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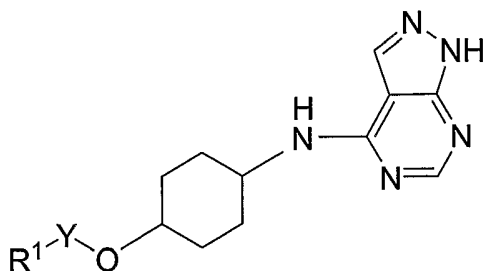
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 4-CYCLOALKYLAMINOPYRAZOLO PYRIMIDINE NMDA/NR2B ANTAGONISTS



(I)

(57) Abstract: Compounds represented by Formula (I): (where R¹ and Y are defined herein) or pharmaceutically acceptable salts thereof, are effective as NMDA/NR2B antagonists useful for treating neurological conditions such as, for example, pain, Parkinson's disease, Alzheimer's disease, epilepsy, depression, anxiety, ischemic brain injury including stroke, and other conditions.



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TITLE OF THE INVENTION

4-CYCLOALKYLAMINOPYRAZOLO PYRIMIDINE NMDA/NR2B ANTAGONISTS

FIELD OF THE INVENTION

5 This invention relates to 4-cycloalkylaminopyrazolo pyrimidine compounds. In particular, this invention relates to 4-cycloalkylaminopyrazolo pyrimidine compounds that are NMDA/NR2B antagonists useful for the treatment of neurological conditions such as pain, Parkinson's disease, Alzheimer's disease, epilepsy, depression, anxiety, ischemic brain injury including stroke, and other conditions.

BACKGROUND OF THE INVENTION

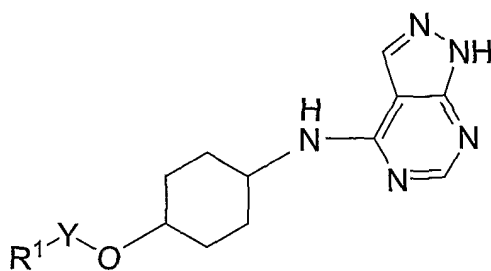
10 Ions such as glutamate play a key role in processes related to chronic pain and pain-associated neurotoxicity – primarily by acting through N-methyl-D-aspartate (“NMDA”) receptors. Thus, inhibition of such action – by employing ion channel antagonists, particularly NMDA antagonists – can be beneficial in the treatment and control of Parkinson's disease and pain.

15 NMDA receptors are heteromeric assemblies of subunits, of which two major subunit families designated NR1 and NR2 have been cloned. Without being bound by theory, it is generally believed that the various functional NMDA receptors in the mammalian central nervous system (“CNS”) are only formed by combinations of NR1 and NR2 subunits, which respectively express glycine and glutamate recognition sites. The NR2 subunit family is in turn divided into four individual subunit types: NR2A, NR2B, NR2C, and NR2D. T. Ishii, et al., *J. Biol. Chem.*, 268:2836-2843 (1993), and D.J. Laurie et al., *Mol. Brain Res.*, 51:23-32 (1997) describe how the various resulting combinations produce a variety of NMDA receptors differing in physiological and pharmacological properties such as ion gating properties, magnesium sensitivity, pharmacological profile, as well as in anatomical distribution.

20 For example, while NR1 is found throughout the brain, NR2 subunits are differentially distributed. In particular, it is believed that the distribution map for NR2B lowers the probability of side effects while treating Parkinson's disease or pain. Thus, it would be desirable to provide novel NMDA antagonists that target the NR2B receptor.

SUMMARY OF THE INVENTION

The present invention relates to 4-cycloalkylaminopyrazolo pyrimidine compounds represented by Formula (Ia):

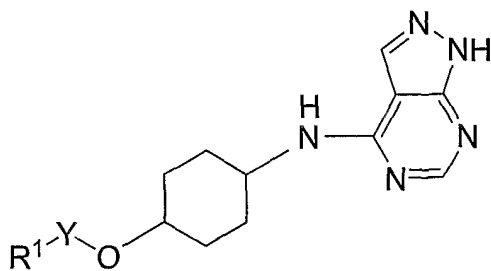


(Ia)

(where R¹ and Y are as defined herein) or pharmaceutically acceptable salts thereof. The present invention also provides pharmaceutical compositions comprising the instant compounds. This invention further provides methods to treat and prevent neurological conditions, including pain, Parkinson's disease, Alzheimer's disease, epilepsy, depression, anxiety, ischemic brain injury including stroke, and other conditions, utilizing the present compounds and compositions.

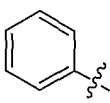
DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are represented by Formula (Ia):



(Ia)

wherein:

R¹ is , unsubstituted or substituted with halogen or -R², where R² is C₁-6alkyl, independently unsubstituted or substituted with one or more halogen;

Y is -C₁-6alkyl, independently unsubstituted or substituted with one or more halogen;

5

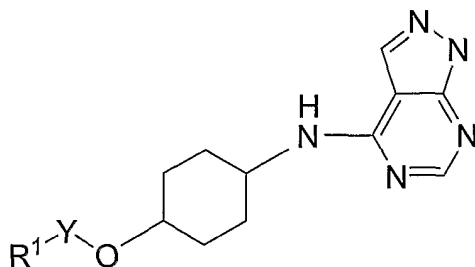
and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

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

The term "aryl", unless specifically stated otherwise, includes optionally substituted multiple and single ring systems such as, for example, phenyl, naphthyl and tolyl.

15

In the structures depicted throughout this application a hydrogen atom on an unsubstituted nitrogen atom may be either expressly shown or implicit. For example, the Formula Ia structure depicted above (with hydrogen atoms at two of the nitrogen atoms) may also be depicted as:



20 The same convention also applies to other generic structures and structures depicting individual species. Of course, nitrogen atoms may also be substituted with atoms and/or moieties other than hydrogen, as set forth elsewhere in this application. Further, multiple enantiomers be depicted to describe the same compound

25 The term "HetAr" includes, for example, heteroaromatic rings such as pyrimidine and pyridine.

The term " $(\text{CH}_2)_0$ " means that the methyl is not present. Thus, " $(\text{CH}_2)_{0-3}$ " means that there are from none to three methyls present – that is, three, two, one, or no methyl present. When no methyl groups are present in a linking alkyl group, the link is a direct bond.

As appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo. Similarly, C_{1-6} , as in C_{1-6} alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_{1-6} alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and hexyl. Likewise, C_0 , as in C_0 alkyl is defined to identify the presence of a direct covalent bond.

The term "substituted" is intended to include substitution at any or all position. Thus, substitution can be made at any of the groups. For example, substituted aryl(C_{1-6})alkyl includes substitution on the aryl group as well as substitution on the alkyl group.

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

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

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

added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

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

As used herein, "pharmaceutically acceptable salts" refer to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula Ia are meant to also include the pharmaceutically acceptable salts.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female, in whom antagonism of CGRP receptor activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought
5 by the researcher, veterinarian, medical doctor or other clinician. As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder.

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

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

The pharmaceutical compositions of the present invention comprise a compound
25 represented by Formula Ia (and/or pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the
30 conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The present invention is further directed to a method for the manufacture of a medicament for the antagonism of NMDA/NR2B receptor activity in humans and animals

comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

In practice, the compounds represented by Formula Ia, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula Ia, and/or pharmaceutically acceptable salt(s) thereof, may also be administered by controlled release means and/or delivery devices.

The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

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

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

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets.

Because of their ease of administration, tablets and capsules are the preferred oral dosage units

whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants.

5 Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.5mg to about 5g of the active ingredient and each
10 cachet or capsule preferably containing from about 0.5mg to about 5g of the active ingredient.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula Ia (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and
15 parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

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

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

Pharmaceutical compositions of the present invention can be in a form suitable
35 for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the

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

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

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

The utility of the compounds in accordance with the present invention as antagonists of NMDA/NR2B receptor activity may be demonstrated by methodology known in the art. Inhibition of the binding to NMDA receptors and functional antagonism of calcium efflux through NMDA channels were determined as follows:

Cell-Based Functional Assay To Determine IC₅₀ of NR2B Antagonists

The ability of selected compounds to inhibit NR1a/NR2B NMDA receptor, as measured by NR1a/NR2B receptor-mediated Ca²⁺ influx, was assessed by the following calcium flux assay procedure:

NR1a/NR2B receptor transfected L(tk-) cells were plated in 96-well format at 3 x 10⁴ cells per well and grown for one to two days in normal growth medium (Dulbeccos MEM with Na pyruvate, 4500 mg glucose, pen/strep, glutamine, 10% FCS and 0.5 mg/mL geneticin). NR1a/NR2B-expression in these cells was induced by the addition of 4-20 nM dexamethasone in the presence of 500 µM ketamine for 16 - 24 hours. Solutions of NR2B antagonists were prepared in DMSO and serially diluted with DMSO to yield 10 solutions differing by 3-fold in

concentration. A 96-well drug plate was prepared by diluting the DMSO solution 250-fold into assay buffer (Hanks Balanced Salt Solution (HBSS) Mg^{2+} free (Gibco #14175-079) containing 20 mM HEPES, 2 mM $CaCl_2$, 0.1 % BSA and 250 μ M Probenecid (Sigma # P-8761)). After induction, the cells were washed twice (Labsystem cell washer, 3 fold dilutions leaving 100 μ L) with assay buffer and loaded with 4 μ M of the calcium fluorescence indicator fluo-3 AM (Molecular Probes # P-1241) in assay buffer containing Pluronic F-127 (Molecular Probes # P-3000) and 10 μ M ketamine at 37 °C for one hour. The cells were then washed eight times with assay buffer leaving 100 μ L of buffer in each well. Fluorescence intensity was immediately measured in a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices) using an excitation of 488 nm and emission at 530 nm. Five seconds after starting the recording of fluorescence intensity, 50 μ L of agonist solution (40 μ M glutamate /glycine, the final concentration 10 μ M) was added and after one minute, when fluorescence signal was stable, 50 μ L of NR2B antagonists and control solutions from the drug plate were added and the fluorescence intensity recorded for another 30 minutes. The IC_{50} values were determined by a non-linear least squares fitting of the endpoint fluorescence values to Equation #1 below.

Equation #1:

$$\text{Endpoint Florescence} = \frac{(Y_{\text{max}} - Y_{\text{min}})}{1 + ([\text{Drug}] / IC_{50})^{nH}} + Y_{\text{min}}$$

where, Y_{min} is average endpoint fluorescence of the control wells containing 1 μ M of AMD-2 and Y_{max} is the average endpoint fluorescence of wells containing 0.1% DMSO in assay buffer.

Binding Assay To Determine K_i NR2B Antagonists

The radioligand binding assay was performed at room temperature in 96-well microtiter plates with a final assay volume of 1.0 mL in 20 mM Hepes buffer (pH 7.4) containing 150 mM NaCl. Solutions of NR2B antagonists were prepared in DMSO and serially diluted with DMSO to yield 20 μ L of each of 10 solutions differing by 3-fold in concentration. Non-specific binding (NSB) was assessed using AMD-1 (10 μ M final concentration), and total binding (TB) was measured by addition of DMSO (2% final concentration). Membranes expressing NR1a/NR2B receptors (40 pM final concentration) and tritiated AMD-2 (1 nM final concentration) were added to all wells of the microtiter plate. After 3 hours of incubation at room temperature,

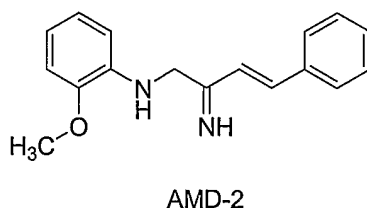
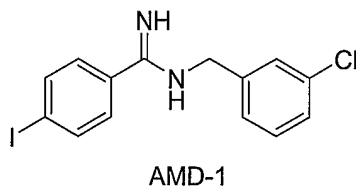
samples are filtered through Packard GF/B filters (presoaked in 0.05% PEI, polyethylenimine Sigma P-3143) and washed 10 times with 1 mL of cold 20 mM Hepes buffer per wash. After vacuum drying of the filter plates, 40 μ L of Packard Microscint-20 was added and bound radioactivity determined in a Packard TopCount. The apparent dissociation constant (K_I), the maximum percentage inhibition ($\%I_{\max}$), the minimum percentage inhibition ($\%I_{\min}$) and the hill slope (nH) were determined by a non-linear least squares fitting the bound radioactivity (CPM bound) to Equation #2 below.

Equation #2:

$$\text{CPM Bound} = \frac{(\text{SB})(\%I_{\max} - \%I_{\min})/100}{(1 + ([\text{Drug}]/(K_I (1 + [\text{AMD-2}]/K_D)))^{nH})} + \text{NSB} + (\text{SB})(100 - \%I_{\max})/100$$

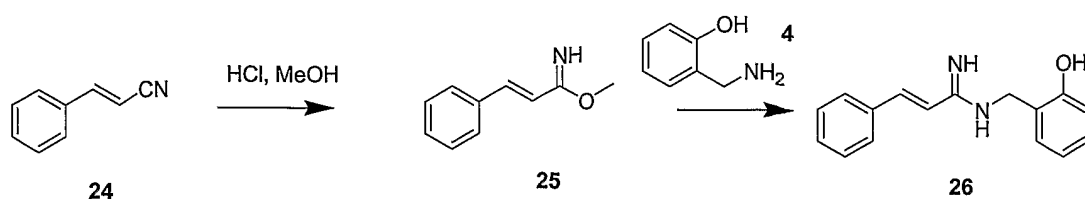
where, K_D is the apparent dissociation constant for the radioligand for the receptor as determined by a hot saturation experiment and SB is the specifically bound radioactivity determined from the difference of TB and NSB control wells.

Synthesis of AMD-1 and AMD-2 may be accomplished according to the following reaction schemes:



The precursor **26** for the synthesis of radiolabelled AMD-1 can be synthesized in accordance with the following procedure:

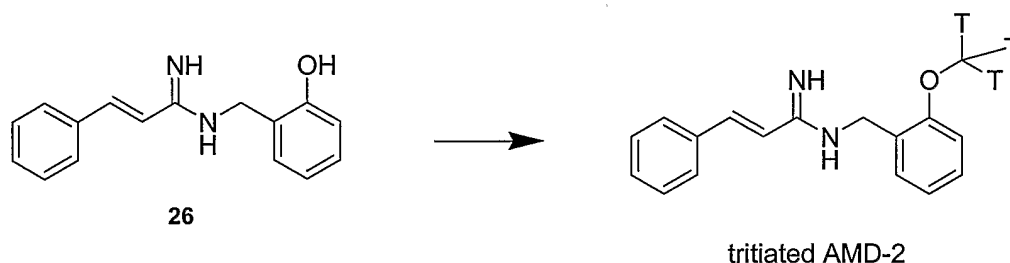
Reaction A



In accordance with the procedures of Reaction A, hydrogen chloride is bubbled through a solution of cinnamionitrile **24** in methanol at room temperature. The volatiles are removed under reduced pressure and the resulting residue is triturated with ether and filtered to yield the intermediate imidate **25**. Imidate **25** is dissolved in methanol at ambient temperature, treated with amine **27** (commercially available from Acros Chemicals) at ambient temperature and stirred under argon. The volatiles are removed under reduced pressure and the residue purified by preparative HPLC or trituration with ether to afford amidine **26**.

Titrated AMD-2 can be synthesized according to the following procedure:

Reaction B

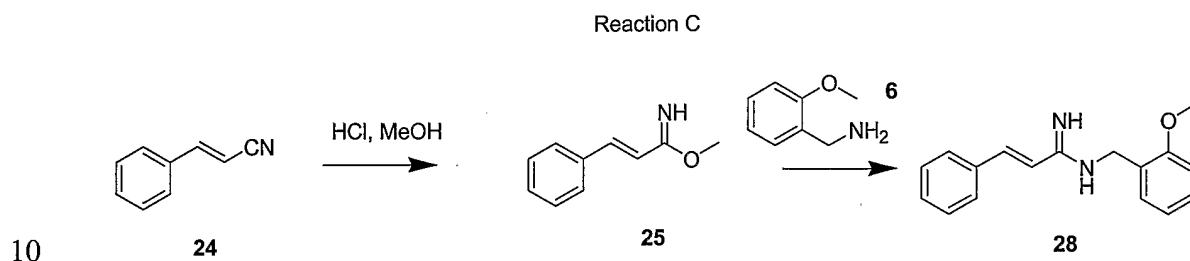


Tritiated AMD-2 was prepared by the following procedure, illustrated above in Reaction B: The precursor **26** (2mg, 0.008mmol) dissolved in dimethylformamide (0.6mL) and potassium carbonate (1.2mg) for 1h. High specific activity tritiated methyl iodide (50mCi, 0.0006mmol, in toluene 1mL, commercially available from American Radiolabeled Chemicals) was added at room temperature and stirred for 2 hours. The reaction mixture was filtered using a Whatman PTFE 0.45µm syringeless filter device to remove any insoluble potassium carbonate, washed with Abs. ethanol (2mL, commercially available from Pharmco), and the combined filtrates were concentrated to dryness at room temperature using a rotary evaporator; this also removed any unreacted tritiated methyl iodide. The residue was purified by HPLC chromatography on a Phenomenx Luna C8 semi-prep column (Luna 5 micro C8(2), 250x10.0

mm) using a gradient system of 20/80 acetonitrile/water with 0.1% trifluoroacetic acid to 100% acetonitrile with 0.1% trifluoroacetic acid in 20min. Total activity of the product was 8mCi. Further purification was effected by absorption onto a Waters C-18 Sep-pak column (Waters Sep-Pak PLUS C18) and elution with water followed by absolute ethanol. The product was
 5 diluted with absolute ethanol (10mL) before submission for final analysis.

AMD-1 can be synthesized according to the general procedure described by C. F. Claiborne et al (Bioorganic & Medchem Letters **13**, 697-700 (2003).

Unlabelled AMD-2 is prepared as follows:



In accordance with Scheme 1b, hydrogen chloride is bubbled through a solution of cinnamitrile **24** in methanol at room temperature. The volatiles are removed under reduced pressure and the resulting residue is triturated with ether and filtered to yield the intermediate
 15 imidate **25**. Imidate **25** is dissolved in methanol at ambient temperature, treated with amine **29** at ambient temperature and stirred under argon. The volatiles are removed under reduced pressure and the residue purified by preparative HPLC or trituration with ether to afford amidine **28**.

The compounds of this invention exhibit IC_{50} and K_I values of less than 50 μM in the functional and binding assays, respectively. It is advantageous that the IC_{50} and K_I values
 20 be less than 5 μM in the functional and binding assays, respectively. It is more advantageous that the IC_{50} and K_I values be less than 1 μM in the functional and binding assays, respectively. It is still more advantageous that the IC_{50} and K_I values be less than 0.1 μM in the functional and binding assays, respectively.

The present compounds are NMDA NR2B receptor antagonists, and as such are
 25 useful for the treatment and prophylaxis of diseases and disorders mediated through the NR2B receptor. Such diseases and disorders include, but are not limited to, Parkinson's disease, neuropathic pain (such as postherpetic neuralgia, nerve injury, the "dynias", e.g., vulvodinia, phantom limb pain, root avulsions, painful diabetic neuropathy, painful traumatic mononeuropathy, painful polyneuropathy), central pain syndromes (potentially caused by

virtually any lesion at any level of the nervous system), and postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, stump pain)), bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain, 5 dysmenorrhea, as well as pain associated with angina, and inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis and gout), headache, migraine and cluster headache, depression, anxiety, schizophrenia, stroke, traumatic brain injury, Alzheimer's disease, cerebral ischemia, amyotrophic lateral sclerosis, Huntington's disease, sensorineural hearing loss, tinnitus, glaucoma, neurological damage caused by epileptic seizures 10 or by neurotoxin poisoning or by impairment of glucose and/or oxygen to the brain, vision loss caused by neurodegeneration of the visual pathway, Restless Leg Syndrome, multi-system atrophy, non-vascular headache, primary hyperalgesia, secondary hyperalgesia, primary allodynia, secondary allodynia, or other pain caused by central sensitization. Compounds of formula I may be used to prevent dyskinesias, particularly the side effects accompanying normal 15 doses of L- Dopa. Furthermore, compounds of formula I may be used to decrease tolerance and/or dependence to opioid treatment of pain, and for treatment of withdrawal syndrome of e.g., alcohol, opioids, and cocaine.

The compounds of this invention are also useful for treating or preventing HIV- and HIV treatment-induced neuropathy, chronic pelvic pain, neuroma pain, complex regional 20 pain syndrome, chronic arthritic pain and related neuralgias, treating or preventing chronic lower back pain, and treating or preventing pain resulting from, or associated with, traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, cancer and chemotherapy.

25 It is understood that compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions, as well as to prevent other conditions mediated through the NMDA NR2B receptor.

Compounds of Formula Ia may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for 30 which compounds of Formula Ia are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula Ia. When a compound of Formula Ia is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula Ia is preferred. Accordingly, the pharmaceutical compositions of the 35 present invention include those that also contain one or more other active ingredients, in addition

to a compound of Formula Ia. Examples of other active ingredients that may be combined with a compound of Formula Ia, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (1) non-steroidal anti-inflammatory agents; (2) COX-2 inhibitors; (3) bradykinin B1 receptor antagonists; (4) sodium channel blockers and antagonists; (5) nitric oxide synthase (NOS) inhibitors; (6) glycine site antagonists; (7) potassium channel openers; (8) AMPA/kainate receptor antagonists; (9) calcium channel antagonists; (10) GABA-A receptor modulators (e.g., a GABA-A receptor agonist); (11) matrix metalloprotease (MMP) inhibitors; (12) thrombolytic agents; (13) opioids such as morphine; (14) neutrophil inhibitory factor (NIF); (15) L-Dopa; (16) carbidopa; (17) levodopa/carbidopa; (18) dopamine agonists such as bromocriptine, pergolide, pramipexole, ropinirole; (19) anticholinergics; (20) amantadine; (21) carbidopa; (22) catechol O-methyltransferase ("COMT") inhibitors such as entacapone and tolcapone; (23) Monoamine oxidase B ("MAO-B") inhibitors; (24) opiate agonists or antagonists; (25) 5HT receptor agonists or antagonists; (26) NMDA receptor agonists or antagonists; (27) NK1 antagonists; (28) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"); (29) tricyclic antidepressant drugs, (30) norepinephrine modulators; (31) lithium; (32) valproate; and (33) neurontin (gabapentin).

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

A formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms can generally contain between from about 1mg to about 1000mg of the active ingredient.

The conditions recited herein can be treated or prevented by the administration of from about 0.01mg to about 140mg of the instant compounds per kilogram of body weight per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the type and severity of the particular disease undergoing therapy. For example, inflammatory pain may be effectively treated by the administration of from about 0.01mg to about 75mg of the present compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Neuropathic pain may be

effectively treated by the administration of from about 0.01mg to about 125mg of the present compound per kilogram of body weight per day, or alternatively about 0.5mg to about 5.5g per patient per day.

The abbreviations used herein are as follows unless specified otherwise:

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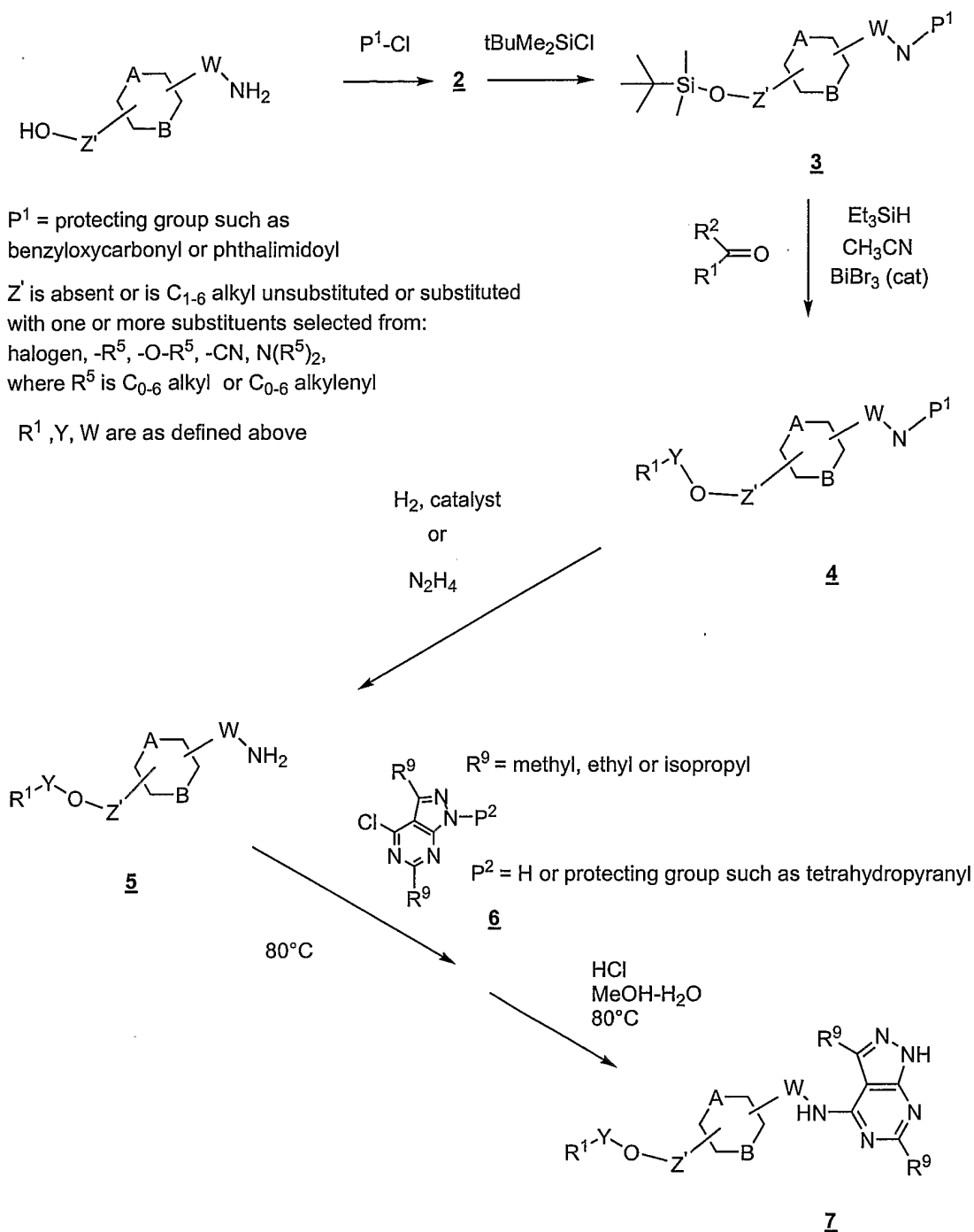
4-MeBnOH	4-Methylbenzyl alcohol
CDI	1,1'-Carbonyldiimidazole
TEA	Triethylamine
TBSCl	t-Butyldimethylsilyl chloride
DMF	Dimethylformamide
(+)-BINAP	(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
NaOtBu	Sodium t-butoxide
DIPEA	Diisopropylethylamine
EtOAc	Ethyl acetate
TBSOTf	t-Butyldimethylsilyl triflate
TBS	t-butyldimethylsilyl
THF	Tetrahydrofuran
DMAP	4-Dimethylaminopyridine
RT	Room temperature
h	Hours
min	Minutes
DCM	Dichloromethane
MeCN	Acetonitrile
iPrOH	2-Propanol
n-BuOH	1-Butanol
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOAt	1-Hydroxy-7-azabenzotriazole

10

The compounds of the present invention can be prepared readily according to the following Schemes and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail. The general procedures for making the compounds claimed in this invention can be readily understood and appreciated by one skilled in the art from viewing the following Schemes.

15

Scheme 1



The synthesis of certain aryl-alkoxy substituted cycloalkanes is depicted in Scheme 1. In the first step, a hydroxy-cycloalkyl-amine **1** is protected with a suitable nitrogen protecting group stable to acidic conditions, such as benzyloxycarbonyl or phthalimidoyl. The

5

butyldimethylsilyloxy, triethylsilyloxy-, triisopropylsilyloxy or trimethylsilyloxy-ether **3** using the standard literature procedures such as the one described in the literature (E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190-91. The trialkylsilyloxy-ether **3** is then reductively alkylated with an aldehyde or ketone in the presence of a trialkylsilane such as

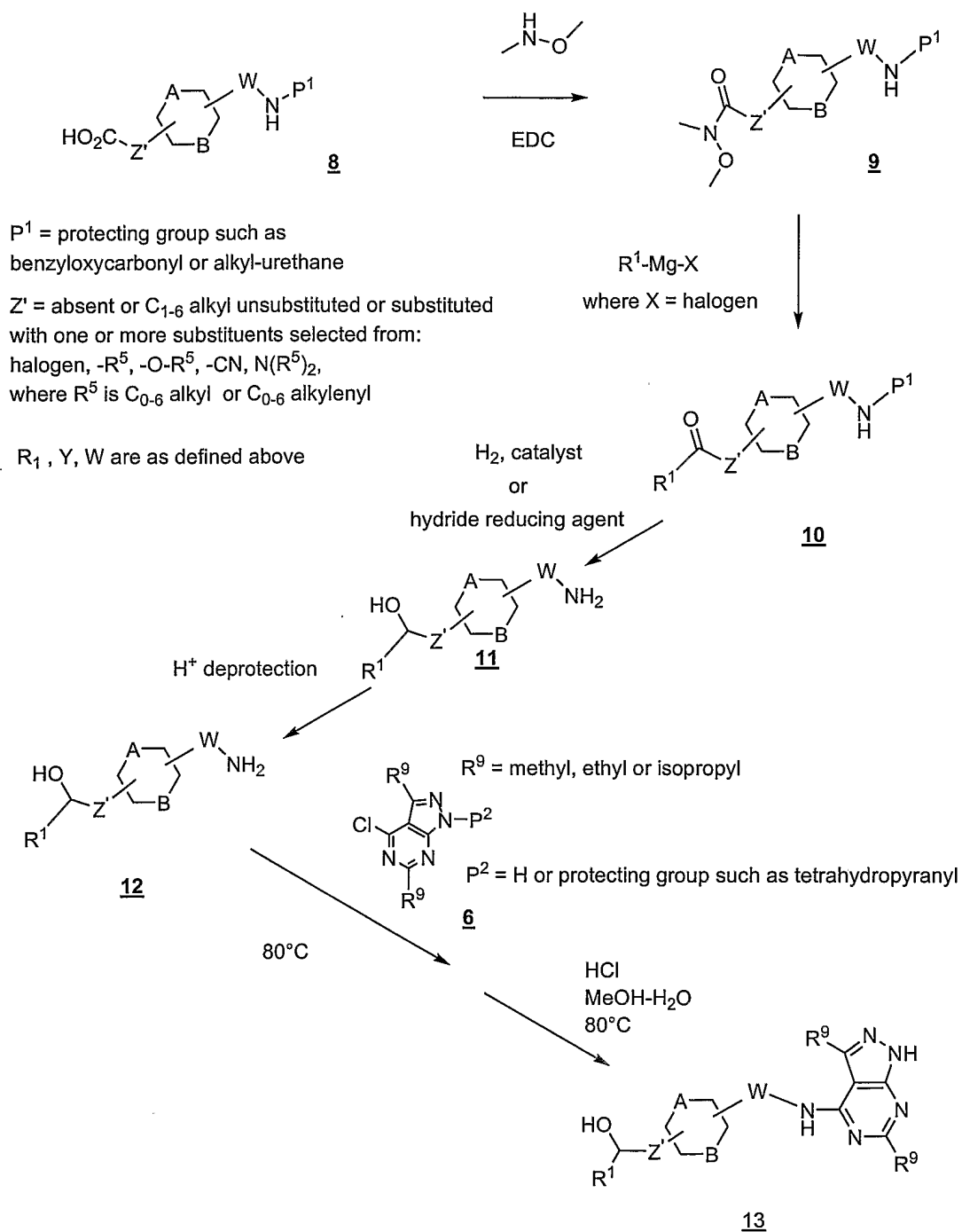
5 triethylsilane or tert-butyldimethylsilane and a suitable aprotic acid catalyst such as trimethylsilyl triflate (S. Hatakeyama, H. Mori, K. Kitano, H. Yamada, and M. Nishizawa, *Tetrahedron Lett.*, **1994**, *35*, 4367-70.), trimethylsilyl bromide or iodide (M. B. Sassaman, K. D. Kotian, G.K. Surya Prakash, and G. A. Olah, *J. Org. Chem.*, **1987**, *52*, 4314-19) yielding an arylalkyl ether **4**. A convenient procedure for generating the trialkylsilyl bromide catalyst in situ, is through the

10 addition of catalytic amounts of bismuth tribromide in acetonitrile solvent (N. Komatsu, J. Ishida, H. Suzuki, *Tetrahedron Lett.*, **1997**, *38*, 7219-22; J. S. Bojwa, X. Jiang, J. Slade, K. Prasad, O. Repic, T. J. Blacklock, *Tetrahedron Lett.* **2002**, *43*, 6709-13). The nitrogen protecting group is removed in the next step using standard methods such as hydrogenolysis, hydrazinolysis or acid hydrolysis, generating the amine-ether **5**. The amine is alkylated with 4-chloro-1H-

15 pyrazolo[3,4-d]pyrimidine **6** (R.K. Robins, *J. Amer. Chem. Soc.*, **78**, 784-790 (1956)) using standard alkylation conditions providing the 4-amino-1H-pyrazolo[3,4-d]pyrimidines **7**. As an alternative, a suitably N-alkoxymethyl protected derivative of **6** such as N-tetrahydropyranyl, N-tetrahydrofuranyl, or N-ethoxyethylidene provides cleaner products and avoids polymeric products arising from further alkylation of the 1H-pyrazolo[3,4-d]pyrimidine N-1 nitrogen. This

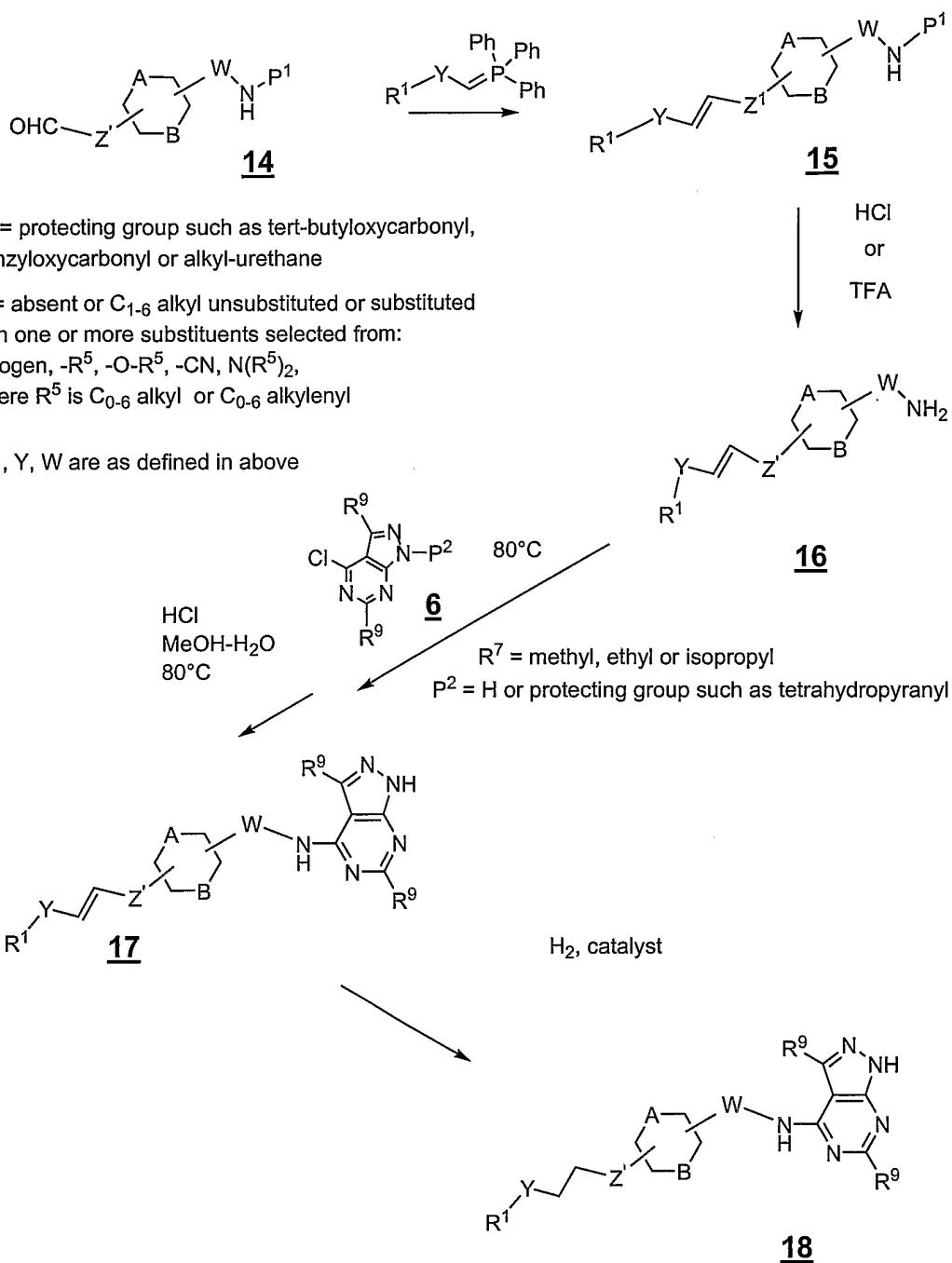
20 type of protecting group is easily removed by brief treatment with aqueous acid in the last step.

Scheme 2



The synthesis of certain aryl-hydroxy-alkyl substituted cycloalkanes is depicted in Scheme 2. In the first step, a carboxy-cycloalkyl-amine is protected with a suitable nitrogen protecting group stable to organomagnesium or organolithium reagents, such as benzyloxycarbonyl or tert-butyloxycarbonyl urethanes. The protected carboxy-cycloalkyl-amine 8 is converted into an N-methoxy-N-methyl amide 9 using the standard literature procedures. The N-methoxy-N-methyl amide is converted into an arylalkyl ketone 10 using an organometallic reagent as described in the literature (S. Nahm and S. M. Weinreb, Tetrahedron Lett., 1981, 22, 3815-3818). The ketone 10 is reduced to alcohol 11 with a hydride reagent such as sodium borohydride or hydrogenated with a catalyst. An alternative procedure is to convert either the N-methoxy-N-methyl amide 9 or the carboxylic acid 8 into an aldehyde derivative 14 which undergoes addition of the organometallic reagent to form the alcohol 11. The nitrogen protecting group is removed in the next step using standard methods such as hydrogenolysis, hydrazinolysis or acid hydrolysis, generating the amine-alcohol 12. The amine 12 is alkylated with 4-chloro-1H-pyrazolo[3,4-d]pyrimidine 6 (R.K. Robins, J. Amer. Chem. Soc., 78, 784-790 (1956)) using standard alkylation conditions providing the 4-amino-1H-pyrazolo[3,4-d]pyrimidines 7. As an alternative, a suitably N-alkoxymethyl protected derivative of 6 such as N-tetrahydropyranyl, N-tetrahydrofuranyl, or N-ethoxyethylidene provides cleaner products and avoids polymeric products arising from further alkylation of the 1H-pyrazolo[3,4-d]pyrimidine N-1 nitrogen. This type of protecting group is easily removed by brief treatment with aqueous acid in the last step.

Scheme 3



The synthesis of certain aryl-alkyl substituted cycloalkanes is depicted in Scheme 3. In the first step, an aldehyde-cycloalkyl-amine **14**, protected with a suitable nitrogen protecting group stable to organomagnesium or organolithium reagents, such as benzyloxycarbonyl or tert-butyloxycarbonyl urethanes, is reacted with a phosphorane reagent

(Wittig reagent) using the standard literature procedures. The resulting olefin-urethane **10** is deprotected using standard methods such as, acid hydrolysis, generating the amine-olefin **16**. The amine **16** is alkylated with 4-chloro-1H-pyrazolo[3,4-d]pyrimidine **6** (R.K. Robins, J. Amer. Chem. Soc., 78, 784-790 (1956)) using standard alkylation conditions providing the 4-amino-1H-pyrazolo[3,4-d]pyrimidines **17**. As an alternative, a suitably N-alkoxymethyl protected derivative of **6** such as N-tetrahydropyranyl, N-tetrahydrofuranyl, or N-ethoxyethylidene provides cleaner products and avoids polymeric products arising from further alkylation of the 1H-pyrazolo[3,4-d]pyrimidine N-1 nitrogen. This type of protecting group is easily removed by brief treatment with aqueous acid in the last step. The olefin **17** is reduced to alkyl-cycloalkyl-4-amino-1H-pyrazolo[3,4-d]pyrimidine **18** hydrogenation over a catalyst.

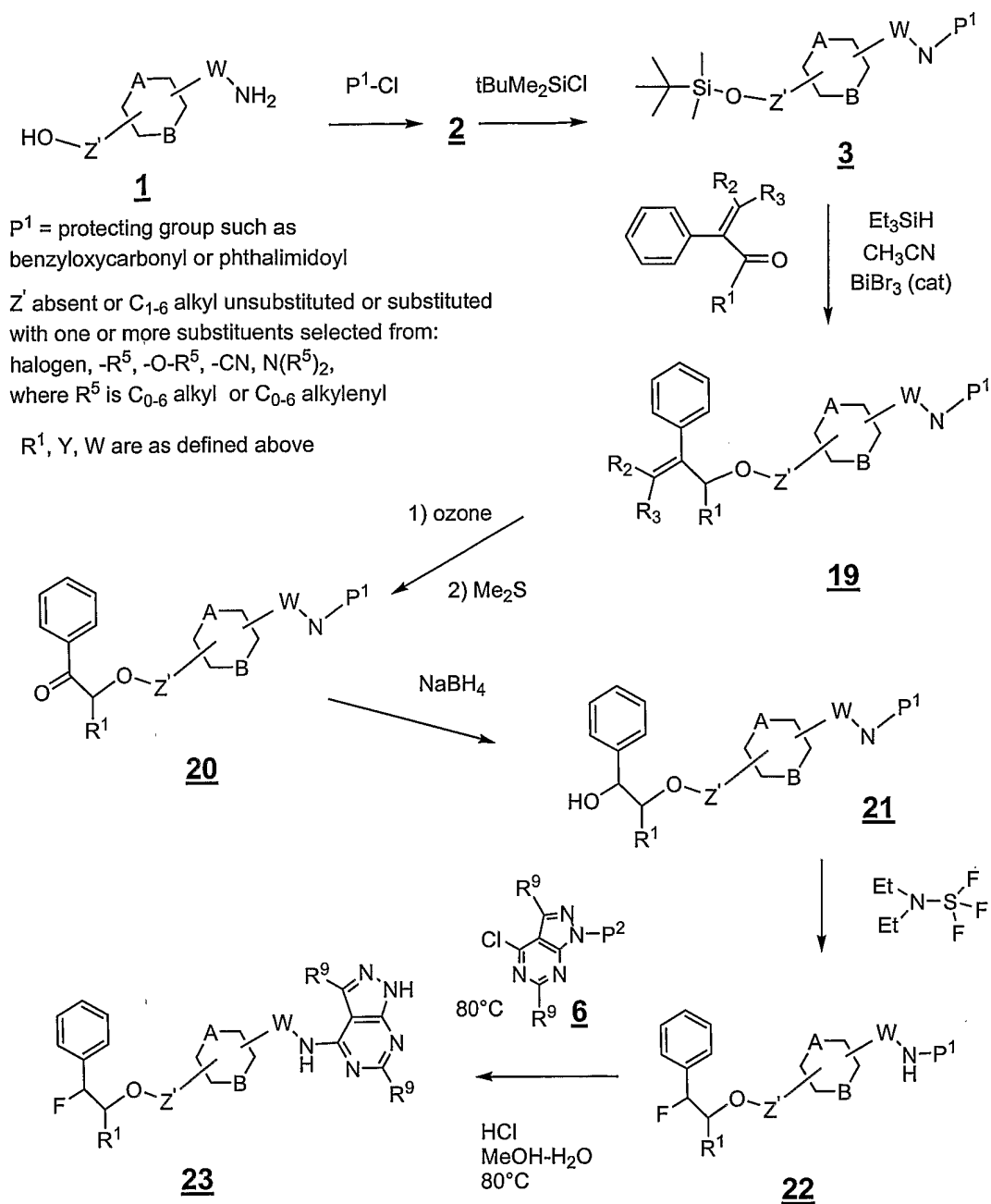
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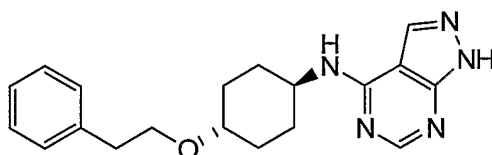
Scheme 4



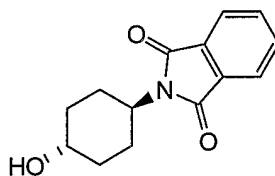
A preferred embodiment is the incorporation of a fluorine substituent into the alkyl-, hydroxy-alkyl or alkoxy side chain or cyclohexane ring. This can be effected by reaction of a hydroxy intermediate such as 11, 21 or 22 with diethylaminosulfur trifluoride [DAST] similar reagent as illustrated in Scheme 4. The incorporation of geminal a difluoro substituent can be effected through the use of diethyl sulfur trifluoride on a ketone intermediate such as 20. The ketone and hydroxy intermediates 20 and 21 can be obtained as shown in Scheme 4 by the ether synthesis described for Scheme 1 substituting an unsaturated aldehyde or ketone in the alkylation step. Cleavage of the olefin intermediate 19 yields the ketone 20 which can be further reduced to give hydroxy intermediate 21 with a hydride reducing agent such as sodium borohydride. Reaction of the hydroxy intermediate 21 with diethyl sulfur trifluoride generates the fluoro compound 22. Conversion of 21 into the 4-amino-1H-pyrazolo[3,4-d]pyrimidine 23 uses the methodology as described in Schemes 1-3 above. The use of a chiral reducing agent further provides a majority of the desired enantiomer of 21. This enantiomerically enhanced form of 21 yields a majority of the desired enantiomer of the chiral fluoro compound 23.

Example 1

trans-(4-Phenethyloxy-cyclohexyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine



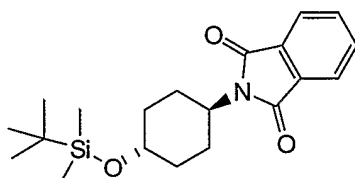
Step 1: trans-2-(4-Hydroxy-cyclohexyl)-isoindole-1,3-dione



A mixture of 31 grams of trans-4-aminocyclohexanol, 550 mL of anhydrous THF, 45 mL of triethylamine and 53 g of N-carboethoxy-phthalimide was heated to reflux for 18 h, cooled, and diluted with 1500 mL of ethyl acetate. The solution was washed with 250 mL of 10% HCl, 100 mL of saturated sodium bicarbonate then dried over magnesium sulfate. Concentration under reduced pressure gave 66 g of product as a white crystalline solid contaminated with ethyl

carbamate. This material was sufficiently pure for the next step, although it could be recrystallized from boiling ethyl acetate-hexane. ¹H NMR (400 MHz, CDCl₃) 7.8 (m, 2H), 7.7 (m, 2H), 4.15 (m, 1H), 3.7 (m, 1H), 2.3 (dd, 2H), 2.1 (d, 2H), 1.78 (d, 2H), 1.4 (dd, 2H).

5 Step 2: trans-2-(4-(tert-Butyl-dimethyl-silyloxy-cyclohexyl)-isoindole-1,3-dione

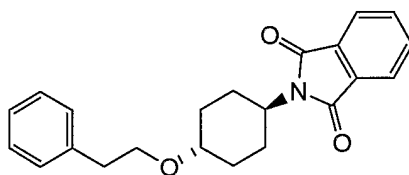


A mixture of 13 g of 2-(4-hydroxy-cyclohexyl)-isoindole-1,3-dione (Compound 1), 10 g of tert-butyldimethylsilyl chloride, 9.3 g of imidazole and 40 mL of DMF was stirred for 24 h.

- 10 The mixture was diluted with 500 mL of ether and washed with 3 x 500 mL portions of water, dried over magnesium sulfate and concentrated under reduced pressure. The product crystallized under vacuum as a white solid: 18.5 g. ¹H NMR (400 MHz, CDCl₃) 7.8 (m, 2H), 7.7 (m, 2H), 4.15 (m, 1H), 3.7 (m, 1H), 2.3 (dd, 2H), 2.1 (d, 2H), 1.78 (d, 2H), 1.4 (dd, 2H), 0.9 (s, 9H), 0.5 (s, 6H).

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Step 3: trans-2-(4-Phenylethyloxy-cyclohexyl)-isoindole-1,3-dione

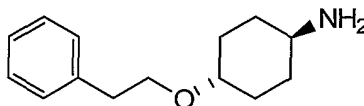


- 20 To a solution of 10 g of ethyl phenylacetate in 100 mL of dry toluene cooled to -78°C under nitrogen was added drop-wise 68 mL of 0.9 M di-isobutyl-aluminum hydride in toluene, keeping the internal temperature below -68°C. When the addition was complete, the reaction was quenched with 200 mL of 10% HCl, and extracted into 2 x 100 mL portions of ether. The combined ether layers were washed with 2 x 100 mL portions of 10% HCl, 100 mL of saturated sodium bicarbonate, diluted with 100 mL of toluene, and dried over magnesium sulfate.

25 Concentration under reduced pressure gave 7.1 g of phenyl acetaldehyde as a volatile liquid. ¹H NMR (400 MHz, CDCl₃) 9.8 (s, 1H), 7.5-7.2 (m, 5H), 3.7 (s, 2H). To a stirred mixture of 10 g

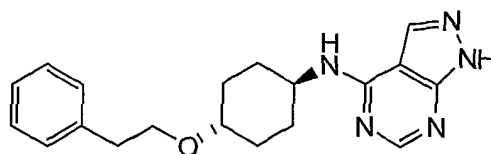
of trans-2-(4-(tert-butyl-dimethyl-silyloxy-cyclohexyl)-isoindole-1,3-dione (Compound 2), 150 mL of anhydrous acetonitrile, 7 mL of triethylsilane and 0.7 g of bismuth tribromide was added 5 g of the freshly prepared phenyl acetaldehyde slowly keeping the temperature at or below 25°C by means of a cooling bath. After stirring for 2 h, the reaction was quenched with 50 mL of saturated sodium bicarbonate and extracted with 3 x 150 mL portions of ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over silica gel eluting with a gradient of 2%-25% ethyl acetate in hexane gave 9.0 g of product as a white crystalline solid: ¹H NMR (400 MHz, CDCl₃) 7.8 (m, 2H), 7.7 (m, 2H), 7.3-7.1 (m, 5H), 4.15 (m, 1H), 3.7 (t, 2H), 3.38 (m, 1H), 2.9 (t, 2H), 2.22 (d, 2H), 2.3 (dd, 2H), 2.18 (d, 2H), 1.78 (d, 2H), 1.4 (dd, 2H).

Step 4: trans 4-Phenylethyloxy-cyclohexylamine



To a solution of 9 g of trans-2-(4-phenylethyloxy-cyclohexyl)-isoindole-1,3-dione in 60 mL of THF and 150 mL of ethanol was added 3.75 mL of hydrazine hydrate and the mixture heated to reflux for 4 h, then 80 mL of 6N HCl was added and the reflux was continued for 1h. The cooled mixture was concentrated under reduced pressure to remove ethanol and filtered. The filter pad was washed with 2 x 50 mL of dilute HCl and the combined filtrates basified to pH 10 with 20% sodium hydroxide and extracted with 3 x 150 mL portions of chloroform. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Further drying under vacuum gave 6 g of product as an oil. MS (m+1) = 220.2; ¹H NMR (400 MHz, CDCl₃) 7.3-7.1 (m, 5H), 3.7 (t, 2H), 3.2 (m, 1H), 2.9 (t, 2H), 2.7 (m, 1H), 2.0 (d, 2H), 1.85 (d, 2H), 1.4 (br s, 2H), 1.3 (dd, 2H), 1.15 (dd, 2H).

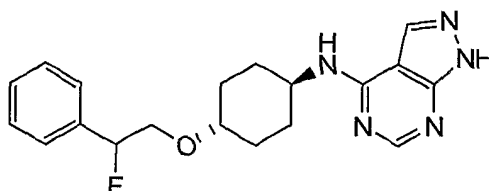
Step 5: trans-(4-Phenethyloxy-cyclohexyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine



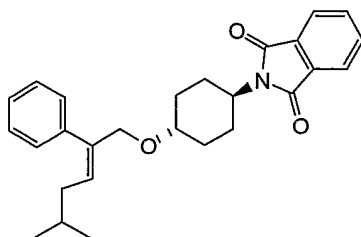
A mixture of 219 mg of trans-4-(2-phenyl-ethoxy)-cyclohexylamine, 154 mg of 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (R.K. Robins, J. Amer. Chem. Soc., 78, 784-790 (1956)), 10 mL of 2-propanol and 0.174 mL of N,N-diisopropyl-ethylamine was heated to 80°C for 12 hours. The mixture was cooled and concentrated under reduced pressure and purified by either preparative TLC eluting with 50:50:5 THF: diethyl ether: NH₄OH or preparative reverse phase chromatography on delta Pak C (C-18 column) eluting with a gradient of 90:10 to 0:100 of 0.1% TFA in H₂O: CH₃CN gave 60-92% of (4-phenethyloxy-cyclohexyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine as a white crystalline solid. MS (m+1) = 338.32; ¹H NMR (400 MHz, CDCl₃) 8.43 (s, 1H), 7.92 (s, 1H), 7.3-7.2 (m, 5H), 3.7 (t, 2H), 3.3 (m, 1H), 2.9 (t, 2H), 2.22 (d, 2H), 2.1 (d, 2H), 1.7 (m, 1H), 1.5 (dd, 2H), 1.4 (m, 2H).

Example 2

trans-[4-(2-Fluoro-2-phenyl-ethoxy-cyclohexyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine

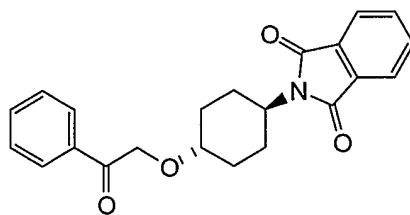


Step 1: trans-2-[4-(5-Methyl-2-phenyl-hex-2-enyloxy)-cyclohexyl]-isoindole-1,3-dione



To a stirred mixture of 1 g of trans-2-(4-(tert-butyl-dimethyl-silyloxy-cyclohexyl)-
 isoindole-1,3-dione, 20 mL of anhydrous acetonitrile, 0.8 mL of triethylsilane and 0.6 g of 5-
 5 methyl-2-phenyl-2-hexenal (commercial, predominantly trans was added) 0.08 g of bismuth
 tribromide. After stirring for 1.3 h, the reaction was quenched with 10 mL of saturated sodium
 bicarbonate and extracted with 3 x 25 mL portions of ethyl acetate. The combined extracts were
 dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over
 silica gel eluting with a gradient of 1%-20% ethyl acetate in hexane gave first 0.30 g of saturated
 product, trans-2-[4-(5-methyl-2-phenyl-hexyloxy)-cyclohexyl]-isoindole-1,3-dione, then 0.50 g
 of product as a resin: ¹H NMR (400 MHz, CDCl₃) 7.8 (m, 2H), 7.7 (m, 2H), 7.3-7.1 (m, 5H),
 5.8 (t, 1H), 4.25 (s, 2H), 4.15 (m, 2H), 3.4 (m, 1H), 2.3 (m, 2H), 2.1 (d, 2H), 1.9 (t, 2H), 1.75 (d,
 2H), 1.65 (m, 1H), 1.35 (m, 2H), 1.3 (t, 2H), 0.9 (d, 6H).

Step 2: trans-2-[4-(2-Oxo-2-phenyl-ethoxy)-cyclohexyl]-isoindole-1,3-dione

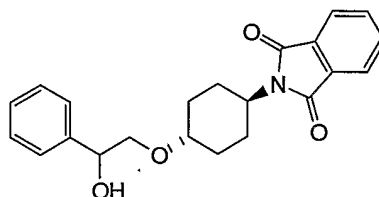


To a stirred solution of 2 g of trans-2-[4-(5-methyl-2-phenyl-hex-2-enyloxy)-
 cyclohexyl]-isoindole-1,3-dione in 100 mL of dichloromethane cooled to -78°C was dispersed a
 stream of ozone from an ozone generator until a blue color persisted. The excess ozone was
 purged with nitrogen until the blue color dissipated, and 5 mL of methyl sulfide was added.
 After warming to room temperature over 30 min, the solution was concentrated under reduced
 pressure. Chromatography over silica gel eluting with a gradient of 2%-30% ethyl acetate in
 hexane gave 1.8 g of product as a white crystalline solid: ¹H NMR (400 MHz, CDCl₃) 8.0 (d,

2H), 7.8 (m, 2H), 7.6 (t, 1H), 7.5 (t, 2H), 4.8 (s, 2H), 4.18 (m, 1H), 3.5 (m, 1H), 2.35 and 2.25 (overlapping dd and d, 4H), 1.8 (d, 2H), 1.5 (dd, 2H).

Step 3: trans-2-[4-(2-Hydroxy-2-phenyl-ethoxy)-cyclohexyl]-isoindole-1,3-dione

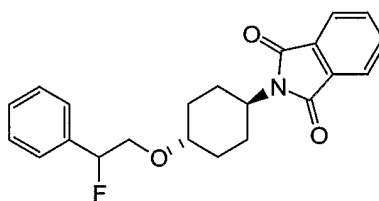
5



A mixture of 1 g of trans-2-[4-(2-oxo-2-phenyl-ethoxy)-cyclohexyl]-isoindole-1,3-dione and 0.1 g of 10% palladium on carbon in 100 mL of ethanol was stirred under 1 atm. of hydrogen overnight. The catalyst was filtered off and the filtrate concentrated to dryness under reduced pressure. Drying under vacuum gave 1.0 g of product as a white crystalline solid: ¹H NMR (400 MHz, CDCl₃) 7.8 (m, 2H), 7.65 (t, 1H), 7.4-7.2 (m, 5H), 4.82 (d, 1H), 4.1 (m, 1H), 3.65 (m, 2H), 3.4 (m, 2H), 2.3 (dd, 2H), 2.2 (m, 2H), 1.8 (d, 2H), 1.4 (dd, 2H).

Step 4: trans-2-[4-(2-Fluoro-2-phenyl-ethoxy)-cyclohexyl]-isoindole-1,3-dione

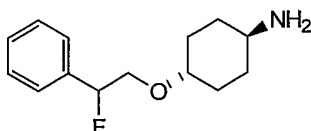
15



To a stirred solution of 1 g of trans-2-[4-(2-hydroxy-2-phenyl-ethoxy)-cyclohexyl]-isoindole-1,3-dione in 100 mL of dichloromethane cooled to -78°C under nitrogen atmosphere was added 1.2 g of diethyl-amino sulfur-trifluoride. The mixture was allowed to warm and stir for 24 h, then quenched with 25 mL of saturated sodium carbonate. After stirring for 15 min, the mixture was diluted with 25 mL of dichloromethane and the layers separated. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The catalyst was filtered off and the filtrate concentrated to dryness under reduced pressure. Chromatography over silica gel eluting with a gradient of 2%-30% ethyl acetate in hexane gave 0.7 g of product as a white crystalline solid: ¹H NMR (400 MHz, CDCl₃) 7.8 (m, 2H), 7.7 (t, 1H), 7.4-7.3 (m,

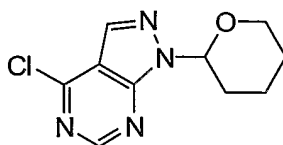
5H), 5.6 (dd, 1H), 4.1 (m, 1H), 3.9-3.65 (complex m, 2H), 3.45 (m, 1H), 2.3 (dd, 2H), 2.2 (m, 2H), 1.8 (d, 2H), 1.4 (dd, 2H).

Step 5: trans-4-(2-Fluoro-2-phenyl-ethoxy)-cyclohexyl-amine



To a solution of 0.7 g of racemic trans-2-[4-(2-fluoro-2-phenyl-ethoxy)-cyclohexyl]-isoindole-1,3-dione in 15 mL of THF and 15 mL of ethanol was added 0.3 mL of hydrazine hydrate and the mixture heated to reflux for 4 h, then 5 mL of 6N HCl was added and the reflux was continued for 1h. The cooled mixture was concentrated under reduced pressure to remove ethanol and filtered. The filter pad was washed with 2 x 10 mL of dilute HCl and the combined filtrates basified to pH 10 with 20% sodium hydroxide and extracted with 3 x 25 mL portions of chloroform. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Further drying under vacuum gave 0.4 g of product as an oil. MS (m+1) = 238.3.

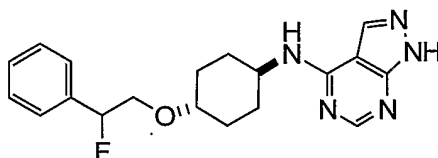
Step 6: 4-Chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine and 4-chloro-2-(tetrahydro-pyran-2-yl)-2H-pyrazolo[3,4-d]pyrimidine



A mixture of 8.5 g of 4-chloro-pyrazolo[3,4-d]pyrimidine, 600 mL of ethyl acetate, and 400 mg of camphor-sulfonic acid was stirred overnight. The mixture was washed with 25 mL of saturated sodium carbonate, dried over magnesium sulfate and concentrated to dryness under reduced pressure. Chromatography over silica gel eluting with a gradient of 1%-20% ethyl acetate in hexane gave 12 g of the 1- THP product as a white crystalline solid which was stored under nitrogen in the freezer: ¹H NMR (400 MHz, CDCl₃) 8.8 (s, 1H), 8.2 (s, 1H), 6.05 (d, 1H). Later fractions eluting with ethyl acetate contained 1.5 g the isomeric 2-THP product: ¹H NMR (400 MHz, CDCl₃) 8.25 (s, 1H), 8.15 (s, 1H), 5.85 (m, 1H). The ratio of the two isomeric

products varied, but either isomer could be used in the alkylation step to generate a 4-alkylamino-pyrazolo[3,4-d]pyrimidine.

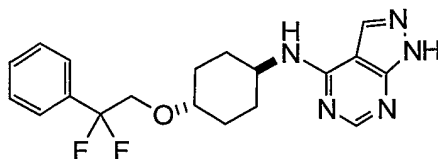
Step 7: trans-[4-(2-Fluoro-2-phenyl-ethoxy)-cyclohexyl]-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine



A mixture of 0.4 g of trans-4-(2-fluoro-2-phenyl-ethoxy)-cyclohexyl-amine, 0.5 g of 4-chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine, and 0.4 mL of N,N-diisopropylethylamine in 25 mL of 2-propanol was heated to reflux under nitrogen overnight. The mixture was cooled and concentrated under reduced pressure. The tan residue was taken up in 200 mL of ethyl acetate, washed with 20 mL of saturated sodium bicarbonate, dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over silica gel eluting with a gradient of 50%-100% ethyl acetate in hexane gave 0.72 g of product as a white solid. The solid was taken up in 75 mL of methanol and 5 mL of 6N HCl and heated at reflux for 15 minutes, cooled and concentrated under reduced pressure to dryness. The solid residue was treated with 10 mL of concentrated aqueous ammonia and again concentrated to dryness. The resulting residue was extracted with 100 mL of chloroform, filtered and concentrated to dryness under reduced pressure. Chromatography over silica gel eluting with a gradient of 1%-5% methanol in ethyl acetate gave 0.45 g of product as a white solid: MS (m+1) = 356.3; ¹H NMR (400 MHz, CDCl₃) 8.4 (s, 1H), 7.9 (s, 1H), 7.4-7.3 (m, 5H), 5.6 (dd, 1H), 3.9-3.65 (complex m, 3H), 3.4 (m, 1H), 2.3 (m, 2H), 2.2 (m, 2H), 1.75-1.4 (m, 4H). Resolution into the pure enantiomers could be performed by isocratic elution on ChiralPak AD at 1 mL/min, eluting with 20% methanol in 2-propanol.

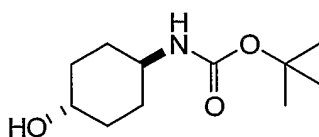
Example 3

trans [4-(2,2-Difluoro-2-phenyl-ethoxy)-cyclohexyl]-carbamic acid tert-butyl ester



Step 1: trans (4-Hydroxy-cyclohexyl)-carbamic acid tert-butyl ester

5

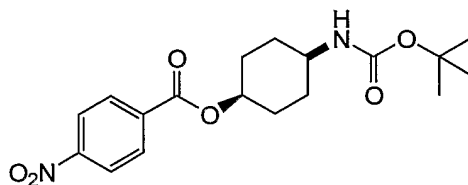


A mixture of 5 g of trans 4-aminocyclohexanol and 9.5 g of di-tert-butyl di-carbonate in 200 mL of THF was heated to reflux for 2 h at which time the mixture became homogeneous.

- 10 The mixture was cooled and concentrated under reduced pressure. Drying under vacuum gave 9.34 g of product as a white crystalline solid; ¹H NMR (400 MHz, CDCl₃) 4.4 (br s, 2H), 3.6 (m, 1H), 3.4 (br s, 1H), 2.0 (t, 4H), 1.45 (s, 9H), 1.4 (dd, 2H), 1.2 (dd, 2H).

Step 2: cis (4-Hydroxy-cyclohexyl)-carbamic acid tert-butyl ester

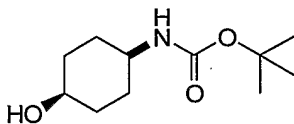
15



To a stirred mixture of 2.2 g of trans (4-hydroxy-cyclohexyl)-carbamic acid tert-butyl ester, 4 g of triphenyl-phosphine, 4.2 g of 4-nitrobenzoic acid, 120 mL of benzene and 10 mL of THF was added 3.5 g of diisopropyl-azo-di-carboxylate over 5 min. The mixture was allowed to stir at room temperature for 4 h and then concentrated under reduced pressure, taken up in 250 mL of dichloromethane and filtered and again concentrated. Chromatography on silica gel eluting with a gradient of 2%-20% ethyl acetate in hexane gave 1.2 g of product as a crystalline solid; ¹H NMR (400 MHz, CDCl₃) 8.3 (d, 2H), 8.2 (d, 2H), 3.8 (br m, 1H), 3.6 (br m, 1H), 2.4 (d, 1H), 2.1-1.6 (complex m, 8H), 1.45 (s, 9H).

25

Step 3: cis (4-Hydroxy-cyclohexyl)-carbamic acid tert-butyl ester



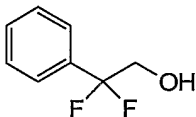
5

A mixture of 1.2 g of cis (4-hydroxy-cyclohexyl)-carbamic acid tert-butyl ester, 20 mL of 2N sodium hydroxide and 50 mL of THF was heated to reflux for 12 h. The mixture was cooled, diluted with 50 mL of water and extracted with 3 x 50 mL portions of ether. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Drying under vacuum gave 0.70 g of product as a white crystalline solid; ¹H NMR (400 MHz, CDCl₃) 4.5 (m, 1H), 3.9 (m, 1H), 3.5 (br s, 1H), 1.6 (m, 8H), 1.42 (s, 9H).

10

Step 4: 2,2-Difluoro-2-phenyl-ethanol

15

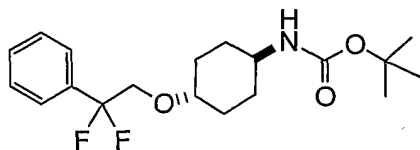


A stirred mixture of 2.2 g of difluoro-2-phenyl acetic acid ethyl ester (W.J. Middleton, E.M. Bingham, J. Org. Chem., 45, 2883-2887 (1980)), and 0.6 g of sodium borohydride in 75 mL of ethanol was kept at room temperature overnight, concentrated to near dryness under reduced pressure carefully acidified with 20 mL of 5% HCl and extracted into 3 x 50 mL of dichloromethane. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Drying under vacuum gave 1.7 g of product as an oil: ¹H NMR (400 MHz, CDCl₃) 7.5 (m, 5H), 4.0 (t, 2H).

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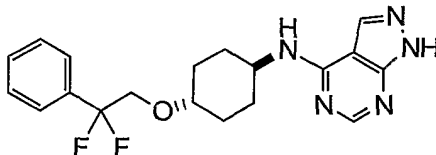
25

Step 5: trans [4-(2,2-Difluoro-2-phenyl-ethoxy)-cyclohexyl]-carbamic acid tert-butyl ester



To a stirred mixture of 0.23 g of g of cis-(4-hydroxy-cyclohexyl)-carbamic acid tert-butyl ester, 0.54 g of 1.1'-(azodicarbonyl)-dipiperidine and 20 mL of benzene was added 0.4 g of tri-n-butyl-phosphine and 1.3 g (8 equivalents) of 2,2-difluoro-2-phenyl-ethanol. The mixture was heated to 60°C overnight, then an additional 0.5 g of 1.1'-(azodicarbonyl)-dipiperidine and 0.4 g of tri-n-butyl-phosphine was added and heating continued for another 24 h. The mixture was cooled, diluted with 25 mL of toluene, filtered and the filter pad washed with 5 mL of toluene. The filtrate was purified by chromatography on silica gel eluting with a gradient of 0%-20% ethyl acetate in hexane gave 0.15 g of product as a resin: ¹H NMR (400 MHz, CDCl₃) 7.5 (m, 5H), 3.95 (m, 2H), 3.4 (m, 1H), 1.95 (m, 2H), 1.6 (m, 6H), 1.45 (s, 9H).

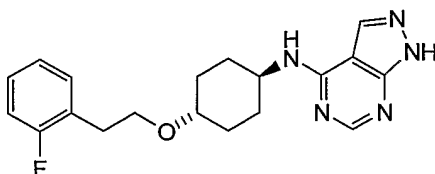
Step 6: trans [4-(2,2-Difluoro-2-phenyl-ethoxy)-cyclohexyl]-carbamic acid tert-butyl ester



A mixture of 0.15 g of trans [4-(2,2-difluoro-2-phenyl-ethoxy)-cyclohexyl]-carbamic acid tert-butyl ester and 10 mL of 4N HCl in dioxane was stirred at room temperature for 4 h then concentrated to dryness under reduced pressure. The resulting HCl salt was taken up in 10 mL of 2-propanol with 0.05 g of 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (R.K. Robins, J. Amer. Chem. Soc., 78, 784-790 (1956)), and 0.3 mL of N,N-diisopropyl-ethylamine and heated to 80°C for 12 hours. The mixture was cooled and concentrated under reduced pressure and the crude product purified by either preparative TLC eluting with 50:50:5 THF: diethyl ether: NH₄OH gave 20 mg of (4-phenethyloxy-cyclohexyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine as a white crystalline solid. MS (m+1) = 374.1; ¹H NMR (400 MHz, CDCl₃) 8.43 (s, 1H), 7.95 (s, 1H), 7.5-7.4 (m, 5H), 3.7 (t, 2H), 3.4 (m, 1H), 2.2 (d, 2H), 2.1 (d, 2H), 1.7 (m, 1H), 1.5 (dd, 2H), 1.4 (m, 2H).

Example 4

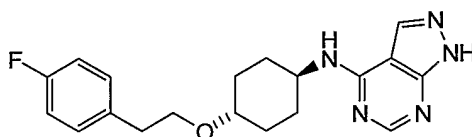
trans-{4-[2-(2-Fluoro-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine



From 2-fluoro-phenylacetic acid ethyl ester, using the procedure described for the preparation of Example 1, Step 3 gave trans-{4-[2-(2-fluoro-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine as a white solid: MS (*m*+1) = 356.1; ¹H NMR (400 MHz, CDCl₃) 8.4 (s, 1H), 7.92 (s, 1H), 7.2 (m, 2H), 7.05 (m, 2H), 4.0 (m, 1H), 3.65 (m, 2H), 3.3 (m, 1H), 2.95 (m, 2H), 2.22 (d, 2H), 2.15 (d, 2H), 1.7 (m, 1H), 1.5 (m, 2H), 1.4 (m, 2H).

Example 5

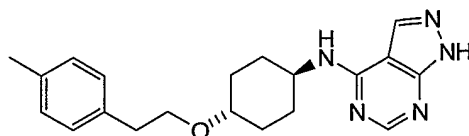
trans-{4-[2-(4-Fluoro-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine



From 4-fluoro-phenylacetic acid methyl ester, using the procedure described for the preparation of Example 1, Step 3 gave trans-{4-[2-(4-fluoro-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine as a white solid: MS (*m*+1) = 356.1; ¹H NMR (400 MHz, CDCl₃) 8.4 (s, 1H), 7.92 (s, 1H), 7.2 (m, 2H), 6.95 (m, 2H), 4.0 (m, 1H), 3.65 (m, 2H), 3.3 (m, 1H), 2.85 (m, 2H), 2.22 (d, 2H), 2.15 (m, 2H), 2.0 (m, 1H), 1.9 (m, 1H), 1.4 (m, 2H).

Example 6

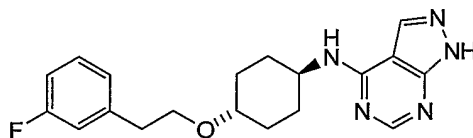
trans-{4-[2-(4-Methyl-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine



From 4-methyl-phenylacetic acid ethyl ester, using the procedure described for the preparation of Example 1, Step 3 gave trans-{4-[2-(4-methyl-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine as a white solid: MS (*m*+1) = 352.2; ¹H NMR (400 MHz, CDCl₃) 8.42 (s, 1H), 7.92 (s, 1H), 7.1 (dd, 4H), 4.0 (m, 1H), 3.68 (m, 2H), 3.3 (m, 1H), 2.85 (m, 2H), 2.35 (s, 3H), 2.22 (d, 2H), 2.15 (d, 2H), 2.0 (m, 1H), 1.4 (m, 4H).

Example 7

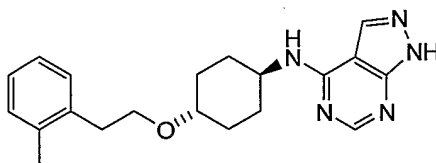
trans-{4-[2-(3-Fluoro-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine



From 3-fluoro-phenylacetic acid methyl ester, using the procedure described for the preparation of Example 1, Step 3 gave trans-{4-[2-(3-fluoro-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine as a white solid: MS (*m*+1) = 356.1; ¹H NMR (400 MHz, CDCl₃) 8.41 (s, 1H), 7.92 (s, 1H), 7.21 (m, 1H), 6.9 (m, 3), 4.1 (m, 1H), 3.68 (m, 2H), 3.3 (m, 1H), 2.85 (m, 2H), 2.22 (d, 2H), 2.15 (d, 2H), 1.6 (m, 1H), 1.45 (m, 2H), 1.2 (m, 2H).

Example 8

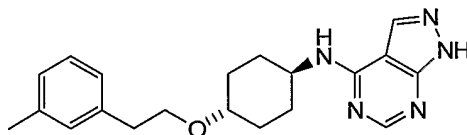
trans-{4-[2-(2-Methyl-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine



From 2-methyl-phenylacetic acid ethyl ester, using the procedure described for the preparation of Example 1, Step 3 gave trans-{4-[2-(2-methyl-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine as a white solid: MS (*m*+1) = 352.1; ¹H NMR (400 MHz, CDCl₃) 8.42 (s, 1H), 7.92 (s, 1H), 7.15 (m, 4H), 4.0 (m, 1H), 3.68 (m, 2H), 3.3 (m, 1H), 2.85 (m, 2H), 2.34 (s, 3H), 2.22 (d, 2H), 2.15 (d, 2H), 1.7 (m, 1H), 1.5 (m, 2H), 1.4 (m, 2H)..

Example 9

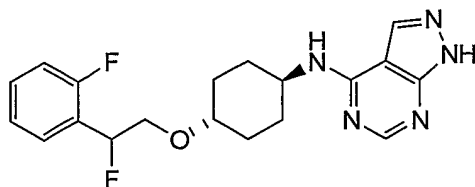
trans-{4-[2-(3-Methyl-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine



From 3-methyl-phenylacetic acid ethyl ester, using the procedure described for the preparation of Example 1, Step 3 gave trans-{4-[2-(3-methyl-phenyl)-ethoxy]-cyclohexyl}-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine as a white solid: MS (*m*+1) = 352.4; ¹H NMR (400 MHz, CDCl₃) 8.42 (s, 1H), 7.92 (s, 1H), 7.2 (m, 1H), 7.0 (m, 3H), 4.0 (m, 1H), 3.68 (m, 2H), 3.3 (m, 1H), 2.85 (m, 2H), 2.33 (s, 3H), 2.22 (d, 2H), 2.15 (d, 2H), 1.7 (m, 1H), 1.5 (m, 2H), 1.4 (m, 2H).\

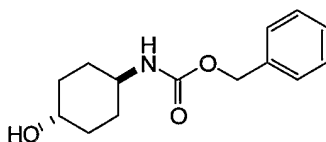
Example 10

trans-[4-(2-Fluoro-2-(2-fluorophenyl)-ethoxy-cyclohexyl)-(1H-pyrazolo[3,4d]pyrimidin-4-yl)-amine



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Step 1: trans (4-Hydroxy-cyclohexyl)-carbamic acid benzyl ester

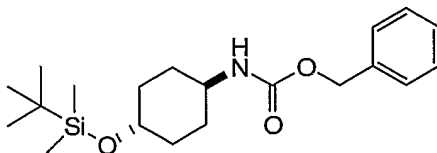


10 To an ice cold mixture of 50 g of trans 4-aminocyclohexanol in 500 mL of ethyl acetate and 500 mL of THF was added 200 mL of saturated sodium carbonate and the 65 mL of benzyl chloroformate drop-wise over 20 min. The mixture was allowed to warm and stir overnight and the precipitated product collected by filtration and washed with 200 mL of water. After drying

15 separated and the aqueous layer extracted with 3 x 100 mL of ethyl acetate. The combined ethyl acetate extracts were dried over magnesium sulfate and concentrated under reduced pressure. Trituration with ether-hexane gave an additional 35.5 g of product as a white crystalline solid. MS (m+1) = 250.4; ¹H NMR (400 MHz, CDCl₃) 7.4-7.3 (m, 5H), 5.1 (s, 2H), 4.6 (s, 1H), 3.6 (m, 1H), 3.5 (m, 1H), 2.0 (dd, 4H), 1.6 (d, 1H), 1.4 (dd, 2H), 1.2 (dd, 2H).

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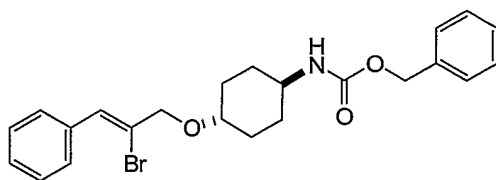
Step 2: trans (4-tert-Butyl-dimethyl-silanyloxy-cyclohexyl)-carbamic acid benzylester



25

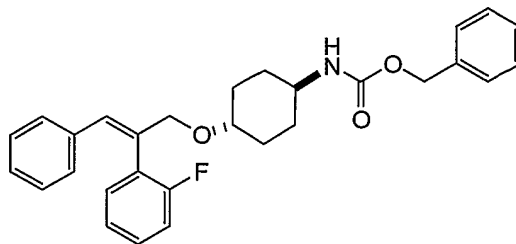
A mixture of 30.5 g of trans-(4-hydroxy-cyclohexyl)-carbamic acid benzylester, 23 g of tert-butyldimethylsilyl chloride, 64 g of imidazole and 55 mL of DMF was stirred for 24 h. The mixture was diluted with 250 mL of ether and washed with 4 x 250 mL portions of water, dried over magnesium sulfate and concentrated under reduced pressure. The product slowly
 5 crystallized under vacuum as a low melting solid: 45 g; ¹H NMR (400 MHz, CDCl₃) 7.4-7.3 (m, 5H), 5.1 (s, 2H), 4.6 (s, 1H), 3.6 (m, 1H), 3.5 (m, 1H), 2.0 (d, 2H), 1.8 (d, 2H), 1.6 (d, 1H), 1.4 (dd, 2H), 1.2 (dd, 2H), 0.9 (s, 9H), 1.05 (s, 6H).

Step 3: trans-[4-(2-Bromo-3-phenyl-allyloxy)-cyclohexyl]-carbamic acid benzyl ester



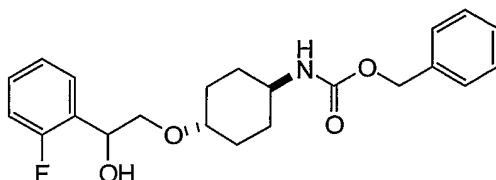
To a stirred mixture of 7.3 g of trans (4-tert-butyl-dimethyl-silanyloxy-cyclohexyl)-carbamic acid benzylester and 5.7 g of 2-bromocinnamaldehyde in 140 mL of anhydrous acetonitrile was added 0.57 g of bismuth tribromide. After 15 min, 5.8 mL of triethyl-silane was
 15 added drop-wise over 15 min. After stirring for 1 h, the reaction was complete by TLC analysis and was quenched with 50 mL of saturated sodium bicarbonate, allowed to stir until the black precipitated bismuth metal was consumed with the formation of a white precipitate and extracted with 3 x 250 mL portions of ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over silica gel eluting with a
 20 gradient of 0%-20% ethyl acetate in hexane gave 7.6 g (90%) of product as a white crystalline solid: MS (m+1) = 444.3; ¹H NMR (400 MHz, CDCl₃) 7.6 (d, 2H), 7.35 (m, 8H), 7.07 (s 1H), 5.08 (s, 2H), 4.6 (s, 1H), 4.28 (s, 2H), 3.6 (m, 1H), 3.4 (m, 1H), 2.06 (d, 4H), 1.48 (dd, 2H), 1.2 (dd, 2H).

Step 4: trans-[4-(2-(2-Fluorophenyl)-3-phenyl-allyloxy)-cyclohexyl]-carbamic acid benzyl ester



A stirred mixture of 0.44 g of trans-[4-(2-bromo-3-phenyl-allyloxy)-cyclohexyl]-carbamic acid benzyl ester, 0.15 g of 2-fluorophenylboronic acid, 0.47 g of barium hydroxide octahydrate, 25 mg of tetrakis-triphenylphosphine palladium, 6 mL of DME and 1 mL of water was heated to reflux for 12 h. The mixture was cooled and partitioned between 10 mL of sodium carbonate and 3 x 20 mL of ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over silica gel eluting with a gradient of 0%-20% ethyl acetate in hexane gave 0.42 g of product as a white crystalline solid: MS (m+1) = 460.4; ¹H NMR (400 MHz, CDCl₃) 7.3-7.2 (m, 9H), 7.1-6.95 (m, 5H), 6.8 (s, 1H), 5.05 (s, 2H), 4.55 (s, 1H), 4.28 (s, 2H), 3.5 (m, 1H), 3.3 (m, 1H), 2.0 (m, 4H), 1.4 (dd, 2H), 1.15 (dd, 2H).

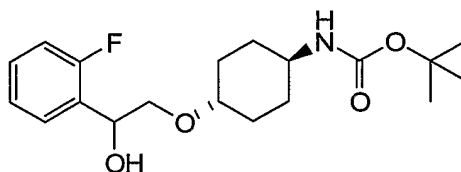
Step 5: trans-[4-(2-Fluoro-2-(2-fluorophenyl)-ethoxy-cyclohexyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine



To a stirred solution of 41 g of trans-[4-(2-(2-fluorophenyl)-3-phenyl-allyloxy)-cyclohexyl]-carbamic acid benzyl ester in 750 mL of dichloromethane and 250 mL of methanol cooled to -78°C was dispersed a stream of ozone from an ozone generator until a blue color persisted. The excess ozone was purged with nitrogen until the blue color dissipated, and 7.8 g of sodium borohydride was added. After warming to room temperature over 30 min, the solution was diluted with 50 mL of water and concentrated under reduced pressure. The residue was treated with 500 mL of 3N hydrochloric acid and extracted into 3 X 500 mL of ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over silica gel eluting with a gradient of 2%-30% ethyl acetate in hexane gave 30 g of product as a white crystalline solid: MS (m+1) = 388.4; ¹H NMR (400 MHz, CDCl₃)

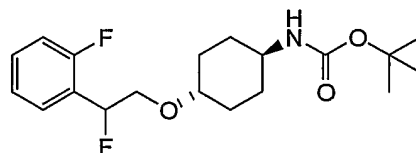
7.53 (m, 1H), 7.33 (m, 5H), 7.25 (m, 1H), 7.14 (m, 1H), 7.0 (m, 1H), 5.15 (d, 1H), 5.07 (s, 2H), 4.6 (m, 1H), 3.7 (d, 1H), 3.5 (br m, 1H), 3.4 (t, 1H), 3.3 (m, 1H), 2.9 (s, 1H), 2.0 (m, 4H), 1.2 (q, 2H), 1.15 (q, 2H).

5 Step 6: *tert*-butyl {*trans*-4-[2-(2-fluorophenyl)-2-hydroxyethoxy]-cyclohexyl} carbamate



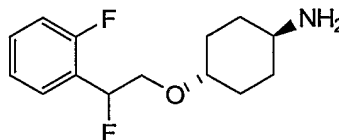
A solution of 26 g of benzyl {*trans*-4-[2-(2-fluorophenyl)-2-hydroxyethoxy]cyclohexyl} carbamate and 19.4 g of di-*tert*-butyldicarbonate in 300 mL of ethanol was stirred with 3 g of 10% palladium on carbon under 1 atm of hydrogen for 18 h.. After removal of the catalyst by filtration and concentration under reduced pressure the product was crystallized by trituration with hexane. Drying under reduced pressure gave 24 g of product as a white crystalline solid: MS (m+1) = 354.4 ; ¹H NMR (400 MHz, CDCl₃) 7.52 (m, 1H), 7.25 (m, 1H), 7.18 (m, 1H), 7.0 (m, 1H), 5.17 (d, 1H), 4.4 (br s, 1H), 3.7 (d, 1H), 3.4 (m, 2H), 3.3 (m, 1H), 2.9 (s, 1H), 2.0 (d, 4H), 1.43 (s, 9H), 1.4 (m, 2H), 1.15 (q, 2H).

Step 7: *tert*-butyl {*trans*-4-[2-fluoro-2-(2-fluorophenyl)ethoxy]cyclohexyl} carbamate



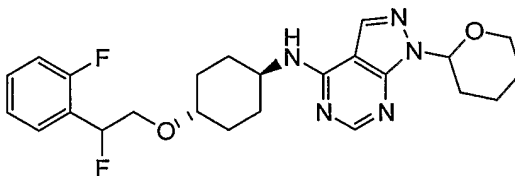
A solution of 18 g of *tert*-butyl {*trans*-4-[2-(2-fluorophenyl)-2-hydroxyethoxy]-cyclohexyl} carbamate in 200 mL of dichloromethane was added over 30 min to a solution of 23 g of diethyl-amino sulfur-trifluoride in 800 mL of dichloromethane cooled to -78°C under nitrogen atmosphere. The mixture was allowed stir for 1 h at -78°C then quenched with 100 mL of saturated sodium carbonate. After stirring for 15 min the layers were separated. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over silica gel eluting with a gradient of 2%-25% ethyl acetate in hexane gave 12 g of product as a white crystalline solid: ¹H NMR (400 MHz, CDCl₃) 7.45 (m, 1H), 7.3 (m, 1H), 7.2 (m, 1H), 7.06 (m, 1H), 5.15 (dm, J_{H-F} = 48 Hz), 4.18 (br s, 1H), 3.65 (complex m, 2H), 3.42 (br s, 1H), 3.3 (m, 1H), 2.0 (d, 4H), 1.42 (s, 9H), 1.4(q, 2H), 1.15 (q, 2H).

Step 8: trans-4-[2-fluoro-2-(2-fluorophenyl)ethoxy]cyclohexanamine



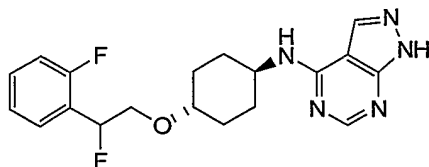
A mixture of 1 g of *tert*-butyl {*trans*-4-[2-fluoro-2-(2-fluorophenyl)ethoxy]-cyclohexyl}carbamate and 10 mL of 4N HCl in dioxane was stirred at room temperature for 3 h then concentrated to dryness under reduced pressure. The white crystalline hydrochloride salt could be converted into the free base by partitioning between 25 mL of 3N sodium hydroxide and 3 x 25 mL portions of chloroform. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Further drying under vacuum gave 0.72 g of product as an oil which crystallized on standing: MS (*m*+1) = 256.4; ¹H NMR (400 MHz, CDCl₃) 7.45 (m, 1H), 7.3 (m, 1H), 7.17 (m, 1H), 7.04 (m, 1H), 5.85 (dd, *J*_{HF} = 47 Hz, 1H), 3.75 (m, 2H), 3.3 (m, 1H), 2.7 (m, 1H), 2.02 (m, 2H), 1.85 (m, 2H), 1.3 (m, 2H), 1.05 (m, 2H).

Step 9: *N*-{trans-4-[2-fluoro-2-(2-fluorophenyl)ethoxy]cyclohexyl}-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



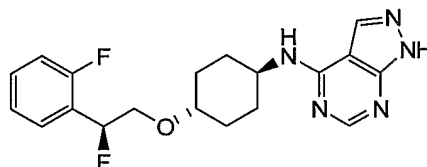
A mixture of 0.52 g *trans*-4-[2-fluoro-2-(2-fluorophenyl)ethoxy]-cyclohexanamine hydrochloride, 0.46 g of 4-chloro-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-*d*]pyrimidine, and 1 g of powdered sodium carbonate in 25 mL of 2-propanol was heated to 80°C under nitrogen overnight. The mixture was cooled, filtered and the solid washed with 3 X 50 mL portions of 10% methanol in chloroform. The combined extracts were concentrated under reduced pressure. Chromatography over silica gel eluting with a gradient of 50%-100% ethyl acetate in hexane gave 0.82 g of product as a white solid: MS (*m*+1) = 458.4.

Step 10 : trans-[4-(2-Fluoro-2-(2-fluorophenyl)-ethoxy-cyclohexyl)-(1H-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine

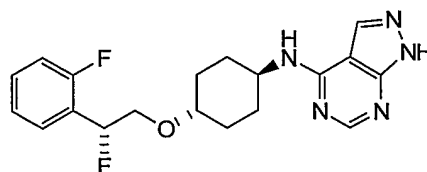


A mixture of 0.82 g of *N*-{*trans*-4-[2-fluoro-2-(2-fluorophenyl)ethoxy]cyclohexyl}-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine in 75 mL of 2-propanol and 2 mL of 12*N* HCl and heated to 90°C for 1 h, cooled and concentrated under reduced pressure to dryness. The solid residue was triturated with 50 mL of ether and filtered. The solid hydrochloride salt was dissolved in 100 mL of methanol and 2 mL of concentrated aqueous ammonia and again concentrated to dryness. The resulting residue was extracted with 100 mL of chloroform, filtered and concentrated to dryness under reduced pressure. Chromatography over silica gel eluting with a gradient of 5%-10% methanol in ethyl acetate gave 0.67 g of product as a white solid: MS (*m*+1) = 374.43; ¹H NMR 8.4 (s, 1H), 7.95 (s, 1H), 7.48 (m, 1H), 7.38 (m, 1H), 7.2 (m, 1H), 7.05 (m, 1H), 5.85 (m, *J*_{HF} = 47 Hz, 1H), 3.8 (m, 3H), 3.42 (br s, 1H), 2.25 (d, 2H), 2.18 (d, 2H), 1.58 (q, 2H), 1.4 (br m, 2H).

Resolution into the pure enantiomers could be performed by isocratic elution on ChiralPak AD at 1 mL/min, eluting with 20% methanol in 2-propanol.



trans-[4-((2*R*)-2-Fluoro-2-(2-fluorophenyl)-ethoxy-cyclohexyl)-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine: [α]_D²⁵ °C = -22.3 ° (*c* = 1, MeOH) MS (*m*+1) = 374.4 ; ¹H NMR (400 MHz, CDCl₃) 8.4 (s, 1H), 7.95 (s, 1H), 7.48 (m, 1H), 7.38 (m, 1H), 7.2 (m, 1H), 7.05 (m, 1H), 5.85 (m, *J*_{HF} = 47 Hz, 1H), 3.8 (m, 3H), 3.42 (br s, 1H), 2.25 (d, 2H), 2.18 (d, 2H), 1.58 (q, 2H), 1.4 (br m, 2H).

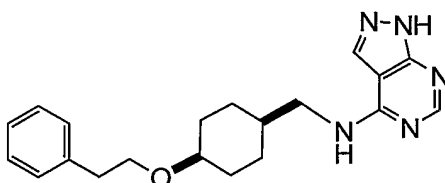


trans-[4-((2*R*)-2-Fluoro-2-(2-fluorophenyl)-ethoxy-cyclohexyl)-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-amine: [α]_D²⁵ °C = -22.3 ° (*c* = 1, MeOH) MS (*m*+1) = 374.4 ; ¹H NMR (400 MHz, CDCl₃) 8.4 (s, 1H), 7.95 (s, 1H), 7.48 (m, 1H), 7.38 (m, 1H), 7.2 (m, 1H), 7.05 (m, 1H), 5.85 (m, *J*_{HF} =

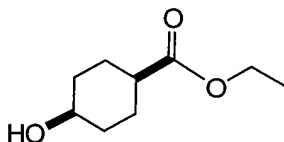
47 Hz, 1H), 3.8 (m, 3H), 3.42 (br s, 1H), 2.25 (d, 2H), 2.18 (d, 2H), 1.58 (q, 2H), 1.4 (br m, 2H).

Example 11

cis-(4-Phenethyloxy-cyclohexylmethyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine

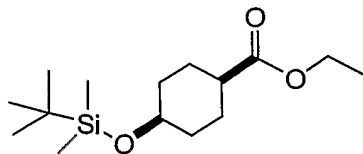


Step 1: cis-4-Hydroxy-cyclohexanecarboxylic acid ethyl ester



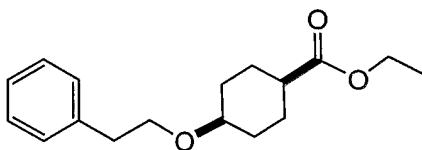
A mixture of 10 g of ethyl 4-hydroxybenzoate, 5 mL of acetic acid, 0.8 g of 5% rhodium on alumina, and 200 mL of ethanol was shaken under 55 psi of hydrogen for 48 h, filtered and concentrated under reduced pressure. The residue was taken up in 200 mL of toluene and again concentrated under reduced pressure to remove acetic acid. Drying under vacuum overnight gave 11 g of product, which was predominantly cis (83:17 cis : trans by HPLC), as a colorless oil: MS (m+1) = 173.2; ¹H NMR (400 MHz, CDCl₃) 4.1 (dd, 2H), 3.9 (m, cis isomer, 0.85 H), 3.6 (m, trans isomer, 0.15 H), 2.4 and 2.2 (m, 1H), 2.0 (m, 2H), 1.62 (m, 6H), 1.2 (t, 3H).

Step 2: cis-4-tert-Butyl-dimethylsilanyloxy-cyclohexanecarboxylic acid ethyl ester



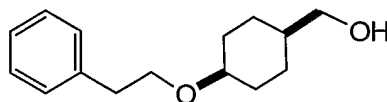
A mixture of 3 g of cis-4-hydroxy-cyclohexanecarboxylic acid ethyl ester, 3 g of imidazole, 33 g of tert-butyldimethylsilyl-chloride, and 6 mL of DMF was stirred under inert atmosphere overnight. The mixture was diluted with 250 mL of water and extracted into 3 x 50 mL portions of ether. The combined ether extracts were washed with 2 x 50 mL of water, dried over magnesium sulfate and concentrated under reduced pressure. Drying under vacuum overnight gave 4.5 g of product as a colorless oil: ¹H NMR (400 MHz, CDCl₃) 4.1 (dd, 2H), 3.58 (m, cis isomer, 0.85 H), 2.2 (m, 1H), 1.95 (m, 4H), 1.6 (m, 1H), 1.5 (m, 1H), 1.22 (m, 6H), 0.9 (s, 9H), 0.04 (s, 6H).

Step 3: cis-2-(4-Phenethyloxy)-cyclohexanecarboxylic acid ethyl ester



From 4 g of cis-4-tert-butyl-dimethylsilyloxy-cyclohexanecarboxylic acid ethyl ester, using the procedure described for Example 1, Step 3 above, gave 3 g of a colorless resin: MS (m+1) = 277.2.

Step 4: cis-(4-Phenethyloxy-cyclohexyl) methanol

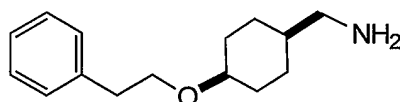


To a stirred, ice cold solution of 3 g of cis-2-(4-phenethyloxy)-cyclohexanecarboxylic acid ethyl ester, in 50 mL of THF was added 10 mL of 1M lithium aluminum hydride in THF. The mixture was allowed to warm to room temperature and stir for 1 h, then cooled in an ice bath and quenched with sequential addition of 0.5 mL of water, 0.5 mL of 1N sodium hydroxide, and 1.5 mL of water. After stirring for 30 min, the mixture was filtered, washed with 2 x 25 mL of

ethyl acetate and combined extracts dried over magnesium sulfate and concentrated under reduced pressure.: MS (m+1) = 235.2, ¹H NMR (400 MHz, CDCl₃) 7.2 (m, 5H), 3.6 (t, 2H), 3.35 (m, 1H), 3.25 (m, 2H), 2.8 (t, 2H), 1.85 (d, 2H), 1.6-1.2 (complex m, 7H).

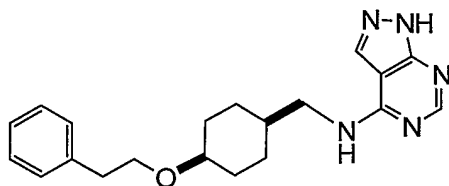
5

Step 5: cis-2-(4-Phenethyloxy-cyclohexyl)-methylamine



10 To a stirred, ice cold solution of 1.2 g of cis-(4-phenethyloxy-cyclohexyl) methanol and 1.5 mL of triethylamine, in 60 mL of dichloromethane was added 1.5 mL of methane-sulfonyl chloride drop-wise over 10 min. The mixture was allowed to stir for 30 min, then concentrated under reduced pressure and diluted with 50 mL of ether and washed with 25 mL of 10% HCl, 25 mL of water, 25 mL of saturated sodium carbonate. The combined extracts were dried over
15 magnesium sulfate and concentrated under reduced pressure. The crude mesylate, 1.6 g, was used without further purification: ¹H NMR (400 MHz, CDCl₃) 7.2 (m, 5H), 4.0 (d, 2H), 3.6 (m, 3H), 3.0 (s, 3H), 2.85 (t, 2H), 1.95 (d, 2H), 1.8-1.2 (complex m, 9H). The mesylate was taken up in 20 mL of DMF and heated to reflux with 2 g of sodium azide to 80°C overnight, cooled, filtered, and concentrated under reduced pressure (bath temp = 60°C) to remove most of the DMF. The
20 residue was diluted with 50 mL of ether and washed with 2 x 50 mL of water, dried over magnesium sulfate and concentrated under reduced pressure. The crude azide, 1.5 g, was used without further purification: ¹H NMR (400 MHz, CDCl₃) 7.2 (m, 5H), 3.6 (t, 2H), 3.56 (m, 1H), 3.1 (d, 2H), 2.95 (t, 2H), 1.95 (d, 2H), 1.8-1.2 (complex m, 9H). To a stirred, ice cold solution of the crude azide in 12 mL of ethanol was added 0.3 g of sodium borohydride and then 0.9 g of
25 nickel chloride hexahydrate. The resulting black mixture was stirred for 2 h, diluted with 50 mL of saturated sodium carbonate and extracted with 3 x 50 mL of chloroform. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Drying under vacuum gave 1.45 g of a thick oil: MS (m+1) = 235.2, ¹H NMR (400 MHz, CDCl₃) 7.2 (m, 5H), 3.6 (t, 2H), 3.55 (m, 1H), 2.88 (t, 2H), 1.85 (d, 2H), 1.7-1.2 (complex m, 7H).

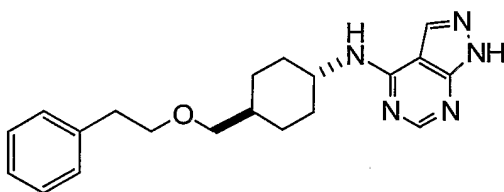
30 Step 6: cis-(4-Phenethyloxy-cyclohexylmethyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine



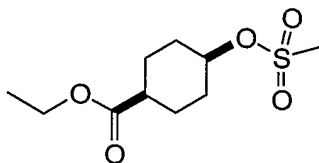
A mixture of 0.3 g of cis-2-(4-phenethyloxy-cyclohexyl)-methylamine, 0.2 g of 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (R.K. Robins, J. Amer. Chem. Soc., 78, 784-790 (1956)), 10 mL of 2-propanol and 0.2 mL of N,N-diisopropyl-ethylamine was heated to 80°C for 12 hours. The mixture was cooled and concentrated under reduced pressure and purified by preparative TLC eluting with 80:20:5 THF: diethyl ether: NH₄OH and preparative reverse phase chromatography on ChiralPak AD eluting with 80:20 hexane (0.1% diethylamine): ethanol gave 0.22 g of product as a white crystalline solid. MS (m+1) = 352.3; ¹H NMR (400 MHz, CDCl₃) 8.4 (s, 1H), 7.92 (s, 1H), 7.2 (m, 5H), 3.6 (t, 2H), 3.55 (m, 1H), 3.5 (m, 2H), 2.85 (t, 2H), 1.9 (m, 2H), 1.7 (m, 1H), 1.8-1.5 (m, 5H), 1.4 (m, 4H).

Example 12

trans-(4-Phenethyloxymethyl-cyclohexyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine



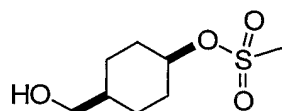
Step 1: cis-4-Methanesulfonyloxy-cyclohexanecarboxylic acid ethyl ester



To a stirred, ice cold solution of 1.8 g of cis-4-hydroxy-cyclohexanecarboxylic acid ethyl ester, and 2.8 mL of triethylamine, in 25 mL of dichloromethane was added 0.85 mL of methanesulfonyl chloride drop-wise over 10 min. The mixture was allowed to stir for 30 min, then concentrated under reduced pressure and diluted with 50 mL of ether and washed with 25 mL of

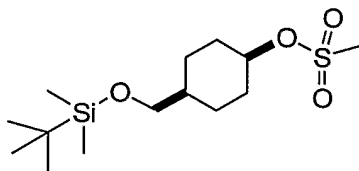
10% HCl, 25 mL of water, 25 mL of saturated sodium carbonate. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. The crude mesylate, 2.5 g, was used without further purification: ¹H NMR (400 MHz, CDCl₃) 4.92 (m, 1H), 4.15 (q, 2H), 3.02 (s, 3H), 2.4 (m, 1H), 2.05 (m, 2H), 1.92 (m, 2H), 1.62-1.4 (complex m, 4H).

5 Step 2: cis-4-Methanesulfonic acid 4-hydroxymethyl-cyclohexyl ester

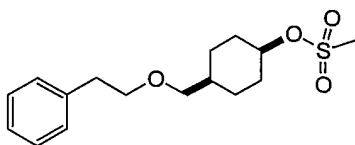


To a stirred solution of 2.5g of cis-4-methanesulfonyloxymethyl-cyclohexanecarboxylic acid ethyl ester in 30 mL of 1, 2-dimethoxyethane was added 10 mL of 1M lithium borohydride in THF. The mixture was allowed to stir for overnight, then cooled in an ice bath and quenched by careful addition of 100 mL of 2N HCl and extracted into 3 x 50 mL portions of ethyl acetate. The combined extracts were washed with 25 mL of saturated sodium carbonate, dried over magnesium sulfate, diluted with 50 mL of toluene and concentrated under reduced pressure. The crude hydroxy-mesylate, 1.8 g, was used without further purification: ¹H NMR (400 MHz, CDCl₃) 5.0 (m, 1H), 4.15 (m, 1H), 3.6 (m, 2H), 3.02 (s, 3H), 2.05 (m, 2H), 1.92 (m, 1H), 1.6 (complex m, 4H), 1.4 (dd, 2H).

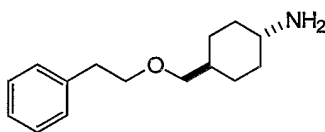
Step 3: cis-Methanesulfonic acid 4-(tert-butyl-dimethyl-silanyloxymethyl)-cyclohexyl ester



A mixture of 1.8 g of cis-4-methanesulfonic acid 4-hydroxymethyl-cyclohexyl, 1.7 g of imidazole, 1.8 g of tert-butyl-dimethylsilyl-chloride, and 4 mL of DMF was stirred under inert atmosphere overnight. The mixture was diluted with 100 mL of water and extracted into 3 x 25 mL portions of ether. The combined ether extracts were washed with 2 x 50 mL of water, dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over silica gel using a gradient elution of 5% to 30% ethyl acetate in hexane gave first a 0.1 g of the trans isomer, 0.5 g of mixed fractions, then 0.9 g of pure cis product as a colorless thick oil: ¹H NMR (400 MHz, CDCl₃) 5.0 (m, 1H), 3.4 (d, 2H), 3.0 (s, 3H), 2.05 (m, 2H), 1.6 (m, 5H), 1.4 (m, 2H), 0.9 (s, 9H), 0.02 (s, 6H).

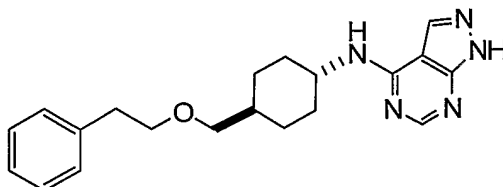
Step 4: cis-Methanesulfonic acid 4-phenethyloxymethyl-cyclohexyl ester

From 0.9 g of cis-methanesulfonic acid 4-(tert-butyl-dimethyl-silanyloxymethyl-cyclohexyl ester, 20 mL of anhydrous acetonitrile, 2.6 mL of triethyl silane, 1.6 mL of phenylacetaldehyde and 0.25 g of bismuth tribromide using the procedure described for Example 1, Step 3 above (chromatography using gradient elution 10%-35% ethyl acetate in hexane), gave 0.8 g of a colorless resin: ¹H NMR (400 MHz, CDCl₃) 7.3-7.2 (m, 5H), 5.0 (m, 1H), 3.62 (t, 2H), 3.28 (d, 2H), 3.0 (s, 3H), 2.88 (t, 2H), 2.05 (m, 2H), 1.65 (m, 4H), 1.58 (m, 1H), 1.4 (m, 2H).

Step 5: trans-4-Phenethyloxymethyl-cyclohexylamine

A stirred mixture of 0.8 g of cis-methanesulfonic acid 4-phenethyloxymethyl-cyclohexyl ester, 10 mL of DMF, and 1.8 g of sodium azide was heated to reflux with to 80°C overnight, cooled, filtered, and concentrated under reduced pressure (bath temp = 60°C) to remove most of the DMF. The residue was diluted with 50 mL of ether and washed with 2 x 50 mL of water, dried over magnesium sulfate and concentrated under reduced pressure. The crude trans-azide, 0.8 g, was used without further purification: ¹H NMR (400 MHz, CDCl₃) 7.25-7.2 (m, 5H), 3.6 (t, 2H), 3.2 (overlapping m, 3H), 2.87 (t, 2H), 2.05 (d, 2H), 1.82 (d, 2H), 1.56 (m, 1H), 1.3 (m, 2H), 1.0 (dd, 2H).

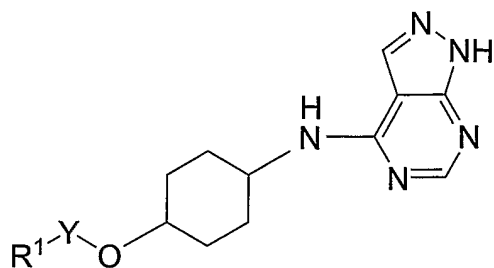
A mixture of 0.8 g of the crude azide and 0.2 g of 10% palladium on carbon in 50 mL of ethanol was stirred under 1 atm of hydrogen for 4 h, filtered and concentrated under reduced pressure. Drying under vacuum gave 0.8 g of a thick oil: MS (m+1) = 235.1, ¹H NMR (400 MHz, CDCl₃) 7.25-7.2 (m, 5H), 3.6 (t, 2H), 3.22 (d, 2H), 2.88 (t, 2H), 2.6 (m, 1H), 1.84 (d, 2H), 1.8 (d, 2H), 1.5 (m, 1H), 1.0 (m, 4H).

Step 6: trans-(4-Phenethyloxymethyl-cyclohexyl)-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-amine

A mixture of 0.13 g of trans-4-phenethyloxymethyl-cyclohexylamine (Compound 45), 0.08 g of
5 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (R.K. Robins, J. Amer. Chem. Soc., 78, 784-790
(1956)), 10 mL of 2-propanol and 0.1 mL of N,N-diisopropyl-ethylamine was heated to 80°C for
12 hours. The mixture was cooled and concentrated under reduced pressure and purified by
preparative TLC eluting with 90:10 THF: NH₄OH: gave 0.15 g of product as a white crystalline
solid. MS (m+1) = 352.1; ¹H NMR (400 MHz, CDCl₃) 8.4 (s, 1H), 7.92 (s, 1H), 7.3-7.2 (m,
10 5H), 3.62 (t, 2H), 3.55 (m, 1H), 3.3 (d, 2H), 2.9 (t, 2H), 2.2 (d, 2H), 2.1 (s, 1H), 1.9 (d, 2H), 1.6
(m, 1H), 1.3 (m, 2H), 1.2 (dd, 2H).

WHAT IS CLAIMED IS:

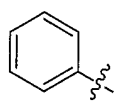
1. A compound having the formula (Ia):



5

(Ia)

wherein:

R¹ is , unsubstituted or substituted with halogen or -R², where R² is C₁-6alkyl, independently unsubstituted or substituted with one or more halogen;

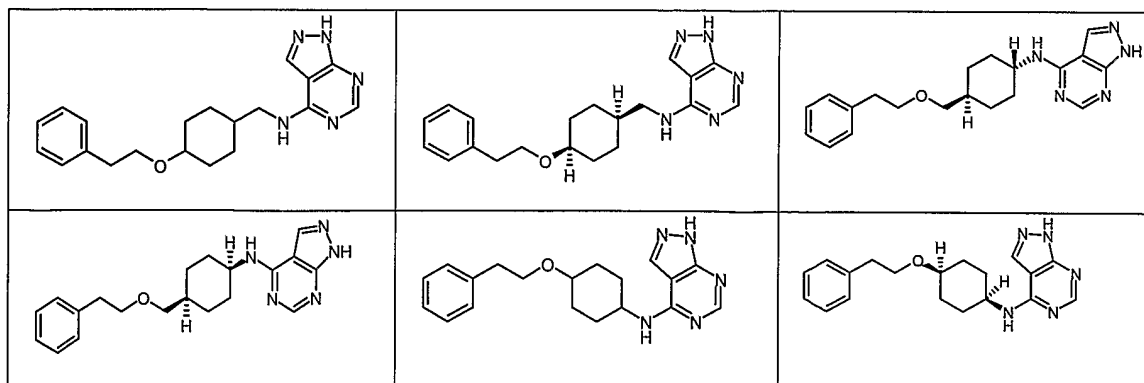
10

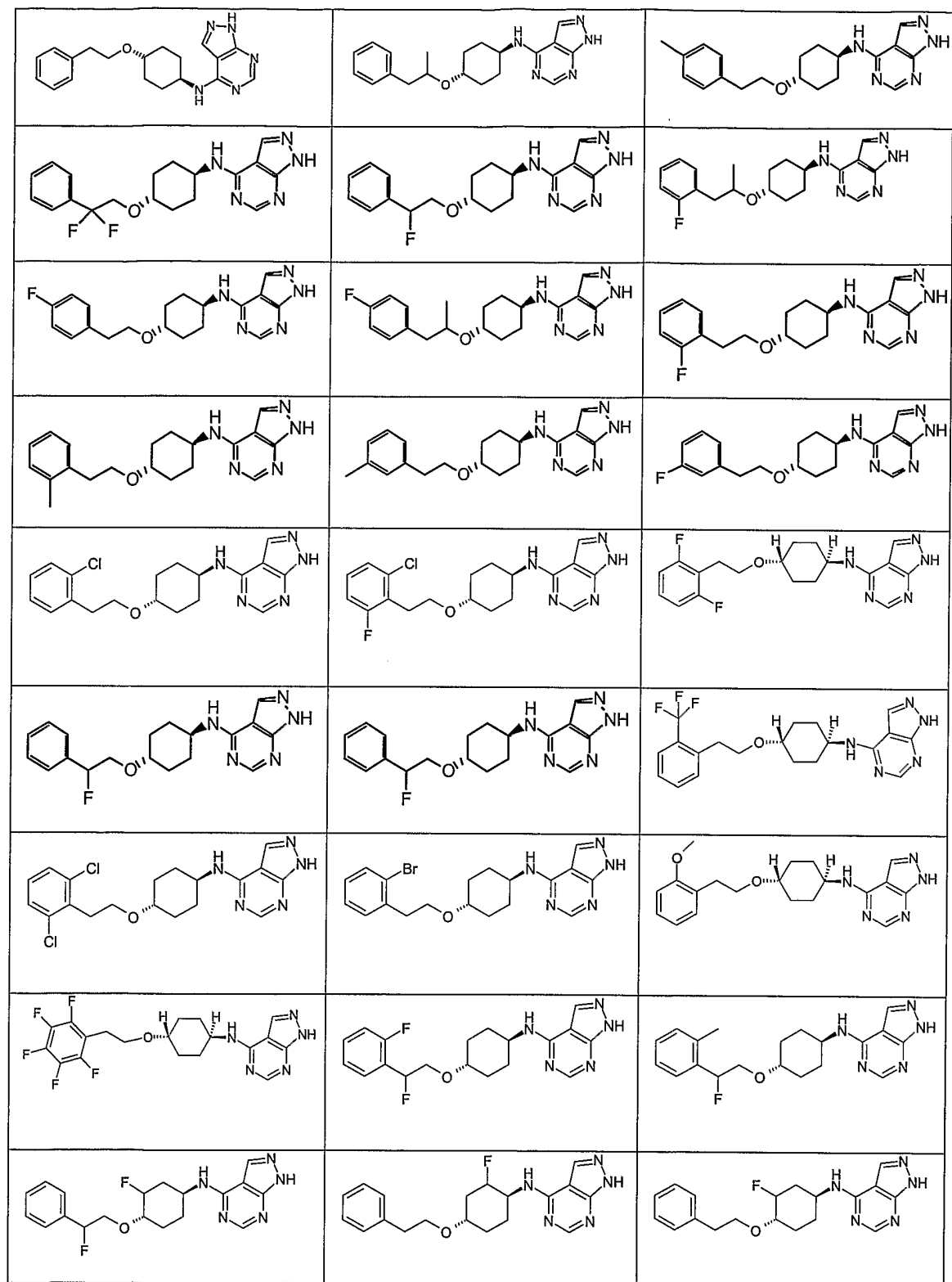
Y is -C₁-6alkyl, independently unsubstituted or substituted with one or more halogen;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

15

2. A compound selected from:





3. A pharmaceutical composition comprising an inert carrier and a therapeutically effective amount of a compound according to Claim 1.

4. The pharmaceutical composition according to Claim 3, further comprising a second therapeutic agent selected from the group consisting of: (i) non-steroidal anti-inflammatory agents; (ii) COX-2 inhibitors; (iii) bradykinin B1 receptor antagonists; (iv) sodium channel blockers and antagonists; (v) nitric oxide synthase (NOS) inhibitors; (vi) glycine site antagonists; (vii) potassium channel openers; (viii) AMPA/kainate receptor antagonists; (ix) calcium channel antagonists; (x) GABA-A receptor modulators (e.g., a GABA-A receptor agonist); (xi) matrix metalloprotease (MMP) inhibitors; (xii) thrombolytic agents; (xiii) opioids such as morphine; (xiv) neutrophil inhibitory factor (NIF); (xv) L-Dopa; (xvi) carbidopa; (xvii) levodopa/carbidopa; (xviii) dopamine agonists such as bromocriptine, pergolide, pramipexole, ropinirole; (xix) anticholinergics; (xx) amantadine; (xxi) carbidopa; (xxii) catechol O-methyltransferase ("COMT") inhibitors such as entacapone and tolcapone; (xxiii) Monoamine oxidase B ("MAO-B") inhibitors; (xiv) opiate agonists or antagonists; (xv) 5HT receptor agonists or antagonists; (xvi) NMDA receptor agonists or antagonists; (xvii) NK1 antagonists; (xviii) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"); (xxix) tricyclic antidepressant drugs, (xxx) norepinephrine modulators; (xxxi) lithium; (xxxii) valproate; and (xxxiii) neurontin (gabapentin).

5. The pharmaceutical composition according to Claim 3 useful for the treatment of pain, Parkinson's disease, Alzheimer's disease, epilepsy, depression, anxiety, and ischemic brain injury including stroke.

6. The pharmaceutical composition according to Claim 3 useful for the treatment of Parkinson's disease.

7. A method for treating or preventing pain, Parkinson's disease, Alzheimer's disease, epilepsy, depression, anxiety, ischemic brain injury including stroke in a patient in need thereof comprising administering to said patient a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

8. A method for treating or preventing chronic, visceral, inflammatory and neuropathic pain syndromes in a patient in need thereof comprising administering to said patient

a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

9. A method for treating or preventing pain resulting from, or associated with, traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, cancer and chemotherapy, in a patient in need thereof comprising administering to said patient a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

10. A method for treating or preventing chronic lower back pain in a patient in need thereof comprising administering to said patient a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

11. A method for treating or preventing phantom limb pain in a patient in need thereof comprising administering to said patient a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

12. A method for treating or preventing HIV- and HIV treatment-induced neuropathy, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and related neuralgias in a patient in need thereof comprising administering to said patient a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

13. A method for treating or preventing epilepsy and partial and generalized tonic seizures in a patient in need thereof comprising administering to said patient a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US2004/025979

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/519

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)

IPC 7 C07D A61K

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, PAJ, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/23389 A (HODGETTS KEVIN JULIAN ; HORVATH RAYMOND F (US); NEUROGEN CORP (US); TR) 5 April 2001 (2001-04-05) page 4 formula IV page 19, lines 1-26; claims 47,49 -----	1-13
A	US 4 904 666 A (FRIEBE WALTER-GUNAR ET AL) 27 February 1990 (1990-02-27) Formula 1 column 1, lines 5-53 -----	1-13
A	US 5 723 608 A (YUAN JUN) 3 March 1998 (1998-03-03) Formula 1 column 1, line 25 - column 2, line 33 ----- -/--	1-13

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

19 November 2004

Date of mailing of the international search report

15/12/2004

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Rudolf, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/025979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROBINS, ROLAND K.: "Potential Purine Antagonists. IX. Further Studies of Some 4,6-Disubstituted Pyrazolo'3,4-d!pyrimidines" J. AM. CHEM. SOC., vol. 79, 1957, pages 6407-6415, XP002306567 table 1	1-13
A	HAMILTON, HARRIET W., BRISTOL, JAMES A.: "C4-substituted 1-beta-D-Ribofuranosylpyrazolo'3,4-d!pyrimidines as Adenosine Agonist Analogues" J. MED. CHEM., vol. 26, 1983, pages 1601-1606, XP002306568 compounds 22,23	1-13
A	RIDEOUT, JANET L., KRENITSKY, THOMAS A., KOSZALKA, GEORGE W., COHN, NAOMI K. ET AL.: "Pyrazolo'3,4-d!pyrimidine Ribonucleosides as Anticoccidials. 2. Synthesis and Activity of Some Nucleosides of 4-(Alkylamino)-1H-pyrazolo'3,4-d!pyrimidines" J. MED. CHEM., vol. 25, 1982, pages 1040-1044, XP002306569 compound 8	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/025979

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. ☒ Claims Nos.: 7-13
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7-13 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/US2004/025979

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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