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(71) Applicant(s)
Merck & Co., Inc.

(72) Inventor(s)
Cube, Rowena V.;Munoz, Benito;Arruda, Jeannie;Wang, Bowei;Bonnefous, Celine;Campbell, Brian T.;Stearns, Brian;Vernier, Jean-Michel;Zhao, Xiumin

(74) Agent / Attorney
Spruson & Ferguson, Level 35 St Martins Tower 31 Market Street, Sydney, NSW, 2000

Metabotropic Glutamate Receptor-5 Modulators

Abstract

Phenyl compounds substituted at the 1-position with a fused bicyclo moiety formed from a five-membered heterocycle fused to a six-membered carbocycle, to a six-membered aryl, or to a six-membered hetaryl, and further optionally substituted at the 3,4 positions, are mGluR5 modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, and panic, as well as in the treatment of pain and other diseases.

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COMPLETE SPECIFICATION

FOR A STANDARD PATENT

Name and Address of Applicant :	Merck & Co., Inc., of 126 East Lincoln Avenue, Rahway, New Jersey, 07065-0907, United States of America
Actual Inventor(s):	Jeannie Arruda Celine Bonnefous Brian T. Campbell Rowena V. Cube Benito Munoz Brian Stearns Jean-Michel Vernier Bowei Wang Xiumin Zhao
Address for Service:	Spruson & Ferguson St Martins Tower Level 35 31 Market Street Sydney NSW 2000 (CCN 3710000177)

Invention Title: Metabotropic glutamate receptor-5 modulators

The following statement is a full description of this invention, including the best method of performing it known to me/us:

TITLE OF THE INVENTION

Metabotropic Glutamate Receptor-5 Modulators

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention is directed to phenyl compounds substituted with a fused-heterobicyclo moeity. In particular, this invention is directed to phenyl compounds substituted at the 1-position with a fused bicyclo moeity formed from a five-membered heterocycle fused to a six-membered carbocycle, to a six-membered aryl, or to a six-membered hetaryl, and further optionally substituted at the 3,4 positions, which are modulators of metabotropic glutamate receptor – subtype 5 ("mGluR5") modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, and panic, as well as in the treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, drug addiction, drug abuse, drug withdrawal and other diseases.

RELATED BACKGROUND

A major excitatory neurotransmitter in the mammalian nervous system is the glutamate molecule, which binds to neurons, thereby activating cell surface receptors. Such surface receptors are characterized as either ionotropic or metabotropic glutamate receptors. The metabotropic glutamate receptors ("mGluR") are G protein-coupled receptors that activate intracellular second messenger systems when bound to glutamate. Activation of mGluR results in a variety of cellular responses. In particular, mgluR1 and mgluR5 activate phospholipase C, which is followed by mobilizing intracellular calcium.

Modulation of metabotropic glutamate receptor subtype 5 (mGluR5) is useful in the treatment of diseases that affect the nervous system (see for example W.P.J.M Spooren et al., *Trends Pharmacol. Sci.*, 22:331-337(2001) and references cited therein). For example, recent evidence demonstrates the involvement of mGluR5 in nociceptive processes and that modulation of mGluR5 using mGluR5-selective compounds is useful in the treatment of various pain states, including acute, persistent and chronic pain [K Walker et al., *Neuropharmacology*, 40:1-9(2001); F.

Bordi, A. Ugolini *Brain Res.*, 871:223-233(2001)], inflammatory pain [K Walker et al., *Neuropharmacology*, 40:10-19(2001); Bhave et al. *Nature Neurosci.* 4:417-423(2001)] and neuropathic pain [Dogrul et al. *Neurosci. Lett.* 292:115-118(2000)].

Further evidence supports the use of modulators of mGluR5 in the treatment of psychiatric and neurological disorders. For example, mGluR5-selective compounds such as 2-methyl-6-(phenylethynyl)-pyridine ("MPEP") are effective in animal models of mood disorders, including anxiety and depression [W.P.J.M Spooren et al., *J. Pharmacol. Exp. Ther.*, 295:1267-1275(2000); E. Tatarczynska et al, *Brit. J. Pharmacol.*, 132:1423-1430(2001); A. Klodzynska et al, *Pol. J. Pharmacol.*, 132:1423-1430(2001)]. Gene expression data from humans indicate that modulation of mGluR5 may be useful for the treatment of schizophrenia [T. Ohnuma et al, *Mol. Brain. Res.*, 56:207-217(1998); *ibid*, *Mol. Brain. Res.*, 85:24-31(2000)]. Studies have also shown a role form GluR5, and the potential utility of mGluR5-modulatory compounds, play in the treatment of movement disorders such as Parkinson's disease [W.P.J.M Spooren et al., *Europ. J. Pharmacol.* 406:403-410(2000); H. Awad et al., *J. Neurosci.* 20:7871-7879(2000); K. Ossawa et al. *Neuropharmacol.* 41:413-420(2001)]. Other research supports a role form GluR5 modulation in the treatment of cognitive dysfunction [G. Riedel et al, *Neuropharmacol.* 39:1943-1951(2000)], epilepsy [A. Chapman et al, *Neuropharmacol.* 39:1567-1574(2000)] and neuroprotection [V. Bruno et al, *Neuropharmacol.* 39:2223-2230(2000)]. Studies with mGluR5 knockout mice and MPEP also suggest that modulation of these receptors may be useful in the treatment of drug addiction, drug abuse and drug withdrawal [C. Chiamulera et al. *Nature Neurosci.* 4:873-874(2001)].

International Patent Publications WO 01/12627 and WO 99/26927 describe heteropolycyclic compounds and their use as metabotropic glutamate receptor antagonists. International Patent Publications WO 96/05818, WO 00/73283, WO 00/20001, and U.S. Patent No. 6,031,003 describe polycyclic compounds active at metabotropic glutamate receptors.

Russian Patent Nos. SU 1824402, SU 1830388, and SU 1806138 describe processes for producing 2-phenylbenzoxazole. Japanese Patent No. JP 07013369 describes an electrophotographic photoreceptor containing oxazole or thiazole derivative charge-transporting agents. International Patent Publication EP 479161 describes the synthesis of heterocyclic compounds. Japanese Patent No. JP 55038302 describes benzoxazole derivatives. German Patent No. DE 2619547 and

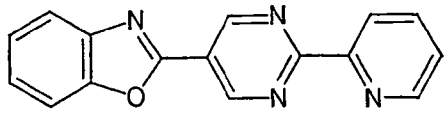
U.S. Patent No. 4, 107,169 describe 2-arylbenzoxazoles and 2-arylbenzothiazoles. U.S. Patent Nos. 3,772,309, and 3,630,972 describe 2-arylbenzazoles and polybenzimidazoles. German Patent Nos. DE 2037998 and DE 2037999 describe benzazoles, benzazolinones, quinolines, indoles, benzothiazoles, benzimidazoles, and benzoxazoles. U.S. Patent No. 3,452,036 and Japanese Patent No. JP 42015938 describe 2-substituted benzoxazoles. Dutch Patent No. NL 6607039 describes herbicidal benzazoles.

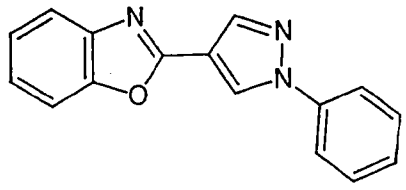
International Patent Publication No. WO 9427601 describes the preparation of [(benzoxazolylphenyl)alkoxy]alkylamines as squalene synthase inhibitors. U.S. Patent No. 3,458,506 describes fluorescent benzazoles compounds containing cyanovinylene groups.

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

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

The following compounds are available from Maybridge plc, Cornwall, England:





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

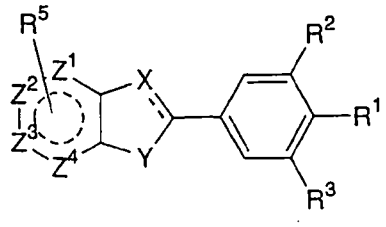
SUMMARY OF THE INVENTION

The present invention is directed to novel phenyl compounds substituted at the 1-position with a fused bicyclo moeity formed from a five-membered heterocycle fused to a six-membered carbocycle, to a six-membered aryl, or to a six-membered hetaryl, and further optionally substituted at the 3,4 positions, which are modulators of metabotropic glutamate receptor-5, useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, and panic, as well as in the treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, drug addiction, drug abuse, drug withdrawal and other diseases. This invention also provides a pharmaceutical composition which includes an effective amount of the novel phenyl compounds substituted with a fused bicyclo moeity formed from a five-membered heterocycle fused to a six-membered carbocycle, to a six-membered aryl, or to a six-membered hetaryl, and a pharmaceutically acceptable carrier.

This invention further provides a method of treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, and panic, as well as a method of treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, drug addiction, drug abuse and drug withdrawal by the administration of an effective amount of the novel phenyl compounds substituted with a fused bicyclo moeity formed from a five-membered heterocycle fused to a six-membered carbocycle, to a six-membered aryl, or to a six-membered hetaryl.

DETAILED DESCRIPTION OF THE INVENTION

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



(I)

or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or NH;

Y is O, or N-R^4;

one of Z^1, Z^2 , Z^3 or Z^2 optionally is N, or NH;

R^1 is -OH, halogen, or –CN; or a –C_{1-6}alkyl, –C_{1-4}alkoxyl, –cycloC_{3-6}alkyl, –C_{0-4}alkyl–phenyl, –C_{0-4}alkyl–pyridyl, –C_{0-4}alkyl–imidazolyl, –C_{0-4}alkyl–pyrazolyl, –C_{0-4}alkyl–triazolyl, –C_{0-4}alkyl–tetrazolyl, –C_{0-4}alkyl–dioxolanyl, –C_{0-4}alkyl–thiazolyl, –C_{0-4}alkyl–piperidinyl, –C_{0-4}alkyl–pyrrolidinyl, –C_{0-4}alkyl–morpholinyl, –C_{0-4}alkyl–pyrimidinyl, –C_{2-6}alkynyl–thiazolyl, or –N(C_{0-4}alkyl)(–C_{0-4}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is hydrogen, halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is -OH, halogen, or –CN; or a –C_{1-6}alkyl, –C_{1-4}alkoxyl, –cycloC_{3-6}alkyl, –C_{0-4}alkyl–phenyl, –C_{0-4}alkyl–pyridyl, –C_{0-4}alkyl–imidazolyl, –C_{0-4}alkyl–pyrazolyl, –C_{0-4}alkyl–triazolyl, –C_{0-4}alkyl–tetrazolyl, –C_{0-4}alkyl–dioxolanyl, –C_{0-4}alkyl–thiazolyl, –C_{0-4}alkyl–piperidinyl, –C_{0-4}alkyl–pyrrolidinyl, –C_{0-4}alkyl–morpholinyl, –C_{0-4}alkyl–pyrimidinyl, –C_{2-6}alkynyl–thiazolyl, or –N(C_{0-4}alkyl)(–C_{0-4}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is hydrogen, halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is –C_{1-6}alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is hydrogen, halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is –C_{1-6}alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –

$N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl$–morpholinyl, or $-C_{0-4}alkyl$–benzoxazolyl;

R^2 is $-C_{0-4}alkyl$–phenyl optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}alkoxyl$ substituents;

R^3 is hydrogen or $-C_{1-4}alkoxyl$;

R^4 is $-C_{0-4}alkyl$; and

R^5 is H, halogen, or $-C_{1-4}alkyl$.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is $-C_{1-6}alkyl$ optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}alkyl$, $-C_{1-4}alkoxyl$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl$–morpholinyl, or $-C_{0-4}alkyl$–benzoxazolyl;

R^2 is hydrogen; or $-C_{1-6}alkyl$ optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}alkoxyl$ substituents;

R^3 is hydrogen or $-C_{1-4}alkoxyl$;

R^4 is $-C_{0-4}alkyl$; and

R^5 is H, halogen, or $-C_{1-4}alkyl$.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is $-C_{1-6}alkyl$ optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}alkyl$, $-C_{1-4}alkoxyl$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl$–morpholinyl, or $-C_{0-4}alkyl$–benzoxazolyl;

R^2 is or $-NO_2$; or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}alkoxyl$ substituents;

R^3 is hydrogen or $-C_{1-4}alkoxyl$;

R^4 is $-C_{0-4}alkyl$; and

R^5 is H, halogen, or $-C_{1-4}alkyl$.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is $-C_{1-6}alkyl$ optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}alkyl$, $-C_{1-4}alkoxyl$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl$–morpholinyl, or $-C_{0-4}alkyl$–benzoxazolyl;

R^2 is $-C_{1-4}alkoxy$–phenyl optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}alkoxyl$ substituents;

R^3 is hydrogen or $-C_{1-4}alkoxyl$;

R^4 is $-C_{0-4}alkyl$; and

R^5 is H, halogen, or $-C_{1-4}alkyl$.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is $-C_{1-6}alkyl$ optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}alkyl$, $-C_{1-4}alkoxyl$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl$–morpholinyl, or $-C_{0-4}alkyl$–benzoxazolyl;

R^2 is $-C_{1-4}alkoxyl$ optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}alkoxyl$ substituents;

R^3 is hydrogen or $-C_{1-4}$alkoxyl;

R^4 is $-C_{0-4}$alkyl; and

R^5 is H, halogen, or $-C_{1-4}$alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is $-$cycloC_{3-6}alkyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}$alkyl–C(O)–O–C_{0-4}alkyl, $-C_{0-4}$alkyl–morpholinyl, or $-C_{0-4}$alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-NO_2$; or $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-C_{0-4}$alkyl–phenyl, or $-C_{1-4}$alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}$alkoxyl substituents;

R^3 is hydrogen or $-C_{1-4}$alkoxyl;

R^4 is $-C_{0-4}$alkyl; and

R^5 is H, halogen, or $-C_{1-4}$alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is $-C_{0-4}$alkyl–triazolyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}$alkyl–C(O)–O–C_{0-4}alkyl, $-C_{0-4}$alkyl–morpholinyl, or $-C_{0-4}$alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-NO_2$; or $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-C_{0-4}$alkyl–phenyl, or $-C_{1-4}$alkoxy–phenyl group, wherein any

of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is –C_{0-4}alkyl–imidazolyl or –C_{0-4}alkyl–pyrazolyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is –C_{0-4}alkyl–tetrazolyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is –C_{0-4}alkyl–pyrrolidinyl or –C_{0-4}alkyl–piperidinyl, optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is –C_{0-4}alkyl–pyridyl or –C_{0-4}alkyl–pyrimidinyl, optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –

OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N;

Y is O;

R^1 is –C_{0-4}alkyl–morpholinyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1 is N;

X is N;

Y is O;

R^1 is -OH, halogen, or –CN; or a –C_{1-6}alkyl, –C_{1-4}alkoxyl, –cycloC_{3-6}alkyl, –C_{0-4}alkyl–phenyl, –C_{0-4}alkyl–pyridyl, –C_{0-4}alkyl–imidazolyl, –C_{0-4}alkyl–pyrazolyl, –C_{0-4}alkyl–triazolyl, –C_{0-4}alkyl–tetrazolyl, –C_{0-4}alkyl–dioxolanyl, –C_{0-4}alkyl–thiazolyl, –C_{0-4}alkyl–piperidinyl, –C_{0-4}alkyl–pyrrolidinyl, –C_{0-4}alkyl–morpholinyl, –C_{0-4}alkyl–pyrimidinyl, –C_{2-6}alkynyl–thiazolyl, or –N(C_{0-4}alkyl)(–C_{0-4}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1 is N;

X is N;

Y is O;

R^1 is –C_{1-6}alkyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1 is N;

X is N;

Y is O;

R^1 is $-C_{0-4}$alkyl–pyridyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}$alkyl–C(O)–O–C_{0-4}alkyl, $-C_{0-4}$alkyl–morpholinyl, or $-C_{0-4}$alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-NO_2$; or $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-C_{0-4}$alkyl–phenyl, or $-C_{1-4}$alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}$alkoxyl substituents;

R^3 is hydrogen or $-C_{1-4}$alkoxyl;

R^4 is $-C_{0-4}$alkyl; and

R^5 is H, halogen, or $-C_{1-4}$alkyl.

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

Z^2 or Z^3 is N;

X is N;

Y is O;

R^1 is -OH, halogen, or –CN; or a $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-$cycloC_{3-6}alkyl, $-C_{0-4}$alkyl–phenyl, $-C_{0-4}$alkyl–pyridyl, $-C_{0-4}$alkyl–imidazolyl, $-C_{0-4}$alkyl–pyrazolyl, $-C_{0-4}$alkyl–triazolyl, $-C_{0-4}$alkyl–tetrazolyl, $-C_{0-4}$alkyl–dioxolanyl, $-C_{0-4}$alkyl–thiazolyl, $-C_{0-4}$alkyl–piperidinyl, $-C_{0-4}$alkyl–pyrrolidinyl, $-C_{0-4}$alkyl–morpholinyl, $-C_{0-4}$alkyl–pyrimidinyl, $-C_{2-6}$alkynyl–thiazolyl, or $-N(C_{0-4}alkyl)(-C_{0-4}alkyl)$ group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}$alkyl–C(O)–O–C_{0-4}alkyl, $-C_{0-4}$alkyl–morpholinyl, or $-C_{0-4}$alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-NO_2$; or $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-C_{0-4}$alkyl–phenyl, or $-C_{1-4}$alkoxy–phenyl group, wherein any

of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^2 or Z^3 is N;

X is N;

Y is O;

R^1 is –C_{0-4}alkyl–pyridyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are CH_2;

X is N;

Y is O;

R^1 is -OH, halogen, or –CN; or a –C_{1-6}alkyl, –C_{1-4}alkoxyl, –cycloC_{3-6}alkyl, –C_{0-4}alkyl–phenyl, –C_{0-4}alkyl–pyridyl, –C_{0-4}alkyl–imidazolyl, –C_{0-4}alkyl–pyrazolyl, –C_{0-4}alkyl–triazolyl, –C_{0-4}alkyl–tetrazolyl, –C_{0-4}alkyl–dioxolanyl, –C_{0-4}alkyl–thiazolyl, –C_{0-4}alkyl–piperidinyl, –C_{0-4}alkyl–pyrrolidinyl, –C_{0-4}alkyl–morpholinyl, –C_{0-4}alkyl–pyrimidinyl, –C_{2-6}alkynyl–thiazolyl, or –N(C_{0-4}alkyl)(–C_{0-4}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-}

6alkyl, $-C_{1-4}$alkoxyl, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl$–morpholinyl, or $-C_{0-4}alkyl$–benzoxazolyl;

R^2 is halogen, –OH, –CN, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-NO_2$; or $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-C_{0-4}alkyl$–phenyl, or $-C_{1-4}alkoxy$–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}$alkoxyl substituents;

R^3 is hydrogen or $-C_{1-4}$alkoxyl;

R^4 is $-C_{0-4}$alkyl; and

R^5 is H, halogen, or $-C_{1-4}$alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are CH_2;

X is N;

Y is O;

R^1 is $-C_{1-6}$alkyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl$–morpholinyl, or $-C_{0-4}alkyl$–benzoxazolyl;

R^2 is halogen, –OH, –CN, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-NO_2$; or $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-C_{0-4}alkyl$–phenyl, or $-C_{1-4}alkoxy$–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}$alkoxyl substituents;

R^3 is hydrogen or $-C_{1-4}$alkoxyl;

R^4 is $-C_{0-4}$alkyl; and

R^5 is H, halogen, or $-C_{1-4}$alkyl.

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

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

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

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

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

The term "hetero" unless specifically stated otherwise includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a heterocycloC_5alkyl is a five-member ring containing from 4 to no carbon atoms. Examples of heteroaryls include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl. Examples of heterocycloalkyls include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "heteroC_{0-4}alkyl" means a heteroalkyl containing 3, 2, 1, or no carbon atoms. However, at least one heteroatom must be present. Thus, as an

example, a heteroC0-4alkyl having no carbon atoms but one N atom would be a -NH– if a bridging group and a –NH_2 if a terminal group. Analogous bridging or terminal groups are clear for an O or S heteroatom.

The term "amine" unless specifically stated otherwise includes primary, secondary and tertiary amines substituted with C0-6alkyl.

The term "carbonyl" unless specifically stated otherwise includes a C0-6alkyl substituent group when the carbonyl is terminal.

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

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

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

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

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared

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

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

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Such additional therapeutic ingredients include, for example, i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) GABA-A receptor modulators, x) dopamine agonists or antagonists, xi) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), xii) tricyclic antidepressant drugs, xiv) norepinephrine modulators, xv) L-

DOPA, xvi) buspirone, xvii) lithium, xviii) valproate, xix) neurontin (gabapentin), xx) olanzapine, xxi) nicotinic agonists or antagonists including nicotine, xxii) muscarinic agonists or antagonists, xxiii) heroin substituting drugs such as methadone, levo-alpha-acetylmethadol, buprenorphine and naltrexone, and xxiv) disulfiram and acamprosate. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

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

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, and panic, as well as being useful in the treatment of pain which are responsive tomgluR5 inhibition, or alternatively about 0.5mg to about 7g per patient per day. For example, schizophrenia, anxiety, depression, and panic may be effectively treated by the administration of from about 0.01mg to 75mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Pain may be effectively treated by the administration of from about 0.01mg to 125mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 5.5g per patient per day. Further, it is understood that themgluR5 inhibiting compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions.

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

about 1000mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

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

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

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

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid

carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

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

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

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

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final

injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

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

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

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

The compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity asmgluR5 inhibitors. Accordingly, another aspect of the invention is the treatment in mammals of, for example, schizophrenia, anxiety, depression, and panic, pain, Parkinson's disease, cognitive dysfunction, epilepsy, drug addiction, drug abuse and drug withdrawal – maladies that are amenable to amelioration through inhibition of mGluR5 – by the

administration of an effective amount of the compounds of this invention. The term "mammals" includes humans, as well as other animals such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than humans is the treatment of clinical correlating afflictions to those above recited examples that are human afflictions.

Further, as described above, the compound of this invention can be utilized in combination with other therapeutic compounds. In particular, the combinations of themgluR5 inhibiting compound of this invention can be advantageously used in combination with i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) GABA-A receptor modulators, x) dopamine agonists or antagonists, xi) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), xii) tricyclic antidepressant drugs, xiii) norepinephrine modulators, xiv) L-DOPA, xv) buspirone, xvi) lithium, xvii) valproate, xviii) neurontin (gabapentin), xix) olanzapine, xx) nicotinic agonists or antagonists including nicotine, xxi) muscarinic agonists or antagonists, xxii) heroin substituting drugs such as methadone, levo-alpha-acetylmethadol, buprenorphine and naltrexone, and xxiii) disulfiram and acamprosate.

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

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

DMF	N,N-dimethylformamide
Dppf	1,1'-bis(diphenylphosphino)-ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_3N	triethylamine
GST	glutathione transferase
HMDS	hexamethyldisilazide
LDA	lithium diisopropylamide
m-CPBA	metachloroperbenzoic acid
MMPP	monoperoxyphthalic acid
MPPM	monoperoxyphthalic acid, magnesium salt $6H_2O$
Ms	methanesulfonyl = mesyl = SO_2Me
Ms0	methanesulfonate = mesylate
NBS	N-bromo succinimide
NSAID	non-steroidal anti-inflammatory drug
o-Tol	ortho-tolyl
OXONE®	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
PCC	pyridinium chlorochromate
$Pd_2(dba)_3$	Bis(dibenzylideneacetone) palladium(0)
PDC	pyridinium dichromate
PDE	Phosphodiesterase
Ph	Phenyl
Phe	Benzenediyl
PMB	para-methoxybenzyl
Pye	Pyridinediyl
rt	room temperature
Rac.	Racemic
SAM	aminosulfonyl or sulfonamide or SO_2NH_2
SEM	2-(trimethylsilyl)ethoxymethoxy
SPA	scintillation proximity assay
TBAF	tetra-n-butylammonium fluoride
Th	2- or 3-thienyl
TFA	trifluoroacetic acid

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

ALKYL GROUP ABBREVIATIONS

Me	=	Methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	Cyclopropyl
c-Bu	=	Cyclobutyl
c-Pen	=	Cyclopentyl
c-Hex	=	Cyclohexyl

ASSAYS DEMONSTRATING BIOLOGICAL ACTIVITY

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

(LM5a cell line) stably expressing hmGluR5a. The assays described in International Patent Publication WO 0116121 can be used.

Calcium Flux Assay

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

Phosphatidylinositol hydrolysis (PI) assays

Inositolphosphate assays were performed as described by Berridge et al. [Berridge et al, *Biochem. J.* 206: 587-5950 (1982); and Nakajima et al., *J. Biol. Chem.* 267:2437-2442 (1992)] with slight modifications. Mouse fibroblast Ltk cells expressing hmGluR5 (hmGluR5/L38- 20 cells) were seeded in 24-well plates at a density of 8x105cells/well. One μCi of [^{3}H]-inositol (Amersham PT6-271; Arlington Heights, Ill.; specific activity = 17.7 Ci/mmol) was added to each well and incubated for 16h at 37°C. Cells were washed twice and incubated for 45min in 0.5mL of standard Hepes buffered saline buffer (HBS; 125mM NaCl, 5mM KCl, 0.62mMmgS0$_4$, 1.8mM $CaCl_2$, 20mM HEPES, 6mM glucose, pH to 7.4). The cells were washed with HBS containing 10mM LiCl, and 400μL buffer added to each well. Cells were incubated at 37°C for 20min. For testing, 50μL of 10X compounds used in the practice of the invention (made in HBS/LiCl (100mM)) was added and

incubated for 10 minutes. Cells were activated by the addition of 10μM glutamate, and the plates left for 1 hour at 37°C. The incubations were terminated by the addition of 1mL ice-cold methanol to each well. In order to isolate inositol phosphates (IPs), the cells were scraped from wells, and placed in numbered glass test tubes. OnemL of chloroform was added to each tube, the tubes were mixed, and the phases separated by centrifugation. IPs were separated on Dowex anion exchange columns (AG 1-X8 100-200 mesh formate form). The upper aqueous layer (750μL) was added to the Dowex columns, and the columns eluted with 3mL of distilled water. The eluents were discarded, and the columns were washed with 10mLs of 60mM ammonium formate/5mM Borax, which was also discarded as waste. Finally, the columns were eluted with 4mL of 800mM ammonium formate/0.1M formic acid, and the samples collected in scintillation vials. Scintillant was added to each vial, and the vials shaken, and counted in a scintillation counter after 2 hours. Phosphatidylinositol hydrolysis in cells treated with certain exemplary compounds was compared to phosphatidylinositol hydrolysis in cells treated with the agonist alone in the absence of compound.

The compounds of this application havemgluR5 inhibitory activity as shown by values of less than 5 μM in the calcium flux assay and values of less than 100 μM in the PI assay. Preferably, the compounds should have values of less than 500nM in the calcium flux assay and values of less than 10 μM in the PI assay. Even more preferably, the compounds should have values of less than 50nM in the calcium flux assay and values of less than 1 μM in the PI assay

Examples 1-80 have mGluR5 inhibitory activity as shown by values of less than 5 μM in the calcium flux assay and values of less than 100 μM in the PI assay.

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

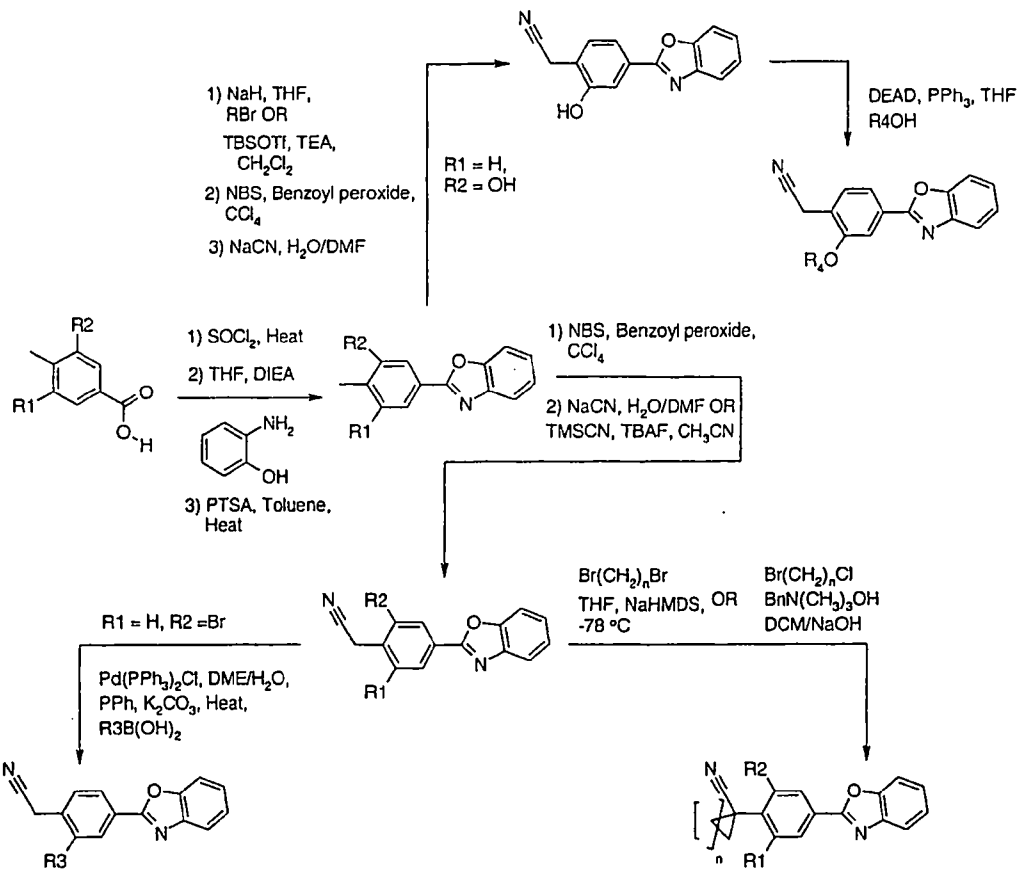
Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room or rt - that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The

melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. When given, yields are for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300MHz, 400MHz or 500MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet;d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations are used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)),mL (milliliters), g (gram(s)),mg (milligrams(s)), mol (moles),mmol (millimoles), eq (equivalent(s)).

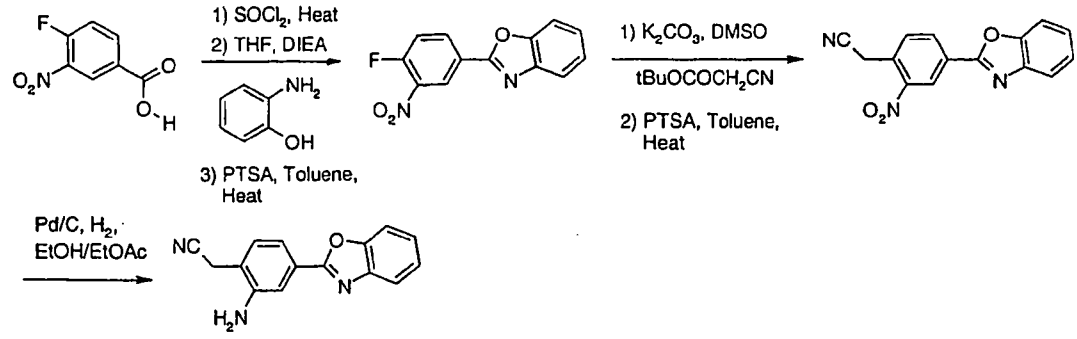
Methods of Synthesis

Compounds of the present invention can be prepared according to the following methods. The substituents are the same as in Formula I except where defined otherwise.

Scheme 1:



Scheme 2:



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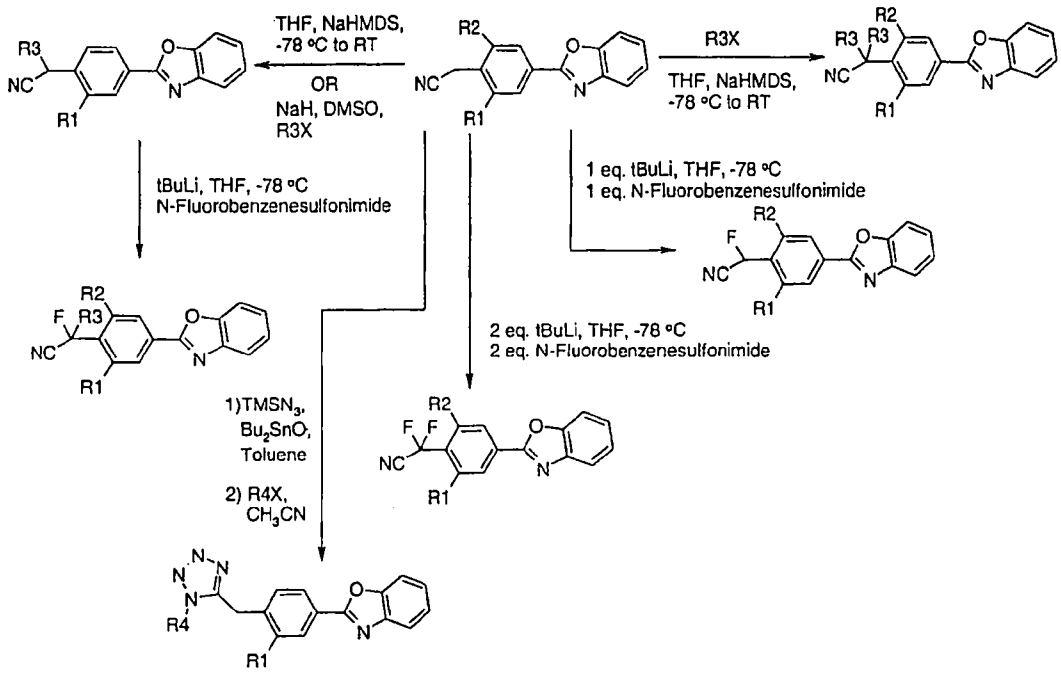

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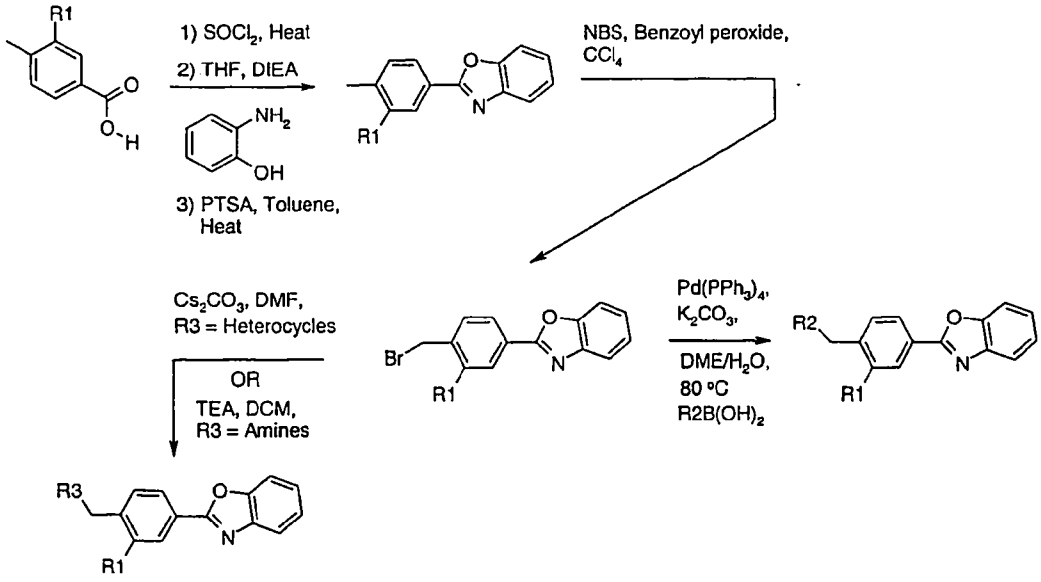

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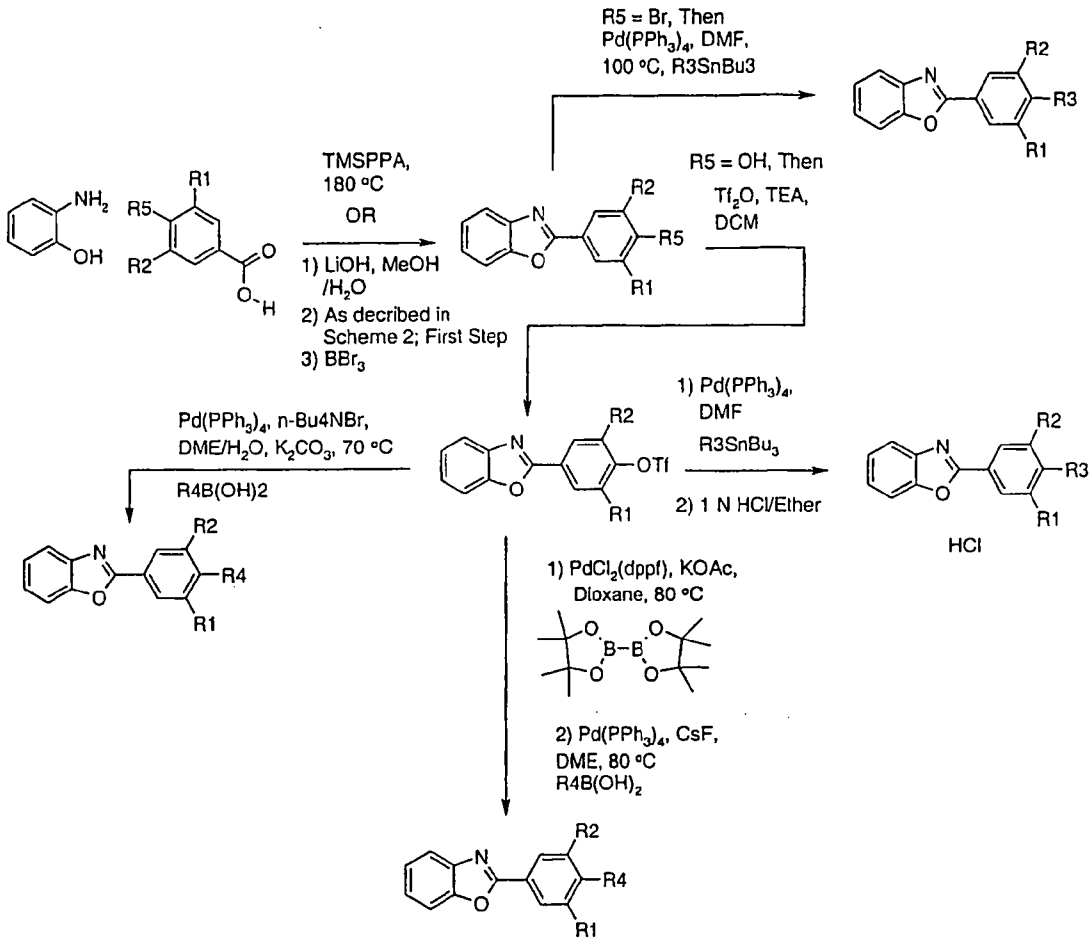

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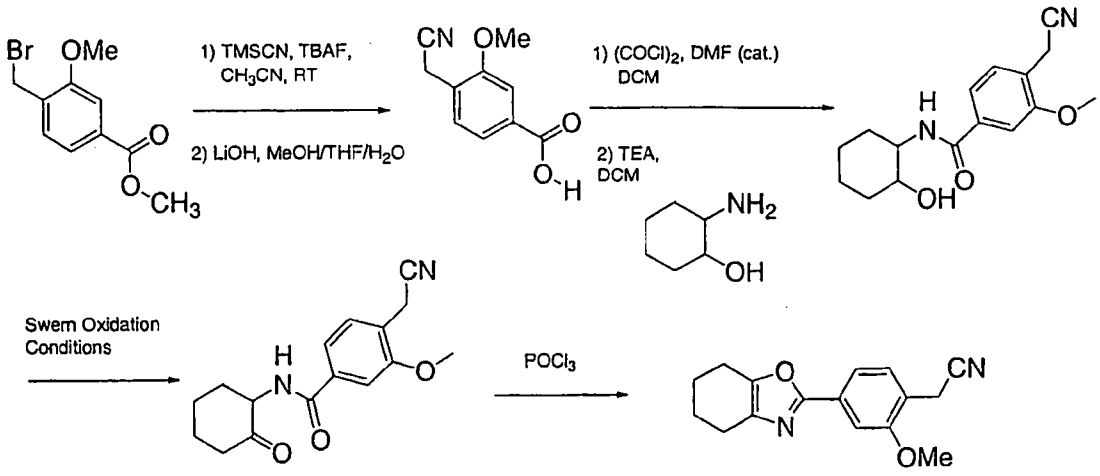

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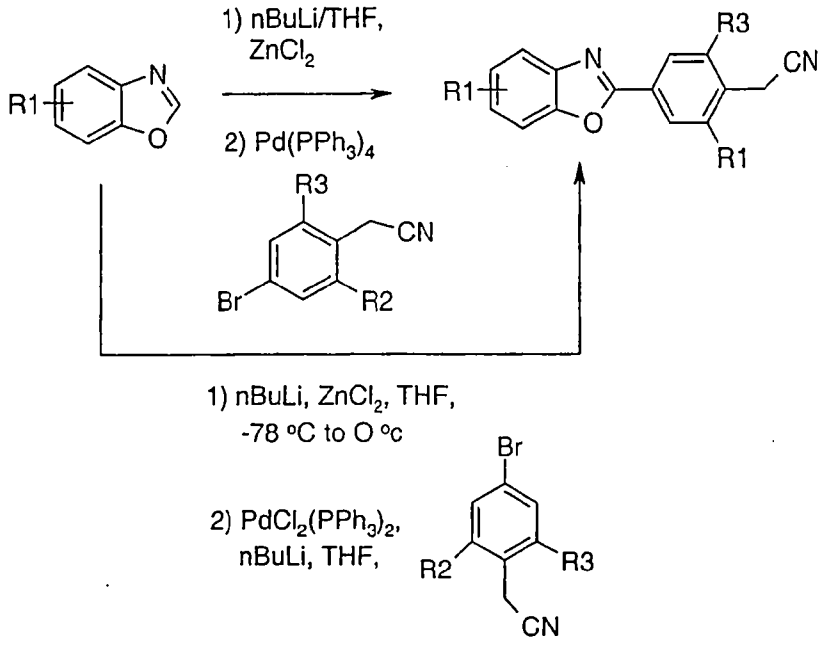

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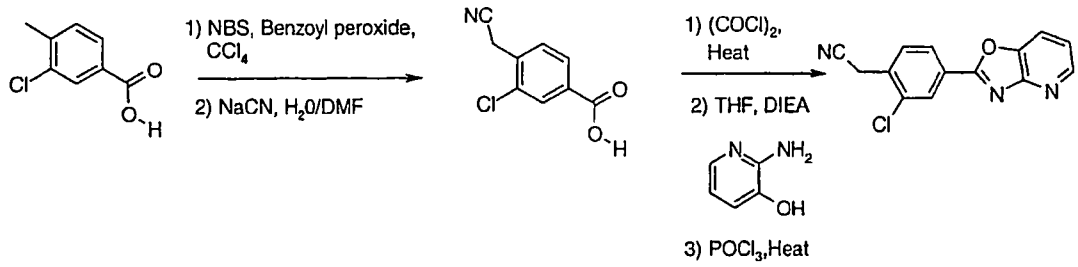
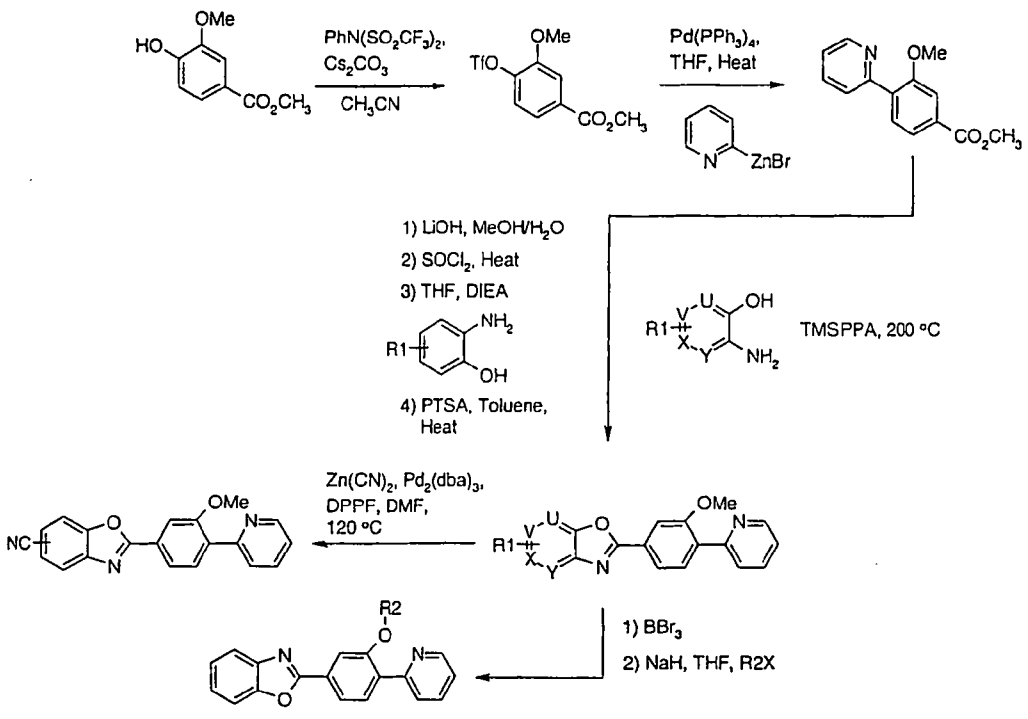
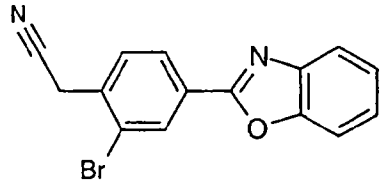


Scheme 9:



Example 1

[4-(1,3-Benzoxazol-2-yl)-2-bromophenyl]acetonitrile



A mixture of 3-bromo-4-methylbenzoic acid (1.0g, 4.7mmol) and thionyl chloride (18mL) was refluxed for 1h and then cooled to rt. The excess thionyl chloride was removed in *vacuo*, the residue was dissolved in THF (10mL), and was added to a cooled (0°C) mixture of 2-aminophenol (510mg, 4.7mmol) and diisopropylethylamine (0.90mL, 5.1mmol) in THF (18mL). The resulting mixture was stirred at rt for 4h. The solvent was then removed and the residue was purified by flash chromatography on silica gel eluting with EtOAc:hexane (1:5 to 1:4) to afford 3-bromo-*N*-(2-hydroxyphenyl)-4-methylbenzamide.

A mixture of 3-bromo-*N*-(2-hydroxyphenyl)-4-methylbenzamide (550mg, 1.8mmol), *p*-toluenesulfonic acid (2.4g, 12.7mmol) in toluene (50mL) was

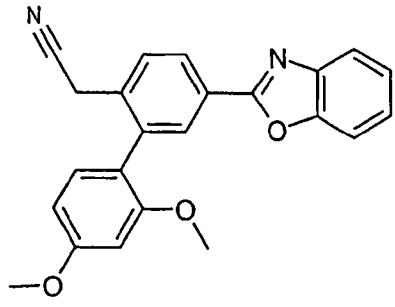
refluxed for 4h, cooled to rt, and filtered through a Celite pad. The filtrate was evaporated to dryness and the residue was purified by flash chromatography on silica gel using a gradient of EtOAc:hexane (0 to 30min: 0 to 15% EtOAc) to afford 2-(3-bromo-4-methylphenyl)-1,3-benzoxazole as a colorless solid. MS (ESI) 288 (M + H)$^+$.

A mixture of 2-(3-bromo-4-methylphenyl)-1,3-benzoxazole (240mg, 0.83mmol), *n*-bromosuccinimide (180mg, 0.99mmol), and benzoyl peroxide (10mg, 0.041mmol) in carbon tetrachloride (15mL) was refluxed for 3h. The white precipitate was filtered and the filtrate was evaporated to dryness. The resulting solid was purified by flash chromatography on silica gel eluting with EtOAc:hexane (1:5) to afford 2-[3-bromo-4-(bromomethyl)phenyl]-1,3-benzoxazole as a yellow solid.

A mixture of 2-[3-bromo-4-(bromomethyl)phenyl]-1,3-benzoxazole (156mg, 0.42mmol), and sodium cyanide (41mg, 0.84mmol) in DMF:H_2O (3:1, 16mL) was stirred at rt for 18h. Water (50mL) was added to the reaction mixture and it was extracted with EtOAc (3x). The organics were combined, washed with brine (2x), dried over Na_2SO_4, and evaporated to dryness to give an orange oil. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc:hexane (0 to 30min: 0 to 20% EtOAc) to afford the desired [4-(1,3-benzoxazol-2-yl)-2-bromophenyl]acetonitrile as a yellow solid (M.p. 190-191°C). ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.50 (s, 1H), 8.22 (dd, 1H), 7.78 (m, 1H), 7.70 (d, 1H), 7.60 (m, 1H), 7.39 (m, 2H), 3.91 (s, 2H). MS (ESI) 313 (M)$^+$.

Example 2

[5-(1,3-Benzoxazol-2-yl)-2',4'-dimethoxy-1,1'-biphenyl-2-yl]acetonitrile

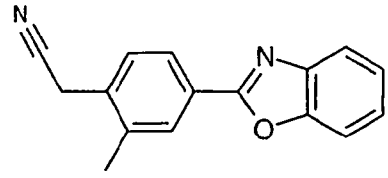


A mixture of 2,4-dimethoxyphenylboronic acid (175mg, 0.96mmol), [4-(1,3-benzoxazol-2-yl)-2-bromophenyl]acetonitrile (example 1) (200mg,

0.64mmol), dichlorobis(triphenylphosphine)palladium(II) (22mg, 0.032mmol), triphenylphosphine (17mg, 0.064mmol), and potassium carbonate (177mg, 1.3mmol) in degassed DME/H_2O (5:1, 12mL) was heated at 83°C for 18h. The mixture was cooled to rt, the two layers were separated and the aqueous layer was extracted with EtOAc (3x). The organics were combined, dried over Na_2SO_4 and evaporated to dryness to give an orange solid. Purification of the crude by flash chromatography on silica gel eluting with a gradient of EtOAc:hexanes (0 to 40min: 0 to 20% EtOAc, 40 to 50min: 50% EtOAc) afforded [5-(1,3-benzoxazol-2-yl)-2',4'-dimethoxy-1,1'-biphenyl-2-yl]acetonitrile as a yellow solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.26 (dd, 1H), 8.15 (s, 1H), 7.77 (m, 1H), 7.70 (d, 1H), 7.57 (m, 1H), 7.36 (m, 2H), 7.16 (d, 1H), 6.62 (dd, 1H), 6.57 (s, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.64 (q, 2H). MS (ESI) 371 $(M + H)^+$.

Example 3

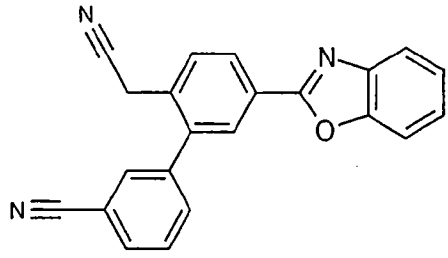
[4-(1,3-Benzoxazol-2-yl)-2-methylphenyl]acetonitrile



A mixture of methane boronic acid (57.6mg, 0.96mmol), [4-(1,3-benzoxazol-2-yl)-2-bromophenyl]acetonitrile (example 1) (200mg, 0.64mmol), dichlorobis (triphenylphosphine)palladium(II) (22.4mg, 0.032mmol), triphenylphosphine (17mg, 0.064mmol), and potassium carbonate (177mg, 1.3mmol) in degassed DME/H_2O (5:1, 12mL) was heated at 80°C for 18h. The mixture was cooled to rt, the two layers were separated and the aqueous layer was extracted with EtOAc (3x). The organics were combined, dried over Na_2SO_4 and evaporated to dryness to give a brown solid. Purification of the crude solid by flash chromatography on silica gel eluting with a gradient of EtOAc:hexanes (0 to 40min: 0 to 25% EtOAc) afforded the desired [4-(1,3-benzoxazol-2-yl)-2-methylphenyl]acetonitrile as a yellow solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.14 (s, 1H), 8.11 (d, 1H), 7.78 (m, 1H), 7.60 (m, 1H), 7.54 (d, 1H), 7.38 (m, 2H), 3.76 (s, 2H), 2.45 (s, 3H). MS (ESI) 249 $(M + H)^+$.

Example 4

5'-(1,3-Benzoxazol-2-yl)-2'-(cyanomethyl)-1,1'-biphenyl-3-carbonitrile



A mixture of 3-bromo-4-methylbenzoic acid (1.0g, 4.7mmol) and thionyl chloride (18mL) was refluxed for 1h and then cooled to rt. The excess thionyl chloride was removed *in vacuo*, the residue was dissolved in THF (10mL), and it was added to a cooled (0°C) mixture of 2-aminophenol (507mg, 4.7mmol) and diisopropylethylamine (0.90mL, 5.1mmol) in THF (18mL). The resulting mixture was stirred at rt for 4h. The solvent was then removed and the residue was purified by flash chromatography on silica gel eluting with EtOAc:hexanes (1:5 to 1:4) to afford 3-bromo-*N*-(2-hydroxyphenyl)-4-methylbenzamide.

A mixture of 3-bromo-*N*-(2-hydroxyphenyl)-4-methylbenzamide (554mg, 1.8mmol), *p*-toluenesulfonic acid (2.41g, 12.7mmol) and toluene (50mL) was refluxed for 4h, cooled to rt, and filtered through a Celite pad. The filtrate was evaporated to dryness and the residue was purified by flash chromatography on silica gel using a gradient of EtOAc:hexanes (0 to 30min:0 to 15% EtOAc) to afford 2-(3-bromo-4-methylphenyl)-1,3-benzoxazole as a colorless solid. MS (ESI) 288 (M^+).

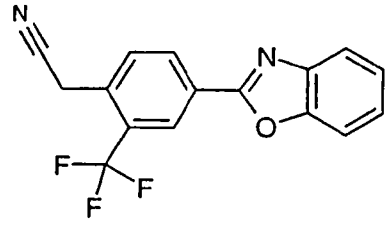
A mixture of 3-cyano-phenylboronic acid (183mg, 1.3mmol), 2-(3-bromo-4-methylphenyl)-1,3-benzoxazole (300mg, 1.04mmol), dichlorobis(triphenylphosphine) palladium(II) (36.5mg, 0.052mmol), triphenylphosphine (27mg, 0.104mmol), and potassium carbonate (287mg, 2.08mmol) in degassed DME/H_2O (5:1, 18mL) was heated to 80°C for 18h. The mixture was cooled to rt and the two layers were separated and the aqueous layer was extracted with EtOAc (3x). The organics were combined, dried over Na_2SO_4, and evaporated to dryness to give a clear solid. Purification of the crude by flash chromatography on silica gel eluting with a gradient of EtOAc:hexanes (0 to 30min: 0 to 20% EtOAc) afforded 5'-(1,3-benzoxazol-2-yl)-2'-methyl-1,1'-biphenyl-3-carbonitrile a colorless solid.

A mixture of 5'-(1,3-benzoxazol-2-yl)-2'-methyl-1,1'-biphenyl-3-carbonitrile (229mg, 0.74mmol), *n*-bromosuccinimide (145mg, 0.81mmol), and benzoyl peroxide (9mg, 0.037mmol) in carbon tetrachloride (15mL) was refluxed for 5h. The solvent was evaporated to dryness and the crude was purified by flash chromatography on silica gel eluting with a gradient of EtOAc:hexanes (0 to 30min: 0 to 20% EtOAc, 30 to 40min: 50% EtOAc) to afford 5'-(1,3-benzoxazol-2-yl)-2'-(bromomethyl)-1,1'-biphenyl-3-carbonitrile as a colorless solid.

A mixture of 5'-(1,3-benzoxazol-2-yl)-2'-(bromomethyl)-1,1'-biphenyl-3-carbonitrile (183mg, 0.47mmol) and sodium cyanide (46mg, 0.94mmol) in DMF:H_2O (5:1, 18mL) and DMF (20mL) was stirred at rt for 3h. H_2O was added to the reaction mixture and it was extracted with EtOAc (3x). The organics were combined, washed with brine (2x), dried over Na_2SO_4, and evaporated to dryness to give an orange oil. The crude was purified by flash chromatography on silica gel eluting with a gradient of EtOAc:hexanes (0 to 30min: 0 to 20% EtOAc) to afford the desired 5'-(1,3-benzoxazol-2-yl)-2'-(cyanomethyl)-1,1'-biphenyl-3-carbonitrile as a colorless solid (M.p. 175-176°C). ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.34 (dd, 1H), 8.18 (s, 1H), 7.77 (m, 3H), 7.67 (m, 3H), 7.60 (m, 1H), 7.40 (m, 2H), 3.69 (s, 2H). MS (ESI) 336 $(M + H)^+$.

Example 5

[4-(1,3-Benzoxazol-2-yl)-2-(trifluoromethyl)phenyl]acetonitrile



A mixture of 4-methyl-3-(trifluoromethyl)benzoic acid (1.0g, 4.9mmol) and thionyl chloride (15mL) was refluxed for 3h and then stirred at rt overnight. The excess thionyl chloride was removed in *vacuo*, the residue was dissolved in THF (20mL), and it was added to a cooled (0°C) solution of 2-aminophenol (0.53g, 4.9mmol) and diisopropylethylamine (1.0mL, 5.9mmol) in anhydrous THF (15mL). The resulting brownish mixture was stirred at rt for 3h. The solvent was then removed and *p*-toluenesulfonic acid (3.7g, 19.6mmol) and toluene

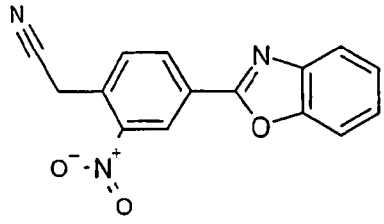
(20mL) were added to the dark oil. The mixture was then refluxed for 3h and the mixture was cooled to rt. The excess *p*-toluenesulfonic acid was filtered through Celite and the filtrate was evaporated to dryness. The crude was purified by flash chromatography on silica gel eluting with EtOAc:hexanes (1:9) to afford 2-[4-methyl-3-(trifluoromethyl)phenyl]-1,3-benzoxazole as a colorless solid.

A mixture of 2-[4-methyl-3-(trifluoromethyl)phenyl]-1,3-benzoxazole (600mg, 2.2mmol), *n*-bromosuccinimide (579mg, 3.25mmol), benzoyl peroxide (26mg, 0.11mmol) in carbon tetrachloride (15mL) was refluxed for 3h and then cooled to rt. The white precipitate was filtered and the filtrate was concentrated to dryness. The crude was purified by flash chromatography on silica gel eluting with EtOAc:hexanes (1:1) to afford 2-[4-(bromomethyl)-3-(trifluoromethyl)phenyl]-1,3-benzoxazole.

To a suspension of 2-[4-(bromomethyl)-3-(trifluoromethyl)phenyl]-1,3-benzoxazole (528mg, 1.5mmol) and cyanotrimethylsilane (0.30mL, 2.2mmol) in acetonitrile (19mL) was added TBAF (1.0M in THF, 2.2mL, 2.2mmol) and the mixture was stirred at rt for 2h. The solvent was removed *in vacuo* and the crude was purified by flash chromatography eluting with EtOAc:hexanes (1:9) to afford the desired [4-(1,3-benzoxazol-2-yl)-2-(trifluoromethyl)phenyl]acetonitrile as a colorless solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.60 (s, 1H), 8.48 (d, 1H), 7.88 (d, 1H), 7.82 (m, 1H), 7.63 (m, 1H), 7.43 (m, 2H), 4.05 (s, 2H). MS (ESI) 303 $(M + H)^+$.

Example 6

[4-(1,3-Benzoxazol-2-yl)-2-nitrophenyl]acetonitrile



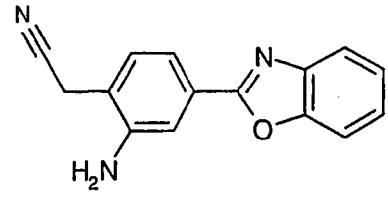
A mixture of 4-fluoro-3-nitrobenzoic acid (2.1g, 11.3mmol) and thionyl chloride (20mL) was refluxed for 3h and then cooled to rt. The excess thionyl chloride was removed and the residue dissolved in 10mL of THF was added to a cooled (0°C) solution of 2-aminophenol (1.24g, 11.3mmol) and diisopropylethylamine (2.4mL, 13.6mmol) in anhydrous THF (20mL). The resulting

mixture was refluxed for 4h and then cooled to rt. The solvent was removed and *p*-toluenesulfonic acid (8.63g, 45.4mmol) and toluene (50mL) were added to afford a dark mixture that was refluxed overnight. The solvent was removed and the crude was purified by flash chromatography on silica gel eluting with hexanes:CH_2Cl_2 (1:5) to afford 2-(4-fluoro-3-nitrophenyl)-1,3-benzoxazole as a colorless solid.

2-(4-fluoro-3-nitrophenyl)-1,3-benzoxazole (200mg, 0.77mmol) was dissolved in DMSO (5mL) and K_2CO_3 (267mg, 1.94mmol) was added. The resulting yellow mixture was warmed to 65°C and *tert*-butylcyanoacetate (137mg, 0.97mmol) was added dropwise. The dark red mixture was heated to 65°C for 30min, cooled to rt, and poured into H_2O. The aqueous layer was acidified to pH 3 (with a 10% aqueous HCl solution) and it was extracted with EtOAc (3x). The organics were combined, washed with brine (2x), dried over Na_2SO_4, and evaporated to dryness. The yellow residue and *p*-toluenesulfonic acid (29.5mg, 0.15mmol) were dissolved in toluene (15mL) and the mixture was refluxed for 20h. After cooling to rt, the mixture was poured in H_2O and the two layers were separated. The aqueous was extracted with EtOAc (3x), the organics were combined, dried over Na_2SO_4, and evaporated to dryness. Purification of the residue by flash chromatography on silica gel eluting with EtOAc:hexanes (3:7 to 2:3 to 1:1) afforded the desired [4-(1,3-benzoxazol-2-yl)-2-nitrophenyl]acetonitrile as an orange solid (M.p. 203°C). ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.79 (s, 1H), 8.57 (dd, 1H), 7.97 (d, 1H), 7.86 (m, 2H), 7.54-7.44 (m, 2H), 4.50 (s, 2H). MS (ESI) 280 $(M + H)^+$.

Example 7

[2-Amino-4-(1,3-benzoxazol-2-yl)phenyl]acetonitrile

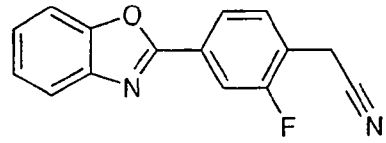


A suspension of [4-(1,3-benzoxazol-2-yl)-2-nitrophenyl]acetonitrile (100mg, 0.36mmol) and Pd/C (20mg) in EtOH/EtOAc (5:1, 60mL) was hydrogenated (35psi) over 2d. The resulting reaction mixture was filtered through Celite and the filtrate was evaporated to dryness. The yellow solid obtained was purified by flash chromatography on silica gel eluting with MeOH:CH_2Cl_2 (1:19) to afford [2-amino-4-

(1,3-benzoxazol-2-yl)phenyl]acetonitrile as an orange solid (M.p.198-199°C). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.77 (m, 1H), 7.71-7.66 (m, 2H), 7.58 (m, 1H), 7.40-7.34 (m, 3H), 3.88 (s, 2H), 3.66 (s, 2H). MS (ESI) 250 $(M + H)^+$.

Example 8

[4-(1,3- Benzoxazol-2-yl)-2-fluorophenyl] acetonitrile

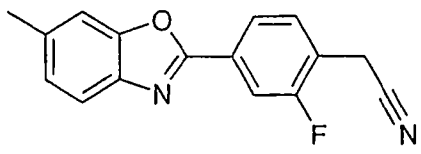


To a stirred solution of 4-bromo-2-fluoro benzyl bromide (1.5g, 5.6mmol) in DMF (50mL) was added sodium cyanide (0.8g, 17mmol). The reaction mixture was stirred at 90°C for 1h, cooled to rt and quenched with brine (50mL). After extraction with EtOAc (3 x 100mL), the organic layers were combined, washed with brine (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, hexanes:EtOAc 5:1) to afford 4-bromo-2-fluoro benzyl cyanide as yellow solid. MS (ESI) 307 $(M + H)^+$.

To a stirred solution of benzoxazole (153mg, 1.3mmol) in 5mL THF at –78°C, was added *n*-Butyllithium (640μL, 2.5M in hexanes, 1.6mmol). The reaction mixture was stirred for 15min at –78°C and $ZnCl_2$ (3.9mL, 1.0M solution in Et_2O, 3.9mmol) was added via a syringe. The reaction was then warmed to 0°C for 1h and a solution of 4-bromo-2-fluoro benzyl cyanide (214mg, 1.0mmol) in THF (2mL) was added, along with Pd (a fine suspension prepared as follows: 200μL *n*-Butyllithium, 2.5M in hexanes added to 144mg $PdCl_2(PPh_3)_2$ in 5mL of THF). The reaction mixture was then stirred at reflux overnight, quenched with sat. $NaHCO_3$ (50mL) and diluted with EtOAc (300mL). The resulting organic layer was washed with H_2O (1 x 50mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue purified by flash chromatography (silica gel, hexanes:EtOAc 5:1) to afford the desired [4-(1,3-benzoxazol-2-yl)-2-fluorophenyl] acetonitrile as a yellow solid. ^{1}H NMR (CD_3OD, 300MHz) δ 8.14 (q, 1H), 8.2 (q, 1H), 7.82 (m, 1H), 7.63 (m,2H), 7.42 (m,2H), 3.85 (s, 2H). MS (ESI) 253 $(M + H)^+$.

Example 9

[2-Fluoro-4-(6-methyl-1,3- benzoxazol-2-yl)phenyl] acetonitrile

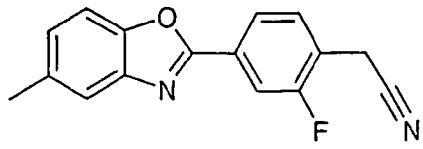


To a stirred solution of 4-bromo-2-fluoro benzyl bromide (1.5g, 5.6mmol) in DMF (50mL) was added sodium cyanide (0.8g, 16.8mmol). The reulting reaction mixture was stirred at 90°C for 1h, cooled to rt, quenched with brine (50mL) and extracted with EtOAc (3 x 100mL). The organic layers were combined, washed with brine (50mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column (silica gel, hexanes:EtOAc 5:1) to afford 4-bromo-2-fluoro benzyl cyanide as yellow solid. MS (ESI) 307 $(M + H)^+$.

To a stirred solution of 6-methylbenzoxazole (173mg, 1.3mmol) in THF (5mL) at –78 °C, was added *n*-Butyllithium (640µL, 2.5M in hexanes, 1.6mmol). The resulting reaction mixture was stirred for 15min at –78 °C and $ZnCl_2$ (3.9mL, 1M in Et_2O, 3.9mmol) was added via a syringe. After warming up the reaction mixture at 0°C for 1h, a solution of 4-bromo-2-fluoro benzyl cyanide (214mg, 1.0mmol) in THF (2mL) was added, along with Pd^0 (a fresh suspension prepared as follows: 200µL *n*-Butyllithium, 2.5M in hexanes added to 144mg of $PdCl_2(PPh_3)_2$ in 5mL of THF). The mixture was then heated under reflux overnight. The mixture was hydrolized with sat. $NaHCO_3$ (50mL) and extracted with EtOAc (3 x 150mL). The organic layers were combined, washed with H_2O (50mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purufied by chromatography on silica gel using a mixture of hexanes:EtOAc (5:1) as eluant to afford [2-fluoro-4-(6-methyl-1,3- benzoxazol-2-yl)phenyl] acetonitrile as yellow solid. ^1H NMR (CD_3OD, 300MHz), δ8.07 (d, 1H), 7.95(d, 1H), 7.64(m, 2H), 7.40(s, 1H), 7.20(d, 1H), 3.90(s, 1H). MS (ESI) 267 $(M + H)^+$.

Example 10

[2-Fluoro-4-(5-methyl-1,3- benzoxazol-2-yl)phenyl] acetonitrile

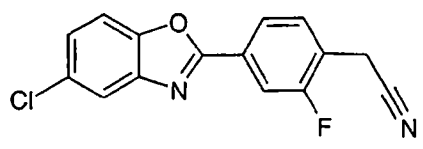


To a stirred solution of 4-bromo-2-fluoro benzyl bromide (1.5g, 5.6mmol) in DMF (50mL) was added sodium cyanide (0.8g, 16.8mmol). The resulting mixture was stirred at 90°C for 1h, cooled at rt and quenched with brine (50mL). After extraction with EtOAc (3 x 50mL), the organic layers were combined, washed with brine (50mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using a mixture of hexanes:EtOAc (5:1) to afford 4-bromo-2-fluoro benzyl cyanide as yellow solid. MS (ESI) 307 $(M + H)^+$.

To a stirred solution of 5-methylbenzoxazole (173mg, 1.3mmol) in THF (5mL) at -78 °C was added n-Butyllithium (640µL, 2.5M in hexanes, 1.6mmol). The reaction mixture was stirred for 15min at –78°C followed by the addition of $ZnCl_2$ (3.9mL, 1M in Et_2O, 3.9mmol) via a syringe. The reaction mixture was warmed at 0 °C for 1h and a solution of 4-bromo-2-fluoro benzyl cyanide (214mg, 1.0mmol) in THF (2mL) was added, along with Pd^0 (a fresh suspension prepared as follows: 200 µL *n*-Butyllithium, 2.5M in hexanes added to 144mg $PdCl_2(PPh_3)_2$ in 5mL of THF). The mixture was refluxed overnight and quenched with sat. $NaHCO_3$ (50mL). After extraction with EtOAc (3x75mL), the organic layers were combined, washed with brine (50mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using a mixture of hexanes:EtOAc (5:1) to afford the desired [2-fluoro-4-(5-methyl-1,3- benzoxazol-2-yl)phenyl] acetonitrile as yellow solid. ^1H NMR (CD_3OD, 300MHz), δ 8.07 (d, 1H), 7.95 (d, 1H), 7.64 (m, 2H), 7.40 (s, 1H), 7.20 (d, 1H), 3.90 (s, 1H). MS (ESI) 267 $(M + H)^+$.

Example 11

[4-(5-Chloro-1,3- benzoxazol-2-yl)-2-fluorophenyl] acetonitrile

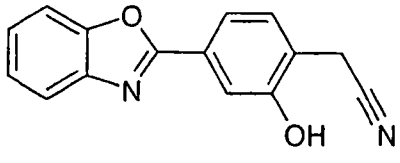


To a stirred solution of 4-bromo-2-fluoro benzyl bromide (1.5g, 5.6mmol) in DMF (50mL) was added sodium cyanide (0.8g, 16.8mmol). The reaction was stirred at 90°C for 1h, and cooled at rt. After quenching with brine (50mL) and diluted with EtOAc (100mL), the EtOAc layer was washed with brine (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, hexanes:EtOAc 5:1) to afford 4-bromo-2-fluoro benzyl cyanide as yellow solid. MS (ESI) 307 $(M + H)^+$.

To a stirred solution of 5-chlorobenzoxazole (200mg, 1.3mmol) in 5mL THF at –78 °C, was added *n*-Butyllithium (640µL, 2.5M in hexane, 1.6mmol). The reaction was stirred for 15min at –78 °C followed by the addition of $ZnCl_2$ (3.9mL, 1M in Et_2O, 3.9mmol) via a syringe. The reaction was then warmed at 0°C for 1h. A solution of 4-bromo-2-fluoro benzyl cyanide (214mg, 1.0mmol) in THF (2mL) was added, along with Pd^0 (a fresh suspension prepared as follows: 200µL, *n*-Butyllithium, 2.5M in hexanes added to 144mg of $PdCl_2(PPh_3)_2$ in 5mL of THF). The reaction was then stirred at reflux overnight and quenched with sat. $NaHCO_3$ (50mL). After diluting the mixture with EtOAc (300mL), the organic extract was washed with H_2O (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, hexanes:EtOAc 5:1) to afford the desired [4-(5-chloro-1,3- benzoxazol-2-yl)-2-fluorophenyl] acetonitrile as yellow solid. ^1H NMR (CD_3OD, 300Hz),δ8.10(d, 1H), 7.99 (d, 1H), 7.79 (d,1H), 7.68 (t, 1H), 7.52 (d, 1H), 7.39 (q, 1H), 3.90 (s, 1H). MS (ESI) 287 $(M + H)^+$.

Example 12

[4-(1,3- Benzoxazol-2-yl)-2-hydroxyphenyl] acetonitrile



To a 100mL round-bottom flask with 3-hydroxy-4-methylbenzoic acid (2.5g, 16.4mmol), was added dropwise $SOCl_2$ (15mL). The reaction was refluxed for 30min and cooled to rt. The excess of $SOCl_2$ was removed *in vacuo* and the oily acid chloride was dissolved in THF (15mL). This resulting solution was added dropwise to a mixture of 2-aminophenol (1.8g, 16.4mmol), triethylamine (1.7g, 16.4mmol) and

THF (30mL) at 0°C. The resulting reaction mixture was then brought to rt for 30min and the resulting precipitate was removed by filtration. The filtrate was concentrated and dried under vacuum. The resulting dark brown solid residue was dissolved in toluene (20mL) and *p*-toluenesulfonic acid (15.6g, 82mmol) was added. The reaction was refluxed overnight, cooled at rt and EtOAc (500mL) was added. The EtOAc solution was washed with brine (3 x 50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallized in EtOAc to afford 5-(1,3-benzoxazol-2-yl)-2-methylphenol as a light yellow solid. MS (ESI) 226 $(M + H)^+$.

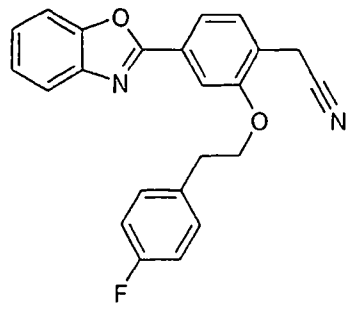
The solution of 5-(1,3-benzoxazol-2-yl)-2-methylphenol (0.8g, 3.5mmol) and triethylamine (0.6mL, 4.3mmol) in CH_2Cl_2 (20mL) was cooled at 0 °C and tert-butyl (900mL, 3.9mmol) was added. The reaction was then warmed to rt for 30min. The mixture was diluted with EtOAc (200mL), washed with H_2O (3X50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 2-(3-{[*tert*-butyl-(dimethyl)silyl]oxy}-4-methylphenyl)-1,3-benzoxazole as light yellow oil.

To 2-(3-{[*tert*-butyl-(dimethyl)silyl]oxy}-4-methylphenyl)-1,3-benzoxazole (1.46g, 4.3mmol) dissolved in CCl_4 (50mL) was added NBS (770mg, 4.3mmol) and benzoyl peroxide (50mg). The reaction mixture was refluxed for 6h and then cooled to rt. The solvent was removed *in vacuo* and the residue was diluted with EtOAc (50mL), washed with brine (50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 2-(3-{[tert-butyl-(dimethysilyl]oxy}-4-bromomethylphenyl)-1,3-benzoxazole as light yellow solid.

The mixture of 2-(3-{[tert-butyl-(dimethyl)silyl]oxy}-4-bromomethylphenyl)-1,3-benzoxazole (1.6g, 3.8mmol) and sodium cyanide (560mg, 11.4mmol) in DMF (10mL) was stirred at 90°C overnight. After cooling to rt, the mixture was diluted with EtOAc (100mL), washed with H_2O (2X50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the desired [4-(1,3-benzoxazol-2-yl)-2-hydroxyphenyl] acetonitrile as yellow solid. ^1H NMR(CD_3OD, 300MHz), δ10.6(s,1H), 7.8(m, 2H), 7.7(m, 2H), 7.5(d, 1H), 7.4(m,2H). MS (ESI) 251 $(M + H)^+$.

Example 13

{4-(1,3- Benzoxazol-2-yl)-2-[2-(4-fluorophenyl) ethoxy]phenyl}acetonitrile



To a 100mL round-bottom flask with 3-hydroxy-4-methylbenzoic acid (2.5g, 16.4mmol), was added $SOCl_2$ (15mL) dropwise. The reaction was refluxed for 30min, cooled to rt and the excess of $SOCl_2$ was removed *in vacuo*. The oily acid chloride was dissolved in THF (15mL) and the solution was added dropwise to a mixture of 2-aminophenol (1.8g, 16.4mmol), triethylamine (1.7g, 16.4mmol) and THF (30mL) at 0°C. The reaction was then warmed to rt for 1h and the precipitate was removed by filtration. The filtrate was concentrated and dried *in vacuo* and the dark brown solid residue was dissolved in toluene (20mL) and *p*-toluenesulfonic acid (15.6g, 82mmol) was added. The reaction was refluxed overnight, cooled to rt and dissolved in EtOAc (500mL). The organic solution was washed with brine (3 x 50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was recrystallized in EtOAc to afford 5-(1,3-benzoxazol-2-yl)-2-methylphenol as a light yellow solid. MS (ESI) 226 $(M + H)^+$.

A solution of 5-(1,3-benzoxazol-2-yl)-2-methylphenol (0.8g, 3.5mmol) and triethylamine (0.6mL, 4.3mmol) in CH_2Cl_2 (20mL) was cooled to 0°C and TBDMS-OTf (900mL, 3.9mmol) was added. The reaction was slowly warmed to rt and EtOAc(200mL) was added. The mixture was washed with H_2O (3 x 50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 2-(3-{[*tert*-butyl-(dimethyl)silyl]oxy}-4-methylphenyl)-1,3-benzoxazole as light yellow oil.

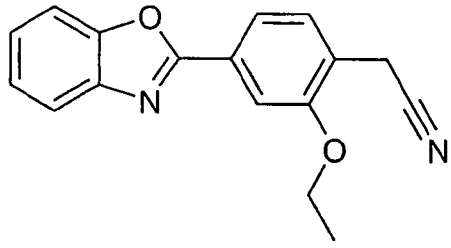
To 2-(3-{[*tert*-butyl-(dimethyl)silyl]oxy}-4-methylphenyl)-1,3-benzoxazole (1.46g, 4.3mmol) in CCl_4 (50mL) was added NBS (770mg, 4.3mmol) and benzoyl peroxide (50mg). The reaction mixture was refluxed for 6h, cooled to rt, and CCl_4 was removed *in vacuo*. The residue was dissolved in EtOAc (50mL), washed with H_2O (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-(3-{[tert-butyl-(dimethyl)silyl]oxy}-4-bromomethylphenyl)-1,3-benzoxazole as light yellow solid.

A mixture of 2-(3-{[tert-butyl-(dimethyl)silyl]oxy}-4-bromomethylphenyl)-1,3-benzoxazole (1.6g, 3.8mmol) and sodium cyanide (560mg, 11.4mmol) in DMF (10mL) was stirred at 90^0C overnight. The reaction was cooled to rt and dissolved in EtOAc (200mL), washed with H_2O (2X50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford [4-(1,3- benzoxazol-2-yl)-2-hydroxyphenyl] acetonitrile as yellow solid. MS (ESI) 251 $(M + H)^+$.

A solution of triphenylphosphine (126mg, 0.48mmol), DEAD (84mg, 0.48mmol) and THF (2mL) was stirred 2h and a solution of [4-(1,3- benzoxazol-2-yl)-2-hydroxyphenyl], acetonitrile (100mg, 0.4mmol) and 4-fluorophenethylalcohol (56mg, 0.4mmol) in THF (2mL) was added. The resulting reaction mixture was stirred overnight and the THF was removed *in vacuo*. The resulting residue was purified on Prep TLC (1000μm) to afford {4-(1,3- benzoxazol-2-yl)-2-[2-(4-fluorophenyl)ethoxy]phenyl}acetonitrile. ^{1}H NMR (CD_3OD, 300MHz), δ 7.88 (d 1H), 7.78 (m, 2H), 7.60 (m, 1H), 7.52 (d, 1H), 7.40 (d, 2H), 7.30 (m, 2H), 7.05 (m, 1H), 4.40 (m, 2H), 3.70 (s,2H), 3.20 (m, 2H). MS (ESI) 373$(M + H)^+$.

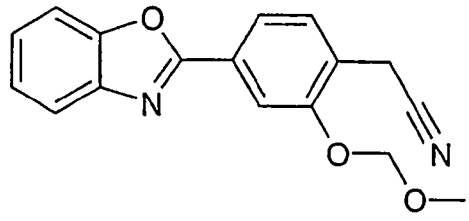
Example 14

[4-(1,3- Benzoxazol-2-yl)-2-ethoxyphenyl] acetonitrile



Example 15

[4-(1,3- Benzoxazol-2-yl)-2-(methoxymethoxy)phenyl] acetonitrile



To a 100mL round-bottom flask with 3-hydroxy-4-methylbenzoic acid (2.5g, 16.4mmol), was added $SOCl_2$ (15mL) dropwise. The reaction was refluxed for 30min, cooled to rt. The excess of $SOCl_2$ was removed *in vacuo* and the oily acid chloride was dissolved in THF (15mL). The resulting solution was added dropwise to a mixture of 2-aminophenol (1.8g, 16.4mmol), triethylamine (1.7g, 16.4mmol) and THF (30mL) at 0°C. The reaction mixture was brought to rt for 30min, after which time, the precipitate was filtered. The filtrate was concentrated and dried *in vacuo*. The dark brown solid residue was dissolved in toluene (20mL) and *p*-toluenesulfonic acid (15.6g, 82mmol) was added. The mixture was refluxed overnight, cooled to rt and EtOAc (500mL) was added. The EtOAc solution was washed with brine (3 x 50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was recrystallized in EtOAc to afford 5-(1,3-benzoxazol-2-yl)-2-methylphenol as a light yellow solid. MS (ESI) 226$(M + H)^+$.

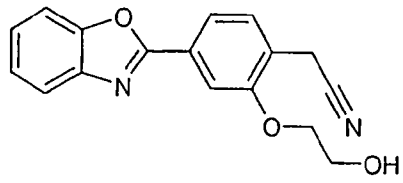
A solution of 5-(1,3-benzoxazol-2-yl)-2-methylphenol (200mg,0.89mmol) in THF (6mL) was cooled to –78°C under Argon and sodium hydride (24mg, 1.0mmol) was added. After 30min at this temperature, bromomethyl ether (225mg,1.8mmol) was added via syringe. The reaction was warmed to rt for 1h. The reaction mixture was concentrated and the residue was purified by flash column (silica gel, hexanes:EtOAc 4:1) to afford 2-[3-(methoxymethoxy)-4-methylphenyl]-1,3-benzoxazole. MS (ESI) 270 $(M + H)^+$.

A solution of 2-[3-(methoxymethoxy)-4-methylphenyl]-1,3-benzoxazole (200mg, 0.74mmol, 84%), NBS (179mg, 0.81mmol), and benzoyl peroxide (50mg) in CCl_4 (10mL), was refluxed for 12h. After cooling to rt, CCl_4 was removed *in vacuo* and residue was purified by flash column (silica gel, hexanes:EtOAc 5:1) to afford 2-[4-(bromomethyl)-3-(methoxymethoxy) phenyl]-1,3-benzoxazole. MS (ESI) 349 $(M + H)^+$.

2-[4-(Bromomethyl)-3-(methoxymethoxy) phenyl]-1,3- benzoxazole (250mg, 0.72mmol) was treated with sodium cyanide (150mg, 2.2mmol) in DMF/H_2O (15mL/1.5mL) at 90°C for 3h and EtOAc (150mL) was added. The EtOAc solution was washed with H_2O (2 x 20mL), brine (2 x 20mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was eluted with flash column (silica gel, hexanes:EtOAc 4:1) to afford the desired [4-(1,3- benzoxazol-2-yl)-2-(methoxymethoxy)phenyl] acetonitrile as a yellow solid. ^1H NMR (CD_3OD, 300MHz), δ 8.02 (d, 2H), 7.95 (m, 1H), 7.80 (m,1 H), 7.63 (m, 1H), 7.57 (d, 2H), 7.40 (m, 2H). MS (ESI) 295 $(M + H)^+$.

Example 16

[4-(1,3- Benzoxazol-2-yl)-2-(hydroxyethoxy)phenyl] acetonitrile



To a 100mL round-bottom flask with 3-hydroxy-4-methylbenzoic acid (2.5g, 16.4mmol) was added $SOCl_2$ (15mL) dropwise. This reaction was refluxed for 30min, cooled to rt and the excess $SOCl_2$ removed *in vacuo*. The oily acid chloride was dissolved in THF (15mL) and the solution was added dropwise to a mixture of 2-aminophenol (1.8g, 16.4mmol), triethylamine(1.7g, 16.4mmol) in THF (30mL) at 0°C. The reaction was then brought to rt for 0.5h and the precipitate was removed by filtration. The filtrate was concentrated and dried *in vacuo*. To the dark brown solid residue was added toluene (20mL) and *p*-toluenesulfonic acid (15.6g, 82mmol). The reaction was refluxed overnight, cooled to rt and dissolved in EtOAc (500mL). The EtOAc solution was washed with H_2O (3x 50mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was recrystallized in EtOAc to afford 5-(1,3-benzoxazol-2-yl)-2-methylphenol as a light yellow solid. MS (ESI) 226 $(M + H)^+$.

A solution of 5-(1,3-benzoxazol-2-yl)-2-methylphenol (355mg, 1.6mmol) in DMF(10mL) was cooled to 0°C and NaH (70mg, 1.7mmol) was added slowly. After 15min, (2-bromoethoxy)(tert-butyl)dimethylsilane (370μL, 1.7mmol) was added. The reaction was then elevated to 90°C for 1h and EtOAc (100mL) was added. The EtOAc solution was washed with brine (3x 20mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column (silica gel, hexanes:EtOAc 1:5) to afford 2-[3-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethoxy)-4-methylphenyl]-1,3-benzoxazole.

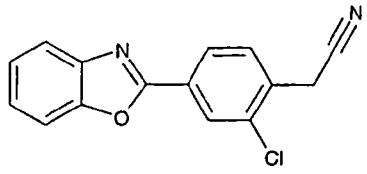
2-[3-(2-{[*Tert*-butyl(dimethyl)silyl]oxy}ethoxy)-4-methylphenyl)]-1,3-benzoxazole (550mg, 1.4mmol) was combined with NBS (255mg, 1.4mmol), benzoyl peroxide (50mg, catalyst) and CCl_4 (30mL). The mixture was refluxed overnight, cooled to rt and EtOAc (200mL) was added. The EtOAc solution was washed with brine (3 x 20mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue

was purified by flash column (silica gel, hexanes:EtOAc 5:1) to afford 2-[4-bromomethylphenyl-3-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethoxy)]-1,3-benzoxazole.

The mixture of 2-[4-bromomethylphenyl-3-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethoxy)]-1,3-benzoxazole(515mg, 1.1mmol) and sodium cyanide (164mg, 3.3mmol) in DMF/H_2O(10mL, 10/1) was stirred at 90°C for 4h, cooled to rt and EtOAc (200mL) was added. The EtOAc solution was washed with brine (3 x 20mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column (silica gel, hexanes:EtOAc 1:1) to afford the desired [4-(1,3- benzoxazol-2-yl)-2-(hydroxyethoxy)phenyl] acetonitrile. ^{1}H NMR (CD_3OD, 300MHz) δ 7.90 (m 1H), 7.80 (m, 2H), 7.62 (m, 1H), 7.49 (d, 1H), 7.40 (m, 2H),4.36(m,2H), 4.10 (m, 2H), 3.78 (s, 2H). MS (ESI) 295 $(M + H)^+$.

Example 17

[4-(1,3-Benzoxazol-2-yl)-2-chlorophenyl]acetonitrile



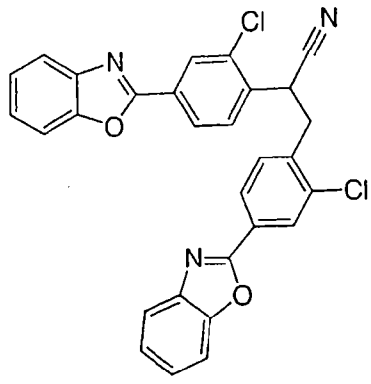
A solution of 2-(3-chloro-4-methylphenyl)-1,3-benzoxazole (780mg, 3.2mmol), *N*-bromosuccinimide (590mg, 3.3mmol) and CCl_4 (30mL) was mixed with a catalytic quantity of benzoyl peroxide. The mixture was heated at reflux for 12h. The reaction mixture was concentrated, and partitioned between saturated aqueous Na_2CO_3 (20mL) and CH_2Cl_2 (20mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20mL). The combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure to afford, after chromatography on silica gel (EtOAc:hexanes 1:9), 2-[4-(bromomethyl)-3-chlorophenyl]-1,3-benzoxazole as a colorless solid.

A slurry of NaCN (435mg, 8.9mmol), 2-[4-(bromomethyl)-3-chlorophenyl]-1,3-benzoxazole (940mg, 2.9mmol), DMF (30mL) and H_2O (30mL) was stirred at rt for 12h. The reaction mixture was poured into brine (250mL) and filtered. The resultant colorless solid was purified by flash chromatography on silica gel (EtOAc:hexanes 1:9) to afford the desired [4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]acetonitrile as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.32 (s,

1H), 8.19 (dd, 1H), 7.77-7.80 (m, 1H), 7.70 (d, 1H), 7.59-7.61 (m, 1H), 7.38-7.41 (m, 2H), 3.92 (s, 2H). MS (ESI) 269 $(M + H)^+$.

Example 18

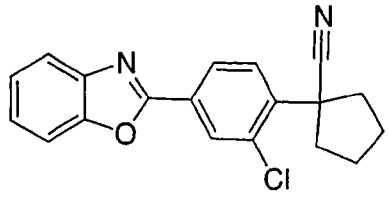
2,3-Bis[4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]propanenitrile



A solution of 2-[4-(bromomethyl)-3-chlorophenyl]-1,3-benzoxazole (150mg, 0.46mmol), KCN (36mg, 0.55mmol), and 18-crown-6 (145mg, 0.55mmol) is refluxed in MeCN (5 mL) for 10 minutes. The reaction is poured into H_2O (100 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic extracts are dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash chromatography (EtOAc:hexanes 1:10) to afford the desired 2,3-bis[4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]propanenitrile as a colorless solid: ^1H NMR ($CDCl_3$, 300MHz) δ 8.32 (dd, 2H), 8.20 (d, 1H), 8.11 (d, 1H), 7.80-7.83 (m, 2H), 7.71 (d, 1H), 7.61-7.63 (m, 2H), 7.39-7.45 (m, 5), 4.85 (t, 1H), 3.40-3.50 (m, 2H). MS (ESI) 511 $(M + H)^+$.

Example 19

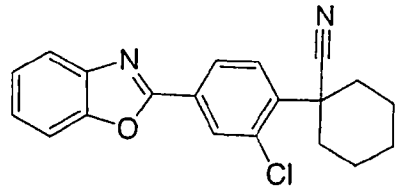
1-[4-(1,3-Benzoxazol-2-yl)-2-chlorophenyl]cyclopentanecarbonitrile



A solution of [4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]acetonitrile (270mg, 1.0mmol) and THF (20mL) was cooled to –78°C. A solution of NaHMDS (3.7mL, 2.2mmol, 0.6M solution in PhMe) was added dropwise via syringe to the reaction. After 15min at –78°C, 1,4-dibromobutane (143µL, 1.2mmol) was added dropwise via syringe. The cooling bath was removed, and the reaction was allowed to warm to rt. The reaction was quenched by the addition of silica gel (600mg) and concentrated to dryness. The residue was purified by flash chromatography on silica gel (EtOAc:hexanes 1:5) to afford the desired 1-[4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]cyclopentanecarbonitrile as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.34 (s, 1H), 8.12 (dd, 1H), 7.77-7.80 (m, 1H), 7.56-7.62 (m, 2H), 7.35-7.42 (m, 2H), 2.71-2.78 (m, 2H), 2.14-2.26 (m, 2H), 1.89-2.01 (m, 4H). MS (ESI) 323 $(M + H)^+$.

Example 20

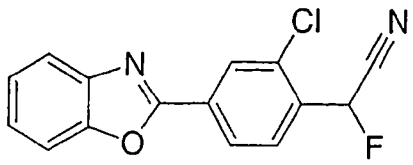
1-[4-(1,3-Benzoxazol-2-yl)-2chlorophenyl] cyclohexanecarbonitrile



Utilizing the general procedure outlined for 1-[4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]cyclopentanecarbonitrile, [4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]acetonitrile (400mg, 1.5mmol) and 1,5-dibromopentane (250µL, 1.8mmol) reacted to afford the desired 1-[4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]cyclohexanecarbonitrile as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.22 (d, 1H), 8.06 (d, 1H), 7.68-7.73 (m, 1H), 7.51-7.55 (m, 2H), 7.28-7.35 (m, 2H), 2.49 (d, 2H), 1.73-2.00 (m, 8H). MS (ESI) 337 $(M+H)^+$.

Example 21

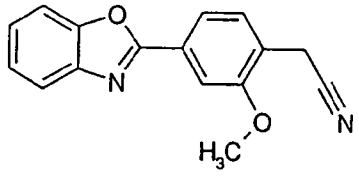
[4-(1,3-Benzoxazol-2-yl)-2-chlorophenyl](fluoro)acetonitrile



A solution of [4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]acetonitrile (98mg, 0.36mmol) and dry THF (5mL) was cooled to –78 °C. A solution of *tert*-butyllithium (500µL, 0.80mmol, 1.7M solution in pentane) was added dropwise via syringe at –78°C. After 1h, a solution of *N*-fluorobenzenesulfonimide (113mg, 0.36mmol) and dry THF (1.5mL) was added dropwise via syringe at –78°C. The cooling bath was removed, and the reaction mixture was gradually allowed to warm to rt, and was maintained at rt for 8h. The reaction was quenched with silica gel (300mg) and concentrated to dryness. The residue was purified by flash chromatography on silica gel (EtOAc:hexanes, 1:3) to afford the desired [4-(1,3-benzoxazol-2-yl)-2-chlorophenyl](fluoro)acetonitrile as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.32 (s, 1H), 8.24 (2, 1H), 7.74-7.84 (m, 2H), 7.56-7.60 (m 1H), 7.35-7.43 (m, 2H), 6.45 (d, 1H). MS (ESI) 287 $(M+H)^+$.

Example 22

2-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]acetonitrile



3-Methoxy-4-methyl benzoic acid (1.2g, 7.2mmol) and thionyl chloride (10mL) was heated to reflux conditions under argon until no starting material was observed by TLC. After cooling mixture to rt and concentration *in vacuo*, the resulting brown oil was dissolved in THF (15mL) and slowly added to a cooled mixture of 2-aminophenol (780mg, 7.1mmol), diisopropylethyl amine (1.5mL, 8.6mmol) and THF (20mL) at 0°C. Reaction mixture was allowed to warm to rt. After one hour, no starting material acid was observed by TLC. After concentrating reaction mixture *in vacuo*, the resulting brown oil was purified by flash chromatography on silica gel, using 1:4 EtOAc:hexanes. This afforded the desired intermediate, *N*-(2-hydroxyphenyl)-3-methoxy-4-methylbenzamide, as a yellow solid.

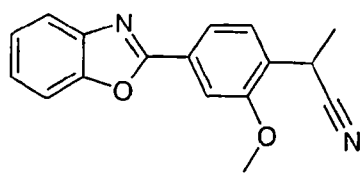
A mixture of *N*-(2-hydroxyphenyl)-3-methoxy-4-methylbenzamide (1.5g, 5.8mmol), toluene (30mL), *p*-toluenesulfonic acid monohydrate (7.6g, 40mmol) and molecular sieves was refluxed overnight. After cooling reaction to rt, filtered washing with warm chloroform and concentrated filtrate *in vacuo*. The resulting brown oil was purified by flash chromatography on silica gel using 1:4 EtOAc:hexanes to give the desired intermediate, 2-(3-methoxy-4-methylphenyl)-1,3-benzoxazole, as a colorless solid.

2-(3-Methoxy-4-methylphenyl)-1,3-benzoxazole (1.0g, 4.1mmol), carbon tetrachloride (18mL), benzoyl peroxide (66mg, 0.3mmol) and N-bromosuccinimide (970mg, 5.4mmol) was heated to reflux conditions under argon and placed under a UV light. After one hour, no starting material was observed by TLC. After cooling mixture to rt, filtered, washing with dichoromethane. After concentrating filtrate *in vacuo*, the resulting colorless solid was purified by flash chromatography, using a gradient elution of 1:4 EtOAc: hexanes to EtOAc. This afforded the desired intermediate, 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole, as a colorless solid.

A mixture of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3 - benzoxazole (318mg, 1mmol), dimethylformamide (7.5mL) and deionzed water (2.5mL) was stirred at rt. Sodium cyanide (150mg, 3.0mmol) was added to reaction. After 3h, dimethylformamide (10mL) was added to help dissolve solids in reaction mixture. Let reaction mixture stir overnight at rt. Workup was done by washing reaction with brine (3 x 30mL), extraction with EtOAc, combined organic extracts, dried (Na_2SO_4), filtered and removed solvent *in vacuo*. Flash chromatography of resulting orange solid on silica gel using a gradient elution of 1:9 EtOAc:hexanes to 1:3 EtOAc:hexanes afforded the desired intermediate, [4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]acetonitrile as a yellow solid. ^{1}H NMR($CDCl_3$, 300MHz) δ 7.86-7.36 (m, 7H), 3.99 (s, 3H), 3.74 (s, 2H), 2.59 – 1.91 (m, 8H). MS (ESI) 265 $(M + H)^+$.

Example 23

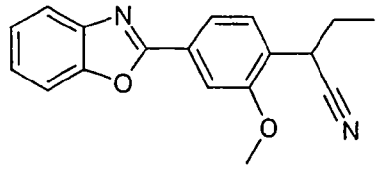
2-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]propanenitrile



4-(1,3-benzoxazol-2-yl)-2-methoxybenzonitrile (22mg, 0.82mmol) was dissolved and cooled to -78°C in THF (8mL) in an oven dried flask flushed with argon. NaHMDS (1.5mL, 0.90mmol) was added and the mixture was stirred at –78°C for 30min. Iodomethane (84μL, 0.90mmol) was added and the mixture was brought to rt and stirred for an additional 45min. The crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford the desired 2-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]propanenitrile as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.89-7.86 (d, 1H), 7.79-7.76 (m, 2H), 7.61-7.56 (m, 2H), 7.40-7.36 (m, 2H), 4.32-4.30 (q, 1H), 4.00 (s, 3H), 1.63-1.61 (d, 1H) MS (ESI) 279 $(M+H)^+$.

Example 24

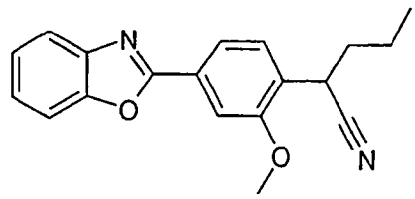
2-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]butanenitrile



Utilizing the general procedure outlined in the synthesis of 2-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]propanenitrile, 4-(1,3-benzoxazol-2-yl)-2-methoxybenzonitrile (300mg, 1.1mmol) was reacted with iodoethane (90μL, 1.1mmol) to afford the desired 2-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]butanenitrile as a yellow solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.87-7.84 (d, 1H), 7.79-7.74 (m, 2H), 7.59-7.53 (m, 2H), 7.37-7.34 (m, 2H), 4.22-4.17 (t, 1H), 3.97 (s, 3H), 1.95-1.89 (m, 2H), 1.13-1.08 (t, 3H). MS (ESI) 293 $(M+H)^+$.

Example 25

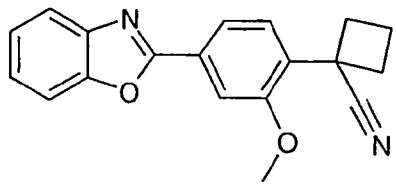
2-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]pentanenitrile



Utilizing the general procedure outlined in the synthesis of 2-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]propanenitrile, 4-(1,3-benzoxazol-2-yl)-2-methoxybenzonitrile (200mg, 0.75mmol) was reacted with 1-iodopropane (73μL, 0.75mmol) to afford the desired 2-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]pentanenitrile as a yellow solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.87-7.84 (d, 1H), 7.79-7.75 (m, 2H), 7.60-7.54 (m, 2H), 7.38-7.35 (m, 2H), 4.27-4.23 (t, 1H), 3.98 (s, 3H), 1.89-1.82 (M, 2H), 1.57-1.53 (m, 2H), 1.00-0.95 (t, 3H). MS (ESI) 307 $(M+H)^+$.

Example 26

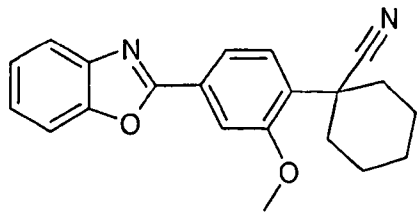
1-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]cyclobutanecarbonitrile



Utilizing the general procedure outlined in the synthesis of 2-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]propanenitrile, 4-(1,3-benzoxazol-2-yl)-2-methoxybenzonitrile (250mg, 0.95mmol) was reacted with 1, 3-Dibromopropane (120μL, 1.1mmol) to afford the desired 1-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]cyclobutanecarbonitrile as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.89-7.87 (m, 3H), 7.62-7.55 (m, 1H) 7.39-7.36 (m, 2H), 7.32-7.26 (m, 1H), 4.05 (s, 3H), 2.90-2.83 (m, 2H), 2.67-2.47 (m, 4H). MS (ESI) 305 $(M+H)^+$.

Example 27

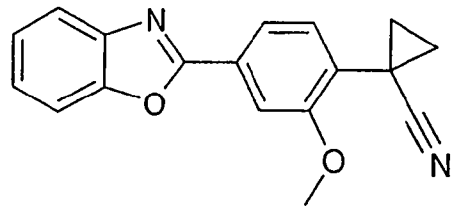
1-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]cyclohexanecarbonitrile



Utilizing the general procedure outlined for the synthesis of 1-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]cyclobutanecarbonitrile, 4-(1,3-benzoxazol-2-yl)-2-methoxybenzonitrile (250mg, 0.95mmol) was reacted with 1, 5-dibromopentane (160μL, 1.1mmol) to afford the desired 1-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]cyclohexanecarbonitrile as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.83-7.75 (m, 3H), 7.59-7.56 (m, 1H) 7.45-7.43 (d, 1H), 7.38-7.34 (m, 2H), 4.04 (s, 3H), 2.41-2.38 (d, 2H), 1.92-1.15 (m, 8H). MS (ESI) 333 $(M+H)^+$.

Example 28

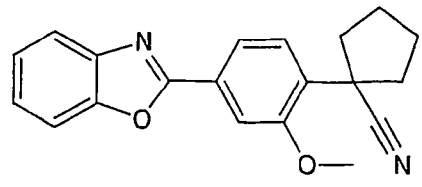
1-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]cyclopropanecarbonitrile



4-(1,3-benzoxazol-2-yl)-2-methoxybenzonitrile (250mg, 0.95mmol) was dissolved in CH_2Cl_2 (5mL). Benzyltrimethylammonium hydroxide (200μL, 0.095mmol) in 50% aqueous NaOH (5mL) was added and the mixture was stirred overnight at rt and then diluted with H_2O. The aqueous mixture was extracted with CH_2Cl_2 (2 x 25mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford the desired 1-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]cyclopropanecarbonitrile as a yellow solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.80-7.78 (m, 3H), 7.60-7.57 (m, 1H), 7.39-7.33 (m, 3H), 4.07 (s, 3H), 1.70-1.66 (t, 2H), 1.34-1.30 (t, 2H). MS (ESI) 291 $(M+H)^+$.

Example 29

1-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]cyclopentanecarbonitrile



3-Methoxy-4-methyl benzoic acid (1.2g, 7.2mmol) and thionyl chloride (10mL) was heated to reflux conditions under argon until no starting material was observed by TLC. After cooling mixture to rt and concentration *in vacuo*, the resulting brown oil was dissolved in THF (15mL) and slowly added to a cooled mixture of 2-aminophenol (780mg, 7.1mmol), diisopropylethyl amine (1.5mL, 8.6mmol) and THF (20mL) at 0°C. Reaction mixture was allowed to warm to rt. After one hour, no starting material acid was observed by TLC. After concentrating reaction mixture *in vacuo*, the resulting brown oil was purified by flash chromatography on silica gel, using 1:4 EtOAc:hexanes. This afforded the desired intermediate, N-(2-hydroxyphenyl)-3-methoxy-4-methylbenzamide, as a yellow solid.

A mixture of *N*-(2-hydroxyphenyl)-3-methoxy-4-methylbenzamide (1.5g, 5.8mmol), toluene (30mL), *p*-toluenesulfonic acid monohydrate (7.6g, 40mmol) and molecular sieves was refluxed overnight. After cooling reaction to rt, filtered washing with warm chloroform and concentrated filtrate *in vacuo*. The resulting brown oil was purified by flash chromatography on silica gel using 1:4 EtOAc:hexanes to give the desired intermediate, 2-(3-methoxy-4-methylphenyl)-1,3-benzoxazole, as a colorless solid.

2-(3-Methoxy-4-methylphenyl)-1,3-benzoxazole (1.0g, 4.1mmol), carbon tetrachloride (18mL), benzoyl peroxide (66mg, 0.3mmol) and N-bromosuccinimide (970mg, 5.4mmol) was heated to reflux conditions under argon and placed under a UV light. After 1h, no starting material was observed by TLC. After cooling mixture to rt, filtered, washing with dichoromethane. After concentrating filtrate *in vacuo*, the resulting colorless solid was purified by flash chromatography, using a gradient elution of 1:4 EtOAc: hexanes to EtOAc. This afforded the desired intermediate, 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole, as a colorless solid.

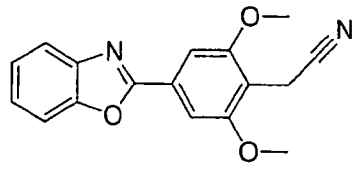
A mixture of, 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3 - benzoxazole (318mg, 1mmol), dimethylformamide (7.5mL) and deionzed water (2.5mL) was stirred at rt. Sodium cyanide (150mg, 3.0mmol) was added to reaction. After 3h, dimethylformamide (10mL) was added to help dissolve solids in reaction mixture. Let reaction mixture stir overnight at rt. Workup was done by washing reaction with brine (3x30mL), extraction with EtOAc, combined organic extracts, dried (Na_2SO_4), filtered and removed solvent *in vacuo*. Flash chromatography of resulting orange solid on silica gel using a gradient elution of 1:9 EtOAc:hexanes to

1:3 EtOAc:hexanes afforded the desired intermediate, [4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]acetonitrile, as a light yellow solid.

[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]acetonitrile (130mg, 0.49mmol) in THF (5.0mL) was cooled to –78°C under argon atmosphere. Sodium bis(trimethylsilyl)amide (1.8mL, 1.08mmol) was added slowly and after fifteen minutes, added 1,4- dibromobutane (0.07mL, 0.59mmol) to dark brown reaction mixture. Let mixture warm to rt overnight. After concentrating reaction mixture *in vacuo*, the resulting pink oil was purified by flash chromatography, using a gradient elution of 1:9 EtOAc:hexanes to 1:4 EtOAc:hexanes. This afforded the desired compound, 1-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]cyclopentanecarbonitrile, as a yellow solid. ^{1}H NMR($CDCl_3$, 300MHz) δ 7.86-7.26 (m, 7H), 4.07 (s, 3H), 2.59 – 1.91 (m, 8H). MS (ESI) 319.1 $(M+H)^+$.

Example 30

[4-(1,3-Benzoxazol-2-yl)-2,6-dimethoxyphenyl]acetonitrile



Thionyl chloride (10mL) and 3,5-dimethoxy-4-methylbenzoic acid (1.0g, 5.1mmol) was refluxed under argon until no starting material was observed by TLC. After cooling reaction mixture to rt, concentrated mixture *in vacuo*. The resulting brown oil was added to a mixture of 2-aminophenol (580mg, 5.3mmol), diisopropylethyl amine (1.1mL, 6.3mmol) and THF (40mL) at 0°C and then brought to rt overnight. After concentrating mixture *in vacuo*, the resulting brown oil was purified by flash chromatography on silica gel, using a gradient elution from 1:9 EtOAc:hexanes to 1:1 EtOAc:hexanes. This afforded the desired intermediate, 3,5-dimethoxy-*N*-(2-methoxyphenyl)-4-methylbenzamide, as a colorless solid.

A mixture of 3,5-dimethoxy-N-(2-methoxyphenyl)-4-methylbenzamide (1.29g, 4.49mmol), toluene (22mL), *p*-toluenesulfonic acid monohydrate (5.9g, 31mmol) and molecular sieves was refluxed until no starting material was observed by TLC. Cooled mixture to rt and filtered, washing with warm chloroform. Removal of solvent from filtrate afforded a yellow solid. Purification of crude solid by flash

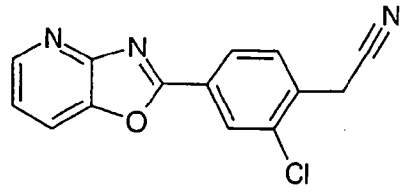
chromatography on silica gel using 1:3 EtOAc:hexanes gave the desired intermediate, 2-(3,5-dimethoxy-4-methylphenyl)-1,3-benzoxazole, as a colorless solid.

A mixture of 2-(3,5-dimethoxy-4-methylphenyl)-1,3-benzoxazole (260mg, 1mmol), carbon tetrachloride (4.2mL), benzoyl peroxide (15mg, 0.06mmol) and N-bromosuccinimide (270mg, 1.5mmol) was heated to reflux conditions under argon overnight. Concentration of cooled reaction mixture *in vacuo* afforded a yellow solid. Flash chromatography on silica gel of crude material using 1:4 EtOAc:hexanes gave the desired intermediate, 2-[4-bromomethyl)-3,5-dimethoxyphenyl]-1,3-benzoxazole, as a colorless solid.

2-[4-bromomethyl)-3,5-dimethoxyphenyl]-1,3-benzoxazole (160mg, 0.46mmol), dimethylformamide (5.0mL), deionized water (1.2mL) and sodium cyanide (77mg, 1.6mmol) was stirred at rt. After no starting material was observed by TLC, washed reaction mixture with brine (3x15mL) and extracted with EtOAc (3x20mL). Combined organic extracts, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 1:4 EtOAc:hexanes to give the desired compound, [4-(1,3-benzoxazol-2-yl)-2,6-dimethoxyphenyl]acetonitrile, as a colorless solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.62 (m,1H), 7.49 (m, 1H), 7.42 (s, 2H), 7.41(m, 1H), 7.40 (m,1H), 4.03 (s, 6H), 3.77 (s, 2H). MS (ESI) 295 $(M + H)^+$.

Example 31

(2-Chloro-4-[1,3]oxazolo[4,5-*b*]pyridin-2-ylphenyl)acetonitrile



A solution of 3-chloro-4-methylbenzoic acid (5.0g, 29mmol), *N*-bromosuccinimide (5.7g, 32mmol), benzoyl peroxide (710mg, 2.9mmol) in CCl_4 (300mL) was heated at reflux for 2.5h. The mixture was concentrated under reduced pressure and dissolved in MTBE. The organic mixture was washed with 1N NaOH (3 x 25mL). The aqueous mixture was acidified with 1N HCl to pH 2 and extracted with

CH_2Cl_2 (3 x 25mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford 4-(bromomethyl)-3-chlorobenzoic acid.

A suspension of 4-(bromomethyl)-3-chlorobenzoic acid (4.0g, 16mmol) in DMF (120mL) and H_2O (40mL) was treated with NaCN (2.4g, 49mmol) and heated to 80°C for 2h. The mixture was cooled to rt and acidified with 1N HCl. The aqueous mixture was extracted with CH_2Cl_2 (3 x 25mL). The combined organic layers were concentrated under reduced pressure and dissolved in MTBE. The organic mixture was washed with H_2O and brine (3 x 25mL), dried over $MgSO_4$, filtered and concentrated to afford 3-chloro-4-(cyanomethyl)benzoyl chloride.

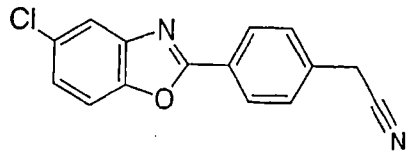
Oxalyl chloride (1.7mL, 19mmol) was added to a suspension of 3-chloro-4-(cyanomethyl)benzoyl chloride (2.5g, 13mmol) in CH_2Cl_2 (120mL). DMF (1 drop) was added to the suspension and the mixture was stirred for 2h at rt. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 3-chloro-4-(cyanomethyl)benzoyl chloride.

The acid chloride was dissolved in CH_2Cl_2 (20mL) and added in solution to a stirring suspension of 2-amino-3-hydroxypyridine (1.4g, 13mmol) and triethylamine (5.4mL, 38mmol) in CH_2Cl_2 (100mL). The mixture was stirred overnight. The reaction mixture was partitioned between CH_2Cl_2 and H_2O. Aqueous mixture was extracted with CH_2Cl_2 (2 x 25mL). Combined organic layers are washed with sat. $NaHCO_3$, and brine (2 x 25mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford 3-chloro-4-(cyanomethyl)-*N*-(3-hydroxypyridin-2-yl)benzamide as a yellow solid. MS (ESI) 288 (M+H).

3-chloro-4-(cyanomethyl)-*N*-(3-hydroxypyridin-2-yl)benzamide (550mg, 1.9mmol) was refluxed in $POCl_3$ (15mL) for 2.5h. Excess $POCl_3$ was removed by distillation and the mixture was cooled to rt. The crude mixture was diluted with H_2O. The aqueous layer was made basic (pH 14) with 1N NaOH and extracted with CH_2Cl_2 (3 x 20mL). The residue was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexane gradient to afford (2-chloro-4-[1,3]oxazolo[4,5-*b*]pyridin-2-ylphenyl)acetonitrile as a colorless solid: ^1H NMR ($CDCl_3$, 300MHz) δ 8.65-8.63 (d, 1H), 8.41 (s,1H), 8.30-8.27 (d, 1H), 7.93-7.90 (d, 2H), 7.77-7.74 (d, 2H), 7.38-7.34 (m, 2H)3.95 (s, 2H). MS (ESI) 270 $(M+H)^+$.

Example 32

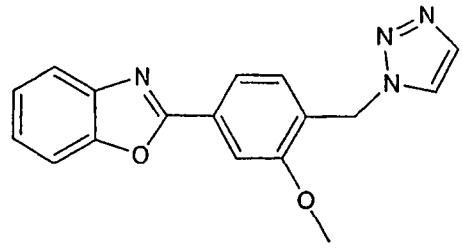
[4-(5-Chloro-1,3-benzoxazol-2-yl)phenyl]acetonitrile



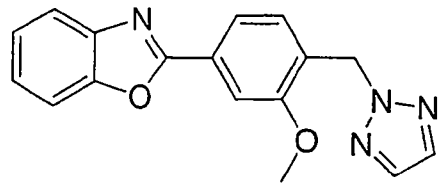
To a solution of 5-chlorobenzoxazole (100mg, 0.65mmol) in anhydrous THF at -78°C under Argon was added *n*-Butyllithium (0.45mL, 1.6M in hexanes). 30min later, zinc chloride (1.95mL, 1.0M in ether) was added. The reaction mixture was warmed to 0°C for 1h and then to 22°C. Then 4-bromophneylphenylacetonitrile (128mg, 0.65mmol) and $Pd(Ph_3P)_4$ (38mg, 0.033mmol) were added. The mixture was heated to reflux for overnight, after which time it was cooled to rt and poured in to a separatory funnel containing EtOAc (50mL), where it was washed with sat. brine (3x20mL). The EtOAc solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 3:1 hexanes:EtOAc to afford a off-colorless solid. ^1H NMR ($CDCl_3$, 300MHz) δ 8.26 (d, 2H), 7.76 (d, 1H), 7.51 (m, 3H), 7.35 (m, 1H), 3.87 (s, 3H). MS (ESI) 269$(M + H)^+$.

Example 33 and 34

2-[3-Methoxy-4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-1,3 benzoxazole



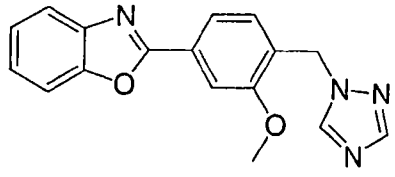
2-[3-Methoxy-4-(2*H*-1,2,3-triazol-2-ylmethyl)phenyl]-1,3-benzoxazole



A slurry of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (300mg, 1.0mmol) and 1*H*-1,2,3-triazole (70mg, 1.0mmol), and Cs_2CO_3 (325mg, 1.0mmol) and MeCN (10mL) was stirred vigorously at rt for 8h. Silica gel (600mg) was added, and the reaction mixture was concentrated to dryness. The residue was purified by flash chromatography on silica gel (linear gradient of EtOAc in hexanes from 0 to 100% over 25min) to afford 2-[3-methoxy-4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole and 2-[3-methoxy-4-(2*H*-1,2,3-triazol-2-ylmethyl)phenyl]-1,3-benzoxazole as colorless solids. 2-[3-methoxy-4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.72-7.78 (m, 3H), 7.69 (s, 1H), 7.59 (s, 1H), 7.53-7.56 (m, 1H), 7.31-7.34 (m, 2H), 7.20 (d, 1H), 5.59 (s, 2H), 3.96 (s, 3H). MS (ESI) 307 (M+H). 2-[3-methoxy-4-(2*H*-1,2,3-triazol-2-ylmethyl)phenyl]-1,3-benzoxazole: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.76-7.80 (m, 3H), 7.68 (s, 1H), 7.56-7.59 (m, 2H), 7.34-7.38 (m, 2H), 7.04 (d, 1H), 5.74 (s, 2H), 3.99 (s, 3H). MS (ESI) 307 $(M+H)^+$.

Example 35

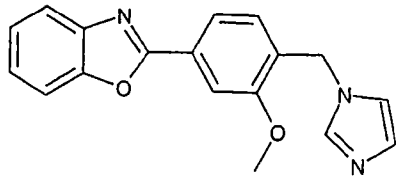
2-[3-Methoxy-4-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole



Utilizing the general procedure outlined for 2-[3-methoxy-4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole, reaction of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (300mg, 1.0mmol) and 1,2,4-triazole (70mg, 1.0mmol) afforded the desired 2-[3-methoxy-4-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.13 (s, 1H), 7.92 (s, 1H), 7.71-7.78 (m, 2H), 7.51-7.54 (m, 1H), 7.29-7.34 (m, 2H), 7.24 (d, 2H), 5.34 (s, 2H), 3.92 (s, 3H). MS (ESI) 307 $(M+H)^+$.

Example 36

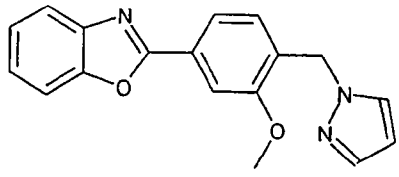
2-[4-(1*H*-Imidazol-1-ylmethyl)-3-methoxyphenyl]-1,3-benzoxazole



Utilizing the general procedure outlined for 2-[3-methoxy-4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole, reaction of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (300mg, 1.0mmol) and imidazole (70mg, 1.0mmol) afforded the desired 2-[4-(1*H*-imidazol-1-ylmethyl)-3-methoxyphenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.57-7.86 (m, 6H), 7.26-7.40 (m, 4H), 5.53 (s, 2H), 4.02 (s, 3H). MS (ESI) 306 $(M+H)^+$.

Example 37

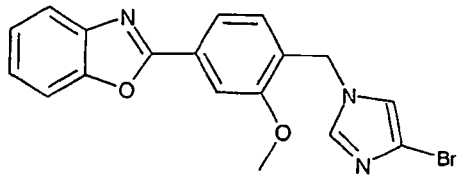
2-[3-Methoxy-4-(1*H*-pyrazol-1-ylmethyl)phenyl]-1,3-benzoxazole



Utilizing the general procedure outlined for 2-[3-methoxy-4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole, reaction of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (300mg, 1.0mmol) and pyrazole (70mg, 1.0mmol) afforded the desired 2-[3-methoxy-4-(1*H*-pyrazol-1-ylmethyl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.60-7.91 (m, 7H), 7.38-7.41 (m, 2H), 6.54 (m, 1H), 5.81 (s, 2H), 4.11 (s, 3H). MS (ESI) 306 $(M+H)^+$.

Example 38

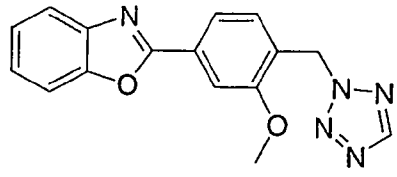
2-{4-[(4-Bromo-1*H*-imidazol-1-yl)methyl]-3-methoxyphenyl}-1,3-benzoxazole



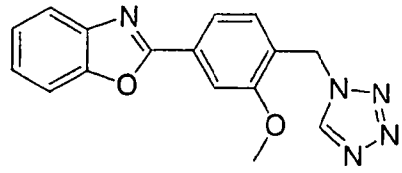
Utilizing the general procedure outlined for 2-[3-methoxy-4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole, reaction of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (300mg, 1.0mmol) and 4-bromo-1*H*-imidazole (150mg, 1.0mmol) afforded the desired 2-{4-[(4-bromo-1*H*-imidazol-1-yl)methyl]-3-methoxyphenyl}-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.94-7.99 (m, 3H), 7.85-7.87 (m, 1H), 7.75-7.78 (m, 1H), 7.65-7.68 (m, 1H), 7.43-7.49 (m, 2H), 7.20 (s, 1H), 5.55 (s, 2H), 4.09 (s, 3H). MS (ESI) 384 $(M+H)^+$.

Example 39 and 40:

2-[3-Methoxy-4-(2*H*-tetrazol-2-ylmethyl)phenyl]-1,3-benzoxazole



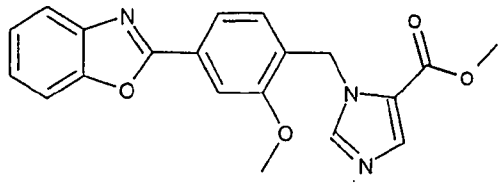
2-[3-Methoxy-4-(1*H*-tetrazol-1-ylmethyl)phenyl]-1,3-benzoxazole



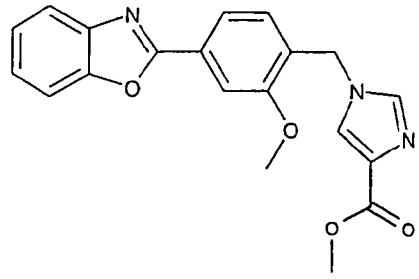
Utilizing the general procedure outlined for 2-[3-methoxy-4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole, reaction of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (300mg, 1.0mmol) and 1*H*-tetrazole (70mg, 1.0mmol) afforded 2-[3-methoxy-4-(2*H*-tetrazol-2-ylmethyl)phenyl]-1,3-benzoxazole and 2-[3-methoxy-4-(1*H*-tetrazol-1-ylmethyl)phenyl]-1,3-benzoxazole as colorless solids. 2-[3-methoxy-4-(2*H*-tetrazol-2-ylmethyl)phenyl]-1,3-benzoxazole: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.52 (s, 1H), 7.72-7.79 (m, 3H), 7.52-7.55 (m, 1H), 7.31-7.34 (m, 2H), 7.21 (d, 1H), 5.86 (s, 2H), 3.93 (s, 3H). MS (ESI) 308 (M+H). 2-[3-methoxy-4-(1*H*-tetrazol-1-ylmethyl)phenyl]-1,3-benzoxazole: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.66 (s, 1H), 7.85 (d, 1H), 7.74-7.83 (m, 2), 7.55-7.59 (m, 1H), 7.41 (d, 1H), 7.34-7.40 (m, 2H), 5.61 (s, 2H), 3.98 (s, 3H). MS (ESI) 308 $(M+H)^+$.

Example 41 and 42:

Methyl 1-[4-(1,3-benzoxazol-2-yl)-2-methoxybenzyl]-1*H*-imidazole-5-carboxylate



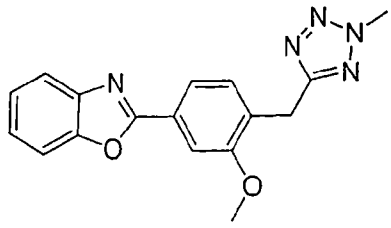
Methyl 1-[4-(1,3-benzoxazol-2-yl)-2-methoxybenzyl]-1*H*-imidazole-4-carboxylate



Utilizing the general procedure outlined for 2-[3-methoxy-4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-1,3-benzoxazole, reaction of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (300mg, 1.0mmol) and methyl 4-imidazole carboxylate (126mg, 1.0mmol) afforded methyl 1-[4-(1,3-benzoxazol-2-yl)-2-methoxybenzyl]-1*H*-imidazole-5-carboxylate and methyl 1-[4-(1,3-benzoxazol-2-yl)-2-methoxybenzyl]-1*H*-imidazole-4-carboxylate as colorless solids. Methyl 1-[4-(1,3-benzoxazol-2-yl)-2-methoxybenzyl]-1*H*-imidazole-5-carboxylate: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.73-7.80 (m, 4H), 7.57-7.60 (m, 1H), 7.34-7.38 (m, 2H), 7.15 (d, 1H), 5.58 (s, 2H), 4.00 (s, 3H), 3.83 (s, 3H). MS (ESI) 364 $(M+H)^+$. Methyl 1-[4-(1,3-benzoxazol-2-yl)-2-methoxybenzyl]-1*H*-imidazole-4-carboxylate: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.75-7.84 (m, 3H), 7.57-7.64 (m, 3H), 7.34-7.38 (m, 2H), 7.18 (d, 1H), 5.17 (s, 2H), 3.97 (s, 3H), 3.86 (s, 3H). MS (ESI) 364 $(M+H)^+$.

Example 43

2-{3-methoxy-4-[(1-methyl-1*H*-tetrazol-5-yl)methyl]phenyl}-1,3-benzoxazole

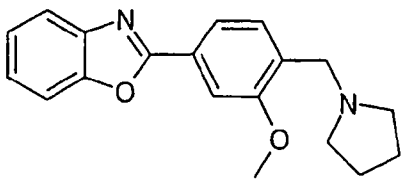


Azidotrimethylsilane (251μL, 1.89mmol) was added to a stirring suspension of 4-(1,3-benzoxazol-2-yl)-2-methoxybenzonitrile (250mg, 0.949mmol) and dibutyltin oxide (24mg, 0.09mmol) in toluene (5mL). The mixture was heated at 110°C overnight. The mixture was cooled to rt and the toluene was removed *in vacuo*. The residue was dissolved in EtOAc and extracted 10% $NaHCO_3$ (3 x 25mL). The combined aqueous extracts were acidified to pH 2 with 3N HCl. The acidic aqueous mixture was extracted with EtOAc (3 x 25mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 2-[3-methoxy-4-(1*H*-tetrazol-5-ylmethyl)phenyl]-1,3-benzoxazole: ^{1}H NMR (DMSO-d_6, 300MHz) δ 7.82-7.78 (m, 3H), 7.75 (s, 1H), 7.46-7.42 (m, 3H), 4.30 (s, 2H), 3.90 (s, 3H). MS (ESI) 308 $(M+H)^+$.

Iodomethane (38μL, 0.42mmol) was added to a stirring solution of 2-[3-methoxy-4-(1*H*-tetrazol-5-ylmethyl)phenyl]-1,3-benzoxazole (130mg, 0.42mmol) and triethylamine (120μL, 0.83mmol) in CH_3CN (5mL). The mixture was stirred at rt overnight. The crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford the desired 2-[3-methoxy-4-(morpholin-4-ylmethyl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.84-7.77 (m, 3H), 7.58 (m 1H), 7.39-7.36 (m, 2H), 7.30-7.27 (d, 1H), 4.32 (s, 2H), 3.96 (s, 6H). MS (ESI) 322 $(M+H)^+$.

Example 44

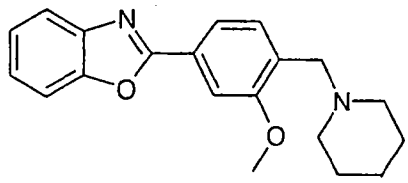
2-[3-Methoxy-4-(pyrrolidin-1-ylmethyl)phenyl]-1,3-benzoxazole



Pyrrolidine (226μL, 2.83mmol) was added to a stirring solution of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (300mg, 0.94mmol) and triethylamine (390μL, 2.8mmol) in CH_2Cl_2 (5mL). The mixture was stirred at rt overnight. Crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford the desired 2-[3-methoxy-4-(pyrrolidin-1-ylmethyl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82-7.80 (m, 1H), 7.77-7.74 (m, 1H), 7.71 (s, 1H), 7.56-7.50 (m, 2H), 7.35-7.30 (m, 2H), 3.94 (s, 3H), 3.71 (s, 2H), 2.59 (s, 4H), 1.81-1.78 (m, 4H). MS (ESI) 309 $(M+H)^+$.

Example 45

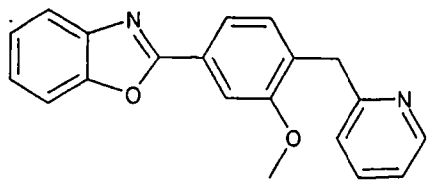
2-[3-Methoxy-4-(piperidin-1-ylmethyl)phenyl]-1,3-benzoxazole



Utilizing the general procedure outlined for 2-[3-methoxy-4-(pyrrolidin-1-ylmethyl)phenyl]-1,3-benzoxazole, 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (300mg, 0.942mmol) was reacted with piperidine (279μL, 2.83mmol) and triethylamine (394μL, 2.83mmol) in CH_2Cl_2 (5mL) to afford the desired 2-[3-methoxy-4-(piperidin-1-ylmethyl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$-d, 300MHz) δ 7.86-7.83 (m, 1H), 7.79-7.76 (m, 1H), 7.73 (s, 1H), 7.61-7.55 (m, 2H), 7.37-7.34 (m, 2H), 3.96 (s, 3H), 3.59 (s, 2H), 2.47 (br, 4H), 1.66-1.58 (m, 4H), 1.46-1.45 (m, 2H). MS (ESI) 323 $(M+H)^+$.

Example 46

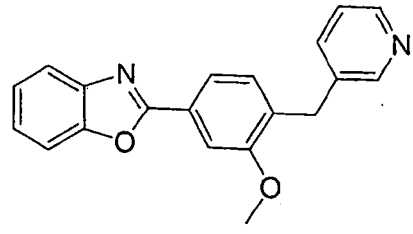
2-[3-Methoxy-4-(pyridin-2-ylmethyl)phenyl]-1,3-benzoxazole



A solution of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (320mg, 1.0mmol) and THF (10mL) was treated with Zn powder (activated by grinding with mortar and pestle), a drop of chlorotrimethylsilane, and a drop of 1,2-dibromoethane. The mixture was heated at reflux for 1h. The resultant organozinc reagent was filtered through a plug of Celite, and transferred to a flask containing 2-bromopyridine (360mg, 2.0mmol) and $Pd(Ph_3P)_4$ (115mg, 0.1mmol). The mixture was degassed with bubbling argon for 15min, and heated at reflux for 12h. The reaction was poured into H_2O (40mL) and extracted with CH_2Cl_2 (2 × 30mL). The organic extracts were dried ($MgSO_4$) and concentrated to afford a colorless solid. Purification of the solid by flash chromatography on silica gel (EtOAc:hexanes 3:1) afforded the desired 2-[3-methoxy-4-(pyridin-2-ylmethyl)phenyl]-1,3-benzoxazole as a yellow solid: ^1H NMR ($CDCl_3$, 300MHz) δ 8.55 (d, 1H), 7.76-7.82 (m, 3H), 7.56-7.62 (d, 2H), 7.32-7.36 (m, 3H), 7.11-7.16 (m, 2H), 4.23 (s, 2H), 3.95 (s, 3H). MS (ESI) 317 $(M+H)^+$.

Example 47

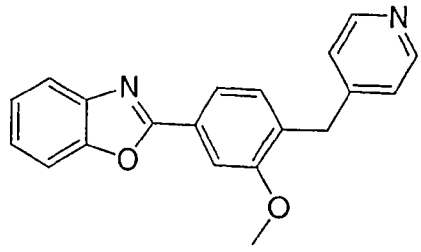
2-[3-Methoxy-4-(pyridin-3-ylmethyl)phenyl]-1,3-benzoxazole



A mixture of 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (190mg, 0.58mmol), 3-pyridylboronic acid (70mg, 0.58mmol), $Pd(Ph_3P)_4$ (70mg, 0.06mmol), K_2CO_3 (200mg, 1.5mmol), DME (6mL) and H_2O (3mL) was degassed with bubbling Ar for 15min. The mixture was heated at 80°C for 1h. The reaction was poured into H_2O (40mL) and extracted with CH_2Cl_2 (2 × 30mL). The organic extracts were dried ($MgSO_4$) and concentrated to afford a colorless solid. Purification of the solid by flash chromatography on silica gel (EtOAc:hexanes 3:1) afforded the desired 2-[3-methoxy-4-(pyridin-3-ylmethyl)phenyl]-1,3-benzoxazole as a yellow solid: ^1H NMR ($CDCl_3$, 300MHz) δ 8.56 (br s, 1H), 8.45 (br d, 1H), 7.74-7.80 (m, 3H), 7.50-7.58 (m, 2H), 7.32-7.37 (m, 2H), 7.17-7.24 (m, 2H), 4.00 (s, 2H), 3.93 (s, 3H). MS (ESI) 317 $(M+H)^+$.

Example 48

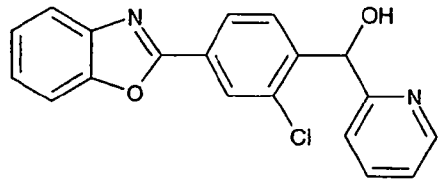
2-[3-Methoxy-4-(pyridin-4-ylmethyl)phenyl]-1,3-benzoxazole



Utilizing the general procedure outlined for 2-[3-methoxy-4-(pyridin-3-ylmethyl)phenyl]-1,3-benzoxazole, 2-[4-(bromomethyl)-3-methoxyphenyl]-1,3-benzoxazole (270mg, 0.81mmol), 4-pyridylboronic acid (100mg, 0.81mmol) reacted to afford the desired 2-[3-methoxy-4-(pyridin-4-ylmethyl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.46 (br s, 2H), 7.75-7.81 (m, 3H), 7.56-7.59 (m, 1H), 7.34-7.36 (m, 2H), 7.22 (d, 1H), 7.13 (d, 2H), 4.00 (s, 2H), 3.92 (s, 3H). MS (ESI) 317 $(M+H)^+$.

Example 49

[4-(1,3-Benzoxazol-2-yl)-2-chlorophenyl](pyridin-2-yl)methanol



A solution of benzoxazole (5.4g, 46mmol) and THF (150mL) was cooled to -78°C. A solution of *n*-butyllithium (29mL, 47mmol, 1.6M solution in hexanes) was added dropwise via syringe over 15min. After 1h at -78°C, a solution of $ZnCl_2$ (95mL, 47mmol, 0.5M solution in ether) was added dropwise via syringe over 5min. The reaction mixture was allowed to warm to rt, and maintained for 1h. 2-Chloro-4-bromobenzonitrile (3.3g, 15mmol) and $Pd(Ph_3P)_4$ (880mg, 0.76mmol) were added to the reaction mixture. The mixture was degassed with bubbling argon for 15min, then heated at reflux for 1h. The reaction was quenched by the addition of 1 N HCl (150mL), and extracted with CH_2Cl_2 (3 × 150mL). The organic extracts were

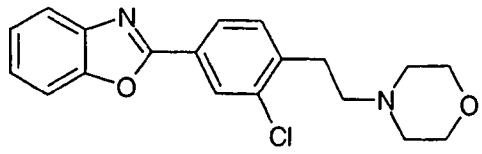
combined, dried ($MgSO_4$), and concentrated to afford, after flash chromatography on silica gel (acetone:hexane 1:5), 4-(1,3-benzoxazol-2-yl)-2-chlorobenzonitrile as a yellow solid.

A solution of 4-(1,3-benzoxazol-2-yl)-2-chlorobenzonitrile (510mg, 2.0mmol) and CH_2Cl_2 was cooled to -78°C. Diisobutylaluminum hydride (2mL, 1.0M solution in PhMe) was added to the reaction dropwise via syringe over 30min. The cooling bath was removed, and the reaction mixture is allowed to warm to rt. The reaction was quenched by the addition of a saturated solution of sodium potassium tartrate (50mL). The resultant slurry was filtered, and the organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to afford, after flash chromatography (acetone:hexane 1:5), 4-(1,3-benzoxazol-2-yl)-2-chlorobenzaldehyde as a yellow solid.

A solution of 2-bromopyridine (110mg, 0.7mmol) and THF (10mL) was cooled to -78°C. *n*-Butyllithium (0.44mL, 0.7mmol, 1.6M solution in THF) was added dropwise via syringe. After 15min, a solution of 4-(1,3-benzoxazol-2-yl)-2-chlorobenzaldehyde (150mg, 0.6mmol) and THF (2mL) was added via syringe, and the reaction was allowed to warm to rt. The reaction is quenched by the addition of H_2O (20mL). The mixture is extracted with EtOAc (3 × 120mL), and the combined organic extracts are dried ($MgSO_4$), and concentrated under reduced pressure to afford, after flash chromatography on silica gel (EtOAc:hexanes 1:1), the desired [4-(1,3-benzoxazol-2-yl)-2-chlorophenyl](pyridin-2-yl)methanol as a colorless solid: ^1H NMR ($CDCl_3$, 300MHz) δ 8.58 (d, 1H), 8.28 (d, 1H), 8.10 (dd, 1H), 7.55-7.55 (m, 4H), 7.23-7.37 (m, 4H). MS (ESI) 337 $(M+H)^+$.

Example 50

2-[3-Chloro-4-(2-morpholin-4-ylethyl)phenyl]-1,3-benzoxazole



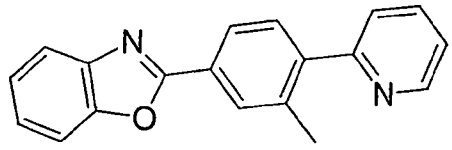
A solution of [4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]acetonitrile (1.11g, 3.88mmol) in CH_2Cl_2 (40mL) was cooled –78°C. Diisobutylaluminum hydride (4.7mL, 4.7mmol, 1.0M solution in PhMe) was added slowly. The mixture

was stirred at –78°C under argon for 3h and allowed to warm slowly to rt overnight. Reaction mixture was cooled to 0°C quenched with acetone and 1N HCl. The mixture was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3 x 100mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford [4-(1,3-benzoxazol-2-yl)-2-chlorophenyl]acetaldehyde.

The crude aldehyde was treated with $NaCNBH_3$ and morpholine in $MeOH/CH_2Cl_2$ (2mL). The crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford the desired 2-[3-chloro-4-(2-morpholin-4-ylethyl)phenyl]-1,3-benzoxazole: ^1H NMR ($CDCl_3$, 300MHz) δ 8.26-8.25 (d, 1H), 8.09-8.06 (m, 1H), 7.79-7.74 (m, 1H), 7.43-7.34 (m, 3H), 3.78-3.75 (m, 4H), 3.05-3.00 (m, 2H), 2.68-2.59 (m, 6H). MS (ESI) 343 $(M+H)^+$.

Example 51

2-(3-Methyl-4-pyridin-2-ylphenyl)-1,3-benzoxazole

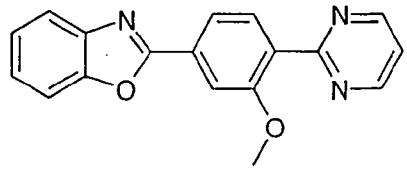


Polyphosphoric acid (100mL) was added to a beaker containing 2-aminophenol (17.7g, 162mmol) and 4-bromo-3-methylbenzoic acid (13.6g, 64mmol). The mixture was heated at 200°C for 1h, then poured into ice water (1L) and allowed to stand overnight. The mixture was filtered and dried to afford 2-(4-bromo-3-methyl(phenyl))-benzoxazole as a colorless solid. A solution of 2-(4-bromo-3-methyl(phenyl))-benzoxazole (670mg, 2.3mmol), 2-(tributylstannyl)pyridine (850mg, 2.3mmol), $Pd(Ph_3P)_4$ (270mg, 0.23mmol) and DMF (23mL) was degassed with bubbling argon for 15min. The reaction mixture was heated at 100°C for 8h. The reaction was cooled to rt, and KF (500mg) and H_2O (250mL) were added. The mixture was extracted with MTBE (3 × 50mL), and the combined organic extracts were washed with water (2 × 20mL), brine (1 × 20mL), dried ($MgSO_4$), and concentrated to afford an oil. Purification of the oil by flash chromatography on silica gel (EtOAc:hexanes 1:2) afforded the desired 2-(3-methyl-4-pyridin-2-ylphenyl)-1,3-benzoxazole as a colorless solid: ^1H NMR ($CDCl_3$, 300MHz) δ 8.91 (d, 1H), 8.52 (t,

1H), 8.19 (s, 1H), 8.15 (d, 1H), 7.97 (br t, 1H), 7.89 (d, 1H), 7.70-7.72 (m, 1H), 7.61 (d, 1H), 7.51-7.54 (m, 1H), 7.30-7.33 (m, 2H), 2.45 (s, 3H), MS (ESI) 287 $(M+H)^+$.

Example 52

2-(3-Methyl-4-pyrimidin-2-ylphenyl)-1,3-benzoxazole

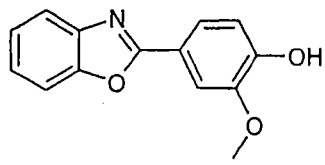


A slurry of 2-(4-bromo-3-methyl(phenyl))-benzoxazole (330mg, 1.1mmol), KOAc (330mg, 3.4mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (93mg, 0.11mmol), bis(pinacolato)diboron (360mg, 1.4mmol), and dioxane (30mL) was degassed with Ar for 15min. The reaction was heated at 80°C for 12h, then quenched by the addition of H_2O (20mL). The mixture was extracted with MTBE (3 x 50mL), and the combined organic extracts were dried (MgSO4), and concentrated under reduced pressure to afford, after flash chromatography on silica gel (EtOAc:hexanes 1:3), 2-[3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole as a colorless solid.

A mixture of 2-[3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (190mg, 0.5mmol), $Pd(Ph_3P)_4$ (60mg, 0.05mmol), CsF (300mg, 2.0mmol), and DME (5mL) was degassed with Ar for 15min. The reaction was heated at 80°C for 12h, then quenched by the addition of H_2O (20mL). The mixture was extracted with MTBE (3 x 50mL), and the combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure to afford, after flash chromatography on silica gel (EtOAc:hexanes 1:1) the desired 2-(3-methyl-4-pyrimidin-2-ylphenyl)-1,3-benzoxazole as a colorless solid: ^1H NMR ($CDCl_3$, 300MHz), δ 8.82 (d, 2H), 7.99-8.20 (m, 2H), 7.98 (d, 2H), 7.75-7.77 (m, 1H), 7.54-7.57 (m, 1H), 7.30-7.35 (m, 2H), 7.20 (t, 1H), 2.64 (s, 3H). MS (ESI) 288 $(M+H)^+$.

Example 53

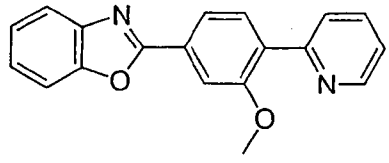
4-(1,3-Benzoxazol-2-yl)-2-methoxyphenol



4-hydroxy-3-methoxybenzoic acid (25g, 149mmol) and 2-amino phenol(16.2g, 149mmol) were combined in a round bottom flask. Trimethylsilyl polyphosphate (80mL) was added neat. The mixture was heated at 180°C for 30min. The mixture is poured over ice and allowed to stir overnight. The suspension was filtered to afford 4-(1,3-benzoxazol-2-yl)-2-methoxyphenol as a pale green solid. MS (ESI) 242 $(M+H)^+$.

Example 54

2-(3-Methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole hydrochloride salt



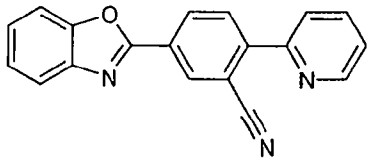
The solution of 4-(1,3-benzoxazol-2-yl)-2-methoxyphenol (7.1g, 29.4mmol) in anhydrous DMF (100mL) was treated with Cs_2CO_3 (9.6g, 29.4mmol) and *N*-phenyl trifluoromethanesulfonimide (10.5g, 29.4mmol) at 22°C for 30min. After which time it was quenched with sat. $NaHCO_3$ (50mL) and diluted with EtOAc (500mL). The EtOAc solution was washed with sat. brine (3 x 100mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with 4:1 hexanes:EtOAc to afford 4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl trifluoromethanesulfonate as a colorless oil. MS (ESI) 374 $(M+H)^+$.

The solution of 4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl trifluoromethanesulfonate (11.7g, 31.3mmol) in anhydrous DMF (150mL) was degassed via Argon for 10min. Then 2-tri-n-butylstannylpyridine (11.5g, 31.3mmol) and $Pd(Ph_3P)_4$ (3.6g, 3.1mmol) were added at 22°C. The resulting mixture was then heated at 100°C for 1h under Argon. Cooled the reaction mixture to 22°C, then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give after purification by flash chromatography (silica gel, 3:1; hexanes:EtOAc) the desired compound as a off-colorless solid which was then disolved in diethyl ether

(200mL) and precipitated as the hydrochloride salt upon treatment with 1M HCl in diethyl ether (20mL). The resulting colorless solid was then treated with EtOAc (1L), heated at refluxing, then cooled to 22°C, collected the solid by filtration to yield a colorless solid as desired compound. (M.p. 215 °C). ^{1}H NMR (CD_3OD, 300MHz) δ 8.88 (m, 1 H), 8.69 (m, 1H), 8.41 (d, 1H), 8.09 (m, 3H), 7.91 (d, 1H), 7.82 (m, 1H), 7.45 (m, 1H), 7.48 (m, 2H), 4.10 (s, 3H). MS (ESI) 303 $(M+H)^+$.

Example 55

5-(1,3-Benzoxazol-2-yl)-2-pyridin-2-yl benzonitrile



To a solution of methyl 3-cyano-4-methoxy-benzoate (1.5g, 7.9mmol) in CH_3OH/H_2O (25mL; 1:1), was added LiOH (2.5g, 60.0mmol). The reaction mixture was refluxed for 2h, cooled at rt and 6M HCl was added dropwise until pH 2 was obtained. The precipitate was collected, washed with H_2O (3 x 20mL), dried *in vacuo* to afford 3-cyano-4-methoxy-benzoic acid. MS (ESI) 178 $(M + H)^+$. To a 100mL round-bottom flask with 3-cyano-4-methoxy-benzoic acid (1.4g, 7.8mmol), was added $SOCl_2$ (15mL) dropwise. The reaction was refluxed for 1h and was cooled to rt. The excess of $SOCl_2$ was removed *in vacuo* and the oily acid chloride was dissolved in THF (15mL). The resulting solution was added dropwise to a mixture of 2-aminophenol (1.3g, 11.7mmol), triethylamine (1.3g, 11.7mmol) and THF (30mL) at 0°C. The reaction was warmed up to rt and stirred an additional 3h. The precipitate was removed by filtration and the filtrate was concentrated and dried *in vacuo*. The dark brown solid residue was dissolved in toluene (20mL) and *p*-toluenesulfonic acid (6.0g, 46.8mmol) was added. The reaction was refluxed overnight, cooled to rt, and EtOAc (300mL) was added. The EtOAc solution was washed with brine (3 x 20mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chhromatography (silica gel, $CHCl_3$:CH_3OH 8:1) to afford 5-(1,3-benzoxazol-2-yl)-2-methoxy benzonitrile. MS (ESI) 251$(M + H)^+$.

To a solution of 5-(1,3-benzoxazol-2-yl)-2-methoxy benzonitrile (270mg, 1.1mmol) in CH_2Cl_2 (5mL) at 0°C, was added BBr_3 (1.0M solution in

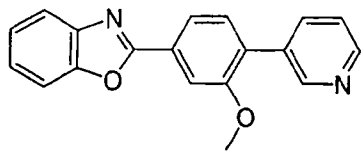
CH_2Cl_2, 430μL, 4.4mmol) dropwise. The reaction was stirred at rt for 4h. EtOAc (150mL) was added, as well as H_2O (30mL). The organic layer was washed with brine (2 x 20mL), dried ($MgSO_4$),concentrated and the crude product was recrystallized in EtOAc to afford 5-(1,3-benzoxazol-2-yl)-2-hydroxy benzonitrile. MS (ESI) 237 $(M + H)^+$.

To a solution of 5-(1,3-benzoxazol-2-yl)-2-hydroxy benzonitrile (230mg, 1.0mmol) and pyridine (154mg, 2mmol) in CH_2Cl_2 (5mL) at 0°C,was added trifluoromethane-sulfonic anhydride (330mg, 1.2mmol) dropwise. The reaction was elevated to rt and stirred for 2h. EtOAc (150mL) was added, as well as H_2O (50mL). The organic layer was washed with brine (2 x 20mL), dried ($MgSO_4$) and the crude material was purified by flash column (silica gel, hexanes:EtOAc 4:1) to afford 4-(1,3-benzoxazol-2-yl)-2-cyanophenyltrifluoromethanesulfonate as yellow oil.

The degassed solution of 4-(1,3-benzoxazol-2-yl)-2-cyanophenyl trifluoromethanesulfonate (300mg, 1.2mmol) in DMF (5mL) was added 2-tri-n-butylstannylpyridine (273mg, 0.74mmol), tetrakis(triphenylphosphine) palladium(0) (150mg, 0.1mmol). The reaction was stirred at 90°C overnight and cooled to rt. EtOAc(100mL) was added, as well as brine (50mL). The organic layer was washed with brine (2 x 20mL), dried ($MgSO_4$), and the crude material was purified on flash column (silica gel, hexanes:EtOAc 3:1) to afford desired 5-(1,3-benzoxazol-2-yl)-2-pyridin-2-yl benzonitrile as pinkish solid. ^1H NMR (CD_3OD, 300MHz), δ 8.85 (d 1H), 8.72 (d, 1H), 8.59 (m, 1H), 8.08 (d, 1H), 7.91 (d, 2H), 7.85 (m, 1H), 7.65 (m, 1H), 7.45 (m, 3H). MS (ESI) 298 $(M + H)^+$.

Example 56

2-(3-Methoxy-4-pyridin-3-ylphenyl)-1,3-benzoxazole

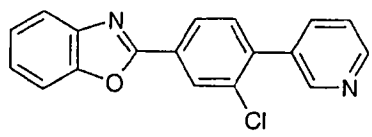


The solution of 4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl trifluoromethanesulfonate (148mg, 0.4mmol) in 6mL of 2:1 DMF:H_2O was degassed via Argon for 10min. Then K_2CO_3 (137mg, 0.99mmol), $Pd(Ph_3P)_4$ (23mg, 0.02mmol), n-Bu_4NBr (128mg, 0.40mmol) and 3-Pyridylboronic acid (73mg, 0.60mmol) were added at 22°C. The resulting mixture was then heated at 75°C for 1h

under Argon. Cooled the reaction mixture to 22°C, then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give after purification by flash chromatography (silica gel, 3:1; hexanes:EtOAc) the desired compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.83 (d, 1H), 8.60 (dd, 1H), 7.92 (m, 3H), 7.81 (m, 1H), 7.62 (m, 1H), 7.48 (d, 1H), 7.39 (m, 3H), 3.98 (s, 3H). MS (ESI) 303 $(M + H)^+$.

Ezample 57

2-(3-Chloro-4-pyridin-3-ylphenyl)-1,3-benzoxazole

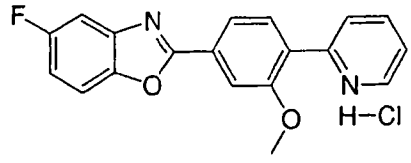


A suspension of 3-chloro-4-hydroxybenzoic acid (20.0g, 11.6mmol) in anhydrous dichloromethane (100mL) was treated with oxalyl chloride(20mL, 23.2mmol) followed by few drops of DMF at 22°C under argon. After 2h stirring, the solution became clear, concentrated to dryness, dissolved in dichloromethane (50mL) and added slowly to a solution of 2-aminophenol (12.6g, 11.6mmol) and TEA (9mL, 11.6mmol) in anhydrous DMC (50mL). After 20min stirring, filtered off salt, concentrated the mixture to afford 4-chloro-3-hydroxy-N-phenylbenzamide as a brown solid. MS (ESI) 264(M + H)+. 4-Chloro-3-hydroxy-N-phenylbenzamide (4g, 15.2 mmol) was treated with $POCl_3$ (5mL) at reflux for 1h. Concentrated and dissolved in dichloromethane (50mL), washed with sat. $NaHCO_3$ (3x25mL) and sat. brine (3x25mL), dried ($MgSO_4$), concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 2:1 hexanes:EtOAc to afford 4-(1,3-benzoxazol-2-yl)-2-chlorophenol as a colorless solid. MS (ESI) 246$(M + H)^+$. The solution of 4-(1,3-benzoxazol-2-yl)-2-methoxyphenol (800mg, 3.3mmol) in anhydrous DMF (10mL) was treated with Cs_2CO_3 (1.1g, 3.2mmol) and *N*-phenyl trifluoromethanesulfonimide (1.2g, 3.2mmol) at 22°C for 30min. After which time it was quenched with sat. $NaHCO_3$ (20mL) and diluted with EtOAc (50mL). The EtOAc solution was washed with sat. brine (3x10mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with 6:1 hexanes:EtOAc to afford 4-(1,3-benzoxazol-2-yl)-2-chlorophenyl trifluoromethanesulfonate a colorless oil. MS (ESI) 378 $(M + H)^+$. The solution of 4-

(1,3-benzoxazol-2-yl)-2-chlorophenyl trifluoromethanesulfonate (150mg, 0.4mmol) in 6mL of 2:1 DMF:H_2O was degassed via Argon for 10min. Then K_2CO_3 (137mg, 0.99mmol), $Pd(Ph_3P)_4$ (23mg, 0.02mmol), n-Bu_4NBr (128mg, 0.40mmol) and 3-Pyridylboronic acid (73mg, 0.60mmol) were added at 22°C. The resulting mixture was then heated at 75°C for 1h under Argon. Cooled the reaction mixture to 22°C, then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give after purification by flash chromatography (silica gel, 3:1; hexanes:EtOAc) the desired compound, as a yellow solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.75 (d, 1H), 6.68 (dd, 1H), 8.42 (d, 1H), 8.24 (dd, 1H), 7.89 (dt, 1H), 7.81 (m, 1H), 7.63 (m, 1H), 7.52 (d, 1H), 7.42 (m, 3H). MS (ESI) 307 $(M + H)^+$.

Example 58

5-Fluoro-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole hydrochloride



To 700mL of degassed CH_3CN was added methyl vanillate (21.1g, 116mmol), *N*-phenyltrifluoromethanesulfonimide (41.3g, 116mmol), and cesium carbonate (37.7g, 116mmol). The mixture was stirred under an argon atmosphere for 48h at which point it was partitioned between EtOAc (750mL) and H_2O (750mL). The organic layer was washed with saturated Na_2CO_3, H_2O, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (1:9 EtOAc / hexanes) to give methyl 3-methoxy-4-{[(trifluoromethyl)sulfonyl]oxy}benzoate as a colorless oil that became a colorless solid upon standing. ^{1}H NMR (DMSO-d_6, 300MHz) δ 7.77 (d, 1H), 7.68 (dd, 1H), 7.59 (d, 1H), 4.00 (s, 3H), 3.91 (s, 3H).

To 300mL of degassed THF was added methyl 3-methoxy-4-{[(trifluoromethyl)sulfonyl]oxy}benzoate (20.95g, 66.7mmol), 2-pyridylzinc bromide (200mL of 0.5M solution in THF, 100mmol), and tetrakis(triphenylphosphine) palladium(0) (5.00g, 4.3mmol). The mixture was degassed with argon for an additional 30 minutes and heated at reflux under an argon atmosphere overnight. The

reaction mixture was cooled to rt and concentrated *in vacuo*. The resultant brown residue was partitioned between EtOAc (1500mL) and 50% saturated $NaHCO_3$ (1000mL). The aqueous layer was extracted with EtOAc (500mL), and the combined organic layers washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (0-25% EtOAc/hexanes) to give methyl 3-methoxy-4-pyridin-2-ylbenzoate as a colorless solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.70 (d, 1H), 7.92-7.83 (m, 3H), 7.70-7.65 (m, 2H), 7.40-7.36 (m, 1H), 3.91 (s, 3H), 3.90 (s, 3H).

To 154mL of a 50/50 solution of MeOH and H_2O was added lithium hydroxide monohydrate (13.85g, 330mmol). The solution was stirred until all of the salt dissolved, at which point methyl 3-methoxy-4-pyridin-2-ylbenzoate (8.02g, 32.9mmol) was added. The mixture was heated at reflux and stirred overnight. The reaction mixture was cooled to rt, neutralized with 6N HCl, and acidified to pH 4 with 1N HCl. A colorless solid crashed out of solution and was filtered to give 3-methoxy-4-pyridin-2-ylbenzoic acid as a colorless solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.70 (d, 1H), 7.92-7.84 (m, 3H), 7.69-7.65 (m, 2H), 7.40-7.36 (m, 1H), 3.91 (s, 3H).

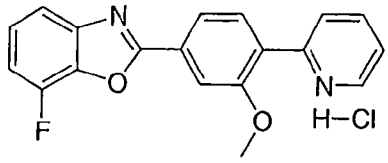
To a stirred solution of 4-fluoro-2-nitrophenol (4.05g, 25.8mmol) in MeOH (200mL) was added tin(II) chloride dihydrate (17.47g, 77.4mmol). The reaction mixture was heated at reflux and monitored by LC/MS. When significant reduction was complete, the reaction mixture was cooled to rt, poured over ice, and made basic (pH 9) with 50% saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 x 200mL) and the combined extracts washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 2-amino-4-fluorophenol as a grayish green solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 6.64 (dd, 1H), 6.47 (dd, 1H), 6.33 (dt, 1H), 4.48 (br s, 1H), 3.78 (br s, 2H).

To 20mL trimethylsilyl polyphosphate was added 2-amino-4-fluorophenol (523mg, 4.11mmol) and 3-methoxy-4-pyridin-2-ylbenzoic acid (857mg, 3.74mmol). The mixture was heated at 200°C for 2h, quenched over ice, and made basic (pH 14) with 1N NaOH. The aqueous phase was extracted with MTBE (300mL), EtOAc (300mL), MTBE (300mL), and CH_2Cl_2 (300mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (0-50% EtOAc/hexanes). The free base was dissolved in ether and HCl (1N in ether) was added. The solution was filtered to give 5-fluoro-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole hydrochloride as a purple solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.87 (d, 1H), 8.34

(t, 1H), 8.18 (d, 1H), 7.97-7.93 (m, 3H), 7.90 (dd, 1H), 7.81-7.75 (m, 2H), 7.37 (dt, 1H), 4.02 (s, 3H); MS (ESI) 321 $(M + H)^+$.

Example 59

7-Fluoro-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole hydrochloride

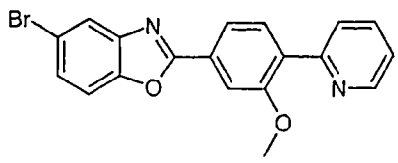


To a stirred slurry of 10% palladium on carbon (2.26g, 2.12mmol) in MeOH (100mL) was added 4-bromo-2-fluoro-6-nitrophenol (5.00g, 21.2mmol). The reaction mixture was stirred under an H_2 atmosphere until significant reduction was seen by TLC. The mixture was filtered through Celite and concentrated *in vacuo*. The resultant solid was triturated with hexanes and reconcentrated to remove residual MeOH and give 2-amino-6-fluorophenol as a dark gray solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 10.86 (br s, 1H), 9.54 (br s, 2H), 7.25-7.19 (m, 1H), 7.13 (d, 1H), 6.94-6.86 (m, 1H).

To 7mL trimethylsilyl polyphosphate was added 2-amino-6-fluorophenol (166mg, 1.31mmol) and 3-methoxy-4-pyridin-2-ylbenzoic acid (300mg, 1.31mmol). The mixture was heated at 200°C for 2h, quenched over ice, and made basic (pH 14) with 1N NaOH. The aqueous phase was extracted with EtOAc (3 x 150mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant oil was taken up in ether and reconcentrated to give a tan solid. The free base was dissolved in ether and HCl (1N in ether) was added. The solution was filtered to give 7-fluoro-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole hydrochloride as a yellow solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.71 (d, 1H), 8.00 (t, 1H), 7.97-7.84 (m, 4H), 7.70 (d, 1H), 7.49-7.37 (m, 3H), 4.00 (s, 3H); MS (ESI) 321 $(M + H)^+$.

Example 60

5-Bromo-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole

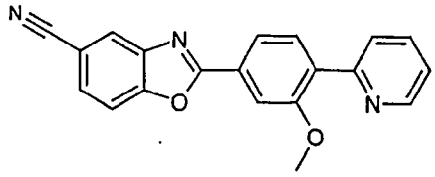


To a stirred solution of 4-bromo-2-nitrophenol (5.00g, 22.9mmol) in MeOH (120mL) was added tin(II) chloride dihydrate (15.53g, 68.8mmol). The reaction mixture was heated at reflux and monitored by LC/MS. When significant reduction was complete, the reaction mixture was cooled to rt, poured over ice, and made basic (pH 9) with 50% saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 x 150mL) and the combined extracts washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 2-amino-4-bromophenol as a dark gray solid. ^1H NMR ($CDCl_3$, 300MHz) δ 9.29 (br s, 1H), 6.71 (d, 1H), 6.56 (d, 1H), 6.49 (dd, 1H), 4.83 (br s, 2H).

To 20mL trimethylsilyl polyphosphate was added 2-amino-4-bromophenol (752mg, 4.00mmol) and 3-methoxy-4-pyridin-2-ylbenzoic acid (916mg, 4.00mmol). The mixture was heated at 200°C for 2h, quenched over ice, and made basic (pH 14) with 1N NaOH. The aqueous phase was extracted with MTBE (3 x 300mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (20-50% EtOAc/hexanes) to give 5-bromo-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole as a pink solid. ^1H NMR (DMSO-d_6, 300MHz) δ 8.71 (d, 1H), 8.10 (d, 1H), 8.00 (t, 1H), 7.97-7.86 (m, 4H), 7.84 (d, 1H), 7.63 (dd, 1H), 7.39 (dt, 1H), 4.00 (s, 3H); MS (ESI) 382 $(M + H)^+$.

Example 61

5-Cyano-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole

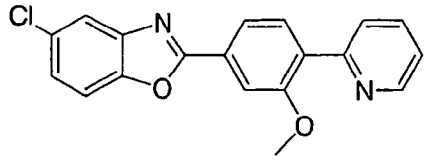


To 1mL of degassed DMF was added 5-bromo-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole (622mg, 1.63mmol), zinc cyanide (115mg, 0.98mmol), tris(dibenzylideneacetone)-dipalladium (0)-chloroform complex (30mg,

0.029mmol), and 1,1'-bisdiphenylphosphinoferrocene (41mg, 0.073mmol). The reaction mixture was degassed with argon for an additional 10min and heated at 120°C under an argon atmosphere for 20h. The mixture was cooled to 80°C, 4mL of a 4:1:4 saturated NH_4Cl:NH_4OH:H_2O solution was added dropwise, and the mixture cooled to rt and stirred overnight. The mixture was cooled to –9°C and filtered, the solid washed with 5mL of a 4:1:5 sat. NH_4Cl:NH_4OH:H_2O solution followed by 5mL H_2O, and dried under vacuum to a dark yellow solid. The crude solid was purified by column chromatography (20-80% EtOAc/hexanes) to give 5-cyano-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole as a tan solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.72 (d, 1H), 8.47 (d, 1H), 8.09-7.85 (m, 7H), 7.40 (ddd, 1H), 4.01 (s, 3H); MS (ESI) 328 $(M + H)^+$.

Example 62

5-Chloro-2-(3-methoxy-4-pyridin-2-ylphenyl)-1,3-benzoxazole hydrochloride



To a suspension of 4-amino-3-methoxy benzoic acid (21g, .125 mole) in H_2SO_4 (2M, 100mL) was added dropwise aqueous sodium nitrite (9.54g, 0.138mole) at 5°C. The mixture was stirred an additional 10min at this temperature. Aqueous potassium iodide (22.9g, 0.138 mole) was added dropwise. The solution was warmed at 40°C until end of the gas evolution. The reaction mixture was cooled at rt and EtOAc (150mL) was added. The aqueous layer was extracted two with EtOAc (2x150mL). The organic layers were combined and washed with a 5% solution of sodium thiosulfate (200mL), brine (200mL), dried ($MgSO_4$) and concentrated under vacuum to give a yellow solid. The crude material was dissolved in MeOH ((400mL), H_2SO_4 was added (8mL) and the reaction was heated under reflux overnight. After classical work-up the crude material was purified by flash chromatography using a mixture of hexane and ethyl acetate (80/20) as eluant to give 22.2 g of pure 4-iodo-3-methoxy-methylbenzoate (0.076 mole, 60.8%). A mixture of 4-iodo-3-methoxy-methylbenzoate (7g, 24mmol), 2-pyridyl zinc bromide (0.5M in

THF, 62mL, 31.2mmol), and tetrakis(triphenylphosphine) palladium (1.4g, 1.2mmol) in THF (40mL) was refluxed for 5h and then stirred at rt overnight. H_2O was added and the solution was filtered through Celite, the pad was washed with EtOAc, and the two layers were separated. The aqueous was washed with EtOAc (2 x 50mL), dried over Na_2SO_4, and evaporated to dryness. The dark residue was purified by flash chromatography on silica gel eluting with EtOAc:hexane (1:5) to afford the desired intermediate, methyl-3-methoxy-4-pyridin-2-yl benzoate, as a yellow solid.

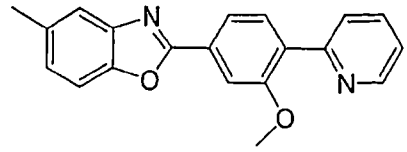
Methyl-3-methoxy-4-pyridin-2-yl benzoate (4.70g, 19.3mmol) and 10% lithium hydroxide in 1:1 water: methanol (14.8mL) was heated to reflux conditions until no starting material was observed by TLC. 6N HCl aqueous solution was added to the cooled mixture until pH 5, A yellow solid precipated was filtered to give the desired intermediate, 3-methoxy-4-pyridin-2-yl benzoic acid, as a grey solid.

3-Methoxy-4-pyridin-2-yl benzoic acid (500mg, 2.2mmol), 2-amino-4-chlorophenol (620mg, 4.3mmol) and trimethyl silylpolyphosphate (2mL) was heated to 180 °C overnight under argon. To the cooled reaction mixture, water (100mL) was added and extracted with EtOAc (4 x 20mL). Set aside organic layer. Filtered aqueous layer through Celite pad and basified filtrate to pH 9 (solid $NaHCO_3$). Extracted with EtOAc (2 x 30mL), combined all organic layers and concentrated *in vacuo*. The resulting orange oil was purified by flash chromatography using a gradient elution of 15:85 ethyl acetate:hexane to 1:1 ethyl acetate:hexane to give the desired intermediate, 5-chloro-2-(3-methoxy-4-pyridin-2-yl phenyl) –1,3-benzoxazole as a colorless solid.

5-Chloro-2-(3-methoxy-4-pyridin-2-yl phenyl)-1,3- benzoxazole (26mg) was stirred in dichloromethane.1.0M HCl in diethyl ether (0.95mL) was added and allowed reaction mixture to stir for 30 minutes. Concentration of reaction mixture *in vacuo* gave the desired compound, 5-chloro-2-(3-methoxy-4-pyridin-2-yl phenyl)-1,3- benzoxazole hydrochloride, as a pink solid. ^{1}H NMR (CD_3OD, 300MHz) δ 8.88-7.46 (m, 10H), 4.11 (s, 3H). MS (ESI) 337 $(M + H)^+$.

Example 63

2-(3-Methoxy-4-pyridin-2-yl phenyl)-5-methyl-1,3-benzoxazole



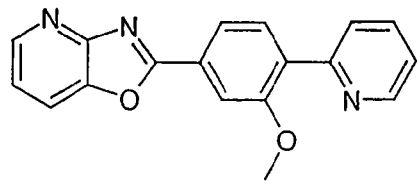
A mixture of A mixture of 4-iodo-3-methoxy-methylbenzoate (see example 62) (7g, 24mmol), 2-pyridyl zinc bromide (0.5M in THF, 62mL, 31.2mmol), and tetrakis(triphenylphosphine)palladium (1.4g, 1.2mmol) in THF (40mL) was refluxed for 5h and then stirred at rt overnight. H_2O was added and the solution was filtered through Celite, the pad was washed with EtOAc, and the two layers were separated. The aqueous was washed with EtOAc (2 x 50mL), dried over Na_2SO_4, and evaporated to dryness. The dark residue was purified by flash chromatography on silica gel eluting with EtOAc:hexane (1:5) to afford the desired intermediate, methyl-3-methoxy-4-pyridin-2-yl benzoate, as a yellow solid.

Methyl-3-methoxy-4-pyridin-2-yl benzoate (4.70g, 19.3mmol) and 10% lithium hydroxide in 1:1 water:methanol (14.8mL) was heated to reflux conditions until no starting material was observed by TLC. 6N HCl aqueous solution was added to the cooled mixture until pH 5, A yellow solid precipated out of solution and was filtered to give the desired intermediate, 3-methoxy-4-pyridin-2-yl benzoic acid, as a grey solid.

3-Methoxy-4-pyridin-2-yl benzoic acid (490mg, 2.1mmol), 2-amino-*p*-cresol (527mg, 4.28mmol) and trimethylsilyl polyphosphate (2mL) was refluxed overnight under argon. Added water (100mL) to the cooled reaction mixture and basified to pH 8 (solid $NaHCO_3$). Extracted with EtOAc (3 x 60mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow residue was purified by flash chromatography using a gradient elution of 1:9 EtOAc: hexanes to 1:4 EtOAc: hexanes to give the desired compound, 2-(3-methoxy-4-pyridin-2-yl phenyl)-5-methyl-1,3-benzoxazole, as a yellow solid. ^1H NMR ($CDCl_3$, 300MHz) δ 8.74 (m, 1H), 7.98 – 7.16 (m, 10H), 4.03 (s, 3H), 2.51 (s, 3H). (ESI) 317 $(M + H)^+$.

Example 64

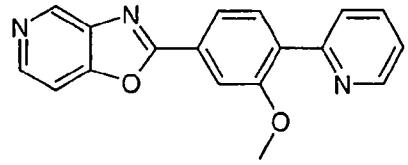
2-(3-Methoxy-4-pyridin-2-ylphenyl)[1,3]oxazolo[4,5-*b*]pyridine



To 5mL of trimethylsilyl polyphosphate was added 2-aminopyridin-3-ol (175mg, 1.59mmol) and 3-methoxy-4-pyridin-2-ylbenzoic acid (344mg, 1.50mmol). The mixture was heated at 200°C for 2h, quenched over ice, and made basic (pH 14) with 1N NaOH. The aqueous phase was extracted with MTBE (3 x 200mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 2-(3-methoxy-4-pyridin-2-ylphenyl)[1,3]oxazolo[4,5-*b*]pyridine as a light yellow solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.72 (d, 1H), 8.58 (d, 1H), 8.30 (d, 1H), 8.05-7.91 (m, 4H), 7.88 (t, 1H), 7.51 (dd, 1H), 7.40 (dd, 1H), 4.02 (s, 3H); MS (ESI) 304 $(M + H)^+$.

Example 65

2-(3-Methoxy-4-pyridin-2-ylphenyl)[1,3]oxazolo[4,5-*c*]pyridine



To a stirred solution of 3-aminopyridine (9.41g, 100mmol) and triethylamine (16.7mL, 120mmol) in CH_2Cl_2 (300mL) at 0°C was added trimethylacetyl chloride (14.8mL, 120mmol) dropwise over 15min. The reaction was warmed to rt and stirred overnight. The mixture was concentrated *in vacuo*, the residue partitioned between EtOAc and H_2O, and the layers separated. The aqueous layer was made basic with saturated $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give *N*-(pyridin-3-yl)-2,2-dimethylpropanamide as a tan solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.57 (d, 1H), 8.33 (dd, 1H), 8.17 (ddd, 1H), 7.69 (br s, 1H), 7.27 (dd, 1H), 1.33 (s, 9H).

To a stirred solution of *N*-(pyridin-3-yl)-2,2-dimethylpropanamide (8.90g, 50.0mmol) in THF (200mL) at –78°C was added n-Butyllithium (50mL,

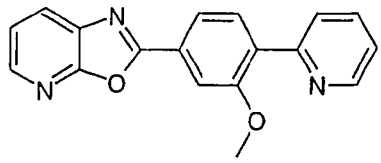
125mmol) dropwise over 30min. After addition, the reaction mixture was warmed to 0°C and stirred an additional 3h. The reaction was then cooled back to –78°C and trimethyl borate (14.2mL, 125mmol) in THF was added dropwise over 15min. After addition, the reaction mixture was warmed to 0°C and stirred an additional 2h. Glacial AcOH (10.8mL, 188mmol) was added to the reaction, followed by dropwise addition of 30 % H_2O_2 (14.3mL, 138mmol). The reaction mixture was warmed to rt and stirred overnight. The mixture was diluted with H_2O and concentrated *in vacuo*. The residue was extracted three times with 10% *i*PrOH / $CHCl_3$, the combined extracts treated with activated charcoal, and the slurry filtered through Celite. The organic layer was washed three times with H_2O, once with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (3-10% MeOH / $CHCl_3$) to give *N*-(4-hydroxypyridin-3-yl)-2,2-dimethylpropanamide as a light yellow solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 11.58 (br s, 1H), 8.76 (br s, 1H), 8.67 (s, 1H), 7.68 (d, 1H), 6.26 (d, 1H), 1.22 (s, 9H).

To a stirring solution of 3N HCl (50mL, 150mmol) was added *N*-(4-hydroxypyridin-3-yl)-2,2-dimethylpropanamide (1.94g, 10.0mmol). The mixture was heated at reflux overnight. After cooling to rt, the mixture was neutralized with 5N NaOH and concentrated *in vacuo*. The residue was taken up in MeOH, the salts filtered out, and the organic layer reconcentrated. The resulting residue was taken up in EtOH, the salts filtered out, and the organic layer reconcentrated to give 3-aminopyridin-4-ol, which was taken into the next step without purification. ^{1}H NMR (DMSO-d_6, 300MHz) δ 12.25 (br s, 1H), 7.35 (dd, 1H), 7.18 (d, 1H), 6.00 (d, 1H), 4.54 (br s, 2H).

To 7mL trimethylsilyl polyphosphate was added 3-aminopyridin-4-ol (330mg, 3.00mmol) and 3-methoxy-4-pyridin-2-ylbenzoic acid (460mg, 2.00mmol). The mixture was heated at 200°C for 2h, quenched over ice, and made basic (pH 14) with 1N NaOH. The aqueous phase was extracted with MTBE (3 x 200mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (50-100% EtOAc/hexanes followed by 10% MeOH/$CHCl_3$) to give 2-(3-Methoxy-4-pyridin-2-ylphenyl)[1,3]oxazolo[4,5-*c*]pyridine as a yellow solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 9.16 (s, 1H), 8.71 (d, 1H), 8.62 (d, 1H), 8.03-7.84 (m, 6H), 7.39 (t, 1H), 4.00 (s, 3H); MS (ESI) 304 $(M + H)^+$.

Example 66

2-(3-Methoxy-4-pyridin-2-ylphenyl)[1,3]oxazolo[5,4-*b*]pyridine

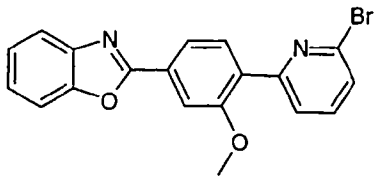


To a stirred slurry of 10% palladium on carbon (1.08g, 1.02mmol) in MeOH (100mL) was added 3-nitropyridin-2-ol (1.42g, 10.2mmol). The reaction mixture was stirred under an H_2 atmosphere until significant reduction was seen by TLC. The mixture was filtered through Celite and concentrated *in vacuo*. The resultant semisolid was triturated with hexanes and concentrated to remove residual MeOH and purified by UV Prep to give 3-aminopyridin-2-ol as a dark brown oil.

To 5mL of trimethylsilyl polyphosphate was added 3-aminopyridin-2-ol (150mg, 1.59mmol) and 3-methoxy-4-pyridin-2-ylbenzoic acid (229mg, 1.0mmol). The mixture was heated at 200°C for 2h, quenched over ice, and made basic (pH 14) with 1N NaOH. The aqueous phase was extracted with EtOAc (3 x 200mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant oil was taken up in a minimum of EtOAc and purified by prep TLC (1:1 EtOAc/hexanes) to give 2-(3-methoxy-4-pyridin-2-ylphenyl)[1,3]oxazolo[5,4-*b*]pyridine as a light yellow solid. ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.73 (dq, 1H), 8.43 (dd, 1H), 8.32 (dd, 1H), 8.02 (d, 1H), 7.99-7.93 (m, 2H), 7.92-7.85 (m, 2H), 7.55 (dd, 1H), 7.40 (ddd, 1H), 4.01 (s, 3H); MS (ESI) 304 (M + H)$^+$.

Example 67

2-[4-(6-Bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole



4-hydroxy-3-methoxybenzoic acid (25g, 150mmol) and 2-amino phenol (16g, 150mmol) were combined in a round bottom flask. Trimethylsilyl

polyphosphate (80mL) was added. The mixture was heated at 180°C for 30min. The mixture was poured over ice and allowed to stir overnight. The suspension was filtered to afford 4-(1,3-benzoxazol-2-yl)-2-methoxyphenol as a pale green solid. MS (ESI) 242 (M+H).

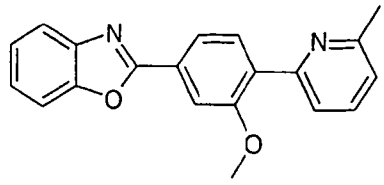
A solution of 4-(1,3-benzoxazol-2-yl)-2-methoxyphenol (7.1g, 29mmol) in anhydrous DMF (100mL) was treated with Cs_2CO_3 (9.6g, 29mmol) and *N*-phenyl trifluoromethanesulfonimide (10g, 29mmol) at 22°C for 30min. The resulting mixture was quenched with saturated aqueous $NaHCO_3$ (50mL) and diluted with EtOAc (500mL). The EtOAc solution was washed with brine (3 x 100mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using and EtOAc/hexanes gradient to afford 4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl trifluoromethanesulfonate as a colorless oil: MS (ESI) 374 $(M+H)^+$.

4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl trifluoromethanesulfonate (480mg, 1.3mmol), potassium acetate (380mg, 3.8mmol), bis(diphenylphosphino)ferrocene palladium dichloride (100mg, 0.13mmol), and bis(pinacolato)diboron (390mg, 1.5mmol) were combined in a 2-neck flask. The flask was evacuated and filled with argon and dioxane (10mL) was added. The suspension was deoxygenated with a stream of argon for 10min. The reaction mixture was stirred under argon at 80°C for 24h. Crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using and EtOAc/hexanes gradient to afford 2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole as an orange solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.83-7.83 (m, 3H), 7.74 (s, 1H), 7.62-7.55 (m, 1H), 7.39-7.36 (m, 2H), 3.98 (s, 3H), 1.39 (s, 12H).

2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (200mg, 0.57mmol) CsF (350mg, 2.3mmol), $Pd(Ph_3P)_4$ (65mg, 0.057mmol), and 2-bromopyridine (140mg, 0.57mmol) were combined in a 2-neck flask. The flask was evacuated and filled with argon and DME (5mL) was added. The suspension was deoxygenated with a stream of argon for 10min. The reaction mixture was stirred under argon at 80°C for 24h. Crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using and EtOAc/hexanes gradient to afford the desired 2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.08-8.05 (d, 1H), 7.98-7.95 (m, 2H), 7.89 (s, 1H), 7.84-7.79 (m, 1H), 7.63-7.60 (m, 1H), 7.45-7.38 (m, 3H), 4.02 (s, 3H). MS (ESI) 382 $(M + H)^+$.

Example 68

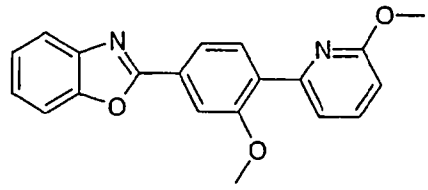
2-[3-Methoxy-4-(6-methylpyridin-2-yl)phenyl]-1,3-benzoxazole



Utilizing the general procedure outlined in the synthesis of 2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole, 2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (200mg, 0.57mmol) was reacted with 2-bromo-6-methylpyridine (65μL, 0.57mmol) to afford the desired 2-[3-methoxy-4-(6-methylpyridin-2-yl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.96-7.95 (m, 2H), 7.89 (s, 1H), 7.82-7.79 (m, 1H), 7.67-7.60 (m, 3H), 7.39-7.36 (m, 2H), 7.14-7.12 (m, 1H), 4.00 (s, 3H), 2.65 (s, 3H). MS (ESI) 317 $(M+H)^+$.

Example 69

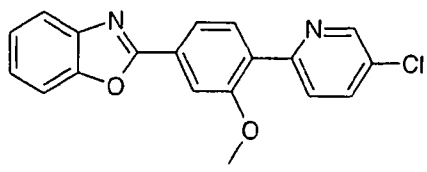
2-[3-Methoxy-4-(6-methoxypyridin-2-yl)phenyl]-1,3-benzoxazole



Utilizing the general procedure outlined in the synthesis of 2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole, 2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (200mg, 0.57mmol) was reacted with 2-bromo-6-methoxypyridine (65μL, 0.57mmol) to afford the desired 2-[3-methoxy-4-(6-methoxypyridin-2-yl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.96-7.95 (m, 2H), 7.89 (s, 1H), 7.82-7.79 (m, 1H), 7.67-7.60 (m, 3H), 7.39-7.36 (m, 2H), 7.14-7.12 (m, 1H), 4.00 (s, 3H), 2.65 (s, 3H). MS (ESI) 333 $(M+H)^+$.

Example 70

2-[4-(5-Chloropyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole

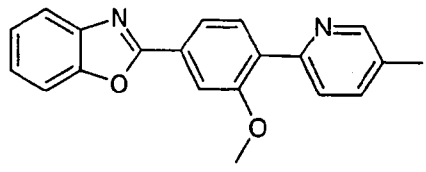


A solution of 5-chloro-2-pyridinol (3.0g, 23mmol), *N*-phenyl trifluoromethanesulfonimide (8.3g, 23mmol), and Cs_2CO_3 (7.5g, 23mmol) in CH_3CN (100mL) was stirred at room temp for 24h. Crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford 4-chlorophenyl-2-trifluoromethanesulfonate as an orange oil: MS (ESI) 262 $(M+H)^+$.

Utilizing the general procedure outlined in the synthesis of 2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole, 2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (100mg, 0.28mmol) was reacted with 4-chlorophenyl trifluoromethanesulfonate (74mg, 0.28mmol) to afford the desired 2-[4-(5-chloropyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole as a colorless solid: ^1H NMR ($CDCl_3$, 300MHz) δ 8.69-8.68 (d, 1H), 7.98 (s, 2H), 7.94-7.90 (m, 2H), 7.86-7.78 (m, 1H), 7.74-7.73 (m, 1H), 7.65-7.58 (m, 1H), 7.40-7.37 (m, 2H), 4.03 (s, 3H). MS (ESI) 337 $(M+H)^+$.

Example 71

2-[3-Methoxy-4-(3-methylpyridin-2-yl)phenyl]-1,3-benzoxazole

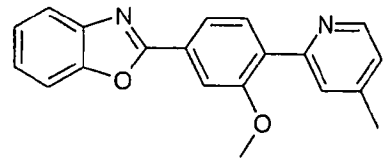


Utilizing the general procedure outlined in the synthesis of 2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole, 2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (150mg, 0.43mmol) was reacted with 2-bromo-5-methylpyridine (73mg, 0.43mmol) to afford the desired 2-[3-methoxy-4-(3-methylpyridin-2-yl)phenyl]-1,3-benzoxazole as a colorless solid:

^{1}H NMR ($CDCl_3$, 300MHz) δ 8.60-8.58 (d, 1H), 7.96-7.90 (m, 3H), 7.80-7.79 (m, 1H), 7.70 (s, 1H), 7.62-7.60 (m, 1H), 7.39-7.36 (m, 2H), 7.10-7.08 (m, 1H), 4.01(s, 3H), 2.43 (s, 3H). MS (ESI) 317 $(M+H)^+$.

Example 72

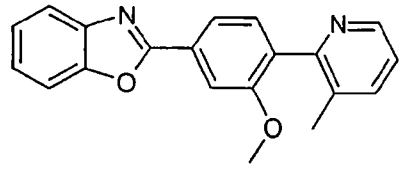
2-[3-Methoxy-4-(4-methylpyridin-2-yl)phenyl]-1,3-benzoxazole



Utilizing the general procedure outlined in the synthesis of 2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole, 2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (150mg, 0.43mmol) was reacted with 2-bromo-4-methylpyridine (47μL, 0.43mmol) to afford the desired 2-[3-methoxy-4-(4-methylpyridin-2-yl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.57 (s, 1H), 7.97-7.96 (m, 2H), 7.89 (s, 1H), 7.82-7.79 (m, 2H), 7.63-7.54 (m, 2H), 7.39-7.36 (m, 2H), 4.01 (s, 3H), 2.39 (s, 3H). MS (ESI) 317 $(M+H)^+$.

Example 73

2-[3-Methoxy-4-(5-methylpyridin-2-yl)phenyl]-1,3-benzoxazole

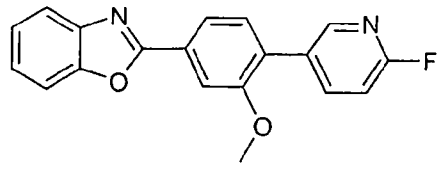


Utilizing the general procedure outlined in the synthesis of 2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole, 2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (200mg, 0.57mmol) was reacted with 2-bromo-3-methylpyridine (63 μL, 0.57mmol) to afford the desired 2-[3-methoxy-4-(5-methylpyridin-2-yl)phenyl]-1,3-benzoxazole as a colorless solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.55-8.53 (d, 1H), 7.98-7.95 (m, 1H), 7.88 (s, 1H),

7.81-7.78 (m, 1H), 7.61-7.56 (m, 2H), 7.46-7.44 (d, 1H), 7.39-7.35 (m, 2H), 7.23-7.19 (m, 1H), 3.91 (s, 3H), 2.19 (s, 3H). MS (ESI) 317 $(M+H)^+$.

Example 74

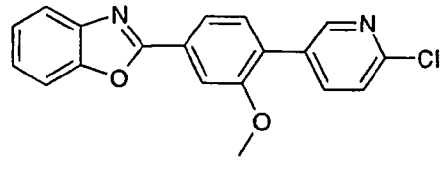
2-[4-(6-Fluoropyridin-3-yl)-3-methoxyphenyl]-1,3-benzoxazole



Utilizing the general procedure outlined in the synthesis of 2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole, 2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (200mg, 0.57mmol) was reacted with 5-bromo-2-fluoropyridine (59μL, 0.57mmol) to afford the desired 2-[4-(6-fluoropyridin-3-yl)-3-methoxyphenyl]-1,3-benzoxazole as a colorless solid: ^1H NMR ($CDCl_3$, 300MHz) δ 8.42 (s, 1H), 8.07-8.00 (m, 1H), 7.97-7.94 (m, 1H), 7.89 (s, 1H), 7.82-7.79 (m, 1H), 7.64-7.59(m, 1H), 7.48-7.45 (d, 1H), 7.41-7.38 (m, 1H), 7.03-6.99 (m, 1H), 3.98 (s, 3H). MS (ESI) 321 $(M+H)^+$.

Example 75

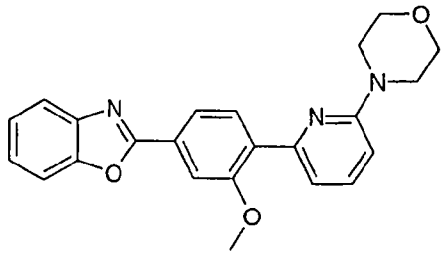
2-[4-(6-Chloropyridin-3-yl)-3-methoxyphenyl]-1,3-benzoxazole



Utilizing the general procedure outlined in the synthesis of 2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole, 2-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazole (100mg, 0.29mmol) was reacted with 5-bromo-2-chloropyridine (55mg, 0.29mmol) and Na_2CO_3 (90mg, 0.86mmol) in DME (2mL), and H_2O (2mL) to afford the desired 2-[4-(6-chloropyridin-3-yl)-3-methoxyphenyl]-1,3-benzoxazole as a colorless solid: ^1H NMR ($CDCl_3$, 300MHz) δ 8.59 (d, 1H), 7.85-7.66 (m, 3H), 7.44-7.78 (m, 1H), 7.56-7.60 (m, 1H), 7.48-7.45 (d, 1H), 7.42-7.38 (m, 3H), 3.98 (s, 3H). MS (ESI) 337 $(M + H)^+$.

Example 76

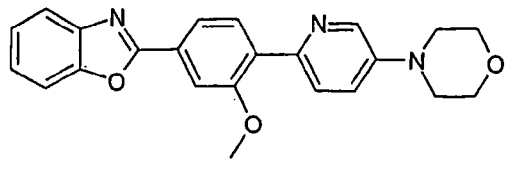
2-[3-Methoxy-4-(6-morpholin-4-ylpyridin-2-yl)phenyl]-1,3-benzoxazole



2-[4-(6-bromopyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole (150mg, 0.39mmol), morpholine (41μL, 0.47mmol), $Pd_2(dba)_3$ (8.2mg, 0.0078mmol), BINAP (9.8mg, 0.016mmol), and NaO*t*Bu (53mg, 0.55mmol) were combined in a sealable tube evacuated and backfilled with argon. Toluene (4mL) was added and the mixture was degassed with a stream of argon for 5min. The tube was sealed and the mixture was heated to 70°C for 18h. Crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford the desired 2-[3-methoxy-4-(6-morpholin-4-ylpyridin-2-yl)phenyl]-1,3-benzoxazole as an orange solid: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.07-8.05 (d, 1H), 7.96-7.95 (m, 1H), 7.88 (s, 1H), 7.83-7.78 (m, 1H), 7.65-7.58 (m, 2H), 7.42-7.36 (m, 3H), 6.65-6.62 (d, 1H), 4.02 (s, 3H), 3.88-3.85 (t, 4H), 3.61-3.58 (t, 4H). MS (ESI) 388 $(M + H)^+$.

Example 77

2-[3-Methoxy-4-(5-morpholin-4-ylpyridin-2-yl)phenyl]-1,3-benzoxazole

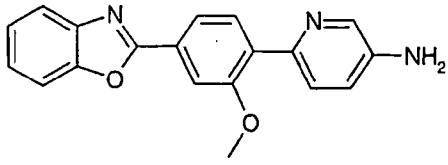


2-[4-(5-chloropyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole (58mg, 0.17mmol), morpholine (18μL, 0.21mmol), $Pd(OAc)_2$ (0.38mg, 0.0017mmol), 1,1'-biphenyl-2-yl[di(*tert*-butyl)]phosphine (1.0mg, 0.0034mmol), and NaO*t*Bu (23mg,

0.24mmol) were combined in a sealable tube evacuated and backfilled with argon. Toluene (800μL) was added and the mixture was degassed with a stream of argon for 5min. The tube was sealed and the mixture was heated to 110°C for 18h. Crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford 2-[3-methoxy-4-(5-morpholin-4-ylpyridin-2-yl)phenyl]-1,3-benzoxazole as a yellow solid. The freebase was dissolved in Et_2O/CH_2Cl_2 and treated with 1N HCl in Et_2O. Resulting yellow solid was filtered and dried under high vacuum to afford the desired 2-[3-methoxy-4-(5-morpholin-4-ylpyridin-2-yl)phenyl]-1,3-benzoxazole hydrochloride as a yellow solid: ^{1}H NMR (CD_3OD, 300MHz) δ 8.33-8.30 (d, 1H), 8.20-8.09 (m, 2H), 8.08-8.02 (m, 2H), 7.87-7.77 (m, 2H), 7.75-7.71 (m, 1H), 7.53-7.42 (m, 2H), 4.10 (s, 3H), 3.89 (t, 4H), 3.49-3.47 (t, 4H). MS (ESI) 388 $(M + H)^+$.

Example 78

6-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]pyridin-3-amine



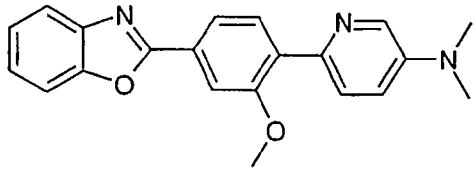
2-[4-(5-chloropyridin-2-yl)-3-methoxyphenyl]-1,3-benzoxazole (100mg, 0.30mmol), benzophenone imine (60μL, 0.36mmol), $Pd_2(dba)_3$ (15mg, 0.015mmol), 1,1'-biphenyl-2-yl(dicyclohexyl)phosphine (10mg, 0.015mmol), NaO*t*Bu (40mg, 0.42mmol) were combined in a sealable tube evacuated and backfilled with argon. Toluene (600μL) was added and the mixture was degassed with a stream of argon for 5min. The tube was sealed and the mixture was heated to 80°C for 24h. Crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford 6-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]-*N*-(diphenylmethylene)pyridin-3-amine as a yellow solid.

6-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]-*N*-(diphenylmethylene)pyridin-3-amine (61mg, 0.13mmol) was dissolved in MeOH (2mL) and NaOAc (25mg, 0.31mmol) and hydroxylamine hydrochloride (16mg, 0.23mmol) were added. The resulting suspension was stirred at rt for 1h. The mixture was partitioned between CH_2Cl_2 and 0.1N aqueous NaOH. Aqueous layer

was extracted with CH_2Cl_2 (3 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford the desired 6-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]pyridin-3-amine: ^1H NMR ($CDCl_3$, 300MHz) δ 8.25-8.24 (d, 1H), 7.95 (s, 2H), 7.86 (s, 1H), 7.80-7.76 (m, 2H), 7.62-7.59 (m, 1H), 7.38-7.35 (m, 2H), 7.07-7.04 (m, 1H), 4.01 (s, 3H). MS (ESI) 318 $(M+H)^+$.

Example 79

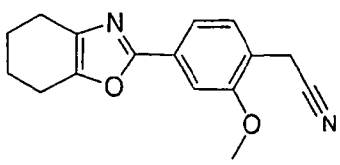
6-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]-*N*,*N*-dimethylpyridin-3-amine



6-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]pyridin-3-amine (22mg, 0.070mmol) was dissolved in MeOH (2mL), and AcOH (2 drops). $NaCNBH_3$ (44mg, 0.70mmol) and formaldehyde (50μL, 0.70mmol) were added and the mixture was stirred overnight. The mixture was partitioned between CH_2Cl_2 and dilute brine. The aqueous layer was extracted with CH_2Cl_2 (3 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude mixture was adsorbed onto silica gel and purified by automated flash chromatography using an EtOAc/hexanes gradient to afford the desired 6-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]-*N*,*N*-dimethylpyridin-3-amine: ^1H NMR ($CDCl_3$, 300MHz) δ 8.24-8.23 (d, 1H), 7.94 (s, 2H), 7.87 (s, 1H), 7.84-7.79 (m, 2H), 7.59 (m, 1H), 7.38-7.35 (m, 2H), 7.07-7.06 (m, 1H), 4.01 (s, 3H), 3.04 (s, 6H). MS (ESI) 346 $(M + H)^+$.

EXAMPLE 80

[2-methoxy-4-(4,5,6,7-tetrahydro-1,3-benzoxazol-2-yl)phenyl]acetonitrile



To a solution of methyl 4-(bromoethyl)-3-methoxy benzoate (25g, 96.5mmol) in acetonitrile (200mL) was added TMSCN (19mL, 144.7mmol) and TBAF (144mL, 1.0M in THF) at 22°C. 20min later, the resulting reaction mixture was concentrated under reduced pressure to give after purification by flash chromatography (silica gel, 4:1; hexanes:EtOAc) the to give methyl 4-(cyanomethyl)-3-ethoxybenzoate as a white solid. MS (ESI) 206 $(M+H)^+$.

A solution of methyl 4-(cyanomethyl)-3-ethoxybenzoate (18g, 88mmol) in 150mL of MeOH:THF:H_2O (3:3:1) was treated with lithium hydroxide monohydrate (11g, 263mmol) at 22°C for overnight. Then 10% aqueous HCl (100mL) was added to quench the reaction, the mixture was extracted with EtOAc (3 x 200mL), the combined organic extracts were washed with brine (100mL) and dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 4-(cyanomethyl)-3-methoxybenzoic acid as a white solid. MS (ESI) 192 $(M+H)^+$.

The 4-(cyanomethyl)-3-methoxybenzoic acid (0.33g, 1.7mmol) was suspended in anhydrous dichloromethane (5mL) and treated with oxalyl chloride(0.3mL, 3.5mmol) followed by few drops of DMF at 22°C under argon. After 2h stirring, the resulting solution was concentrated to dryness, dissolved in dichloromethane (5mL), and added slowly to a solution of trans-2-aminocyclohexanol hydrochloride (0.26g, 1.7mmol) and TEA (0.5mL, 3.5mmol) in anhydrous dichloromethane (10mL). After 20min stirring, filtered off salt, and concentrated to afford 4-(cyanomethyl)-*N*-[(2*R*)-2-hydroxycyclohexyl]-3-methoxybenzamide as a yellow solid. MS (ESI) 289 $(M+H)^+$.

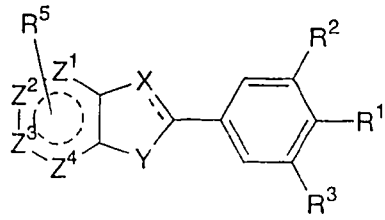
To a solution of oxalyl chloride (0.2mL, 2.2mmol) in anhydrous dichloromethane (2mL) at –78°C was added DMSO (0.32mL, 4.5mmol) under Argon. The solution was maintained for 10min where upon a solution of 4-(cyanomethyl)-*N*-[(2*R*)-2-hydroxycyclohexyl]-3-methoxybenzamide (430mg, 1.5mmol) in anhydrous dichloromethane (13mL) was added dropwide. The reaction was stirred at –78°C for 30min, whereupon TEA (1mL, 7.5mmol) was added. The reaction was warmed to 22°C for 2h. Then, 50mL dichloromethane was added to the mixture, washed with sat $NaHCO_3$ (3 x 15mL) and sat. brine (3 x 15mL), dried ($MgSO_4$), and concentrated to afford a yellow solid of 4-(cyanomethyl)-3-methoxy-*N*-(2-oxocyclohexyl)benzamide. MS (ESI) 287 $(M+H)^+$.

4-(cyanomethyl)-3-methoxy-*N*-(2-oxocyclohexyl)benzamide (0.8g, 2.8mmol) was treated with $POCl_3$ (5mL) at reflux for 1h. The resulting mixture was concentrated and dissolved in dichloromethane (50mL), washed with sat. $NaHCO_3$ (3

x 15mL) and sat. brine (3x15mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with 2:1 hexanes:EtOAc to afford the desired compound, [2-methoxy-4-(4,5,6,7-tetrahydro-1,3-benzoxazol-2-yl)phenyl]acetonitrile, the desired compound, as white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.58 (dd, 1H), 7.53 (m, 1H), 7.42 (d, 1H), 3.95 (s, 3H), 3.72 (s, 2H), 2.71 (m, 2H), 2.62 (m, 2H), 1.87 (m, 4H). MS (ESI) 269 $(M+H)^+$.

The claims defining the invention are as follows:

1. A compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or NH;

Y is O, or N-R^4;

one of Z^1, Z^2 , Z^3 or Z^2 optionally is N, or NH;

R^1 is -OH, halogen, or –CN; or a –C_{1-6}alkyl, –C_{1-4}alkoxyl, –cycloC_{3-6}alkyl, –C_{0-4}alkyl–phenyl, –C_{0-4}alkyl–pyridyl, –C_{0-4}alkyl–imidazolyl, –C_{0-4}alkyl–pyrazolyl, –C_{0-4}alkyl–triazolyl, –C_{0-4}alkyl–tetrazolyl, –C_{0-4}alkyl–dioxolanyl, –C_{0-4}alkyl–thiazolyl, –C_{0-4}alkyl–piperidinyl, –C_{0-4}alkyl–pyrrolidinyl, –C_{0-4}alkyl–morpholinyl, –C_{0-4}alkyl–pyrimidinyl, –C_{2-6}alkynyl–thiazolyl, or –N(C_{0-4}alkyl)(–C_{0-4}alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl;

R^2 is hydrogen, halogen, –OH, –CN, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –NO_2; or –C_{1-6}alkyl, –C_{1-4}alkoxyl, –C_{0-4}alkyl–phenyl, or –C_{1-4}alkoxy–phenyl group, wherein any of the groups is optionally substituted with 1-3 independently halogen, -OH, –CN, or –C_{1-4}alkoxyl substituents;

R^3 is hydrogen or –C_{1-4}alkoxyl;

R^4 is –C_{0-4}alkyl; and

R^5 is H, halogen, or –C_{1-4}alkyl.

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

Z^1, Z^2, Z^3, and Z^4 are each CH;

X is N; and

Y is O.

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

R^1 is $-C_{1-6}$alkyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl$–morpholinyl, or $-C_{0-4}alkyl$–benzoxazolyl.

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

R^2 is $-C_{0-4}alkyl$–phenyl optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}$alkoxyl substituents.

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

R^2 is $-C_{1-6}$alkyl optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}$alkoxyl substituents.

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

R^2 is NO_2 or $-N(C_{0-4}alkyl)(-C_{0-4}alkyl)$ optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}$alkoxyl substituents.

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

R^2 is $-C_{1-6}$alkoxy-phenyl optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}$alkoxyl substituents.

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

R^2 is $-C_{1-6}$alkoxyl optionally substituted with 1-3 independently halogen, -OH, –CN, or $-C_{1-4}$alkoxyl substituents.

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

R^1 is –cycloC_{3-6}alkyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl.

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

R^1 is –C_{0-4}alkyl–triazolyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl.

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

R^1 is –C_{0-4}alkyl–imidazolyl or –C_{0-4}alkyl–pyrazolyl, optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl.

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

R^1 is –C_{0-4}alkyl–tetrazolyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl.

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

R^1 is –C_{0-4}alkyl–pyrrolidinyl or –C_{0-4}alkyl–piperidinyl, optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, –C_{1-6}alkyl, –C_{1-4}alkoxyl, –N(C_{0-4}alkyl)(C_{0-4}alkyl), –C_{0-4}alkyl–C(O)–O–C_{0-4}alkyl, –C_{0-4}alkyl–morpholinyl, or –C_{0-4}alkyl–benzoxazolyl.

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

R^1 is $-C_{0-4}alkyl-$pyridyl or $-C_{0-4}alkyl-$pyrimidinyl, optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}alkyl$, $-C_{1-4}alkoxyl$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl-$morpholinyl, or $-C_{0-4}alkyl-$benzoxazolyl.

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

R^1 is $-C_{0-4}alkyl-$morpholinyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}alkyl$, $-C_{1-4}alkoxyl$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl-$morpholinyl, or $-C_{0-4}alkyl-$benzoxazolyl.

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

Z^1 is N;

X is N; and

Y is O.

17. The compound according to Claim 16, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-C_{1-6}alkyl$ optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}alkyl$, $-C_{1-4}alkoxyl$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl-$morpholinyl, or $-C_{0-4}alkyl-$benzoxazolyl.

18. The compound according to Claim 16, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-C_{0-4}alkyl-$pyridyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}alkyl$, $-C_{1-4}alkoxyl$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}alkyl-C(O)-O-C_{0-4}alkyl$, $-C_{0-4}alkyl-$morpholinyl, or $-C_{0-4}alkyl-$benzoxazolyl.

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

Z^2 or Z^3 is N;

X is N; and

Y is O.

20. The compound according to Claim 19, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-C_{0-4}$alkyl–pyridyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}$alkyl–C(O)–O–C_{0-4}alkyl, $-C_{0-4}$alkyl–morpholinyl, or $-C_{0-4}$alkyl–benzoxazolyl.

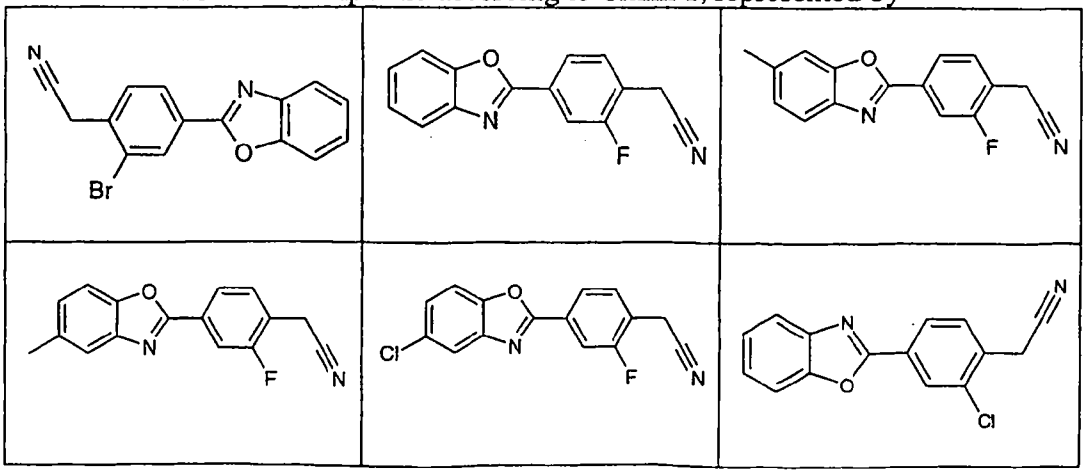
21. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein:

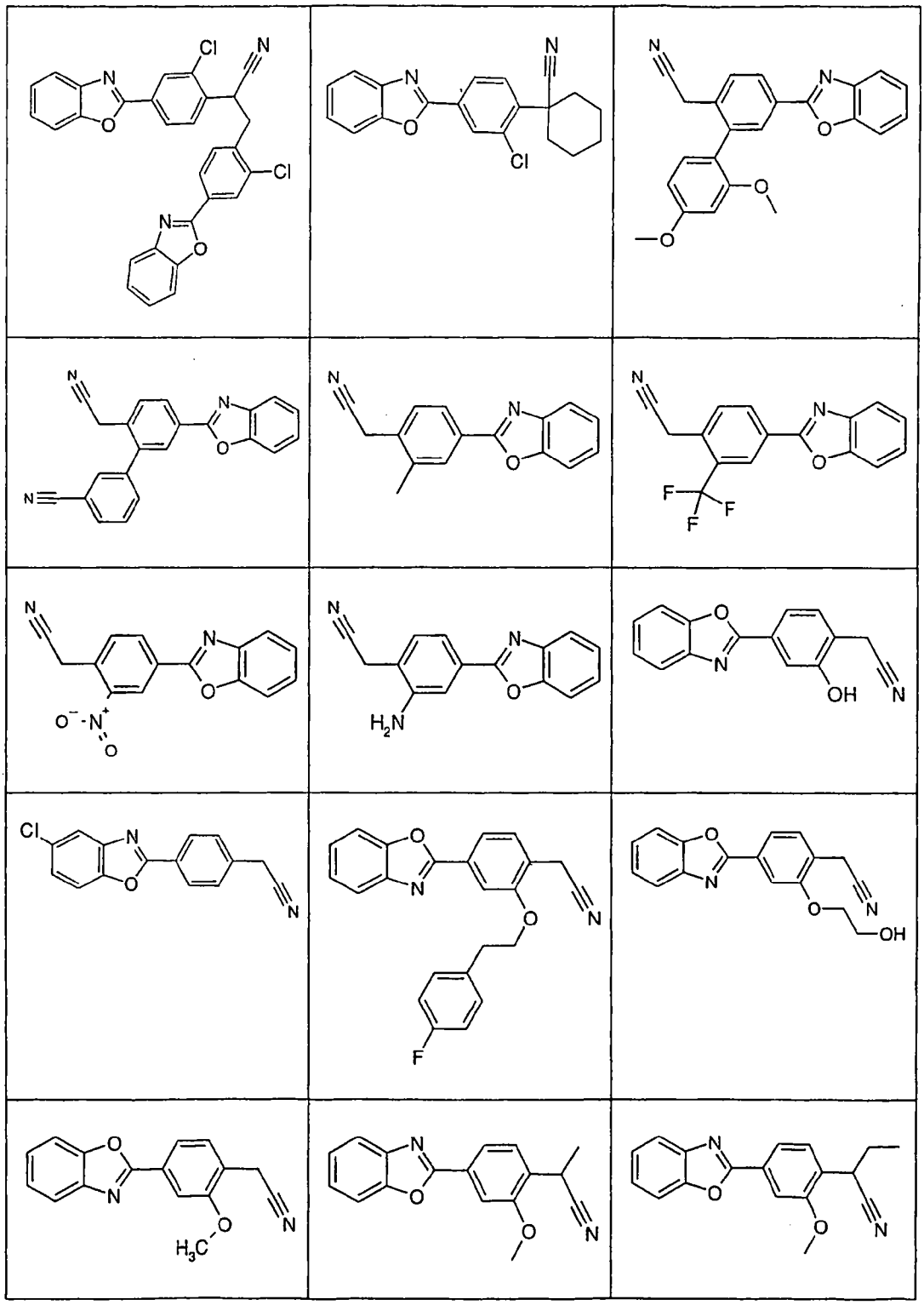
Z^1, Z^2, Z^3, and Z^4 are CH_2.

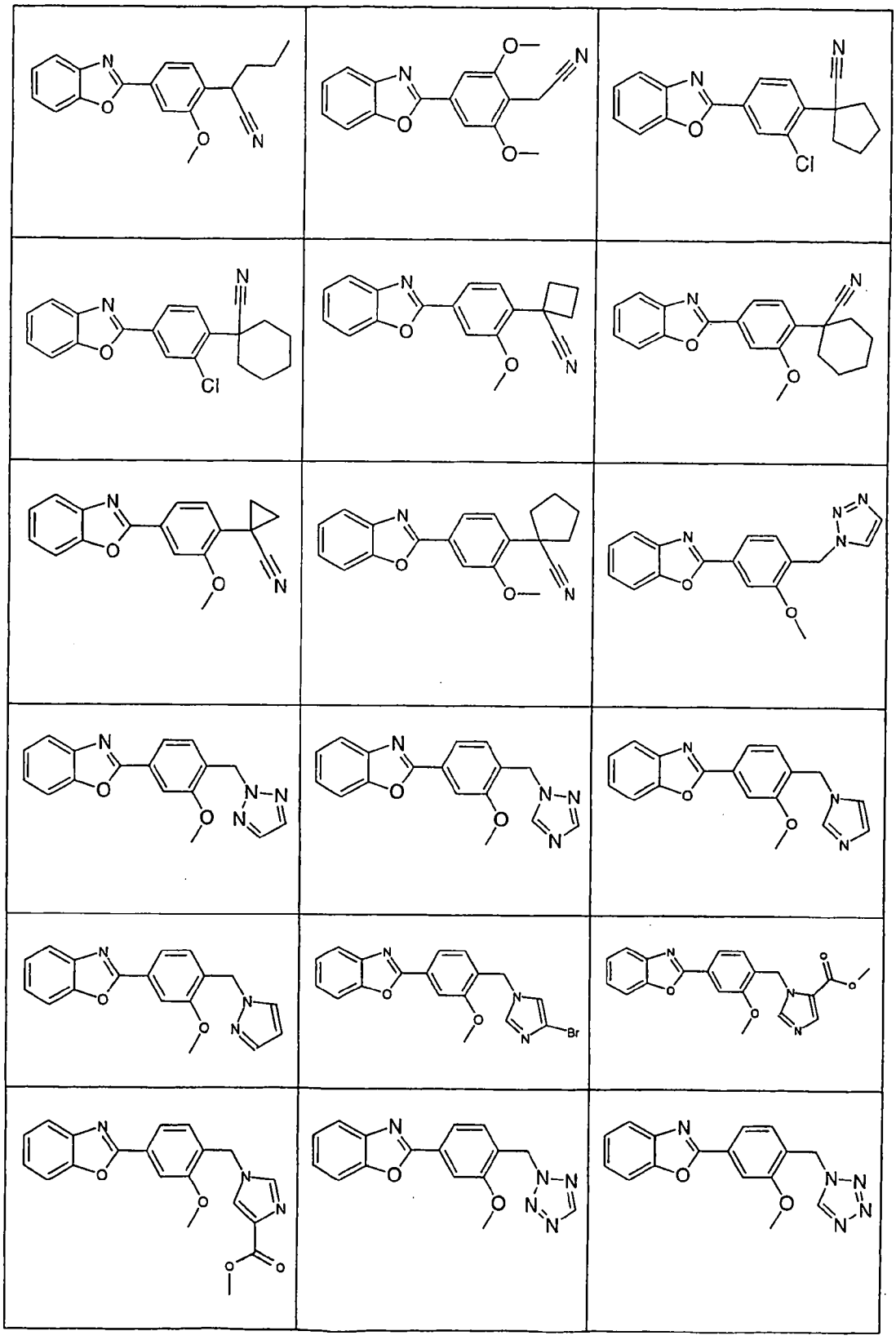
22. The compound according to Claim 21, or a pharmaceutically acceptable salt thereof, wherein;

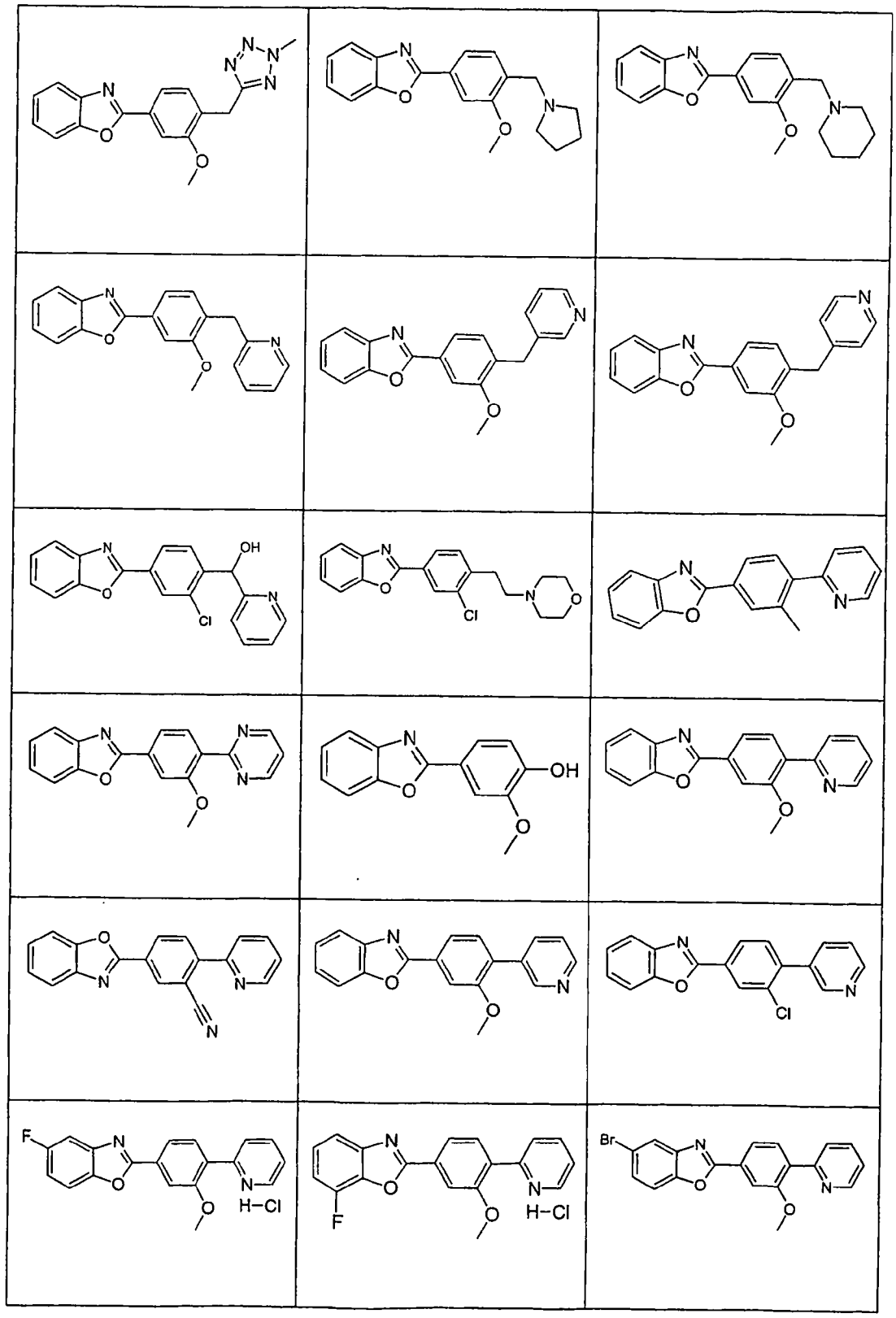
R^1 is $-C_{1-6}$alkyl optionally substituted with 1-5 substituents; wherein each substituent is independently halogen, –OH, –CN, $-C_{1-6}$alkyl, $-C_{1-4}$alkoxyl, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-C_{0-4}$alkyl–C(O)–O–C_{0-4}alkyl, $-C_{0-4}$alkyl–morpholinyl, or $-C_{0-4}$alkyl–benzoxazolyl.

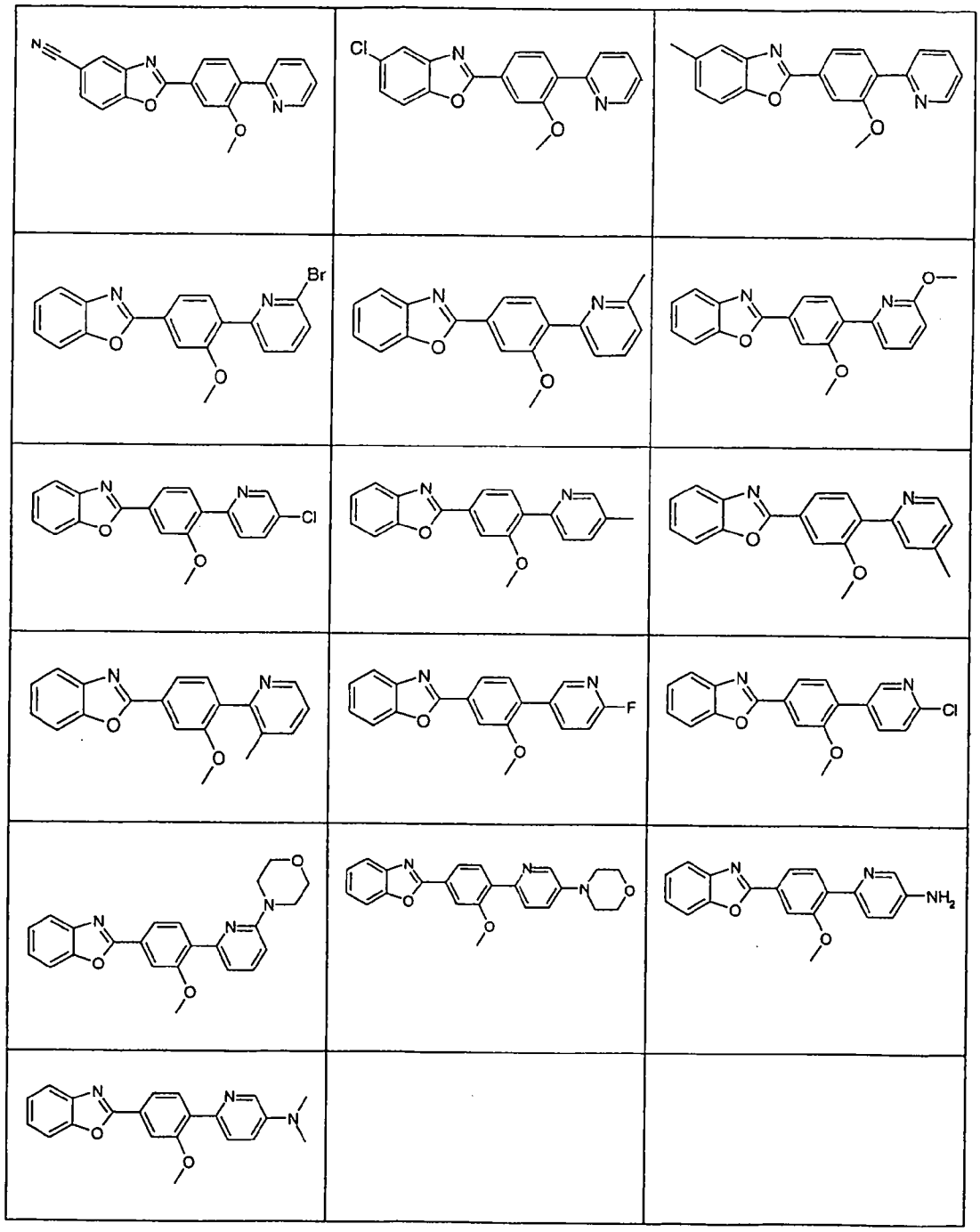
23. The compound according to Claim 1, represented by





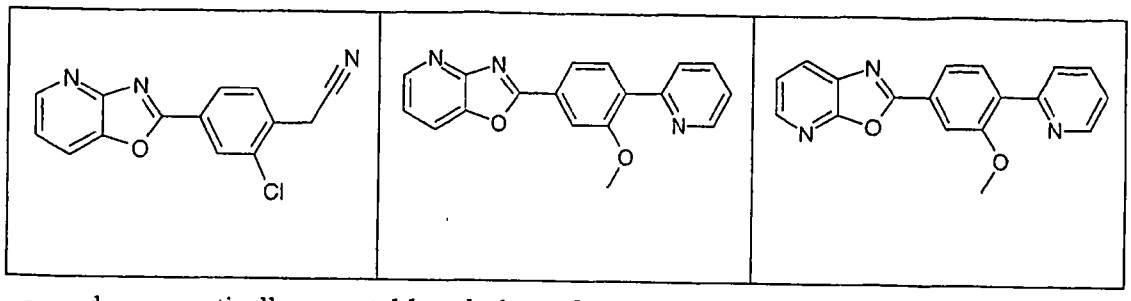






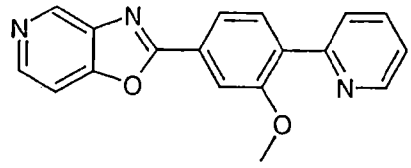
or a pharmaceutically acceptable salt thereof.

24. The compound according to Claim 1 represented by



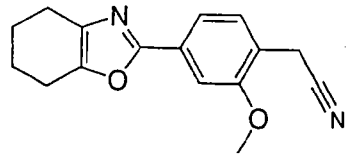
or a pharmaceutically acceptable salt thereof.

25. The compound according to Claim 1 represented by



or a pharmaceutically acceptable salt thereof.

26. The compound according to Claim 1 represented by



or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising a therapeutically effective amount of

the compound according to claim 1 or a pharmaceutically acceptable salt thereof; and

a pharmaceutically acceptable carrier.

28. The pharmaceutical composition according to claim 27, further comprising i) an opiate agonist, ii) an opiate antagonist, iii) a calcium channel antagonist, iv) a 5HT receptor agonist, v) a 5HT receptor antagonist, vi) a sodium channel antagonist, vii) an NMDA receptor agonist, viii) an NMDA receptor antagonist, ix) a COX-2 selective inhibitor, x) an NK1 antagonist, xi) a non-steroidal

anti-inflammatory drug, xii) a GABA-A receptor modulator, xiii) a dopamine agonist, xiv) a dopamine antagonist, xv) a selective serotonin reuptake inhibitor, xvi) a tricyclic antidepressant drug, xvii) a norepinephrine modulator, xviii) L-DOPA, xix) buspirone, xx) a lithium salt, xxi) valproate, xxii) neurontin, xxiii) olanzapine, xxiv) a nicotinic agonist, xxv) a nicotinic antagonist, xxvi) a muscarinic agonist, xxvii) a muscarinic antagonist, xxviii) a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), xxix) a heroin substituting drug, xxx) disulfiram, or xxxi) acamprosate.

29. The pharmaceutical composition according to claim 28, wherein said heroin substituting drug is methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone.

30. A method of treatment or prevention of pain comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

31. A method of treatment or prevention of a pain disorder wherein said pain disorder is acute pain, persistent pain, chronic pain, inflammatory pain, or neuropathic pain, comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

32. A method of treatment or prevention of anxiety, depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia or panic comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

33. A method of treatment or prevention of disorders of extrapyramidal motor function comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

34. The method of claim 16 wherein said disorder of extrapyramidal motor function is Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, or tardive dyskinesia.

35. A method of treatment or prevention of anxiety disorders comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

36. The method of claim 35 wherein said anxiety disorder is panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder, or nonspecified anxiety disorder.

37. A method of treatment or prevention of neuropathic pain comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

38. A method of treatment or prevention of Parkinson's Disease comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

39. A method of treatment or prevention of depression comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

40. A method of treatment or prevention of epilepsy comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

41. A method of treatment or prevention of inflammatory pain comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

42. A method of treatment or prevention of cognitive dysfunction comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

43. A method of treatment or prevention of drug addiction, drug abuse and drug withdrawal comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

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Merck & Co., Inc.

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON