(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2007 (22.02.2007)

PCT

(10) International Publication Number
WO 2007/021309 A1

(51) International Patent Classification:

C07D 209/46 (2006.01)	*C07D 413/04* (2006.01)
C07D 401/04 (2006.01)	*C07D 413/14* (2006.01)
C07D 401/06 (2006.01)	*A61K 31/4245* (2006.01)
C07D 401/12 (2006.01)	*A61K 31/4439* (2006.01)
C07D 401/14 (2006.01)	*A61K 31/4035* (2006.01)
C07D 403/06 (2006.01)	*A61K 31/506* (2006.01)
C07D 403/12 (2006.01)	*A61P 25/00* (2006.01)

(21) International Application Number:
PCT/US2006/005247

(22) International Filing Date:
15 February 2006 (15.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/US2005/028760
12 August 2005 (12.08.2005) US

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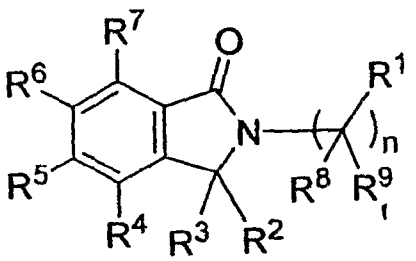
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED ISOINDOLONES AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR POTENTIATORS



(I)

(57) Abstract: The present invention is directed to compounds of formula (I), wherein R^1 is a ring, R^5 is a specified substituent, and n is from 1 to 8. The invention also relates to the use of the compounds in therapy as metabotropic glutamate receptors modulators, particularly in neurological and psychiatric disorders.

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SUBSTITUTED ISOINDOLONES AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR POTENTIATORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is related to PCT Application PCT/US05/28760, filed August 12, 2005, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

The present invention relates to novel compounds that function as potentiators of glutamate receptors, methods for their preparation, pharmaceutical compositions containing them and their use in therapy.

The metabotropic glutamate receptors (mGluR) constitute a family of GTP-binding-protein (G-protein) coupled receptors that are activated by glutamate, and have important roles in synaptic activity in the central nervous system, including neural plasticity, neural development and neurodegeneration.

Activation of mGluRs in intact mammalian neurons elicits one or more of the following responses: activation of phospholipase C; increases in phosphoinositide (PI) hydrolysis; intracellular calcium release; activation of phospholipase D; activation or inhibition of adenyl cyclase; increases or decreases in the formation of cyclic adenosine monophosphate (cAMP); activation of guanylyl cyclase; increases in the formation of cyclic guanosine monophosphate (cGMP); activation of phospholipase A_2; increases in arachidonic acid release; and increases or decreases in the activity of voltage- and ligand-gated ion channels (Schoepp *et al.*, 1993, Trends Pharmacol. Sci., 14:13 ; Schoepp, 1994, Neurochem. Int., 24:439; Pin *et al.*, 1995, Neuropharmacology 34:1; Bordi & Ugolini, 1999, Prog. Neurobiol. 59:55).

Eight mGluR subtypes have been identified, which are divided into three groups based upon primary sequence similarity, signal transduction linkages, and pharmacological profile. Group-I includes mGluR1 and mGluR5, which activate phospholipase C and the generation of an intracellular calcium signal. The Group-II (mGluR2 and mGluR3) and Group-III

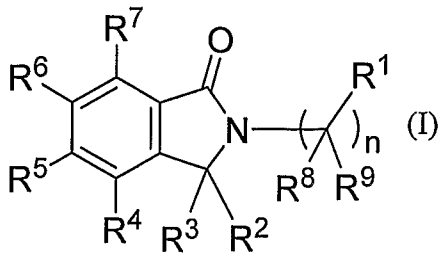
(mGluR4, mGluR6, mGluR7, and mGluR8) mGluRs mediate an inhibition of adenylyl cyclase activity and cyclic AMP levels. For a review, *see* Pin *et al.*, 1999, Eur. J. Pharmacol., 375:277-294.

Activity of mGluR family receptors are implicated in a number of normal processes in the mammalian CNS, and are important targets for compounds for the treatment of a variety of neurological and psychiatric disorders. Activation of mGluRs is required for induction of hippocampal long-term potentiation and cerebellar long-term depression (Bashir *et al.*, 1993, Nature, 363:347 ; Bortolotto *et al.*, 1994, Nature, 368:740 ; Aiba *et al.*, 1994, Cell, 79:365 ; Aiba *et al.*, 1994, Cell, 79:377). A role for mGluR activation in nociception and analgesia also has been demonstrated (Meller *et al.*, 1993, Neuroreport, 4: 879; Bordi & Ugolini, 1999, Brain Res., 871:223). In addition, mGluR activation has been suggested to play a modulatory role in a variety of other normal processes including synaptic transmission, neuronal development, apoptotic neuronal death, synaptic plasticity, spatial learning, olfactory memory, central control of cardiac activity, waking, motor control and control of the vestibulo-ocular reflex (Nakanishi, 1994, Neuron, 13:1031; Pin *et al.*, 1995, Neuropharmacology, *supra*; Knopfel *et al.*, 1995, J. Med. Chem., 38:1417).

Recent advances in the elucidation of the neurophysiological roles of mGluRs have established these receptors as promising drug targets in the therapy of acute and chronic neurological and psychiatric disorders and chronic and acute pain disorders. Because of the physiological and pathophysiological significance of the mGluRs, there is a need for new drugs and compounds that can modulate mGluR function.

SUMMARY OF THE INVENTION

We have identified a class of compounds that modulate mGluR function. In one aspect the invention provides compounds of formula I,



(I)

wherein:

R^1 is a 3- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of N, O and S, wherein said ring may be substituted by one or more A;

R^2 and R^3 are independently selected from the group consisting of H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, heterocycloalkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-aryl, C_{1-6}-alkyl-heteroaryl, C_{1-6}-alkyl-heterocycloalkyl, and C_{1-6}-alkyl-C_{3-8}-cycloalkyl, wherein R^2 and R^3 may be substituted by one or more A;

R^4 and R^6 are independently selected from the group consisting of H, hydroxy, F, Cl, Br, I, nitro, cyano, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, aryl, C_{1-6}-alkylaryl, OC_{0-6}-alkylaryl, $(CO)R^{10}$, $O(CO)R^{10}$, $O(CO)OR^{10}$, $C(O)OR^{10}$, $O(CNR^{10})OR^{11}$, C_{1-6}-alkylOR^{10}, OC_{2-6}-alkylOR^{10}, C_{1-6}-alkyl$(CO)R^{10}$, OC_{1-6}-alkyl$(CO)R^{10}$, C_{0-6}-alkylCO_2R^{10}, OC_{1-6}-alkylCO_2R^{10}, C_{1-6}-alkylcyano, OC_{2-6}-alkylcyano, C_{0-6}-alkyl$NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}R^{11}$, C_{1-6}-alkyl$(CO)NR^{10}R^{11}$, OC_{1-6}-alkyl$(CO)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)R^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)NR^{10}R^{11}$, C_{0-6}-alkylSR^{10}, OC_{2-6}-alkylSR^{10}, C_{0-6}-alkyl$(SO)R^{10}$, OC_{2-6}-alkyl$(SO)R^{10}$, C_{0-6}-alkylSO_2R^{10}, OC_{2-6}-alkylSO_2R^{10}, C_{0-6}-alkyl$(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$(SO_2)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)R^{11}$, OC_{2-6}-alkyl$NR^{10}(SO_2)R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, $(CO)NR^{10}R^{11}$, $O(CO)NR^{10}R^{11}$, $NR^{10}OR^{11}$, C_{0-6}-alkyl$NR^{10}(CO)OR^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)OR^{11}$, SO_3R^{10} and a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of N, O and S, wherein R^4 and R^6 may be substituted by one or more A, and wherein any cycloalkyl or aryl is optionally

fused to a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of C, N, O and S;

R^5 is selected from the group consisting of CN, OC_{0-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, C_{0-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{0-6}-alkylheteroaryl, OC_{0-6}-alkylheteroaryl, heterocycloalkyl, C_{1-6}-alkylheterocycloalkyl, OC_{0-6}-alkylheterocycloalkyl and $C(O)R_{10}$, wherein any cyclic moiety is substituted by one or more B;

R^7 is selected from the group consisting of H, F, Cl, Br, I, nitro, cyano, OC_{1-4}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, and C_{3-8}-cycloalkyl;

R^8 and R^9 are independently selected from the group consisting of H, F, Cl, Br, I, nitro, cyano, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, and OC_{2-6}-alkynyl,
or, where n is greater than 1,
two or more R^8 and/or R^9 on adjacent carbon atoms may be absent to form an alkenyl or alkynyl moiety;

R^{10} and R^{11} are independently selected from the group consisting of H, hydroxy, oxo, F, Cl, Br, I, nitro, cyano, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, aryl, C_{1-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{0-6}-alkyl-heterocycloalkyl, OC_{1-6}-alkyl-heterocycloalkyl, heteroaryl, C_{1-6}alkylheteroaryl, heterocycloalkyl-C_{1-6}-alkylaryl and heterocycloalkyl-C_{1-6}-alkylheteroaryl, wherein any cyclic moiety is optionally fused to a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of C, N, O and S and any cyclic moiety is optionally substituted with a substituent selected from alkyl, halo, hydroxyl, Oalkyl, haloalkyl and Ohaloalkyl;

A is selected from the group consisting of H, hydroxy, F, Cl, Br, I, nitro, cyano, oxo, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, aryl, C_{1-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{1-6}-alkyl-heterocyclyl, C_{1-6}-alkyl-heterocycloalkyl, OC_{0-6}-alkyl-heterocycloalkyl, $(CO)R^{10}$, $O(CO)R^{10}$, $O(CO)OR^{10}$, $O(CNR^{10})OR^{11}$, C_{1-6}-alkylOR^{10}, OC_{2-6}-alkylOR^{10}, C_{1-6}-alkyl$(CO)R^{10}$, OC_{1-6}-alkyl$(CO)R^{10}$, C_{0-6}-alkylCO_2R^{10}, OC_{1-6}-alkylCO_2R^{10}, C_{1-6}-alkylcyano, OC_{2-6}-alkylcyano, C_{0-6}-alkyl$NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}R^{11}$, C_{0-6}-alkyl$(CO)NR^{10}R^{11}$, OC_{1-6}-alkyl$(CO)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)R^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)NR^{10}R^{11}$, C_{0-6}-alkylSR^{10}, OC_{2-6}-alkylSR^{10}, C_{0-6}-alkyl$(SO)R^{10}$, OC_{2-6}-alkyl$(SO)R^{10}$, C_{1-6}-alkylSO_2R^{10}, OC_{2-6}-alkylSO_2R^{10}, C_{0-6}-alkyl$(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$(SO_2)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)R^{11}$, OC_{2-6}-alkyl$NR^{10}(SO_2)R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, $(CO)NR^{10}R^{11}$, $O(CO)NR^{10}R^{11}$, $NR^{10}OR^{11}$, C_{0-6}-alkyl$NR^{10}(CO)OR^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)OR^{11}$, SO_3R^{10} and a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of N, O and S, wherein said 5- to 7-membered ring is optionally substituted by one or more of R^{10} and R^{11};

B is selected from the group consisting of C_{0-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, C_{0-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{1-6}-alkylheterocycloalkyl, OC_{0-6}-alkylheterocycloalkyl, C_{1-6}-alkylheteroaryl and OC_{1-6}-alkylheteroaryl, wherein any cyclic moiety is substituted with at least one substituent selected from the group consisting of halo, alkyl, alkylhalo, alkoxy, oxo, COR, CO_2R, SO_2R and CN;

R is selected from the group consisting of H and alkyl;

and

n is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

or a pharmaceutically acceptable salt, hydrate, solvate, optical isomer, or combination thereof.

The invention also provides processes for the preparation of compounds of formula I.

The invention further provides a pharmaceutical composition comprising a compound according to formula I together with a pharmaceutically acceptable carrier or excipient; in another aspect the invention provides a method for the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction in an animal in need of such treatment. The method comprises the step of administering to the animal a therapeutically effective amount of a compound of formula I or a pharmaceutical composition thereof.

The invention also provides for the use of a compound according to formula I, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of any of the conditions discussed herein. Further, the invention provides a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is based upon the discovery of compounds that exhibit activity as pharmaceuticals, in particular as modulators of metabotropic glutamate receptors. More particularly, the compounds of the present invention exhibit activity as potentiators of the mGluR2 receptor, and are useful in therapy, in particular for the treatment of neurological and psychiatric disorders associated with glutamate dysfunction.

Definitions

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry*, Sections A, B, C, D, E, F, and H, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures. Optionally, a name of a compound may be generated using a

chemical naming program: ACD/ChemSketch, Version 5.09/September 2001, Advanced Chemistry Development, Inc., Toronto, Canada.

The term "alkyl" as used herein means a straight- or branched-chain hydrocarbon radical having, for example, from one to six carbon atoms, and includes methyl, ethyl, propyl, isopropyl, t-butyl and the like.

The term "alkenyl" as used herein means a straight- or branched-chain alkenyl radical having, for example, from two to six carbon atoms, and includes ethenyl, 1-propenyl, 1-butenyl and the like.

The term "alkynyl" as used herein means a straight- or branched-chain alkynyl radical having, for example, from two to six carbon atoms, and includes 1-propynyl (propargyl), 1-butynyl and the like.

The term "cycloalkyl" as used herein means a cyclic group (which may be unsaturated) having, for example, from three to seven carbon atoms, and includes cyclopropyl, cyclohexyl, cyclohexenyl and the like.

The term "heterocycloalkyl" as used herein means, for example, a three- to seven-membered cyclic group (which may be unsaturated) having at least one heteroatom selected from the group consisting of N, S and O, and includes piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl and the like.

The term "alkoxy" as used herein means a straight- or branched-chain alkoxy radical having, for example, from one to six carbon atoms and includes methoxy, ethoxy, propyloxy, isopropyloxy, *t*-butoxy and the like.

The term "halo" as used herein means halogen and includes fluoro, chloro, bromo, iodo and the like, in both radioactive and non-radioactive forms.

The term "aryl" as used herein means an aromatic group having, for example, five to twelve atoms, and includes phenyl, naphthyl and the like.

The term "heteroaryl" means an aromatic group which includes at least one heteroatom selected from the group consisting of N, S and O, and includes groups and includes pyridyl, indolyl, furyl, benzofuryl, thienyl, benzothienyl, quinolyl, oxazolyl and the like.

The term "alkanoyl" as used herein means a straight- or branched-chain alkanoyl radical having, for example, from two to seven atoms, and includes acetyl, propionyl, butyryl and the like.

The term "cycloalkenyl" as used herein means an unsaturated cylcloaklyl group having, for example, from four to seven carbon atoms, and includes cyclopent-1-enyl, cyclohex-1-enyl and the like.

The terms "alkylaryl", "alkylheteroaryl " and "alkylcycloalkyl " refer to an alkyl radical substituted with an aryl, heteroaryl or cycloalkyl group, and includes 2-phenethyl, 3-cyclohexyl propyl and the like.

The term "5- to 7-membered ring that may contain one or more heteroatoms independently selected from N, O and S" includes aromatic and heteroaromatic rings, as well as carbocyclic and heterocyclic rings which may be saturated or unsaturated, and includes furyl, isoxazolyl, oxazolyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolyl, triazolyl, morpholinyl, piperazinyl, piperidinyl, homopiperidinyl, tetrahydropyranyl, phenyl, cyclohexyl, cycloheptyl, cyclopentyl, cyclohexanyl and the like.

The term "pharmaceutically acceptable salt" means either an acid addition salt or a basic addition salt which is compatible with the treatment of patients.

A "pharmaceutically acceptable acid addition salt" is any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formula I or any of its intermediates.

Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di- and tricarboxylic acids. Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid and other sulfonic acids such as methanesulfonic acid and 2-hydroxyethanesulfonic acid. Either the mono- or di-acid salts can be formed, and such salts can exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of these compounds are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection criteria for the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts e.g. oxalates may be used for example in the isolation of compounds of Formula I for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

A "pharmaceutically acceptable basic addition salt" is any non-toxic organic or inorganic base addition salt of the acid compounds represented by Formula I or any of its intermediates. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium or barium hydroxides. Illustrative organic bases which form suitable salts include aliphatic, alicyclic or aromatic organic amines such as methylamine, trimethyl amine and picoline or ammonia. The selection of the appropriate salt may be important so that an ester functionality, if any, elsewhere in the molecule is not hydrolyzed. The selection criteria for the appropriate salt will be known to one skilled in the art.

"Solvate" means a compound of Formula I or the pharmaceutically acceptable salt of a compound of Formula I wherein molecules of a suitable solvent are incorporated in a crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered as the solvate. Examples of suitable solvents are ethanol, water and the like. When water is the solvent, the molecule is referred to as a hydrate.

The term "stereoisomers" is a general term for all isomers of the individual molecules that differ only in the orientation of their atoms in space. It includes mirror image isomers (enantiomers), geometric (cis/trans) isomers and isomers of compounds with more than one chiral centre that are not mirror images of one another (diastereomers).

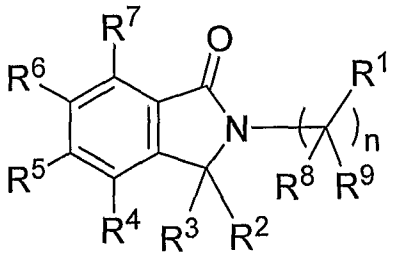
The term "treat" or "treating" means to alleviate symptoms, eliminate the causation of the symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder or condition.

The term "therapeutically effective amount" means an amount of the compound which is effective in treating the named disorder or condition.

The term "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant or other material which is mixed with the active ingredient in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the patient. One example of such a carrier is a pharmaceutically acceptable oil typically used for parenteral administration.

Compounds

Compounds of the invention conform generally to formula I:



(I)

wherein:

R^1 is a 3- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of N, O and S, wherein said ring may be substituted by one or more A;

R^2 and R^3 are independently selected from the group consisting of H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, heterocycloalkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-aryl, C_{1-6}-alkyl-heteroaryl, C_{1-6}-alkyl-heterocycloalkyl, and C_{1-6}-alkyl-C_{3-8}-cycloalkyl, wherein R^2 and R^3 may be substituted by one or more A;

R^4 and R^6 are independently selected from the group consisting of H, hydroxy, F, Cl, Br, I, nitro, cyano, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, aryl, C_{1-6}-alkylaryl, OC_{0-6}-alkylaryl, $(CO)R^{10}$, $O(CO)R^{10}$, $O(CO)OR^{10}$, $C(O)OR^{10}$, $O(CNR^{10})OR^{11}$, C_{1-6}-alkylOR^{10}, OC_{2-6}-alkylOR^{10}, C_{1-6}-alkyl$(CO)R^{10}$, OC_{1-6}-alkyl$(CO)R^{10}$, C_{0-6}-alkylCO_2R^{10}, OC_{1-6}-alkylCO_2R^{10}, C_{1-6}-alkylcyano, OC_{2-6}-alkylcyano, C_{0-6}-alkyl$NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}R^{11}$, C_{1-6}-alkyl$(CO)NR^{10}R^{11}$, OC_{1-6}-alkyl$(CO)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)R^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)NR^{10}R^{11}$, C_{0-6}-alkylSR^{10}, OC_{2-6}-alkylSR^{10}, C_{0-6}-alkyl$(SO)R^{10}$, OC_{2-6}-alkyl$(SO)R^{10}$, C_{0-6}-alkylSO_2R^{10}, OC_{2-6}-alkylSO_2R^{10}, C_{0-6}-alkyl$(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$(SO_2)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)R^{11}$, OC_{2-6}-alkyl$NR^{10}(SO_2)R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, $(CO)NR^{10}R^{11}$, $O(CO)NR^{10}R^{11}$, $NR^{10}OR^{11}$, C_{0-6}-alkyl$NR^{10}(CO)OR^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)OR^{11}$, SO_3R^{10} and a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of N, O and S, wherein R^4 and R^6 may be substituted by one or more A, and wherein any cycloalkyl or aryl is optionally fused to a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of C, N, O and S;

R^5 is selected from the group consisting of CN, OC_{0-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, C_{0-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{0-6}-alkylheteroaryl, OC_{0-6}-alkylheteroaryl, heterocycloalkyl, C_{1-6}-alkylheterocycloalkyl, OC_{0-6}-alkylheterocycloalkyl and $C(O)R_{10}$, wherein any cyclic moiety is substituted by one or more B;

R^7 is selected from the group consisting of H, F, Cl, Br, I, nitro, cyano, OC_{1-4}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, and C_{3-8}-cycloalkyl;

R^8 and R^9 are independently selected from the group consisting of H, F, Cl, Br, I, nitro, cyano, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, and OC_{2-6}-alkynyl,
or, where n is greater than 1,
two or more R^8 and/or R^9 on adjacent carbon atoms may be absent to form an alkenyl or alkynyl moiety;

R^{10} and R^{11} are independently selected from the group consisting of H, hydroxy, oxo, F, Cl, Br, I, nitro, cyano, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, aryl, C_{1-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{0-6}-alkyl-heterocycloalkyl, OC_{1-6}-alkyl-heterocycloalkyl, heteroaryl, C_{1-6}alkylheteroaryl, heterocycloalkyl-C_{1-6}-alkylaryl and heterocycloalkyl-C_{1-6}-alkylheteroaryl, wherein any cyclic moiety is optionally fused to a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of C, N, O and S and any cyclic moiety is optionally substituted with a substituent selected from alkyl, halo, hydroxyl, Oalkyl, haloalkyl and Ohaloalkyl;

A is selected from the group consisting of H, hydroxy, F, Cl, Br, I, nitro, cyano, oxo, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, aryl, C_{1-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{1-6}-alkyl-heterocyclyl, C_{1-6}-alkyl-heterocycloalkyl, OC_{0-6}-alkyl-heterocycloalkyl, $(CO)R^{10}$, $O(CO)R^{10}$, $O(CO)OR^{10}$, $O(CNR^{10})OR^{11}$, C_{1-6}-alkylOR^{10}, OC_{2-6}-alkylOR^{10}, C_{1-6}-alkyl$(CO)R^{10}$, OC_{1-6}-alkyl$(CO)R^{10}$, C_{0-6}-alkylCO_2R^{10}, OC_{1-6}-alkylCO_2R^{10}, C_{1-6}-alkylcyano, OC_{2-6}-alkylcyano, C_{0-6}-alkyl$NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}R^{11}$, C_{0-6}-alkyl$(CO)NR^{10}R^{11}$, OC_{1-6}-alkyl$(CO)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)R^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)NR^{10}R^{11}$, C_{0-6}-alkylSR^{10}, OC_{2-6}-alkylSR^{10}, C_{0-6}-alkyl$(SO)R^{10}$, OC_{2-6}-alkyl$(SO)R^{10}$, C_{1-6}-alkylSO_2R^{10}, OC_{2-6}-alkylSO_2R^{10}, C_{0-6}-

alkyl(SO_2)$NR^{10}R^{11}$, OC_{2-6}-alkyl(SO_2)$NR^{10}R^{11}$, C_{0-6}-alkylNR^{10}(SO_2)R^{11}, OC_{2-6}-alkylNR^{10}(SO_2)R^{11}, C_{0-6}-alkylNR^{10}(SO_2)$NR^{10}R^{11}$, OC_{2-6}-alkylNR^{10}(SO_2)$NR^{10}R^{11}$, (CO)$NR^{10}R^{11}$, O(CO)$NR^{10}R^{11}$, $NR^{10}OR^{11}$, C_{0-6}-alkylNR^{10}(CO)OR^{11}, OC_{2-6}-alkylNR^{10}(CO)OR^{11}, SO_3R^{10} and a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of N, O and S, wherein said 5- to 7-membered ring is optionally substituted by one or more of R^{10} and R^{11};

B is selected from the group consisting of C_{0-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, C_{0-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{1-6}-alkylheterocycloalkyl, OC_{0-6}-alkylheterocycloalkyl, C_{1-6}-alkylheteroaryl and OC_{1-6}-alkylheteroaryl, wherein any cyclic moiety is substituted with at least one substituent selected from the group consisting of halo, alkyl, alkylhalo, alkoxy, oxo, COR, CO_2R, SO_2R and CN;

R is selected from the group consisting of H and alkyl;

and

n is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

or a pharmaceutically acceptable salt, hydrate, solvate, optical isomer, or combination thereof;

with the proviso that the compound is not selected from the group consisting of:
5-(4-Benzyl-piperazine-1-carbonyl)-7-methyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
7-Methyl-5-(4-pyridin-4-ylmethyl-piperazine-1-carbonyl)-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
7-Methyl-5-[4-(2-pyridin-4-yl-ethyl)piperazine-1-carbonyl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
4-{4-[7-Methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile,

2-Benzyl-1-oxo-2,3-dihydro-1H-isoindole-5-carbonitrile,
7-Chloro-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile,
7-Methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile,
7-Methyl-1-oxo-2-(4-chloro-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile,
1-Oxo-2-(4-trifluoromethoxy-benzyl)-7-trifluoromethyl-2,3-dihydro-1H-isoindole-5-carbonitrile,
3-Oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-4,6-dicarbonitrile,
7-Iodo-5-methoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
2-Benzyl-5-methoxy-2,3-dihydro-isoindol-1-one, and
7-Chloro-5-methoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one.

It will be understood by those of skill in the art that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated by those of skill in the art that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of formula I. It will further be understood that the present invention encompasses tautomers of the compounds of formula I.

It will also be understood by those of skill in the art that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of formula I.

Within the scope of the invention are also salts of the compounds of formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention are obtained using standard procedures well known in the art, for example, by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It is also possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

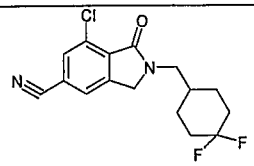
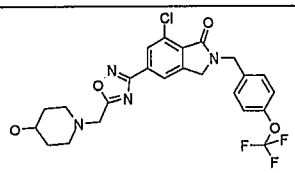
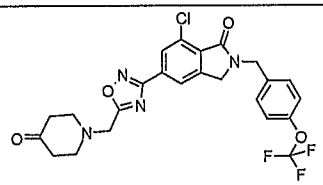
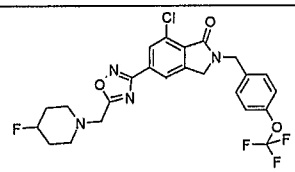
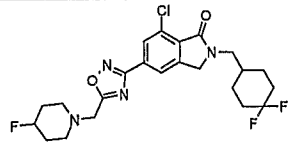
In one embodiment of the present invention, the compound of formula I may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

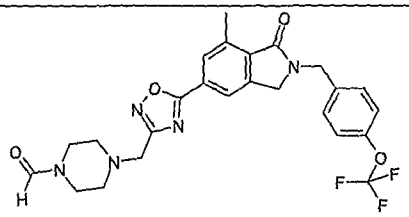
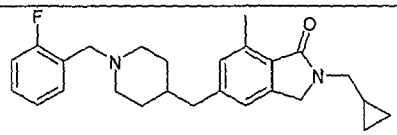
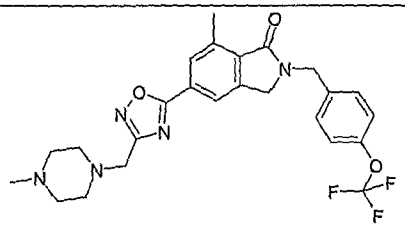
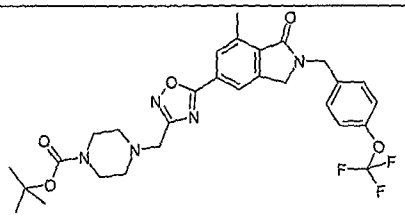
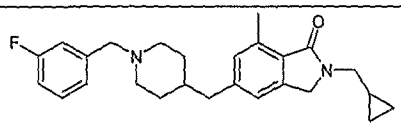
In a particular embodiment of the invention, R^5 is selected from the group consisting of heterocycloalkyl and C_{1-6}alkylheterocycloalkyl.

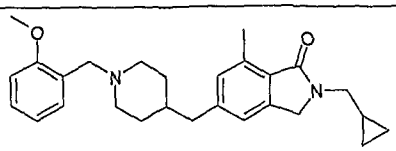
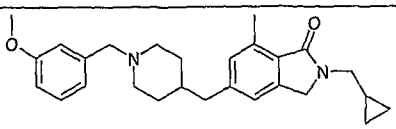
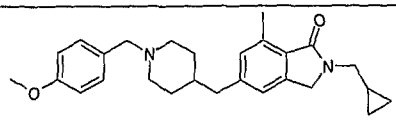
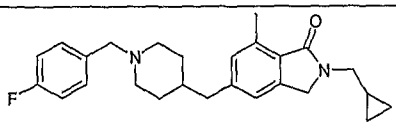
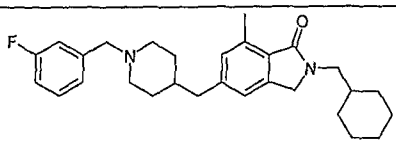
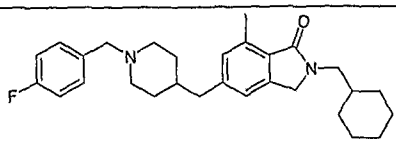
In a particular embodiment of the invention, B is selected from the group consisting of C_{0-6}alkylaryl, C_{1-6}alkylheteroaryl and C_{0-6}alkylheterocycloalkyl.

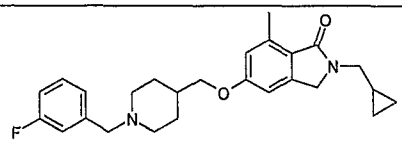
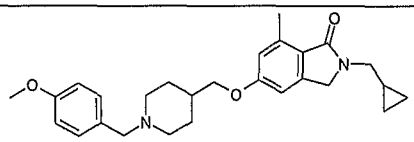
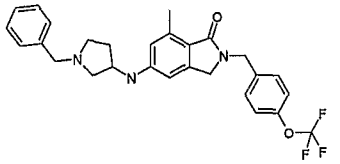
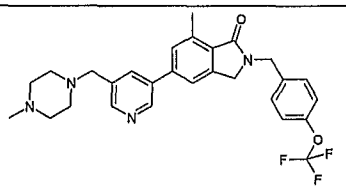
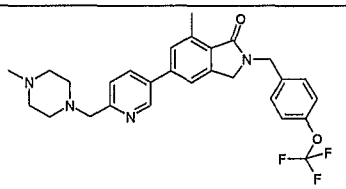
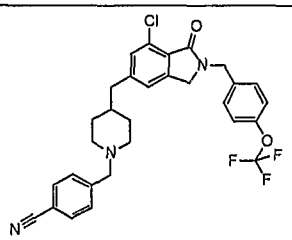
Specific examples of the present invention include the compounds shown in the following table, their pharmaceutically acceptable salts, hydrates, solvates, optical isomers, and combinations thereof:

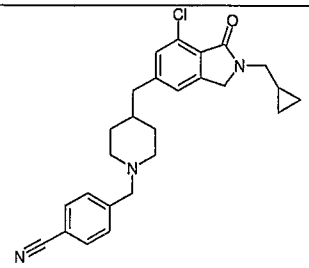
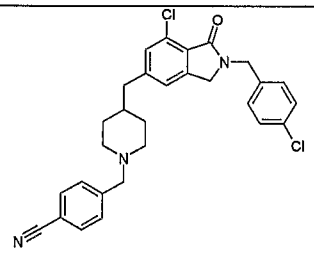
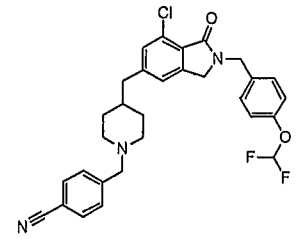
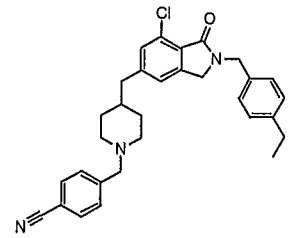
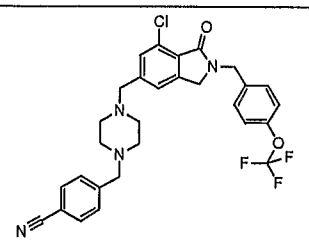
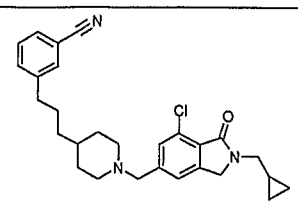
Example No.	Structure	Name

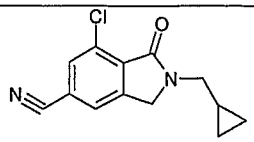
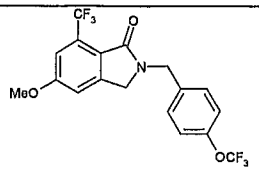
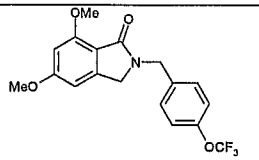
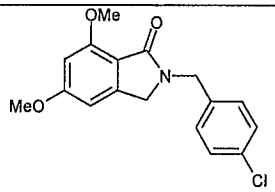
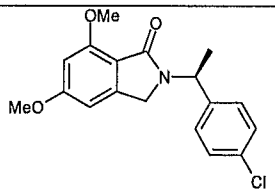
Example No.	Structure	Name
5		7-Chloro-2-[(4,4-difluoro-cyclohexyl) methyl]-1-oxoisoindoline-5-carbonitrile
8.1		7-Chloro-5-[5-(4-hydroxy-piperidin-1-yl methyl)-[1,2,4] oxadiazol-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one
8.2		7-Chloro-5-[5-(4-oxo-piperidin-1-yl methyl)-[1,2,4]oxadiazol-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one
8.3		7-Chloro-5-[5-(4-fluoro-piperidin-1-yl methyl)-[1,2,4] oxadiazol-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one
8.4		7-Chloro-2-(4,4-difluoro-cyclohexyl-methyl)-5-[5-(4-fluoro-piperidin-1-ylmethyl)-[1,2,4]oxadiazol-3-yl]-2,3-dihydro-isoindol-1-one

Example No.	Structure	Name
10.4		4-{5-[7-Methyl-1-oxo-2-(4-trifluoro-methoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-ylmethyl}-piperazine-1-carbaldehyde
11		2-Cyclopropylmethyl-5-[1-(2-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one
12.2		7-Methyl-5-[3-(4-methyl-piperazin-1-ylmethyl)-[1,2,4] oxadiazol-5-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one
12.3		4-{5-[7-Methyl-1-oxo-2-(4-trifluoro-methoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-yl methyl}-piperazine-1-carboxylic acid tert-butyl ester
13.1		2-Cyclopropylmethyl-5-[1-(3-fluoro-benzyl)-piperidin-4-yl methyl]-7-methyl-2,3-dihydro-isoindol-1-one

Example No.	Structure	Name
13.2		2-Cyclopropylmethyl-5-[1-(2-methoxy-benzyl)-piperidin-4-yl methyl]-7-methyl-2,3-dihydro-isoindol-1-one
13.3		2-Cyclopropylmethyl-5-[1-(3-methoxy-benzyl)-piperidin-4-yl methyl]-7-methyl-2,3-dihydro-isoindol-1-one
13.4		2-Cyclopropylmethyl-5-[1-(4-methoxy-benzyl)-piperidin-4-yl methyl]-7-methyl-2,3-dihydro-isoindol-1-one
13.5		2-Cyclopropylmethyl-5-[1-(4-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one
13.6		2-Cyclohexylmethyl-5-[1-(3-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one
13.7		2-Cyclohexylmethyl-5-[1-(4-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one

Example No.	Structure	Name
13.8		2-Cyclopropylmethyl-5-[1-(3-fluoro-benzyl)-piperidin-4-ylmethoxy]-7-methyl-2,3-dihydro-isoindol-1-one
13.9		2-Cyclopropylmethyl-5-[1-(4-methoxybenzyl)-piperidin-4-ylmethoxy]-7-methyl-2,3-dihydro-isoindol-1-one
15		5-(1-Benzyl-pyrrolidin-3-ylamino)-7-methyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one
16.1		7-Methyl-5-[5-(4-methyl-piperazin-1-yl methyl)-pyridin-3-yl] 2-(4-trifluoro methoxy-benzyl)-2,3-dihydro-isoindol-1-one
16.2		7-Methyl-5-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-2-(4-trifluoro methoxy-benzyl)-2,3-dihydro-isoindol-1-one
17.1		4-{4-[7-Chloro-1-oxo-2-(4-trifluoro methoxy-benzyl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile

Example No.	Structure	Name
17.2		4-[4-(7-Chloro-2-cyclopropylmethyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl methyl)-piperidine-1-ylmethyl]-benzonitrile
17.3		4-{4-[7-Chloro-2-(4-chloro-benzyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl methyl]-piperidin-1-ylmethyl}-benzonitrile
17.4		4-{4-[7-Chloro-2-(4-difluoromethoxy-benzyl)-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile
17.5		4-{4-[7-Chloro-2-(4-ethyl-benzyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl methyl]-piperidin-1-ylmethyl}-benzonitrile
18.1		4-{4-[7-Chloro-1-oxo-2-(4-trifluoro methoxy-benzyl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperazin-1-methyl}-nicotinonitrile
18.2		3-{3-[1-(7-Chloro-2-cyclopropylmethyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl methyl)-piperidin-4-yl]-propyl}-benzonitrile

Example No.	Structure	Name
19		7-Chloro-2-cyclopropylmethyl-1-oxo-2,3-dihydro-1H-isoindole-5-carbonitrile
20		5-Fluoro-2-(4-ethyl-benzyl)-7-trifluoro methyl-2,3-dihydro-isoindol-1-one
21		5,7-Dimethoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1one
22		5,7-Dimethoxy-2-(4-chloro-benzyl)-2,3-dihydro-isoindol-1one
23		5,7-Dimethoxy-2-[1-(4-chloro-phenyl)-ethyl]-2,3-dihydro-isoindol-1one

Pharmaceutical Compositions

The compounds of the present invention may be formulated into conventional pharmaceutical composition comprising a compound of formula I, or a pharmaceuetically acceptable salt or solvate thereof, in associaton with a pharmaceutically acceptable carrier or excipient. The pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents. A solid carrier can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers include, but are not limited to, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art. Exemplary compositions intended for oral use may contain one or more coloring, sweetening, flavoring and/or preservative agents.

Depending on the mode of administration, the pharmaceutical composition will include from about 0.05%w (percent by weight) to about 99%w, more particularly, from about 0.10%w to 50%w, of the compound of the invention, all percentages by weight being based on the total weight of the composition.

A therapeutically effective amount for the practice of the present invention can be determined by one of ordinary skill in the art using known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented.

Medical Use

We have discovered that the compounds of the present invention exhibit activity as pharmaceuticals, in particular as modulators of metabotropic glutamate receptors. More particularly, the compounds of the present invention exhibit activity as potentiators of the mGluR2 receptor, and are useful in therapy, in particular for the treatment of neurological and psychiatric disorders associated with glutamate dysfunction in an animal.

More specifically, the neurological and psychiatric disorders include, but are not limited to, disorders such as cerebral deficit subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy,

cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, cerebral deficits secondary to prolonged status epilepticus, 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, social phobia, obsessive compulsive disorder, and post-traumatic stress disorder (PTSD)), mood disorders (including depression, mania, bipolar disorders), circadian rhythm disorders (including jet lag and shift work), 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, inflammatory pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, and conduct disorder.

The invention thus provides a use of any of the compounds according to formula I, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

Additionally, the invention provides a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to formula I or a pharmaceutically acceptable salt or solvate thereof, is administered to a patient in need of such treatment. The invention also provides a compound of formula I or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of the present invention further encompasses the administration of an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or

chronic, or to mitigate a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

In use for therapy in a warm-blooded animal such as a human, the compounds of the present invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints. In preferred embodiments of the invention, the route of administration is oral, intravenous, or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, who determines the individual regimen and dosage level for a particular patient.

As mentioned above, the compounds described herein may be provided or delivered in a form suitable for oral use, for example, in a tablet, lozenge, hard and soft capsule, aqueous solution, oily solution, emulsion, and suspension. Alternatively, the compounds may be formulated into a topical administration, for example, as a cream, ointment, gel, spray, or aqueous solution, oily solution, emulsion or suspension. The compounds described herein also may be provided in a form that is suitable for nasal administration, for example, as a nasal spray, nasal drops, or dry powder. The compounds can be administered to the vagina or rectum in the form of a suppository. The compounds described herein also may be administered parentally, for example, by intravenous, intravesicular, subcutaneous, or intramuscular injection or infusion. The compounds can be administered by insufflation (for example as a finely divided powder). The compounds may also be administered transdermally or sublingually.

In addition to their use in therapeutic medicine, the compounds of formula I, or salts thereof, are useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of mGluR-related activity in

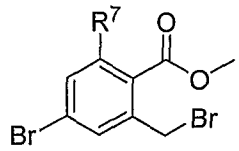
laboratory animals as part of the search for new therapeutics agents. Such animals include, for example, cats, dogs, rabbits, monkeys, rats and mice.

Process for Preparing

Compounds of the present invention can be prepared by various synthetic processes. The selection of a particular process to prepare a given compound is within the purview of the person of skill in the art. The choice of particular structural features and/or substituents may therefore influence the selection of one process over another.

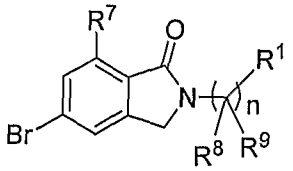
Within these general guidelines, the following processes can be used to prepare exemplary subsets of compounds of this invention. Unless indicated otherwise, the variables described in the following schemes and processes have the same definitions as those given for formula I above.

In one process, for example, a compound of formula Ia:



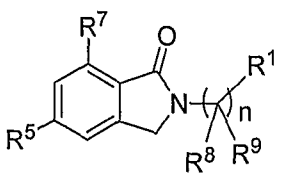
(Ia)

is cyclized in the presence of an amine of the formula $R^1(CR^8CR^9)_nNH_2$ to give a compound of formula Ib:



(Ib).

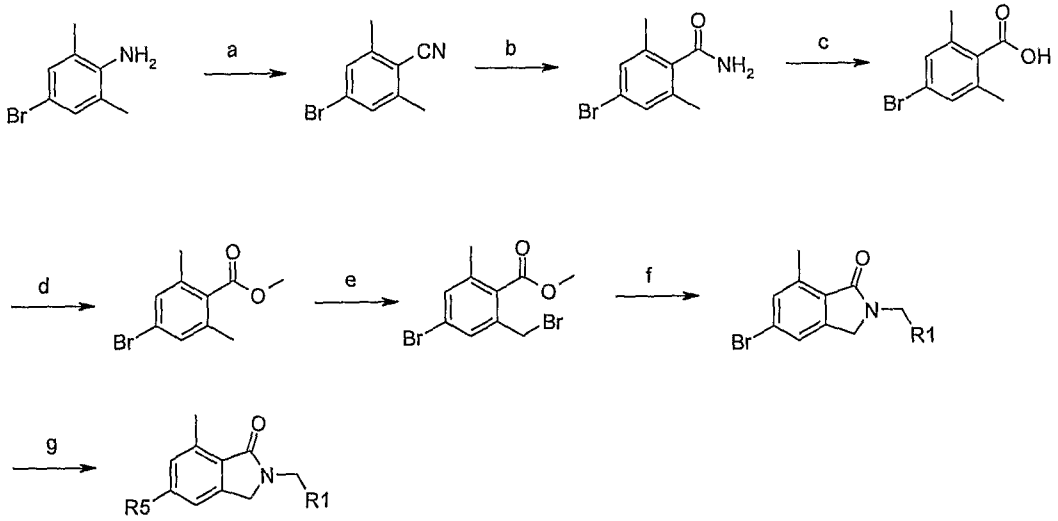
A compound of formula Ib is then cross-coupled with a suitable reagent containing R^5 to yield a a compound according to formula Ic:



(Ic).

In one embodiment of this process, 5-substituted-7-methyl isoindolones are synthesized as depicted in Scheme 1 below. 4-bromo-2,6-dimethylaniline is converted to the corresponding nitrile under Sandmeyer reaction conditions. The nitrile is then hydrolyzed to the acid in a stepwise fashion. The amide can be obtained by basic hydrolysis. The amide is then diazotized and hydrolyzed with nitrososulphuric acid to provide the benzoic acid, which is subsequently protected as the methyl ester using standard conditions. The benzylic methyl group is monobrominated with N-bromosuccinimide using benzoyl peroxide as the radical initiator. This resultant intermediate is cyclized to the isoindolone with the appropriate amine in the presence of a base such as potassium carbonate. Finally, substituent R^5 was introduced at C5 of the isoindolone using typical Buchwald, Suzuki or Stille cross-coupling reaction conditions and reagents.

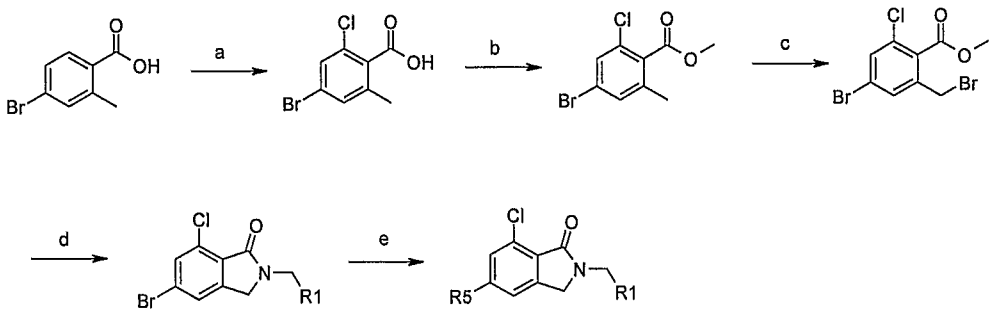
Scheme 1



(a) NaCN, CuCN, HCl; (b) NaOH; (c) nitrososulphuric acid; (d) MeI, K_2CO_3; (e) NBS, $(PhCO_2)_2$; (f) $R1CH_2NH_2$, K_2CO_3; (g) R5H, BINAP, $PdCl_2(dppf)$, NaOtBu OR $R5B(OH)_2$, $PdCl_2(dppf)$, K_2CO_3 OR $R5SnBu_3$, $Pd(PPh_3)_4$

In another embodiment of this process, 5-substituted-7-chloro isoindolones are synthesized as depicted in Scheme 2 below. 4-bromo-2-methylbenzoic acid is chlorinated *ortho* to the acid using *N*-chlorosuccinimide and a palladium catalyst. In the manner analogous to that described above (Scheme 1), this acid was then esterified, brominated, and cyclized to yield the isoindolone intermediate. Substituent R^5 is introduced similarly.

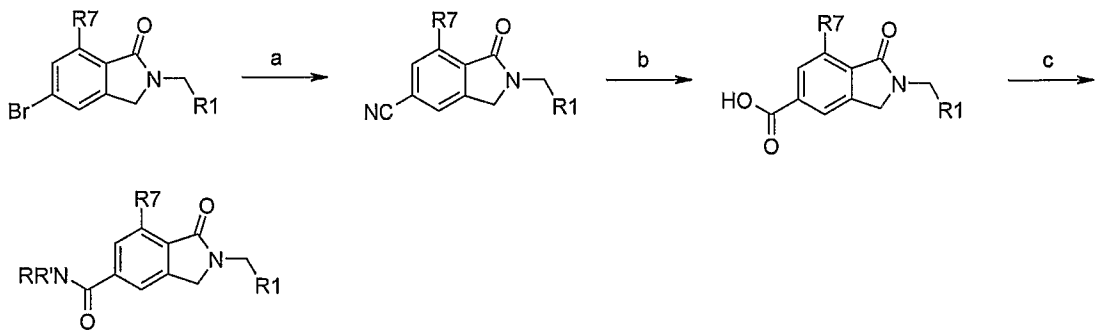
Scheme 2



(a) NCS, $Pd(OAc)_2$; (b) MeI, K_2CO_3; (c) NBS, $(PhCO_2)_2$; (d) $R1CH_2NH_2$, K_2CO_3;
(e) R5H, BINAP, $PdCl_2(dppf)$, NaOtBu OR $R5B(OH)_2$, $PdCl_2(dppf)$, K_2CO_3 OR $R5SnBu_3$, $Pd(PPh_3)_4$

In yet another embodiment of this process, isoindolones that are substituted with an amide at C5 can be prepared as depicted in Scheme 3 below. Thus, an appropriately substituted 5-bromoisoindolone is converted to the corresponding nitrile using zinc cyanide in the presence of a palladium catalyst. The nitrile is then hydrolyzed under basic conditions to provide the benzoic acid, which was then coupled with various amines using methodologies that are well-known in the art to provide the final compounds.

Scheme 3

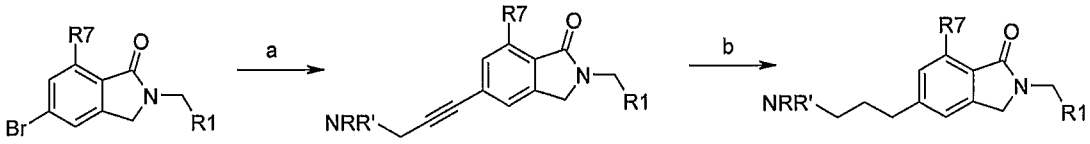


(a) $Zn(CN)_2$, $Pd(PPh_3)_4$; (b) NaOH; (c) RR'NH, EDCI

In still another embodiment, the process as described above can be adapted for the preparation of amino-propargyl and amino-alkyl isoindolones. Thus, suitable 5-bromoisoindolones are first subjected to Sonogashira coupling conditions with various

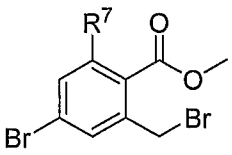
propargyl amines as shown in Scheme 4. The resulting alkyne then can be hydrogenated using routine methodologies to provide the amino-alkyl substituted product. In Scheme 4, R and R' correspond to substituents as defined herein for R^{10} and R^{11}.

Scheme 4



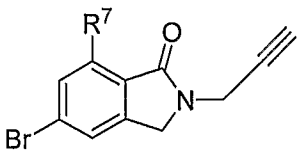
(a) $RR'NCH_2CCH$, CuI, $Pd(PPh_3)_4$, Et_3N; (b) H_2, Pd(C)

Another process according to this invention adapts some of the foregoing synthetic methodology for the preparation of compounds bearing N-propargylic substituents. Thus, a compound of the formula Ia:



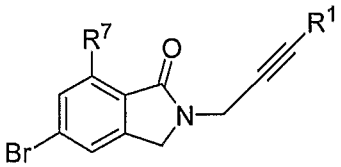
(Ia)

is cyclized in the presence of propargyl amine into a compound of the formula Id:



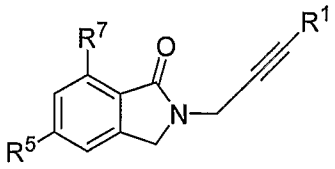
(Id).

Coupling a compound of formula Id with a reagent comprising R^1 gives a compound of formula Ie:



(Ie),

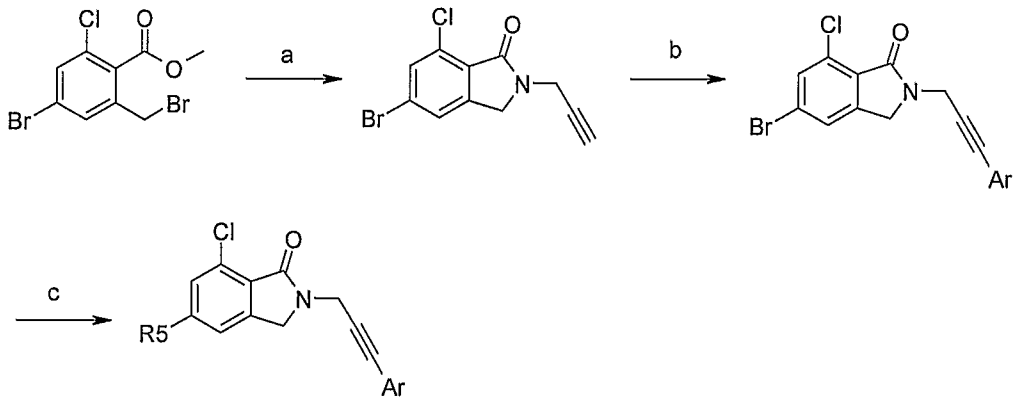
R^1 preferably is an aryl group. A compound of formula Ie is then cross-coupled with a reagent comprising R^5, thereby yielding a compound according to formula If:



(If).

One embodiment of this process is shown in Scheme 5 below. The terminal alkyne is coupled with various aryl groups using standard Sonogashira coupling conditions. Finally, substituent R^5 was introduced at C5 using typical Buchwald, Suzuki or Stille cross-coupling reaction conditions as indicated in Scheme 5.

Scheme 5

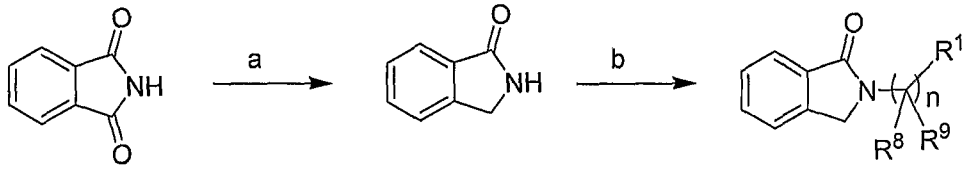


(a) propargyl amine, K_2CO_3; (b) ArI, CuI, $Pd(PPh_3)_4$, Et_3N;
(c) R5H, BINAP, $PdCl_2(dppf)$, NaOtBu OR $R5B(OH)_2$, $PdCl_2(dppf)$, K_2CO_3 OR $R5SnBu_3$, $Pd(PPh_3)_4$

Another process of the invention contemplates the preparation of compounds of formula I that are unsubstituted on the isoindolone aromatic ring. This subset of compounds are be straightforwardly prepared as depicted below in Scheme 6. Thus, phthalimide is reduced, for example with tin under acidic conditions, to provide isoindolinone. This intermediate is alkylated with various electrophiles under basic conditions to provide the desired final

products. In Scheme 6, X can be any suitable leaving group such as, for example, halo, such as bromo and iodo; and tosylate.

Scheme 6



(a) Sn, HCl, AcOH; (b) $R^1(CR^8R^9)_nX$, Cs_2CO_3, 18-crown-6

Many variations of the foregoing processes and additions thereto appear throughout the examples that follow. The person of ordinary skill in the art thus will appreciate that the compounds of this invention can be prepared by following or adapting one or more of the processes disclosed herein.

The invention is further illustrated by way of the following examples, which are intended to elaborate several embodiments of the invention. These examples are not intended to, nor are they to be construed to, limit the scope of the invention. It will be clear that the invention may be practiced otherwise than as particularly described herein. Numerous modifications and variations of the present invention are possible in view of the teachings herein and, therefore, are within the scope of the invention.

General methods

All starting materials are commercially available or earlier described in the literature.

The ^1H and ^{13}C NMR spectra were recorded either on Bruker 300, Bruker DPX400 or Varian +400 spectrometers operating at 300, 400 and 400 MHz for ^1H NMR respectively, using TMS or the residual solvent signal as reference, in deuterated chloroform as solvent unless otherwise indicated. All reported chemical shifts are in ppm on the delta-scale, and the fine splitting of the signals as appearing in the recordings (s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet).

Analytical in line liquid chromatography separations followed by mass spectra detections, were recorded on a Waters LCMS consisting of an Alliance 2795 (LC) and a ZQ single quadropole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source operated in a positive and/or negative ion mode. The ion spray voltage was ±3 kV and the mass spectrometer was scanned from m/z 100-700 at a scan time of 0.8 s. To the column, X-Terra MS, Waters, C8, 2.1 x 50mm, 3.5 mm, was applied a linear gradient from 5 % to 100% acetonitrile in10 mM ammonium acetate (aq.), or in 0.1% TFA (aq.).

Preparative reversed phase chromatography was run on a Gilson autopreparative HPLC with a diode array detector using an XTerra MS C8, 19x300mm, 7mm as column.

Purification by a chromatotron was performed on rotating silica gel / gypsum (Merck, 60 PF-254 with calcium sulphate) coated glass sheets, with coating layer of 1, 2, or 4 mm using a TC Research 7924T chromatotron.

Purification of products were also done using Chem Elut Extraction Columns (Varian, cat #1219-8002), Mega BE-SI (Bond Elut Silica) SPE Columns (Varian, cat # 12256018; 12256026; 12256034), or by flash chromatography in silica-filled glass columns.

Microwave heating was performed in a Smith Synthesizer Single-mode microwave cavity producing continuous irradiation at 2450 MHz (Personal Chemistry AB, Uppsala, Sweden).

The pharmacological properties of the compounds of the invention can be analyzed using standard assays for functional activity. Examples of glutamate receptor assays are well known in the art as described in, for example, Aramori *et al.*, 1992, Neuron, 8:757; Tanabe *et al.*, 1992, Neuron, 8:169; Miller *et al.*, 1995, J. Neuroscience, 15:6103; Balazs, *et al.*, 1997, J. Neurochemistry, 1997,69:151. The methodology described in these publications is incorporated herein by reference. Conveniently, the compounds of the invention can be studied by means of an assay that measures the mobilization of intracellular calcium, $[Ca^{2+}]_i$ in cells expressing mGluR2.

Fluorometric Imaging Plate Reader (FLIPR) analysis was used to detect allosteric activators of mGluR2 via calcium mobilization. A clonal HEK 293 cell line expressing a chimeric mGluR2/CaR construct comprising the extracellular and transmembrane domains of human mGluR2 and the intracellular domain of the human calcium receptor, fused to the promiscuous chimeric protein $G_{\alpha qi5}$ was used. Activation of this construct by agonists or allosteric activators resulted in stimulation of the PLC pathway and the subsequent mobilization of intracellular Ca^{2+} which was measured via FLIPR analysis. At 24-hours prior to analysis, the cells were trypsinized and plated in DMEM at 100,000 cells/well in black sided, clear-bottom, collagen I coated, 96-well plates. The plates were incubated under 5% CO_2 at 37°C overnight. Cells were loaded with 6μM fluo-3 acetoxymethylester (Molecular Probes, Eugene Oregon) for 60 minutes at room temperature. All assays were performed in a buffer containing 126mM NaCl, 5mM KCl, 1mM $MgCl_2$, 1mM $CaCl_2$, 20mM Hepes, 0.06μM DCG-IV (a Group II mGluR selective agonist), supplemented with 1.0mg/ml D-glucose and 1.0mg/ml BSA fraction IV (pH 7.4).

FLIPR experiments were done using a laser setting of 0.8 W and a 0.4 second CCD camera shutter speed. Extracellular fluo-3 was washed off and cells were maintained in 160 μL of buffer and placed in the FLIPR. An addition of test compound (0.01μM to 30μM in duplicate) was made after 10 seconds of baseline fluorescent readings were recorded on FLIPR. Fluorescent signals were then recorded for an additional 75 seconds at which point a second addition of DCG-IV (0.2μM) was made and fluorescent signals were recorded for an additional 65 seconds. Fluorescent signals were measured as the peak height of the response within the sample period. Data was analyzed using Assay Explorer, and EC_{50} and E_{max} values (relative to maximum DCG-IV effect) were calculated using a four parameter logistic equation.

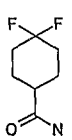
A [^{35}S]-GTPγS binding assay was used to functionally assay mGluR2 receptor activation. The allosteric activator activity of compounds at the human mGluR2 receptor were measured using a [^{35}S]-GTPγS binding assay with membranes prepared from CHO cells which stably express the human mGluR2. The assay is based upon the principle that agonists bind to G-

protein coupled receptors to stimulate GDP-GTP exchange at the G-protein. Since [^{35}S]-GTPγS is a non-hydrolyzable GTP analog, it can be used to provide an index of GDP-GTP exchange and, thus, receptor activation. The GTPγS binding assay therefore provides a quantitative measure of receptor activation.

Membranes were prepared from CHO cells stably transfected with human mGluR2. Membranes (30 μg protein) were incubated with test compound (3nM to 300μM) for 15 minutes at room temperature prior to the addition of 1 μM glutamate, and incubated for 30 min at 30°C in 500 μl assay buffer (20 mM HEPES, 100mM NaCl, 10mM $MgCl_2$), containing 30μM GDP and 0.1nM [^{35}S]-GTPγS (1250 Ci/mmol). Reactions were carried out in triplicate in 2 ml polypropylene 96-well plates. Reactions were terminated by vacuum filtration using a Packard 96-well harvester and Unifilter-96, GF/B filter microplates. The filter plates were washed 4 x 1.5 ml with ice-cold wash buffer (10mM sodium phosphate buffer, pH 7.4). The filter plates were dried and 35 μl of scintillation fluid (Microscint 20) was added to each well. The amount of radioactivity bound was determined by counting plates on the Packard TopCount. Data was analyzed using GraphPad Prism, and EC_{50} and E_{max} values (relative to the maximum glutamate effect) were calculated using non-linear regression.

Generally, the compounds of the present invention were active in assays described herein at concentrations (or with EC_{50} values) less than 10 μM. For example, compounds of Examples 8.3, 10.4, 11 and 13.7 and have EC50 values 75, 230, 84 and 28 nM, respectively.

Example 1: 4,4-Difluorocyclohexanecarboxamide

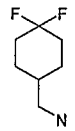


A suspension of ethyl 4,4-difluorocyclohexanecarboxylate (2500mg, 13mmol) in ammonium hydroxide (28%, 50 ml) was stirred at 60 °C overnight. After removal of solvent, the residue was washed with water. The precipitate was obtained as product (white solid, 800 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.31-5.45 (br, 2H), 2.02-2.27 (m, 3H), 1.92-2.02 (m, 2H), 1.72-

1.87 (m, 4H). The mother liquor was acidified with 1N HCl to pH<1. The compound was extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous sodium sulphate, filtered, condensed. 4,4-difluorocyclohexanecarboxylic acid was obtained as a 1200 mg of white solid which was further converted to 4,4-difluorocyclohexanecarboxamide by following procedure.

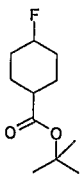
To a solution of 4,4-difluorocyclohexanecarboxylic acid (1.35g, 8.22 mmol) in THF (50 ml), 4-methylmorpholine (831 mg, 8.22 mmol)was added at –70 °C. followed by isobutyl chloridocarbonate (1140 mg, 8.22 mmol). 10 mins later, ammonium hydroxide (28 %, 10 ml) was adde. The resulting mixture was allowed to warm up to 0°C. After removal of all solvents, the residue was washed with water, hexanes to provide a 1.06 g of white solid which was 4,4-difluorocyclohexanecarboxamide. Total yield was 82%.

Example 2: [(4,4-Difluorocyclohexyl)methyl]amine



4,4-difluorocyclohexanecarboxamide (1.32g, 8.10 mmol) was stirred in the solution of lithium borohydrate (1M, 30 ml) under nitrogen overnight. Then, the reaction mixture was refluxed for 4 hours. After cooled to room temperature, it was poured into ice-water slowly. After filtration, the product was extracted with dichloromethane from filtrate. Combined organic layers were water, brine, dried over anhydrous sodium sulphate, filtered and condensed to provide a 934 mg of colorless oil (82%). δ 2.53 (d, 2H), 1.98-2.09 (m, 2H), 1.73-1.82 (m, 6H), 1.17-1.29 (m, 3H).

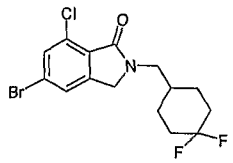
Example 3: Tert-butyl 4-fluorocyclohexanecarboxylate



To a solution of tert-butyl 4-hydroxycyclohexanecarboxylate (1500mg, 7.45mmol) in dichloromethane (anhydrous, 20 ml), DAST was (1571 mg, 22.4 mmol) added at 0°C. The

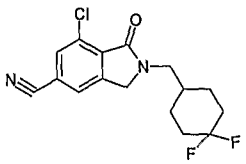
resulting mixture was stirred at 0°C for 3 hours. The mixture was diluted with dichloromethane , quenched with sodium bicarbonate. The organic layer was separated, the aquous phase was extracted with EtOAc. The combined organic layer were washed with water, brine, dried with androus sodium sulphate. The product was purified (flash chromatography, 10 to 20% EtOAc/hexanes) and obtained as a 210 mg of yellow oil (25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60-5.80 (m, 1H), 4.99-5.09 (m, 2H), 4.73 (d, 2H), 3.34 (br, 2H), 2.29-2.32 (m, 2H), 1.44-1.46 (m, 9H).

Example 4: 5-Bromo-7-chloro-2-[(4,4-difluorocyclohexyl)methyl]isoindolin-1-one



4-Bromo-2-bromomethyl-6-chlorobenzoic acid methyl ester (3.5 g, 9.35 mmol), (4,4-difluorocyclohexyl)methylamine (1.7 g, 11.39 mmol) and K_2CO_3 (3.15 g, 22.78 mmol) were stirred in toluene (10 mL) at 95 °C for 12 hours. The reaction was partitioned between ethyl acetate and water and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography (10-25% EtOAc/Hexanes) to afford the title compound as a yellow foam (2.2 g, 45%), ^{1}H NMR (300 MHz, $CDCl_3$): 7.58 (s, 1H), 7.50 (s, 1H), 4.36 (s, 2H), 3.48 (d, 2H), 2.10-2.14 (m, 2H), 1.64-1.82 (m, 5H), 1.35-1.447 (m, 2H)

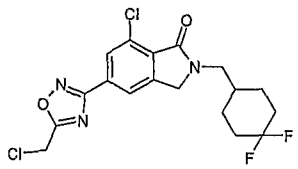
Example 5: 7-Chloro-2-[(4,4-difluorocyclohexyl)methyl]-1-oxoisoindoline-5-carbonitrile



5-bromo-7-chloro-2-[(4,4-difluorocyclohexyl)methyl]isoindolin-1-one (1.14 g, 3.01 mmol) was set stirring in DMF (10 mL) under argon and $Zn(CN)_2$ (389 mg, 3.31 mmol) and $Pd(PPh_3)_4$ (347 mg, 0.3 mmol) were added. The reaction was stirred at 80 °C for 1.5 hours. The reaction was partitioned between ethyl acetate and water and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under

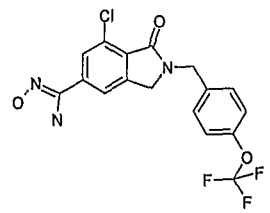
reduced pressure and the product was purified by column chromatography (40% EtOAc/Hexanes) to afford the title compound as a yellow foam (60 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (s, 1H), 7.65 (s, 1H), 4.45 (s, 2H), 3.53 (d, 2H), 2.11-2.15 (m, 2H), 1.66-1.91 (m, 5H), 1.41-1.50 (m, 2H)

Example 6: 7-Chloro-5-[5-(chloromethyl)-1,2,4-oxadiazol-3-yl]-2-[(4,4-difluoro-cyclohexyl) methyl]isoindolin-1-one



To a solution of 7-Chloro-N-hydroxy-1-oxo-2-[(4,4-difluorocyclohexyl)methyl]-2,3-dihydro-1H-isoindole-5-carboxamidine (450 mg, 1.26 mmol) in acetonitrile (10 ml), chloroacetyl chloride (170 mg, 1.51 mmol) was added, followed by K_2CO_3 (260 mg, 1.89 mmol). The mixture was stirred overnight. After diluter with EtOAc (20ml), it was washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated to provide a yellow foam. This foam was stirred in DMF (2 ml) at 140°C for 3 hours. After cooled to room temperature, it was diluted with water (5 ml). The product was extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated. The product was purified by column chromatography (40to 60 % EtOAc in hexanes) to yield the title compound as a white solid

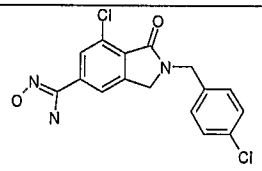
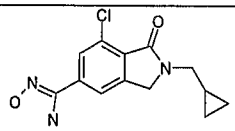
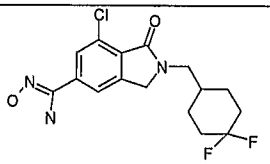
Example 7.1: 7-Chloro-N-hydroxy-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxamidine



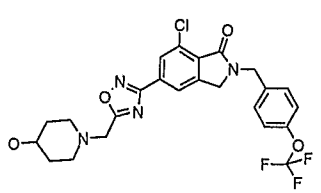
To a suspension of 7-chloro-1-oxo-2-[4-(trifluoromethoxy)benzyl]isoindoline-5-carbonitrile (500 mg, 1.36mmol) in ethanol (2 ml), 8-hydroxyquinoline (495 mg, 3.41 mmol) was added, followed by a solution of hydroxylamine hydrochloride (199 mg, 2.86 mmol) in water (1ml)

and a solution of sodium carbonate (230 mg, 2.2 mmol) in water (1ml). The resulting mixture was refluxed for 4 hours. After removal of solvents, the residue was loaded to a flash chromatography. The product was purified (20% EtOAc / hexanes to 2% ammonia in MeOH/ EtOAc) and obtained a 500 mg of greenish foam (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.04 (s, 1H) 7.48-7.61 (m, 2H), 7.28-7.36 (m, 2H), 7.17-7.21 (m, 2H), 6.04 (br, 1H), 4.77 (s, 2H), 4.22 (s, 2H).

The following compounds were made in a similar manner:

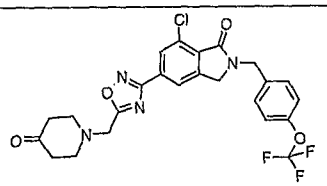
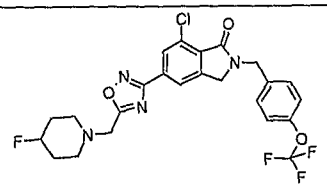
Example	Structure	Name	Yield
7.2		7-Chloro-2-(4-chlorobenzyl)-N'-hydroxy-1-oxoisoindoline-5-carboximidamide	930 mg, (85%), brown solid
NMR	10.04 (s, 1H), 7.76-7.80 (m, 2H), 7.29-7.43 (m, 4H), 6.02 (s, 2H), 4.70 (s, 2H), 4.38 (s, 2H).		
7.3		7-Chloro-2-(cyclopropylmethyl)-N'-hydroxy-1-oxoisoindoline-5-carboximidamide	700 mg, (80%), brown solid
NMR	10.01 (s, 1H), 7.77-7.83 (m, 2H), 5.90 (s, 2H), 4.54 (s, 2H), 3.40 (d, 2H), 0.99-1.06 (m, 1H), 0.53-0.58 (m, 2H), 0.33-0.39 (m, 2H).		
7.4		7-Chloro-2-[(4,4-difluorocyclohexyl)methyl]-N'-hydroxy-1-oxoisoindoline-5-carboximidamide	800 mg, (87%), yellow solid
NMR	10.01 (s, 1H), 7.59-4.63 (m, 2H), 4.92 (s, 2H), 4.42 (s, 2H), 3.51 (d, 2H), 2.10-2.15 (m, 1H), 1.61-1.81 (m, 6H), 1.40-1.45 (m, 2H).		

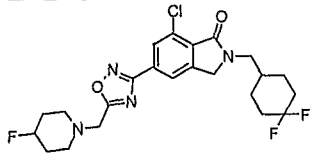
Example 8.1: 7-Chloro-5-[5-(4-hydroxy-piperidin-1-ylmethyl)-[1,2,4]oxadiazol-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one



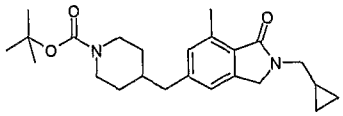
To a mixture of 4-Hydroxy piperidine (9.9mg, 0.098mmol), 7-chloro-5-chloromethyl-[1,2,4]oxadiazol-3-yl)-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one (30 mg, 0.065 mmol) and potassium carbonate (27 mg, 0.195 mmol) was added acetonitrile (3.0mL). The mixture was allowed to stir at room temperature overnight. Water (2.0mL) was added and the product was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated. Column chromatography provided the title compound as a yellow oil, 16.7 mg (49%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 8.04 (s, 1H), 7.38-7.41 (m, 2H), 7.20-7.23 (m, 2H), 4.82 (s, 2H), 4.34 (s, 2H), 3.95 (s, 2H), 3.75 (br, 1H), 2.90-2.93 (m, 2H), 2.42-2.50 (m, 2H), 1.94-1.99 (m, 2H), 1.64-1.74 (m, 3H)

The following compounds were prepared in a similar manner:

Example	Structure	Name	Yield
8.2		7-Chloro-5-[5-(4-oxo-piperidin-1-ylmethyl)-[1,2,4]oxadiazol-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one	23.8 mg (70%), yellow oil
NMR	8.19 (s, 1H), 8.04 (s, 1H), 7.37-7.41 (m, 2H), 7.20-7.23 (m, 2H), 4.82 (s, 2H), 4.34 (m, 2H), 4.10 (s, 2H), 3.00 (t, 2H), 2.56 (t, 2H)		
8.3		7-Chloro-5-[5-(4-fluoro-piperidin-1-ylmethyl)-[1,2,4]oxadiazol-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one	22.1 mg (50%), yellow oil
NMR	8.19 (s, 1H), 8.02 (s, 1H), 7.32-7.40 (m, 2H), 7.11-7.19 (m, 2H), 4.79 (s, 2H), 4.30 (s, 2H), 3.94 (s, 2H), 3.75 (br, 1H), 2.85-2.95 (m, 2H), 2.40-2.50 1.85-1.95 (m, 2H), 1.60-1.75 (m, 2H)		

8.4		7-Chloro-2-(4,4-difluoro-cyclohexylmethyl)-5-[5-(4-fluoro-piperidin-1-ylmethyl)-[1,2,4] oxadiazol-3-yl]-2,3-dihydro-isoindol-1-one	33.2 mg (95%), white solid
NMR	8.50 (s, 1H), 8.24 (s, 1H), 4.68 (s, 2H), 3.94 (s, 2H), 3.75 (br, 1H), 2.89-3.54 (m, 2H), 2.80-3.00 (m, 2H), 2.45-2.55 (m, 2H), 2.05-2.2 (m, 2H), 1.85-1.95 (m, 3H), 1.35-1.85 (m, 8H)		

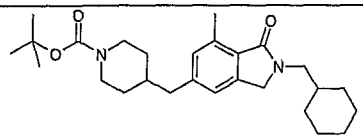
Example 9.1: 4-(2-Cyclopropylmethyl-7-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester



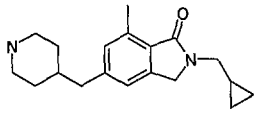
To a purged (Argon) sample of 4-Methylene-piperidine-1-carboxylic acid tert-butyl ester (727mg, 3.68mmol) was added 9-BBN (11.32mL, 5.66mmol). The mixture was stirred at 60°C for two hours. After cooling to room temperature this solution was added to 5-Bromo-7-methyl-2-cyclopropylmethyl-2,3-dihydro-isoindol-1-one (794mg, 2.83mmol), $Pd(dppf)Cl_2$ (115mg, 0.142mmol), DMF (25mL), potassium carbonate (1.17g, 8.49mmol) and water (2.5mL). The mixture was allowed to stir at 75°C for 1.5 hours. The mixture was then cooled to room temperature and poured into water (3mL). The product was extracted with ethyl acetate. The combined organic layers were washed with water three times, brine, dried over sodium sulphate, filtered and concentrated. Column chromatography (30% Ethyl acetate/hexanes) provided the title compound as a light yellow oil (777mg, 53%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (s, 1H), 6.94 (s, 1H), 4.39 (s, 2H), 3.42 (d, 2H), 2.68 (s, 3H), 2.57 (s, 2H), 2.54 (d, 2H), 1.70-1.62 (m, 4H), 1.43 (s, 9H), 1.09 (d, 1H), 1.01 (m, 1H), 0.56-0.5(m, 2H), 0.31-0.29 (m, 2H).

The following compound was prepared in a similar manner:

Example	Structure	Name	Yield

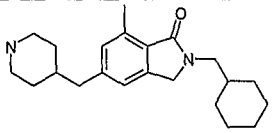
9.2		4-(2-Cyclohexylmethyl-7-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester	658mg 48% colourless solid
NMR	7.00 (s, 2H), 6.97 (s, 1H), 4.31 (s, 2H), 3.42-3.40 (d, 2H), 2.71 (s, 3H), 2.65-2.57 (m, 4H), 1.73-1.61 (m, 9H), 1.47 (s, 9H), 1.25-0.90 (m, 7H)		

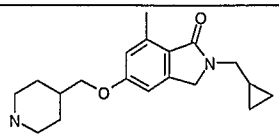
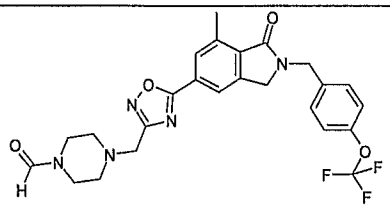
Example 10.1: 2-Cyclopropylmethyl-7-methyl-5-piperidin-4-ylmethyl-2,3-dihydro-isoindol-1-one



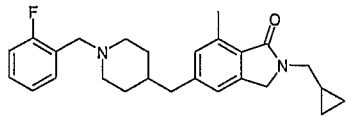
4-[7-Methyl-1-oxo-2-cycopropylmethyl-2,3-dihydro-1H-isoindol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester (777mg, 1.95mmol) was dissolved in formic acid (10 mL) and stirred at room temperature for 0.5 hours. The formic acid was removed under reduced pressure and the product was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrate to afford the title compound (578mg, 99%) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (s, 1H), 6.95 (s, 1H), 4.40 (s, 2H), 3.43 (d, 2H), 3.07-3.03 (d, 2H), 2.69 (s, 3H), 2.56-2.38 (m, 4H), 2.38 (br s, 1H), 1.64-1.61 (m, 4H), 1.19-1.15 (m, 2H), 1.02 (m, 1H), 0.57-0.53 (m, 2H), 0.34-0.30 (m, 2H).

The following compounds were prepared in a similar manner:

Example	Structure	Name	Yield
10.2		2-Cyclohexylmethyl-7-methyl-5-piperidin-4-ylmethyl-2,3-dihydro-isoindol-1-one	501mg 99% brown oil
NMR	7.01 (s, 1H), 6.97 (s, 1H), 4.30 (s, 2H), 3.42-3.40 (d, 2H), 3.14-3.10 (d, 2H), 2.71 (s, 3H), 2.63-2.57 (m, 4H), 1.73-1.67 (m, 9H), 1.30-1.19 (m, 4H), 1.05-1.02 (m, 3H).		

10.3		2-Cyclopropylmethyl-7-methyl-5-(piperidin-4-ylmethoxy)-2,3-dihydro-isoindol-1-one	294mg 94% yellow solid
NMR	6.74 (s, 1H), 6.70 (s, 1H), 4.38 (s, 2H), 3.83-3.81 (d, 2H), 3.43-3.41 (d, 2H), 3.17-3.13 (d, 2H), 2.71-2.64 (m, 5H), 2.37 (br s, 1H), 1.95-1.82 (m, 3H), 1.36-1.28 (m, 2H), 1.02 (m, 1H), 0.57-0.53 (m, 2H), 0.33-0.29 (m, 2H).		
10.4		4-{5-[7-Methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4] oxadiazol-3-ylmethyl}-piperazine-1-carbaldehyde	30mg 52% yellow solid
NMR	8.05 (s, 2H), 8.00 (s, 1H), 7.39-7.38 (d, 2H), 7.23-7.20 (d, 2H), 4.82 (s, 2H), 4.34 (s, 2H), 3.84 (s, 2H), 3.66-3.63 (m, 2H), 3.48-3.45 (m, 2H), 2.86 (s, 3H), 2.68-2.62 (m, 4H).		

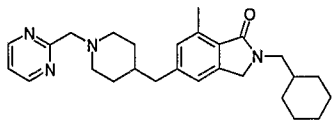
Example 11. 2-Cyclopropylmethyl-5-[1-(2-fluorobenzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one



To a mixture of 2-Fluorobenzyl bromide (47μL, 0.377mmol), 7-methyl-5-piperidin-4-ylmethyl-2-cyclohexylpropyl-2,3-dihydro-isoindol-1-one (75mg, 0.251mmol) and potassium carbonate (104mg, 0.753mmol) was added acetonitrile (3.0mL). The mixture was stirred at 80°C for 4 hours. 1 scoop of Sodium ter-butoxide (~200mg) was added and stirring continued overnight at 80°C. The mixture was cooled to rrom temperature, water (2.0mL) was added and the product was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated. Column chromatography provided the title compound as a yellow oil (6.6mg, 6%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (m, 1H), 7.23-7.13 (m, 1H), 7.11-7.00 (m, 3H), 6.96 (s, 1H), 4.41 (s, 2H), 3.61 (s, 2H),

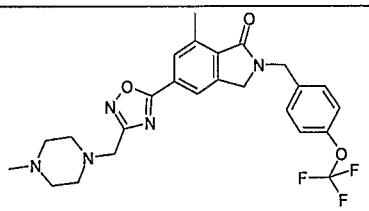
3.46-3.44 (d, 2H), 2.95-2.92 (d, 2H), 2.70(s, 3H), 2.59-2.57 (d, 2H), 2.01-1.98 (t, 2H), 1.65-1.61 (m, 3H), 1.38-1.27 (m, 2H), 1.04 (m, 1H), 0.60-0.55 (m, 2H), 0.36-0.32 (m, 2H).

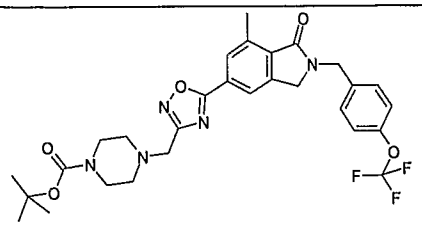
Example 12.1: 2-Cyclohexylmethyl-7-methyl-5-(1-pyrimidin-2-ylmethyl-piperidin-4-ylmethyl)-2,3-dihydro-isoindol-1-one



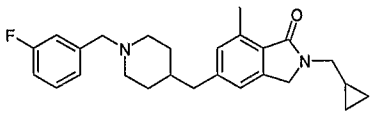
To a mixture of 2-Chloromethyl pyrimidine (32mg, 0.247mmol), 2-Cyclohexylmethyl-7-methyl-5-piperidin-4-ylmethyl-2,3-dihydro-isoindol-1-one (56mg, 0.164mmol) and cesium carbonate (160mg, 0.492mmol) was added acetonitrile (3.0mL). The mixture was allowed to stir at room temperature overnight. Water (2.0mL) was added and the product was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated. Column chromatography provided the title compound as a yellow oil (48mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76-8.72 (d, 2H), 7.18 (t, 1H), 6.99 (s, 1H), 6.95 (s, 1H), 4.30 (s, 2H), 3.78 (s, 2H), 3.40-3.37 (d, 2H), 2.97-2.93 (d, 2H), 2.70 (s, 3H), 2.58-2.56 (d, 2H), 2.10-2.05 (t, 2H)1.71-1.42 (m, 10H), 1.26-1.13 (m, 4H), 1.09-0.98 (m, 2H).

The following compounds were prepared in a similar manner:

Example	Structure	Name	Yield
12.2		7-Methyl-5-[3-(4-methyl-piperazin-1-ylmethyl)-[1,2,4]oxadiazol-5-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one	50mg 88% colourless solid
NMR	8.04 (s, 1H), 7.99 (s, 1H), 7.39-7.34 (c, 2H), 7.22-7.19 (d, 1H), 4.80 (s, 2H), 4.33 (s, 2H), 3.79 (s, 3H), 2.78-2.68 (br s, 4H), 2.62-2.51 (br s, 4H), 2.30 (s, 3H).		

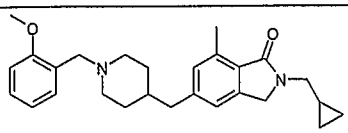
12.3		4-{5-[7-Methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4] oxadiazol-3-ylmethyl}-piperazine-1-carboxylic acid tert-butyl ester	60mg colourless solid
NMR	8.05 (s, 1H), 8.00 (s, 1H), 7.36-7.36 (d, 2H), 7.23-7.20 (d, 2H), 4.81 (s, 2H), 4.34 (s, 2H), 3.80 (s, 2H)3.52-3.47 (m, 4H), 2.85 (s, 3H), 2.60-2.57 (m, 4H), 1.46 (s, 9H).		

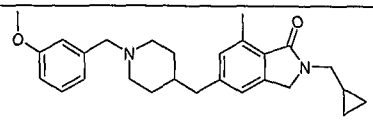
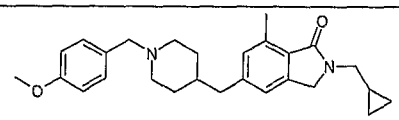
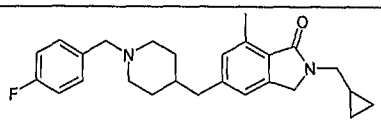
Example 13.1: 2-Cyclopropylmethyl-5-[1-(3-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one

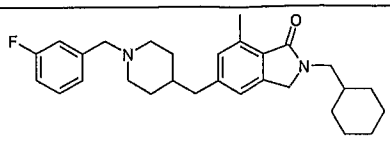
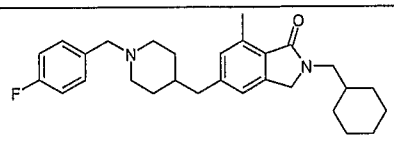
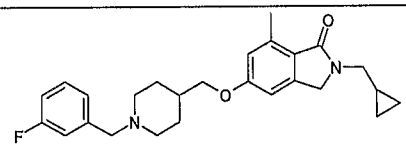
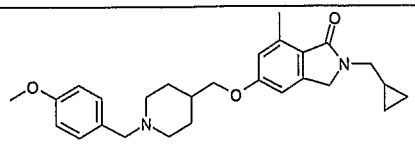


To a solution of 2-Cyclopropylmethyl-7-methyl-5-piperidin-4-ylmethyl-2,3-dihydro-isoindol-1-one (30mg, 0.101mmol) in methanol (2mL) was slowly added acetic acid (1mL). After stirring at room temperature for 5 minutes, 3-Fluoro-benzaldehyde (12.8μL, 0.121mmol) and sodium cyanoborohydride (8μL, 0.111mmol) were added dropwisely. The mixture stirred at room temperature for 2 hours and was neutralized with saturated sodium bicarbonate (10mL). The aqueous mixture was extracted with dichloromethane and the organics were dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography (10-40% ethyl acetate in hexanes) provided the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.23 (m, 1H), 7.09-7.03 (m, 3H), 6.97-6.92 (m, 2H), 4.41 (s, 2H), 3.48-3.44 (m, 4H), 2.88-2.85 (d, 2H), 2.71 (s, 3H), 2.60-2.57 (d, 2H), 1.93 (t, 2H), 1.64-1.50 (m, 3H), 1.36-1.28 (m, 2H), 1.04 (m, 1H), 0.60-0.55 (m, 2H), 0.34-0.32 (m, 2H)

The following compounds were prepared in a similar manner:

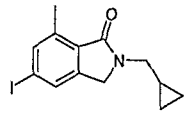
Example	Structure	Name	Yield
13.2		2-Cyclopropylmethyl-5-[1-(2-methoxybenzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-	7.3mg 11%

		isoindol-1-one	colourless oil
NMR	7.36-7.34 (d, 1H), 7.23.-7.20 (m, 1H), 7.02 (s, 1H), 6.96-6.85 (m, 3H), 4.41 (s, 2H), 3.81 (s, 3H), 3.55 (s, 2H), 3.46-3.43 (d, 2H), 2.95-2.91 (d, 2H), 2.70 (s, 3H), 2.60-2.57 (d, 2H), 1.98 (t, 2H), 1.70 (br s, 2H), 1.63-1.59 (m, 3H), 1.39-1.37 (m, 2H), 1.04 (m, 1H), 0.60-0.55 (m, 2H), 0.36-0.32 (m, 2H)		
13.3		2-Cyclopropylmethyl-5-[1-(3-methoxybenzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one	40mg 60% yellow oil
NMR	7.26-7.20 (m, 1H), 7.03 (s, 1H), 6.97 (s, 1H), 6.91-6.89 (m, 3H), 4.41 (s, 2H), 3.82 (s, 3H), 3.47-3.44 (m, 4H), 2.90-2.86 (d, 2H), 2.71 (s, 3H), 2.59-2.57 (d, 2H), 1.92 (t, 2H), 1.64-1.59 (m, 3H), 1.36-1.35 (m, 2H), 1.04 (m, 1H), 0.59-0.55 (m, 2H), 0.36-0.32 (m, 2H)		
13.4		2-Cyclopropylmethyl-5-[1-(4-methoxybenzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one	23mg 34% yellow oil
NMR	7.23-7.21 (d, 2H), 7.02 (s, 1H), 6.96 (s, 1H), 6.87-6.84 (, 2H), 4.41 (s, 2H), 3.82 (s, 3H), 3.46-3.44 (m, 4H), 2.89-2.85 (d, 2H), 2.70 (s, 3H), 2.58-2.56 (d, 2H), 1.91 (t, 2H), 1.63-1.59 (m, 3H), 1.34-1.32 (m, 2H), 1.04 (m, 1H), 0.59-0.55 (m, 2H), 0.36-0.32 (m, 2H)		
13.5		2-Cyclopropylmethyl-5-[1-(4-fluorobenzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one	36mg 35% light yellow oil
NMR	7.29-7.24 (m, 2H), 7.02-6.97 (m, 4H), 4.41 (s, 2H), 3.61 (s, 2H), 3.46-3.44 (m, 4H), 2.87-2.83 (d, 2H), 2.70(s, 3H), 2.59-2.57 (d, 2H), 1.90-1.86 (t, 2H), 1.63-1.59 (m, 3H),		

	1.34-1.30 (m, 2H), 1.04 (m, 1H), 0.60-0.55 (m, 2H), 0.35-0.32 (m, 2H)		
13.6		2-Cyclohexylmethyl-5-[1-(3-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one	34mg 43% colourless oil
NMR	7.30-7.23 (m, 1H), 7.09-7.04 (m, 2H), 7.00-6.92 (m, 3H), 4.29 (s, 2H), 3.48 (s, 2H), 3.41-3.39 (d, 2H), 2.88-2.84 (d, 2H), 2.70 (s, 3H), 2.59-2.57 (d, 2H), 1.96-1.89 (t, 2H), 1.73-1.60 (m, 8H), 1.35-1.19 (m, 6H), 1.05 (m, 2H)		
13.7		2-Cyclohexylmethyl-5-[1-(4-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one	26mg 33% light yellow oil
NMR	7.29-7.24 (m, 2H), 7.03-6.96 (m, 4H), 4.29 (s, 2H), 3.45 (s, 2H), 3.41-3.39 (d, 2H), 2.87-2.83 (d, 2H), 2.70 (s, 3H), 2.58-2.56 (d, 2H), 1.90-1.86 (t, 2H), 1.76-1.59 (m, 9H), 1.34-1.19 (m, 5H), 1.06 (m, 2H)		
13.8		2-Cyclopropylmethyl-5-[1-(3-fluorobenzyl)-piperidin-4-ylmethoxy]-7-methyl-2,3-dihydro-isoindol-1-one	27mg 26% yellow oil
NMR	7.32-7.25 (m, 1H), 7.11-7.08 (m, 2H), 6.98-6.95 (m, 1H), 6.75-6.72 (d, 2H), 4.38 (s, 2H), 3.86-3.84 (d, 2H), 3.52 (s, 2H), 3.44-3.42 (d, 2H), 2.96-2.92 (d, 2H), 2.70(s, 3H), 2.07-2.04 (t, 2H), 1.85-1.82 (m, 3H), 1.45 (m, 2H), 1.04 (m, 1H), 0.59-0.55 (m, 2H), 0.35-0.31 (m, 2H)		
13.9		2-Cyclopropylmethyl-5-[1-(4-methoxy -benzyl)-piperidin-4-ylmethoxy]-7-m ethyl-2,3-dihydro-isoindol-1-one	24mg 39% yellow oil
NMR	7.28-7.22 (m, 1H), 7.11-7.08 (m, 2H), 6.94-6.91 (m, 2H), 6.83-6.81 (d, 1H), 6.79-6.71 (d, 2H), 4.38 (s, 2H), 3.86-3.83 (m, 5H), 3.52 (s, 2H), 3.44-3.42 (d, 2H), 2.98-2.94 (d, 2H), 2.70 (s, 3H), 2.06-1.99 (t, 2H), 1.85-1.82 (m, 3H), 1.46-1.42 (m, 2H), 1.03 (m,		

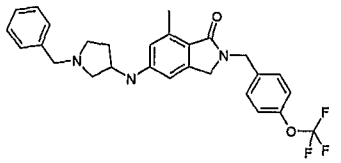
	1H), 0.59-0.56 (m, 2H), 0.35-0.31 (m, 2H)

Example 14: 2-Cyclopropylmethyl-5-iodo-7-methyl-2,3-dihydro-isoindol-1-one



To a solution of 5-Bromo-7-methyl-2-cyclopropylmethyl-2,3-dihydro-isoindol-1-one (1.0g, 3.56mmol) in butanol (10 ml), (1R, 2R)-N,N'-dimethylcyclohexane-1,2-diamine (204 mg, 1.42mmol), copper(I) iodide (140mg, 0.714mmol) and sodium iodide (1.08g, 14.3 mmol) were added. The resulting mixture was stirred at 120°C overnight. After cooling, the mixture was diluted with ethyl acetate, washed with water, brine, dried over anhydrous sodium sulphate, filtered, concentrated. Column chromatography (30% EtOAc/Hexanes) provided the title compound (1.07g, 92%) as a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.59 (s, 1H), 4.42 (s, 2H), 3.46-3.44 (d, 2H), 2.70 (s, 3H), 1.04-1.02 (m, 1H), 0.61-0.57 (m, 2H), 0.34-0.31 (m, 2H)

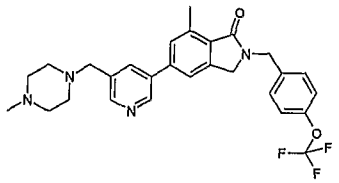
Example 15: 5-(1-Benzyl-pyrrolidin-3-ylamino)-7-methyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one



3-Amino-1-benzyl-pyrrolidine (57mg, 0.325mmol), 5-Bromo-7-methyl-2-(4-trifluoromethoxybenzyl)-2,3-dihydro-isoindol-1-one (100mg, 0.25mmol), NaO^{t}Bu (168mg, 1.75mmol), BINAP (16mg, 0.025mmol) and $Pd_2(dba)_3$ (23mg, 0.025 mmol) were dissolved in anhydrous toluene (5mL). The mixture was immersed in a 110°C oil bath. After eighteen hours, the reaction was cooled and poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The compound was purified by column chromatography (50% EtOAc/Hexanes) to provide the title compound as a yellow gum (87mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.34 (m, 7H), 7.18 (d, 2H), 6.34 (d, 2H), 4.72 (s, 2H), 4.33 (d, 1H), 4.12 (s, 2H), 4.04 (m, 1H), 3.64

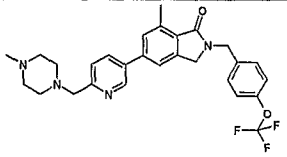
(collapsed dd, 2H), 2.75-2.83 (m, 2H), 2.66 (s, 3H), 2.58 (dd, 1H), 2.45 (ddd, 1H), 2.32-2.42 (m, 1H), 1.67-1.70 (m, 1H).

Example 16.1: 7-Methyl-5-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-2-(4-rifluoromethoxybenzyl)-2,3-dihydro-isoindol-1-one

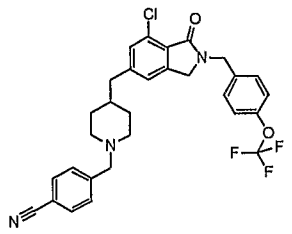


Methanesulfonic acid 5-[7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-pyridin-3-ylmethyl ester (36mg, 0.071mmol) was dissolved in THF (5mL). N-Methyl piperazine (24uL, 0.213mmol) was added and the mixture stirred at 50°C for 18hrs. The mixture was cooled, diluted with water, and extracted with ethyl acetate. The organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography (5% 2M NH_3 in $MeOH/CH_2Cl_2$) provided the title compound (24mg, 67%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.56 (s, 1H), 7.86 (s, 1H), 7.42 (d, 2H), 7.37 (d, 2H), 7.19 (d, 2H), 4.82 (s, 2H), 4.32 (s, 2H), 3.60 (s, 2H), 2.85 (s, 3H), 2.52-2.42 (br s, 8H), 2.30 (s, 3H).

The following compound was prepared in a similar manner:

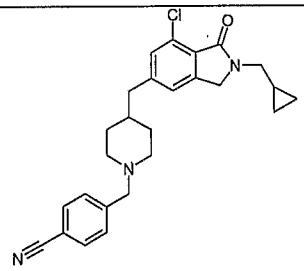
Example	Structure	Name	Yield
16.2		7-Methyl-5-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one	48mg, 80% brown oil
NMR	8.78 (s, 1H), 7.85 (s, 1H), 7.50 (d, 1H), 7.40-7.34 (m, 4H), 7.20 (d, 2H), 4.81 (s, 2H), 4.32 (s, 2H), 3.73 (s, 2H), 2.84 (s, 3H), 2.60-2.52 (br d, 8H), 2.31 (s, 3H)		

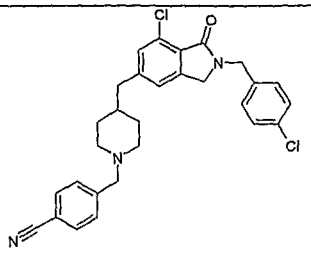
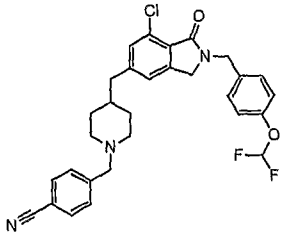
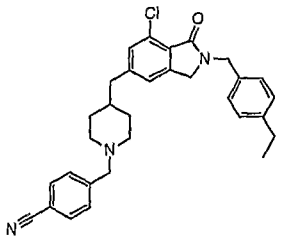
Example 17.1: 4-{4-[7-Chloro-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile



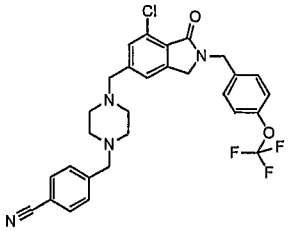
To a mixture of 4-Cyano-benzyl bromide (12mg, 0.06mmol), 7-chloro-5-piperidin-4-ylmethyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one (30.0mg, 0.06mmol) and potassium carbonate (42mg, 0.3mmol) was added acetonitrile (3.0mL). The mixture was allowed to stir at room temperature overnight. Water (2.0mL) was added and the product was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated. Column chromatography provided the title compound as a brown oil (39.0mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, 2H), 7.27-7.59 (m, 4H), 7.17-7.20 (m, 3H), 7.05 (s, 1H), 4.77 (s, 2H), 4.22 (s, 2H), 3.53 (s, 2H), 2.80-2.84 (m, 2H), 2.58-2.60 (m, 2H), 1.91 (t, 2H), 1.56-1.62 (m, 3H), 1.27-1.34 (m, 2H).

The following compounds were prepared in a similar manner:

Example	Structure	Name	Yield
17.2		4-[4-(7-Chloro-2-cyclopropylmethyl-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl)-piperidine-1-ylmethyl]-benzonitrile	21.1 mg, 82.4%, brown oil
NMR	7.59-7.62 (m, 2H), 7.45 (d, 2H), 7.18 (s, 1H), 7.11 (s, 1H), 4.43 (s, 2H), 3.53 (s, 2H), 3.46 (d, 2H), 2.81-2.85 (m, 2H), 2.60-2.62 (m, 2H), 1.92-1.99 (m, 2H), 1.50-1.64 (m, 3H), 1.27-1.35 (m, 2H), 0.98-1.05 (m, 1H), 0.55-0.60 (m, 2H), 0.33-0.35 (m, 2H)		

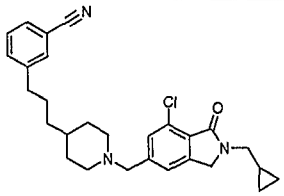
17.3		4-{4-[7-Chloro-2-(4-chloro-benzyl)-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile	81.8 mg, 97.1%, yellow oil
NMR	7.58-7.62 (m, 2H), 7.42-7.50 (m, 2H), 7.24-7.32 (m, 4H), 7.18 (s, 1H), 7.04 (s, 1H), 4.73 (s, 2H), 4.19 (s, 2H), 3.51 (s, 2H), 2.79-2.83 (m, 2H), 2.57-59 (m, 2H), 1.90-1.97 (m, 2H), 1.49-1.61 (m, 2H), 1.24-1.37 (m, 3H)		
17.4		4-{4-[7-Chloro-2-(4-difluoromethoxy-benzyl)- 1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile	35.2mg, 72.9%, yellow oil
NMR	7.59-7.61 (m, 2H), 7.42-7.45 (m, 2H), 7.30-7.35 (m, 2H), 7.19 (s, 1H), 7.05-7.11 (m, 3H), 6.26-6.75 (t, 1H), 4.75 (s, 2H), 4.21 (s, 2H), 3.52 (s, 2H), 2.79-2.83 (m, 2H), 2.58-2.60 (m, 2H), 1.88-1.98 (m, 2H), 1.51-1.62 (m, 3H), 1.25-1.37 (m, 2H)		
17.5		4-{4-[7-Chloro-2-(4-ethyl-benzyl)-1 -oxo-2,3-dihydro-1H-isoindol-5-ylme thyl]-piperidin-1-ylmethyl}-benzoni trile	16.2mg, 43.3%, yellow oil
NMR	7.59-7.62 (m, 2H), 7.42-7.48(m, 2H), 7.24-7.28 (m, 2H), 7.16-7.18 (m, 3H), 7.02 (s, 1H), 4.74 (s, 2H), 4.19 (s, 2H), 3.52 (s, 2H), 2.79-2.83 (m, 2H), 2.57-2.68 (m, 4H), 1.90-1.98 (m, 2H), 1.51-1.61 (m, 3H), 1.21-1.36 (m, 5H)		

Example 18.1: 4-{4-[7-Chloro-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperazin-1-methyl}-nicotinonitrile

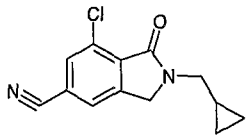


4-(Piperazin-1-ylmethyl)benzonitrile (30mg, 0.094mmol) was dissolved in dichloromethane (2.0mL) and 7-Chloro-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carbaldehyde (20.0mg, 0.054mmol) was added. The mixture was stirred for ten minutes and sodium triacetoxy borohydride (16.1mg, 0.076mmol) was added and the reaction was allowed to stir overnight. The reaction was then diluted with dichloromethane, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered and concentrated. Column chromatography (20% MeOH/EtOAc) provided the title compound as a yellow oil (17.9mg, 32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.63 (m, 2H), 7.34-7.47 (m, 5H), 7.27-7.28 (m, 1H), 7.18-7.21 (m, 2H), 4.78 (m, 2H), 4.24 (s, 2H), 3.55-3.57 (m, 4H), 2.48-2.53 (m, 8H).

The following compound was prepared in a similar manner:

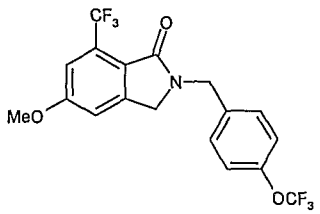
Example	Structure	Name	Yield
18.2		3-{3-[1-(7-Chloro-2-cyclopropylmethyl-1-oxo-2,3-dihydro-1H-isoindol-5- ylmethyl)-piperidin-4-yl]-propyl}-b enzonitrile	13mg, 70.3%, yellow oil
NMR	7.41-7.50 (3H), 7.34-7.38 (m, 2H), 4.44 (s, 2H), 3.52 (s, 2H), 3.46 (d, 2H), 2.84-2.87 (m, 2H), 2.64 (t, 2H), 1.85-1.98 (m, 3H), 1.65-1.68 (m, 4H), 1.26-1.30 (m, 4H), 1.02-1.08 (m, 1H), 0.55-0.61 (m, 2H), 0.33-0.37 (m, 2H)		

Example 19: 7-Chloro-2-cyclopropylmethyl-1-oxo-2,3-dihydro-1H-isoindole-5-carbonitrile



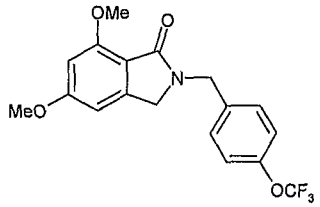
5-Bromo-7-chloro-2-cyclopropylmethyl-2,3-dihydro-isoindol-1-one (360mg, 1.20mmol) was set stirring in DMF (15 mL) under argon and $Zn(CN)_2$ (154mg, 1.32mmol) and $Pd(PPh_3)_4$ (139mg, 0.12mmol) were added. The reaction was stirred at 80 °C for 1.5 hours. The reaction was partitioned between ethyl acetate and water and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography (40% EtOAc/Hexanes) to afford a yellow solid (142.6mg, 82%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (s, 2H), 7.36 (d, 2H), 7.22 (s, 2H), 4.80 (s, 2H), 4.30 (s, 2H), 2.81 (s, 3H).

Example 20: 7-Trifluoromethyl-5-methoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one



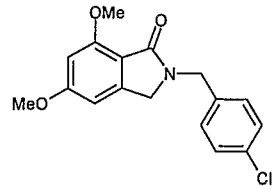
A mixture of 7-trifluoromethyl-5-bromo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one (0.060 g, 0.15 mmol), and 30% sodium methoxide-methanol (0.21 mL) in methanol (4 mL) was stirred at 100 °C for 1h. Workup and silica gel column chromatography using 30% ethyl acetate in hexane afforded 7-trifluoromethyl-5-methoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one (0.043 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.88 (s, 3H), 4.25 (s, 2H), 4.76 (s, 2H), 7.02 (s, 1H), 7.17 (d, 2H), 7.28 (s, 1H), 7.37 (d, 2H).

Example 21: 5,7-Dimethoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1one



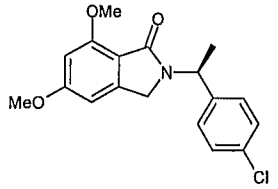
To a solution of 4-bromo-5,7-Dimethoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1one (0.200 g, 0.45 mmol) in benzene under N2 atmosphere was added 2,2'-azobis(2-methyl proponitrile) AIBN (5.0 mg), followed by tributyl tin hydride (0.238 mL, 0.9 mmol). The resulting mixture was refluxed in an oil bath for 2 h. The reaction was monitored by GC-MS for the disappearance of starting material. The reaction mixture was cooled to room temperature and stirred with potassium fluoride (200 mg) for 45 min. The solids were filtered and the filtrate was concentrated. The resulting material was purified using column chromatography (typically 40% ethyl acetate in hexanes) to give 5,7-Dimethoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1one (0.106 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 3H), 3.95 (s, 3H), 4.17 (s, 2H), 4.72 (s, 2H), 6.43 (d, 2H), 7.16 (d, 2H), 7.32 (d, 2H). GC-MS: m/z 367 $(M)^+$, 349 $(M-18)^+$.

Example 22: 5,7-Dimethoxy-2-(4-chloro-benzyl)-2,3-dihydro-isoindol-1one



To a solution of 4-bromo-5,7-Dimethoxy-2-(4-chloro-benzyl)-2,3-dihydro-isoindol-1one (0.100 g, 0.25 mmol) in benzene under N2 atmosphere was added 2,2'-azobis(2-methyl proponitrile) AIBN (5.0 mg), followed by tributyl tin hydride (0.132 mL, 0.5 mmol). The resulting mixture was refluxed in an oil bath for 2 h. The reaction was monitored by GC-MS for the disappearance of starting material. The reaction mixture was cooled to room temperature and stirred with potassium fluoride (200 mg) for 45 min. The solids were filtered and the filtrate was concentrated. The resulting material was purified using column chromatography (typically 40% ethyl acetate in hexanes) to give 5,7-Dimethoxy-2-(4-chloro-benzyl)-2,3-dihydro-isoindol-1one (0.035 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 3H), 3.95 (s, 3H), 4.15 (s, 2H), 4.69 (s, 2H), 6.43 (d, 2H), 7.25 (m, 4H). GC-MS: m/z 317 $(M)^+$, 299 $(M-18)^+$.

Example 23: 5,7-Dimethoxy-2-[1-(4-chloro-phenyl)-ethyl]-2,3-dihydro-isoindol-1one

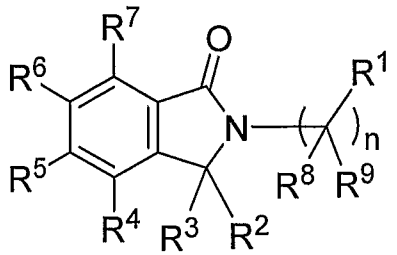


To a solution of 4-bromo-5,7-Dimethoxy-2-[1-(4-chloro-phenyl)-ethyl]-2,3-dihydro-isoindol-1one (0.112 g, 0.27 mmol) in benzene under N2 atmosphere was added 2,2'-azobis(2-methyl proponitrile) AIBN (5.0 mg), followed by tributyl tin hydride (0.145 mL, 0.55 mmol). The resulting mixture was refluxed in an oil bath for 2 h. The reaction was monitored by GC-MS for the disappearance of starting material. The reaction mixture was cooled to room temperature and stirred with potassium fluoride (200 mg) for 45 min. The solids were filtered and the filtrate was concentrated. The resulting material was purified using column chromatography (typically 40% ethyl acetate in hexanes) to give 5,7-Dimethoxy-2-[1-(4-chloro-phenyl)-ethyl]-2,3-dihydro-isoindol-1one (0.056 g, 63%). ^{1}H NMR (300 MHz,

$CDCl_3$): δ (ppm) 1.43 (d, 3H), 3.63 (s, 3H), 3.68 (d, 1H), 3.74 (s, 3H), 3.99 (d, 1H), 5.53 (q, 1H), 6.23 (dd, 2H), 7.15 (m, 4H). GC-MS: m/z 331 $(M)^+$, 316 $(M-15)^+$.

WHAT IS CLAIMED IS:

1. A compound according to formula I:



(I)

wherein:

R^1 is a 3- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of N, O and S, wherein said ring may be substituted by one or more A;

R^2 and R^3 are independently selected from the group consisting of H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, heterocycloalkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-aryl, C_{1-6}-alkyl-heteroaryl, C_{1-6}-alkyl-heterocycloalkyl, and C_{1-6}-alkyl-C_{3-8}-cycloalkyl, wherein R^2 and R^3 may be substituted by one or more A;

R^4 and R^6 are independently selected from the group consisting of H, hydroxy, F, Cl, Br, I, nitro, cyano, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, aryl, C_{1-6}-alkylaryl, OC_{0-6}-alkylaryl, $(CO)R^{10}$, $O(CO)R^{10}$, $O(CO)OR^{10}$, $C(O)OR^{10}$, $O(CNR^{10})OR^{11}$, C_{1-6}-alkylOR^{10}, OC_{2-6}-alkylOR^{10}, C_{1-6}-alkyl$(CO)R^{10}$, OC_{1-6}-alkyl$(CO)R^{10}$, C_{0-6}-alkylCO_2R^{10}, OC_{1-6}-alkylCO_2R^{10}, C_{1-6}-alkylcyano, OC_{2-6}-alkylcyano, C_{0-6}-alkyl$NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}R^{11}$, C_{1-6}-alkyl$(CO)NR^{10}R^{11}$, OC_{1-6}-alkyl$(CO)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)R^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)NR^{10}R^{11}$, C_{0-6}-alkylSR^{10}, OC_{2-6}-alkylSR^{10}, C_{0-6}-alkyl$(SO)R^{10}$, OC_{2-6}-alkyl$(SO)R^{10}$, C_{0-6}-alkylSO_2R^{10}, OC_{2-6}-alkylSO_2R^{10}, C_{0-6}-alkyl$(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$(SO_2)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)R^{11}$,

OC_{2-6}-alkyl$NR^{10}(SO_2)R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, $(CO)NR^{10}R^{11}$, $O(CO)NR^{10}R^{11}$, $NR^{10}OR^{11}$, C_{0-6}-alkyl$NR^{10}(CO)OR^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)OR^{11}$, SO_3R^{10} and a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of N, O and S, wherein R^4 and R^6 may be substituted by one or more A, and wherein any cycloalkyl or aryl is optionally fused to a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of C, N, O and S;

R^5 is selected from the group consisting of CN, OC_{0-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, C_{0-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{0-6}-alkylheteroaryl, OC_{0-6}-alkylheteroaryl, heterocycloalkyl, C_{1-6}-alkylheterocycloalkyl, OC_{0-6}-alkylheterocycloalkyl and $C(O)R_{10}$, wherein any cyclic moiety is substituted by one or more B;

R^7 is selected from the group consisting of H, F, Cl, Br, I, nitro, cyano, OC_{1-4}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, and C_{3-8}-cycloalkyl;

R^8 and R^9 are independently selected from the group consisting of H, F, Cl, Br, I, nitro, cyano, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, and OC_{2-6}-alkynyl,
or, where n is greater than 1, two or more R^8 and/or R^9 on adjacent carbon atoms may be absent to form an alkenyl or alkynyl moiety;

R^{10} and R^{11} are independently selected from the group consisting of H, hydroxy, oxo, F, Cl, Br, I, nitro, cyano, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, aryl, C_{1-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{0-6}-alkyl-heterocycloalkyl, OC_{1-6}-alkyl-heterocycloalkyl, heteroaryl, C_{1-6}alkylheteroaryl, heterocycloalkyl-C_{1-6}-alkylaryl and heterocycloalkyl-C_{1-6}-alkylheteroaryl, wherein any cyclic moiety is optionally fused to a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the

group consisting of C, N, O and S and any cyclic moiety is optionally substituted with a substituent selected from alkyl, halo, hydroxyl, Oalkyl, haloalkyl and Ohaloalkyl;

A is selected from the group consisting of H, hydroxy, F, Cl, Br, I, nitro, cyano, oxo, C_{1-6}-alkyl, C_{1-6}-alkylhalo, OC_{1-6}alkyl, OC_{1-6}-alkylhalo, C_{2-6}-alkenyl, OC_{2-6}-alkenyl, C_{2-6}-alkynyl, OC_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{1-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, aryl, C_{1-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{1-6}-alkyl-heterocyclyl, C_{1-6}-alkyl-heterocycloalkyl, OC_{0-6}-alkyl-heterocycloalkyl, $(CO)R^{10}$, $O(CO)R^{10}$, $O(CO)OR^{10}$, $O(CNR^{10})OR^{11}$, C_{1-6}-alkylOR^{10}, OC_{2-6}-alkylOR^{10}, C_{1-6}-alkyl$(CO)R^{10}$, OC_{1-6}-alkyl$(CO)R^{10}$, C_{0-6}-alkylCO_2R^{10}, OC_{1-6}-alkylCO_2R^{10}, C_{1-6}-alkylcyano, OC_{2-6}-alkylcyano, C_{0-6}-alkyl$NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}R^{11}$, C_{0-6}-alkyl$(CO)NR^{10}R^{11}$, OC_{1-6}-alkyl$(CO)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)R^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)R^{11}$, C_{0-6}-alkyl$NR^{10}(CO)NR^{10}R^{11}$, C_{0-6}-alkylSR^{10}, OC_{2-6}-alkylSR^{10}, C_{0-6}-alkyl$(SO)R^{10}$, OC_{2-6}-alkyl$(SO)R^{10}$, C_{1-6}-alkylSO_2R^{10}, OC_{2-6}-alkylSO_2R^{10}, C_{0-6}-alkyl$(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$(SO_2)NR^{10}R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)R^{11}$, OC_{2-6}-alkyl$NR^{10}(SO_2)R^{11}$, C_{0-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, OC_{2-6}-alkyl$NR^{10}(SO_2)NR^{10}R^{11}$, $(CO)NR^{10}R^{11}$, $O(CO)NR^{10}R^{11}$, $NR^{10}OR^{11}$, C_{0-6}-alkyl$NR^{10}(CO)OR^{11}$, OC_{2-6}-alkyl$NR^{10}(CO)OR^{11}$, SO_3R^{10} and a 5- to 7-membered ring that may contain one or more heteroatoms independently selected from the group consisting of N, O and S, wherein said 5- to 7-membered ring is optionally substituted by one or more of R^{10} and R^{11};

B is selected from the group consisting of C_{0-6}-alkyl-C_{3-8}-cycloalkyl, OC_{0-6}-alkyl-C_{3-8}-cycloalkyl, C_{0-6}-alkylaryl, OC_{0-6}-alkylaryl, C_{1-6}-alkylheterocycloalkyl, OC_{0-6}-alkylheterocycloalkyl, C_{1-6}-alkylheteroaryl and OC_{1-6}-alkylheteroaryl, wherein any cyclic moiety is substituted with at least one substituent selected from the group consisting of halo, alkyl, alkylhalo, alkoxy, oxo, COR, CO_2R, SO_2R and CN;

R is selected from the group consisting of H and alkyl;
and
n is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;
or a pharmaceutically acceptable salt, hydrate, solvate, optical isomer, or combination thereof;

with the proviso that the compound is not selected from the group consisting of:
5-(4-Benzyl-piperazine-1-carbonyl)-7-methyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
7-Methyl-5-(4-pyridin-4-ylmethyl-piperazine-1-carbonyl)-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
7-Methyl-5-[4-(2-pyridin-4-yl-ethyl)piperazine-1-carbonyl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
4-{4-[7-Methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile,
2-Benzyl-1-oxo-2,3-dihydro-1H-isoindole-5-carbonitrile,
7-Chloro-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile,
7-Methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile,
7-Methyl-1-oxo-2-(4-chloro-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile,
1-Oxo-2-(4-trifluoromethoxy-benzyl)-7-trifluoromethyl-2,3-dihydro-1H-isoindole-5-carbonitrile,
3-Oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-4,6-dicarbonitrile,
7-Iodo-5-methoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
2-Benzyl-5-methoxy-2,3-dihydro-isoindol-1-one, and
7-Chloro-5-methoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one.

2. A compound selected from the group consisting of:
7-Chloro-2-[(4,4-difluorocyclohexyl)methyl]-1-oxoisoindoline- 5-carbonitrile,
7-Chloro-5-[5-(4-hydroxy-piperidin-1-ylmethyl)-[1,2,4] oxadiazol-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
7-Chloro-5-[5-(4-oxo-piperidin-1-ylmethyl)-[1,2,4]oxadiazol-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
7-Chloro-5-[5-(4-fluoro-piperidin-1-ylmethyl)-[1,2,4] oxadiazol-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
7-Chloro-2-(4,4-difluoro-cyclohexyl-methyl)-5-[5-(4-fluoro-piperidin-1-ylmethyl)-[1,2,4]oxadiazol-3-yl]-2,3-dihydro-isoindol-1-one,

4-{5-[7-Methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-ylmethyl}-piperazine-1-carbaldehyde,

2-Cyclopropylmethyl-5-[1-(2-fluorobenzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one,

7-Methyl-5-[3-(4-methyl-piperazin-1-ylmethyl)-[1,2,4] oxadiazol-5-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,

4-{5-[7-Methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-ylmethyl}-piperazine-1-carboxylic acid tert-butyl ester,

2-Cyclopropylmethyl-5-[1-(3-fluoro-benzyl)-piperidin-4-yl methyl]-7-methyl-2,3-dihydro-isoindol-1-one,

2-Cyclopropylmethyl-5-[1-(2-methoxy-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one,

2-Cyclopropylmethyl-5-[1-(3-methoxy-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one,

2-Cyclopropylmethyl-5-[1-(4-methoxy-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one,

2-Cyclopropylmethyl-5-[1-(4-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one,

2-Cyclohexylmethyl-5-[1-(3-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one,

2-Cyclohexylmethyl-5-[1-(4-fluoro-benzyl)-piperidin-4-ylmethyl]-7-methyl-2,3-dihydro-isoindol-1-one,

2-Cyclopropylmethyl-5-[1-(3-fluoro-benzyl)-piperidin-4-ylmethoxy]-7-methyl-2,3-dihydro-isoindol-1-one,

2-Cyclopropylmethyl-5-[1-(4-methoxybenzyl)-piperidin-4-ylmethoxy]-7-methyl-2,3-dihydro-isoindol-1-one,

5-(1-Benzyl-pyrrolidin-3-ylamino)-7-methyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,

7-Methyl-5-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl] 2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,

7-Methyl-5-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one,
4-{4-[7-Chloro-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile,
4-[4-(7-Chloro-2-cyclopropylmethyl-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl)-piperidine-1-ylmethyl]-benzonitrile,
4-{4-[7-Chloro-2-(4-chloro-benzyl)-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile,
4-{4-[7-Chloro-2-(4-difluoromethoxy-benzyl)- 1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile,
4-{4-[7-Chloro-2-(4-ethyl-benzyl)-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperidin-1-ylmethyl}-benzonitrile,
4-{4-[7-Chloro-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-piperazin-1-methyl}-nicotinonitrile,
3-{3-[1-(7-Chloro-2-cyclopropylmethyl-1-oxo-2,3-dihydro-1H-isoindol-5-ylmethyl)-piperidin-4-yl]-propyl}-benzonitrile,
7-Chloro-2-cyclopropylmethyl-1-oxo-2,3-dihydro-1H-isoindole-5-carbonitrile,
5-Fluoro-2-(4-ethyl-benzyl)-7-trifluoromethyl-2,3-dihydro-isoindol-1-one,
5,7-Dimethoxy-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1one,
5,7-Dimethoxy-2-(4-chloro-benzyl)-2,3-dihydro-isoindol-1one, and
5,7-Dimethoxy-2-[1-(4-chloro-phenyl)-ethyl]-2,3-dihydro-isoindol-1one;
or a pharmaceutically acceptable salt, hydrate, solvate, optical isomer, or combination thereof.

3. A pharmaceutical composition comprising a compound according to any one of claims 1 – 2 and a pharmaceutically acceptable carrier or excipient.

4. A compound according to any one of claims 1 – 2 for use as a medicament.

5. The use of a compound according to any one of claims 1 – 2 in the manufacture of a medicament for the therapy of neurological and psychiatric disorders associated with glutamate dysfunction.

6. The use of claim 5, wherein the neurological and psychiatric disorders are selected from cerebral deficit subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia, AIDS-induced dementia, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, cerebral deficits secondary to prolonged status epilepticus, migraine, migraine headache, urinary incontinence, substance tolerance, substance withdrawal, psychosis, schizophrenia, anxiety, generalized anxiety disorder, panic disorder, social phobia, obsessive compulsive disorder, and post-traumatic stress disorder (PTSD), mood disorders, depression, mania, bipolar disorders, circadian rhythm disorders, jet lag, shift work, trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain, acute pain, chronic pain, severe pain, intractable pain, neuropathic pain, inflammatory pain, and post-traumatic pain, tardive dyskinesia, sleep disorders, narcolepsy, attention deficit/hyperactivity disorder, and conduct disorder.

7. A method for the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction in an animal in need of such treatment, comprising the step of administering to said animal a therapeutically effective amount of a compound according to any one of claims 1 – 2.

8. A method for the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction in an animal in need of such treatment, comprising the step of administering to said animal a therapeutically effective amount of a pharmaceutical composition according to claim 3.

9. The method according to claim 7 or 8, wherein the neurological and psychiatric disorders are selected from cerebral deficit subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia, AIDS-induced dementia, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, cerebral deficits secondary to prolonged status epilepticus, migraine, migraine headache, urinary incontinence, substance tolerance, substance withdrawal, psychosis, schizophrenia, anxiety, generalized anxiety disorder, panic disorder, social phobia, obsessive compulsive disorder, and post-traumatic stress disorder (PTSD), mood disorders, depression, mania, bipolar disorders, circadian rhythm disorders, jet lag, shift work, trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain, acute pain, chronic pain, severe pain, intractable pain, neuropathic pain, inflammatory pain, and post-traumatic pain, tardive dyskinesia, sleep disorders, narcolepsy, attention deficit/hyperactivity disorder, and conduct disorder.

10. The method according to claim 9, wherein the neurological and psychiatric disorders are selected from Alzheimer's disease, cerebral deficits secondary to prolonged status epilepticus, substance tolerance, substance withdrawal, psychosis, schizophrenia, anxiety, generalized anxiety disorder, panic disorder, social phobia, obsessive compulsive disorder, and post-traumatic stress disorder (PTSD), mood disorders, depression, mania, and bipolar disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/005247

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/46 C07D401/04 C07D401/06 C07D401/12 C07D401/14
C07D403/06 C07D403/12 C07D413/04 C07D413/14 A61K31/4245
A61K31/4439 A61K31/4035 A61K31/506 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARR N ET AL: "Palladium-assisted organic reactions. VIII. Simple syntheses of 2,3-disubstituted phthalimidines" JOURNAL OF ORGANOMETALLIC CHEMISTRY, vol. 302, no. 1, 11 March 1986 (1986-03-11), pages 117-126, XP002383544 the whole document, particularly page 120, scheme 1, compounds 4d and 4g	1
X	US 5 681 954 A (YAMAMOTO K ET AL) 28 October 1997 (1997-10-28) the whole document, particularly examples 8 and 10	1,3-10
X	WO 2004/031178 A (PFIZER LIMITED) 15 April 2004 (2004-04-15) the whole document, particularly example 6	1,3-10

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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

Date of the actual completion of the international search	Date of mailing of the international search report
2 June 2006	28/06/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/005247

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOARAU C ET AL: "A versatile synthesis of poly- and diversely substituted isoindolin-1-ones" SYNTHESIS, no. 5, 2000, pages 655-660, XP002383545 the whole document, particularly page 656, compound 1c	1
X	RYS V ET AL: "A short total synthesis of the alkaloids piperolactam C, goniopedaline, and stigmalactam" EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol. 7, April 2003 (2003-04), pages 1231-1237, XP002383546 the whole document, particularly compounds 15-19	1
X	CLAYDEN J ET AL: "Dearomatizing anionic cyclization of substituted N-cumyl-N-benzyl-benzamides on treatment with LDA: synthesis of partially saturated substituted isoindolones" ORGANIC LETTERS, vol. 2, no. 26, 2000, pages 4229-4232, XP002345295 the whole document, particularly compound 11	1
X	COUTURE A ET AL: "Diastereoselective addition of metalated isoindolin-1-ones to aldehydes. Stereoselective preparation of (E)-3-arylideneisoindolin-1-on" TETRAHEDRON LETTERS, vol. 43, no. 12, 18 March 2002 (2002-03-18), pages 2207-2210, XP004344002 the whole document, particularly compounds 8 and 20	1
X	CASAGRANDE C ET AL: "Synthesis of some isoindolines and 1,2,3,4-tetrahydroisoquinolines and their evaluation as alpha-adrenergic and adrenergic neuron blocking agents" IL FARMACO, EDIZIONE SCIENTIFICA, vol. 27, no. 6, June 1972 (1972-06), pages 445-470, XP000571647 the whole document, particularly page 449, compounds XXVI-XXVIII	1,3-10
P,X	WO 2005/085216 A (NISSAN CHEMICAL INDUSTRIES, LTD.) 15 September 2005 (2005-09-15) the whole document, particularly abstract and page 332, compound 6-070	1,3-10

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/005247

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/085214 A (BANYU PHARMACEUTICAL CO., LTD) 15 September 2005 (2005-09-15) the whole document, particularly abstract and pages 133, 135, 177, 178, 180, 184-188, 194, 199, 202, 207 and 226	1,3-10
P,X	WO 2005/074643 A (SMITH BEECHAM CORPORATION) 18 August 2005 (2005-08-18) the whole document, particularly example 40	1,3-10
E	WO 2006/020879 A (ASTRAZENECA AB ET AL) 23 February 2006 (2006-02-23) the whole document	1-10
A	WO 99/26927 A (NPS PHARMACEUTICALS, INC.) 3 June 1999 (1999-06-03) the whole document	1,7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/005247

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/005247

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 1551828 A1	13-07-2005
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		MX PA05002735 A	23-05-2005
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		AU 2004202776 A1	22-07-2004
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		EP 1037878 A2	27-09-2000
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