The compounds of the present invention may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment, or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bees wax, mineral oil, diluents such as water and alcohol, and emulsifiers, and stabilizers. Topical formulations may contain a concentration of the formula I or its pharmaceutical salt from about 0.1 to about 10% w/v (weight per unit volume).

The compounds of formula I are potentiators of metabotropic glutamate (mGlu) receptor function, in particular they are potentiators of mGlu2 receptors. That is the compounds of formula I increase mGlu2 receptor response to glutamate or a glutamate agonist, enhancing the function of the receptors. The behavior of the potentiators of formula I at mGlu2 receptors is shown in Example A which is suitable to identify potentiators useful for carrying out the present invention. Thus, the potentiators of the present invention are expected to be useful in the treatment of various neurological and psychiatric disorders associated with glutamate dysfunction described to be treated herein and others that can be treated by such potentiators as are appreciated by those skilled in the art.

Example A

Potentiation of Glutamate-Induced Increase in Intracellular Calcium with a mGlu2 Expressing Cell Line.

Cell lines expressing human mGlu2 receptors are derived as previously described (Desai, Burnett, Mayne, Schoepp, *Mol. Pharmacol.* 48, 648-657, 1995) and cultured in DMEM with 5% dialyzed fetal bovine serum, 1 mM glutamine, 1 mM sodium pyruvate, 50 μg/mL Geneticin G418, and 0.2 mg/mL hygromycin B. Confluent cultures are passaged weekly. These cells are referred to as RGT cells for Rat Glutamate Transporter, and have been co-transfected with the glutamate/aspartate transporter GLAST. The RGT cell line expressing the mGlu2 receptors is stably transfected with the promiscuous G-protein, Galpha15 to change the signaling pathway to the mGlu2 receptor to one that could be easily measured through release of intracellular calcium. Thus, intracellular calcium levels are monitored before and after the addition of drugs on a Fluorometric Imaging Plate Reader (i.e. FLIPR, Molecular Devices). The following buffer is used throughout as an assay buffer: 10 mM KCl, 138 mM NaCl, 5 mM $CaCl_2$, 1 mM $MgCl_2$, 4

mM Na H_2PO_4, 10 mM Glucose, 10 mM HEPES, pH 7.4. Cells that had been plated 48 hours prior at a density of 30-40,000 cells per well in a 96-well plate are loaded with a calcium-sensitive dye for 90 minutes at 25 °C. Fluo-3 (2 mM in DMSO, Molecular Probes) are mixed with a equal volume of 10% pluronic acid in DMSO, and diluted to 8 μM into the buffer described above containing 10% fetal bovine serum to make the loading buffer. Following loading of the cells, the loading buffer is removed and replaced with assay buffer prior to drug addition and monitoring on the FLIPR. The resulting signal from the addition of compounds of formula (I) and submaximal concentrations of a glutamate-site agonist (e.g. 1 μM glutamate) is determined by taking the difference of the maximal fluorescent peak height minus the background fluorescence in each well and expressing the results as a percent of the signal seen with a maximal glutamate response (30 μM glutamate, typically about 30-50,000 Relative Fluorescent Units). Least squares curve fitting with a four-parameter equation is then applied to the resulting dose-% response curve to determine the resulting EC_{50} values.

Exemplified compounds of formula I typically affect the potentiation of mGlu2 receptors with EC_{50} values less than 12.5 μM. More specifically, examples 21, 22, 27, and 84 affect the potentiation of mGlu2 receptors with EC_{50} values less than 350 nM.

Compounds of formula I are modulators of leukotriene receptor function, in particular they are antagonists of leukotriene receptors. That is the compounds of formula I antagonize the cysteinyl-leukotriene D4 (LTD4) receptor. The behavior of the antagonism of the cysteinyl-leukotriene D4 (LTD4) receptor by compounds of formula I is shown in Example B which is suitable to identify antagonists useful for carrying out the present invention. Thus, the leukotriene antagonists of the present invention are useful in the treatment of various inflammatory and allergic disorders mediated by leukotrienes and described to be treated herein and other disorders that can be treated by such antagonists as are appreciated by those skilled in the art.

Example B

Antagonism of Cysteinyl-leukotriene D4 (LTD4) –Induced Increase in Intracellular Calcium within a Cysteinyl-Leukotriene 1 (CysLT1) Receptor Expressing Cell Line.

Cell lines expressing the human CysLT1 receptor [AV12-664 (ATCC-9595)] are derived and maintained in culture media: DMEM with 5% dialyzed fetal bovine serum, 1 mM glutamine, and 1 mM sodium pyruvate. Confluent cultures are passaged weekly.

Intracellular calcium levels are monitored in the CysLT1-expressing cells with the addition of LTD4, with or without prior exposure to the compounds being tested as antagonists with a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices). The following buffer is used throughout as an assay buffer: Hanks Buffered Saline Solution without phenol red (GIBCO), with 10 mM HEPES pH 7.4. Cells that had been plated 48 hours prior at a density of 20-25,000 cells per well in a 96-well plate are loaded with a calcium-sensitive dye for 90 minutes at 25 °C. Fluo-3 (2 mM in DMSO, Molecular Probes) is mixed with an equal volume of 10% pluronic acid in DMSO, and diluted to 8 μM in the buffer described above containing 10% fetal bovine serum to make the loading buffer. Following loading of the cells, the buffer is removed and replaced with assay buffer prior to drug addition and monitoring on the FLIPR for several minutes. The resulting signal from the addition of 6 nM LTD4 (provides approximately 90% of the maximal signal with 25 nM LTD4) is determined by taking the difference of the maximal fluorescent peak height minus the background fluorescence in each well and expressing the results as a percent of the signal seen without pretreatment of the test compound(s). Least squares curve fitting with a four-parameter equation is applied to the resulting dose-% inhibition curve to determine the resulting IC_{50} values.

Exemplified compounds of formula I typically affect the antagonism of CysLT1 receptors with IC_{50} values less than 12.5 μM. More specifically, examples 21, 27 and 84 affect the antagonism of CysLT1 receptors with IC_{50} values less than 150 nM.

In one embodiment of the present invention provides methods of treating neurological and psychiatric disorders associated with glutamate dysfunction, comprising administering to a patient in need thereof an effective amount of a potentiator of metabotropic glutamate 2 receptors.

Specifically, the present invention provides a method of treating neurological and psychiatric disorders associated with glutamate dysfunction, comprising administering to a patient in need thereof an effective amount of a potentiator of the mGlu2 receptor and/or antagonist of the CysLT1 receptor, that is, the present invention provides methods using an effective amount of a potentiator of mGlu2 receptors and/or antagonist of the CysLT1 receptor.

In a preferred embodiment the present invention provides a method of treating migraine, comprising administering to a patient in need thereof an effective amount of a compound of formula I.

In another preferred embodiment the present invention provides a method of treating anxiety, comprising administering to a patient in need thereof an effective amount of a compound of formula I.

Particularly preferred anxiety disorders are generalized anxiety disorder, panic disorder, and obsessive compulsive disorder.

In another preferred embodiment the present invention provides a method of treating schizophrenia, comprising administering to a patient in need thereof an effective amount of a compound of formula I.

In yet another preferred embodiment the present invention provides a method of treating epilepsy, comprising administering to a patient in need thereof an effective amount of a compound of formula I.

Because the compounds of formula I enhance the normal physiological function of the mGlu receptors, the compounds of formula I are useful for the treatment of a variety of neurological and psychiatric disorders associated with glutamate dysfunction, including: acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, multiple sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity (including tremors) seizures, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), mood disorders (including depression, mania, bipolar disorders), trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic pain states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep

disorders (including narcolepsy), attention deficit/hyperactivity disorder, and conduct disorder.

At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV™) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool for identifying many of the disorders described herein. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders described herein and that these systems evolve with medical scientific progress.

The compounds of formula I potentiate mGlu receptor response, in particular mGlu2 receptor response, to glutamate and glutamate agonists. Such agonists are easily recognized and some are available in the art. Schoepp, D.D., Jane, D.E., Monn, J.A., *Neuropharmacology* 38: 1431-1476, (1999).

Thus, a more particular embodiment, it is understood that the present invention extends to a method of potentiating the action of a glutamate receptor agonist at the Group II mGlu receptors, comprising administering to a patient in need thereof an effective amount of a mGlu2 potentiator, in particular a compound of formula I, in combination with a potentiated amount of an mGlu receptor agonist. Such a combination may be advantageous in that it may augment the activity and selectivity of mGlu agonist.

As used herein, the term "patient" refers to a warm blooded animal such as a mammal which is afflicted with one or more neurological and psychiatric disorders associated with glutamate dysfunction. It is understood that guinea pigs, dogs, cats, rats, mice, horses, cattle, sheep, and humans, particularly humans, are examples of animals within the scope of the meaning of the term. It is also understood that this invention relates specifically to the potentiation of mammalian metabotropic glutamate receptors.

It is also recognized that one skilled in the art may affect the neurological and psychiatric disorders by treating a patient presently afflicted with the disorders or by prophylactically treating a patient afflicted with the disorders with an effective amount of the compound of formula I. Thus, the terms "treatment" and "treating" are intended to refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the neurological and psychiatric disorders described herein, but does not necessarily indicate a total elimination of all disorder symptoms, and

is intended to include prophylactic treatment of such neurological and psychiatric disorders.

As used herein, the term "effective amount" of a compound of formula I refers to an amount, that is, the dosage which is effective in treating the neurological and psychiatric disorders described herein.

The attending diagnostician, as one skilled in the art, can readily determine an effective amount by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining an effective amount, the dose of a compound of formula I, a number of factors are considered by the attending diagnostician, including, but not limited to: the compound of formula I to be administered; the co-administration of an mGlu agonist, if used; the species of mammal; its size, age, and general health; the specific disorder involved; the degree of involvement or the severity of the disorder; the response of the individual patient; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of other concomitant medication; and other relevant circumstances.

An effective amount of a compound of formula I is expected to vary from about 0.01 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day. Preferred amounts may be determined by one skilled in the art.

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

The attending diagnostician, as one skilled in the art, can readily determine a potentiated amount by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining a potentiated amount, the dose of an mGlu agonist to be administered in combination with a compound of formula I, a number of factors are considered by the attending diagnostician, including, but not limited to: the mGlu agonist selected to be administered, including its potency and selectivity; the compound of formula I to be co-administered; the species of mammal; its size, age, and

general health; the specific disorder involved; the degree of involvement or the severity of the disorder; the response of the individual patient; the modes of administration; the bioavailability characteristics of the preparations administered; the dose regimens selected; the use of other concomitant medication; and other relevant circumstances.

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

Of the neurological and psychiatric disorders associated with glutamate dysfunction which are treated according to the present invention, the treatment of migraine, anxiety, schizophrenia, and epilepsy are particularly preferred. Particularly preferred anxiety disorders are generalized anxiety disorder, panic disorder, and obsessive compulsive disorder.

Thus, in a preferred embodiment the present invention provides a method of treating migraine, comprising administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof.

In one of the available sources of diagnostic tools, *Dorland's Medical Dictionary* (23rd Ed., 1982, W. B. Saunders Company, Philidelphia, PA), migraine is defined as a symptom complex of periodic headaches, usually temporal and unilateral, often with irritability, nausea, vomiting, constipation or diarrhea, and photophobia. As used herein the term "migraine" includes these periodic headaches, both temporal and unilateral, the associated irritability, nausea, vomiting, constipation or diarrhea, photophobia, and other associated symptoms. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders, including migraine, and that these systems evolve with medical scientific progress.

In another preferred embodiment the present invention provides a method of treating anxiety, comprising administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof.

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

A number of preclinical laboratory animal models for migraine and anxiety have been described. One commonly used model of migraine is the dural extravasation model that has been described by Phebus et al., Life Sci., 61(21), 2117-2126 (1997) which can be used to evaluate the present compounds.

Example C

Animal Model of Dural Plasma Protein Extravasation (PPE).

Male Harlan Sprague-Dawley rats (250-350 g) are anesthetized with sodium pentobarbital (65 mg/kg, i.p.) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -2.5 mm. Following a midline sagital scalp incision, two pairs of bilateral holes are drilled through the skull (3.2 mm posterially, 1.8 and 3.8 mm laterally, all coordinates referenced to bregma). Pairs of stainless steel stimulating electrodes, insulated except at the tips (Rhodes Medical Systems, Inc.), are lowered through the holes in both hemispheres to a depth of 9.2 mm.

The femoral vein is exposed and a dose of the test compound is injected intravenously (i.v.) at a dosing volume of 1 mL/kg. Approximately 8 minutes post i.v. injection, a 20 mg/kg dose of Fluorescein isothiocyanate–bovine serum albumin (FITC-BSA) is also injected intravenously. The FITC-BSA functions as a marker for protein extravasation. Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion is stimulated for 5 minutes at a current intensity of 1.0 mA (5 Hz, 5 msec

duration) with a Model S48 Grass Instrument Stimulator with PSIU6 photoelectric isolation unit (Grass-Telefactor).

Alternatively, rats fasted overnight are dosed orally with test compound via gavage at a volume of 2 mL/kg. Approximately 50 minutes later the animals are anesthetized and placed in the stereotaxic frame as described above. Exactly 58 minutes post-p.o. dosing, the animals are dosed with FITC-BSA (20 mg/kg, i.v.). Exactly one hour post-p.o. dosing, the animals are stimulated as described above.

Five minutes following stimulation, the animals are killed by exsanguination with 40 mL of saline. The top of the skull is removed to facilitate the collection of the dural membranes. The membrane samples are removed from both hemispheres, rinsed with water, and spread flat on microscopic slides. Once dried, the tissues are coverslipped with a 70% glycerol/water solution.

A fluorescence microscope (Zeiss) equipped with a grating monochromator and a spectrophotometer is used to quantify the amount of FITC-BSA in each sample. An excitation wavelength of approximately 490 nm is utilized and the emission intensity at 535 nm was determined. The microscope is equipped with a motorized stage and also interfaced with a personal computer. This facilitates the computer-controlled movement of the stage with fluorescence measurements at 25 points (500 mm steps) on each dural sample. The mean and standard deviation of the measurements are determined by the computer.

The extravasation induced by the electrical stimulation of the trigeminal ganglion is an ipsilateral effect (i.e. occurs only on the side of the dura in which the trigeminal ganglion was stimulated). This allows the use of the other (unstimulated) half of the dura as a control. The ratio of the amount of extravasation in the dura from the stimulated side, over the amount of extravasation in the unstimulated side, is calculated. Control animals dosed only with saline, yield a ratio of approximately 2.0. In contrast, a compound which effectively prevented the extravasation in the dura from the stimulated side would yield a ratio of approximately 1.0.

Examples 21, 22, 27 and 84 affect extravasation in the dura with ID_{100} values less than or equal to 0.1 mg/kg p.o.

The fear potentiated startle response model has been extensively used as a model of anxiety and can be used to evaluate the present compounds. Davis, *Psychopharmacol.*,

62, 1 (1979); Davis, *Behav. Neurosci.*, 100, 814 (1986); Davis, *Tr. Pharmacol. Sci.*, 13, 35 (1992).

Example D

Fear Potentiated Startle Paradigm.

Male Sprague-Dawley rats weighing 325-400 g are purchased from Harlan Sprague-Dawley, Inc. (Cumberland, IN) and given a one week acclimation period before testing. Rats are individually housed with food and water ad libitum in an animal room on a 12-hour light/dark cycle with lights on between 6:00 A.M. and 6:00 P.M. The test compound of formula I is prepared in a suspension of 5% ethanol, 0.5% CMC, 0.5% Tween 80 and 99% water. 2*S*-2-amino-2-(1S,2S-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl) propionic acid is prepared in sterile water. Control rats are given the respective vehicle.

The fear potentiated startle paradigm is conducted over three consecutive days. All three days begin with a 5-minute adaptation period before the trial starts. On day one (baseline startle) after the adaptation period, the animal receives 30 trials of 120dB auditory noise. The mean startle amplitude (V_{mean}) is used to assign animals to groups with similar means before conditioning begins. Day two consists of conditioning the animals. Each animal receives 0.5 mA of shock for 500 msec preceded by a 5 second presentation of light which remains on for the duration of the shock. Ten presentations of the light and shock are administered. Day three is the testing trial where drug administration occurs prior to testing. Twenty-four hours after conditioning, startle testing sessions are conducted. Ten trials of acoustic startle (120 dB), non-light paired, are presented at the beginning of the session. This is followed by 20 random trials of the noise alone and 20 random trials of noise preceded by light. Excluding the first 10 trials, the startle response amplitudes for each trial type are averaged for each animal. Data is presented as the difference between light + noise and noise-alone. Differences in startle response amplitudes are analyzed by JMP statistical software using a One-way Anova (analysis of variance, t-test). Group differences are considered to be significant at $p<0.05$.

In another preferred embodiment the present invention provides a method of treating epilepsy, comprising administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof.

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

Various electroshock-induces models has been extensively used as a model of seizure disorders.

Example E

Electroshock-induced seizures.

Application of electrical stimulation by corneal electrodes to mice can induce tonic hindlimb-extensor seizures. Blockade of tonic extensor seizures induced by electroshock is considered predictive for drugs which block seizure propagation and may be effective in preventing various seizures in humans, including epileptic seizures.

Vehicle or a dose of a test drug are administered to groups of 5 to 10 mice each. Thirty minutes later, electroshock (10 mA, 0.2 sec duration) is administered by transcorneal electrodes. The number of mice exhibiting tonic extensor seizures in each group is recorded. The data are reported as the percentage of mice that are protected from seizures.

The chemical nomenclature used in the examples and preparations is derived from one or more standard conventions. The skilled artisan will recognize the technical meaning when names are derived from two or more conventions.

The terms used in the examples and preparations have their normal meanings unless otherwise designated. For example, "°C" refers to degrees Celsius; "N" refers to normal or normality; "M" refers to molar or molarity; "mol" refers to mole or moles; "mmol" refers to millimole or millimoles; "mmol" refers to micromole or micromoles; "kg" refers to kilogram or kilograms; "g" refers to gram or grams; "mg" refers to microgram or micrograms; "mg" refers to milligram or milligrams; "mL" refers to microliter or microliters; "mL" refers milliliter or milliliters; "L" refers to liter or liters; "bp" refers to boiling point; "mp" refers to melting point; "brine" refers to a saturated aqueous sodium chloride solution; "h or hr" refers to hour or hours; "min" refers to minute or minutes; "MS" refers to mass spectrometry; "NMR" refers to nuclear magnetic resonance spectroscopy; "TFA" refers to trifluoroacetic acid; "CH_2Cl_2" or "DCM" refers to dichloromethane; "DCE" refers to dichloroethane; "MeOH" refers to methanol; "NH_4OH" refers to a concentrated aqueous ammonia solution; "HCl" refers to hydrogen chloride; "MTBE" refers to *tert*-butyl methyl ether; "DSC" refers to differential scanning calorimetery; "DMEM" refers to Dulbecco's modified eagle medium. Chemical shifts are give in δ and NMR spectra were obtained in $CDCl_3$, unless otherwise indicated.

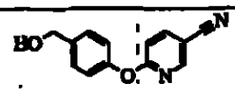
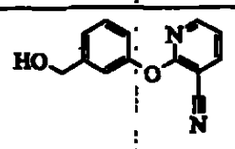
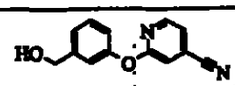
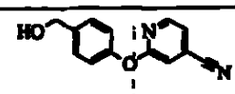
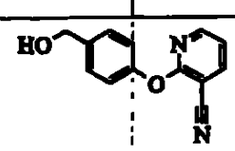
Preparation 1

Synthesis of 6-(3-hydroxymethyl-phenoxy)-nicotinonitrile.

Add 3-hydroxybenzyl alcohol (0.99 g, 7.94 mmol) and potassium carbonate (1.50 g, 10.83 mmol) to 6-chloronicotinitrile (1.00 g, 7.22 mmol) in dimethylacetamide (25 mL) and stir. Heat to 100 °C for 4 hrs. Let cool to ambient temperature and pour into water (100 mL). Extract with diethyl ether (3 x 100 mL). Combine the organic layers and wash with 1N NaOH (2 x 50 mL) and dry over magnesium sulfate. Filter and concentrate under reduced pressure to give the product (1.63 g, 99%): ^{1}H NMR ($CDCl_3$) 8.49 (d, J = 2.2 Hz, 1H), 7.95 (dd, J = 2.2 Hz, 8.7 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.29 (s, 1H), 7.21 (s, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 4.77 (s, 2H).

The following compounds are prepared essentially as described in Preparation 1.

Prep. No.	Chemical name	Structure	Physical data

Prep. No.	Chemical name	Structure	Physical data
2	6-(4-Hydroxymethyl-phenoxy)-nicotinonitrile		^{1}H NMR ($CDCl_3$) 8.49 (d, 2.1 Hz, 1H), 7.96 (d6, J = 2,4 Hz, 8.6 Hz, 1H), 7.49 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.6 Hz, 1H), 4.77 (s, 2H).
3	2-(3-Hydroxymethyl-phenoxy)-nicotinonitrile		^{1}H NMR ($CDCl_3$) 8.33 (dd, J = 2.1 Hz, 4.9 Hz, 1H), 8.04 (dd, J = 1.9 Hz, 7.5 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.24 (s, 1H), 7.16-7.11 (m, 2H), 4.75 (s, 2H).
4	2-(3-Hydroxymethyl-phenoxy)-isonicotinonitrile		^{1}H NMR ($CDCl_3$) 8.35 (d, J = 5.1 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.31-7.27 (m, 1H), 7.24 (d, J = 5.1 Hz, 1H), 7.21-7.18 (m, 2H), 7.09 (d, J = 8.1 Hz, 1H), 4.77 (s, 2H).
5	2-(4-Hydroxymethyl-phenoxy)-isonicotinonitrile		^{1}H NMR ($CDCl_3$) 8.35 (d, J = 5.0 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 5.0 Hz, 1H), 7.20 (s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 4.76 (s, 2H).
6	2-(4-Hydroxymethyl-phenoxy)-nicotinonitrile		^{1}H NMR ($CDCl_3$) 8.35 (dd, J = 2.0 Hz, 5.0 Hz, 1H), 8.05 (dd, J = 2.0 Hz, 7.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.22