGlu) receptors that act as ligand-gated ionic channels. Via activation of the iGlu receptors, glutamate is thought to regulate fast neuronal transmission within the synapse of two connecting neurons in the CNS. The second general type of receptor is the G-protein or second messenger-linked "metabotropic" glutamate (mGluR) receptor. Both types of receptors appear not only to mediate normal synaptic transmission along excitatory pathways, but also participate in the modification of synaptic connections during development and throughout life. Schoepp, Bockaert, and Sladeczek, Trends in Pharmacol. Sci., 11, 508 (1990); McDonald and Johnson, Brain Research Reviews, 15, 41 (1990).

The present invention relates to potentiators of mGlu receptors, in particular mGluR2 receptors. The mGluR receptors belong to the Type III G- protein coupled receptor (GPCR) superfamily. This superfamily of GPCR's including the calcium-sensing receptors, $GABA_B$ receptors and pheromone receptors, which are unique in that they are activated by binding of effectors to the amino-terminus portion of the receptor protein. The mGlu receptors are thought to mediate glutamate's demonstrated ability to modulate intracellular signal transduction pathways. Ozawa, Kamiya and Tsuzuski, Prog. Neurobio., 54, 581 (1998). They have been demonstrated to be localized both pre- and post-synaptically where they can regulate neurotransmitter release, either glutamate or other neurotransmitters, or modify the post-synaptic response of neurotransmitters, respectively.

At present, there are eight distinct mGlu receptors that have been positively identified, cloned, and their sequences reported. These are further subdivided based on their amino acid sequence homology, their ability to effect certain signal transduction mechanisms, and their known pharmacological properties. Ozawa, Kamiya and Tsuzuski, Prog. Neurobio., 54,

581 (1998). For instance, the Group I mGluR receptors, which include the mGlulR and mGlu5R, are known to activate phospholipase C (PLC) via Gαq-proteins thereby resulting in the increased hydrolysis of phosphoinositides and intracellular calcium mobilization. There are several compounds that are reported to activate the Group I mGlu receptors including DHPG, (R/S)-3,5-dihydroxyphenylglycine. Schoepp, Goldworthy, Johnson, Salhoff and Baker, J. Neurochem., 63, 769 (1994); Ito, et al., keurorep., 3, 1013 (1992). The Group II mGlu receptors consist of the two distinct receptors, mGluR2 and mGluR3 receptors. Both have been found to be negatively coupled to adenylate cyclase via activation of Gαi-protein. These receptors can be activated by a selective compound such as 1S,2S,SR,6S-2 aminobicyclo[3.1.0]hexane-2,6-dicarboxylate. Monn, et al., J. Med. Chem., 40, 528 (1997); Schoepp, et al., Neuropharmacol., 36, 1 (1997). This activitation leads to inhibition of glutamate release in the synapse (Cartmell et al, J Neurochem 75, 889 (2000)). Similarly, the Group III mGlu receptors, including mGluR4, mGluR6, mGluR7 and mGluR8, are negatively coupled to adenylate cyclase via Gαi and are potently activated by L-AP4 (L- (+) -2-amino-4-phosphonobutyric acid). Schoepp, Neurochem. Int., 24, 439 (1994).

Nonselective mGluR2/mGluR3 receptor agonists (Monn, et al., J. Med. Chem., 43, 4893, (2000)) have shown efficacy in numerous animal models of anxiety and psychosis as well as human clinical trials in schizophrenia patients; Patil et al, Nature Medicine, 13, 1102 (2007). Recent reports indicate that mGluR2 but not the mGluR3 receptor mediates the actions of the dual mGluR2/mGluR3 agonist LY379268 in mouse models predictive of antipsychotic activity. Woolley et al, Psycopharmacology, 196, 431 (2008). Additionally, recent animal studies demonstrate that selective potentiation of the mGluR2 receptor has similar effects to such non-selective agonists (Galici et al, Journal of Pharmacology and Experimental Therapeutics, 315, 1181 (2005)) suggesting an alternative strategy concerning the discovery of selective, positive allosteric modulators (PAMs or allosteric potentiators) of mGluR2 (Johnson et al, J. Med. Chem. 46, 3189, (2003); Pinkerton et al., J. Med. Chem., 47, 4595 (2004). These potentiators act by enabling the receptor to produce an enhanced response to endogenous glutamate. Such allosteric potentiators do not bind at the glutamate binding site also known as the "orthosteric site", and may benefit by binding to a site other than the highly conserved orthosteric site. A potential advantage to this approach includes the opportunity to have a distinct pharmacological profile by enhancing the activity of the endogenous ligand upon its binding to the orthosteric site. The pharmacological distinctions include the potential for pharmacological specificity between related receptor types that share the same endogenous ligand. In addition, positive allosteric

modulators of mGluR2 have been shown to potentiate the response of mGluR2 agonists such as LY379268 (Johnson et. Al. Biochemical Soc. Trans. 32, 881 (2004) and this represents an alternative strategy for treatment using mGluR2 selective PAMs.

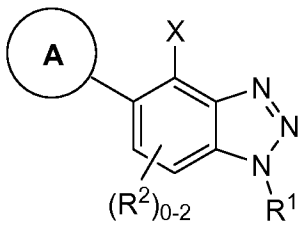
It has become increasingly clear that there is a link between modulation of excitatory amino acid receptors, including the glutamatergic system, through changes in glutamate release or alteration in postsynaptic receptor activation, and a variety of neurological and psychiatric disorders. e.g. Monaghan, Bridges and Cotman, Ann. Rev. Pharmacol. Toxicol., 29, 365-402 (1989); Schoepp and Sacann, Neurobio. Aging, 15, 261-263 (1994); Meldrum and Garthwaite, Tr. Pharmacol. Sci., 11, 379-387 (1990). The medical consequences of such glutamate dysfunction make the abatement of these neurological processes an important therapeutic goal.

SUMMARY OF THE INVENTION

The present invention is directed to biaryl benzotriazole derivatives which are potentiators of metabotropic glutamate receptors, particularly the mGluR2 receptor, and which are useful in the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction and diseases in which metabotropic glutamate receptors are involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which metabotropic glutamate receptors are involved.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses compounds according to Formula I



I

wherein:

X is selected from halo, methyl and -CN;

R^1 is selected from the group consisting of:

(1) C_{1-8}alkyl,

(2) C_{2-8}alkenyl,

(3) C_{2-8}alkynyl,

(4) C_{1-8}haloalkyl,

(5) C_{3-6}cycloalkyl-$(CH_2)_p$-, wherein p is 0, 1, 2, 3 or 4, and

(6) 4-(2-methylbenzamido)benzyl;

each R^2 is independently selected from the group consisting of: halo, OH, C_{1-4}alkyl, C_{1-4}alkoxy, CF_3 and –CN;

A is selected from aryl, heteroaryl and heterocycle, wherein said aryl, heteroaryl and heterocycle are optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions;

aryl at each occurrence is independently selected from the group consisting of: phenyl, naphthyl, anthryl and phenanthryl;

heteroaryl at each occurrence independently means a 5- or 6-membered monocyclic aromatic or 9- or 10-membered bicyclic aromatic, wherein at least one atom in the aromatic is selected from N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide, and the remaining atoms are selected from C, N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide;

heterocycle at each occurrence independently means a 5- or 6-membered monocyclic non-aromatic ring or 9- or 10-membered bicyclic non- or partially-aromatic ring, each optionally substituted with oxo, wherein at least one atom is selected from N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide, and the remaining atoms are selected from C, N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide;

each R^3 is independently selected from the group consisting of:

(1) halo,

(2) C_{1-8}alkyl,

(3) C_{2-6}alkenyl,

(4) C_{2-6}alkynyl,

(5) C_{3-6}cycloalkyl,

(6) C_{1-6}alkoxy,

(7) C_{3-6}cycloalkoxy,

(8) -CN,

(9) -OH,

(10) -C(O)-O-C_{1-4}alkyl,

(11) -C(O)-C_{1-4}alkyl,

(12) -$N(R)_2$,

(13) -C(O)-$N(R)_2$,

(14) -$S(O)_k$-C_{1-4}alkyl, wherein k is 0, 1 or 2,

(15) -aryl,

(16) -heteroaryl,

(17) -heterocycle,

(18) -C(O)-aryl,

(19) -N(R)-aryl,

(20) benzyl,

(21) benzyloxy,

(22) aryl-O-,

(23) heteroaryl-O-,

(24) heterocycle-O-

(23) -CO_2H,

(24) -SH,

(25) -SO_2N(R)R,

(26) -N(R)C(O)N(R)R,

(27) -N(R)C(O)C_{1-4}alkyl,

(28) -N(R)SO_2N(R)R,

(29) -$B(OH)_2$,

(30) heterocycle-CH_2-,

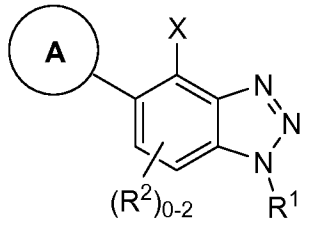
(31) heteroaryl-CH_2- and

(32) -N(R)C(O)-O-C_{1-4}alkyl,

wherein groups (2) to (7), (15) to (24), (30), (31) and (32) above are optionally substituted from one up to the maximum number of substitutable positions with one or more substituents independently selected from the group consisting of: OH, CN, halo, carboxy, -C(O)-O-C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino, phenyl and heterocycle, and each R is independently selected from the group consisting of: H and C_{1-4}alkyl;

and pharmaceutically acceptable salts thereof.

The invention also encompasses a genus of compounds of Formula I



I

wherein:

X is selected from halo, methyl and -CN;

R^1 is selected from the group consisting of:

(1) C_{1-8}alkyl,

(2) C_{2-8}alkenyl,

(3) C_{2-8}alkynyl,

(4) C_{1-8}haloalkyl,

(5) C_{3-6}cycloalkyl-$(CH_2)_p$-, wherein p is 0, 1, 2, 3 or 4, and

(6) 4-(2-methylbenzamido)benzyl;

each R^2 is independently selected from the group consisting of: halo, OH, C_{1-4}alkyl, C_{1-4}alkoxy, CF_3 and –CN;

A is selected from aryl, heteroaryl and heterocycle, wherein said aryl, heteroaryl and heterocycle are optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions;

aryl at each occurrence is independently selected from the group consisting of: phenyl, naphthyl, anthryl and phenanthryl;

heteroaryl at each occurrence independently means a 5- or 6-membered monocyclic aromatic or 9- or 10-membered bicyclic aromatic, wherein at least one atom in the aromatic is selected from N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide, and the remaining atoms are selected from C, N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide;

heterocycle at each occurrence independently means a 5- or 6-membered monocyclic non-aromatic ring or 9- or 10-membered bicyclic non- or partially-aromatic ring, each optionally

substituted with oxo, wherein at least one atom is selected from N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide, and the remaining atoms are selected from C, N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide;

each R^3 is independently selected from the group consisting of:

(1) halo,
(2) C_{1-8}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}alkynyl,
(5) C_{3-6}cycloalkyl,
(6) C_{1-6}alkoxy,
(7) C_{3-6}cycloalkoxy,
(8) -CN,
(9) -OH,
(10) -C(O)-O-C_{1-4}alkyl,
(11) -C(O)-C_{1-4}alkyl,
(12) -$N(R)_2$,
(13) -C(O)-$N(R)_2$,
(14) -$S(O)_k$-C_{1-4}alkyl, wherein k is 0, 1 or 2,
(15) -aryl,
(16) -heteroaryl,
(17) -heterocycle,
(18) -C(O)-aryl,
(19) -N(R)-aryl,
(20) benzyl,
(21) benzyloxy,
(22) aryl-O-,
(23) heteroaryl-O-,
(24) heterocycle-O-
(23) -CO_2H,
(24) -SH,
(25) -SO_2N(R)R,
(26) -N(R)C(O)N(R)R,

(27) -N(R)C(O)C_{1-4}alkyl,

(28) -N(R)SO_2N(R)R,

(29) -$B(OH)_2$,

(30) heterocycle-CH_2- and

(31) heteroaryl-CH_2-,

wherein groups (2) to (7), (15) to (24), (30) and (31) above are optionally substituted from one up to the maximum number of substitutable positions with one or more substituents independently selected from the group consisting of: OH, CN, halo, carboxy, -C(O)-O-C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino, phenyl and heterocycle, and each R is independently selected from the group consisting of: H and C_{1-4}alkyl;

and pharmaceutically acceptable salts thereof.

Within the genus, the invention encompasses a first subgenus of compounds of Formula I wherein X is Br.

Within the first subgenus, the invention encompasses a first class of compounds of Formula I wherein R^1 is 2,2-dimethylpropyl.

Also within the first subgenus, the invention encompasses a second class of compounds of Formula I wherein R^1 is cyclopropylmethyl.

Also within the first subgenus, the invention encompasses a third class of compounds of Formula I wherein R^1 is 4,4,4-trifluorobutyl

Also within the genus, the invention encompasses a second sub-genus of compounds of Formula I wherein **A** is phenyl, optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions.

Within the second subgenus, the invention encompasses a fourth class of compounds of Formula I wherein each R^3 is independently selected from the group consisting of: halo, C_{1-4}alkyl, C_{1-4}alkoxy, -CF_3, -OCF_3, -NH_2, -CN, -OH, -CH_2-OH, -CH_2-O-CH_3, -C(O)OC_{1-4}alkyl, -OCH_2-C(O)-OH, -NH-C(O)-C_{1-4}alkyl and phenyl, optionally substituted with 1 to 5 substituents independenly selected from halo and methyl.

Also within the genus, the invention encompasses a third sub-genus of compounds of Formula I wherein **A** is selected from pyridine, pyrimidine, pyridazine and triazine, optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions.

Within the third subgenus, the invention encompasses a fifth class of compounds of Formula I wherein each R^3 is independently selected from the group consisting of: halo, C_{1-4}alkyl, C_{1-4}alkoxy, $-CF_3$, $-OCF_3$, $-NH_2$, -CN, -OH, $-CH_2$-OH, $-CH_2$-O-CH_3, $-C(O)OC_{1-4}$alkyl, $-OCH_2$-C(O)-OH, -NH-C(O)-C_{1-4}alkyl, phenyl optionally substituted with 1 to 5 substituents independenly selected from halo and methyl, and pyridyl optionally substituted with 1 to 4 substituents independenly selected from halo and methyl.

Also within the genus, the invention encompasses a fourth sub-genus of compounds of Formula I wherein **A** is selected from pyrazole, oxadiazole, thiadiazole, furan, thiophene, pyrrole, triazole, oxazole, thiazole, imidazole, isoxazole and isothiazole, optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions.

Within the fourth subgenus, the invention encompasses a sixth class of compounds of Formula I wherein each R^3 is independently selected from the group consisting of: halo, C_{1-4}alkyl, C_{1-4}alkoxy, $-CF_3$, $-OCF_3$, $-NH_2$, -CN, -OH, $-CH_2$-OH, $-CH_2$-O-CH_3, $-C(O)OC_{1-4}$alkyl, $-OCH_2$-C(O)-OH, -NH-C(O)-C_{1-4}alkyl, phenyl optionally substituted with 1 to 5 substituents independenly selected from halo and methyl, and pyridyl optionally substituted with 1 to 4 substituents independently selected from halo and methyl.

Also within the genus, the invention encompasses a fifth subgenus of compounds of Formula I wherein: X is selected from Br and Cl; R^1 is selected from the group consisting of: 2,2-dimethylpropyl and cyclopropylmethyl; R^2 is not present; **A** is phenyl optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions; each R^3 is independently selected from the group consisting of: (1) C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted with hydroxy; (2) –CN, (3) halo, (4) $-CF_3$, (5) methoxy, (6) tetrahydro-2H-pyranyloxy and (7) pyridinyloxy, said pyridinyloxy optionally substituted with halo; and pharmaceutically acceptable salts thereof.

Also within the genus, the invention encompasses a sixth subgenus of compounds of Formula I wherein: X is selected from Br and Cl; R^1 is selected from the group consisting of: 2,2-dimethylpropyl and cyclopropylmethyl; R^2 is not present; **A** is selected from the group consisting of: pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzisoxazolyl, triazolyl[1,5-a]pyridinyl, triazolyl[4,3-a]pyridinyl, pyrrolo[2,3-b]pyridinyl, indazolyl and 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, wherein **A** is optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions; each R^3 is independently selected from the group consisting of: (1) C_{1-4}alkyl, said C_{1-4}alkyl optionally

substituted with hydroxy; (2) –CN, (3) halo, (4) -CF_3, (5) methoxy, (6) tetrahydro-2H-pyranyloxy and (7) pyridinyloxy, said pyridinyloxy optionally substituted with halo; and pharmaceutically acceptable salts thereof.

The invention also encompasses compounds of Formula I wherein **A** is 3,4-dihydro-2H-chromene optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions.

In another embodiment, the invention encompasses compounds of Formula I wherein X is Cl and R^1 is cyclopropylmethyl. Within this embodiment, the invention encompasses compounds of Formula I wherein **A** is selected from phenyl, pyridine and pyrimidine, optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions. Further within this embodiment, R^2 is not present; and each R^3 is independently selected from the group consisting of: (1) C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted with hydroxy and 1 to 3 halo; (2) –CN, (3) halo, (4) C_{1-4}alkoxy, (5) methylsulfanyl, (6) methylsulfinyl, (7) methylsulfonyl, (8) -C(O)-$N(R)_2$, (9) -C(O)-O-C_{1-4}alkyl, (10) piperazinyl, (11) 4-methylpiperazinyl, (12) piperazinylmethyl, (13) 4-methylpiperazinylmethyl, (14) morpholinyl and (15) morpholinylmethyl.

The invention also encompasses a compound selected from the following group:
4-bromo-1-(2,2-dimethylpropyl)-5-(1-methyl-1H- -pyrazol-4-yl)-1H-1,2,3-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-phenyl-1*H*-benzotriazole;
3-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]-4-fluorobenzonitrile;
4-[4-chloro-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]isoquinoline;
4-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]isoquinoline;
3-[4-chloro-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-chloro-1-(2,2-dimethylpropyl)-5-phenyl-1*H*-benzotriazole;
5-(1-benzofuran-3-yl)-4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazole;
{4-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}methanol;
4-bromo-1-(2,2-dimethylpropyl)-5-(3-methyl-1,2-benzisoxazol-5-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-[1,2,4]triazolo[1,5-a]pyridin-6-yl-1*H*-benzotriazole;
4-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-bromo-1-(2,2-dimethylpropyl)-5-pyridin-4-yl-1*H*-benzotriazole;
6-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]quinoline;
4-bromo-1-(2,2-dimethylpropyl)-5-(1*H*-pyrrolo[2,3-b]pyridin-5-yl)-1*H*-benzotriazole;

4-bromo-1-(2,2-dimethylpropyl)-5-[1,2,4]triazolo[1,5-a]pyridin-7-yl-1*H*-benzotriazole;
3-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile;
2-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-bromo-1-(2,2-dimethylpropyl)-5-pyridin-3-yl-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(4-methylpyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-pyrimidin-5-yl-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(2-methylpyridin-4-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(6-methylpyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(2-fluoropyridin-4-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-1H-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(5-fluoropyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(2-fluoropyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(6-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(6-fluoropyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(1*H*-indazol-5-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(2-methoxypyrimidin-5-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(5-methoxypyridin-3-yl)-1*H*-benzotriazole;
5-(1-benzofuran-2-yl)-4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazole;
5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridine-2-carbonitrile;
5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridine-2-carbonitrile;
4-bromo-1-(2,2-dimethylpropyl)-5-(4-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-[1,2,4]triazolo[4,3-a]pyridin-6-yl-1*H*-benzotriazole;
2-{3-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]phenyl}propan-2-ol;
4-bromo-5-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-1-(2,2-dimethylpropyl)-1*H*-benzotriazole;
{5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}methanol;
5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]isoquinoline;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-4-carbonitrile;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-4-fluorobenzonitrile;
6-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]quinoline;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridinium trifluoroacetate;

2-{3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}propan-2-ol;
5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridine-3-carbonitrile;
4-bromo-5-[3-chloro-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl]-1-(cyclopropylmethyl)-1*H*-benzotriazole; and
4-bromo-5-{4-[(2-chloropyridin-4-yl)oxy]phenyl}-1-(cyclopropylmethyl)-1*H*-1,2,3-benzotriazole;
4-bromo-1-(cyclopropylmethyl)-5-(2-methoxy-6-methylpyridin-3-yl)-1*H*-benzotriazole;
7-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3,4-dihydro-2*H*-chromen-4-ol;
4-bromo-1-(cyclopropylmethyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl] yridine-2(1*H*)-one;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-1-methylpyridin-2(1*H*)-one;
4-bromo-1-(cyclopropylmethyl)-5-(2-methoxy-6-methylpyridin-3-yl)-1*H*-benzotriazole;
{4-[4-bromo-1-(2-methylpropyl)-1*H*-benzotriazol-5-yl]phenyl}methanol;
{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluorophenyl}methanol;
{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-fluorophenyl}methanol;
{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-(methylsulfanyl)phenyl}methanol;
{5-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]thiophen-2-yl}methanol;
{5-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluoropyridin-2-yl}methanol;
{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-(methylsulfonyl)phenyl}methanol;
4-Chloro-1-(cyclopropylmethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-benzotriazole;
7-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2,3-dihydro-4*H*-chromen-4-one;
4-chloro-1-(cyclopropylmethyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-fluoropyridin-3-yl)-1*H*-benzotriazole;
4-chloro-5-(2-chloropyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(pyrimidin-5-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(thiophen-2-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[2-(methylsulfanyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[3-(methylsulfanyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[3-(methylsulfinyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[3-(methylsulfonyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[2-(methylsulfinyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[2-(methylsulfonyl)phenyl]-1*H*-benzotriazole;
3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzamide;

2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzamide;
3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-*N*-methylbenzamide;
3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-*N,N*-dimethylbenzamide;
2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-*N,N*-dimethylbenzamide;
{3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}methanol;
4-chloro-1-(cyclopropylmethyl)-5-(6-fluoro-2-methylpyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-fluoro-6-methylpyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(6-fluoropyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-piperazin-1-ylpyridin-4-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(6-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(3-fluoropyridin-4-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-methylpyridin-3-yl)-1*H*-benzotriazole;
methyl 5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-2-carboxylate;
4-chloro-1-(cyclopropylmethyl)-5-(6-morpholin-4-ylpyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(6-piperazin-1-ylpyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(3-fluorophenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(4-fluorophenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-methylphenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(3-methylphenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(4-methylphenyl)-1*H*-benzotriazole;
4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-benzotriazole;
2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-chloro-1-(cyclopropylmethyl)-5-pyridin-3-yl-1*H*-benzotriazole;
methyl 4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluorobenzoate;
4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzoic acid;
4-chloro-1-(cyclopropylmethyl)-5-[2-(morpholin-4-ylmethyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-pyridin-4-yl-1*H*-benzotriazole;
{2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}methanol;
4-chloro-1-(cyclopropylmethyl)-5-(2-morpholin-4-ylpyridin-3-yl)-1*H*-benzotriazole;
tert-butyl {5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}carbamate;
4-chloro-1-(cyclopropylmethyl)-5-(2-methylpyridin-4-yl)-1*H*-benzotriazole;

5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-2-carbonitrile;
4-chloro-1-(cyclopropylmethyl)-5-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-ethoxypyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(6-methylpyridin-3-yl)-1*H*-benzotriazole;
methyl 4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-fluorobenzoate;
4-chloro-5-(6-chloro-2-fluoropyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;
4-chloro-5-(2-chloro-6-methylpyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-fluorophenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-pyridin-2-yl-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-fluoropyridin-4-yl)-1*H*-benzotriazole;
7-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-4-methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine;
4-chloro-5-(3-chloro-2-morpholin-4-ylpyridin-4-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(3-fluoro-2-morpholin-4-ylpyridin-4-yl)-1*H*-benzotriazole;
2-{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-3-yl}propan-2-ol;
4-chloro-1-(cyclopropylmethyl)-5-(2-methoxypyridin-4-yl)-1*H*-benzotriazole;
4-chloro-5-(6-chloropyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(5-fluoropyridin-3-yl)-1*H*-benzotriazole;
tert-butyl 4-{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}piperazine-1-carboxylate;
ethyl 5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-3-carboxylate;
4-chloro-1-(cyclopropylmethyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[4-(1-methoxyethyl)phenyl]-1*H*-benzotriazole;
1-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}-2,2-difluoroethanol;
1-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}-2,2,2-trifluoroethanol;
{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-methylphenyl}methanol;
2-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}propan-2-ol;
5-[4-(tert-butoxymethyl)phenyl]-4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazole;
{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}methanol;
{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-6-fluoropyridin-2-yl}methanol;
{3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}methanol;
{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluorophenyl}methanol;

4-chloro-1-(cyclopropylmethyl)-5-{6-[1-(methoxymethoxy)-1-methylethyl]pyridin-3-yl}-1*H*-benzotriazole;

1-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}ethanol; and

2-{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}propan-2-ol;

and pharmaceutically acceptable salts of any of the foregoing compounds.

The invention also encompasses a pharmaceutical composition comprising a compound of Formula I in combination with a pharmaceutically acceptable carrier.

The invention also encompasses a method for treating a neurological or psychiatric disorder associated with glutamate dysfunction in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound of Formula I. The invention also encompasses this method wherein the neurological or psychiatric disorder associated with glutamate dysfunction is schizophrenia.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, 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, octyl, nonyl, and the like.

"Haloalkyl" means alkyl as defined above wherein one more hydrogen atoms are replaced by halo.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Cycloalkyl" means mono-, bi- or tri-cyclic structures, optionally combined with linear or branched structures, having the indicated number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1- bicyclo[4.4.0]decyl, and the like.

"Alkoxy" means alkoxy groups of a straight or branched having the indicated number of carbon atoms. C_{1-6}alkoxy, for example, includes methoxy, ethoxy, propoxy, isopropoxy, and the like.

"Cycloalkoxy" means cycloalkyl as defined above bonded to an oxygen atom, such as cyclopropyloxy.

Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, and the like.

"Halogen" and "halo" includes fluorine, chlorine, bromine and iodine.

The compounds of the present invention are potentiators of metabotropic glutamate (mGluR) receptor function, in particular they are potentiators of mGluR2 receptors. That is, the compounds of the present invention do not appear to bind at the glutamate recognition site on the mGluR receptor, but in the presence of glutamate or a glutamate agonist, the compounds of the present invention increase mGluR receptor response. The present potentiators are expected to have their effect at mGluR receptors by virtue of their ability to increase the response of such receptors to glutamate or glutamate agonists, enhancing the function of the receptors. It is recognized that the compounds of the present invention would be expected to increase the effectiveness of glutamate and glutamate agonists of the mGluR2 receptor. Thus, the potentiators of the present invention are expected to be useful in the treatment of various neurological and psychiatric disorders associated with glutamate dysfunction described to be treated herein and others that can be treated by such potentiators as are appreciated by those skilled in the art.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. Any formulas, structures or names of compounds described in this specification that do not specify a particular stereochemistry are meant to encompass any and all existing isomers as described above and mixtures thereof in any proportion. When stereochemistry is specified, the invention is meant to encompass that particular isomer in pure form or as part of a mixture with other isomers in any proportion.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

In the compounds of generic Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (1H) and deuterium (2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, 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, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include 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. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include a pharmaceutically acceptable salts.

Exemplifying the invention are Examples 1 to 143, described herein. The subject compounds are useful in a method of potentiating metabotorpic glutamate receptor activity in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the subject compounds disclosed herein as potentiators of metabotropic glutamate receptor activity. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention.

The present invention is further directed to a method for the manufacture of a medicament for potentiating metabotropic glutamate receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female, in whom potentiation of metabotropic glutamate receptor activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. It is recognized that one skilled in the art may affect the neurological and psychiatric disorders by treating a patient presently afflicted with the disorders or by prophylactically treating a patient afflicted with the disorders with an effective amount of the compound of the present invention. As used herein, the terms "treatment" and "treating" refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the neurological and psychiatric disorders described herein, but does not necessarily indicate a total elimination of all disorder symptoms, as well as the prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as potentiators of metabotropic glutamate receptor activity, in particular mGluR2 activity, may be demonstrated by methodology known in the art. Activity as potentiators of mGluR2 activity may be determined as follows. The compounds of the present invention may be tested in a

fluorescence laser imaging plate reader (FLIPR) based assay. This assay is a common functional assay to monitor Ca^{2+} mobilization in whole cells expressing recombinant receptor coupled with a promiscuous G-protein. CHO dhfr- cells stably expressing recombinant human mGluR2 and Gα16 loaded with Fluo-4 AM (Invitrogen, Carlsbad CA) are treated with dose responses of compounds and the Ca^{2+} response is monitored on a FLIPR384 (Molecular Devices, Sunnydale CA) for agonist activity. The potentiation response is monitored after a subsequent addition of an EC20 concentration of glutamate (900 nM). The maximum calcium response at each concentration of compound for agonist or potentiation are plotted as dose responses and the curves are fitted with a four parameters logistic equation giving EC50 and Hill coefficient using the iterative non linear curve fitting software program.

The compounds of the present invention may also be tested in a [^{35}S]-GTPγS assay. The stimulation of [^{35}S]-GTPγS binding is a common functional assay to monitor Gαi-coupled receptor in native and recombinant receptor membrane preparation. Membrane from cells stably expressing hmGlu2 CHO-K1 (50μg) are incubated in a 96 well plate for 1 hour in the presence of GTPγS^{35} (0.05nM), GDP (5μM) and compounds. The reaction is stopped by rapid filtration over Unifilter GF/B plate (Packard, Bioscience, Meriden CT) using a 96-well cell harvester (Brandel Gaithersburg, MD). The filter plates are counted using Topcount counter (Packard, Bioscience, Meriden CT, USA). When compounds are evaluated as potentiators they are tested in the presence of glutamate (1μM). The activation (agonist) or the potentiation of glutamate (potentiator) curves are fitted with a four parameters logistic equation giving EC_{50} and Hill coefficient using the iterative non linear curve fitting software GraphPad (San Diego CA, USA).

In particular, Examples 1 to 143 were tested and demonstrated activity in potentiating the mGluR2 receptor in the FLIPR assay, generally with an EC_{50} of less than about 10 μM. Compounds within the present invention had activity in potentiating the mGluR2 receptor in the FLIPR and GTPγS assays with an EC_{50} of less than about 1 μM. Examples 1 to 143 resulted in a minimum 1.8-fold potentiation of glutamate response in the presence of an EC20 concentration of glutamate (900nM). Such results are indicative of the intrinsic activity of the compounds in use as potentiators of mGluR2 receptor activity.

Representative FLIPR EC_{50} Values

Ex.	EC50	N

Ex.	EC50	N
3	52 nM	2
18	130 nM	2
26	699 nM	2
39	46 nM	2
45	15 nM	2
61	12 nM	2
52	8 nM	2
142	23 nM	2
80	57 nM	2
92	79 nM	2
131	25 nM	2
72	137 nM	2
86	2270 nM	1
112	1030 nM	1
119	2340 nM	1

Metabotropic glutamate receptors including the mGluR2 receptor have been implicated in a wide range of biological functions. This has suggested a potential role for these receptors in a variety of disease processes in humans or other species.

The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with glutamate dysfunction, including one or more of the following conditions or diseases: acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and

obsessive compulsive disorder), mood disorders (including depression, mania, bipolar disorders), trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic pain states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), autism, autism spectrum disorders, attention deficit/hyperactivity disorder, and conduct disorder.

In an embodiment the present invention provides a method for treating migraine, comprising: administering to a patient in need thereof an effective amount of a compound of formula I. In another embodiment the present invention provides a method for preventing or treating anxiety, comprising: administering to a patient in need thereof an effective amount of a compound of formula I. Particular anxiety disorders of the invention are generalized anxiety disorder, panic disorder, and obsessive compulsive disorder. In another embodiment the present invention provides a method for treating schizophrenia, comprising: administering to a patient in need thereof an effective amount of a compound of formula I. In yet another embodiment the present invention provides a method for treating epilepsy, comprising: administering to a patient in need thereof an effective amount of a compound of formula I.

In an embodiment, the present invention provides a method for the treatment of schizophrenia comprising: administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof. In one of the available sources of diagnostic tools, The Merck Manual (2006-2007), schizophrenia is characterized by psychosis (loss of contact with reality), hallucinations (false perceptions), delusions (false beliefs), disorganized speech and behavior, flattened affect (restricted range of emotions), cognitive deficits (impaired reasoning and problem solving), and occupational and social dysfunction. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders, including migraine, and that these systems evolve with medical scientific progress

Thus, in an embodiment the present invention provides a method for treating migraine, comprising: administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof. In one of the available sources of diagnostic tools, Dorland's Medical Dictionary (23'd Ed., 1982, W. B. Saunders Company, Philidelphia, PA), migraine is defined as a symptom complex of periodic headaches, usually temporal and unilateral, often with irritability, nausea, vomiting, constipation or diarrhea, and photophobia. As used herein the term "migraine" includes these periodic headaches, both temporal and unilateral, the associated irritability, nausea, vomiting, constipation or diarrhea,

photophobia, and other associated symptoms. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders, including migraine, and that these systems evolve with medical scientific progress.

In another embodiment the present invention provides a method for treating anxiety, comprising: administering to a patient in need thereof an effective amount of a compound of Formula I or a pharmaceutical composition thereof. At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool including anxiety and related disorders. These include: panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive- compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder and anxiety disorder not otherwise specified. As used herein the term "anxiety" includes treatment of those anxiety disorders and related disorder as described in the DSM-IV. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders, and particular anxiety, and that these systems evolve with medical scientific progress. Thus, the term "anxiety" is intended to include like disorders that are described in other diagnostic sources.

In another embodiment the present invention provides a method for treating depression, comprising: administering to a patient in need thereof an effective amount of a compound of Formula I or a pharmaceutical composition thereof. At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool including depression and related disorders. Depressive disorders include, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, anxiety and phobias; seasonal affective disorder; or bipolar disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder. As used herein the term "depression" includes treatment of those depression disorders and related disorder as described in the DSM-IV.

In another embodiment the present invention provides a method for treating epilepsy, comprising: administering to a patient in need thereof an effective amount of a compound of Formula I or a pharmaceutical composition thereof. At present, there are several types and subtypes of seizures associated with epilepsy, including idiopathic, symptomatic, and cryptogenic. These epileptic seizures can be focal (partial) or generalized. They can also be simple or complex. Epilepsy is described in the art, such as Epilepsy: A comprehensive textbook. Ed. By Jerome Engel, Jr. and Timothy A. Pedley. (Lippincott-Raven, Philadelphia, 1997). At present, the International Classification of Diseases, Ninth Revision, (ICD-9) provides a diagnostic tool including epilepsy and related disorders. These include: generalized nonconvulsive epilepsy, generalized convulsive epilepsy, petit mal status epilepticus, grand mal status epilepticus, partial epilepsy with impairment of consciousness, partial epilepsy without impairment of consciousness, infantile spasms, epilepsy partialis continua, other forms of epilepsy, epilepsy, unspecified, NOS. As used herein the term "epilepsy" includes these all types and subtypes. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders, including epilepsy, and that these systems evolve with medical scientific progress.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents, including an mGluR agonist.

The term "potentiated amount" refers to an amount of an mGluR agonist, that is, the dosage of agonist which is effective in treating the neurological and psychiatric disorders described herein when administered in combination with an effective amount of a compound of the present invention. A potentiated amount is expected to be less than the amount that is required to provided the same effect when the mGluR agonist is administered without an effective amount of a compound of the present invention.

A potentiated amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining a potentiated amount, the dose of an mGluR agonist to be administered in combination with a compound of formula I, a number of factors are considered by the attending diagnostician, including, but not limited to: the mGluR agonist

selected to be administered, including its potency and selectivity; the compound of formula I to be coadministered; the species of mammal; its size, age, and general health; the specific disorder involved; the degree of involvement or the severity of the disorder; the response of the individual patient; the modes of administration; the bioavailability characteristics of the preparations administered; the dose regimens selected; the use of other concomitant medication; and other relevant circumstances.

A potentiated amount of an mGluR agonist to be administered in combination with an effective amount of a compound of formula I is expected to vary from about 0.1 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day and is expected to be less than the amount that is required to provided the same effect when administered without an effective amount of a compound of formula I. Preferred amounts of a co-administered mGlu agonist are able to be determined by one skilled in the art.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form may be utilized containing such other drugs and the compound of Formula I. However, the combination therapy may also includes therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds.

Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such

other drugs may be administered, by a route and in an amount commonly used, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention may be utilized. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical

composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Oily suspensions may be formulated by suspending the active ingredient in a suitable oil. Oil-in-water emulsions may also be employed. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives.

Pharmaceutical compositions of the present compounds may be in the form of a sterile injectable aqueous or yridine s suspension. The compounds of the present invention may also be administered in the form of suppositories for rectal administration. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention may be employed. The compounds of the present invention may also be

formulated for administered by inhalation. The compounds of the present invention may also be administered by a transdermal patch by methods known in the art.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment, prevention, control, amelioration, or reduction of risk of conditions which require potentiation of metabotorpic glutamate receptor activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

When treating, preventing, controlling, ameliorating, or reducing the risk of neurological and psychiatric disorders associated with glutamate dysfunction or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of

administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein. The compounds of the present invention can be prepared in a variety of fashions.

All patents, publications and pending patent applications identified are hereby incorporated by reference.

Abbreviations used in the description of the chemistry and in the Examples that follow are: Ac2O (acetic anhydride); AcOH (acetic acid); AEBSF (p-aminoethylbenzenesulfonyl fluoride); Boc (di-tert-butyl carbamate); $(Boc)_2O$ (di-tert-butyl dicarbonate); BSA (bovine serum albumin); BuLi (n-Butyl lithium); CDCl3 (chloroform-d); CuI (copper iodide); CuSO4 (copper sulfate); DBU (1,8-DIAZABICYCLO[5.4.0]UNDEC-7-ENE); DCE (dichloroethane); DCM (dichloromethane); DEAD (diethyl azodicarboxylate); DIPEA (diisopropylethylamine); DMBA (1,3-dimethylbarbituric acid); DMF (N,N-dimethylformamide); DMP (Dess-Martin periodinane); DMSO (dimethyl sulfoxide); DPPA (diphenylphosphoryl azide); DTT (dithiothreitol); EDTA (ethylene-diamine-tetra-acetic acid); EGTA (ethylene-glycol-tetra-acetic acid); Et2O (diethylether); EtOAc (ethyl acetate); EtOH (ethanol); HOAc (acetic acid); HPLC (high-performance liquid chromatography); HRMS (high resolution mass spectrum); LAH (lithium aluminum hydride); LCMS (liquid chromatograph-mass spectrometer); LHMDS (lithium bis(trimethylsilyl)amide); LRMS (low resolution mass spectrum); mCPBA (3-chloroperoxybenzoic acid); MeOH (methanol); MP-B(CN)H3 (Macroporous cyanoborohydride); NaHCO3 (sodium bicarbonate); Na2SO4 (sodium sulfate); Na(Oac)3BH (sodium triacetoxyborohydride); NH4Oac (ammonium acetate); NBS (N-bromosuccinamide); NFSi (N-fluorobenzenesulfonimide); NMP (1-methyl-2-pyrrolidinone); NMR (nuclear magnetic resonance); PBS (phosphate buffered saline); PCR (polymerase chain reaction); Pd(dppf) ([1,1'-bis(diphenylphosphino)ferrocene] palladium); Pd(Ph3)4 (palladium(0) tetrakis-triphenylphosphine); POCl3 (phosphorous oxychloride); PS-DIEA (polystyrene diisopropylethylamine); PS-PPh3 (polystyrene-triphenyl phosphine); PTSA (para-toluene sulfonic acid); Pyr (pyridine); Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); TBAF (tetrabutylammonium fluoride); T-BuOH (tert-butanol); THF (tetrahydrofuran); Tf (trifluoromethanesulfonyl); TFA (trifluoroacteic acid); and TMSCH2N2 (trimethylsilyldiazomethane).

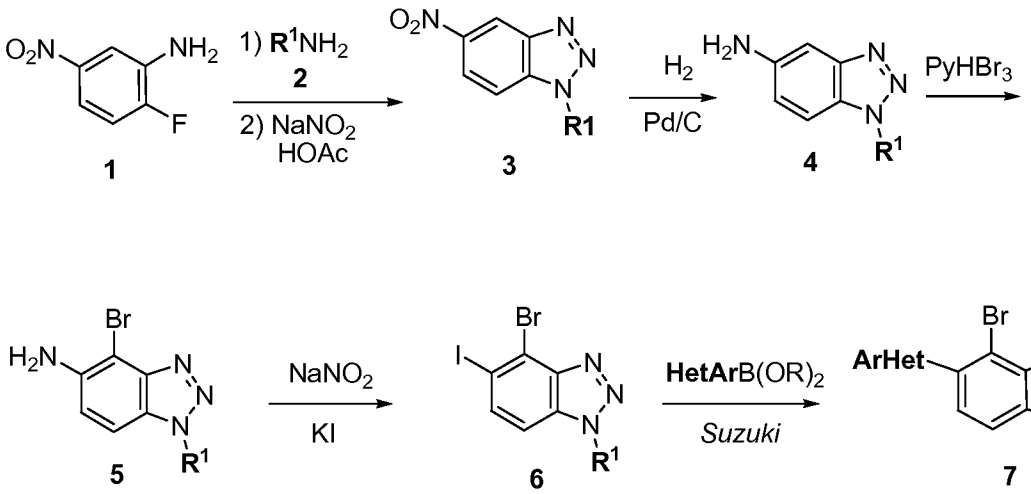
The compounds of this invention may be prepared by employing reactions as shown in the following Reaction Schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative Reaction Schemes below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the Reaction Schemes do not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are optionally allowed under the definitions of Formula A hereinabove.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in Reaction Scheme I.

SYNOPSIS OF REACTION SCHEMES

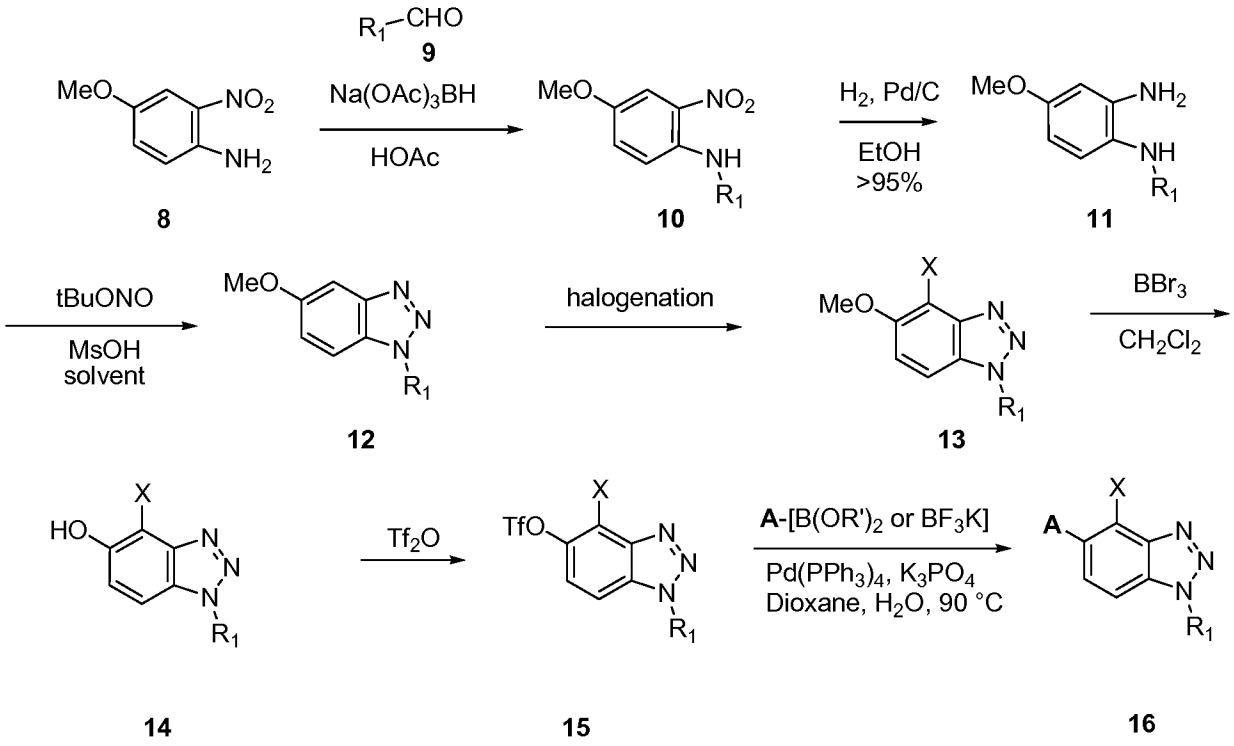
As shown in Reaction Scheme I, 2-fluoro-5-nitroaniline (**1**) can undergo an aromatic nucleophilic substitution with amine **2** to provide a nitrodianiline intermediate which cyclizes to form 5-nitrobenzotriazole (**3**) under diazotization conditions with $NaNO_2$. Hydrogenation of **3** with Pd/C as catalyst provides 5-aminobenzotriazole (**4**) which upon treatment with pyridium tribromide, yields 5-amino-4-bromobenzotriazole (**5**). Sandmeyer reaction of **5** with KI gives 4-bromo-5-iodobenzotriazole (**6**). Finally, compound **6** can be selectively coupled with boronic acid/esters via Suzuki coupling to provide the biaryl benzotrizole **7**.

Reaction Scheme I



As shown in Reaction Scheme II, nitroaniline (**8**) can be reacted with various aldehydes (**9**) to give substituted anilines (**10**). Catalytic hydrogenation can be used to reduce the nitro group to the amine (**11**) followed by cyclization to the benzotriazole with *t*-butyl nitrite. Various strategies can be employed to substituted at the C-4 position to give (**13**), with halogenation being an example. From the halogen, a Me or CN can be installed using Pd-catalyzed couplings with tetramethyl tin or zinc (II) cyanide respectively. Deprotection of the methyl ether can be effected by boron tribromide to give the phenol (**14**). The phenol can be treated with triflic anhydride to give **15**, which can be subsequently coupled to a variety aryl metals using palladium to give invention compounds **16.**

Reaction Scheme II



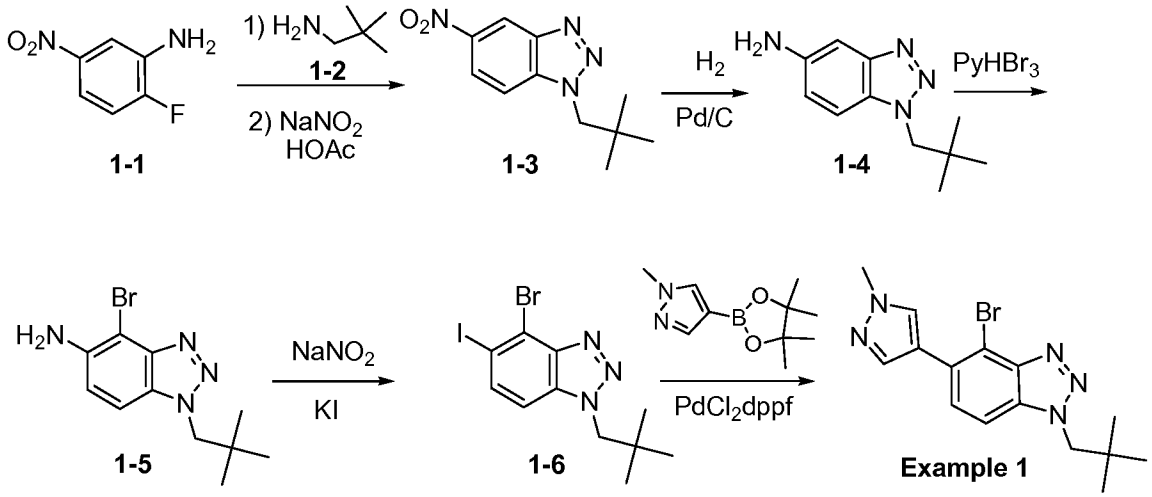
EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof. The reagents utilized in synthesizing the compounds depicted in the following Tables are either commercially available or are readily prepared by one of ordinary skill in the art.

EXAMPLE 1

4-bromo-1-(2,2-dimethylpropyl)-5-(1-methyl-1H- -pyrazol-4-yl)-1H-1,2,3-benzotriazole

Scheme 1



Step 1: 1-(2,2-dimethylpropyl)-5-nitro-*1H* -1,2,3-benzotriazole (**1-3**)

2-Fluoro-5-nitroaniline (**1-1**) (10.22 g, 65.5 mmol, 1.0 equiv.) was dissolved in anhydrous DMSO (100 ml), and then treated with neopentylamine (**1-2**) (7.71 ml, 65.5 mmol, 1.0 equiv.). The reaction mixture was heated at 120 °C for 2 days. The reaction mixture was cooled to room temperature and treated with acetic acid (25 ml), followed by addition of 0.65 M aqueous solution of sodium nitrite (121 ml, 79 mmol, 1.2equiv.). The mixture was then neutralized to pH7 with NaOH (1N) aqueous and diluted with water, which caused precipitation. The solid was collected on top of filter and washed twice with water. The crude solid was purified with normal phase silica gel chromatography (EtOAc/Hexane gradient from 0 to 100%) to yield 1-(2,2-dimethylpropyl)-5-nitro-1H -1,2,3-benzotriazole (**1-3**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (d, 1H, J = 2.0 Hz), 8.40 (dd, 1H, J = 9.1, 2.0 Hz), 7.62 (d, 1H, J = 9.1 Hz), 4.47 (s, 2H), 1.07 (s, 9H) ppm. LRMS m/z (M+H) 235.1 found, 235.3 required.

Step 2: 1-(2,2-Dimethylpropyl)-1H-1,2,3-benzotriazol-5-amine (**1-4**)

1-(2,2-Dimethylpropyl)-5-nitro-1H -1,2,3-benzotriazole (**1-3**) (4.46 g, 19.04 mmol, 1.0equiv.) was dissolved in ethanol (50 ml) and flushed with N_2, then charged with 10% Pd/C (2.026 g, 1.904 mmol, 0.1equiv.). After purging with first N_2 then H_2, a hydrogen balloon was attached. After stirring at room temperature for 5 hrs. The reaction mixture was filtered through a Celite funnel. The residue was washed with MeOH several times. The filtrate was

concentrated to give 1-1-(2,2-dimethylpropyl)-1H-1,2,3-benzotriazol-5-amine (**1-4**). LRMS m/z (M+H) 205.0 found, 205.3 required.

Step 3: 4-bromo-1-(2,2-dimethylpropyl)-1H-1,2,3-benzotriazol-5-amine (**1-5**)

1-(2,2-dimethylpropyl)-1H-1,2,3-benzotriazol-5-amine (**1-4**) (3.52 g, 17.23 mmol, 1.0 equiv.) was dissolved in $CHCl_3$ (172 ml) and treated with pyridinium tribromide (5.51 g, 17.23 mmol, 1.0equiv.). The reaction mixture was stirred at room temperature until LCMS showed almost only product. The solid was collected on top of filter, and washed with hexane. The solid was taken up in Et_2O/EtOAc, and neutralized with aqueous saturated $NaHCO_3$. The organic layers were combined and dried over anhydrous $MgSO_4$, filtered and concentrated to 4-bromo-1-(2,2-dimethylpropyl)-1H-1,2,3-benzotriazol-5-amine (**1-5**) as pale white solid. ^1H NMR (500 MHz, CD_3OD) δ 7.30 (d, 1H, J = 8.8 Hz), 7.07 (sb, 3H), 7.02 (d, 1H, J = 8.8 Hz), 4.34 (s, 2H), 1.03 (s, 9H) ppm. LRMS m/z (M+H) 283.0 and 285.0 (intensity ratio ~1:1) found, 283.1 and 285.1 required.

Step 4: 4-bromo-1-(2,2-dimethylpropyl)-5-iodo-1H-1,2,3-benzotriazol-5-amine (**1-6**)

To a solution of p-toluenesulfonic acid monohydrate (510 mg, 2.68 mmol) in acetonitrile (3574 µl), was added 4-bromo-1-(2,2-dimethylpropyl)-1H-1,2,3-benzotriazol-5-amine (**1-5**) (253 mg, 0.893 mmol). The resulting suspension was cooled to 10-15 °C. To this suspension, was added aqueous solution of sodium nitrite (537 µl, 1.787 mmol) and KI (536 µl, 2.234 mmol). The reaction mixture was stirred for 10 minutes before it was warmed to 20 °C. To the reaction mixture was then diluted with water and neutralized with $NaHCO_3$ (1 M) to pH 9-10 followed by treatment with 3M aqueous solution of $Na_2S_2O_3$ (6 mL). The precipitated aromatic iodide was collected on top of filter, and washed with cold Et_2O and hexanes. The crude product was purified with normal phase silica gel chromatography using (EtOAc/hexanes gradient) to obtain 4-bromo-1-(2,2-dimethylpropyl)-5-iodo-1H-1,2,3-benzotriazol-5-amine (**1-6**). ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, 1H, J = 8.7 Hz), 7.25 (d, 1H, J = 9.0 Hz), 4.36 (s, 2H), 1.04 (s, 9H) ppm. LRMS m/z (M+H) 393.8 and 395.8 found, 393.9 and 395.9 required.

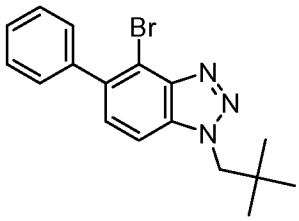
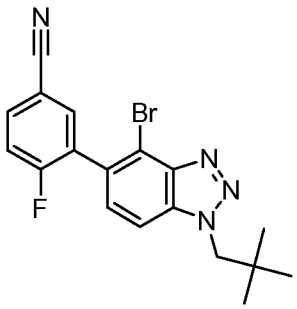
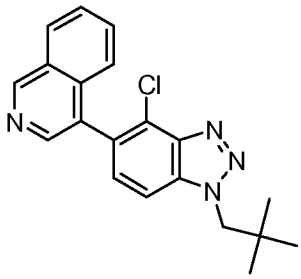
Step 5: 4-bromo-1-(2,2-dimethylpropyl)-5-(1-methyl-1H- -pyrazol-4-yl)-1H-1,2,3-benzotriazole (Example 1)

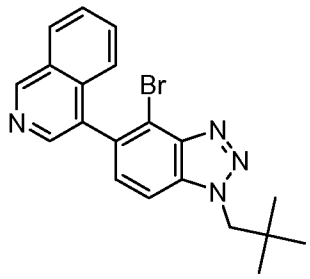
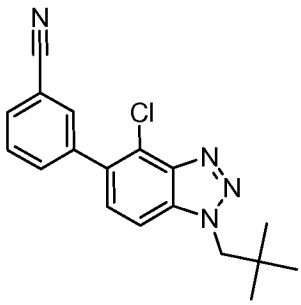
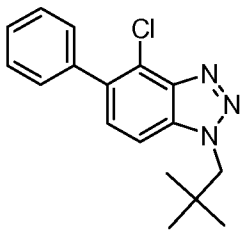
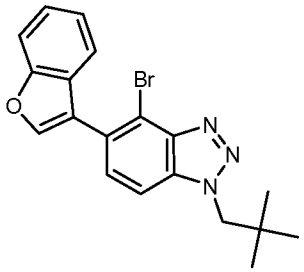
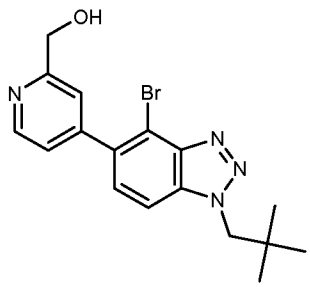
To a suspension of 4-bromo-1-(2,2-dimethylpropyl)-5-iodo-1H-1,2,3-benzotriazol-5-amine (**1-6**) (20 mg, 0.051 mmol, 1.0 equiv.), 1-methyl-4-(4,4,5,5-tetramethyl-

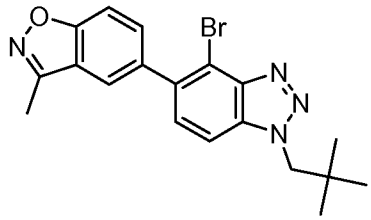
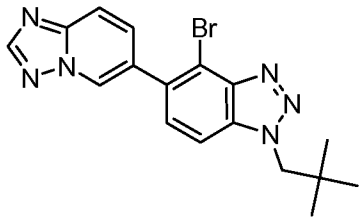
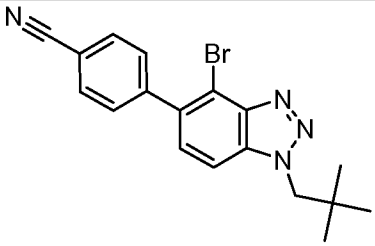
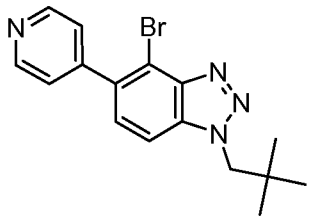
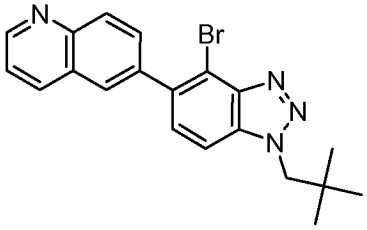
1,3,2-dioxaborolan-2-yl)-1H-pyrazole (11.09 mg, 0.053 mmol, 1.05equiv.), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (4.14 mg, 5.08 μmol, 0.1equiv.) in 1,4-dioxane (0.5 ml), was added a 1M aqueous solution of Cs_2CO_3 (0.102 ml, 0.102 mmol, 2.0equiv.). The reaction mixture was irradiated at 100 °C in microwave reactorfor 10 minutes. The mixture was purified by reverse phase HPLC (H_2O/ CH_3CN gradient containing 0.1% TFA) to afford Example 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.87 (s, 1H), 7.53 (d, 1H, J = 8.6 Hz), 7.46 (d, 1H, J = 8.6 Hz), 4.41 (s, 2H), 4.04 (s, 3H), 1.07 (s, 9H). LRMS m/z (M+H) 348.0 and 350.0 found, 348.1 and 350.1 required.

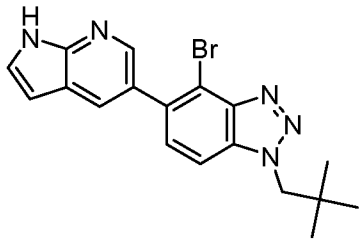
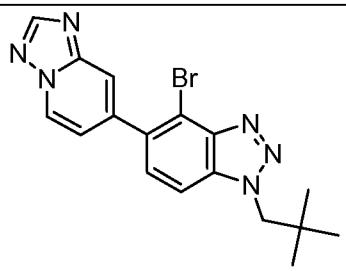
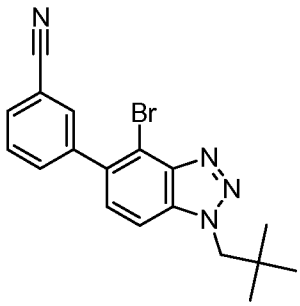
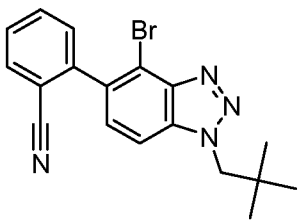
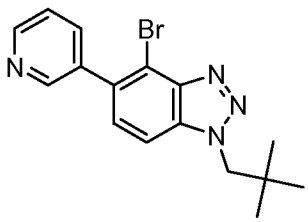
The compounds shown in Table 1 were synthesized according to the Reaction Scheme 1 and Example 1. The compounds below were isolated as a TFA salt or neutral species.

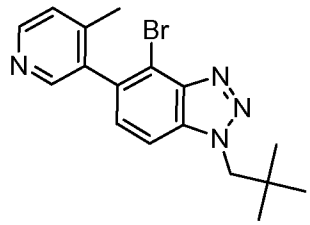
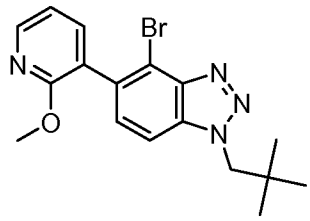
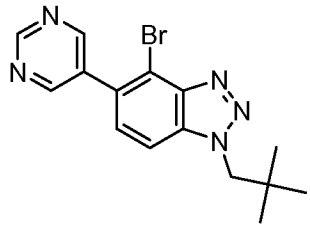
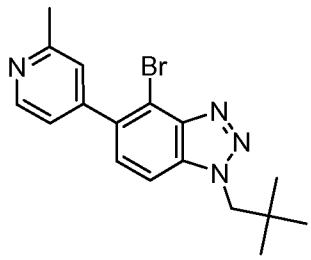
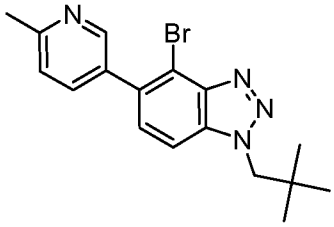
Table 1

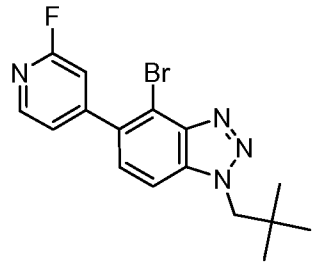
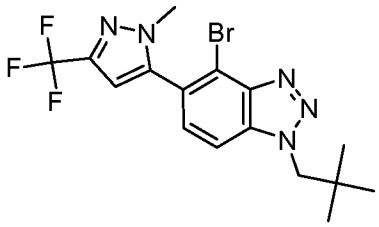
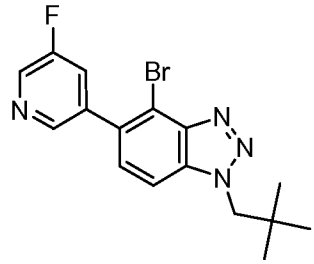
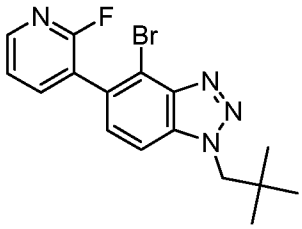
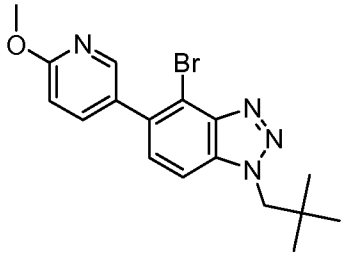
Ex.	Structure	Name	LRMS *m/z* (M+H)
2		4-bromo-1-(2,2-dimethylpropyl)-5-phenyl-1*H*-benzotriazole	LRMS *m/z* (M+H) 344.0 and 346.0 (intensity ratio ~1:1) found, 344.1 and 346.1 required.
3		3-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]-4-fluorobenzonitrile	LRMS *m/z* (M+H) 387.0 and 389.0 (intensity ratio ~1:1) found, 387.1 and 389.1 required.
4		4-[4-chloro-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]isoquinoline	LRMS *m/z* (M+H) 351.0 found, 351.1 required.

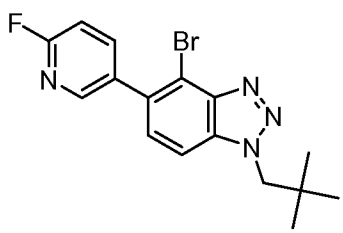
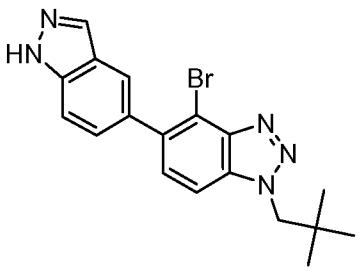
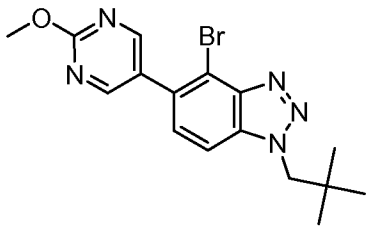
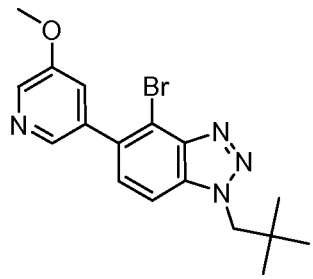
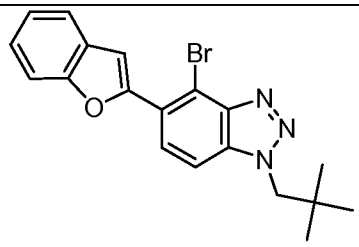
Ex.	Structure	Name	LRMS *m/z* (M+H)
5		4-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]isoquinoline	LRMS *m/z* (M+H) 395.0 and 397.0 (intensity ratio ~1:1) found, 395.1 and 397.1 required.
6		3-[4-chloro-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile	LRMS *m/z* (M+H) 325.0 found, 325.1 required.
7		4-chloro-1-(2,2-dimethylpropyl)-5-phenyl-1*H*-benzotriazole	LRMS *m/z* (M+H) 300.1 found, 300.1 required.
8		5-(1-benzofuran-3-yl)-4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 384.1 and 386.1 (intensity ratio ~1:1) found, 384.1 and 386.1 required.
9		{4-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl] yridine-2-yl}methanol	LRMS *m/z* (M+H) 375.1 and 377.1 (intensity ratio ~1:1) found, 375.1 and 377.1 required.

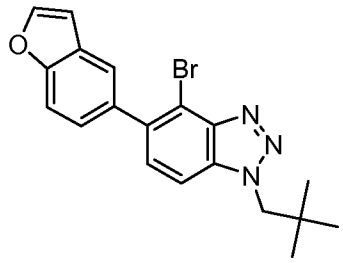
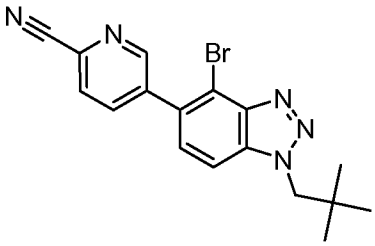
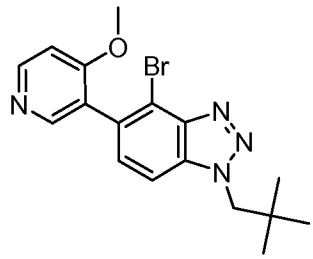
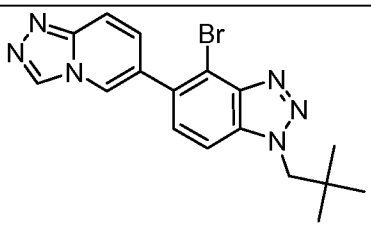
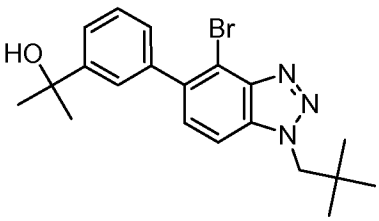
Ex.	Structure	Name	LRMS *m/z* (M+H)
10		4-bromo-1-(2,2-dimethylpropyl)-5-(3-methyl-1,2-benzisoxazol-5-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 399.1 and 401.1 (intensity ratio ~1:1) found, 399.1 and 401.1 required.
11		4-bromo-1-(2,2-dimethylpropyl)-5-[1,2,4]triazolo[1,5-a] yridine-6-yl-1*H*-benzotriazole	LRMS *m/z* (M+H) 385.1 and 387.1 (intensity ratio ~1:1) found, 385.1 and 387.1 required.
12		4-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile	LRMS *m/z* (M+H) 369.1 and 371.1 (intensity ratio ~1:1) found, 369.1 and 371.1 required.
13		4-bromo-1-(2,2-dimethylpropyl)-5-pyridin-4-yl-1*H*-benzotriazole	LRMS *m/z* (M+H) 345.1 and 347.1 (intensity ratio ~1:1) found, 345.1 and 347.1 required.
14		6-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]quinoline	LRMS *m/z* (M+H) 359.1 and 361.1 (intensity ratio ~1:1) found, 395.1 and 397.1 required.

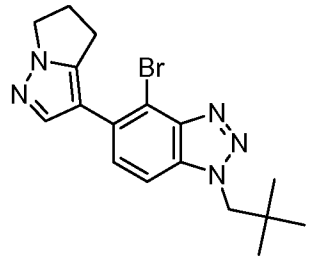
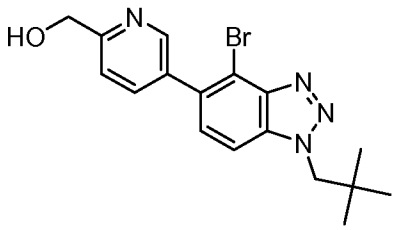
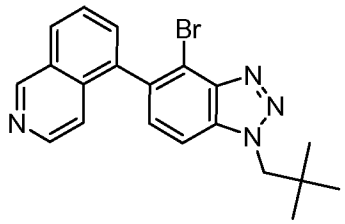
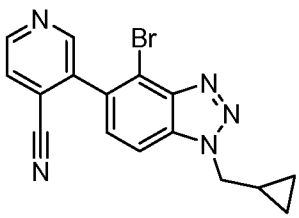
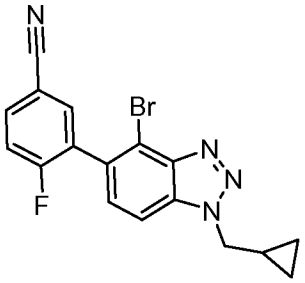
Ex.	Structure	Name	LRMS *m/z* (M+H)
15		4-bromo-1-(2,2-dimethylpropyl)-5-(1*H*-pyrrolo[2,3-b] yridine-5-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 384.1 and 386.1 (intensity ratio ~1:1) found, 384.1 and 386.1 required.
16		4-bromo-1-(2,2-dimethylpropyl)-5-[1,2,4]triazolo[1,5-a] yridine-7-yl-1*H*-benzotriazole	LRMS *m/z* (M+H) 385.1 and 387.1 (intensity ratio ~1:1) found, 385.1 and 387.1 required.
17		3-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile	LRMS *m/z* (M+H) 369.1 and 371.1 (intensity ratio ~1:1) found, 369.1 and 371.1 required.
18		2-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile	LRMS *m/z* (M+H) 369.1 and 371.1 (intensity ratio ~1:1) found, 369.1 and 371.1 required.
19		4-bromo-1-(2,2-dimethylpropyl)-5-pyridin-3-yl-1*H*-benzotriazole	LRMS *m/z* (M+H) 345.1 and 347.1 (intensity ratio ~1:1) found, 345.1 and 347.1 required.

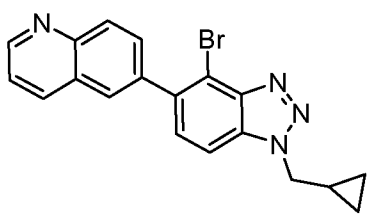
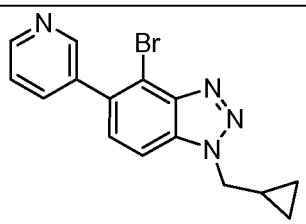
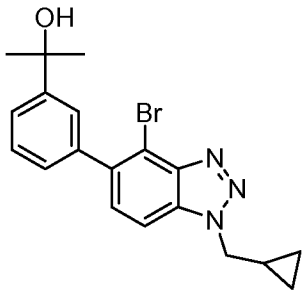
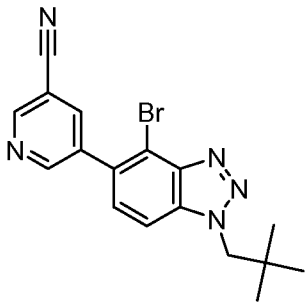
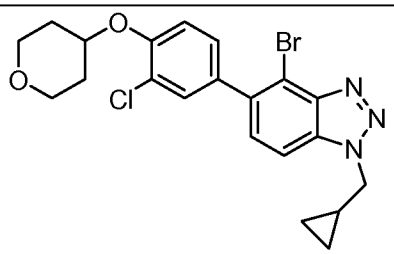
Ex.	Structure	Name	LRMS *m/z* (M+H)
20		4-bromo-1-(2,2-dimethylpropyl)-5-(4-methylpyridin-3-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 359.1 and 361.1 (intensity ratio ~1:1) found, 359.1 and 361.1 required.
21		4-bromo-1-(2,2-dimethylpropyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 375.1 and 377.1 (intensity ratio ~1:1) found, 375.1 and 377.1 required.
22		4-bromo-1-(2,2-dimethylpropyl)-5-pyrimidin-5-yl-1*H*-benzotriazole	LRMS *m/z* (M+H) 346.1 and 348.1 (intensity ratio ~1:1) found, 346.1 and 348.1 required.
23		4-bromo-1-(2,2-dimethylpropyl)-5-(2-methylpyridin-4-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 359.1 and 361.1 (intensity ratio ~1:1) found, 359.1 and 361.1 required.
24		4-bromo-1-(2,2-dimethylpropyl)-5-(6-methylpyridin-3-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 359.1 and 361.1 (intensity ratio ~1:1) found, 359.1 and 361.1 required.

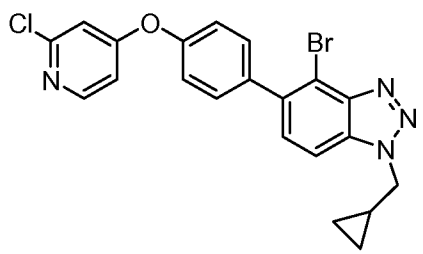
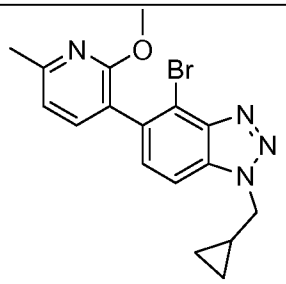
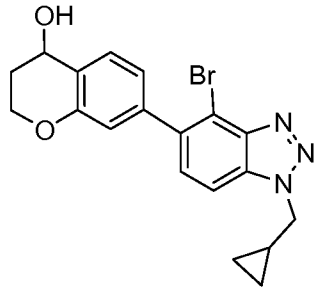
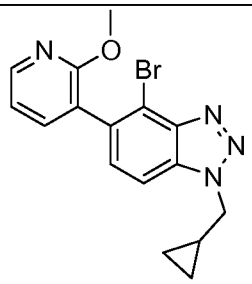
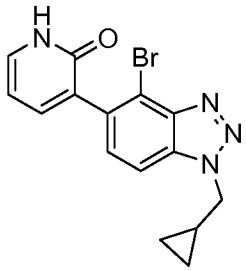
Ex.	Structure	Name	LRMS *m/z* (M+H)
25		4-bromo-1-(2,2-dimethylpropyl)-5-(2-fluoropyridin-4-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 363.1 and 365.1 (intensity ratio ~1:1) found, 363.1 and 365.1 required.
26		4-bromo-1-(2,2-dimethylpropyl)-5-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-1H-benzotriazole	LRMS *m/z* (M+H) 416.1 and 418.1 (intensity ratio ~1:1) found, 416.1 and 418.1 required.
27		4-bromo-1-(2,2-dimethylpropyl)-5-(5-fluoropyridin-3-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 363.1 and 365.1 (intensity ratio ~1:1) found, 363.1 and 365.1 required.
28		4-bromo-1-(2,2-dimethylpropyl)-5-(2-fluoropyridin-3-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 363.1 and 365.1 (intensity ratio ~1:1) found, 363.1 and 365.1 required.
29		4-bromo-1-(2,2-dimethylpropyl)-5-(6-methoxypyridin-3-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 375.1 and 377.1 (intensity ratio ~1:1) found, 375.1 and 377.1 required.

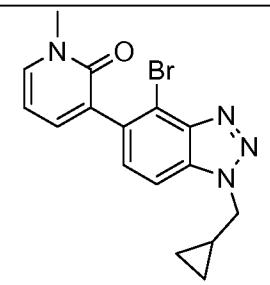
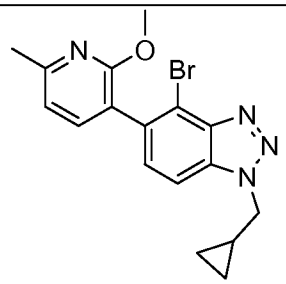
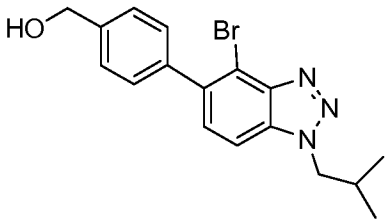
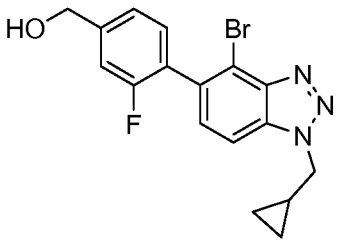
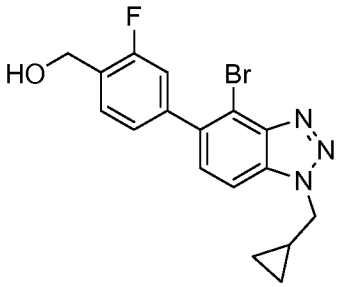
Ex.	Structure	Name	LRMS *m/z* (M+H)
30		4-bromo-1-(2,2-dimethylpropyl)-5-(6-fluoropyridin-3-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 363.1 and 365.1 (intensity ratio ~1:1) found, 363.1 and 365.1 required.
31		4-bromo-1-(2,2-dimethylpropyl)-5-(1*H*-indazol-5-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 384.1 and 386.1 (intensity ratio ~1:1) found, 384.1 and 386.1 required.
32		4-bromo-1-(2,2-dimethylpropyl)-5-(2-methoxypyrimidin-5-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 376.1 and 378.1 (intensity ratio ~1:1) found, 376.1 and 378.1 required.
33		4-bromo-1-(2,2-dimethylpropyl)-5-(5-methoxypyridin-3-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 375.1 and 377.1 (intensity ratio ~1:1) found, 375.1 and 377.1 required.
34		5-(1-benzofuran-2-yl)-4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 384.1 and 386.1 (intensity ratio ~1:1) found, 384.1 and 386.1 required.

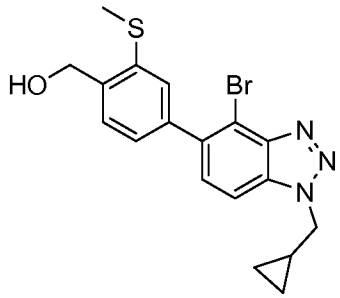
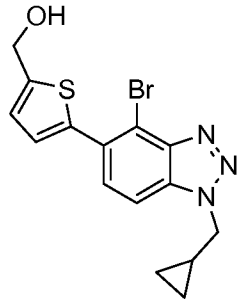
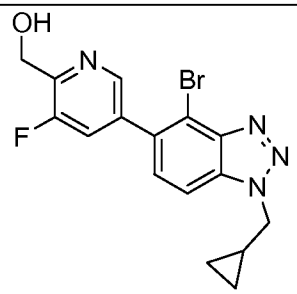
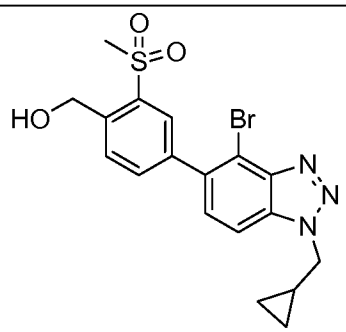
Ex.	Structure	Name	LRMS *m/z* (M+H)
35		5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridine-2-carbonitrile	LRMS *m/z* (M+H) 384.1 and 386.1 (intensity ratio ~1:1) found, 384.1 and 386.1 required.
36		5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridine-2-carbonitrile	LRMS *m/z* (M+H) 370.1 and 372.1 (intensity ratio ~1:1) found, 370.1 and 372.1 required.
37		4-bromo-1-(2,2-dimethylpropyl)-5-(4-methoxypyridin-3-yl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 375.1 and 377.1 (intensity ratio ~1:1) found, 375.1 and 377.1 required.
38		4-bromo-1-(2,2-dimethylpropyl)-5-[1,2,4]triazolo[4,3-a] yridine-6-yl-1*H*-benzotriazole	LRMS *m/z* (M+H) 385.1 and 387.1 (intensity ratio ~1:1) found, 385.1 and 387.1 required.
39		2-{3-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]phenyl}propan-2-ol	LRMS *m/z* (M+H) 402.1 and 404.1 (intensity ratio ~1:1) found, 402.1 and 404.1 required.

Ex.	Structure	Name	LRMS *m/z* (M+H)
40		4-bromo-5-(5,6-dihydro-4H-pyrrolo[1,2-b] yridine-3-yl)-1-(2,2-dimethylpropyl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 374.1 and 376.1 (intensity ratio ~1:1) found, 374.1 and 376.1 required.
41		{5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl] yridine-2-yl}methanol	LRMS *m/z* (M+H) 375.1 and 377.1 (intensity ratio ~1:1) found, 375.1 and 377.1 required.
42		5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]isoquinoline	LRMS *m/z* (M+H) 395.1 and 397.1 (intensity ratio ~1:1) found, 395.1 and 397.1 required.
43		3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-4-carbonitrile	LRMS *m/z* (M+H) 354.0 and 356.0 (intensity ratio ~1:1) found, 354.0 and 356.0 required.
44		3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-4-fluorobenzonitrile	LRMS *m/z* (M+H) 370.9 and 372.9 (intensity ratio ~1:1) found, 371.0 and 373.0 required.

Ex.	Structure	Name	LRMS *m/z* (M+H)
45		6-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]quinoline	LRMS *m/z* (M+H) 378.9 and 380.9 (intensity ratio ~1:1) found, 379.0 and 381.0 required.
46		3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridinium trifluoroacetate	LRMS *m/z* (M+H) 329.0 and 331.0 (intensity ratio ~1:1) found, 329.0 and 331.0 required.
47		2-{3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}propan-2-ol	LRMS *m/z* (M+H) 386.0 and 388.0 (intensity ratio ~1:1) found, 386.1 and 388.1 required.
48		5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridine-3-carbonitrile	LRMS *m/z* (M+H) 370.0 and 372.0 (intensity ratio ~1:1) found, 370.1 and 372.1 required.
49		4-bromo-5-[3-chloro-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl]-1-(cyclopropylmethyl)-1*H*-benzotriazole	LRMS *m/z* (M+H) 462.0 and 464.0 (intensity ratio ~3:4) found, 462.1 and 464.1 required.

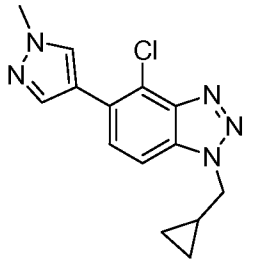
Ex.	Structure	Name	LRMS *m/z* (M+H)
50		4-bromo-5-{4-[(2-chloropyridin-4-yl)oxy]phenyl}-1-(cyclopropylmethyl)-1*H*-1,2,3-benzotriazole	LRMS *m/z* (M+H) 455.0 and 457.0 (intensity ratio ~3:4) found, 455.0 and 457.0 required.
51		4-bromo-1-(cyclopropylmethyl)-5-(2-methoxy-6-methylpyridin-3-yl)-1*H*-benzotriazole	LRMS m/z (M+H) 375.2 found, 375.1 required
52		7-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3,4-dihydro-2*H*-chromen-4-ol	LRMS m/z (M+H) 401.1 found, 401.8 required
53		4-bromo-1-(cyclopropylmethyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole	LRMS m/z (M+H) 361.1 found, 361.1 required
54		3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl] yridine-2(1*H*)-one	LRMS m/z (M+H) 347.1 found, 347.1 required

Ex.	Structure	Name	LRMS *m/z* (M+H)
55		3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-1-methylpyridin-2(1*H*)-one	LRMS m/z (M+H) 361.1 found, 361.1 required
56		4-bromo-1-(cyclopropylmethyl)-5-(2-methoxy-6-methylpyridin-3-yl)-1*H*-benzotriazole	LRMS m/z (M+H) 375.2 found, 375.1 required
57		{4-[4-bromo-1-(2-methylpropyl)-1*H*-benzotriazol-5-yl]phenyl}methanol	LRMS m/z (M+H) 361.9 found, 360.3 required
58		{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluorophenyl}methanol	LRMS m/z (M+H) 378.1 found, 378 required
59		{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-fluorophenyl}methanol	LRMS m/z (M+H) 376.1 found, 376.1 required

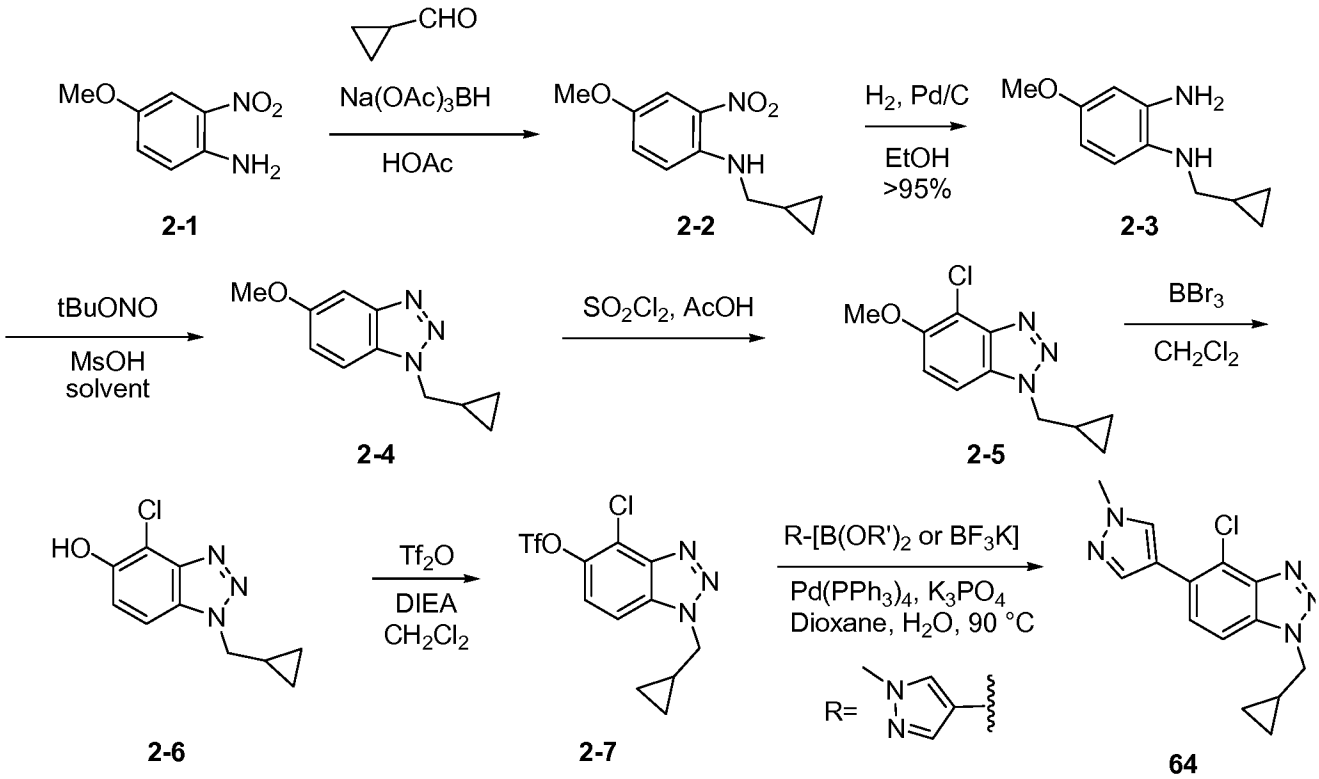
Ex.	Structure	Name	LRMS *m/z* (M+H)
60		{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-(methylsulfanyl)phenyl}methanol	LRMS m/z (M+H) 406.1 found, 406.1 required
61		{5-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]thiophen-2-yl}methanol	LRMS m/z (M+H) 366.1 found, 366.1 required
62		{5-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluoropyridin-2-yl}methanol	LRMS m/z (M+H) 379.1 found, 379.1 required
63		{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-(methylsulfonyl)phenyl}methanol	LRMS m/z (M+H) 437.8 found, 437.1 required

Example 64

4-Chloro-1-(cyclopropylmethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-benzotriazole



Preparation of Example 64:



Step 1 **Preparation of *N*-(cyclopropylmethyl)-4-methoxy-2-nitroaniline (2-2):**

To a 5 L vessel was charged 4-methoxy-2-nitroaniline (160 g, 952 mmol) in dichloromethane (2.44 L). The reaction mixture was cooled to 10 °C and cyclopropanecarboxyaldehyde (100 g, 143 mmol) was added in four 25 gram portions. The vessel was charged with acetic acid (300 ml, 523 mmol) via an addition funnel fitted on the reactor and charged to the reaction mixture over 20 minutes. After 45 minutes, the vessel was charged with sodium triacetoxyborohydride (444 g, 209 mmol) portionwise. The mixture was warmed to ambient temperature over 4 hours and was stirred for an additional 14 hours. The mixture was treated with saturated aqueous sodium bicarbonate (100 mL) and poured into

sodium bicarbonate (4 L) and dichloromethane. The organic extract was concentrated *in vacuo*, providing the titled compound.

Step 2 Preparation of N^1-(cyclopropylmethyl)-4-methoxybenzene-1,2-diamine (2-3):

N-(Cyclopropylmethyl)-4-methoxy-2-nitroaniline (175 g) was dissolved in ethanol (1750 mL) and was added to a 4.0 L Hast 'C" Shaker can. The mixture was cooled to 10 °C and treated with 3% Pt/0.6%VG/C, deGussa (4.5 g). The vessel was sparged under nitrogen and then sparged three times with hydrogen at a setting of 40 psi and agitated for 2.5 hours. To a pre-washed solka-flok with ethanol, the reaction mixture was filtered through solka-flok through a sintered glass funnel to have about a ½ inch depth of solka-flok. The solka-flok was then washed with 1 L ethanol and concentrated *in vacuo*, providing the titled compound.

Step 3 Preparation of 1-(cyclopropylmethyl)-5-methoxy-1*H*-benzotriazole (2-4):

N^1-(Cyclopropylmethyl)-4-methoxybenzene-1,2-diamine (10.8 g, 56.2 mmol) was dissolved in ethanol (80 mL) and treated with methanesulfonic acid (3.65 ml, 56.2 mmol) followed by isoamyl nitrite (7.56 ml, 56.2 mmol). The mixture was stirred for 15 minutes, diluted with ethyl acetate (1500 mL) and washed with saturated bicarbonate solution (500 mL x 2). The organic extracts were concentrated *in vacuo*, providing a dark solid. The residue was purified by silica gel gradient chromatography (5-50% ethyl acetate in heptanes), providing the titled compound as a tan solid.

Step 4 Preparation of 4-chloro-1-(cyclopropylmethyl)-5-methoxy-1*H*-benzotriazole (2-5):

1-(Cyclopropylmethyl)-5-methoxy-1*H*-benzotriazole (10 g, 49 mmol) was dissolved in acetic acid (100 mL), cooled to 0 °C and treated with sulfuryl dichloride (4.8 mL, 59 mmol, 1.2 equiv) over three minutes. The mixture was warmed to ambient temperature over three hours and stirred for an additional 14 hours. The mixture was diluted with ethyl acetate and washed with aqueous saturated sodium bicarbonate. The organic layer was dried with magnesium sulfate, filtered and partially concentrated in vacuo to ~30 mL, which was then treated with water. The resulting precipitate was filtered, collected and dried *in vacuo*, providing the titled compound.

Step 5 Preparation of 4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-ol (2-6):

4-Chloro-1-(cyclopropylmethyl)-5-methoxy-1*H*-benzotriazole (10.5 g, 44.2 mmol) was dissolved in dichloromethane (200 mL), cooled to 0 °C and treated with boron tribromide (88 mL, 1M dichloromethane solution, 88 mmol, 2 equiv). The ice bath was removed and the mixture was stirred for 4 hours at ambient temperature. The mixture was slowly treated with water (10 mL) and then treated with sodium hydroxide (1N aqueous) until pH >10. After stirring for an additional 30 minutes, ammonium chloride (aqueous saturated) was added until the pH of the mixture was adjusted to pH 6–7. The aqueous mixture was extracted exhaustively with dichloromethane containing 5% methanol. The combined organic extracts were dried with sodium sulfate, filtered and concentrated *in vacuo*, providing the titled compound as a light brown solid.

Step 6 Preparation of 4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl trifluoromethanesulfonate (2-7):

4-Chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-ol (2.91 g, 13.0 mmol) was suspended in dichloromethane (40 mL), cooled to 0 °C and treated with *N,N*-diisopropylethylamine (4.55 mL, 26.0 mmol, 2 equiv). The mixture was treated with trifluoromethanesulfonic anhydride (2.86 mL, 16.9 mmol, 1.3 equiv) and stirred for 30 minutes. The mixture was poured into ammonium chloride (100 mL, aqueous saturated) and extracted with dichloromethane (2 X 150 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel gradient chromatography (100:0 to 1:1; hexanes : ethyl acetate), providing the titled compound as a light brown solid.

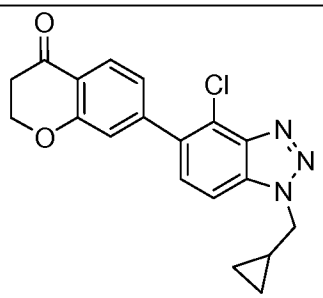
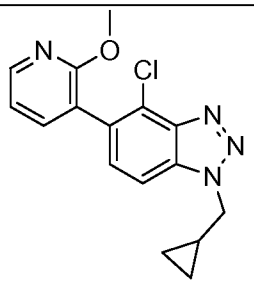
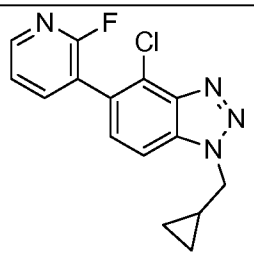
Step 7 Preparation of 4-chloro-1-(cyclopropylmethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-benzotriazole (Example 64):

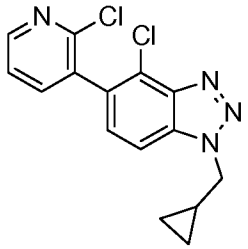
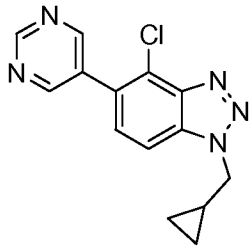
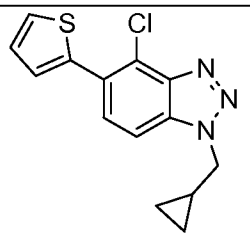
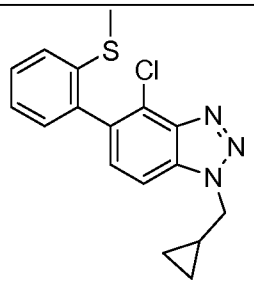
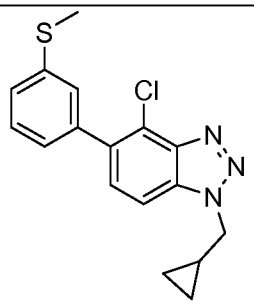
4-Chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl trifluoromethanesulfonate (54 mg, 0.15 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (32 mg, 0.152 mmol, 1 equiv), potassium phosphate (97 mg, 0.45 mmol, 3 equiv) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol, 0.1 equiv) were combined in degassed dioxane (1 mL) and water (0.1 mL) and placed into a preheated oil bath at 90 °C for 1 hour. The mixture was cooled to ambient temperature, poured into sodium bicarbonate (15 mL, aqueous saturated) and extracted with ethyl acetate (2 X 25 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by

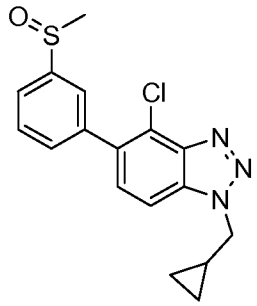
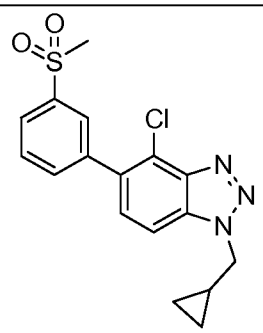
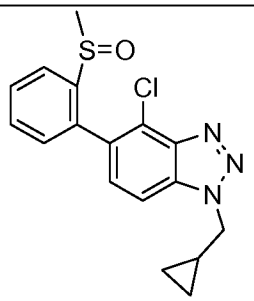
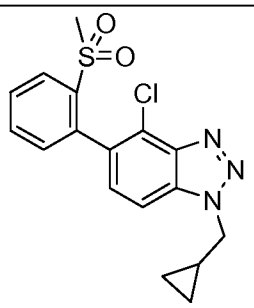
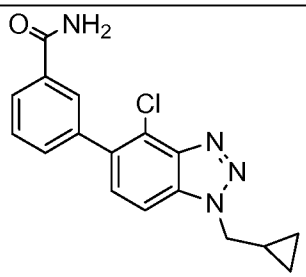
silica gel gradient chromatography (100:0 to 0:100; hexanes : ethyl acetate), providing the titled compound as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, s), 7.85 (1H, s), 7.61 (1H, d, *J* = 8.6 Hz), 7.48 (1H, d, *J* = 8.6 Hz), 4.53 (2H, d, *J* = 7.2 Hz), 4.01 (3H, s), 1.46–1.36 (1H, m), 0.70–0.65 (2H, m), 0.52–0.48 (2H, m) ppm; high resolution mass spectrometry (ES+) *m/z* 288.1016 [$(M+H)^+$; calculated for $C_{14}H_{15}ClN_5$: 288.1011].

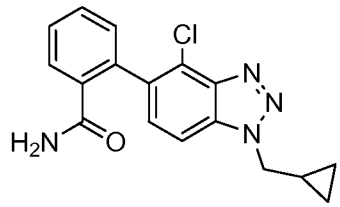
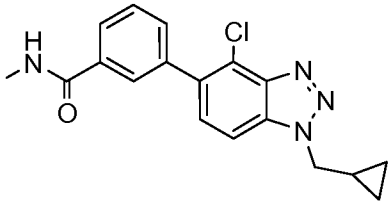
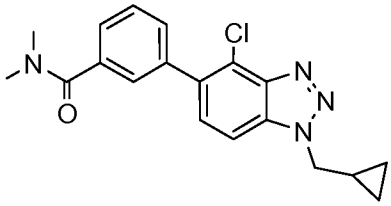
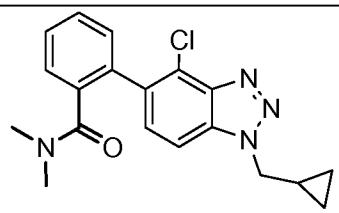
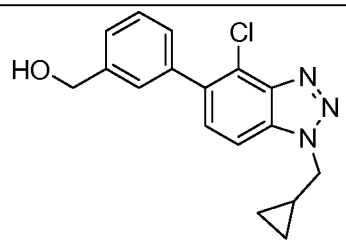
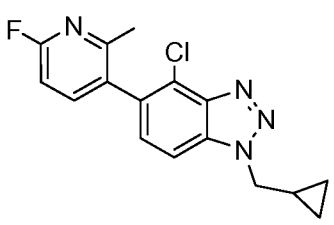
The following compounds were prepared according to the general procedure described in **Example 64**, substituting the appropriate boronate ester, boronic acid or potassium trifluoroborate salt for 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (Step 7). The starting materials are either commercially available, known in the literature or may be prepared from commercially available reagents using conventional reactions well known in the art.

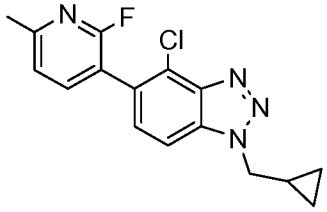
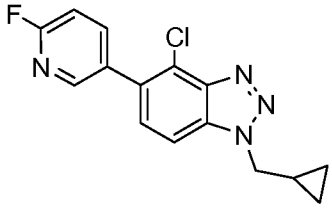
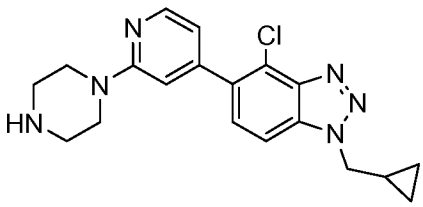
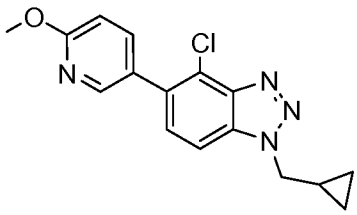
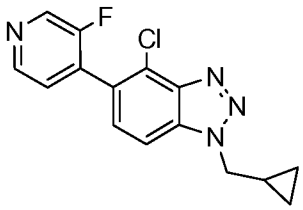
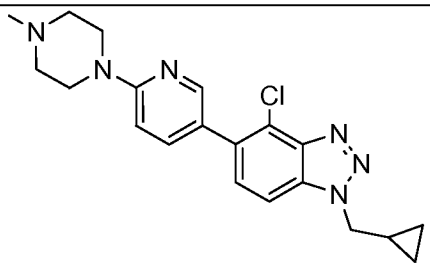
Table 2

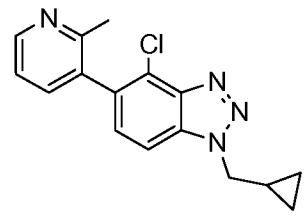
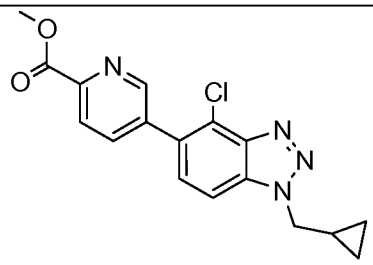
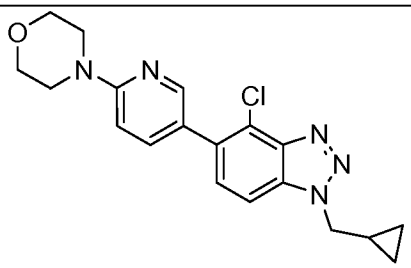
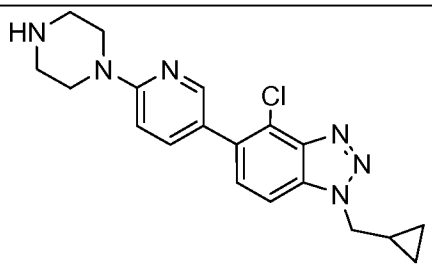
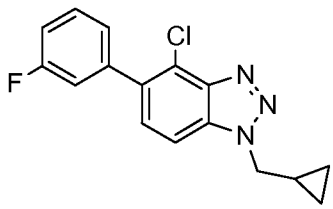
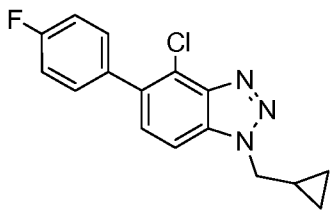
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
65		7-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2,3-dihydro-4*H*-chromen-4-one	$C_{19}H_{17}ClN_3O_2$ [M+H] Calc'd 355.1, found 354.0
66		4-chloro-1-(cyclopropylmethyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole	$C_{16}H_{16}ClN_4O$ [M+H] Calc'd 317.2 found 317.1
67		4-chloro-1-(cyclopropylmethyl)-5-(2-fluoropyridin-3-yl)-1*H*-benzotriazole	$C_{15}H_{13}ClFN_4$ [M+H] Calc'd 305.2 found 305.0

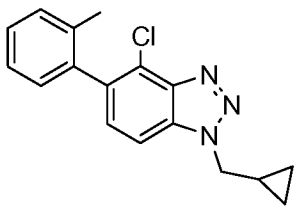
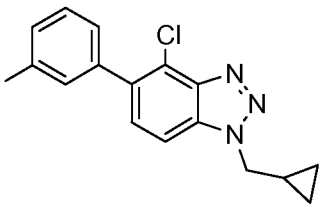
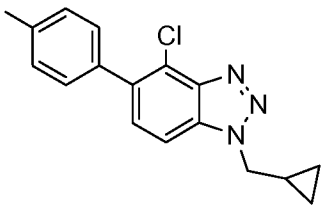
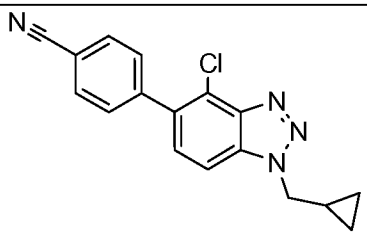
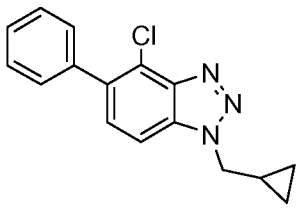
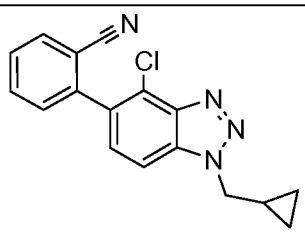
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
68		4-chloro-5-(2-chloropyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole	$C_{15}H_{13}Cl_2N_4$ [M+H] Calc'd 319.1 found 319.1
69		4-chloro-1-(cyclopropylmethyl)-5-(pyrimidin-5-yl)-1*H*-benzotriazole	$C_{14}H_{13}ClN_5$ [M+H] Calc'd 286.1 found 286.1
70		4-chloro-1-(cyclopropylmethyl)-5-(thiophen-2-yl)-1*H*-benzotriazole	$C_{14}H_{13}ClN_3S$ [M+H] Calc'd 290.1 found 290.1
71		4-chloro-1-(cyclopropylmethyl)-5-[2-(methylsulfanyl)phenyl]-1*H*-benzotriazole	$C_{17}H_{17}ClN_3S$ [M+H] Calc'd 330.1 found 330.1
72		4-chloro-1-(cyclopropylmethyl)-5-[3-(methylsulfanyl)phenyl]-1*H*-benzotriazole	$C_{17}H_{17}ClN_3S$ [M+H] Calc'd 330.1 found 330.1

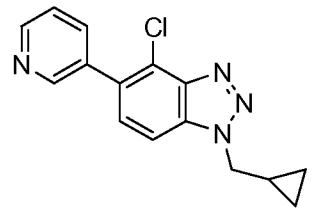
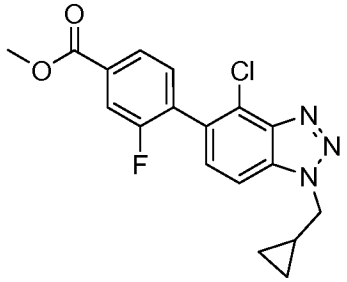
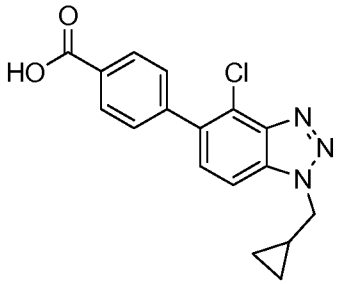
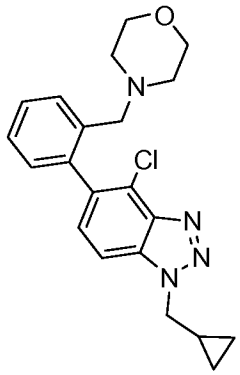
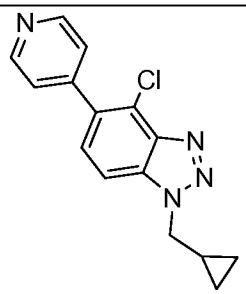
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
73		4-chloro-1-(cyclopropylmethyl)-5-[3-(methylsulfinyl)phenyl]-1*H*-benzotriazole	$C_{17}H_{16}ClN_3OS$ [M+H] Calc'd 346.1 found 346.1
74		4-chloro-1-(cyclopropylmethyl)-5-[3-(methylsulfonyl)phenyl]-1*H*-benzotriazole	$C_{17}H_{16}ClN_3O_2S$ [M+H] Calc'd 362.1 found 362.1
75		4-chloro-1-(cyclopropylmethyl)-5-[2-(methylsulfinyl)phenyl]-1*H*-benzotriazole	$C_{17}H_{17}ClN_3OS$ [M+H] Calc'd 346.1 found 346.1
76		4-chloro-1-(cyclopropylmethyl)-5-[2-(methylsulfonyl)phenyl]-1*H*-benzotriazole	$C_{17}H_{17}ClN_3O_2S$ [M+H] Calc'd 362.1 found 362.1
77		3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzamide	$C_{17}H_{16}ClN_4O$ [M+H] Calc'd 327.1011 found 327.1007

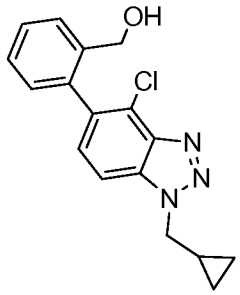
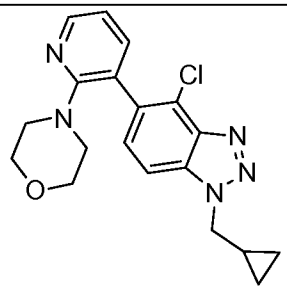
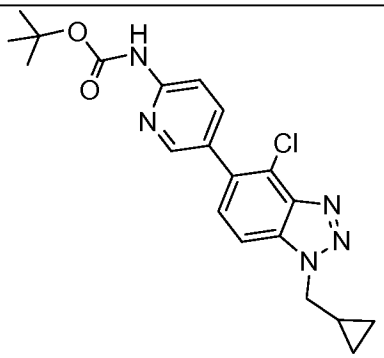
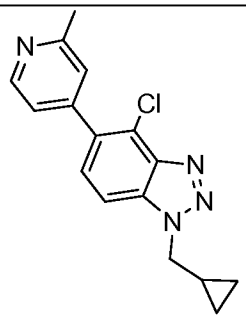
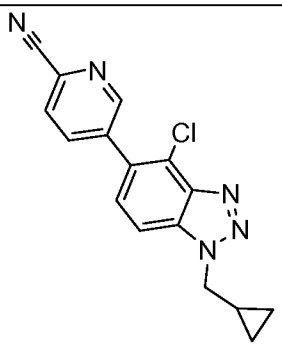
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
78		2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzamide	$C_{17}H_{16}ClN_4O$ [M+H] Calc'd 327.1011 found 327.1007
79		3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-*N*-methylbenzamide	$C_{18}H_{18}ClN_4O$ [M+H] Calc'd 341.1167 found 341.1164
80		3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-*N,N*-dimethylbenzamide	$C_{19}H_{20}ClN_4O$ [M+H] Calc'd 355.1323 found 355.1320
81		2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-*N,N*-dimethylbenzamide	$C_{19}H_{20}ClN_4O$ [M+H] Calc'd 355.1323 found 355.1320
82		{3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}methanol	$C_{17}H_{17}ClN_3O$ [M+H] calc'd 314.1058 found 314.1049
83		4-chloro-1-(cyclopropylmethyl)-5-(6-fluoro-2-methylpyridin-3-yl)-1*H*-benzotriazole	$C_{16}H_{15}ClFN_4$ [M+H] calc'd 317.0967 found 317.0961

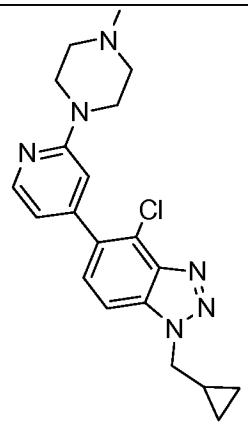
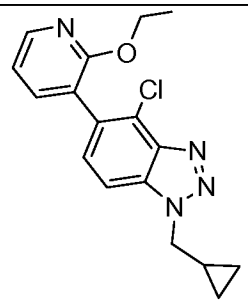
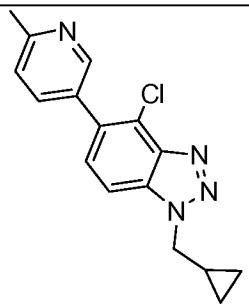
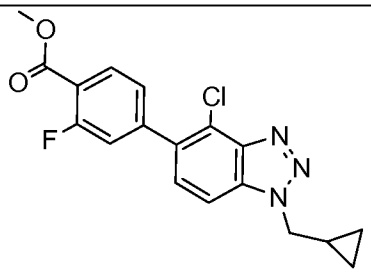
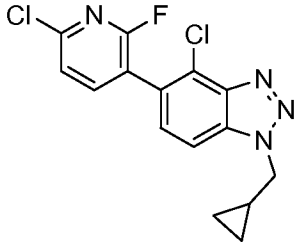
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
84		4-chloro-1-(cyclopropylmethyl)-5-(2-fluoro-6-methylpyridin-3-yl)-1*H*-benzotriazole	$C_{16}H_{15}ClFN_4$ [M+H] calc'd 317.0967 found 317.0963
85		4-chloro-1-(cyclopropylmethyl)-5-(6-fluoropyridin-3-yl)-1*H*-benzotriazole	$C_{15}H_{13}ClFN_4$ [M+H] calc'd 303.0811 found 303.0804
86		4-chloro-1-(cyclopropylmethyl)-5-(2-piperazin-1-ylpyridin-4-yl)-1*H*-benzotriazole	$C_{19}H_{22}ClN_6$ [M+H] calc'd 369.1592 found 369.1580
87		4-chloro-1-(cyclopropylmethyl)-5-(6-methoxypyridin-3-yl)-1*H*-benzotriazole	$C_{16}H_{16}ClN_4O$ [M+H] calc'd 315.1007 found 315.1004
88		4-chloro-1-(cyclopropylmethyl)-5-(3-fluoropyridin-4-yl)-1*H*-benzotriazole	$C_{15}H_{13}ClFN_4$ [M+H] calc'd 303.0811 Found 303.0804
89		4-chloro-1-(cyclopropylmethyl)-5-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1*H*-benzotriazole	$C_{20}H_{24}ClN_6$ [M+H] calc'd 383.1745 found 383.1737

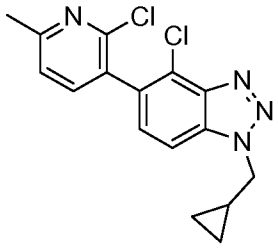
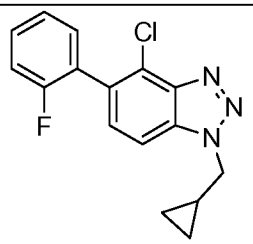
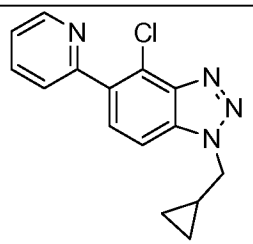
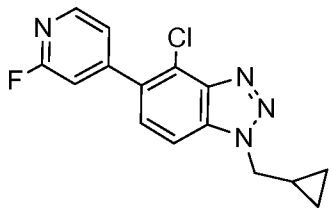
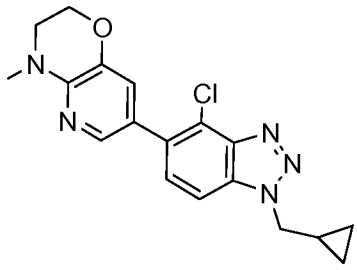
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
90		4-chloro-1-(cyclopropylmethyl)-5-(2-methylpyridin-3-yl)-1*H*-benzotriazole	$C_{16}H_{16}ClN_4$ [M+H] calc'd 299.1058 found 299.1057
91		methyl 5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-2-carboxylate	$C_{17}H_{16}ClN_4O_2$ [M+H] calc'd 343.0956 found 343.0950
92		4-chloro-1-(cyclopropylmethyl)-5-(6-morpholin-4-ylpyridin-3-yl)-1*H*-benzotriazole	$C_{19}H_{21}ClN_5O$ [M+H] calc'd 370.1429 found 370.1418
93		4-chloro-1-(cyclopropylmethyl)-5-(6-piperazin-1-ylpyridin-3-yl)-1*H*-benzotriazole	$C_{19}H_{22}ClN_6$ [M+H] calc'd 369.1589 found 369.1580
94		4-chloro-1-(cyclopropylmethyl)-5-(3-fluorophenyl)-1*H*-benzotriazole	$C_{16}H_{14}ClFN_3$ [M+H] calc'd 302.0855 found 302.0850
95		4-chloro-1-(cyclopropylmethyl)-5-(4-fluorophenyl)-1*H*-benzotriazole	$C_{16}H_{14}ClFN_3$ [M+H] calc'd 302.0855 found 302.0851

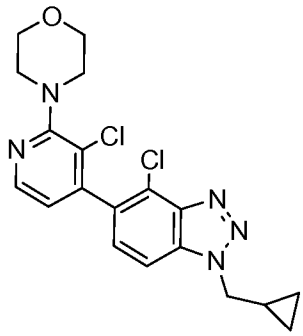
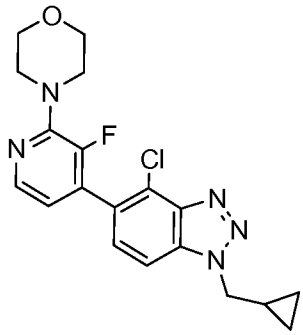
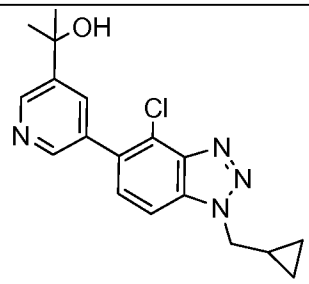
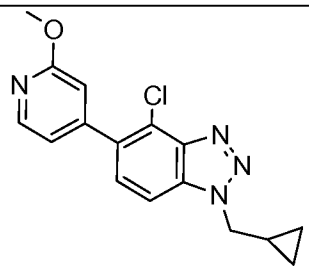
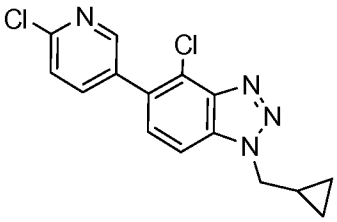
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
96		4-chloro-1-(cyclopropylmethyl)-5-(2-methylphenyl)-1*H*-benzotriazole	$C_{17}H_{17}ClN_3$ [M+H] calc'd 298.1106 found 298.1106
97		4-chloro-1-(cyclopropylmethyl)-5-(3-methylphenyl)-1*H*-benzotriazole	$C_{17}H_{17}ClN_3$ [M+H] calc'd 298.1106 found 298.1106
98		4-chloro-1-(cyclopropylmethyl)-5-(4-methylphenyl)-1*H*-benzotriazole	$C_{17}H_{17}ClN_3$ [M+H] calc'd 298.1106 found 298.1105
99		4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzonitrile	$C_{17}H_{15}ClN_4$ [M+H] calc'd 309.0902 found 309.0900
100		4-chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-benzotriazole	$C_{16}H_{15}ClN_3$ [M+H] calc'd 284.0949 found 284.0948
101		2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzonitrile	$C_{17}H_{14}ClN_4$ [M+H] calc'd 309.0902 found 309.0901

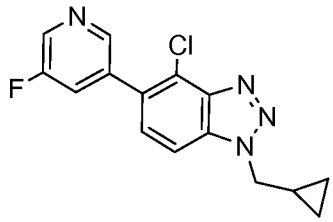
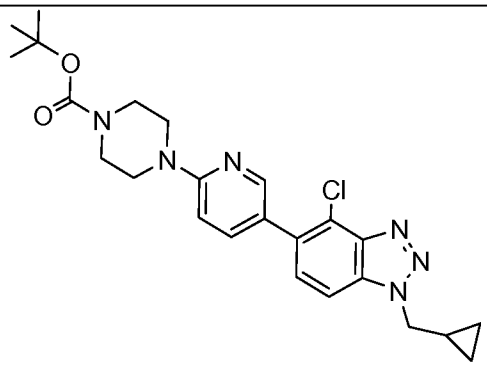
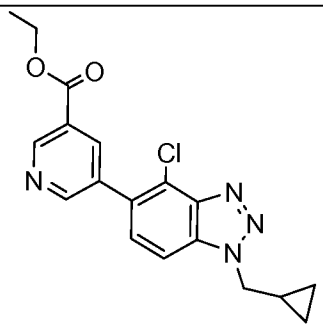
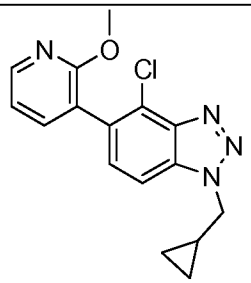
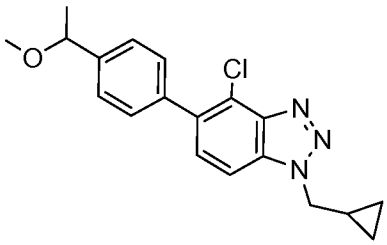
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
102		4-chloro-1-(cyclopropylmethyl)-5-pyridin-3-yl-1*H*-benzotriazole	$C_{15}H_{14}ClN_4$ [M+H] calc'd 285.0902 found 285.0898
103		methyl 4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluorobenzoate	$C_{18}H_{16}ClFN_3O_2$ [M+H] calc'd 360.0910 found 360.0907
104		4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzoic acid	$C_{17}H_{15}ClN_3O_2$ [M+H] calc'd 328.0847 found. 328.0846
105		4-chloro-1-(cyclopropylmethyl)-5-[2-(morpholin-4-ylmethyl)phenyl]-1*H*-benzotriazole	$C_{21}H_{24}ClN_4O$ [M+H] calc'd 383.1633 found 383.1629
106		4-chloro-1-(cyclopropylmethyl)-5-pyridin-4-yl-1*H*-benzotriazole	$C_{15}H_{14}ClN_4$ [M+H] calc'd 285.0902 found 285.0898

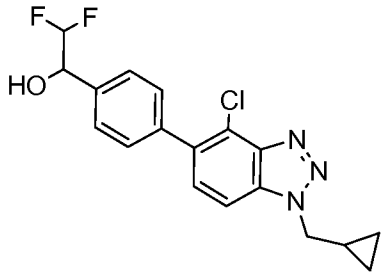
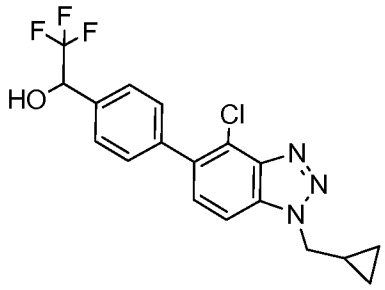
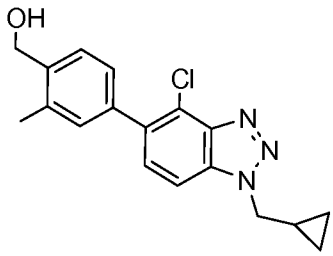
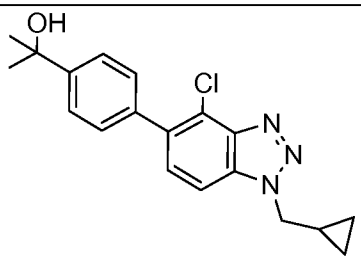
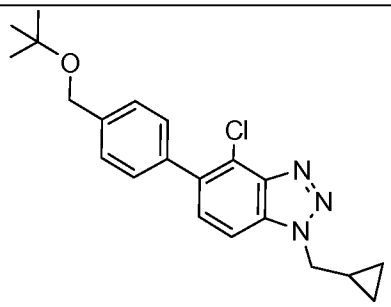
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
107		{2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}methanol	$C_{17}H_{17}ClN_3O$ [M+H] calc'd 314.1055 found 314.1053
108		4-chloro-1-(cyclopropylmethyl)-5-(2-morpholin-4-ylpyridin-3-yl)-1*H*-benzotriazole	$C_{19}H_{21}ClN_5O$ [M+H] calc'd 370.1429 found 370.1423
109		*tert*-butyl {5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}carbamate	$C_{20}H_{23}ClN_5O_2$ [M+H] calc'd 400.1535 found 400.1532
110		4-chloro-1-(cyclopropylmethyl)-5-(2-methylpyridin-4-yl)-1*H*-benzotriazole	$C_{16}H_{16}ClN_4$ [M+H] calc'd 299.1058 found 299.1053
111		5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-2-carbonitrile	$C_{16}H_{13}ClN_5$ [M+H] calc'd 310.0854 found 310.0853

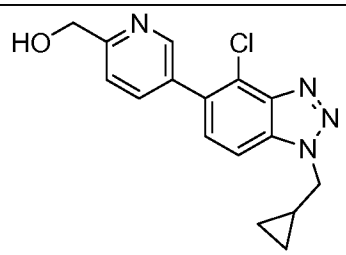
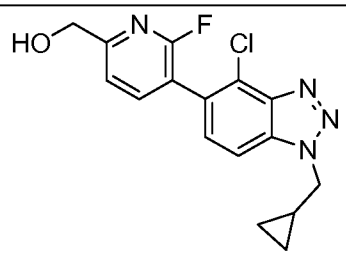
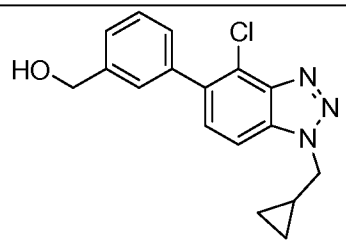
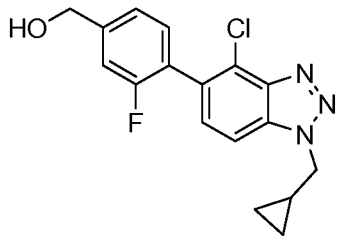
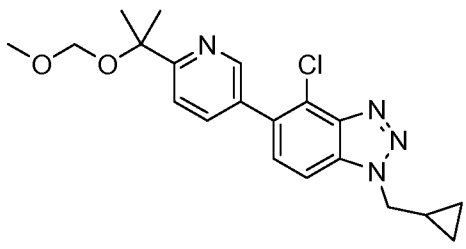
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
112		4-chloro-1-(cyclopropylmethyl)-5-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1*H*-benzotriazole	$C_{20}H_{24}ClN_6$ [M+H] calc'd 383.1745 found 383.1745
113		4-chloro-1-(cyclopropylmethyl)-5-(2-ethoxypyridin-3-yl)-1*H*-benzotriazole	$C_{17}H_{18}ClN_4O$ [M+H] calc'd 329.1164 found 329.1161
114		4-chloro-1-(cyclopropylmethyl)-5-(6-methylpyridin-3-yl)-1*H*-benzotriazole	$C_{16}H_{16}ClN_4$ [M+H] calc'd 299.1058 found 299.1054
115		methyl 4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-fluorobenzoate	$C_{18}H_{16}ClFN_3O_2$ [M+H] Calc'd 360.0913 found 360.0910
116		4-chloro-5-(6-chloro-2-fluoropyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole	$C_{15}H_{12}C_{l2}FN_4$ [M+H] Calc'd 337.0 found 337.1

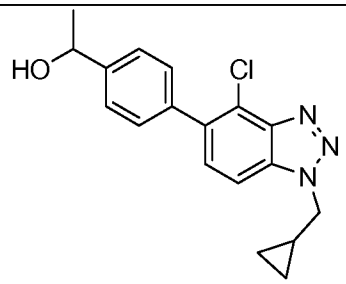
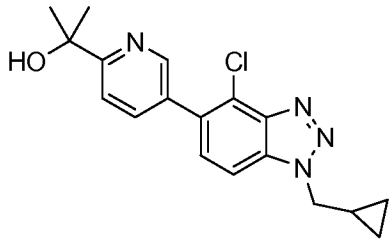
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
117		4-chloro-5-(2-chloro-6-methylpyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole	$C_{16}H_{15}C_{l2}N_4$ [M+H] Calc'd 333.0672 found 333.0678
118		4-chloro-1-(cyclopropylmethyl)-5-(2-fluorophenyl)-1*H*-benzotriazole	$C_{16}H_{14}ClFN_3$ [M+H] Calc'd 302.0859 found 302.0855
119		4-chloro-1-(cyclopropylmethyl)-5-pyridin-2-yl-1*H*-benzotriazole	$C_{15}H_{14}ClN_4$ [M+H] Calc'd 285.0905 found 285.0902
120		4-chloro-1-(cyclopropylmethyl)-5-(2-fluoropyridin-4-yl)-1*H*-benzotriazole	$C_{15}H_{13}ClFN_4$ [M+H] Calc'd 303.0811 found 303.0807
121		7-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-4-methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine	$C_{18}H_{19}ClN_5O$ [M+H] Calc'd 356.1276 found 356.1273

Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
122		4-chloro-5-(3-chloro-2-morpholin-4-ylpyridin-4-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole	$C_{19}H_{20}C_{l2}N_5O$ [M+H] Calc'd 404.1042 found 404.1039
123		4-chloro-1-(cyclopropylmethyl)-5-(3-fluoro-2-morpholin-4-ylpyridin-4-yl)-1*H*-benzotriazole	$C_{19}H_{20}ClFN_5O$ [M+H] Calc'd 388.1338 found 338.1335
124		2-{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-3-yl}propan-2-ol	$C_{18}H_{20}ClN_4O$ [M+H] Calc'd 343.1323 found 343.1324
125		4-chloro-1-(cyclopropylmethyl)-5-(2-methoxypyridin-4-yl)-1*H*-benzotriazole	$C_{16}H_{16}ClN_4O$ [M+H] Calc'd 315.1010 found 315.1009
126		4-chloro-5-(6-chloropyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole	$C_{15}H_{13}C_{l2}N_4$ [M+H] Calc'd 319.0515 found 319.0513

Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
127		4-chloro-1-(cyclopropylmethyl)-5-(5-fluoropyridin-3-yl)-1*H*-benzotriazole	$C_{15}H_{13}ClFN_4$ [M+H] Calc'd 303.0811 found 303.0811
128		*tert*-butyl 4-{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}piperazine-1-carboxylate	$C_{24}H_{30}ClN_6O_2$ [M+H] Calc'd 469.2115 found 469.2120
129		ethyl 5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-3-carboxylate	$C_{18}H_{18}ClN_4O_2$ [M+H] Calc'd 357.1116 found 357.1115
130		4-chloro-1-(cyclopropylmethyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole	$C_{16}H_{16}ClN_4O$ [M+H] Calc'd 315.1 found 315.2
131		4-chloro-1-(cyclopropylmethyl)-5-[4-(1-methoxyethyl)phenyl]-1*H*-benzotriazole	$C_{19}H_{20}ClN_3O$ Calc'd 342.137 found 342.1371

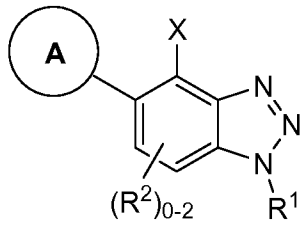
Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
132		1-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}-2,2-difluoroethanol	$C_{18}H_{16}ClF_2N_3O$ Calc'd 364.1026 found 364.1029
133		1-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}-2,2,2-trifluoroethanol	$C_{18}H_{15}ClF_3N_3O$ Calc'd 382.0932 found 382.0932
134		{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-methylphenyl}methanol	$C_{18}H_{18}ClN_3O$ Calc'd 328.1214 found 328.1212
135		2-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}propan-2-ol	$C_{19}H_{20}ClN_3O$ Calc'd 342.137 found 342.1374
136		5-[4-(*tert*-butoxymethyl)phenyl]-4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazole	$C_{21}H_{24}ClN_3O$ Calc'd 370.1683 found 370.1687

Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
137		{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}methanol	$C_{16}H_{15}ClN_4O$ Calc'd 315.1010 found 315.1010
138		{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-6-fluoropyridin-2-yl}methanol	$C_{16}H_{14}ClFN_4O$ Calc'd 333.0916 found 333.0913
139		{3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}methanol	$C_{17}H_{17}ClN_3O$ calc. 314.1055 found 314.1049
140		{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluorophenyl}methanol	$C_{17}H_{16}ClFN_3O$ calc. 332.0960 found 332.0964
141		4-chloro-1-(cyclopropylmethyl)-5-{6-[1-(methoxymethoxy)-1-methylethyl]pyridin-3-yl}-1*H*-benzotriazole	$C_{20}H_{24}ClN_4O_2$ [M+H] calc. 387.1582 found 387.1592

Ex.	Structure	Name	LRMS or HRMS *m/z* (M+H)
142		1-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}ethanol	$C_{18}H_{19}ClN_3O$ [M+H] calc. 328.1211 found 328.1209
143		2-{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}propan-2-ol	$C_{18}H_{20}ClN_4O$ [M+H] calc. 343.132 found 343.132

WHAT IS CLAIMED IS:

1. A compound according to Formula I



I

wherein:

X is selected from halo, methyl and -CN;

R^1 is selected from the group consisting of:

(1) C_{1-8}alkyl,
(2) C_{2-8}alkenyl,
(3) C_{2-8}alkynyl,
(4) C_{1-8}haloalkyl,
(5) C_{3-6}cycloalkyl-$(CH_2)_p$-, wherein p is 0, 1, 2, 3 or 4, and
(6) 4-(2-methylbenzamido)benzyl;

each R^2 is independently selected from the group consisting of: halo, OH, C_{1-4}alkyl, C_{1-4}alkoxy, CF_3 and –CN;

A is selected from aryl, heteroaryl and heterocycle, wherein said aryl, heteroaryl and heterocycle are optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions;

aryl at each occurrence is independently selected from the group consisting of: phenyl, naphthyl, anthryl and phenanthryl;

heteroaryl at each occurrence independently means a 5- or 6-membered monocyclic aromatic or 9- or 10-membered bicyclic aromatic, wherein at least one atom in the aromatic is selected from N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide, and the remaining atoms are selected from C, N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide;

heterocycle at each occurrence independently means a 5- or 6-membered monocyclic non-aromatic ring or 9- or 10-membered bicyclic non- or partially-aromatic ring, each optionally substituted with oxo, wherein at least one atom is selected from N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide, and the remaining atoms are selected from C, N(R), O and S, the sulfur optionally oxidized to sulfone or sulfoxide;

each R^3 is independently selected from the group consisting of:

(1) halo,
(2) C_{1-8}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}alkynyl,
(5) C_{3-6}cycloalkyl,
(6) C_{1-6}alkoxy,
(7) C_{3-6}cycloalkoxy,
(8) -CN,
(9) -OH,
(10) -C(O)-O-C_{1-4}alkyl,
(11) -C(O)-C_{1-4}alkyl,
(12) -$N(R)_2$,
(13) -C(O)-$N(R)_2$,
(14) -$S(O)_k$-C_{1-4}alkyl, wherein k is 0, 1 or 2,
(15) -aryl,
(16) -heteroaryl,
(17) -heterocycle,

(18) -C(O)-aryl,
(19) -N(R)-aryl,
(20) benzyl,
(21) benzyloxy,
(22) aryl-O-,
(23) heteroaryl-O-,
(24) heterocycle-O-
(23) $-CO_2H$,
(24) -SH,
(25) $-SO_2N(R)R$,
(26) -N(R)C(O)N(R)R,
(27) $-N(R)C(O)C_{1-4}alkyl$,
(28) $-N(R)SO_2N(R)R$,
(29) $-B(OH)_2$,
(30) heterocycle-CH_2-,
(31) heteroaryl-CH_2- and
(32) $-N(R)C(O)-O-C_{1-4}alkyl$,

wherein groups (2) to (7), (15) to (24), (30), (31) and (32) above are optionally substituted from one up to the maximum number of substitutable positions with one or more substituents independently selected from the group consisting of: OH, CN, halo, carboxy, $-C(O)-O-C_{1-4}alkyl$, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkylamino$, phenyl and heterocycle, and each R is independently selected from the group consisting of: H and $C_{1-4}alkyl$;

and pharmaceutically acceptable salts thereof.

2. The compound according to Claim 1 wherein each R^3 is independently selected from the group consisting of:

(1) halo,
(2) $C_{1-8}alkyl$,
(3) $C_{2-6}alkenyl$,
(4) $C_{2-6}alkynyl$,

(5) C_{3-6}cycloalkyl,

(6) C_{1-6}alkoxy,

(7) C_{3-6}cycloalkoxy,

(8) -CN,

(9) -OH,

(10) -C(O)-O-C_{1-4}alkyl,

(11) -C(O)-C_{1-4}alkyl,

(12) -$N(R)_2$,

(13) -C(O)-$N(R)_2$,

(14) -$S(O)_k$-C_{1-4}alkyl, wherein k is 0, 1 or 2,

(15) -aryl,

(16) -heteroaryl,

(17) -heterocycle,

(18) -C(O)-aryl,

(19) -N(R)-aryl,

(20) benzyl,

(21) benzyloxy,

(22) aryl-O-,

(23) heteroaryl-O-,

(24) heterocycle-O-

(23) -CO_2H,

(24) -SH,

(25) -SO_2N(R)R,

(26) -N(R)C(O)N(R)R,

(27) -N(R)C(O)C_{1-4}alkyl,

(28) -N(R)SO_2N(R)R,

(29) -$B(OH)_2$,

(30) heterocycle-CH_2- and

(31) heteroaryl-CH_2-,

wherein groups (2) to (7), (15) to (24), (30) and (31) above are optionally substituted from one up to the maximum number of substitutable positions with one or more substituents

independently selected from the group consisting of: OH, CN, halo, carboxy, -C(O)-O-C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino, phenyl and heterocycle, and each R is independently selected from the group consisting of: H and C_{1-4}alkyl.

3. The compound according to Claim 2 wherein X is Br.

4. The compound according to Claim 3 wherein R^1 is 2,2-dimethylpropyl.

5. The compound according to Claim 3 wherein R^1 is cyclopropylmethyl.

6. The compound according to Claim 3 wherein R^1 is 4,4,4-trifluorobuty

7. The compound according to Claim 2 wherein **A** is phenyl, optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions.

8. The compound according to Claim 7 wherein each R^3 is independently selected from the group consisting of: halo, C_{1-4}alkyl, C_{1-4}alkoxy, -CF_3, -OCF_3, -NH_2, -CN, -OH, -CH_2-OH, -CH_2-O-CH_3, -C(O)OC_{1-4}alkyl, -OCH_2-C(O)-OH, -NH-C(O)-C_{1-4}alkyl and phenyl, optionally substituted with 1 to 5 substituents independenly selected from halo and methyl.

9. The compound according to Claim 2 wherein **A** is selected from pyridine, pyrimidine, pyridazine and triazine, optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions.

10. The compound according to Claim 9 wherein each R^3 is independently selected from the group consisting of: halo, C_{1-4}alkyl, C_{1-4}alkoxy, -CF_3, -OCF_3, -NH_2, -CN, -OH, -CH_2-OH, -CH_2-O-CH_3, -C(O)OC_{1-4}alkyl, -OCH_2-C(O)-OH, -NH-C(O)-C_{1-4}alkyl, phenyl optionally substituted with 1 to 5 substituents independenly selected from halo and methyl, and pyridyl optionally substituted with 1 to 4 substituents independenly selected from halo and methyl.

11. The compound according to Claim 2 wherein **A** is selected from pyrazole, oxadiazole, thiadiazole, furan, thiophene, pyrrole, triazole, oxazole, thiazole, imidazole, isoxazole and isothiazole, optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions.

12. The compound according to Claim 11 wherein each R^3 is independently selected from the group consisting of: halo, C_{1-4}alkyl, C_{1-4}alkoxy, $-CF_3$, $-OCF_3$, $-NH_2$, -CN, -OH, $-CH_2$-OH, $-CH_2$-O-CH_3, -C(O)OC_{1-4}alkyl, $-OCH_2$-C(O)-OH, -NH-C(O)-C_{1-4}alkyl, phenyl optionally substituted with 1 to 5 substituents independenly selected from halo and methyl, and pyridyl optionally substituted with 1 to 4 substituents independently selected from halo and methyl.

13. The compound according to Claim 2 wherein:

X is selected from Br and Cl;

R^1 is selected from the group consisting of: 2,2-dimethylpropyl and cyclopropylmethyl;

R^2 is not present.

A is phenyl optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions;

each R^3 is independently selected from the group consisting of: (1) C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted with hydroxy; (2) –CN, (3) halo, (4) $-CF_3$, (5) methoxy, (6) tetrahydro-2H-pyranyloxy and (7) pyridinyloxy, said pyridinyloxy optionally substituted with halo;

and pharmaceutically acceptable salts thereof.

14. The compound according to Claim 2 wherein:

X is selected from Br and Cl;

R^1 is selected from the group consisting of: 2,2-dimethylpropyl and cyclopropylmethyl;

R^2 is not present.

A is selected from the group consisting of: pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzisoxazolyl, triazolyl[1,5-a]pyridinyl, triazolyl[4,3-a]pyridinyl, pyrrolo[2,3-b]pyridinyl, indazolyl and 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, wherein **A** is optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions;

each R^3 is independently selected from the group consisting of: (1) C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted with hydroxy; (2) –CN, (3) halo, (4) $-CF_3$, (5) methoxy, (6) tetrahydro-2H-pyranyloxy and (7) pyridinyloxy, said pyridinyloxy optionally substituted with halo;

and pharmaceutically acceptable salts thereof.

15. The compound according to Claim 1 wherein **A** is 3,4-dihydro-2H-chromene optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions.

16. The compound according to Claim 1 wherein X is Cl and R^1 is cyclopropylmethyl.

17. The compound according to Claim 16 wherein **A** is selected from phenyl, pyridine and pyrimidine, optionally substituted with one or more R^3 groups up to the maximum number of substitutable positions.

18. The compound according to Claim 17, wherein:

R^2 is not present; and each R^3 is independently selected from the group consisting of: (1) C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted with hydroxy and 1 to 3 halo; (2) –CN, (3) halo, (4)

C_{1-4}alkoxy, (5) methylsulfanyl, (6) methylsulfinyl, (7) methylsulfonyl, (8) -C(O)-$N(R)_2$, (9) -C(O)-O-C_{1-4}alkyl, (10) piperazinyl, (11) 4-methylpiperazinyl, (12) piperazinylmethyl, (13) 4-methylpiperazinylmethyl, (14) morpholinyl and (15) morpholinylmethyl.

19. A compound according to Claim 1 selected from the following group:
4-bromo-1-(2,2-dimethylpropyl)-5-(1-methyl-1H- -pyrazol-4-yl)-1H-1,2,3-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-phenyl-1*H*-benzotriazole;
3-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]-4-fluorobenzonitrile;
4-[4-chloro-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]isoquinoline;
4-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]isoquinoline;
3-[4-chloro-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-chloro-1-(2,2-dimethylpropyl)-5-phenyl-1*H*-benzotriazole;
5-(1-benzofuran-3-yl)-4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazole;
{4-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}methanol;
4-bromo-1-(2,2-dimethylpropyl)-5-(3-methyl-1,2-benzisoxazol-5-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-[1,2,4]triazolo[1,5-a]pyridin-6-yl-1*H*-benzotriazole;
4-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-bromo-1-(2,2-dimethylpropyl)-5-pyridin-4-yl-1*H*-benzotriazole;
6-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]quinoline;
4-bromo-1-(2,2-dimethylpropyl)-5-(1*H*-pyrrolo[2,3-b]pyridin-5-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-[1,2,4]triazolo[1,5-a]pyridin-7-yl-1*H*-benzotriazole;
3-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile;
2-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-bromo-1-(2,2-dimethylpropyl)-5-pyridin-3-yl-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(4-methylpyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-pyrimidin-5-yl-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(2-methylpyridin-4-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(6-methylpyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(2-fluoropyridin-4-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-1H-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(5-fluoropyridin-3-yl)-1*H*-benzotriazole;

4-bromo-1-(2,2-dimethylpropyl)-5-(2-fluoropyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(6-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(6-fluoropyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(1*H*-indazol-5-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(2-methoxypyrimidin-5-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-(5-methoxypyridin-3-yl)-1*H*-benzotriazole;
5-(1-benzofuran-2-yl)-4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazole;
5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridine-2-carbonitrile;
5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridine-2-carbonitrile;
4-bromo-1-(2,2-dimethylpropyl)-5-(4-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-bromo-1-(2,2-dimethylpropyl)-5-[1,2,4]triazolo[4,3-a]pyridin-6-yl-1*H*-benzotriazole;
2-{3-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]phenyl}propan-2-ol;
4-bromo-5-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-1-(2,2-dimethylpropyl)-1*H*-benzotriazole;
{5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}methanol;
5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]isoquinoline;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-4-carbonitrile;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-4-fluorobenzonitrile;
6-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]quinoline;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridinium trifluoroacetate;
2-{3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}propan-2-ol;
5-[4-bromo-1-(2,2-dimethylpropyl)-1*H*-benzotriazol-5-yl]pyridine-3-carbonitrile;
4-bromo-5-[3-chloro-4-(tetrahydro-2*H*-pyran-4-yloxy)phenyl]-1-(cyclopropylmethyl)-1*H*-benzotriazole; and
4-bromo-5-{4-[(2-chloropyridin-4-yl)oxy]phenyl}-1-(cyclopropylmethyl)-1*H*-1,2,3-benzotriazole;
4-bromo-1-(cyclopropylmethyl)-5-(2-methoxy-6-methylpyridin-3-yl)-1*H*-benzotriazole;
7-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3,4-dihydro-2*H*-chromen-4-ol;
4-bromo-1-(cyclopropylmethyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl] yridine-2(1*H*)-one;
3-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-1-methylpyridin-2(1*H*)-one;
4-bromo-1-(cyclopropylmethyl)-5-(2-methoxy-6-methylpyridin-3-yl)-1*H*-benzotriazole;
{4-[4-bromo-1-(2-methylpropyl)-1*H*-benzotriazol-5-yl]phenyl}methanol;

{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluorophenyl}methanol;
{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-fluorophenyl}methanol;
{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-(methylsulfanyl)phenyl}methanol;
{5-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]thiophen-2-yl}methanol;
{5-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluoropyridin-2-yl}methanol;
{4-[4-bromo-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-(methylsulfonyl)phenyl}methanol;
4-Chloro-1-(cyclopropylmethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-benzotriazole;
7-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2,3-dihydro-4*H*-chromen-4-one;
4-chloro-1-(cyclopropylmethyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-fluoropyridin-3-yl)-1*H*-benzotriazole;
4-chloro-5-(2-chloropyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(pyrimidin-5-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(thiophen-2-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[2-(methylsulfanyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[3-(methylsulfanyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[3-(methylsulfinyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[3-(methylsulfonyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[2-(methylsulfinyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[2-(methylsulfonyl)phenyl]-1*H*-benzotriazole;
3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzamide;
2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzamide;
3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-*N*-methylbenzamide;
3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-*N,N*-dimethylbenzamide;
2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-*N,N*-dimethylbenzamide;
{3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}methanol;
4-chloro-1-(cyclopropylmethyl)-5-(6-fluoro-2-methylpyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-fluoro-6-methylpyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(6-fluoropyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-piperazin-1-ylpyridin-4-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(6-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(3-fluoropyridin-4-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-methylpyridin-3-yl)-1*H*-benzotriazole;

methyl 5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-2-carboxylate;
4-chloro-1-(cyclopropylmethyl)-5-(6-morpholin-4-ylpyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(6-piperazin-1-ylpyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(3-fluorophenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(4-fluorophenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-methylphenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(3-methylphenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(4-methylphenyl)-1*H*-benzotriazole;
4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-benzotriazole;
2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzonitrile;
4-chloro-1-(cyclopropylmethyl)-5-pyridin-3-yl-1*H*-benzotriazole;
methyl 4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluorobenzoate;
4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]benzoic acid;
4-chloro-1-(cyclopropylmethyl)-5-[2-(morpholin-4-ylmethyl)phenyl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-pyridin-4-yl-1*H*-benzotriazole;
{2-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}methanol;
4-chloro-1-(cyclopropylmethyl)-5-(2-morpholin-4-ylpyridin-3-yl)-1*H*-benzotriazole;
tert-butyl {5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}carbamate;
4-chloro-1-(cyclopropylmethyl)-5-(2-methylpyridin-4-yl)-1*H*-benzotriazole;
5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-2-carbonitrile;
4-chloro-1-(cyclopropylmethyl)-5-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-ethoxypyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(6-methylpyridin-3-yl)-1*H*-benzotriazole;
methyl 4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-fluorobenzoate;
4-chloro-5-(6-chloro-2-fluoropyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;
4-chloro-5-(2-chloro-6-methylpyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-fluorophenyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-pyridin-2-yl-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(2-fluoropyridin-4-yl)-1*H*-benzotriazole;
7-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-4-methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine;
4-chloro-5-(3-chloro-2-morpholin-4-ylpyridin-4-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;

4-chloro-1-(cyclopropylmethyl)-5-(3-fluoro-2-morpholin-4-ylpyridin-4-yl)-1*H*-benzotriazole;
2-{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-3-yl}propan-2-ol;
4-chloro-1-(cyclopropylmethyl)-5-(2-methoxypyridin-4-yl)-1*H*-benzotriazole;
4-chloro-5-(6-chloropyridin-3-yl)-1-(cyclopropylmethyl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-(5-fluoropyridin-3-yl)-1*H*-benzotriazole;
tert-butyl 4-{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}piperazine-1-carboxylate;
ethyl 5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridine-3-carboxylate;
4-chloro-1-(cyclopropylmethyl)-5-(2-methoxypyridin-3-yl)-1*H*-benzotriazole;
4-chloro-1-(cyclopropylmethyl)-5-[4-(1-methoxyethyl)phenyl]-1*H*-benzotriazole;
1-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}-2,2-difluoroethanol;
1-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}-2,2,2-trifluoroethanol;
{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-2-methylphenyl}methanol;
2-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}propan-2-ol;
5-[4-(tert-butoxymethyl)phenyl]-4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazole;
{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}methanol;
{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-6-fluoropyridin-2-yl}methanol;
{3-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}methanol;
{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]-3-fluorophenyl}methanol;
4-chloro-1-(cyclopropylmethyl)-5-{6-[1-(methoxymethoxy)-1-methylethyl]pyridin-3-yl}-1*H*-benzotriazole;
1-{4-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]phenyl}ethanol; and
2-{5-[4-chloro-1-(cyclopropylmethyl)-1*H*-benzotriazol-5-yl]pyridin-2-yl}propan-2-ol;

and pharmaceutically acceptable salts of any of the foregoing compounds.

20. A pharmaceutical composition comprising a compound according to Claim 1 in combination with a pharmaceutically acceptable carrier.

21. A method for treating a neurological or psychiatric disorder associated with glutamate dysfunction in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound according to Claim 1.

22. The method according to Claim 21 wherein the neurological or psychiatric disorder associated with glutamate dysfunction is schizophrenia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/36598

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 413/00 (2010.01)
USPC - 544/143
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 544/143

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 544/143,132,405,366,333

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB, USPT, EPAB, JPAB)
Search terms: biaryl, benzotriazole, metabotropic glutamate rececptor, mGLUR2, CNS, psychiatric, schizophrnia, dimethylpropyl, pyrazol, fluorobenzonitrile, isoquinoline, fluoropyridine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,664,395 B2 (LETAVIC et al) 16 December 2003 (16.12.2003); entire document, especially para [0013]	1-22
Y	US 2008/0194656 A1 (BERWAER et al) 15 August 2008 (14.08.2008); entire document, especially abstract	1-22
Y	US 2006/0122240 A1 (Semple et al) 08 June 2006 (08.06.2006); entire document, especially abstract	4-6,13,14,16-19

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2010 (15.07.2010)	27 JUL 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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