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(54) Title: NOVEL BREATHING CONTROL MODULATING COMPOUNDS, AND METHODS OF USING SAME

(57) Abstract: The present invention includes pyrimido[5,4-*d*]pyrimidines that are useful in the prevention and/or treatment of breathing control diseases or disorders in a subject in need thereof. The present invention also includes a method of preventing and/or treating a respiratory disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the invention. The present invention further includes a method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the invention.

TITLE OF THE INVENTION

Novel Breathing Control Modulating Compounds, and Methods of Using Same

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 61/792,185, filed March 15, 2013, which application is hereby incorporated by reference in its entirety herein.

BACKGROUND OF THE INVENTION

Normal control of breathing is a complex process that involves, in part, the body's interpretation and response to chemical stimuli such as carbon dioxide, pH and oxygen levels in blood, tissues and the brain. Normal breathing control is also affected by other factors such as wakefulness (*i.e.*, whether the patient is awake or sleeping), emotion, posture and vocalization. Within the brain medulla, there are respiratory control centers that interpret various feed-forward and feed-back signals that affect respiration by issuing commands to the muscles that perform the work of breathing. Key muscle groups are located in the abdomen, diaphragm, pharynx and thorax. Sensors located centrally and peripherally then provide input to the brain's central respiration control areas that enables response to changing metabolic requirements.

For example, ventilation sufficient to meet the body's metabolic needs is maintained primarily by the body's rapid response to changes in carbon dioxide (CO_2) levels. Increased CO_2 levels (hypercapnia) signal the body to increase breathing rate and depth, resulting in higher blood oxygen levels and subsequent lower blood CO_2 levels. Conversely, low CO_2 levels (hypocapnia) can result in periods of hypopnea (decreased breathing) or, in the extreme case, apnea (no breathing) since the stimulation to breathe is diminished.

There are many diseases in which loss of normal breathing control is a primary or secondary feature of the disease. Examples of diseases with a primary loss of breathing control are sleep apneas (central, mixed or obstructive; where the breathing repeatedly stops for 10 to 60 seconds) and congenital central hypoventilation syndrome. Secondary loss of breathing control may be due to chronic cardio-pulmonary diseases (*e.g.*, heart failure, chronic bronchitis, emphysema, and impending respiratory failure), excessive weight (*e.g.*, obesity-hypoventilation syndrome), certain drugs (*e.g.*, anesthetics, sedatives, sleeping aids, anxiolytics, hypnotics, alcohol, and narcotic analgesics and/or factors that affect the neurological system (*e.g.*, stroke, tumor, trauma, radiation damage, and ALS). In

chronic obstructive pulmonary diseases where the body is exposed to chronically high levels of carbon dioxide, the body adapts to the respiratory acidosis (lower pH) by a kidney mediated retention of bicarbonate, which has the effect of partially neutralizing the CO_2/pH respiratory stimulation. Thus, the patient is unable to mount a normal ventilatory response to changes in metabolic demand.

Sleep disordered breathing is an example of where abnormalities in the control of breathing lead to a serious and prevalent disease in humans. Sleep apnea is characterized by frequent periods of no or partial breathing. Key factors that contribute to these apneas include anatomical factors (*e.g.*, obesity), decreased hypercapnic and hypoxic ventilatory responses (*e.g.*, decreased response to high carbon dioxide and low oxygen levels, respectively) and loss of "wakefulness" (*i.e.*, respiratory drive to both lungs and/or to pharyngeal dilator muscles during sleep). Apneic events result in hypoxia (and the associated oxidative stress) and eventually severe cardiovascular consequences (high blood pressure, stroke, heart attack).

Estimates for U.S. individuals afflicted with conditions wherein there is compromised respiratory control include sleep apneas (15-20 millions); obesity-hypoventilation syndrome (3-5 millions); chronic heart disease (5 millions); chronic obstructive pulmonary disease (COPD)/chronic bronchitis (10 millions); drug-induced hypoventilation (2-10 millions); and mechanical ventilation weaning (0.5 million).

Drugs are most often eliminated by biotransformation and/or excretion into urine, feces or bile. The liver is the major organ for xenobiotic biotransformation, and is thereby important in characterizing the metabolic stability, toxicology, and drug-drug interaction properties of drugs. Drug metabolism is achieved via two major liver-located enzyme reactions: Phase I and Phase II reactions. Phase I enzymes include the cytochrome P450 (CYP450) family of enzymes, which are located in the smooth endoplasmic reticulum. The basic processes in Phase I reactions are oxidation, reduction and/or hydrolysis, many of which are catalyzed by the CYP450 system and require NADPH as a cofactor. Phase II enzymes are located in the cytoplasm and endoplasmic reticulum, and perform conjugation reactions including glucuronic acid, glutathione, sulfate, and glutamine conjugations. Phase II reactions generally inactivate the drug if it is not already therapeutically inactive following Phase I metabolism, and also make the drug more water soluble to facilitate its elimination. Some drugs are metabolized by Phase I or Phase II enzymes alone, whereas others are metabolized by both Phase I and Phase II enzymes (Baranczewski *et al.*, 2006, Pharmacol. Rep. 58:453-472). Microsomes are subcellular liver tissue fractions (membrane vesicles of

the smooth endoplasmic reticulum) and contain the Phase I CYP450 family of enzymes. Compounds undergo only Phase I metabolism in liver microsomes in the presence of NADPH cofactors. Significant parent-drug disappearance in the presence of liver microsomes thus indicates that the drug will be significantly modified by the CYP450 enzymes in the body (Rodrigues, 1994, Biochem, Pharm. 48(12):2147).

The purpose of a pharmacokinetic (PK) study is to use drug concentration-time profiles and associated pharmacokinetic parameters to understand how the drug is processed, modified, distributed and/or eliminated upon administration to an animal. In drug discovery, a pharmacokinetic study is performed to (1) guide dosage regimen design for animal efficacy and toxicity studies, (2) understand and interpret pharmacology and toxicology study results, and (3) select the drug candidates with desired pharmacokinetic properties for the disease indication intended. The PK data from the animal studies can be extrapolated to predict PK profiles in humans so as to select and optimize dosage regimens for a drug candidate in human clinical trials.

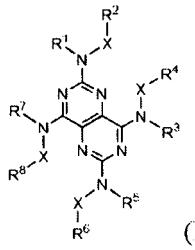
There is a need in the art for novel compounds useful for restoring all or part of the body's normal breathing control system in response to changes in CO_2 and/or oxygen levels, with minimal side effects. Further, there is a need in the art for novel compounds useful for restoring all or part of the body's normal breathing control system, that possess suitable metabolic stability and suitable pharmacokinetic properties, such as oral bioavailability. Further, there is a need in the art for novel compounds useful for restoring all or part of the body's normal breathing control system, that can be administered orally and used in a chronic manner, as well as acutely, via methods including intravenous administration. The present invention addresses and meets these needs.

BRIEF SUMMARY OF THE INVENTION

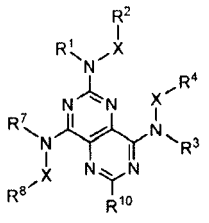
The invention provides a compound or salt thereof. The invention further provides a pharmaceutical composition comprising the compound of the invention and at least one pharmaceutically acceptable carrier. The invention further provides a method of preventing or treating a breathing control disorder or disease in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and at least one compound of the invention or salt thereof. The invention further provides a method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical

composition comprising at least one pharmaceutically acceptable carrier and at least one compound of the invention or salt thereof. The invention further provides a method of preparing N^2-N^6-bis-cyclopropylmethyl N^4, N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**).

In certain embodiments, the compound is selected from the group consisting of:

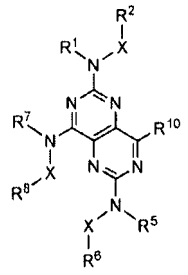
a compound of formula (I):  (I), wherein in formula (I):

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl; each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; and, each occurrence of X is independently alkyl or substituted alkyl;

a compound of formula (II):  (II), wherein in formula (II):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl; each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; each occurrence

of R^9 is independently alkyl, or substituted alkyl; R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy; and,



a compound of formula (III): (III), wherein in formula (III):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl; or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl; each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; each occurrence of R^9 is independently alkyl or substituted alkyl; and R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy; and any combinations thereof.

In certain embodiments, the compound is selected from the group consisting of: N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine; N-(6-Chloro-4,8-*bis*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine; N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine; N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl)-hydroxylamine; N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-

tetraamine; 6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; 2-(4,8-Bis-*n*-propylamino-6-methylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol; N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine; N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; 6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; 2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol; N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; 2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine; 2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol; N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; 6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine; N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine; N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine; N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; 2-Chloro-6-(N,N'-dimethyl-

hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine; 6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; 6-Benzyloxy-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; 4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ol; 4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile; N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; 6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; 4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid; N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-amidine; N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; 6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; 6-Methoxy-N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; 6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile; N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine 2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine; N^4,N^8-Diethyl-N^2,N^6-Di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; 6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d] pyrimidine-2,4,8-triamine; 6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine; N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d] pyrimidine-2,4,8-triamine; N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine; (4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester; (4,8-Bis-methylamino-6-*n*-

propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid; N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide; (6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester; a salt or solvate thereof, and any combinations thereof.

In certain embodiments, the salt is selected from the group consisting of sulfate, hydrogen sulfate, hemisulfate, chloride, bromide, iodide, nitrate, carbonate, phosphate, hydrogen phosphate, dihydrogen phosphate, formate, acetate, propionate, succinate, glycolate, gluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, 4-hydroxybenzoate, phenylacetate, mandelate, pamoate, methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, trifluoromethanesulfonate, 2-hydroxyethanesulfonate, *p*-toluenesulfonate, sulfanilate, cyclohexylaminosulfonate, stearate, alginate, β-hydroxybutyrate, salicylate, galactarate, galacturonate, saccharin, saccharate, glycerophosphonate, and any combinations thereof.

In certain embodiments, the composition of the invention further comprises at least one agent selected from the group consisting of doxapram and enantiomers thereof, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients, benzodiazepine receptor agonists, orexin antagonists, tricyclic antidepressants, serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids, orexins, melatonin agonists, ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics. In other embodiments, the compound and the agent are physically mixed in the composition. In yet other embodiments, the compound and the agent are physically separated in the composition.

In certain embodiments, the composition of the invention further comprises at least one agent known to cause changes in breathing control. In other embodiments, the at least one agent is selected from the group consisting of opioid narcotics, benzodiazepines, sedatives, sleeping aids, hypnotics, propofol, and any combinations thereof. In yet other embodiments, the compound and the agent are physically mixed in the composition. In yet other embodiments, the compound and the agent are physically separated in the composition.

In certain embodiments, the composition allows for modified delivery of the compound following oral administration to a subject. In other embodiments, the composition minimizes delivery of the compound to the stomach of the subject and maximizes delivery of the compound to the intestine of the subject. In yet other embodiments, the composition

includes an enteric coating. In yet other embodiments, the compound is contained in a pharmaceutically suitable capsule. In yet other embodiments, the capsule contains granules or powder of the compound, or an admixture of the compound with an excipient. In yet other embodiments, the excipient comprises a binder, disintegrant, diluent, buffer, lubricant, glidant, antioxidant, antimicrobial preservative, colorant, or flavorant. In yet other embodiments, the capsule is enterically coated but the granules or powders of the compound are not enterically coated. In yet other embodiments, the granules or powders of the compound are coated with an enteric coating before being placed into the capsule. In yet other embodiments, the granules or powders of the compound are coated with a multiplicity of enteric coatings, as to provide delivery of drug to different regions of the intestine of the subject. In yet other embodiments, at least a portion of the granules or powders of the compound are enterically coated. In yet other embodiments, the capsule is coated with an enteric coating that is different from the enteric coating that coats the granules or powders of the compound. In yet other embodiments, the compound is coated onto a base particle, whereby a core comprising the drug as a coating over the base particle is formed. In yet other embodiments, the base particle is not enterically coated and the composition is contained in a pharmaceutically acceptable capsule that is enterically coated. In yet other embodiments, the core is coated with an enteric coating, thereby forming an enterically coated bead. In yet other embodiments, the enterically coated bead is contained in a pharmaceutically acceptable capsule. In yet other embodiments, the capsule contains beads coated with a multiplicity of enteric coatings, so that the capsule provides delivery of the compound to different regions of the intestine of the subject. In yet other embodiments, the contents of the capsule are dissolved or suspended in a pharmaceutically acceptable liquid as to provide a liquid-filled capsule. In yet other embodiments, the capsule is enterically coated but the liquid formulation contained within does not comprise an enteric coating. In yet other embodiments, the granules or powders of the compound are enterically coated. In yet other embodiments, the granules or powders of the compound are coated with a multiplicity of enteric coatings, as to provide delivery of drug to different regions of the intestine of the subject. In yet other embodiments, the enteric coating applied to the capsule differs from the enteric coating applied to any of the granules or powders of the compound. In yet other embodiments, the compound is coated onto a base particle to form a core comprising the compound as a coating over the base particle, wherein the core is suspended in a pharmaceutically acceptable liquid, and wherein the suspended core is placed in a capsule. In yet other embodiments, the capsule is enterically coated but the core is not enterically coated.

In yet other embodiments, the capsule and the core are enterically coated.

In certain embodiments, the destabilization is associated with a breathing control disorder or disease.

In certain embodiments, the breathing control disorder or disease is selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, altitude sickness, hypoxia, hypercapnia, chronic obstructive pulmonary disease (COPD), sudden infant death syndrome (SIDS), congenital central hypoventilation syndrome, Alzheimer's disease, Parkinson's disease, stroke, Duchenne muscular dystrophy, and brain and spinal cord traumatic injury. In other embodiments, the respiratory depression is caused by an anesthetic, a sedative, a sleeping aid, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic.

In certain embodiments, the subject is further administered at least one additional agent useful for treating the breathing disorder or disease. In other embodiments, the at least one additional agent is selected from the group consisting of doxapram and enantiomers thereof, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients, benzodiazepine receptor agonists, orexin antagonists, tricyclic antidepressants, serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids, orexins, melatonin agonists, ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics. In yet other embodiments, the compound and the agent are separately administered to the subject. In yet other embodiments, the compound and the agent are co-administered to the subject, further wherein the compound and the agent are physically mixed or physically separated when administered to the subject.

In certain embodiments, the subject is further administered at least one additional therapeutic agent known to change normal breathing control in the subject. In other embodiments, the at least one additional agent is selected from the group consisting of opioid narcotics, benzodiazepines, sedatives, sleeping aids, hypnotics, propofol, and any combinations thereof. In yet other embodiments, the composition is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject.

In certain embodiments, the subject is a mammal or bird. In other embodiments, the mammal is a human. In yet other embodiments, the composition is

administered to the subject by a nasal, inhalational, topical, oral, buccal, rectal, pleural, peritoneal, vaginal, intramuscular, subcutaneous, transdermal, epidural, intrathecal, intratracheal, otic, intraocular or intravenous route. In yet other embodiments, the composition is orally administered to the subject.

In certain embodiment, the compound is N^2-N^6-bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine and wherein the X-ray powder diffraction spectrum of the compound comprises 2Θ values (in degrees) of about 8.12, 9.59, 12.60, 15.02, 16.33, 17.40, 18.98, 20.68, 21.72, 22.28, 23.98, 25.24, and 26.70.

In certain embodiments, the method of preparing (**84**) comprises reacting 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-*d*]pyrimidine-4,8-diamine and cyclopropylmethylamine in a solvent. In other embodiments, the reaction is run under heating and (**84**) precipitates from the solvent once the reaction system is cooled to room temperature. In yet other embodiments, the solvent comprises *n*-butanol. In yet other embodiments, the precipitated (**84**) is recrystallized from *n*-butanol. In yet other embodiments, the recrystallized (**84**) has a X-ray powder diffraction spectrum comprising 2Θ values (in degrees) of about 8.12, 9.59, 12.60, 15.02, 16.33, 17.40, 18.98, 20.68, 21.72, 22.28, 23.98, 25.24, and 26.70. In yet other embodiments, the 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-*d*]pyrimidine-4,8-diamine is prepared by reacting 2,4,6,8-tetrachloro-pyrimido[5,4-*d*]pyrimidine and methylamine in a solvent. . In yet other embodiments, the ratio of equivalents of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine to methylamine is about 1 : 4.5.

BRIEF DESCRIPTION OF THE DRAWINGS

For the purpose of illustrating the invention, there are depicted in the drawings certain embodiments of the invention. However, the invention is not limited to the precise arrangements and instrumentalities of the embodiments depicted in the drawings.

Figure 1 is a graph illustrating the effect of compound (**4a**) on minute volume in an anesthetized rat spirometry screening assay.

Figure 2 is a graph illustrating the effect of compound (**4a**) on respiratory rate in an anesthetized rat spirometry screening assay.

Figure 3 is a graph illustrating the effect of compound (**4a**) on tidal volume in an anesthetized rat spirometry screening assay.

Figure 4 is a bar graph illustrating the dose-dependent effect of compound (**4a**)

on minute volume (based on a two-minute average) in an anesthetized rat spirometry screening assay.

Figure 5 is a graph illustrating the effect of compound (**4a**) on pulse rate in an anesthetized rat spirometry screening assay.

Figure 6 is a graph illustrating the effect of compound (**4a**) on blood pressure in an anesthetized rat spirometry screening assay.

Figure 7 is a graph illustrating the effect of compound (**27a**) on minute volume in an anesthetized rat spirometry screening assay.

Figure 8 is a graph illustrating the effect of compound (**27a**) on respiratory rate in an anesthetized rat spirometry screening assay.

Figure 9 is a graph illustrating the effect of compound (**27a**) on tidal volume in an anesthetized rat spirometry screening assay.

Figure 10 is a bar graph illustrating the dose-dependent effect of compound (**27a**) on minute volume (based on a two-minute average) in an anesthetized rat spirometry screening assay.

Figure 11 is a graph illustrating the effect of compound (**27a**) on pulse rate in an anesthetized rat spirometry screening assay.

Figure 12 is a graph illustrating the effect of compound (**27a**) on blood pressure in an anesthetized rat spirometry screening assay.

Figure 13 is a graph illustrating the XRPD for N^2,N^6-bis-cyclopropylmethyl N^4, N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**) as crystallized from *n*-butanol. The ordinate corresponds to intensity in arbitrary units, and the abscissa corresponds to position (2 Theta), Copper (Cu).

Figure 14 is a graph illustrating the finding that compound (**27a**) reduced apnea frequency in rats chronically treated with morphine, versus treatment with a vehicle. The marked decrease in apnea at the 12:00-12:30 PM time bin, across all groups, was caused by overt stimulation (awakening) from dosing via oral gavage.

Figure 15 is a graph illustrating the finding that compound (**27a**) reduced the number of apneas per hr expressed as a percent change from baseline (pre-drug) in rats chronically administered morphine, versus treatment with a vehicle. The marked decrease in apnea at the 30 min post-treatment time, across all groups, was caused by overt stimulation (awakening) from dosing via oral gavage.

Figure 16 is a bar graph illustrating the finding that compound (**27a**) reduced the the number of apneas per hr in rats chronically administered morphine, versus treatment

with a vehicle.

Figure 17 is a bar graph illustrating the finding that compound (**27a**) did not cause an increase in minute volume compared to a vehicle-treated group.

Figure 18 is a graph illustrating the finding that compound (**27a**) did not cause an increase in ventilation per unit time compared to baseline, nor to treatment with a vehicle. The marked increase in minute volume at the (12:00-12:30) 30 min post-treatment time, across all groups, was caused by overt stimulation from dosing via oral gavage.

Figure 19 is a graph illustrating the finding that compound (**85a**) reduced apnea frequency in rats chronically treated with morphine, versus treatment with a vehicle. The decrease in apnea at the 12:00-12:30 PM time bin, across all groups, was caused by overt stimulation (awakening) from dosing via oral gavage.

Figure 20 is a graph illustrating the finding that compound (**85a**) reduced the number of apneas per hr expressed as a percent change from baseline (pre-drug), in rats chronically treated with morphine, versus treatment with a vehicle. The marked decrease in apnea at the 30 min post-treatment time, across all groups, was caused by overt stimulation (awakening) from dosing via oral gavage.

Figure 21 is a bar graph illustrating the finding that compound (**85a**) reduced the the number of apneas per hr in rats chronically treated with morphine, versus treatment with a vehicle.

Figure 22 is a bar graph illustrating the finding that compound (**85a**) did not cause an increase in minute volume compared to a vehicle-treated group.

Figure 23 is a graph illustrating the finding that compound (**85a**) did not cause an increase in ventilation per unit time compared to treatment with a vehicle. The marked increase in minute volume at the (12:00-12:30) 30 min post-treatment time, across all groups, was caused by overt stimulation from dosing via oral gavage.

Figure 24 is a graph illustrating the finding that compound (**137a**) reduced apnea frequency in rats chronically treated with morphine, versus treatment with a vehicle. (Note: The decrease in apnea at the 12:00-12:30 PM time bin, across all groups, is caused by overt stimulation (awakening) from dosing via oral gavage).

Figure 25 is a graph illustrating the finding that compound (**137a**) reduced the number of apneas per hr expressed as a percent change from baseline (pre-drug), in rats chronically treated with morphine, versus treatment with a vehicle. The marked decrease in apnea at the 30 min post-treatment time, across all groups, was caused by overt stimulation (awakening) from dosing via oral gavage.

Figure 26 is a bar graph illustrating the finding that compound (**137a**) reduced the number of apneas per hr in rats chronically treated with morphine, versus treatment with a vehicle.

Figure 27 is a bar graph illustrating the finding that compound (**137a**) at a low dose did not cause an increase in minute volume compared to a vehicle-treated group. Compound **137a** caused an increase in minute volume at the higher dose.

Figure 28 is a graph illustrating the finding that compound (**137a**) did not cause an increase in ventilation per unit time compared to treatment with a vehicle. The marked increase in minute volume at the (12:00-12:30) 30 min post-treatment time, across all groups, was caused by overt stimulation from dosing via oral gavage.

Figure 29 is a graph illustrating the finding that compound (**145a**) reduced apnea frequency in rats chronically treated with morphine, versus treatment with a vehicle. The decrease in apnea at the 12:00-12:30 PM time bin, across all groups, is caused by overt stimulation (awakening) from dosing via oral gavage.

Figure 30 is a graph illustrating the finding that compound (**145a**) reduced the number of apneas per hr expressed as a percent change from baseline (pre-drug), in rats chronically treated with morphine, versus treatment with a vehicle. The marked decrease in apnea at the 30 min post-treatment time, across all groups, was caused by overt stimulation (awakening) from dosing via oral gavage.

Figure 31 is a bar graph illustrating the finding that compound (**145a**) reduced the number of apneas per hr in rats chronically treated with morphine, versus treatment with a vehicle.

Figure 32 is a bar graph illustrating the finding that compound (**145a**) did not cause an increase in minute volume compared to a vehicle-treated group.

Figure 33 is a graph illustrating the finding that compound (**145a**) did not cause an increase in ventilation per unit time compared to treatment with a vehicle. The marked increase in minute volume at the (12:00-12:30) 30 min post-treatment time, across all groups, was caused by overt stimulation from dosing via oral gavage).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the discovery that the compounds of the invention are orally bioavailable breathing control modulators and useful in the prevention or treatment of breathing control disorders or diseases. Further, the compounds of the invention are orally bioavailable breathing control modulators suitable for chronic use in the prevention

or treatment of breathing control disorders or diseases. Further, the compounds of the invention are breathing control modulators and useful in the prevention or treatment of breathing control disorders or diseases upon oral administration.

In one aspect, the compounds of the invention prevent changes to the body's normal breathing control system, as a result of disorders and diseases and in response to changes in CO_2 and/or oxygen levels, with minimal side effects. In another aspect, the compounds of the invention decrease the incidence and severity of breathing control disturbances, such as sleep apneas. In yet another aspect, the compounds of the invention decrease the incidence of apneic events and/or decrease the duration of apneic events. In yet another aspect, the compounds of the invention have good metabolic stability and oral bioavailability. In yet another aspect, the compounds of the invention do not interfere with the effectiveness of therapies that may cause changes to breathing control, such as opioid analgesia. Such breathing control-altering therapies benefit from administration of agents that support or restore normal breathing function.

In one aspect, the compounds of the invention represent an improvement over previously reported breathing control modulating compounds, such as the compounds disclosed in U.S. Application No. 13/306,349. In one aspect, the compounds of the invention have improved microsomal stability and metabolic stability over the compounds taught in the prior art. In another aspect, the compounds of the invention have improved oral bioavailability over the compounds taught in the prior art. In another aspect, the compounds of the invention have improved pharmacological activities over the compounds taught in the prior art. In yet another aspect, the compounds of the invention display a developable cytochrome P450 profile (metabolism) and low activity at cardiac channels such as, but not limited to, hERG.

In one embodiment, the breathing control disorder or disease is selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, altitude sickness, hypoxia, hypercapnia, chronic obstructive pulmonary disease (COPD) and sudden infant death syndrome (SIDS). In another embodiment, the respiratory depression is caused by an anesthetic, sedative, sleeping aid, anxiolytic agent, hypnotic agent, alcohol or narcotic. In yet another embodiment, the respiratory depression is caused by genetic factors as manifested in congenital central hypoventilation syndrome. In yet another embodiment, the respiratory depression is caused by neurological conditions such as Alzheimer's disease, Parkinson's disease, stroke, Duchenne muscular dystrophy, and brain or spinal cord traumatic

injury.

Definitions

As used herein, each of the following terms has the meaning associated with it in this section. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in animal pharmacology, pharmaceutical science, separation science and organic chemistry are those well-known and commonly employed in the art.

As used herein, the articles "a" and "an" refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

As used herein, the term "about" is understood by persons of ordinary skill in the art and varies to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term "about" is meant to encompass variations of ±20% or ±10%, more preferably ±5%, even more preferably ±1 %, and still more preferably ±0.1 % from the specified value, as such variations are appropriate to perform the disclosed methods.

As used herein, a "subject" may be a human or non-human mammal or a bird. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and murine mammals. Preferably, the subject is human.

In a non-limiting embodiment, the following terminology used to report blood gas measurements is well known to those skilled in the art and may be defined as such: minute ventilation (MV) is a measure of breathing volume per unit time and is given herein as mL/min; pCO_2 is partial pressure of carbon dioxide (gas) in (arterial) blood measured in mm Hg (millimeters of Hg); pO_2 is partial pressure of oxygen (gas) in (arterial) blood measured in mmHg (millimeters of Hg); SaO_2 is the percentage of oxyhemoglobin saturation (oxygen gas bound to hemoglobin) that correlates to the percentage of hemoglobin binding sites in the bloodstream occupied by oxygen; end-tidal CO_2 is the measurement of exhaled carbon dioxide gas as detected using calorimetry, capnometry, or capnography techniques.

As used herein, the term ED_{50} refers to the effective dose of a formulation that produces 50 % of the maximal effect in subjects that are administered that formulation.

As used herein, the term "CYP450" or "P450" as applied to enzymes refers to cytochrome P450 (or P450) family of enzymes.

As used herein, a "disease" is a state of health of a subject wherein the subject cannot maintain homeostasis, and wherein if the disease is not ameliorated then the subject 's health continues to deteriorate.

As used herein, a "disorder" in a subject is a state of health in which the subject is able to maintain homeostasis, but in which the subject 's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the subject's state of health.

As used herein, an "effective amount," "therapeutically effective amount" or "pharmaceutically effective amount" of a compound is that amount of compound that is sufficient to provide a beneficial effect to the subject to which the compound is administered.

The terms "treat," "treating" and "treatment," as used herein, means reducing the frequency or severity with which symptoms of a disease or condition are experienced by a subject by virtue of administering an agent or compound to the subject.

The term "prevent," "preventing" or "prevention," as used herein, means avoiding or delaying the onset of symptoms associated with a disease or condition in a subject that has not developed such symptoms at the time the administering of an agent or compound commences. Disease, condition and disorder are used interchangeably herein.

As used herein, the term "pharmaceutically acceptable" refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound useful within the invention, and is relatively non-toxic, *i.e.*, the material may be administered to a subject without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the language "pharmaceutically acceptable salt" refers to a salt of the administered compound prepared from pharmaceutically acceptable non-toxic acids and bases, including inorganic acids, inorganic bases, organic acids, inorganic bases, solvates, hydrates, and clathrates thereof.

As used herein, the term "composition" or "pharmaceutical composition" refers to a mixture of at least one compound useful within the invention with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a subject.

As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the

invention within or to the subject such that it may perform its intended function. Typically, such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation, including the compound useful within the invention, and not injurious to the subject. Some examples of materials that may serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations. As used herein, "pharmaceutically acceptable carrier" also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound useful within the invention, and are physiologically acceptable to the subject. Supplementary active compounds may also be incorporated into the compositions. The "pharmaceutically acceptable carrier" may further include a pharmaceutically acceptable salt of the compound useful within the invention. Other additional ingredients that may be included in the pharmaceutical compositions used in the practice of the invention are known in the art and described, for example in Remington's Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

In one aspect, the terms "co-administered" and "co-administration" as relating to a subject refer to administering to the subject a compound of the invention or salt thereof along with a compound that may also treat breathing control disorders and/or with a compound that is useful in treating other medical conditions but which in themselves may alter breathing control. In one embodiment, the co-administered compounds are administered separately, or in any kind of combination as part of a single therapeutic approach. The co-administered compound may be formulated in any kind of combinations as mixtures of solids and liquids under a variety of solid, gel, and liquid formulations, and as a solution.

By the term "specifically bind" or "specifically binds," as used herein, is

meant that a first molecule preferentially binds to a second molecule (*e.g.*, a particular receptor or enzyme), but does not necessarily bind only to that second molecule.

As used herein, the term "alkyl" by itself or as part of another substituent means, unless otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms designated (*i.e.*, C_1-C_{10} means one to ten carbon atoms) and includes straight, branched chain, or cyclic substituent groups. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hexyl, and cyclopropylmethyl. Most preferred is (C_1-C_6)alkyl, such as, but not limited to, ethyl, methyl, isopropyl, isobutyl, n-pentyl, n-hexyl and cyclopropylmethyl.

As used herein, the term "cycloalkyl" by itself or as part of another substituent means, unless otherwise stated, a cyclic chain hydrocarbon having the number of carbon atoms designated (*i.e.*, C_3-C_6 means a cyclic group comprising a ring group consisting of three to six carbon atoms) and includes straight, branched chain or cyclic substituent groups. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Most preferred is (C_3-C_6)cycloalkyl, such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "alkenyl" employed alone or in combination with other terms means, unless otherwise stated, a stable mono-unsaturated or di-unsaturated straight chain or branched chain hydrocarbon group having the stated number of carbon atoms. Examples include vinyl, propenyl (or allyl), crotyl, isopentenyl, butadienyl, 1,3-pentadienyl, 1,4-pentadienyl, and the higher homologs and isomers. A functional group representing an alkene is exemplified by $-CH_2-CH=CH_2$.

As used herein, the term "alkynyl" employed alone or in combination with other terms means, unless otherwise stated, a stable straight chain or branched chain hydrocarbon group with a triple carbon-carbon bond, having the stated number of carbon atoms. Non-limiting examples include ethynyl and propynyl, and the higher homologs and isomers. The term "propargylic" refers to a group exemplified by $-CH_2-C\equiv CH$. The term "homopropargylic" refers to a group exemplified by $-CH_2CH_2-C\equiv CH$. The term "substituted propargylic" refers to a group exemplified by $-CR_2-C\equiv CR$, wherein each occurrence of R is independently H, alkyl, substituted alkyl, alkenyl or substituted alkenyl, with the proviso that at least one R group is not hydrogen. The term "substituted homopropargylic" refers to a group exemplified by $-CR_2CR_2-C\equiv CR$, wherein each occurrence of R is independently H, alkyl, substituted alkyl, alkenyl or substituted alkenyl, with the proviso that at least one R group is not hydrogen.

As used herein, the term "substituted alkyl," "substituted cycloalkyl," "substituted alkenyl" or "substituted alkynyl" means alkyl, cycloalkyl, alkenyl or alkynyl, as defined above, substituted by one, two or three substituents selected from the group consisting of halogen, -OH, alkoxy, tetrahydro-2-H-pyranyl, $-NH_2$, $-N(CH_3)_2$, (1-methyl-imidazol-2-yl), pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, -C(=O)OH, trifluoromethyl, -C≡N, -C(=O)O(C_1-C_4)alkyl, -C(=O)NH_2, -C(=O)NH(C_1-C_4)alkyl, -C(=O)N((C_1-C_4)alkyl)$_2$, $-SO_2NH_2$, -C(=NH)NH_2, and $-NO_2$, preferably containing one or two substituents selected from halogen, -OH, alkoxy, $-NH_2$, trifluoromethyl, $-N(CH_3)_2$, and -C(=O)OH, more preferably selected from halogen, alkoxy and -OH. Examples of substituted alkyls include, but are not limited to, 2,2-difluoropropyl, 2-carboxycyclopentyl and 3-chloropropyl.

As used herein, the term "alkoxy" employed alone or in combination with other terms means, unless otherwise stated, an alkyl group having the designated number of carbon atoms, as defined above, connected to the rest of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy (isopropoxy) and the higher homologs and isomers. Preferred are (C_1-C_3)alkoxy, such as, but not limited to, ethoxy and methoxy.

As used herein, the term "halo" or "halogen" employed alone or as part of another substituent means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine, more preferably, fluorine or chlorine.

As used herein, the term "heteroalkyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain alkyl group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may be optionally oxidized and the nitrogen heteroatom may be optionally quaternized. The heteroatom(s) may be placed at any position of the heteroalkyl group, including between the rest of the heteroalkyl group and the fragment to which it is attached, as well as attached to the most distal carbon atom in the heteroalkyl group. Examples include: $-O-CH_2-CH_2-CH_3$, $-CH_2-CH_2-CH_2-OH$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-S-CH_2-CH_3$, and $-CH_2CH_2-S(=O)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$, or $-CH_2-CH_2-S-S-CH_3$

As used herein, the term "heteroalkenyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain monounsaturated or di-unsaturated hydrocarbon group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S,

and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. Up to two heteroatoms may be placed consecutively. Examples include -CH=CH-O-CH_3, -CH=CH-CH_2-OH, -CH_2-CH=N-OCH_3, -CH=CH-N(CH_3)-CH_3, and -CH_2-CH=CH-CH_2-SH.

As used herein, the term "aromatic" refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, *i.e.* having (4n+2) delocalized π (pi) electrons, where n is an integer.

As used herein, the term "aryl" employed alone or in combination with other terms means, unless otherwise stated, a carbocyclic aromatic system containing one or more rings (typically one, two or three rings) wherein such rings may be attached together in a pendent manner, such as a biphenyl, or may be fused, such as naphthalene. Examples include phenyl, anthracyl, and naphthyl. Preferred are phenyl and naphthyl, most preferred is phenyl.

As used herein, the term "aryl-(C_1-C_3)alkyl" means a functional group wherein a one to three carbon alkylene chain is attached to an aryl group, *e.g.*, -CH_2CH_2-phenyl or –CH_2-phenyl (benzyl). Preferred is aryl-CH_2- and aryl-CH(CH_3)-. The term "substituted aryl-(C_1-C_3)alkyl" means an aryl-(C_1-C_3)alkyl functional group in which the aryl group is substituted. Preferred is substituted aryl(CH_2)-. Similarly, the term "heteroaryl-(C_1-C_3)alkyl" means a functional group wherein a one to three carbon alkylene chain is attached to a heteroaryl group, *e.g.*, -CH_2CH_2-pyridyl. Preferred is heteroaryl-(CH_2)-. The term "substituted heteroaryl-(C_1-C_3)alkyl" means a heteroaryl-(C_1-C_3)alkyl functional group in which the heteroaryl group is substituted. Preferred is substituted heteroaryl-(CH_2)-.

As used herein, the term "heterocycle" or "heterocyclyl" or "heterocyclic" by itself or as part of another substituent means, unless otherwise stated, an unsubstituted or substituted, stable, mono- or multi-cyclic heterocyclic ring system that consists of carbon atoms and at least one heteroatom selected from the group consisting of N, O, and S, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen atom may be optionally quaternized. The heterocyclic system may be attached, unless otherwise stated, at any heteroatom or carbon atom that affords a stable structure. A heterocycle may be aromatic or non-aromatic in nature. In one embodiment, the heterocycle is a heteroaryl.

As used herein, the term "heteroaryl" or "heteroaromatic" refers to a heterocycle having aromatic character. A polycyclic heteroaryl may include one or more

rings that are partially saturated. Examples include tetrahydroquinoline and 2,3-dihydrobenzofuryl.

Examples of non-aromatic heterocycles include monocyclic groups such as aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazoline, pyrazolidine, dioxolane, sulfolane, 2,3-dihydrofuran, 2,5-dihydrofuran, tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydropyridine, 1,4-dihydropyridine, piperazine, morpholine, thiomorpholine, pyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane, homopiperazine, homopiperidine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin and hexamethyleneoxide.

Examples of heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl (such as, but not limited to, 2- and 4-pyrimidinyl), pyridazinyl, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

Examples of polycyclic heterocycles include indolyl (such as, but not limited to, 3-, 4-, 5-, 6- and 7-indolyl), indolinyl, quinolyl, tetrahydroquinolyl, isoquinolyl (such as, but not limited to, 1- and 5-isoquinolyl), 1,2,3,4-tetrahydroisoquinolyl, cinnolinyl, quinoxalinyl (such as, but not limited to, 2- and 5-quinoxalinyl), quinazolinyl, phthalazinyl, 1,8-naphthyridinyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarin, 1,5-naphthyridinyl, benzofuryl (such as, but not limited to, 3-, 4-, 5-, 6- and 7-benzofuryl), 2,3-dihydrobenzofuryl, 1,2-benzisoxazolyl, benzothienyl (such as, but not limited to, 3-, 4-, 5-, 6-, and 7-benzothienyl), benzoxazolyl, benzothiazolyl (such as, but not limited to, 2-benzothiazolyl and 5-benzothiazolyl), purinyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl.

The aforementioned listing of heterocyclyl and heteroaryl moieties is intended to be representative and not limiting.

As used herein, the term "substituted" means that an atom or group of atoms has replaced hydrogen as the substituent attached to another group.

For aryl, aryl-(C_1-C_3)alkyl and heterocyclyl groups, the term "substituted" as applied to the rings of these groups refers to any level of substitution, namely mono-, di-, tri-, tetra-, or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. In one embodiment, the substituents vary in number between one and four. In another embodiment, the substituents vary in number between one and three. In yet another embodiment, the substituents vary in number between one and two. In yet another embodiment, the

substituents are independently selected from the group consisting of C_{1-6} alkyl, -OH, C_{1-6} alkoxy, halo, amino, acetamido and nitro. As used herein, where a substituent is an alkyl or alkoxy group, the carbon chain may be branched, straight or cyclic, with straight being preferred.

The following abbreviations are used herein:

δ (delta): delta (ppm); μL (μl): microliter;

ABG: arterial blood gas; AcOH: acetic acid;

ASV: adaptive servo ventilation; AUC: area under (the) curve;

BiPAP: bi-level positive airway pressure; nBuOH: *n*-butanol;

2-BuOH: 2-butanol; $CHCl_3$: chloroform;

$CDCl_3$: chloroform-d; CH_2Cl_2: dichloromethane or methylene chloride;

CPAP: continous positive airway pressure; DIPEA: N,N-diisopropylethylamine;

DMAc: N,N-dimethylacetamide; DMSO: dimethylsulfoxide;

EPAP: expiratory positive airway pressure; EtOAc: ethyl acetate;

EtOH: ethanol; Et_2O: (di)ethyl ether;

f: frequency (of respiration); F (%): bioavailability (percent)

HCl: hydrochloric acid or a hydrochloride salt;

hERG: human Ether-a-go-go Related Gene (Kv11.1 ion channel)

H_2SO_4: sulfuric acid; HLM: human liver microsomes;

HPLC: high pressure liquid chromatography;

ICU: intensive care unit; IPA: isopropanol (or 2-propanol);

IPAP: inspiratory positive airway pressure;

LCMS: liquid chromatography-mass spectrometry;

MBP: mean blood pressure; MeCN or CH_3CN: acetonitrile;

MEK: methyl ethyl ketone; MeOH or CH_3OH: methanol;

MIBK: methyl *iso*-butyl ketone; min: minute

mL (or mL): milliliter; mpk: mg/kg;

MTBE: methyl-*tert*-butyl ether; MV: minute volume;

MS: mass spectrometry; NaCl: sodium chloride;

NaHMDS: sodium hexamethyldisilazide; $NaHCO_3$: sodium bicarbonate;

NaOH: sodium hydroxide; Na_2SO_4: sodium sulfate;

NAVA: neurally adjusted ventilatory assist;

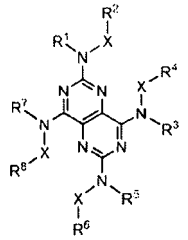
NIPPV: non-invasive positive pressure ventilation;

NMR: nuclear magnetic resonance; PAV: proportional assist ventilation;
PE or pet ether: petroleum ether; ppm: part per million;
iPrOAc: isopropyl acetate; nPrOH: n-propanol;
RLM: rat liver microsomes; RR: respiratory rate;
THF: tetrahydrofuran; TV: tidal volume;
V_E: minute (expired) volume; XRPD: x-ray powder diffraction (spectrum);
%y: percent yield.

"Instructional material" as that term is used herein includes a publication, a recording, a diagram, or any other medium of expression that can be used to communicate the usefulness of the composition and/or compound of the invention in a kit. The instructional material of the kit may, for example, be affixed to a container that contains the compound and/or composition of the invention or be shipped together with a container that contains the compound and/or composition. Alternatively, the instructional material may be shipped separately from the container with the intention that the recipient uses the instructional material and the compound cooperatively. Delivery of the instructional material may be, for example, by physical delivery of the publication or other medium of expression communicating the usefulness of the kit, or may alternatively be achieved by electronic transmission, for example by means of a computer, such as by electronic mail, or download from a website.

Compounds and Compositions of the Invention

The invention includes a compound of formula (I) or a salt thereof:



(I), wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a

biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; and,

each occurrence of X is independently alkyl or substituted alkyl.

In one embodiment, R^1, R^3, R^5 and R^7 are H.

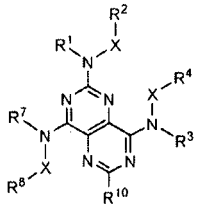
In one embodiment, R^1, R^3, R^5 and R^7 are H; X is O; and R^2, R^4, R^6 and R^8 are alkyl or substituted alkyl. In another embodiment, R^1, R^3, R^5 and R^7 are H; X is O; and R^2, R^4, R^6 and R^8 are H. In yet another embodiment, R^1, R^3, R^5 and R^7 are alkyl or substituted alkyl; X is O; and R^2, R^4, R^6 and R^8 are H.

In one embodiment, R^1, R^3, R^5 and R^7 are H; X is NH; and R^2, R^4, R^6 and R^8 are alkyl or substituted alkyl. In another embodiment, R^1, R^3, R^5 and R^7 are H; X is NH; and R^2, R^4, R^6 and R^8 are H.

In one embodiment, R^1, R^3, R^5 and R^7 are H; X is NR^9; and R^2, R^4, R^6 and R^8 are alkyl or substituted alkyl. In another embodiment, R^1, R^3, R^5 and R^7 are H; X is NR^9; and R^2, R^4, R^6 and R^8 are H. In yet another embodiment, R^1, R^3, R^5 and R^7 are alkyl or substituted alkyl; X is NR^9; and R^2, R^4, R^6 and R^8 are alkyl or substituted alkyl.

In one embodiment, R^1, R^3, R^5 and R^7 are H; X is bond; and R^2, R^4, R^6 and R^8 are alkyl or substituted alkyl.

The invention also includes a compound of formula (II) or a salt thereof:



(II), wherein:

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

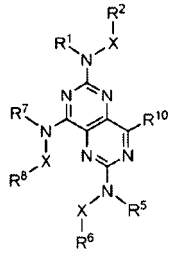
each occurrence of X is independently selected from the group consisting of bond,

NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl;

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy.

The invention also includes a compound of formula (III) or a salt thereof:



(III), wherein:

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl;

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy.

In one embodiment, the compound of the invention is selected from the group consisting of:

N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine;

N-(6-Chloro-4,8-*bis*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-

hydroxylamine;

N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-n-propylamino-pyrimido[5,4-d] pyrimidine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl)-hydroxylamine;

N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-(4,8-Bis-*n*-propylamino-6-methylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol;

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine;

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol;

N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-

tetraamine;

2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol;

N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-Chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Benzyloxy-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ol;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid;

N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-

amidine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methoxy-N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

N^4,N^8-Diethyl-N^2,N^6-Di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid;

N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide;

(6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester;

any salt or solvate thereof, and any combinations thereof.

In one embodiment, the salt is selected from the group consisting of sulfate, hydrogen sulfate, chloride, bromide, iodide, nitrate, carbonate, phosphate, hydrogen phosphate, dihydrogen phosphate, formate, acetate, propionate, succinate, glycolate, gluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, 4-hydroxybenzoate, phenylacetate, mandelate, pamoate, methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, trifluoromethanesulfonate, 2-hydroxyethanesulfonate, *p*-toluenesulfonate, sulfanilate, cyclohexylaminosulfonate, stearate, alginate, β-hydroxybutyrate, salicylate, galactarate, galacturonate, saccharin, saccharate, and glycerophosphonate. In certain embodiments, salts may be comprised of one or more molar equivalent of salt former with respect to any molecule of the invention.

In one embodiment, the at least one compound of the invention is a component of a pharmaceutical composition further including at least one pharmaceutically acceptable carrier.

The compounds of the invention may possess one or more stereocenters, and each stereocenter may exist independently in either the (R) or (S) configuration. In one embodiment, compounds described herein are present in optically active or racemic forms. The compounds described herein encompass racemic, optically-active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful properties described herein. Preparation of optically active forms is achieved in any suitable manner, including by way of non-limiting example, by resolution of the racemic form with recrystallization techniques, synthesis from optically-active starting materials, chiral synthesis, or chromatographic separation using a chiral stationary phase. In one embodiment, a mixture of one or more isomer is utilized as the therapeutic compound described herein. In another embodiment, compounds described herein contain one or more chiral centers. These compounds are prepared by any means, including stereoselective synthesis, enantioselective synthesis and/or separation of a mixture of enantiomers and/ or diastereomers. Resolution of compounds and isomers thereof is achieved by any means including, by way of non-limiting example, chemical processes, enzymatic processes, fractional crystallization, distillation, and chromatography.

The methods and formulations described herein include the use of N-oxides (if appropriate), crystalline forms (also known as polymorphs), solvates, amorphous phases, and/or pharmaceutically acceptable salts of compounds having the structure of any compound of the invention, as well as metabolites and active metabolites of these compounds having the

same type of activity. Solvates include water, ether (e.g., tetrahydrofuran, methyl tert-butyl ether) or alcohol (e.g., ethanol) solvates, acetates and the like. In one embodiment, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, and ethanol. In another embodiment, the compounds described herein exist in unsolvated form. In one embodiment, the compounds of the invention exist as tautomers. All tautomers are included within the scope of the compounds recited herein.

In one embodiment, compounds described herein are prepared as prodrugs. A "prodrug" is an agent converted into the parent drug *in vivo*. In one embodiment, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In another embodiment, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

In one embodiment, sites on, for example, the aromatic ring portion of compounds of the invention are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the aromatic ring structures may reduce, minimize or eliminate this metabolic pathway. In one embodiment, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a deuterium, a halogen, or an alkyl group.

Compounds described herein also include isotopically-labeled compounds wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds described herein include and are not limited to ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{36}Cl, ^{18}F, ^{123}I, ^{125}I, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, and ^{35}S. In one embodiment, the isotope comprises deuterium. In certain embodiments, isotopically-labeled compounds are useful in drug and/or substrate tissue distribution studies. In another embodiment, substitution with heavier isotopes such as deuterium affords greater metabolic stability (for example, increased in vivo half-life or reduced dosage requirements). In yet another embodiment, substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, is useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds are prepared by any suitable method or by processes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Isotopical labeling should not eb construced to be limited to the compounds of the invention, but rather applies to the compounds that may be used in combination with the compounds of the invention, such as but not limited to acetazolamide,

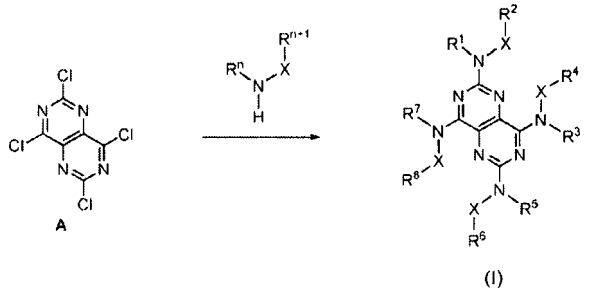
almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients, benzodiazepine receptor agonists, orexin antagonists, tricyclic antidepressants, serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids, orexins, melatonin agonists, ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics. In certain embodiments, the oxybate salt is isotopically labeled with one or more deuteriums at the C-α position.

In one embodiment, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Preparation of the Compounds of the Invention

The compounds of the invention may be prepared according to the general methodology illustrated in the synthetic schemes described below. The reagents and conditions described herein may be modified to allow the preparation of the compounds of the invention, and such modifications are known to those skilled in the art. The scheme included herein are intended to illustrate but not limit the chemistry and methodologies that one skilled in the art may use to make compounds of the invention.

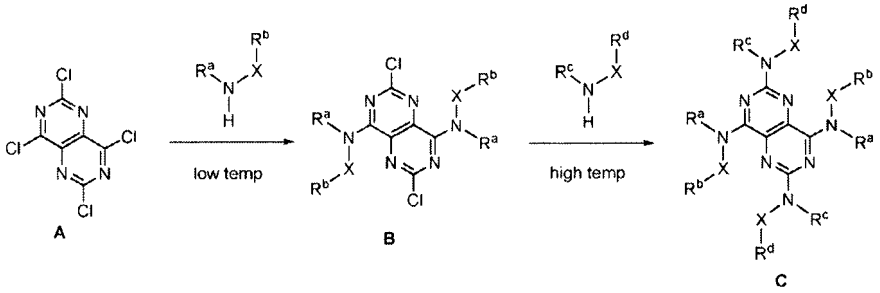
In a non-limiting example, compounds of formula (I) may be prepared by the additions of: (i) a primary alkylamine or a secondary alkylamine or an allylic amine or a propargylic amine, or (ii) a N-alkoxy-N-alkylamine, or (iii) an appropriately substituted hydrazine to suitably chlorinated intermediate (**A**) (Scheme 1).



Scheme 1. (n = 1, 3, 5 and 7)

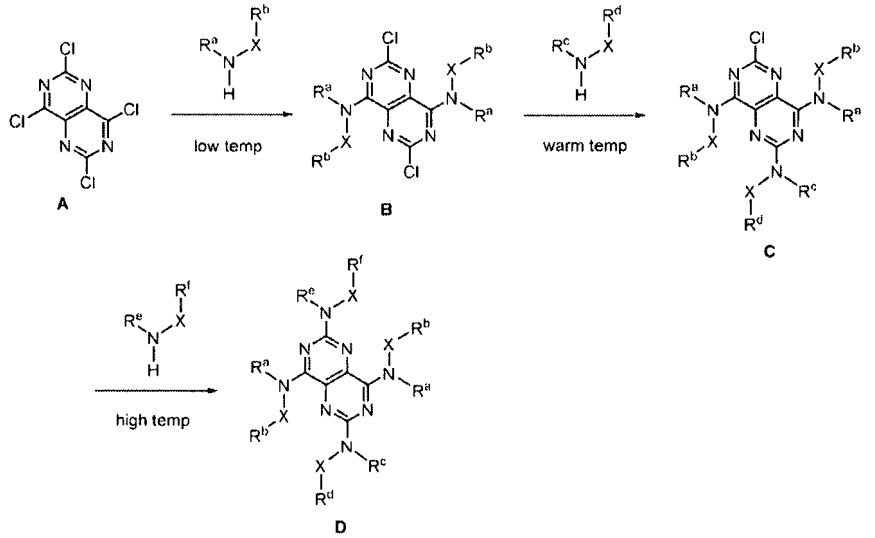
In a non-limiting example, compounds of formulae (I)-(III) may be prepared by the successive additions of: (i) a primary alkylamine or a secondary alkylamine or an allylic amine or a propargylic amine, and (ii) a N-alkoxy-N-alkylamine or (iii) an appropriately substituted hydrazine to suitably chlorinated intermediate (**A**) (Scheme 2). Reaction temperature can be used to direct the order of installation of substituents onto the

pyrimido[5,4-d]pyrimidine core. For example, low temperatures, such as 0°C to ambient temperature (approximately 20°C) selectively installs substituents at centers adjacent to the ring junction (alpha positions), yielding compound (**B**), whereas higher temperatures (approximately 80-100°C) add substituents to positions farther removed (beta positions) from the ring junction and less activated towards nucleophilic displacement. Thus, tetra-substituted pyrimido[5,4-d] pyrimidine compounds (**C**) may be obtained with dissimilar substituents (Scheme 2). Quenching the reaction appropriately may afford tri-substituted pyrimido[5,4-d]pyrimidine compounds.



Scheme 2.

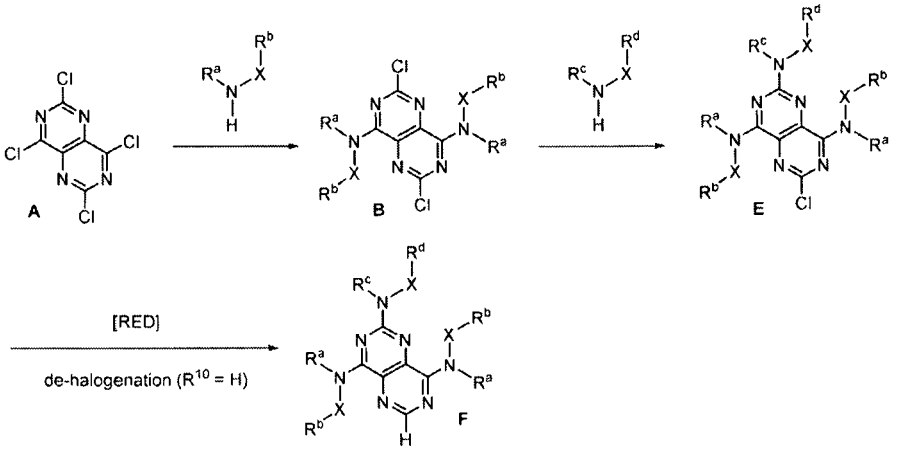
In a non-limiting example, compounds of formula (I) may be obtained with dissimilar substituents (**D**, Scheme 3) by attaching two identical alkylamino substituents in the first step and then attaching a third alkylamino substituent, dissimilar to the previous groups, in the second step and lastly, attaching a fourth alkylamino substituent that is dissimilar from the previous groups.



Scheme 3.

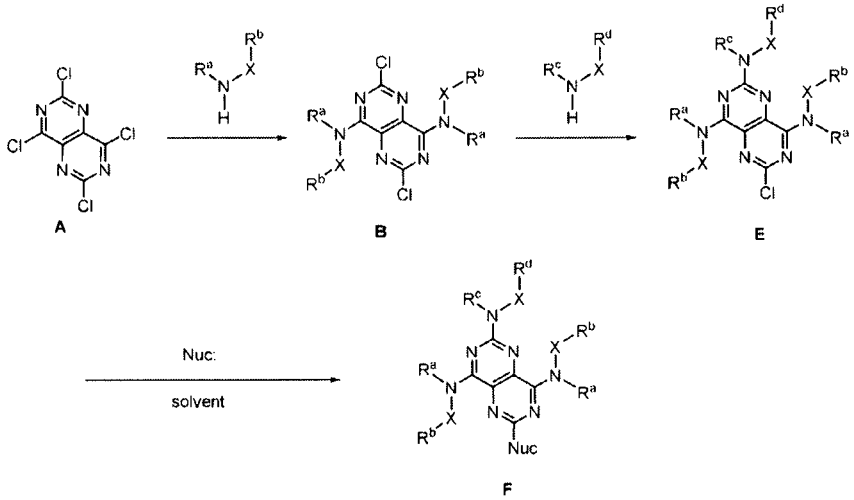
In a non-limiting example, compounds of formula (II)-(III) may be prepared

by the successive additions of: (i) a primary alkylamine or a secondary alkylamine or an allylic amine or a propargylic amine, and (ii) a N-alkoxy-N-alkylamine or (iii) an appropriately substituted hydrazine to suitably chlorinated intermediate (**A**), to provide mono-chloro pyrimido[5,4-d]pyrimidine compounds (**E**), which may be further dehalogenated /reduced to produce tri-substituted pyrimido[5,4-d]pyrimidine compounds (**F**) of formula (II) (Scheme 4).



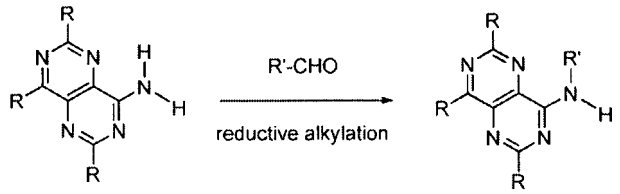
Scheme 4.

In a non-limiting example, compounds of formulae (I)-(III) may be obtained via halide displacement with nucleophiles to produce pyrimido[5,4-d] pyrimidine compounds which contain halogen, cyano, amidino, amido, hydrazino, hydroxyl, alkyl, substituted alkyl, alkoxy or substituted alkoxy, carboxylic acid, carboxamido, ether or thioether substituents.



Scheme 5.

In a non-limiting example, compounds of formulae (I)-(III) may be obtained via reductive amination of amino-substituted pyrimido[5,4-d] pyrimidine compounds.



Scheme 6.

Salts

The compounds described herein may form salts with acids, and such salts are included in the present invention. In one embodiment, the salts are pharmaceutically acceptable salts. The term "salts" embraces addition salts of free acids that are useful within the methods of the invention. The term "pharmaceutically acceptable salt" refers to salts that possess toxicity profiles within a range that affords utility in pharmaceutical applications. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present invention, such as for example utility in process of synthesis, purification or formulation of compounds useful within the methods of the invention.

Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include sulfate, hydrogen sulfate, hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids (including hydrogen phosphate and dihydrogen phosphate). Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β-hydroxybutyric, salicylic, galactaric, galacturonic acid, glycerophosphonic acids and saccharin (*e.g.*, saccharinate, saccharate). Salts may be comprised of a fraction of one, one or more than one molar equivalent of acid or base with respect to any compound of the invention.

Suitable pharmaceutically acceptable base addition salts of compounds of the invention include, for example, metallic salts including alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from

basic amines such as, for example, N,N'-dibenzylethylene-diamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

Molecules of the invention may be isolated as crystalline or amorphous free bases. Such crystalline or amorphous free bases may be obtained directly during the processing step wherein the final amine is attached during the synthetic process, and may also or alternatively be obtained by separately dissolving and crystallizing, and/or precipating, the free base from a suitable solvent or mixture of solvents. Suitable solvents may include, but are not limited to, MeCN, MEK, MIBK, EtOAc, iPrOAc, water, heptane, MTBE, cyclohexane, toluene, MeOH, EtOH, n-PrOH, IPA, nBuOH, 2-BuOH, isoamyl alcohol, and THF.

Combination and Concurrent Therapies

In one embodiment, the compounds of the invention are useful in the methods of present invention when used concurrently with at least one additional compound useful for preventing and/or treating breathing control disorders.

In one embodiment, the compounds of the invention are useful in the methods of present invention in combination with at least one additional compound useful for preventing and/or treating breathing control disorders.

These additional compounds may comprise compounds of the present invention or other compounds, such as commercially available compounds, known to treat, prevent, or reduce the symptoms of breathing disorders. In one embodiment, the combination of at least one compound of the invention or a salt thereof and at least one additional compound useful for preventing and/or treating breathing disorders has additive, complementary or synergistic effects in the prevention and/or treatment of disordered breathing, and in the prevention and/or treatment of sleep-related breathing disorders.

In a non-limiting example, the compounds of the invention or a salt thereof may be used concurrently or in combination with one or more of the following drugs: doxapram, enantiomers of doxapram, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients (such as eszopiclone and zolpidem), benzodiazepine receptor agonists (*e.g.*, zolpidem, zaleplon, estazolam, flurazepam, quazepam, temazepam, triazolam) orexin antagonists (*e.g.*, suvorexant), tricyclic antidepressants (*e.g.*, doxepin), serotonergic

modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids (such as, but not limited to, dronabinol), orexins, melatonin agonists (such as ramelteon), compounds known as ampakines, sodium oxybate, modafinil, and armodafinil.

In a non-limiting example, the compounds of the invention or a salt thereof may be used concurrently or in combination with inhaled therapeutics such as oxygen and carbon dioxide as for the treatment of sleep disordered breathing.

Non-limiting examples of ampakines are the pyrrolidine derivative racetam drugs such as piracetam and aniracetam; the "CX-" series of drugs which encompass a range of benzoylpiperidine and benzoylpyrrolidine structures, such as CX-516 (6-(piperidin-1-yl-carbonyl)quinoxaline), CX-546 (2,3-dihydro-1,4-benzodioxin-7-yl-(1-piperidyl)-methanone), CX-614 (2H,3H,6aH-pyrrolidino(2,1-3',2')-1,3-oxazino-(6',5'-5,4)benzo(e)1,4-dioxan-10-one), CX-691 (2,1,3-benzoxadiazol-6-yl-piperidin-1-yl-methanone), CX-717, CX-701, CX-1739, CX-1763, and CX-1837; benzothiazide derivatives such as cyclothiazide and IDRA-21 (7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide); biarylpropylsulfonamides such as LY-392,098, LY-404,187 (N-[2-(4'-cyanobiphenyl-4-yl)propyl]propane-2-sulfonamide), LY-451,646 and LY-503,430 (4'-{(1S)-1-fluoro-2-[(isopropylsulfonyl)amino]-1-methylethyl}-N-methylbiphenyl-4-carboxamide).

In one embodiment, the invention includes a composition comprising a compound of the invention and at least one agent selected from the group consisting of doxapram, enantiomers of doxapram, enantiomers of doxapram, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients (such as eszopiclone or zolpidem), benzodiazepine receptor agonists (such as zolpidem, zaleplon, estazolam, flurazepam, quazepam, temazepam, or triazolam), orexin antagonists (*e.g.* suvorexant), tricyclic antidepressants (such as doxepin), serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids (such as but not limited to dronabinol), orexins, melatonin agonists (such as ramelteon), compounds known as ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics such as oxygen and carbon dioxide gases.

In another non-limiting example, the compounds of the invention or a salt thereof may be used concurrently or in combination with one or more of the following drugs and drug classes known to cause changes in breathing control: opioid narcotics (such as morphine, fentanyl, codeine, hydromorphone, hydrocodone, oxymorphone, oxycodone, meperidine, butorphanol, carfentanil, buprenorphine, methadone, nalbuphine, propoxyphene,

pentazocine, remifentanil, alfentanil, sufentanil and tapentadol); benzodiazepines (such as midazolam); and sedatives (such as zolipidem and eszopiclone); propofol; sodium oxybate, modafinil, and armodafinil. In one embodiment, the invention includes a composition comprising a compound of the invention and at least one agent known to cause changes in breathing control. In one embodiment, the at least one agent is selected from the group consisting of opioid narcotics, benzodiazepines, sedatives, sleeping aids and propofol.

In another non-limiting example, the compounds of the invention or a salt thereof may be used concurrently or in combination with one or more of the following drugs and drug classes known to either aid the onset of sleep, maintain sleep and/or alter arousal threshold: zolipidem, zaleplon, eszopiclone, ramelteon, estazolam, temazepam doxepin, phenobarbital and other barbiturates, diphenhydramine, doxylamine and related compounds, sodium oxybate, modafinil and armodafinil, for example. The combination of a sleep promoting/stabilizing drug and the compounds of the invention may act additively or synergistically to improve indices of sleep disordered breathing. In one embodiment, the compounds of the invention stabilize respiratory pattern (*i.e.*, decrease variation in respiratory rate and tidal volume on a breath by breath basis) and respiratory drive (*i.e.*, decrease fluctuations in the neural control of the respiratory muscles), thereby decreasing the incidence of central and obstructive apneas whilst the sleep promoting/stabilizing drug prevents patient arousal from sleep if residual apneas persist. Blood gas derangements associated with a residual apnea may elicit chemoreceptor stimulation, which in turn elicits generalized central nervous system arousal. Patients with a low arousal threshold from sleep wake early and often (*i.e.*, experience sleep fragmentation), and these patients experience a ventilatory overshoot due to the sudden awakening in excess of the level of chemoreceptor stimulation. Sleep promoting/stabilizing drugs delay cortical arousal and permit a more appropriate ventilatory response to apnea-induced chemoreceptor stimulation. The patient benefits from delayed arousal from sleep because sleep fragmentation decreases and hyperventilation-driven central apneas decrease.

As used herein, combination of two or more compounds may refer to a composition wherein the individual compounds are physically mixed or wherein the individual compounds are physically separated. A combination therapy encompasses administering the components separately to produce the desired additive, complementary or synergistic effects.

In one embodiment, the compound and the agent are physically mixed in the composition. In another embodiment, the compound and the agent are physically separated

in the composition.

In one embodiment, the compound of the invention is co-administered with a compound that is used to treat another disorders but causes loss of breathing control. In this aspect, the compound of the invention blocks or otherwise reduces depressive effects on normal breathing control caused by the compound with which they are co-administered. Such compound that treats another disorder but depresses breathing control includes but is not limited to anesthetics, sedatives, sleeping aids, anxiolytics, hypnotics, alcohol, and narcotic analgesics. The co-administered compound may be administered individually, or a combined composition as a mixture of solids and/or liquids in a solid, gel or liquid formulation or as a solution, according to methods known to those familiar with the art.

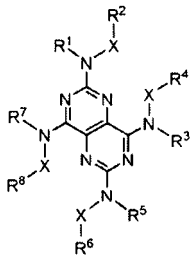
In one embodiment, a compound of the present invention may be co-administered with at least one additional compound useful for treating breathing control disorders and with at least one compound that is used to treat other disorder but causes a loss of breathing control. In this aspect, the compound of the invention works in an additive, complementary or synergistic manner with the co-administered breathing control agent to block or otherwise reduce depressive effects on normal breathing control caused by other compounds with which they are combined.

A synergistic effect may be calculated, for example, using suitable methods such as, for example, the Sigmoid-E_{max} equation (Holford & Scheiner, 19981, Clin. Pharmacokinet. 6: 429-453), the equation of Loewe additivity (Loewe & Muischnek, 1926, Arch. Exp. Pathol Pharmacol. 114: 313-326), the median-effect equation (Chou & Talalay, 1984, Adv. Enzyme Regul. 22: 27-55), and through the use of isobolograms (Tallarida & Raffa, 1996, Life Sci. 58: 23-28). Each equation referred to above may be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

In one embodiment, a compound of the present invention may be packaged with at least one additional compound useful for treating breathing control disorders. In another embodiment, a compound of the present invention may be packaged with a therapeutic agent known to cause changes in breathing control, such as, but not limited to, anesthetics, sedatives, anxiolytics, hypnotics, alcohol, and narcotic analgesics. A co-package may be based upon, but not limited to, dosage units.

Methods of the Invention

In one aspect, the present invention includes a method of preventing or treating a breathing control disorder or disease in a subject in need thereof. The method includes administering to the subject an effective amount of a pharmaceutical formulation comprising at least a pharmaceutically acceptable carrier and at least one compound or salt thereof selected from the group consisting of:



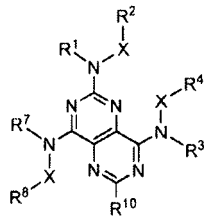
a compound of formula (I): (I), wherein in formula (I)

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; and,

each occurrence of R^9 is independently alkyl or substituted alkyl;



a compound of formula (II): (II), wherein in formula (II):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

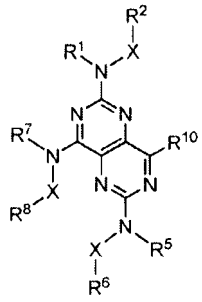
or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a

biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl;

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy; and,

a compound of formula (III):  (III), wherein in formula (III):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl;

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy.

In another aspect, the present invention includes a method of preventing destabilization of or stabilizing breathing rhythm in a subject in need thereof. The method includes administering to the subject an effective amount of a pharmaceutical formulation comprising at least a pharmaceutically acceptable carrier and at least one compound of the invention or a salt thereof.

In one embodiment, administering the formulation of the invention stabilizes

the breathing rhythm of the subject. In another embodiment, administering the formulation of the invention increases minute ventilation in the subject.

In one embodiment, the destabilization is associated with a breathing control disorder or disease.

In one embodiment, the breathing disorder or disease is selected from the group consisting of narcotic-induced respiratory depression, anesthetic-induced respiratory depression, sedative-induced respiratory depression, sleeping aid-induced respiratory depression, anxiolytic-induced respiratory depression, hypnotic-induced respiratory depression, alcohol-induced respiratory depression, analgesic-induced respiratory depression, sleep apnea (includes but not limited to mixed central, obstructive, anatomical), apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, altitude sickness, hypoxia, hypercapnia, chronic obstructive pulmonary disease (COPD), sudden infant death syndrome (SIDS), Alzheimer's disease, Parkinson's disease, stroke, Duchenne muscular dystrophy, and brain and spinal cord traumatic injury. In another embodiment, the respiratory depression is caused by an anesthetic, a sedative, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic. In yet another embodiment, the compounds of the invention or a salt thereof may be used concurrently or in combination with one or more of the following drugs and drug classes known to either aid the onset of sleep, maintain sleep and/or alter arousal threshold: zolipidem, zaleplon, eszopiclone, ramelteon, estazolam, temazepam doxepin, phenobarbital and other barbiturates, diphenhydramine, doxylamine and related compounds for example.

In one embodiment, the subject is further administered at least one additional compound useful for preventing or treating the breathing disorder or disease. In another embodiment, the at least one additional compound is selected from the group consisting of doxapram, enantiomers of doxapram, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives such as eszopiclone and zolpidem, benzodiazepine receptor agonists (*e.g.*, zolpidem, zaleplon, estazolam, flurazepam, quazepam, temazepam, triazolam), orexin antagonists (*e.g.*, suvorexant), tricyclic antidepressants (*e.g.*, doxepin), serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids (such as but not limited to dronabinol), orexins, melatonin agonists (such as ramelteon), compounds known as ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics.

In yet another embodiment, the formulation is administered to the subject in conjunction with the use of a mechanical ventilation device or positive airway pressure

device. In one embodiment, the formulation is administered to the subject by an inhalational, topical, oral, nasal, buccal, rectal, pleural, peritoneal, vaginal, intramuscular, subcutaneous, transdermal, epidural, intrathecal, intratracheal, otic, intraocular or intravenous route. In another embodiment, the subject is a bird or a mammal including but not limited to mouse, rat, ferret, guinea pig, non-human primate (such as monkey), dog, cat, horse, cow, pig and other farm animals. In one embodiment, the subject is a human.

In one embodiment, the compound of the invention is selected from the group consisting of:

N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine;

N-(6-Chloro-4,8-*bis*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine;

N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-n-propylamino-pyrimido[5,4-d] pyrimidine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl)-hydroxylamine;

N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-(4,8-Bis-*n*-propylamino-6-methylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol;

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine;

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol;

N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol;

N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
2-Chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;
6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
6-Benzyloxy-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ol;
4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;
N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid;
N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-amidine;
N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
6-Methoxy-N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;
N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine
2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;
N^4,N^8-Diethyl-N^2,N^6-Di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-

tetraamine;

N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d] pyrimidine-2,4,8-triamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid;

N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide;

(6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester;

any salt thereof, and any combinations thereof.

Pharmaceutical Compositions and Formulations

The invention also encompasses the use of pharmaceutical compositions of at least one compound of the invention or a salt thereof to practice the methods of the invention.

Such a pharmaceutical composition may consist of at least one compound of the invention or a salt thereof, in a form suitable for administration to a subject, or the pharmaceutical composition may comprise at least one compound of the invention or a salt thereof, and one or more pharmaceutically acceptable carriers, one or more additional ingredients, or some combination of these. The at least one compound of the invention may be present in the pharmaceutical composition in the form of a physiologically acceptable salt, such as in combination with a physiologically acceptable cation or anion, as is well known in the art.

In an embodiment, the pharmaceutical compositions useful for practicing the method of the invention may be administered to deliver a dose of between 1 ng/kg/day and 100 mg/kg/day. In another embodiment, the pharmaceutical compositions useful for practicing the invention may be administered to deliver a dose of between 1 ng/kg/day and 1,000 mg/kg/day.

The relative amounts of the active ingredient, the pharmaceutically acceptable

carrier, and any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

Pharmaceutical compositions that are useful in the methods of the invention may be suitably developed for nasal, inhalational, oral, rectal, vaginal, pleural, peritoneal, parenteral, topical, transdermal, pulmonary, intranasal, buccal, ophthalmic, epidural, intrathecal, intratracheal, otic, intraocular, intravenous or another route of administration. A composition useful within the methods of the invention may be directly administered to the brain, the brainstem, or any other part of the central nervous system of a mammal or bird. Other contemplated formulations include projected nanoparticles, microspheres, liposomal preparations, coated particles, polymer conjugates, resealed erythrocytes containing the active ingredient, and immunologically-based formulations. Additionally, constituents and or processes useful within the methods of the invention enables the pharmaceutical compositions of at least one compound of the invention or a salt thereof to be combined or processed with other substances into a pharmaceutical matrix to easily process insoluble materials, to improve the bioavailability of compounds of the inventions or salts, the ability to create controlled and or sustained release product, and the ability to create compounds that are extremely homogeneous. By way of example, implementing hot melt extrusion, solid solutions, solid dispersions, size reduction technologies, molecular complexes (e.g. cyclodextrins, and others), microparticulate, particle and formulation coating processes. It is understood that in all the constituents and or process a skill artisan can utilize amorphous or crystalline phases. The route(s) of administration will be readily apparent to the skilled artisan and will depend upon any number of factors including the type and severity of the disease being treated, the type and age of the veterinary or human patient being treated, and the like.

The formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology and pharmaceutics. In general, such preparatory methods include the step of bringing the active ingredient into association with a carrier or one or more other accessory ingredients, and then, if necessary or desirable, shaping or packaging the product into a desired single-dose or multi-dose unit.

As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the

active ingredient is generally equal to the dosage of the active ingredient that would be administered to a subject or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage. The unit dosage form may be for a single daily dose or one of multiple daily doses (*e.g.*, about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form may be the same or different for each dose.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for ethical administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions of the invention is contemplated include, but are not limited to, humans and other primates, mammals including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, and dogs.

In one embodiment, the compositions of the invention are formulated using one or more pharmaceutically acceptable excipients or carriers. In one embodiment, the pharmaceutical compositions of the invention comprise a therapeutically effective amount of at least one compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers, which are useful, include, but are not limited to, glycerol, water, saline, ethanol, recombinant human albumin (e.g. Recombumin®), solubilized gelatins (e.g. Gelofusine®), and other pharmaceutically acceptable salt solutions such as phosphates and salts of organic acids. Examples of these and other pharmaceutically acceptable carriers are described in Remington's Pharmaceutical Sciences (1991, Mack Publication Co., New Jersey).

The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), recombinant human albumin, solubilized gelatins, suitable mixtures thereof, and vegetable oils. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be

preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions may be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate or gelatin.

Formulations may be employed in admixtures with conventional excipients, *i.e.*, pharmaceutically acceptable organic or inorganic carrier substances suitable for oral, parenteral, nasal, inhalational, intravenous, subcutaneous, transdermal enteral, or any other suitable mode of administration, known to the art. The pharmaceutical preparations may be sterilized and if desired mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or fragrance-conferring substances and the like. They may also be combined where desired with other active agents, *e.g.*, other analgesic, anxiolytics or hypnotic agents. As used herein, "additional ingredients" include, but are not limited to, one or more ingredients that may be used as a pharmaceutical carrier.

The composition of the invention may comprise a preservative from about 0.005% to 2.0% by total weight of the composition. The preservative is used to prevent spoilage in the case of exposure to contaminants in the environment. Examples of preservatives useful in accordance with the invention include but are not limited to those selected from the group consisting of benzyl alcohol, sorbic acid, parabens, imidurea and combinations thereof. A particularly preferred preservative is a combination of about 0.5% to 2.0% benzyl alcohol and 0.05% to 0.5% sorbic acid.

The composition preferably includes an antioxidant and a chelating agent which inhibit the degradation of the compound. Preferred antioxidants for some compounds are BHT, BHA, alpha-tocopherol and ascorbic acid in the preferred range of about 0.01% to 0.3% and more preferably BHT in the range of 0.03% to 0.1% by weight by total weight of the composition. Preferably, the chelating agent is present in an amount of from 0.01% to 0.5% by weight by total weight of the composition. Particularly preferred chelating agents include edetate salts (*e.g.* disodium edetate) and citric acid in the weight range of about 0.01% to 0.20% and more preferably in the range of 0.02% to 0.10% by weight by total weight of the composition. The chelating agent is useful for chelating metal ions in the composition which may be detrimental to the shelf life of the formulation. While BHT and disodium edetate are the particularly preferred antioxidant and chelating agent, respectively, for some compounds, other suitable and equivalent antioxidants and chelating agents may be substituted therefore as would be known to those skilled in the art.

Liquid suspensions may be prepared using conventional methods to achieve suspension of the active ingredient in an aqueous or oily vehicle. Aqueous vehicles include, for example, water, and isotonic saline. Oily vehicles include, for example, almond oil, oily esters, ethyl alcohol, vegetable oils such as arachis, olive, sesame, or coconut oil, fractionated vegetable oils, and mineral oils such as liquid paraffin. Liquid suspensions may further comprise one or more additional ingredients including, but not limited to, suspending agents, dispersing or wetting agents, emulsifying agents, demulcents, preservatives, buffers, salts, flavorings, coloring agents, and sweetening agents. Oily suspensions may further comprise a thickening agent. Known suspending agents include, but are not limited to, sorbitol syrup, hydrogenated edible fats, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, and cellulose derivatives such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose. Known dispersing or wetting agents include, but are not limited to, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with a fatty acid, with a long chain aliphatic alcohol, with a partial ester derived from a fatty acid and a hexitol, or with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene stearate, heptadecaethyleneoxycetanol, polyoxyethylene sorbitol monooleate, and polyoxyethylene sorbitan monooleate, respectively). Known emulsifying agents include, but are not limited to, lecithin, acacia and other ionic or non ionic surfactants. Known preservatives include, but are not limited to, methyl, ethyl, or *n*-propyl para-hydroxybenzoates, ascorbic acid, and sorbic acid.

Liquid solutions of the active ingredient in aqueous or oily solvents may be prepared in substantially the same manner as liquid suspensions, the primary difference being that the active ingredient is dissolved, rather than suspended in the solvent. As used herein, an "oily" liquid is one which comprises a carbon-containing liquid molecule and which exhibits a less polar character than water. Liquid solutions of the pharmaceutical composition of the invention may comprise each of the components described with regard to liquid suspensions, it being understood that suspending agents will not necessarily aid dissolution of the active ingredient in the solvent. Aqueous solvents include, for example, water, and isotonic saline. Oily solvents include, for example, almond oil, oily esters, ethyl alcohol, vegetable oils such as arachis, olive, sesame, or coconut oil, fractionated vegetable oils, and mineral oils such as liquid paraffin.

Powdered and granular formulations of a pharmaceutical preparation of the invention may be prepared using known methods. Such formulations may be administered directly to a subject, used, for example, to form tablets, to fill capsules, or to prepare an

aqueous or oily suspension or solution by addition of an aqueous or oily vehicle thereto. Each of these formulations may further comprise one or more of dispersing or wetting agent, a suspending agent, ionic and non-ionic surfactants, and a preservative. Additional excipients, such as fillers and sweetening, flavoring, or coloring agents, may also be included in these formulations.

A pharmaceutical composition of the invention may also be prepared, packaged, or sold in the form of oil-in-water emulsion or a water-in-oil emulsion. The oily phase may be a vegetable oil such as olive or arachis oil, a mineral oil such as liquid paraffin, or a combination of these. Such compositions may further comprise one or more emulsifying agents such as naturally occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soybean or lecithin phosphatide, esters or partial esters derived from combinations of fatty acids and hexitol anhydrides such as sorbitan monooleate, and condensation products of such partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. These emulsions may also contain additional ingredients including, for example, sweetening or flavoring agents.

Methods for impregnating or coating a material with a chemical composition are known in the art, and include, but are not limited to methods of depositing or binding a chemical composition onto a surface, methods of incorporating a chemical composition into the structure of a material during the synthesis of the material (*i.e.*, such as with a physiologically degradable material), and methods of absorbing an aqueous or oily solution or suspension into an absorbent material, with or without subsequent drying. Methods for mixing components include physical milling, the use of pellets in solid and suspension formulations and mixing in a transdermal patch, as known to those skilled in the art.

Administration/Dosing

The regimen of administration may affect what constitutes an effective amount. The therapeutic formulations may be administered to the patient either prior to or after the onset of a breathing disorder event. Further, several divided dosages, as well as staggered dosages may be administered daily or sequentially, or the dose may be continuously infused, or may be a bolus injection. Further, the dosages of the therapeutic formulations may be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

Administration of the compositions of the present invention to a patient, preferably a mammal, more preferably a human, may be carried out using known procedures,

at dosages and for periods of time effective to treat a breathing control disorder in the patient. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the activity of the particular compound employed; the time of administration; the rate of excretion of the compound; the duration of the treatment; other drugs, compounds or materials used in combination with the compound; the state of the disease or disorder, age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well-known in the medical arts. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A non-limiting example of an effective dose range for a therapeutic compound of the invention is from about 0.01 mg/kg to 100 mg/kg of body weight/per day. One of ordinary skill in the art would be able to study the relevant factors and make the determination regarding the effective amount of the therapeutic compound without undue experimentation.

The compound can be administered to an animal as frequently as several times daily, or it may be administered less frequently, such as once a day, once a week, once every two weeks, once a month, or even less frequently, such as once every several months or even once a year or less. It is understood that the amount of compound dosed per day may be administered, in non-limiting examples, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days. For example, with every other day administration, a 5 mg per day dose may be initiated on Monday with a first subsequent 5 mg per day dose administered on Wednesday, a second subsequent 5 mg per day dose administered on Friday, and so on. The frequency of the dose will be readily apparent to the skilled artisan and will depend upon any number of factors, such as, but not limited to, the type and severity of the disease being treated, the type and age of the animal, etc.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

A medical doctor, *e.g.*, physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the

dosage until the desired effect is achieved.

In particular embodiments, it is especially advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding/formulating such a therapeutic compound for the treatment of breathing disorders in a patient.

In one embodiment, the compositions of the invention are administered to the patient in dosages that range from one to five times per day or more. In another embodiment, the compositions of the invention are administered to the patient in range of dosages that include, but are not limited to, once every day, every two, days, every three days to once a week, and once every two weeks. It will be readily apparent to one skilled in the art that the frequency of administration of the various combination compositions of the invention will vary from subject to subject depending on many factors including, but not limited to, age, disease or disorder to be treated, gender, overall health, and other factors. Thus, the invention should not be construed to be limited to any particular dosage regime and the precise dosage and composition to be administered to any patient will be determined by the attending physician taking all other factors about the patient into account.

Compounds of the invention for administration may be in the range of from about 1 μg to about 7,500 mg, about 20 μg to about 7,000 mg, about 40 μg to about 6,500 mg, about 80 μg to about 6,000 mg, about 100 μg to about 5,500 mg, about 200 μg to about 5,000 mg, about 400 μg to about 4,000 mg, about 800 μg to about 3,000 mg, about 1 mg to about 2,500 mg, about 2 mg to about 2,000 mg, about 5 mg to about 1,000 mg, about 10 mg to about 750 mg, about 20 mg to about 600 mg, about 30 mg to about 500 mg, about 40 mg to about 400 mg, about 50 mg to about 300 mg, about 60 mg to about 250 mg, about 70 mg to about 200 mg, about 80 mg to about 150 mg, and any and all whole or partial increments there-in-between.

In some embodiments, the dose of a compound of the invention is from about 0.5 μg and about 5,000 mg. In some embodiments, a dose of a compound of the invention

used in compositions described herein is less than about 5,000 mg, or less than about 4,000 mg, or less than about 3,000 mg, or less than about 2,000 mg, or less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 200 mg, or less than about 50 mg. Similarly, in some embodiments, a dose of a second compound as described herein is less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 400 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than about 40 mg, or less than about 30 mg, or less than about 25 mg, or less than about 20 mg, or less than about 15 mg, or less than about 10 mg, or less than about 5 mg, or less than about 2 mg, or less than about 1 mg, or less than about 0.5 mg, and any and all whole or partial increments thereof.

In one embodiment, the present invention is directed to a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a compound of the invention, alone or in combination with a second pharmaceutical agent; and instructions for using the compound to treat, prevent, or reduce one or more symptoms of breathing disorder in a patient.

The term "container" includes any receptacle for holding the pharmaceutical composition or to add protection to manage stability and or water-uptake. For example, in one embodiment, the container is the packaging that contains the pharmaceutical composition such as liquid (solution and suspension), semisolid, lyophilized solid, solution and powder or lyophilized formulation present in dual chambers. In other embodiments, the container is not the packaging that contains the pharmaceutical composition, *i.e.*, the container is a receptacle, such as a box or vial that contains the packaged pharmaceutical composition or unpackaged pharmaceutical composition and the instructions for use of the pharmaceutical composition. Moreover, packaging techniques are well known in the art. It should be understood that the instructions for use of the pharmaceutical composition may be contained on the packaging containing the pharmaceutical composition, and as such the instructions form an increased functional relationship to the packaged product. However, it should be understood that the instructions may contain information pertaining to the compound's ability to perform its intended function, *e.g.*, treating, preventing, or reducing a breathing disorder in a patient.

Routes of Administration

Routes of administration of any of the compositions of the invention include inhalational, oral, nasal, rectal, parenteral, sublingual, transdermal, transmucosal (*e.g.*,

sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (*e.g.*, trans- and perivaginally), (intra)nasal, and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, epidural, intrapleural, intraperitoneal, intratracheal, otic, intraocular, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration.

Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, emulsions, dispersions, suspensions, solutions, sterile solutions for injection, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and compositions that would be useful in the present invention are not limited to the particular formulations and compositions that are described herein.

Oral Administration

In one embodiment, compounds of the invention may be formulated to prepare a pharmaceutical composition for oral administration. In further embodiments, the composition for oral administration may be designed to promote a modified release of the drug, such that the location, extent and rate of exposure of the compound when ingested are modulated. Factors that affect the target zone for exposure of a drug may be the drug's pH or enzymatic stability, reactivity with other drugs (*e.g.*, certain antibiotics), solubility as a salt or free base, ionization behavior, and pharmacodynamic and pharmacokinetic behaviors in specific environments. Some drugs are better absorbed in the duodenum or other intestinal locations.

Delayed release is a particularly useful mode of modified release that delivers drug in its most concentrated form to the duodenum or other intestinal location. In a preferred embodiment, compounds of the present invention are formulated to promote delivery to the duodenum and, optionally, other intestinal locations. Delayed release may be achieved using compositions that include a enteric coatings. Enteric coatings are insoluble in highly acidic environments, with the polyacidic coating remaining non-ionized and intact at gastric pH. However, under mildly acidic (> pH 5.5), neutral or mildly alkaline conditions (pH 6.5-7.6) of the duodenum or other intestinal regions, the coating ionizes, swells and breaks down, exposing the coated entity to the environment. Coating options exist to allow ionization at or near a specific pH (*e.g.* Eudragit L-110, ionization threshold pH 6.0; Eudragit

S-100, ioization threshold pH 7.0).

In a further embodiment, compounds of the present invention may be formulated with an enteric coating which has been modified by adding plasticizers to the polymer before coating. The plasticizers may be added to adjust resistance to chipping or cracking of the coating, while also lowering the glass transition temperature of the coating to enable smooth and even spreadability of the coating during its application. Suitable plasticizers include polyethylene glycol 8000 (PEG 8000), triethyl citrate (TEC), and triacetin, which may be incorporated into the polymeric enteric coating agent.

Compounds of the present invention may be enterically formulated under a variety of dosage forms, including (but not limited to) capsules, granules of the active drug itself, beads, and tablets. In one embodiment, the composition may comprise a drug encapsulated in a capsule that is enterically coated to release the drug in the duodenum or other intestinal environment. In one aspect of the invention, pharmaceutically acceptable capsules include hard capsules, which may be composed of plant derived polysaccharides, starches, and cellulose, or gelatin. In another embodiment, pharmaceutically acceptable capsules include soft gelatin capsules. The gelatin capsule may be composed of animal–derived collagen or from a hypromellose, a modified form of cellulose, and manufactured using optional mixtures of gelatin, water and plasticizers such as sorbitol or glycerol

In one embodiment, molecules of the invention may be encapsulated in pure granular or powdered form, with no carriers, excipients or other pharmaceutically acceptable additives. In other embodiments, molecules of the invention may be encapsulated together with one or more pharmaceutically acceptable carriers, excipients,. antioxidants (*e.g.*, sodium metabisulfite, butylated hydroxy toluene [BHT]), antifungals, (*e.g.*, benzoic and ascorbic acids and their salts, and phenolic compounds such as methyl, ethyl, propyl and butyl p-hydroxybenzoate (parabens)), antimicrobial preservatives (*e.g.*, sodium benzoate, sorbic acid), colorants, and flavorants. The excipients may aid in capsule-filling behavior, stability, and in the distribution of the drug when the capsule disintegrates in the body. In another embodiment, granules and/or powders of compounds of the present invention may be enterically coated before being placed in a capsule. The enterically coated granules and/or powders placed in the capsule may feature one or several types of enteric coating to enable delivery of the drug to different regions of the intestine. The capsule may lack enteric coating or may be coated with an enteric coating matching or differing entirely from the coating applied to any of the enterically coated material inside the capsule.

In a further embodiment, molecules of the invention may be encapsulated in a

liquid in the form of a solution or suspension in water or various pharmaceutically acceptable oils or other dispersion medium (*e.g.*, mineral oil, sesame oil, safflower oil, coconut oils), optionally with such excipients as cosolvents (*e.g.*, propylene glycol, glycerol), solubility enhancers (*e.g.*, sorbitol, dextrose), wetting agents (*e.g.*; polysorbates [Tweens], sorbitan esters [Span], hydrophobic colloids [cellulose derivatives], thickening agents (*e.g.*, methylcellulose, microcrystalline cellulose), buffers (*e.g.*, disodium hydrogen phosphate), antioxidants (*e.g.*, butylated hydroxy toluene [BHT], citric acid, potassium sorbate), antifungals (*e.g.*, benzoic and ascorbic acids and their salts, and phenolic compounds such as methyl, ethyl, propyl and butyl p-hydroxybenzoate (parabens)) antimicrobial preservatives (*e.g.*, sodium benzoate, sorbic acid), colorants and flavorants. In some embodiments, compounds of the present invention may be formulated for liquid filled capsules in the form of the pure drug as granules and/or powders in the liquid. In a related embodiment, the capsule contained the drug in liquid may be enterically coated. In another embodiment, granules and/or powders of compounds of the invention may be enterically coated before being placed in a liquid and the combination placed in a capsule. The enterically coated granules and/or powder may feature one or several types of enteric coating to enable deliver of the drug to different regions of the intestine. The capsule may lack enteric coating or may be coated with an enteric coating matching or differing entirely from the coating applied to any of the enterically coated material inside the capsule.

In another embodiment, molecules of the present invention may be encapsulated in a capsule comprised of material which affords post-gastric drug delivery without the need for the separate application of an enteric coating (*e.g.*, Entericare enteric softgels). The molecules may be encapsulated in such capsules as granules or powders with or without excipients, and as solutions or suspensions as described above.

In some embodiments, the solid particles of the compounds of the present invention, as a variety of particle sizes and particle size distributions, may be admixed with excipients such as microcrystalline cellulose or lactose and formed as a bead which comprise the drug-containing core onto which the enteric coating is applied. In some embodiments, molecules of the current invention may be formed as a suspension or solution including , optionally, buffers (*e.g.*, aq. 1 N HCl with tris hydroxymethyl aminomethane [TRIS]), and binders (*e.g.*, Opadry Clear Coat Powder) and coated onto a base particle, for example sugar beads (*e.g.*, Sugar Spheres, NF particles) to form a bead. In another embodiment, the beads may be enterically coated. In yet another embodiment, molecules of the invention may be formulated as enterically coated beads, as described above, and the beads further formulated

by encapsulation. In a further embodiment, a combination of beads with different types of enteric coating may be encapsulated, such that once released from the capsule, compounds of the invention are made available in a controlled manner at different regions ranging from the duodenum to other parts of the intestine. The capsule may lack enteric coating or may be coated with an enteric coating matching or differing entirely from the coating applied to any of the enterically coated material inside the capsule.

In a further embodiment, compounds of the present invention may be formulated as tablets or caplets which alone or in combination with other formulation components deliver drug to the duodenum or other intestinal region. In one embodiment, compounds of the invention are formulated as tablets or caplets which are enterically coated and which constitute the dosage form administered. In another embodiment, tablets or caplets of suitable size and shape may be placed inside a capsule. In one such embodiment, the capsule may be enterically coated and contain non-enterically coated tablets or caplets which are released from the capsule in the duodenum or other intestinal region. In yet another such embodiment, the capsule may be designed to disintegrate in the stomach and release entericallly coated tablets or caplets for subsequent delivery to duodenum or other intestinal regions. In yet another such embodiment, the capsule and tablets or caplets contained within may both be enterically coated to provide further control over the release of the tablets or caplets from the capsule, and the subsequent release of the drug from the tablet or caplet. In a further related embodiment., tablets or caplets featuring a variety of enteric coating may combined and place in a capsule which itself may optionally be enterically coated as well. Materials which are useful for enteric coatings for tablets and caplets include but are not limited to those described above for application to capsules.

Enteric coatings may permit premature drug release in acidic media. In a still further embodiment, compounds of the present invention may be formulated such that a subcoating is applied before the enteric coating is applied. The subcoating may comprise application to the enteric substrate of a soluble subcoating agent, examples of which are hydroxypropylmethylcellulose, povidone, hydroxypropyl cellulose, polyethylene glycol 3350, 4500, 8000, methyl cellulose, pseudo ethylcellulose and amylopectin. A thin subcoating layer on the enteric substrate impedes water penetration through the enteric coating on the capsule shell or into the core where the active ingredient is located, preventing premature drug release. The subcoating may also promote the release of the drug in a basic environment by moderating the acidic microenvironment at the interface between the core and the enteric coating. In some embodiments, compounds of the present invention are

formulated with a subcoating containing organic acids intended to promote more rapid polymer dissolution of a capsule as the coating degrades in environments with pH 5-6, promoting a rapid release of the drug in basic media.

For oral application, particularly suitable are tablets, dragees, liquids, drops, capsules, caplets and gelcaps. Other formulations suitable for oral administration include, but are not limited to, a powdered or granular formulation, an aqueous or oily suspension, an aqueous or oily solution, a paste, a gel, toothpaste, a mouthwash, a coating, an oral rinse, or an emulsion. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic, generally recognized as safe (GRAS), pharmaceutically excipients which are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate.

Tablets may be non-coated or they may be coated using known methods to achieve delayed disintegration in the gastrointestinal tract of a subject, thereby providing sustained release and absorption of the active ingredient. By way of example, a material such as glyceryl monostearate or glyceryl distearate may be used to coat tablets. Further by way of example, tablets may be coated using methods described in U.S. Patents Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotically controlled release tablets. Tablets may further comprise a sweetening agent, a flavoring agent, a coloring agent, a preservative, or some combination of these in order to provide for pharmaceutically elegant and palatable preparation.

Hard capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin. Such hard capsules comprise the active ingredient, and may further comprise additional ingredients including, for example, an inert solid diluent such as calcium carbonate, calcium phosphate, or kaolin.

Soft gelatin capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin from animal–derived collagen or from a hypromellose, a modified form of cellulose, and manufactured using optional mixtures of gelatin, water and plasticizers such as sorbitol or glycerol. Such soft capsules comprise the active ingredient, which may be mixed with water or an oil medium such as peanut oil, liquid paraffin, or olive oil.

For oral administration, the compounds of the invention may be in the form of

tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents; fillers; lubricants; disintegrates; or wetting agents. If desired, the tablets may be coated using suitable methods and coating materials such as OPADRY™ film coating systems available from Colorcon, West Point, Pa. (*e.g.*, OPADRY™ OY Type, OYC Type, Organic Enteric OY-P Type, Aqueous Enteric OY-A Type, OY-PM Type and OPADRY™ White, 32K18400). It is understood that similar type of film coating or polymeric products from other companies can be used.

A tablet comprising the active ingredient may, for example, be made by compressing or molding the active ingredient, optionally with one or more additional ingredients. Compressed tablets may be prepared by compressing, in a suitable device, the active ingredient in a free-flowing form such as a powder or granular preparation, optionally mixed with one or more of a binder, a lubricant, an excipient, a surface active agent, and a dispersing agent. Molded tablets may be made by molding, in a suitable device, a mixture of the active ingredient, a pharmaceutically acceptable carrier, and at least sufficient liquid to moisten the mixture. Pharmaceutically acceptable excipients used in the manufacture of tablets include, but are not limited to, inert diluents, granulating and disintegrating agents, binding agents, and lubricating agents. Known dispersing agents include, but are not limited to, potato starch and sodium starch glycolate. Known surface-active agents include, but are not limited to, sodium lauryl sulphate. Known diluents include, but are not limited to, calcium carbonate, sodium carbonate, lactose, microcrystalline cellulose, calcium phosphate, calcium hydrogen phosphate, and sodium phosphate. Known granulating and disintegrating agents include, but are not limited to, corn starch and alginic acid. Known binding agents include, but are not limited to, gelatin, acacia, pre-gelatinized maize starch, polyvinylpyrrolidone, and hydroxypropyl methylcellulose. Known lubricating agents include, but are not limited to, magnesium stearate, stearic acid, silica, and talc.

Granulating techniques are well known in the pharmaceutical art for modifying starting powders or other particulate materials of an active ingredient. The powders are typically mixed with a binder material into larger permanent free-flowing agglomerates or granules referred to as a "granulation." For example, solvent-using "wet" granulation processes are generally characterized in that the powders are combined with a binder material and moistened with water or an organic solvent under conditions resulting in the formation of a wet granulated mass from which the solvent must then be evaporated.

Melt granulation generally consists in the use of materials that are solid or semi-solid at room temperature (*i.e.*, having a relatively low softening or melting point range)

to promote granulation of powdered or other materials, essentially in the absence of added water or other liquid solvents. The low melting solids, when heated to a temperature in the melting point range, liquefy to act as a binder or granulating medium. The liquefied solid spreads itself over the surface of powdered materials with which it is contacted, and on cooling, forms a solid granulated mass in which the initial materials are bound together. The resulting melt granulation may then be provided to a tablet press or be encapsulated for preparing the oral dosage form. Melt granulation improves the dissolution rate and bioavailability of an active (*i.e.*, drug) by forming a solid dispersion or solid solution.

U.S. Patent No. 5,169,645 discloses directly compressible wax-containing granules having improved flow properties. The granules are obtained when waxes are admixed in the melt with certain flow improving additives, followed by cooling and granulation of the admixture. In certain embodiments, only the wax itself melts in the melt combination of the wax(es) and additives(s), and in other cases both the wax(es) and the additives(s) will melt.

The present invention also includes a multi-layer tablet comprising a layer providing for the delayed release of one or more compounds useful within the methods of the invention, and a further layer providing for the immediate release of one or more compounds useful within the methods of the invention. Using a wax/pH-sensitive polymer mix, a gastric insoluble composition may be obtained in which the active ingredient is entrapped, ensuring its delayed release.

Parenteral Administration

As used herein, "parenteral administration" of a pharmaceutical composition includes any route of administration characterized by physical breaching of a tissue of a subject and administration of the pharmaceutical composition through the breach in the tissue. Parenteral administration thus includes, but is not limited to, administration of a pharmaceutical composition by injection of the composition, by application of the composition through a surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, but is not limited to, subcutaneous, intravenous, intraperitoneal, intramuscular, intrasternal injection, and kidney dialytic infusion techniques.

Formulations of a pharmaceutical composition suitable for parenteral administration comprise the active ingredient combined with a pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration.

Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as in ampules or in multi-dose containers containing a preservative. Injectable formulations may also be prepared, packaged, or sold in devices such as patient-controlled analgesia (PCA) devices. Formulations for parenteral administration include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations. Such formulations may further comprise one or more additional ingredients including, but not limited to, suspending, stabilizing, or dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (*i.e.*, powder or granular) form for reconstitution with a suitable vehicle (*e.g.*, sterile pyrogen-free water) prior to parenteral administration of the reconstituted composition.

The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the known art, and may comprise, in addition to the active ingredient, additional ingredients such as the dispersing agents, wetting agents, or suspending agents described herein. Such sterile injectable formulations may be prepared using a non-toxic parenterally-acceptable diluent or solvent, such as water or 1,3-butane diol, for example. Other acceptable diluents and solvents include, but are not limited to, Ringer's solution, isotonic sodium chloride solution, and fixed oils such as synthetic mono- or di-glycerides. Other parentally-administrable formulations which are useful include those which comprise the active ingredient in a recombinant human albumin, a fluidized gelatin, or in a microcrystalline form, in a liposomal preparation, or as a component of a biodegradable polymer system. Compositions for sustained release or implantation may comprise pharmaceutically acceptable polymeric or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

Topical Administration

An obstacle for topical administration of pharmaceuticals is the stratum corneum layer of the epidermis. The stratum corneum is a highly resistant layer comprised of protein, cholesterol, sphingolipids, free fatty acids and various other lipids, and includes cornified and living cells. One of the factors that limit the penetration rate (flux) of a compound through the stratum corneum is the amount of the active substance that can be loaded or applied onto the skin surface. The greater the amount of active substance which is applied per unit of area of the skin, the greater the concentration gradient between the skin surface and the lower layers of the skin, and in turn the greater the diffusion force of the

active substance through the skin. Therefore, a formulation containing a greater concentration of the active substance is more likely to result in penetration of the active substance through the skin, and more of it, and at a more consistent rate, than a formulation having a lesser concentration, all other things being equal.

Formulations suitable for topical administration include, but are not limited to, liquid or semi-liquid preparations such as liniments, lotions, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes, and solutions or suspensions. Topically administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

Enhancers of permeation may be used. These materials increase the rate of penetration of drugs across the skin. Typical enhancers in the art include ethanol, glycerol monolaurate, PGML (polyethylene glycol monolaurate), dimethylsulfoxide, and the like. Other enhancers include oleic acid, oleyl alcohol, ethoxydiglycol, laurocapram, alkanecarboxylic acids, dimethylsulfoxide, polar lipids, or N-methyl-2-pyrrolidone.

One acceptable vehicle for topical delivery of some of the compositions of the invention may contain liposomes. The composition of the liposomes and their use are known in the art (for example, see Constanza, U.S. Patent No. 6,323,219).

In alternative embodiments, the topically active pharmaceutical composition may be optionally combined with other ingredients such as adjuvants, anti-oxidants, chelating agents, surfactants, foaming agents, wetting agents, emulsifying agents, viscosifiers, buffering agents, preservatives, and the like. In another embodiment, a permeation or penetration enhancer is included in the composition and is effective in improving the percutaneous penetration of the active ingredient into and through the stratum corneum with respect to a composition lacking the permeation enhancer. Various permeation enhancers, including oleic acid, oleyl alcohol, ethoxydiglycol, laurocapram, alkanecarboxylic acids, dimethylsulfoxide, polar lipids, or N-methyl-2-pyrrolidone, are known to those of skill in the art. In another aspect, the composition may further comprise a hydrotropic agent, which functions to increase disorder in the structure of the stratum corneum, and thus allows increased transport across the stratum corneum. Various hydrotropic agents such as isopropyl alcohol, propylene glycol, or sodium xylene sulfonate, are known to those of skill in the art.

The topically active pharmaceutical composition should be applied in an

amount effective to affect desired changes. As used herein "amount effective" shall mean an amount sufficient to cover the region of skin surface where a change is desired. An active compound should be present in the amount of from about 0.0001% to about 15% by weight volume of the composition. More preferable, it should be present in an amount from about 0.0005% to about 5% of the composition; most preferably, it should be present in an amount of from about 0.001% to about 1% of the composition. Such compounds may be synthetically-or naturally derived.

Buccal Administration

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) of the active ingredient, the balance comprising an orally dissolvable or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise a powder or an aerosolized or atomized solution or suspension comprising the active ingredient. Such powdered, aerosolized, or aerosolized formulations, when dispersed, preferably have an average particle or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein. The examples of formulations described herein are not exhaustive and it is understood that the invention includes additional modifications of these and other formulations not described herein, but which are known to those of skill in the art.

Rectal Administration

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for rectal administration. Such a composition may be in the form of, for example, a suppository, a retention enema preparation, and a solution for rectal or colonic irrigation.

Suppository formulations may be made by combining the active ingredient with a non-irritating pharmaceutically acceptable excipient which is solid at ordinary room temperature (*i.e.*, about 20°C) and which is liquid at the rectal temperature of the subject (*i.e.*, about 37°C in a healthy human). Suitable pharmaceutically acceptable excipients include, but are not limited to, cocoa butter, polyethylene glycols, and various glycerides. Suppository formulations may further comprise various additional ingredients including, but not limited to, antioxidants, and preservatives.

Retention enema preparations or solutions for rectal or colonic irrigation may be made by combining the active ingredient with a pharmaceutically acceptable liquid carrier. As is well known in the art, enema preparations may be administered using, and may be packaged within, a delivery device adapted to the rectal anatomy of the subject. Enema preparations may further comprise various additional ingredients including, but not limited to, antioxidants, and preservatives.

Additional Administration Forms

Additional dosage forms of this invention include dosage forms as described in U.S. Patents Nos. 6,340,475, 6,488,962, 6,451,808, 5,972,389, 5,582,837, and 5,007,790. Additional dosage forms of this invention also include dosage forms as described in U.S. Patent Applications Nos. 20030147952, 20030104062, 20030104053, 20030044466, 20030039688, and 20020051820. Additional dosage forms of this invention also include dosage forms as described in PCT Applications Nos. WO 03/35041, WO 03/35040, WO 03/35029, WO 03/35177, WO 03/35039, WO 02/96404, WO 02/32416, WO 01/97783, WO 01/56544, WO 01/32217, WO 98/55107, WO 98/11879, WO 97/47285, WO 93/18755, and WO 90/11757.

Controlled Release Formulations and Drug Delivery Systems

In further embodiments, the composition may be designed to promote controlled release of the drug, such that the location, extent and rate of exposure of the compound when administered are modulated. Factors that affect the target zone for exposure of an orally administered drug may be the drug's pH, enzymatic stability, reactivity with other drugs (e.g., certain antibiotics), solubility as a salt or free base, ionization behavior, and pharmacodynamic and pharmacokinetic behaviors in specific environments.

Controlled- or sustained-release formulations of a pharmaceutical composition of the invention may be made using conventional technology. In some cases, the dosage forms to be used can be provided as slow or controlled-release of one or more active ingredients therein using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the pharmaceutical compositions of the invention. Thus, single unit dosage forms suitable for oral administration, such as tablets, capsules, gelcaps, and caplets, that are adapted for controlled-

release are encompassed by the present invention.

Most controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include targeted delivery within the gastrointestinal tract upon oral administration, extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood level of the drug, and thus can affect the occurrence of side effects.

Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body.

Controlled-release of an active ingredient can be stimulated by various inducers, for example water, pH, temperature, enzymes, bacteria, or other physiological conditions or compounds. The term "controlled-release component" in the context of the present invention is defined herein as a compound or compounds, including, but not limited to, polymers, polymer matrices, gels, permeable membranes, liposomes, or microspheres or a combination thereof that facilitates the controlled-release of the active ingredient.

In certain embodiments, the formulations of the present invention may be, but are not limited to, short-term, rapid-offset, as well as controlled, for example, sustained release, delayed release and pulsatile release formulations. The active drug substance can also be coated on an implantable medical device to be eluted or be released using a remotely activated system.

The term sustained release is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that may, although not necessarily, result in substantially constant blood levels of a drug over an extended time period. The period of time may be as long as a month or more and should be a release that is longer that the same amount of agent administered in bolus form.

For sustained release, the compounds may be formulated with a suitable

polymer or hydrophobic material which provides sustained release properties to the compounds. As such, the compounds for use the method of the invention may be administered in the form of microparticles, for example, by injection or in the form of wafers or discs by implantation (drug embedded in polymeric matrices).

In a preferred embodiment of the invention, the compounds of the invention are administered to a patient, alone or in combination with another pharmaceutical agent, using a sustained release formulation.

The term delayed release is used herein in its conventional sense to refer to a drug formulation that provides for an initial release of the drug after some delay following drug administration and that may, although not necessarily, includes a delay of from about 10 minutes up to about 24 hours.

The term pulsatile release is used herein in its conventional sense to refer to a drug formulation that provides release of the drug in such a way as to produce pulsed plasma profiles of the drug after drug administration.

The term immediate release is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration.

As used herein, short-term refers to any period of time up to and including about 24 hours, about 12 hours, about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes and any or all whole or partial increments thereof after drug administration after drug administration.

As used herein, rapid-offset refers to any period of time up to and including about 24 hours, about 12 hours, about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes, and any and all whole or partial increments thereof after drug administration.

Some drugs are better absorbed in the duodenum or other intestinal locations. A particularly useful mode of controlled release is one that minimizes release of drug in the stomach while delivering drug in its most concentrated form to the duodenum or other intestinal locations. In a preferred embodiment, compounds of the present invention are formulated to promote delivery to the duodenum and, optionally, other intestinal locations. Controlled release that delivers drug to the duodenum or other intestinal regions may be achieved using compositions that include enteric coatings. Enteric coatings are insoluble in highly acidic environments, often comprising a polyacidic coating which remains non-

ionized and intact at gastric pH. However, under mildly acidic (> pH 5.5), neutral or mildly alkaline conditions (pH 6.5-7.6) of the duodenum or other intestinal regions, the coating ionizes, swells and breaks down, exposing the coated entity to the environment. Coating options exist to allow ionization at or near a specific pH (*e.g.*, Eudragit L-110, ionization threshold pH 6.0; Eudragit S-100, ioization threshold pH 7.0). It is understood that similar type or grade of film coating or polymeric products from other companies can be used.

In a further embodiment, compounds of the present invention may be formulated with an enteric coating, which has been modified by adding plasticizers to the polymer before coating. The plasticizers may be added to adjust resistance to chipping or cracking of the coating, while also lowering the glass transition temperature of the coating to enable smooth and even spreadability of the coating during its application. Suitable plasticizers include polyethylene glycol 8000 (PEG 8000), triethyl citrate (TEC), and triacetin, which may be incorporated into the polymeric enteric coating agent.

Compounds of the present invention may be enterically formulated under a variety of dosage forms, including (but not limited to) capsules, granules of the active drug itself, beads, micro spheres, and tablets. In one embodiment, the composition may comprise a drug encapsulated in a capsule that is enterically coated to release the drug in the duodenum or other intestinal environment. In one aspect of the invention, pharmaceutically acceptable capsules include hard capsules. In another embodiment, pharmaceutically acceptable capsules include soft gelatin capsules.

In one embodiment, molecules of the invention may be encapsulated in pure granular or powdered form, with no carriers, excipients or other pharmaceutically acceptable additives. In other embodiments, molecules of the invention may be encapsulated together with one or more pharmaceutically acceptable carriers, excipients, antioxidants, antifungals, (*e.g.*, benzoic and ascorbic acids and their salts, and phenolic compounds such as methyl, ethyl, propyl and butyl p-hydroxybenzoate (parabens)), antimicrobial preservatives , colorants, and flavorants. The excipients may aid in capsule-filling behavior, stability, and in the distribution of the drug when the capsule disintegrates in the body. In another embodiment, granules and/or powders of compounds of the present invention may be enterically coated before being placed in a capsule. The enterically coated granules and/or powders placed in the capsule may feature one or several types of enteric coating to enable delivery of the drug to different regions of the intestine. The capsule may lack enteric coating or may be coated with an enteric coating matching or differing entirely from the coating applied to any of the enterically coated materials inside the capsule.

In a further embodiment, molecules of the invention may be encapsulated in a liquid in the form of a solution or suspension in water or various pharmaceutically acceptable oils or other dispersion medium, optionally with such excipients as cosolvents (*e.g.*, PEG 300, PEG 400, propylene glycol, glycerol, tween 80, ethanol), solubility enhancers (e.g., sorbitol, dextrose), wetting agents (thickening agent, buffers (*e.g.*, disodium hydrogen phosphate), antioxidants, antifungals, preservatives, colorants and flavorants. In some embodiments, compounds of the present invention may be formulated for liquid filled capsules in the form of the pure drug as granules and/or powders in the liquid. In a related embodiment, the capsule containing the drug in liquid may be enterically coated. In another embodiment, granules and/or powders of compounds of the invention may be enterically coated before being placed in a liquid and the combination placed in a capsule. The enterically coated granules and/or powder may feature one or several types of enteric coating to enable delivery of the drug to different regions of the intestine. The capsule may lack enteric coating or may be coated with an enteric coating matching or differing entirely from the coating applied to any of the enterically coated materials inside the capsule.

In another embodiment, molecules of the present invention may be encapsulated in a capsule comprised of material that affords post-gastric drug delivery without the need for the separate application of an enteric coating (e.g., Entericare enteric softgels). The molecules may be encapsulated in such capsules as granules or powders with or without excipients, and as solutions or suspensions as described above.

In some embodiments, the solid particles of the compounds of the present invention, as a variety of particle sizes and particle size distributions, may be admixed with excipients such as microcrystalline cellulose or lactose and formed as a bead which comprises the drug-containing core onto which the enteric coating is applied. In some embodiments, molecules of the current invention may be formed as a suspension or solution including, optionally, buffers (e.g., aq. 1N HCl with trishydroxymethylaminomethane [TRIS]), and binders (e.g., Opadry Clear Coat Powder) and coated onto a base particle, for example sugar beads (e.g., Sugar Spheres, NF particles) to form a bead. In another embodiment, the beads may be enterically coated. In yet another embodiment, molecules of the invention may be formulated as enterically coated beads, as described above, and the beads further formulated by encapsulation. In a further embodiment, a combination of beads with different types of enteric coating may be encapsulated, such that once released from the capsule compounds of the invention are made available in a controlled manner at different regions ranging from the duodenum to other parts of the intestine. The capsule may lack

enteric coating or may be coated with an enteric coating matching or differing entirely from the coating applied to any of the enterically coated materials inside the capsule.

In a further embodiment, compounds of the present invention may be formulated as tablets or caplets which alone or in combination with other formulation components deliver drug to the duodenum or other intestinal region. In one embodiment, compounds of the invention are formulated as tablets or caplets which are enterically coated and which constitute the dosage form administered. In another embodiment, tablets or caplets of suitable size and shape may be placed inside a capsule. In one such embodiment, the capsule may be enterically coated and contain non-enterically coated tablets or caplets which are released from the capsule in the duodenum or other intestinal region. In yet another such embodiment, the capsule may be designed to disintegrate in the stomach and release entericallly coated tablets or caplets for subsequent delivery to duodenum or other intestinal regions. In yet another such embodiment, the capsule and tablets or caplets contained within may both be enterically coated to provide further control over the release of the tablets or caplets from the capsule, and the subsequent release of the drug from the tablet or caplet. In a further related embodiment, tablets or caplets featuring a variety of enteric coating may combined and place in a capsule which itself may optionally be enterically coated as well. Materials which are useful for enteric coatings for tablets and caplets include but are not limited to those described above for application to capsules.

Enteric coatings may permit premature drug release in acidic media. In a still further embodiment, compounds of the present invention may be formulated such that a subcoating is applied before the enteric coating is applied. The subcoating may comprise application to the enteric substrate of a soluble subcoating agent, examples of which are hydroxypropylmethylcellulose, povidone, hydroxypropyl cellulose, polyethylene glycol 3350, 4500, 8000, methyl cellulose, pseudo ethylcellulose and amylopectin. It is understood that similar type of synthetic and semisynthetic polymeric products from other companies can be used. A thin subcoating layer on the enteric substrate impedes water penetration through the enteric coating on the capsule shell or into the core where the active ingredient is located, preventing premature drug release. The subcoating may also promote the release of the drug in a basic environment by moderating the acidic microenvironment at the interface between the core and the enteric coating. In some embodiments, compounds of the present invention are formulated with a subcoating containing organic acids intended to promote more rapid polymer dissolution of a capsule as the coating degrades in environments with pH 5-6, promoting a rapid release of the drug in basic media.

Mechanical Devices

In one aspect of the invention, a method of treating a patient without normal ventilation and normal breathing control comprises administering the composition useful within the invention as described herein, and additionally treating the patient using a device to support breathing. Such devices include, but are not limited to, ventilation devices, CPAP and BiPAP devices.

Mechanical ventilation is a method to mechanically assist or replace spontaneous breathing. Mechanical ventilation is typically used after an invasive intubation, a procedure wherein an endotracheal or tracheostomy tube is inserted into the airway. It is normally used in acute settings, such as in the ICU, for a short period of time during a serious illness. It may also be used at home or in a nursing or rehabilitation institution, if patients have chronic illnesses that require long-term ventilation assistance. The main form of mechanical ventilation is positive pressure ventilation, which works by increasing the pressure in the patient's airway and thus forcing air into the lungs. Less common today are negative pressure ventilators (for example, the "iron lung") that create a negative pressure environment around the patient's chest, thus sucking air into the lungs. Mechanical ventilation is often a life-saving intervention, but carries many potential complications including pneumothorax, airway injury, alveolar damage, and ventilator-associated pneumonia. For this reason the pressure and volume of gas used is strictly controlled, and discontinued as soon as possible. Types of mechanical ventilation are: conventional positiove pressure ventilation, high frequency ventilation, non-invasive ventilation (non-invasive positive pressure ventilation or NIPPV), proportional assist ventilation (PAV), adaptive servo ventilation (ASV) and neurally adjusted ventilatory assist (NAVA).

Non-invasive ventilation refers to all modalities that assist ventilation without the use of an endotracheal tube. Non-invasive ventilation is primarily aimed at minimizing patient discomfort and the complications associated with invasive ventilation, and is often used in cardiac disease, exacerbations of chronic pulmonary disease, sleep apnea, and neuromuscular diseases. Non-invasive ventilation refers only to the patient interface and not the mode of ventilation used; modes may include spontaneous or control modes and may be either pressure or volume cycled modes. Some commonly used modes of NIPPV include:

(a) Continuous positive airway pressure (CPAP): This kind of machine has been used mainly by patients for the treatment of sleep apnea at home, but now is in widespread use across intensive care units as a form of ventilation support. The CPAP machine stops upper

airway obstruction by delivering a stream of compressed air via a hose to a nasal pillow, nose mask or full-face mask, splinting the airway open (keeping it open under air pressure) so that unobstructed breathing becomes possible, reducing and/or preventing apneas and hypopneas. When the machine is turned on, but prior to the mask being placed on the head, a flow of air comes through the mask. After the mask is placed on the head, it is sealed to the face and the air stops flowing. At this point, it is only the air pressure that accomplishes the desired result. This has the additional benefit of reducing or eliminating the extremely loud snoring that sometimes accompanies sleep apnea.

(b) Bi-level positive airway pressure (BIPAP): Pressures alternate between inspiratory positive airway pressure (IPAP) and a lower expiratory positive airway pressure (EPAP), triggered by patient effort. On many such devices, backup rates may be set, which deliver IPAP pressures even if patients fail to initiate a breath.

(c) Intermittent positive pressure ventilation (IPPV), via mouthpiece or mask.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents were considered to be within the scope of this invention and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, *e.g.*, nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that, wherever values and ranges are provided herein, the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, all values and ranges encompassed by these values and ranges are meant to be encompassed within the scope of the present invention. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application. The description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range and, when appropriate, partial integers of the numerical values within ranges. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This

applies regardless of the breadth of the range.

The following examples further illustrate aspects of the present invention. However, they are in no way a limitation of the teachings or disclosure of the present invention as set forth herein.

EXAMPLES

The invention is now described with reference to the following Examples. These Examples are provided for the purpose of illustration only, and the invention is not limited to these Examples, but rather encompasses all variations that are evident as a result of the teachings provided herein.

Materials:

Unless otherwise noted, all remaining starting materials were obtained from commercial suppliers and used without purification. Final products are typically isolated as acid addition salts unless noted otherwise.

Example 1: N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (3) and corresponding hydrochloride salt (4a) (Scheme 7)

2,6-Dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**2**):

To a solution of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine (**1**) (2.20 g, 8.15 mmol) in THF (55 mL), *n*-propylamine (2.68 mL, 32.60 mmol) in THF (15 mL) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for 1 h. After this time, water (50 mL) was added and the resultant precipitate was filtered, washed with water (30 mL) and dried over P_2O_5 to yield 2,6-dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-4,8-diamine (**2**) (2.49 g, 97%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 6.92-6.85 (2H, m), 3.56 (4H, td, J=7.3, 6.2 Hz), 1.73 (4H, sextet, J=7.3 Hz), 1.02 (6H, t, J=7.3 Hz). ESI-MS (m/z): 315, 317, 319 $[M+H]^+$.

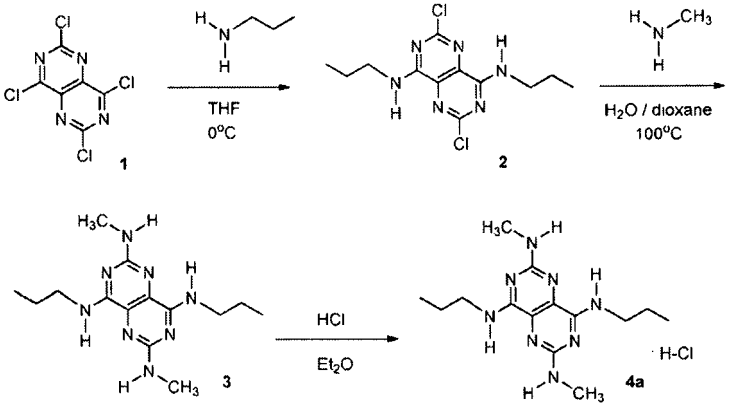
N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**3**):

The mixture of 2,6-dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-4,8-diamine (**2**) (316 mg, 1.00 mmol) and methylamine (40% water solution) (2.00 mL, 718 mg, 23.15 mmole) in 1,4-dioxane (3 mL) was heated at 100°C for 65h. After this time, the volatiles were removed by evaporation, and the residue was partitioned between CH_2Cl_2 (40 mL) and water (20 mL). The water phase was extracted with CH_2Cl_2 (2 x 30 mL). The

combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (98:2) to yield N^2,N^6-dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**3**) (220 mg, 72%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 6.53 (2H, br s), 4.60 (2H, br s), 3.46 (4H, q, J=6.7 Hz), 2.97 (6H, d, J=4.5 Hz), 1.69 (4H, sextet, J=7.5 Hz), 1.00 (6H, t, J=7.5 Hz). ESI-MS (m/z): 305 $[M+H]^+$.

N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**4a**):

A 2M HCl/diethyl ether solution (0.35 mL, 0.70 mmol) was added to a suspension of N^2,N^6-dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**3**) (212 mg, 0.70 mmol) in methanol (15 mL). The mixture was stirred for 0.5 h at 0°C and the resultant precipitate were filtered, washed with methanol (3 mL) to yield N^2,N^6-dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**4a**) (230 mg, 96%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 9.70-9.41 (1H, m), 7.86-7.37 (1H, m), 6.63 (1.3H, br s), 4.97-4.68 (0.7H, m) ,3.77-3.38 (4H, m), 3.15-2.86 (6H, m), 1.93-1.68 (4H, m), 1.04 (6H, t, J=7.3 Hz). ESI-MS (m/z): 305 $[M+H]^+$; melting point: 229-232 °C.



Scheme 7.

Example 2: N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (5) and corresponding hydrochloride salt (6a) (Scheme 8)

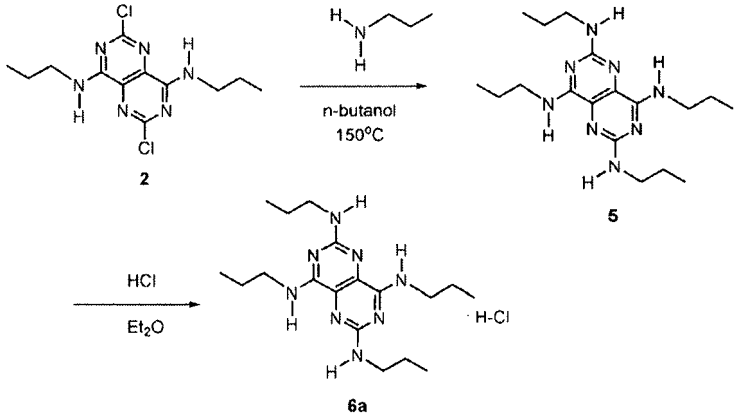
N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**5**):

A mixture of 2,6-dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**2**) (338 mg, 1.07 mmol), K_2CO_3 (296 mg, 2.14 mmol) and *n*-propylamine (2.20 mL) in *n*-butanol (4 mL) was heated at 150°C for 45 h. After this time, the volatiles were removed by evaporation and the residue was partitioned between EtOAc (50 mL) and a saturated

$NaHCO_3$ solution (30 mL). The water phase was extracted with EtOAc (2 x 40 mL). The combined organic extracts were washed with water (50 mL), and then with a brine solution (50 mL), and lastly dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (98:2) to yield N^2,N^4,N^6,N^8-tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**5**) (235 mg, 61%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 6.47 (2H, br s), 4.61(2H, br s), 3.53-3.40, (4H, m), 3.40-3.26 (4H, m), 1.76-1.54 (8H, m), 1.00 (6H, t, J=7.4 Hz), 0.99 (6H, t, J=7.4 Hz). ESI-MS (m/z): 361 $[M+H]^+$.

N^2, N^4, N^6, N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**6a**):

N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**5**) and 2M HCl/diethyl ether in CH_2Cl_2/MeOH (15/1) were reacted using the procedure described for compound (**4a**) to yield N^2,N^4,N^6,N^8-tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**6a**) in quantitative yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 9.55 (0.7H, br s), 7.75-7.36 (1.3H, m), 6.71 (1.3H, s), 4.85 (0.7H, br s), 3.72-3.21 (8H, m), 1.90-1.52 (8H, m), 1.03 (6H, t, J=7.3 Hz), 0.98 (6H, t, J=7.3 Hz). ESI-MS (m/z): 361 $[M+H]^+$; melting point: 208-211 °C.



Scheme 8.

Example 3: N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (7) and corresponding hydrochloride salt (8a)

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**7**):

2,6-Dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**2**) and *n*-butylamine were reacted using the procedure described for compound (**3**) to yield N^2, N^6-di-*n*-butyl-N^4, N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**7**) in 85%

yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.46 (2H, br s), 4.57 (2H, br s), 3.51-3.42 (4H, m), 3.42-3.32 (4H, m), 1.69 (4H, sextet, J=7.4 Hz), 1.63-1.54 (4H, m), 1.48-1.37 (4H, m), 1.00 (6H, t, J=7.4 Hz), 0.96 (6H, t, J=7.4 Hz). ESI-MS (m/z): 389 $[M+H]^+$.

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**8a**):

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**7**) and 2M HCl/diethyl ether in CH_2Cl_2/MeOH (15/1) were reacted using the procedure described for compound (**4a**) to yield N^2,N^6-di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**8a**) in quantitative yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.95 (0.5H, s), 9.54 (0.5H, br s), 7.67 (1H, br s), 7.45 (1H, br s), 6.69 (1.2H, s), 4.82 (0.8H, br s), 3.69-3.29 (8H, m), 1.85-1.67 (4H, m), 1.65-1.52 (4H, m), 1.41 (4H, sextet, J=7.3 Hz), 1.02 (6H, t, J=7.3 Hz), 0.95 (6H, t, J=7.4 Hz). ESI-MS (m/z): 389 $[M+H]^+$; melting point: 205-208 °C.

Example 4: N^2, N^6-Di-*i*-propyl-N^4, N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (9) and corresponding hydrochloride salt (10a)

N^2, N^6-Di-*i*-propyl-N^4, N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**9**):

2,6-Dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**2**) and *i*-propylamine were reacted using the procedure described for compound (**3**) to yield N^2,N^6-di-*i*-propyl-N^4, N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**9**) in 85% yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 6.45 (2H, br s), 4.44 (2H, br s), 4.20-4.05 (2H, m), 3.50-3.37 (4H, m), 1.68 (4H, sextet, J=7.4 Hz), 1.23 (12H, d, J=6.5 Hz), 1.00 (6H, t, J=7.4 Hz). ESI-MS (m/z): 361 $[M+H]^+$.

N^2, N^6-Di-*i*-propyl-N^4, N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**10a**):

N^2,N^6-Di-*n*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**9**) and 2M HCl/diethyl ether in CH_2Cl_2/MeOH (15/1) were reacted using the procedure described for compound (**4a**) to yield N^2,N^6-di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**10a**) in 81% yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.90 (0.6H, s), 9.58 (0.4H, s), 7.71 (1H, s), 7.48-7.40 (1H, m), 6.50 (1H, d, J=7.4 Hz), 4.68 (1H, d, J=7.4 Hz), 4.29-4.02 (2H, m), 3.64-3.42 (4H, m), 1.80-1.68 (4H, m), 1.28 (7.2H, d, J=6.6 Hz), 1.23 (4.8H, d, J=6.6 Hz), 1.04-0.97 (6H, m). ESI-MS (m/z): 361 $[M+H]^+$; melting point: 158-161 °C.

Example 5: N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (12) and corresponding hydrochloride salt (13a) (Scheme 9)

2,6-Dichloro-N^4-*n*-propyl- N^8- prop-2-ynyl-pyrimido[5,4-d]pyrimidine-4, 8-diamine (**11**):

n-Propylamine (283 µL, 3.45 mmol) in THF (15 mL) was added dropwise to a mixture of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine (**1**) (930 mg, 3.45 mmol) and K_2CO_3 (477 mg, 3.45 mmol) in THF (20 mL) at -78°C during 30 min. The reaction mixture was allowed to reach ambient temperature, and then propargylamine (442 µL, 6.90 mmol) was added. The mixture was stirred for 1h. After this time, water (50 mL) was added and the resulting suspension was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with water (50 mL), and then with a brine solution (50 mL) and lastly dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (99:1) to PE/EtOAc (9:1) to yield 2,6-dichloro-N^4-*n*-propyl- N^8- prop-2-ynyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**11**) (740 mg, 70%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.01-6.95 (1H, m), 6.95-6.87 (1H, m), 4.39 (2H, dd, J=5.5, 2.6 Hz), 3.56 (2H, td, J=7.3, 6.1 Hz), 2.33 (1H, t, J=2.6 Hz), 1.73 (2H, sextet, J=7.3 Hz), 1.04 (3H, t, J=7.3 Hz). ESI-MS (m/z): 311, 313, 315 $[M+H]^+$.

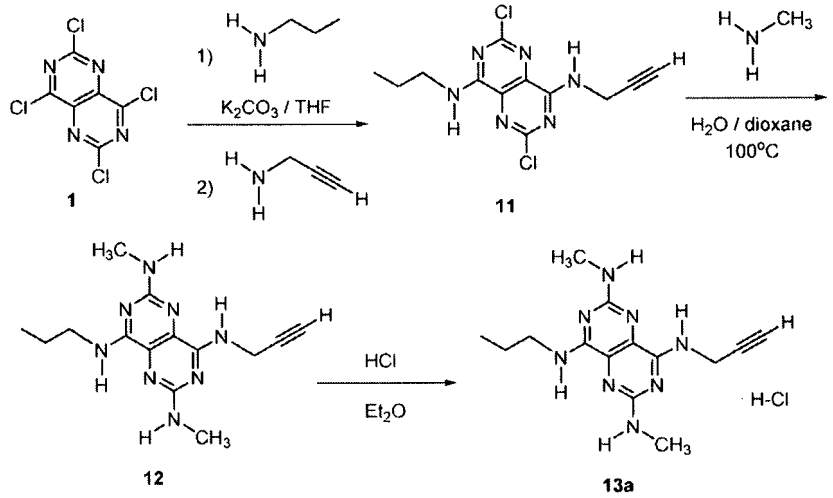
N^2, N^6-Dimethyl-N^4-*n*-propyl- N^8- prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**12**):

A mixture of 2,6-dichloro-N^4-*n*-propyl- N^8- prop-2-ynyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**11**) (312 mg, 1.00 mmol) and methylamine (40% water solution) (2.00 mL) in 1,4-dioxane (3 mL) was heated at 100°C for 30 h. The volatiles were removed by evaporation, and the residue was partitioned between CH_2Cl_2 (40 mL) and water (20 mL). The water phase was then extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (98:2) to yield N^2,N^6-dimethyl-N^4-*n*-propyl-N^8- prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**12**) (150 mg, 50%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.68-6.44 (2H, m), 4.65 (2H, br s), 4.32 (2H, dd, J=5.7, 2.6 Hz), 3.50-3.42 (2H, m), 2.98 (3H, s), 2.97 (3H, s), 2.24 (1H, t, J=2.6 Hz), 1.69 (2H, sextet, J=7.4 Hz), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 301 $[M+H]^+$.

N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8- prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

hydrochloride (**13a**):

N^2,N^6-dimethyl-N^4-*n*-propyl-N^8- prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**12**) and 2M HCl/diethyl ether in CH_2Cl_2/MeOH (15/1) were reacted using the procedure described for compound (**4a**) to yield N^2,N^6-dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**13a**) quantitative yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 10.2-9.4 (1H, m), 8.3-7.4 (1H, m), 6.92-6.45 (1.6H, m), 5.18-74.73 (0.4H, m), 4.48-4.25 (2H, m), 3.70-3.50 (2H, m), 3.19-2.92 (6H, m), 2.36-2.20 (1H, m), 1.90-1.72 (2H, m), 1.04 (3H, t, J=7.4 Hz). ESI-MS (m/z): 301 $[M+H]^+$; melting point: 210-212 °C.



Scheme 9.

Example 6: N^2,N^6-Bis(N-methoxy(N-methyl)amino)-N^4-*n*-propylamino-N^8-prop-2-ynyl-amino-pyrimido[5,4-d]pyrimidine (14) and corresponding hydrochloride salt (15a)

N^2,N^6-Bis(methoxy(methyl)amino)-N^4-*n*-propylamino-N^8-prop-2-ynylamino-pyrimido[5,4-d]pyrimidine (**14**):

A mixture of 2,6-dichloro-N^4-*n*-propyl-N^8- prop-2-ynyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**11**) (350 mg, 1.12 mmol), N,O-dimethylhydroxylamine hydrochloride (3.28 g, 33.60 mmol) and N,N-diisopropylethylamine (5.85 mL, 33.60 mmol) in 1,4-dioxane (15 mL) was heated at 90°C for 60 h. The reaction mixture was then cooled, and a saturated $NaHCO_3$ solution (30 mL) was added. The resultant precipitate was filtered and dissolved in CH_2Cl_2. This solution was washed with water (2 x 20mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (95:5) to yield N^2,N^6-bis(N-methoxy(N-methyl)amino)-N^4-*n*-propylamino-N^8-

prop-2-ynylamino-pyrimido[5,4-d]pyrimidine (**14**) (156 mg, 39%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.84 (1H, t, J=5.6 Hz), 6.80 (1H, t, J=6.0 Hz), 4.52 (2H, dd, J=5.6, 2.5 Hz), 4.04 (3H, s), 4.04(3H, s), 3.71-3.64 (2H, m), 3.49 (3H, s), 3.48 (3H, s), 2.40 (1H, t, J=2.5 Hz), 1.87 (2H, sextet, J=7.4 Hz), 1.16 (3H, t, J=7.4 Hz). ESI-MS (m/z): 361 $[M+H]^+$.

N^2,N^6-Bis(N-methoxy(N-methyl)amino)-N^4-*n*-propylamino-N^8-prop-2-ynylamino-pyrimido[5,4-d]pyrimidine hydrochloride (**15a**):

N^2,N^6-Bis(N-methoxy(N-methyl)amino)-N^4-*n*-propylamino-N^8-prop-2-ynylamino-pyrimido[5,4-d]pyrimidine (**14**) and 2M HCl/diethyl ether in MeOH were reacted using the procedure described for compound (**4a**) to yield N^2,N^6-bis(N-methoxy (N-methyl) amino)-N^4-*n*-propylamino-N^8-prop-2-ynylamino-pyrimido[5,4-d]pyrimidine hydrochloride (**15a**) in 90% yield. 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 9.63 (1H, br s), 9.29 (1H, br s), 4.31 (2H, dd, J=5.2, 2.3 Hz), 3.82 (3H, s), 3.81 (3H, s), 3.53-3.47 (2H, m), 3.41 (3H, s), 3.38 (3H, s), 3.23 (1H, t, J=2.3 Hz), 1.66 (2H, sextet, J=7.4 Hz), 0.92 (3H, t, J=7.4 Hz). ESI-MS (m/z): 361 $[M+H]^+$; melting point: 176-177 °C.

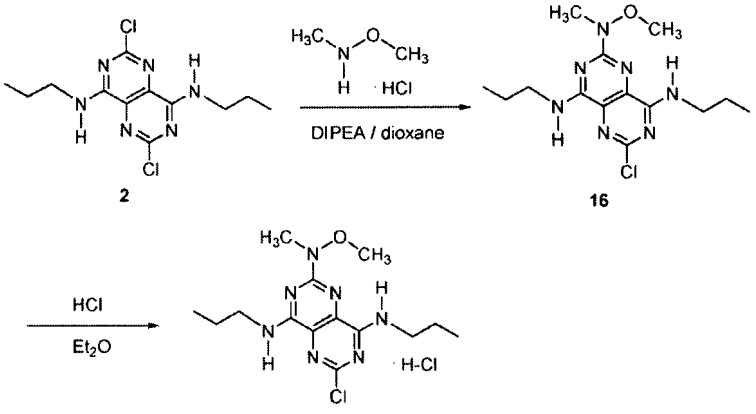
Example 7: N-(6-Chloro-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine (16) and corresponding hydrochloride salt (17a) (Scheme 10)

N-(6-Chloro-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine (**16**):

A mixture of 2,6-dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**2**) (316 mg, 1.00 mmol), N,O-dimethylhydroxylamine hydrochloride (975 mg, 10.00 mmol) and N,N-diisopropylethylamine (1.74 mL, 10.00 mmol) in 1,4-dioxane (10 mL) was heated at 90°C for 5 h. The reaction mixture was cooled and a saturated $NaHCO_3$ solution (30 mL) was added. The resulting suspension was extracted with CH_2Cl_2 (3 x 20mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (98:2) to yield N-(6-chloro-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine (**16**) (237 mg, 70%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.87-6.77(1H, m), 6.68-6.64 (1H, t, J=5.6 Hz), 3.86 (3H, s), 3.58-3.47 (4H, m), 3.36 (3H, s), 1.77-1.65 (4H, m), 1.02 (3H, t, J=7.4 Hz), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 340, 342 $[M+H]^+$.

N-(6-Chloro-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine hydrochloride (**17a**):

N-(6-Chloro-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine (**16**) and 2M HCl/diethyl ether in diethyl ether were reacted using procedure described for compound (**4a**) to yield N-(6-chloro-4,8-bis-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine hydrochloride (**17a**) in 90% yield. 400 MHz ^{1}H NMR (DMSO-d6, ppm): δ 9.27-8.15 (2H, m), 3.81 (3H, s), 3.49-3.32 (7H, m), 1.70-1.54 (4H, m), 0.95-0.84 (6H, m). ESI-MS (m/z): 340, 342 $[M+H]^+$; melting point: 142-145 °C.



Scheme 10.

Example 8: N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine (18) and corresponding hydrochloride salt (19a) (Scheme 11)

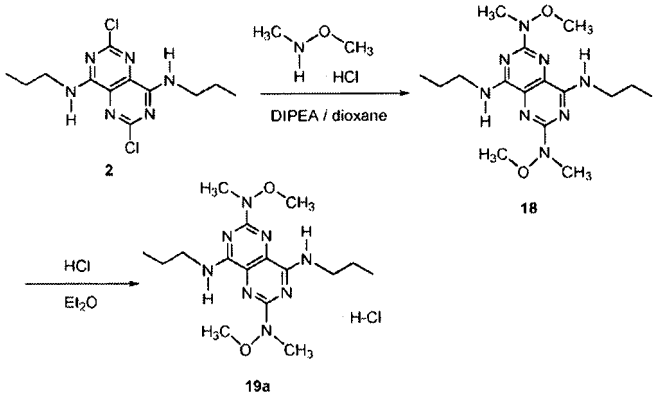
N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine (**18**):

2,6-Dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**2**) and N,O-dimethylhydroxylamine hydrochloride were reacted using the procedure described for compound (**14**) to yield N^2,N^6-bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine (**18**) in 94% yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm): d 6.62 (2H, t, J=5.9 Hz), 3.88 (6H, s), 3.55-3.48 (4H, m), 3.32 (6H, s), 1.71 (4H, sextet, J=7.4 Hz), 1.00 (6H, t, J=7.4 Hz). ESI-MS (m/z): 365 $[M+H]^+$.

N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine hydrochloride (**19a**):

N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine (**18**) and 2M HCl/diethyl ether in MeOH were reacted using the procedure described for compound (**4a**) to yield N^2,N^6-bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine (hydrochloride (**19a**) in 94% yield. 400

MHz ^{1}H NMR ($CDCl_3$, ppm): δ 12.79 (1H, br s), 11.7-8.3 (2H, m), 3.94 (6H, s), 3.61-3.50 (4H, m), 3.42 (6H, s),1.84-1.71 (4H, m), 1.04-0.94 (6H, m). ESI-MS (m/z): 365 $[M+H]^+$.



2 18 19a

Scheme 11.

Example 9: N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (21) and corresponding hydrochloride salt (22a) (Scheme 12)

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**):

A mixture of 2,6-dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**2**) (1.00 g, 3.17 mmol) and 2M methylamine/THF (8 mL) was heated at 60 °C for 21 h. The volatiles were removed by evaporation and the residue was partitioned between EtOAc (30 mL) and a saturated $NaHCO_3$ solution (30 mL). The water phase was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water (50 mL), and then with a brine solution (50 mL) and lastly dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed to yield 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido [5,4-d]pyrimidine-2,4,8-triamine (**20**) (975mg, 99%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 6.80-6.71 (1H, m), 6.52 (1H, t, J=5.1 Hz), 4.93-4.85 (1H, m), 3.54 (2H, td, J=7.3, 6.1 Hz), 3.49-3.42 (2H, m), 3.00 (3H, d, J=5.1 Hz), 1.77-1.63 (4H, m), 1.03 (3H, t, J=7.4 Hz), 1.01 (3H, t, J=7.4 Hz). ESI-MS (m/z): 310, 312 $[M+H]^+$.

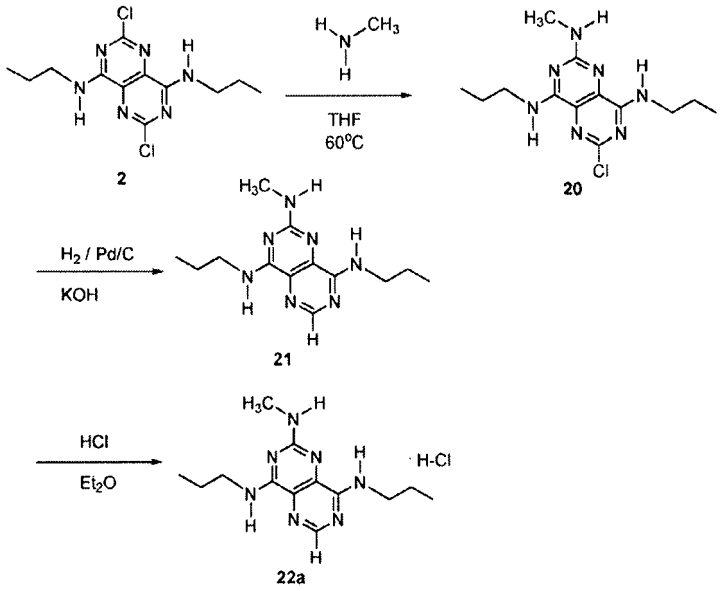
N^2-Methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**21**):

A mixture of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (440 mg, 1.42 mmol), KOH (319 mg, 5.68 mmol) and 10% Pd/C (310 mg) in THF (20 mL) was hydrogenated at 30 psi for 72 h. The reaction mixture was filtered, and the filtrate was evaporated. The residue was dissolved in EtOAc (80 mL), washed with water (3 x 30 mL), and then with a brine solution (30 mL) and lastly dried over solid anhydrous Na_2SO_4. After filtration the solvent was removed in vacuo and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to

CH_2Cl_2/EtOH (98:2) to yield N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**21**) (360 mg, 92%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.25 (1H, s), 6.74-6.56 (2H, m), 4.92 (1H, br s), 3.56-3.48 (4H, m), 3.00 (3H, d, J=5.1 Hz), 1.78-1.63 (4H, m), 1.02 (3H, t, J=7.3 Hz), 1.00 (3H, t, J=7.3 Hz). ESI-MS (m/z): 276 $[M+H]^+$.

N^2-Methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine hydrochloride (**22a**):

N^2-Methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**21**)and 2M HCl/diethyl ether in diethyl ether were reacted using the procedure described for compound (**4a**) to yield N^2-methyl-N^4,N^8-di-n-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine hydrochloride (**22a**) in 91% yield. 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 13.8-13.0 (1H, br s), 9.78-8.83 (1H, m), 8.56 (1H, br s), 8.41 (1H, s), 7.33 (1H, br s), 3.55-3.35 (4H, m, overlapped with water), 2.99 (3H, s), 1.71-1.60 (4H, m), 0.95 (3H, t, J=7.3 Hz), 0.91 (3H, t, J=7.3 Hz). ESI-MS (m/z): 276 $[M+H]^+$; melting point: 139-142 °C.



Scheme 12.

Example 10: O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-hydroxylamine (23) and corresponding hydrochloride salt (24a)

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-hydroxylamine (**23**):

A mixture of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (300 mg, 0.97 mmol), N,O-dimethylhydroxylamine hydrochloride (426 mg, 4.37 mmol) and N,N-diisopropylethylamine (722 µL, 4.37 mmol) in 1,4-dioxane (10 mL) was heated at 90°C for 60 h. The reaction mixture was cooled, and a

saturated $NaHCO_3$ solution (30 mL) was added. The resulting suspension was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (30mL), and then with a brine solution (20 mL) and lastly dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (95:5) to yield of O,N-dimethyl-N-(6-methylamino-4,8-bis-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-hydroxylamine (**23**) (175 mg, 54%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.57 (2H, br s), 4.67 (1H, br s), 3.88 (3H, s), 3.54-3.43 (4H, m), 3.30 (3H, s), 2.98 (3H, d, J=5.1 Hz), 1.76-1.64 (4H, m), 1.01 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 335 $[M+H]^+$.

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-hydroxylamine hydrochloride (**24a**):

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-hydroxylamine (**23**) and 2M HCl/diethyl ether in diethyl ether were reacted using the procedure described for compound (**3a**) to yield O,N-dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-hydroxylamine hydrochloride (**24a**) in 90% yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm): 13.24 (0.2H, br s), 8.26 (1.8H, br s), 6.71-6.63 (1H, m), 3.89 (3H, s), 3.66-3.60 (2H, m), 3.57-3.51 (2H, m), 3.37 (3H, s), 3.06 (3H, d, J=4.8 Hz), 1.85-1.74 (4H, m), 1.03 (3H, t, J=7.4 Hz), 1.02 (3H, t, J=7.4 Hz). ESI-MS (m/z): 335 $[M+H]^+$; melting point: 182-185 °C.

Example 11: N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (26) and corresponding hydrochloride salt (27a) (Scheme 13)

2,6-Dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**):

A 2M methylamine/THF (2.10 mL, 4.2 mmol) solution was added to a solution of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine (**1**) (250 mg, 0.93 mmol) in THF (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 h. After this time, water (10 mL) was added and the precipitate was filtered, washed with water (10 mL) and dried over P_2O_5 to yield 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) (230 mg, 95%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.90 (2H, br s), 3.16 (6H, d, J=5.0 Hz). ESI-MS (m/z): 259, 261, 263 $[M+H]^+$.

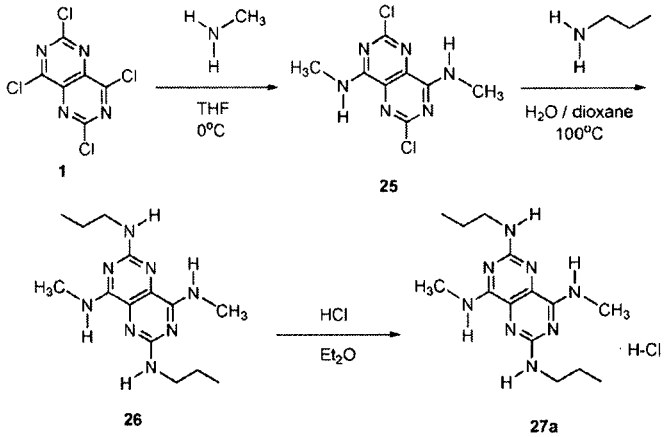
N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**26**):

2,6-Dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) and *n*-propylamine were reacted using the procedure described for compound **3** to yield N^2,N^6-di-

n-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**26**) in 90% yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.49-6.38 (2H, m), 4.64 (2H, t, J=5.2 Hz), 3.38-3.33 (4H, m), 3.06 (6H, d, J=5.2 Hz), 1.63 (4H, sextet, J=7.3 Hz), 0.99 (6H, t, J=7.3 Hz). ESI-MS (m/z): 305 $[M+H]^+$.

N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**27a**):

N^2,N^6-Di-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**26**) and 2M HCl/diethyl ether in diethyl ether/1,4-dioxane (5/1) were reacted using the procedure described for compound (**4a**) to yield N^2,N^6-di-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**27a**) in 88% yield. 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.00 (0.3H, s), 9.65 (0.7H, s), 7.70 (1H, s), 7.44 (1H, s), 6.65 (1.3H, s), 4.89 (0.7H, s), 3.50-3.43 (3H, m), 3.39-3.30 (1H, m), 3.21-3.20 (4H, m), 3.08-3.03 (2H, m), 1.71-1.59 (4H, m), 0.99 (6H, t, J=7.5 Hz). ESI-MS (m/z): 305 $[M+H]^+$; melting point: 237-240 °C.



Scheme 13.

Example 12: N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (28) and corresponding hydrochloride salt (29a) (Scheme 14)

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine hydrochloride (**20a**)

A 2M HCl /diethyl ether (260 µL, 0.52 mmol) was added to the solution of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) (160 mg, 0.52 mmol) in diethyl ether (10 mL). The mixture was stirred for 0.5 h at 0°C, and the resultant precipitate was filtered, washed with diethyl ether (3 mL) and dried to yield 6-chloro-N^2-methyl-N^4,N^8-di-$_n$-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine hydrochloride

(**20a**) (160 mg, 89%y). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 9.44 (1H, br s) 8.96 (1H, br s), 7.37 (1H, br s), 3.78-3.12 (4H, m, overlapped with water), 2.97 (3H, s), 1.71-1.56 (4H, m), 0.95 (3H, t, J=7.3 Hz), 0.89 (3H, t, J=7.3 Hz). ESI-MS (m/z): 310, 312 $[M+H]^+$; melting point: 209-212 °C.

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**28**):

A mixture of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (310 mg, 1.00 mmol) and dimethylamine (40% water solution, 2.25 mL) in 1,4-dioxane (2.5 mL) was heated at 105°C for 16 h in a closed vial. The volatiles were removed by evaporation, and the residue was partitioned between CH_2Cl_2 (35 mL) and a saturated $NaHCO_3$ solution (30 mL). The water phase was extracted with CH_2Cl_2 (2 x 35 mL), and the combined organic extracts were washed with water (40 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (95:5) to PE/EtOAc (85:15) to yield N^2,N^2,N^6-trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**28**) (280 mg, 88%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 400 MHz ^{1}H NMR ($CDCl_3$, ppm): 6.61-6.40 (2H, m), 4.57 (1H, br s), 3.54-3.43 (4H, m), 3.15 (6H, s), 2.97 (3H, d, J=5.0 Hz), 1.76-1.65 (4H, m), 1.01 (3H, t, J=7.4 Hz), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 319 $[M+H]^+$.

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**29a**):

A 2M HCl /diethyl ether solution (0.41 mL, 0.82 mmol) was added to a solution of N^2,N^2,N^6-trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**28**) (264 mg, 0.83 mmol) in methanol (20 mL). The mixture was stirred for 0.5 h at 0°C, and then the volatiles were removed under reduced pressure to yield N^2,N^2,N^6-trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**29a**) (292 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.08 (1H, br s), 12.41 (0.3H, s), 8.4-7.2 (1.7H, br s), 6.59 (1H, s), 3.65-3.59 (2H, m), 3.56-3.48 (2H, m), 3.22 (6H, s), 3.04 (2H, d, J=4.8 Hz), 1.84-1.73 (4H, m), 1.03 (3H, t, J=7.4 Hz), 1.02 (3H, t, J=7.4 Hz). ESI-MS (m/z): 319 $[M+H]^+$; melting point: 241-243 °C.

Example 13: N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (30) and corresponding hydrochloride salt (31a) (Scheme 14)

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

(30):

A mixture of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (300 mg, 0.97 mmol) and diethylamine (500 µL) in 1,4-dioxane (2.5 mL) was heated in a closed vial at 120°C for 48 h. An additional portion of diethylamine (500 µL) was added and heating at 120°C was continued for 48 h. The volatiles were removed by evaporation, and the residue was partitioned between CH_2Cl_2 (35 mL) and a saturated $NaHCO_3$ solution (30 mL). The water phase was extracted with CH_2Cl_2 (2 x 30 mL), and the combined organic extracts were washed with water (40 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (95:5) to give N^2,N^2-diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**30**) (130 mg, 39%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.52 (1H, br s), 6.45 (1H, br s), 4.53 (1H, br s), 3.67-3.57 (4H, m), 3.52-3.42 (4H, m), 2.97 (3H, d, J=4.4 Hz), 1.75-1.63 (4H, m), 1.19 (6H, t, J=7.0 Hz), 1.00 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 347 $[M+H]^+$.

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**31a**):

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**30**) (110 mg, 0.32 mmol) was treated with 2M HCl /diethyl ether using the procedure described for compound **20a** to yield N^2,N^2-diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**31a**) (110 mg, 89%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.91 (1H, s), 7.56 (1H, br s), 7.51-7.43 (1H, m), 6.62-6.50 (1H, m), 3.65-3.54 (6H, m), 3.53-3.45 (2H, m), 3.04 (3H, d, J=4.8 Hz), 1.83-1.68 (4H, m), 1.18 (6H, t, J=7.0 Hz), 1.03 (3H, t, J=7.1 Hz), 1.01 (3H, t, J=7.1 Hz). ESI-MS (m/z): 347 $[M+H]^+$; melting point: 202-204 °C.

Example 14: 2-(6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol (32) and corresponding hydrochloride salt (33a) (Scheme 14)

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) (257 mg, 0.83 mmol) and 2-aminoethanol were reacted using the procedure described for compound **40** to yield 2-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol (**32**) (200 mg, 72%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.64 (1H, br s), 6.28 (1H, br s), 5.08 (1H, t, J=5.2 Hz), 4.86-4.37 (2H, m), 3.85-3.80 (2H, m),

3.60-3.53 (2H, m), 3.49-3.41 (4H, m), 2.96 (3H, d, J=5.2 Hz), 1.75-1.62 (4H, m), 1.01 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 335 $[M+H]^+$.

2-(6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol (**32**) (190 mg, 0.57 mmol)) was treated with 2M HCl /diethyl ether in methanol using the procedure described for compound (**29a**) (210 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 15.1-13.7 (1H, m), 8.00-7.31 (1.5H, m), 6.95 (0.5H, br s) ,6.64 (1H, br s), 5.5-4.7 (1H, m), 3.86-3.81 (2H, m), 3.70-3.45 (6H, m), 3.04 (3H, s), 3.0-2.5 (1H, br s), 1.83-1.71 (4H, m), 1.03 (6H, t, J=7.4 Hz). ESI-MS (m/z): 335 $[M+H]^+$; melting point: 194-196 °C.

Example 15: N^2-(2-Methoxyethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (34) and corresponding hydrochloride salt (35a) (Scheme 14)

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**34**) was prepared from 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) (300 mg, 0.97 mmol) and 2-methoxy-ethylamine in n-butanol using the procedure described for compound (**9**) (215 mg, 64%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.61-6.40 (2H, m), 4.93 (1H, s), 4.59 (1H, br s), 3.63-3.53 (4H, m), 3.50-3.41 (4H, m), 3.39 (3H, s), 2.97 (3H, d, J=5.2 Hz), 1.74-1.63 (4H, m), 1.00 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 349 $[M+H]^+$.

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**34**) (200 mg, 0.57 mmol)) was treated with 2M HCl /diethyl ether in methanol using the procedure described for compound (**29a**) (178 mg, 81%y). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 9.3-8.0 (1H, m), 6.94 (2H, br s), 6.2-4.5 (2H, br s), 3.60-3.54 (2H, m), 3.51-3.41 (6H, m), 3.27 (3H, s), 2.92 (3H, s), 1.70-1.59 (4H, m), 0.93 (6H, t, J=7.4 Hz). ESI-MS (m/z): 349 $[M+H]^+$; melting point: 214-216 °C.

Example 16: N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (36) and corresponding hydrochloride salt (37a) (Scheme 14)

N^2-(2-Isopropoxy-ethyl)- N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**36**) (249 mg, 0.80 mmol) was prepared from 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) and 2-isopropyl-

ethylamine using procedure described for compound (**40**) (165 mg 55%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.55-6.42 (2H, m), 4.97-4.89 (1H, m), 4.60 (1H, br s), 3.66-3.54 (5H, m), 3.50-3.40 (4H, m), 2.96 (3H, d, J=5.0 Hz), 1.74-1.63 (4H, m), 1.18 (6H, d, J=6.3 Hz), 1.00 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 377 $[M+H]^+$.

N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**36**) (140 mg, 0.37 mmol) was treated with 2M HCl /diethyl ether in methanol using the procedure described for compound (**29a**) (152 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): 15.4-13.8 (1H, m), 10.1-9.2 (0.5H, m), 8.11-7.35 (1.5H, m), 7.01-6.56 (1H, m), 5.37-4.65 (1H, m), 3.70-3.42 (9H, m), 3.03 (3H, s), 1.85-1.70 (4H, m), 1.18 (6H, d, J=6.2 Hz), 1.03 (3H, t, J=7.4 Hz), 1.02 (3H, t, J=7.4 Hz). ESI-MS (m/z): 377 $[M+H]^+$; melting point: 154-156 °C.

Example 17: N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (38) and corresponding hydrochloride salt (39a) (Scheme 14)

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**38**):

A mixture of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (300 mg, 0.97 mmol), 3,3,3-trifluoropropylamine hydrochloride (435 mg, 2.91 mmol) and N,N-diisopropylethylamine (503μL, 2.91 mmol) in *n*-butanol (1.5 mL) was heated in a closed vial at 140°C for 24 h. A saturated $NaHCO_3$ solution (5 mL) was added and the resulting suspension was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (20 mL), and then with a brine solution (10 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (5:1) to PE/EtOAc (3:1) to give N^8-methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**38**) (300 mg, 80%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.58 (1H, br s), 6.45 (1H, br s), 4.79 (1H, s), 4.63 (1H, br s), 3.66 (2H, dt, J=7.4, 6.4 Hz), 3.49-3.43 (4H, m), 2.98 (3H, d, J=5.2 Hz), 2.55-2.43 (2H, m), 1.70 (2H, sextet, J=7.4 Hz), 1.69 (2H, sextet, J=7.4 Hz), 1.01 (6H, t, J=7.4 Hz). ESI-MS (m/z): 387 $[M+H]^+$.

N^8-Methyl- N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**39a**):

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**38**) (290 mg, 0.75 mmol) was treated with 2M HCl /diethyl ether in diethyl ether/ ethanol (15/1) using the procedure described for compound (**20a**) to produce N^8-methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**39a**) (293 mg, 92%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 9.75 (1H, br s), 9.50 (1H, br s), 6.87 (1H, br s), 6.62 (1H, s), 3.79 (2H, dt, J=7.4, 6.7 Hz), 3.68-3.59 (4H, m), 3.08 (3H, d, J=4.8 Hz), 2.54-2.41 (2H, m), 1.89-1.78 (4H, m), 1.06 (3H, t, J=7.4 Hz), 1.05 (3H, t, J=7.4 Hz). ESI-MS (m/z): 387 $[M+H]^+$; melting point: 259-260 °C.

Example 18: N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (40) and corresponding hydrochloride salt (41a) (Scheme 14)

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**40**):

A mixture of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (250 mg, 0.81 mmol) and morpholine (2.0 mL) was heated in a closed vial at 105°C for 16 h. A saturated $NaHCO_3$ solution (15 mL) was added and the resulting suspension was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with water (2 x 15 mL), and then with a brine solution (20 mL), and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (98:2) to give N^2-methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**40**) (265 mg, 91%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.65-6.37 (2H, m), 4.65 (1H, br s), 3.83-3.67 (8H, m), 3.54-3.40 (4H, m), 2.97 (3H, s), 1.76-1.63 (4H, m), 1.00 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 361 $[M+H]^+$.

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**41a**):

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**40**) (250 mg, 0.69 mmol) was treated with 2M HCl /diethyl ether in methanol using the procedure described for compound (**20a**) (226 mg, 82%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.07 (1H, br s), 7.72 (1H, s), 7.48-7.39 (1H, m), 6.66-6.54 (1H, m), 3.82-3.71 (8H, m), 3.61 (2H, q, J=7.8 Hz), 3.53-3.45 (2H, m), 3.05 (3H, d, J=4.8 Hz), 1.82-1.70 (4H, m), 1.03 (3H, t, J=7.4 Hz), 1.02 (3H, t, J=7.4 Hz). ESI-MS (m/z): 361 $[M+H]^+$; melting point: 240-242 °C.

Example 19: N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (42) and corresponding hydrochloride salt (43a) (Scheme 14)

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine was prepared from 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (250 mg, 0.81 mmol) and piperidine using procedure described for compound (**40**) (240 mg, 83%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.49 (2H, br s), 4.59 (1H, br s), 3.83-3.65 (4H, m), 3.59-3.38 (4H, m), 2.96 (3H, s), 1.75-1.64 (4H, m), 1.64-1.54 (6H, m), 1.00 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 359 $[M+H]^+$.

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**42**) (220 mg, 0.61 mmol) was treated with 2M HCl /diethyl ether in methanol were reacted using the procedure described for compound (**29a**) (242 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.8-13.8 (1.2H, m), 12.51 (0.8H, br s), 6.65-6.54 (1H, m), 4.06-3.72 (4H, m), 3.66-3.58 (2H, m), 3.57-3.48 (2H, m), 3.05 (3H, d, J=4.8 Hz), 1.80 (4H, sextet, J=7.4 Hz), 1.73-1.62 (6H, m), 1.03 (3H, t, J=7.4 Hz), 1.02 (3H, t, J=7.4 Hz). ESI-MS (m/z): 359 $[M+H]^+$; melting point: 220-222 °C.

Example 20: N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (44) and corresponding dihydrochloride salt (45a) (Scheme 14)

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) (160 mg, 0.52 mmol) and pyrrolidine were reacted using procedure described for compound (**40**) (135 mg, 76%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.76-6.32 (2H, m), 4.58 (1H, br s), 3.74- 3.34 (8H, m), 2.97 (3H, s), 1.98-1.90 (4H, m), 1.76-1.64 (4H, m), 1.00 (6H, t, J=7.4 Hz). ESI-MS (m/z): 345 $[M+H]^+$.

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**44**) (125 mg, 0.36 mmol) was treated with 2M HCl /diethyl ether in methanol using the procedure described for compound (**20a**) (76 mg, 50%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.66 (1H, s), 12.34 (1H, s), 11.72 (1H, br s), 9.39 (1H, br s), 6.69-6.58 (1H, m), 4.26-3.95 (2H, m), 3.83-3.51 (6H, m), 3.06 (3H, d, J=4.7 Hz), 2.21-1.92 (4H, m), 1.91-1.75 (4H, m), 1.07-0.99 (6H, m). ESI-MS (m/z): 345 $[M+H]^+$; melting point: 243-245 °C.

Example 21: N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4-

d] pyrimidine-2,4,8-triamine (46) and corresponding hydrochloride salt (47a) (Scheme 14)

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) (260 mg, 0.84 mmol) and 4-methoxypiperidine were reacted using procedure described for compound **40** to produce N^2-methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine (**46**) (270 mg, 83%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.49 (2H, s), 4.62 (1H, br s), 4.42-4.30 (2H, m), 3.54-3.35 (5H, m), 3.39 (3H, s), 3.29-3.17 (2H, m), 2.98 (3H, d, J=4.4 Hz), 2.01-1.91 (2H, m), 1.76-1.63 (4H, m), 1.62-1.50 (2H, m), 1.00 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 389 $[M+H]^+$.

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**46**) (240 mg, 0.62 mmol) was treated with 2M HCl /diethyl ether in methanol using the procedure described for compound (**20a**) (262 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.99 (1H, br s), 7.66 (1H, br s), 7.47 (1H, br s), 6.63-6.56 (1H, m), 4.28-4.16 (2H, m), 3.64-3.57 (2H, m), 3.53-3.32 (5H, m), 3.39 (3H, s), 3.04 (3H, d, J=5.0 Hz), 1.98-1.89 (2H, m), 1.82-1.70 (4H, m), 1.64-1.52 (2H, m), 1.05-0.98 (6H, m). ESI-MS (m/z): 389 $[M+H]^+$; melting point: 221-223 °C.

Example 22: N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido [5,4-d]pyrimidine-2,4,6,8-tetraamine (48) and corresponding hydrochloride salt (49a) (Scheme 14)

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**48**):

A mixture of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (250 mg, 0.81 mmol) and 3-chloro-2-methyl-benzylamine (315 mg, 2.02 mmol) in *n*-butanol (2.0 mL) was heated in a closed vial at 145°C for 23 h. The reaction mixture was cooled and a saturated $NaHCO_3$ solution (20 mL) was added. The resulting suspension was extracted with CH_2Cl_2 (3 x 15mL). The combined organic extracts were washed with water (20 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (98:2) to give N^2-(3-chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**48**) (200 mg, 58%). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.33-7.24 (2H, m), 7.07 (1H, dd,

J=7.8, 7.8 Hz), 6.60-6.48 (1H, m), 6.47-6.34 (1H, m), 4.87-4.74 (1H, m), 4.65-4.54 (1H, m), 4.59 (2H, d, J=5.7 Hz), 3.49-3.39 (4H, m), 2.97 (3H, d, J=5.1 Hz), 2.43 (3H, s), 1.67 (2H, sextet, J=7.3 Hz), 1.66 (2H, sextet, J=7.3 Hz), 0.98 (3H, t, J=7.3 Hz), 0.98 (3H, t, J=7.3 Hz). ESI-MS (m/z): 429, 431 $[M+H]^+$.

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**49a**):

N^2-(3-chloro-2-methyl-benzyl)- N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine hydrochloride (**30**) (140 mg, 0.33 mmol) was treated with 2M HCl /diethyl ether using the procedure described for compound (**29a**) to produce N^2-(3-chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**49a**) (140 mg, 91%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 15.5-14.8 (0.4H, m), 14.39-13.95 (0.6H, m), 9.8-9.4 (0.4H, m), 7.86-7.36 (1H, m), 7.31 (1H, d, J=7.8 Hz), 7.23-7.17 (1H, m), 7.2-7.0 (0.6H, m), 7.09 (1H, dd, J=7.8, 7.8 Hz), 6.72-6.49 (1H, m), 5.16-4.79 (1H, m), 4.77-4.47 (2H, m), 3.70-3.37 (4H, m), 3.13-2.89 (3H, m), 2.42 (3H, s), 1.89-1.61 (4H, m), 1.08-0.94 (6H, m). ESI-MS (m/z): 429, 431 $[M+H]^+$; melting point: 193-196 °C.

Example 23: N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (50) and corresponding hydrochloride salt (51a) (Scheme 14)

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) (250 mg, 0.81 mmol) and 3,4-dichlorobenzylamine were reacted in DMSO using the procedure described for compound (**48**) to produce N^2-(3,4-dichloro-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**50**) (260 mg, 71%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.49 (1H, d, J=2.0 Hz), 7.36 (1H, d, J=8.2 Hz), 7.21 (1H, dd, J=8.2, 2.0 Hz), 6.58 (1H, s), 6.38 (1H, s), 5.08 (1H, s), 4.67 (1H, s), 4.54 (2H, d, J=6.0 Hz), 3.46-3.40 (4H, m), 2.96 (3H, d, J=5.1 Hz), 1.71-1.61 (4H, m), 0.98 (3H, t, J=7.4 Hz), 0.97 (3H, t, J=7.4 Hz). ESI-MS (m/z): 449, 451, 453 $[M+H]^+$.

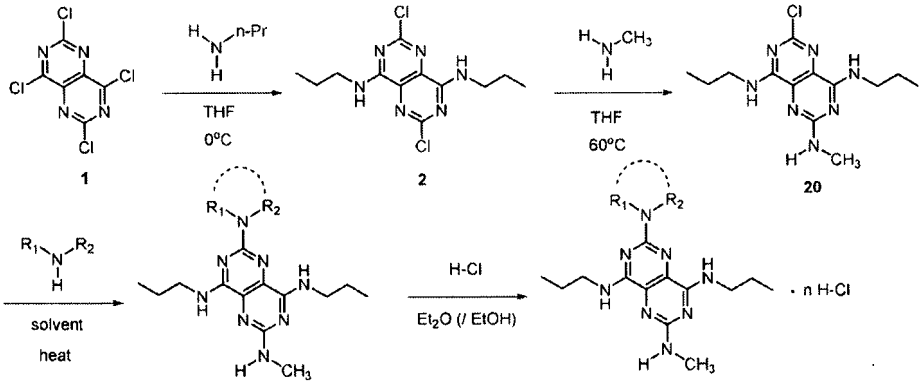
N^2-(3,4-Dichloro-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**50**) (240 mg, 0.53 mmol) was treated with 2M HCl /diethyl ether in diethyl ether using the procedure described for compound (**20a**). The product was crystallized from ethanol to give N^2-(3,4-dichloro-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**51a**) (200 mg, 78%y). 400

MHz ^{1}H NMR (DMSO-d_6, ppm): δ 13.5-12.3 (1H, m), 8.87 (1H, br s), 8.5-7.9 (1H, br s), 7.9-6.6 (3H, m), 7.68 (1H, s), 7.58 (1H, d, J=8.2 Hz), 4.57 (2H, s), 3.62-3.36 (4H, m, overlapped with water), 2.96 (3H, s), 1.75-1.41 (4H, m), 1.00-0.75 (6H, m). ESI-MS (m/z): 449, 451, 453 $[M+H]^+$; melting point: 176-179 °C.

Example 24: N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (52) and corresponding hydrochloride salt (53a) (Scheme 14)

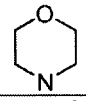
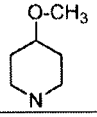
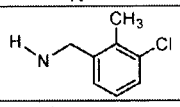
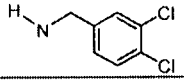
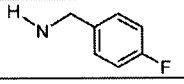
6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) (360 mg, 1.16 mmol) and 4-fluorobenzylamine were reacted in *n*-butanol using the procedure described for compound (**48**) to produce N^2-(4-fluoro-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**52**) (169 mg, 37%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): 7.39-7.30 (2H, m), 7.06-6.93 (2H, m), 6.56 (1H, br s), 6.43 (1H, br s), 4.95 (1H, br s), 4.72-4.48 (3H, m), 3.50-3.37 (4H, m), 2.97 (3H, d, J=5.2 Hz), 1.67 (4H, sextet, J=7.5 Hz), 0.98 (6H, t, J=7.5 Hz). ESI-MS (m/z): 399 $[M+H]^+$.

N^2-(4-Fluoro-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4,-d] pyrimidine-2,4,8-triamine (**52**) (160 mg, 0.40 mmol) and 2M HCl/diethyl ether in methanol were reacted using the procedure described for (**20a**) (145 mg, 83%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 15.32-14.86 (1.5H, m), 9.79-9.43 (1.5H, m), 7.35-7.21 (2H, m), 7.13 (1H, br s), 7.07-6.98 (2H, m), 6.61 (1H, s), 4.62 (2H, s), 3.69-3.49 (4H, m), 3.07 (3H, s), 1.89-1.69 (4H, m), 1.09-0.96 (6H, m). ESI-MS (m/z): 399 $[M+H]^+$; melting point: 187-189°C.



Scheme 14.

Table 1. 2-Substituted N^4,N^8-di-*n*-propyl-N^6-methyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamines and corresponding hydrochloride salts.

Cmpd #	R_1-N-R_2 / H-Cl
28 / 29a	CH_3-N-CH_3
30 / 31a	CH_3-CH_2-N-CH_2-CH_3
32 / 33a	H-N-CH_2-CH_3-OH
34 / 35a	H-N-CH_2-CH_3-O-CH_3
36 / 37a	H-N-CH_2-CH_3-O-$CH(CH_3)_2$
38 / 39a	H-N-CH_2-CH_2-CF_3
40 / 41a	
42 / 43 a	
44 / 45a	
46 / 47a	
48 / 49a	
50 / 51a	
52 / 53a	

Example 25: N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (55) and hydrochloride salt (56a) (Scheme 15)

2,6-Dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**):

A 2M methylamine/THF (2.10 mL, 4.2 mmol) was added to a solution of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine (**1**) (250 mg, 0.93 mmol) in THF (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 h. Water (10 mL) was then added and the resultant precipitate was filtered, washed with water (10 mL) and lastly dried over P_2O_5 to give 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) (230 mg, 95%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.90 (2H, br s), 3.16 (6H, d, J=5.0 Hz). ESI-MS (m/z): 259, 261, 263 $[M+H]^+$.

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**54**):

A mixture of 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) (325 mg, 3.17 mmol) and *n*-propylamine (206 µL, 2.5 mmol) in *n*-butanol (5 mL) was heated in a closed vial at 90°C for 8 h. The volatiles were removed by evaporation,

and the residue was partitioned between EtOAc (20 mL) and a saturated $NaHCO_3$ solution (20 mL). The aqueous phase was separated and then extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with water (30 mL), and then with a brine solution (30 mL) and lastly dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was filtered through silica gel pad using PE/EtOAc (5:1) as eluent to give 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**54**) (320 mg, 91%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.72 (1H, br s), 6.49 (1H, br s), 4.97 (1H, t, J=5.4 Hz), 3.42-3.35 (2H, m), 3.14 (3H, d, J=5.2 Hz), 3.04 (3H, d, J=5.0 Hz), 1.69-1.59 (2H, m), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 282, 284 $[M+H]^+$.

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**55**):

A mixture of 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (300 mg, 1.06 mmol) and dimethylamine (40% water solution, 5.0 mL) in *n*-butanol (5.0 mL) was heated in a closed vial at 135°C for 36 h. The volatiles were removed by evaporation and the residue was partitioned between CH_2Cl_2 (35 mL) and a saturated $NaHCO_3$ solution (30 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 35 mL). The combined organic extracts were washed with water (40 mL) and dried over solid anhydrous Na_2SO_4. After flitration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (99:1) to PE/EtOAc (1:99) to give N^2,N^2,N^4,N^8-tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**55**) (245 mg, 80%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.48 (1H, s), 6.40 (1H, s), 4.64 (1H, s), 3.39-3.32 (2H, m), 3.16 (6H, s), 3.08 (3H, d, J=5.3 Hz), 3.06 (3H, d, J=5.3 Hz), 1.63 (2H, sextet, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 291 $[M+H]^+$.

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**56a**):

N^2,N^2,N^4,N^8-tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**55**) (240 mg, 0.83 mmol) was treated with 2M HCl /diethyl ether in diethyl ether/ ethanol (1/2) using the procedure described for compound (**20a**) (216 mg, 80%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.87 (1H, s), 7.62 (1H, s), 7.46 (1H, s), 6.64 (1H, s), 3.49-3.42 (2H, m), 3.20 (3H, d, J=5.2 Hz), 3.15 (6H, s), 3.08 (3H, d, J=4.6 Hz), 1.66 (2H, sextet, J=7.2 Hz), 0.98 (3H, t, J=7.2 Hz). ESI-MS (m/z): 291 $[M+H]^+$; melting point: 285 °C (dec.).

Example 26: N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-

2,4,6,8-tetraamine (57) and hydrochloride salt (58a) (Scheme 15)

A mixture of 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (225 mg, 0.80 mmol) and diallylamine (2.0 mL) was heated in a closed vial at 120°C for 144 h. A saturated $NaHCO_3$ solution (15 mL) was added and the resulting suspension was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with water (2 x 15 mL), and then with a brine solution (20 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (10:1) to PE/EtOAc (1:1) to give N^2,N^2-diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**57**) (170 mg, 62%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.50-6.30 (2H, m), 5.90 (2H, ddt, J=17.2, 10.2, 5.8 Hz), 5.16 (2H, ddt, J=17.2, 1.6, 1.6 Hz), 5.11 (2H, ddt, J=10.2, 1.6, 1.6 Hz), 4.62 (1H, br s), 4.26-4.22 (4H, m), 3.39-3.32 (2H, m), 3.07 (3H, d, J=5.0 Hz), 3.06 (3H, d, J=5.0 Hz), 1.68-1.57 (2H, m) 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 343 $[M+H]^+$.

N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**57**) (150 mg 0.44 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using the procedure described for compound (**20a**) (130 mg, 78%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.91 (1H, s), 7.68 (1H, s), 7.39 (1H, s), 6.65 (1H, t, J=5.3 Hz), 5.92-5.78 (2H, m), 5.18-5.14 (2H, m), 5.14-5.11 (2H, m), 4.20 (4H, d, J=5.6 Hz), 3.47 (2H, q, J=6.7 Hz), 3.19 (3H, d, J=5.3 Hz), 3.07 (3H, d, J=4.6 Hz) ,1.71-1.60 (2H, m), 0.98 (3H, t, J=7.4 Hz). ESI-MS (m/z): 343 $[M+H]^+$; melting point: 199-201 °C.

Example 27: 2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol (59) and corresponding hydrochloride salt (60a) (Scheme 15)

A mixture of 6-chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (300 mg, 1.06 mmol) and (2-hydroxyethyl)-methylamine (510 µL, 6.36 mmol) in *n*-butanol (5.0 mL) was heated in a closed vial at 115°C for 48 h. The reaction mixture was cooled and a saturated $NaHCO_3$ solution (20 mL) was added. The resulting suspension was extracted with CH_2Cl_2 (3 x 15mL). The combined organic extracts were washed with water (20 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (5:1) to PE/EtOAc (1:1) to give 2-[(4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol (**59**) (300 mg, 88%y).

400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.52 (1H, br s), 6.30 (1H, br s), 5.15-4.82 (1H, br s), 4.66 (1H, s), 3.95-3.84 (2H, m), 3.81-3.70 (2H, m), 3.44-3.30 (2H, m), 3.21 (3H, s), 3.08 (6H, s), 1.69-1.57 (2H, m), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 321 $[M+H]^+$.

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol (**59**) (300 mg, 0.94 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using the procedure described for compound (**20a**) (270 mg, 81%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.83 (1H, s), 7.83 (1H, s), 7.44 (1H, s), 6.72-6.60 (1H, m), 3.92-3.85 (2H, m), 3.84-3.77 (2H, m), 3.50-3.40 (2H, m), 3.26 (1H, s), 3.22-3.17 (6H, m), 3.06 (3H, d, J=4.7 Hz), 1.71-1.60 (2H, m), 0.98 (3H, t, J=7.4 Hz). ESI-MS (m/z): 321 $[M+H]^+$; melting point: 246-248 °C.

Example 28: N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (61) and corresponding hydrochloride salt (62a) (Scheme 15)

6-Chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**54**) (300 mg, 1.06 mmol) and 2-isopropoxy-ethylamine were heated for 144 h according to the procedure described for compound (**59**) to produce N^2-(2-isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**61**) (210 mg, 57%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.43 (2H, br s), 5.01-4.91 (1H, m), 4.64 (1H, s), 3.67-3.54 (5H, m), 3.39-3.32 (2H, m), 3.07 (3H, d, J=4.5 Hz), 3.05 (3H, d, J=4.5 Hz), 1.68-1.58 (2H, m), 1.18 (6H, d, J=6.1 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 349 $[M+H]^+$.

N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**61**) (190 mg, 0.55 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using the procedure described for compound (**20a**) (190 mg, 89%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.5-7.2 (2H, m), 7.0-6.3 (2H, m), 5.23 (1H, br s), 3.61-3.56 (4H, m), 3.62 (1H, septet, J=6.1 Hz), 3.50-3.37 (2H, m), 3.25-3.04 (6H, m), 1.72-1.60 (2H, m), 1.19 (6H, d, J=6.1 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 349 $[M+H]^+$; melting point: 150-152 °C.

Example 29: 2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine (63) and corresponding hydrochloride salt (64a) (Scheme 15)

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-

triamine (**54**) (300 mg, 1.06 mmol) was reacted with N,N,N'-trimethyl-ethane-1,2-diamine by heating for 78 h according to the procedure described for compound (**60**) to produce 2-[N-(2-dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine (**63**) (310 mg, 84%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.60 (1H, s), 6.45 (1H, s), 4.76 (1H, s), 3.82-3.76 (2H, m), 3.39-3.32 (2H, m), 3.16 (3H, s), 3.07 (3H, d, J=5.0 Hz), 3.06 (3H, d, J=5.0 Hz), 2.56-2.54 (2H, m), 2.34 (6H, s), 1.68-1.58 (2H, m), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 348 $[M+H]^+$.

2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine (**63**) (292 mg, 0.84mmol) was treated with 2M HCl /diethyl ether in diethyl ether /ethanol (1/1) using procedure described for compound (**29a**) (322 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.3-7.6 (1H, br s), 7.17 (1H, s), 5.75 (1H, s), 4.06-3.97 (2H, m), 3.45-3.38 (2H, m), 3.17 (3H, s), 3.14 (3H, d, J=4.9 Hz), 3.07 (3H, d, J=4.9 Hz), 2.95-2.86 (2H, m), 2.60 (6H, s), 1.69-1.59 (2H, m), 0.98 (3H, t, J=7.4 Hz). ESI-MS (m/z): 348 $[M+H]^+$.

Example 30: 2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol (65) and corresponding hydrochloride salt (66a)

(Scheme 15)

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol (**65**):

A mixture of 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (275 mg, 0.98 mmol) and 2-(2-hydroxyethylamino)-ethanol (385 µL, 3.88 mmol) in *n*-butanol (5.0 mL) was heated in a closed vial at 135°C for 100 h. The volatiles were removed by evaporation, and the residue was partitioned between CH_2Cl_2 (35 mL) and a saturated $NaHCO_3$ solution (30 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (20 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (99:1) to PE/EtOAc (1:99) to give 2-[(4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol (**65**) (217 mg, 63%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.71-6.64 (1H, m), 6.12-6.06 (1H, m), 5.03- 4.86 (2H, m), 4.75-4.66 (1H, m), 3.92-3.87 (4H, m), 3.82-3.76 (4H, m), 3.38-3.31 (2H, m), 3.07 (3H, d, J=5.2 Hz), 3.05 (3H, d, J=5.1 Hz), 1.62 (2H, sextet, J=7.4 Hz), 0.98 (3H, t, J=7.4 Hz). ESI-

MS (m/z): 351 $[M+H]^+$.

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol hydrochloride (**66a**):

2-[(4,8-Bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol (**65**) (206 mg, 0.59 mmol) was treated with 2M HCl /diethyl ether in diethyl ether /ethanol (1/1) using procedure described for compound (**20a**) (215 mg, 95%y). 400 MHz ^{1}H NMR (D_2O, ppm): δ 3.85-3.79 (4H, m), 3.76-3.71 (4H, m), 3.41-3.35 (2H, m), 3.08 (3H, s), 2.99 (3H, s), 1.65 (2H, sextet, J=7.4 Hz), 0.97 (3H, t, J=7.4 Hz). ESI-MS (m/z): 351 $[M+H]^+$; melting point: 220-222 °C.

Example 31: N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (67) and corresponding hydrochloride salt (68a) (Scheme 15)

6-Chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**54**) (275 mg, 0.97 mmol) was reacted with bis-(2-methoxyethyl)-amine by heating for 78 h according to the procedure described for compound (**60**) to produce N^2,N^2-bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**67**) (220 mg, 60%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.46-6.31 (2H, m), 4.69-4.57(1H, m), 3.86-3.80 (4H, m), 3.62 (4H, t, J=6.3 Hz), 3.39-3.32 (2H, m), 3.38 (6H, s), 3.09-3.03 (6H, m), 1.63 (2H, sextet, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 379 $[M+H]^+$.

N^2,N^2-bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**67**) (205 mg, 0.65 mmol) was treated with 2M HCl /diethyl ether in diethyl ether using procedure described for compound (**20a**) (210 mg, 94%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.66-6.60 (1H, m), 3.91-3.82 (4H, m), 3.59 (4H, t, J=6.0 Hz), 3.49-3.43 (2H, m), 3.35 (6H, s), 3.19 (3H, d, J=5.2 Hz), 3.07 (3H, d, J=4.7 Hz), 1.66 (2H, sextet, J=7.4 Hz), 0.98 (3H, t, J=7.4). ESI-MS (m/z): 379 $[M+H]^+$; melting point: 196-198 °C.

Example 32: 6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine (70) and corresponding hydrochloride salt (71a) (Scheme 15)

6-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-N^4,N^8-dimethyl-N^2-*n*-propyl- pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**69**):

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**54**) (230 mg, 0.82 mmol) and 4-piperidone ethylene ketal (314 µL, 2.45 mmol) in n-butanol (5.0 mL) were heated at 120°C in a closed vial for 24 h. The reaction mixture was cooled, and saturated $NaHCO_3$ solution (20 mL) was added. The resulting suspension was extracted with EtOAc (3 x 15mL). The combined organic extracts were washed with water (40 mL), and then with a brine solution (30 mL), and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOAc (3:2) to give 6-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-N^4,N^8-dimethyl-N^2-*n*-propyl pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**69**) (309 mg, 97%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.50-6.35 (2H, m), 4.66 (1H, br s), 4.00 (4H, s), 3.93-3.89 (4H, m), 3.36 (2H, td, J=7.2, 6.1 Hz), 3.07 (3H, d, J=5.1 Hz), 3.06 (3H, d, J=5.3 Hz), 1.77-1.72 (4H, m), 1.67-1.57 (2H, m), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 389 $[M+H]^+$.

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine (**70**):

A mixture of 6-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-N^4,N^8-dimethyl-N^2-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**69**) (300 mg, 0.77 mmol) and 4N HCl (6 mL) in THF (5 mL) was stirred at room temperature for 20 h. The pH of the solution was adjusted to 9 by the addition of a saturated $NaHCO_3$ solution. The resulting suspension was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (40 mL), then with a brine solution (30 mL), and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from $CHCl_3$ to $CHCl_3$/EtOAc (9:1) to give 6-(4-oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine (**70**) (213 mg, 80%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.49 (1H, s), 6.41 (1H, s), 4.70 (1H, s), 4.15-4.08 (4H, m), 3.41-3.33 (2H, m), 3.10 (3H, d, J=5.1 Hz), 3.08 (3H, d, J=5.2 Hz), 2.49 (4H, t, J=6.1 Hz), 1.64 (2H, sextet, J=7.4 Hz), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 345 $[M+H]^+$.

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine hydrochloride (**71a**):

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d] pyrimidine-2,4,8-triamine (**70**) (213 mg, 0.62 mmol) was treated with 2M HCl /diethyl ether in diethyl ether using procedure described for compound (**20a**) (210 mg, 89%y). 400 MHz

^{1}H NMR ($CDCl_3$, ppm): δ 14.08 (1H, s), 7.87 (1H, s), 7.41 (1H, s), 6.75-6.62 (1H, m), 4.15-4.07 (4H, m), 3.53-3.42 (2H, m), 3.22 (3H, d, J=5.1 Hz), 3.09 (3H, d, J=4.5 Hz), 2.51 (4H, t, J=6.1 Hz), 1.67 (2H, sextet, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 345 $[M+H]^+$; melting point: 267 °C (dec.).

Example 33: N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido [5,4-d]pyrimidine-2,4,8-triamine (72) and corresponding hydrochloride (73a) (Scheme 15)

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**54**) (221 mg, 0.78 mmol) was reacted with 3-trifluoromethyl-piperidine (311 µL, 2.34 mmol) according to the procedure described for compound (**69**) to produce N^2-(3-trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido [5,4-d]pyrimidine-2,4,8-triamine (**72**) (285 mg, 91%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): 6.52-6.32 (2H, m), 5.02-4.94 (1H, m), 4.82-4.74 (1H, m), 4.67 (1H, br s), 3.41-3.31 (2H, m), 3.08 (3H, d, J=5.0 Hz), 3.07 (3H, d, J=5.1 Hz), 2.84-2.71 (2H, m), 2.39-2.24 (1H, m), 2.13-2.01 (1H, m), 1.85-1.74 (1H, m), 1.70-1.47 (4H, m), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 399 $[M+H]^+$.

N^2-(3-trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido [5,4-d]pyrimidine-2,4,8-triamine (**72**) (283 mg, 0.71mmol) was treated with 2M HCl /diethyl ether in diethyl ether using procedure described for compound (**20a**) (215 mg, 70%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.21 (1H, s), 13.2-12.6 (0.5H, br s), 8.6-8.0 (1.5H, br s), 6.73-6.55 (1H, m), 4.91-4.83 (1H, m), 4.83-4.71 (1H, m), 3.52-3.42 (2H, m), 3.20 (3H, d, J=5.1 Hz), 3.11 (3H, d, J=4.6 Hz), 3.08-2.92 (2H, m), 2.38-2.22 (1H, m), 2.15-2.04 (1H, m), 1.94-1.83 (1H, m), 1.73-1.47 (4H, m), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 399 $[M+H]^+$; melting point: 270 °C (dec.).

Example 34: N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine (74) and corresponding hydrochloride salt (75a) (Scheme 15)

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d] pyrimidine-2,4,8-triamine (**74**):

A mixture of 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (282 mg, 1.00 mmol) and thiomorpholine 1,1-dioxide (406

mg, 3.00 mmol) in *n*-butanol (5.0 mL) was heated in a closed vial at 130°C for 48 h. The reaction mixture was cooled and a saturated $NaHCO_3$ solution (20 mL) was added. The resulting suspension was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (30 mL), and then with a brine solution (30 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using $CHCl_3$ as an eluent to give N^2-6-*n*-propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine (**74**) (378 mg, 99%). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.55 (1H, s), 6.31 (1H, s), 4.80-4.67 (1H, m), 4.43-4.24 (4H, m), 3.41-3.32 (2H, m), 3.07 (6H, d, J=5.1 Hz), 3.10-3.02 (4H, m), 1.69-1.55 (2H, m), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 381 $[M+H]^+$.

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine hydrochloride (**75a**):

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine (375 mg, 0.97 mmol)was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (198 mg, 48%y). 400 MHz ^{1}H NMR ($CDCl_3$/TFA, ppm): δ 9.79 (1H, s), 9.30-8.90 (1H, m), 7.65-7.14 (1H, m), 4.57-4.43 (4H, m), 3.51 (2H, t, J=7.4Hz), 3.39-3.29 (4H, m), 3.23 (3H, s), 3.21 (3H, d, J=4.5 Hz), 1.68 (2H, sextet, J=7.4 Hz), 0.98 (3H, t, J=7.4 Hz). ESI-MS (m/z): 381 $[M+H]^+$; melting point >300 °C.

Example 35: N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (76) and corresponding hydrochloride salt (77a) (Scheme 15)

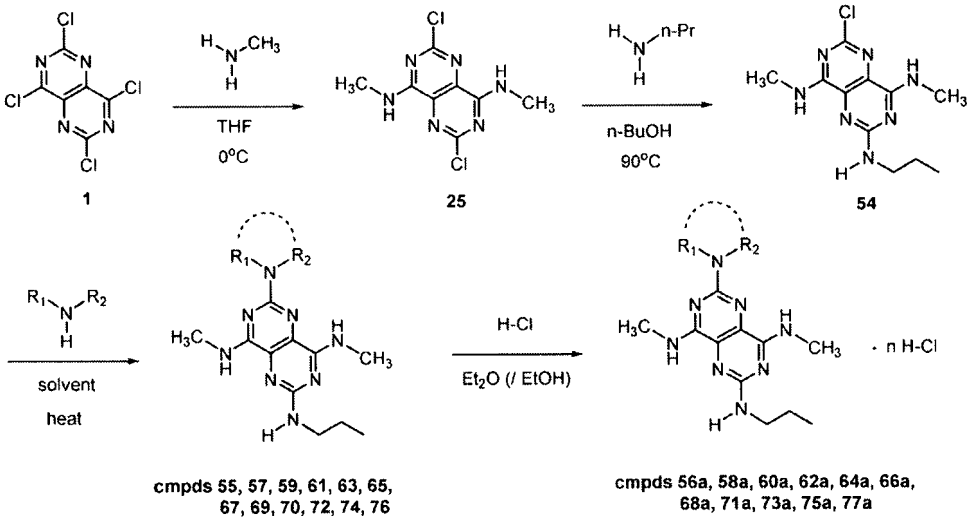
N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**76**):

A mixture of 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (282 mg, 1.00 mmol), 4,4-difluoro-piperidine hydrochloride (158 mg, 2.91 mmol) and N,N-diisopropylethylamine (345µL, 2.00 mmol) in 1,4-dioxane (4 mL) was heated in a closed vial at 120°C for 48 h. Additional portions of 4,4-difluoro-piperidine hydrochloride (158 mg, 2.91 mmol) and N,N-diisopropylethylamine (345µL, 2.00 mmol) were added and heating was continued for 18 h. After cooling, a saturated $NaHCO_3$ solution (5 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with water (20 mL), then with a brine

solution (10 mL), and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (7:1) to PE/EtOAc (1:1) to give N^2-*n*-propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**76**) (303 mg, 83%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.52-6.34 (2H, m), 4.69 (1H, br s), 3.96-3.91 (4H, m), 3.39-3.33 (2H, m), 3.08 (3H, d, J=5.1 Hz), 3.07 (3H, d, J=5.1 Hz), 2.04-1.94 (4H, m), 1.63 (2H, sextet, J=7.3 Hz), 0.99 (3H, t, J=7.3 Hz). ESI-MS (m/z): 367 $[M+H]^+$.

N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine hydrochloride (**77**):

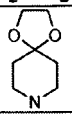
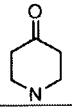
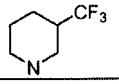
N^2-*n*-propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**76**) (303 mg, 0.83 mmol) was treated with 2M HCl/diethyl ether in diethyl ether using procedure described for (**20a**) (319 mg, 96%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.20-7.40 (3H, m), 6.82-6.57 (1H, m), 3.97-3.90 (4H, m), 3.48-3.42 (2H, m), 3.19 (3H, d, J=5.1 Hz), 3.06 (3H, d, J=5.1 Hz), 2.05-1.93 (4H, m), 1.65 (2H, sextet, J=7.3 Hz), 0.97 (3H, t, J=7.3 Hz). ESI-MS (m/z): 367 $[M+H]^+$; melting point: 290 °C (dec.).



Scheme 15.

Table 2. 2-Substituted N^4,N^8-dimethyl-N^6-n-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamines and corresponding hydrochloride salts

Cmpd #	$_{,1}$-N-R_2 / H-Cl
55 / 56a	CH_3-N-CH_3
57 / 58a	CH_2=CH-CH_2-N-CH_2-CH=CH_2
59 / 60a	CH_3-N-CH_2-CH_2-OH
61 / 62a	H-N-CH_2-CH_2-O-CH(CH_3)$_2$
63 / 64a	CH_3-N-CH_2-CH_2-N(CH_3)$_2$

65 / 66a	H-N-(CH_2-CH_2-OH)$_2$
67 / 68a	H-N-(CH_2-CH_2-OCH_3)$_2$
69	
70 / 71a	
72/ 73a	
74 / 75a	
1. 76 / 77a	2. 

Example 36: N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (78) and corresponding hydrochloride salt (79a) (Scheme 16)

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**78**):

A mixture of 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) (310 mg, 1.35 mmol) and methylamine (40% water solution, 1.0 mL) in *n*-butanol (1.0 mL) was heated in a closed vial at 125°C for 20 h. The reaction mixture was cooled, and water (10 mL) was added. The resulting precipitate was filtered, washed with water (10 mL), and dried. The product was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (97:3) to give N^2,N^4,N^6,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**78**) (230 mg, 69%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.48 (2H, br s), 4.62 (2H, br s), 3.07 (6H, d, J=5.1 Hz), 2.97 (6H, d, J=5.1 Hz). ESI-MS (m/z): 249 $[M+H]^+$.

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**79a**):

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**78**) (220 mg, 0.89 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (200 mg, 80%y). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 9.2-7.9 (3H, m), 7.5-6.3 (2H, br s), 2.99 (6H, s), 2.92 (6H, s). ESI-MS (m/z): 249 $[M+H]^+$; melting point > 300 °C.

Example 37: N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-

tetraamine hydrochloride (80) and corresponding hydrochloride salt (81a) (Scheme 16)

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**80**):

A mixture of 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) and ethylamine (70% water solution, 1.0 mL) in *n*-butanol (1.0 mL) was heated in a closed vial at 140°C for 24 h. After cooling, a saturated $NaHCO_3$ solution (20 mL) was added, and the resulting suspension was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with water (20 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (98:2) to give N^2,N^6-diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**80**) (130 mg, 41%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.45 (2H, br s), 4.59 (2H, br s), 3.48-3.36 (4H, m), 3.06 (6H, d, J=5.0 Hz), 1.23 (6H, t, J=7.2). ESI-MS (m/z): 277 $[M+H]^+$.

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**81a**):

N^2,N^6-diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**80**) (120 mg, 0.43 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (90 mg, 67%y). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 9.2-8.2 (3H, m), 7.6-6.5 (2H, m), 3.49-3.37 (4H, m), 3.06-2.90 (6H, m), 1.14 (6H, t, J=7.2 Hz). ESI-MS (m/z): 277 $[M+H]^+$; melting point: 256-258 °C.

Example 38: N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (82) and corresponding hydrochloride salt (83a) (Scheme 16)

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**82**):

2,6-Dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) (250 mg, 0.96 mmol) and *n*-butylamine (6 eq.) in *n*-butanol were reacted according to the procedure described for compound (**80**). After recrystallization from EtOAc / petroleum ether, N^2,N^6-di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**82**) was obtained (110 mg, 34%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.43 (2H, br s), 4.61 (2H, br s), 3.43-3.53 (4H, m), 3.06 (6H, d, J=5.0 Hz), 1.64-1.54 (4H, m), 1.49-1.37 (4H, m), 0.96 (6H, t, J=7.4 Hz). ESI-MS (m/z): 333 $[M+H]^+$.

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**83a**):

N^2,N^6-di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-

tetraamine (**82**) (100 mg, 0.30 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**29a**) (110 mg, ~100%y). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 9.2-7.8 (3H, m), 7.4-6.5 (2H, m), 3.48-3.32 (4H, m), 2.99 (6H, s), 1.59-1.46 (4H, m), 1.42-1.27 (4H, m), 0.90 (6H, t, J=7.3 Hz). ESI-MS (m/z): 333 $[M+H]^+$; melting point: 199-201 °C.

Example 39: N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (84) and corresponding hydrochloride salt (85a) (Scheme 16)

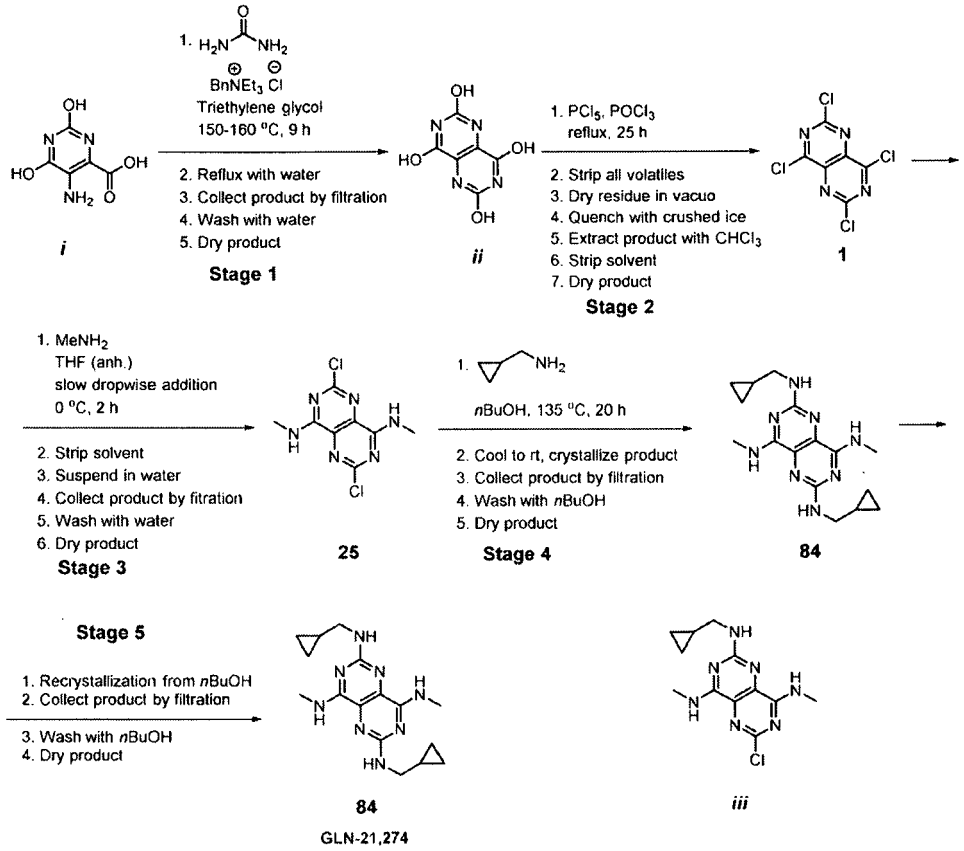
N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**):

A mixture of 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) (2.0 g, 7.72 mmol) and cyclopropylmethylamine (4.0 mL, 46.31 mmol) in *n*-butanol (15.0 mL) was heated in a closed vial at 130°C for 34 h. After cooling, a saturated $NaHCO_3$ solution (100 mL) and water (100 mL) was added, and the resulting suspension was extracted with $CHCl_3$ (3 x 200 mL). The combined organic extracts were washed with water (150 mL), and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (96:4) to give N^2,N^6-bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**) (1.35 g, 53%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.43 (2H, br s), 4.78 (2H, br s), 3.25 (4H, dd, J=6.8, 5.6 Hz), 3.07 (6H, d, J=5.2 Hz), 1.15-1.04 (2H, m), 0.54-0.49 (4H, m), 0.27-0.22 (4H, m). ESI-MS (m/z): 329 $[M+H]^+$.

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**85a**):

A 2.5 M HCl /EtOH solution (3.2 mL, 8.0 mmol) was added to the suspension of N^2,N^6-bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**) (2.63 g, 8.01 mmol) in CH_2Cl_2/EtOH (100 mL/100 mL). The mixture was stirred for 0.5 h at room temperature and then volatiles were removed under reduced pressure. The residue was treated with diethyl ether (30 mL). The resultant precipitate were filtered, washed with diethyl ether (15 mL),then with petroleum ether (15 mL) and dried to give N^2,N^6-bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**85a**) (2.75 g, 94%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.1-12.7 (1H, br s), 8.85 (1H, s), 8.04 (1H, br s), 7.42-6.62 (2H, m), 3.30-3.18 (4H, m), 3.07-2.88 (6H, m),

1.15-1.03 (2H, m), 0.50-0.37 (4H, m), 0.33-0.17 (4H, m). ESI-MS (m/z): 329 $[M+H]^+$; melting point: 264-265 °C.



Scheme 16.

Example 39A: Preparation of N^2-N^6-Biscyclopropylmethyl-N^4, N^8-dimethyl-pyrimido [5,4-d]pyrimidine-2,4,6,8-tetraamine (84) (Scheme 16)

Stage 1. Pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraol (ii)

A 250 mL, three-necked round bottom flask with a magnetic stir bar, temperature probe and an air condenser was charged with 5-aminoorotic acid (*i*) (15 g, 87.6 mmol, 1 equiv.), urea (42 g, 701 mmol, 8 equiv.), benzyltriethylammonium chloride (0.3 g, 1.3 mmol, 0.015 equiv.) and triethylene glycol (13 mL). The suspension was heated with stirring and maintained at 150-160°C (reaction mixture temperature) for 9 h. The initially viscous, heterogeneous mixture became more homogeneous and easily stirrable after heating for 10 minutes. After 3-4 h of heating the reaction mixture formed a thick, lumpy paste and toward the end of the heating period became unstirrable. Sublimation of urea occurred during the heating period. The course of the reaction was monitored by detecting the evolution of gaseous NH_3 with a wetted pH-indicator paper.

After reaction completion (no further NH_3 evolution), the mixture was cooled to 90°C and water (120 mL) was added. The mixture was stirred at reflux for 1 h, during which time the initial pasty mass converted to a thin suspension. The mixture was cooled to room temperature, filtered, and the brown solid product washed with water (3 x 50 mL). The product was dried under air for 16 h at 60°C yielding pyrimido[5,4-*d*]pyrimidine-2,4,6,8-tetraol (***ii***) (16.8 g, 98%y), as a brown powder. The product was used as is in the next step.

Stage 2: 2,4,6,8-Tetrachloro-pyrimido[5,4-d]pyrimidine (1)

A 1 L round bottom flask with a magnetic stir bar, a reflux condenser and a $CaCl_2$ drying tube was charged with pyrimido[5,4-*d*]pyrimidine-2,4,6,8-tetraol (***ii***) (23.9 g, 122 mmol, 1 equiv), PCl_5 (152 g, 732 mmol, 6 equiv) and $POCl_3$ (387.3 mL, 4150 mmol, 34 equi.). The resulting suspension was refluxed for 25 h at 145°C. At the end of the reflux period the reaction mixture became completely homogeneous. Precipitation of solids occurred upon cooling to room temperature. The reflux condenser was replaced by a distillation still head, and all volatiles were distilled off at atmospheric pressure and 145°C. When distillation ceased, the distilling flask was cooled to room temperature and water aspirator vacuum was applied to partially dry the product. The viscous product, while still in the distillation flask, was further dried for 30 min at 145°C under vacuum. The product, while in the distillation flask, was cooled to room temperature, and crushed ice (350 mL) was introduced, resulting in the generation of heat and the boiling of the ice turned to water. The resulting slurry was cooled to room temperature, mixed with 400 mL of chloroform, and the emulsified mixture filtered through a glass frit. The filtrate comprised a clear lower organic layer, a middle emulsified layer and an upper aqueous layer. The organic layer was separated and saved and other two layers were combined and extracted with four additional 200 mL portions of chloroform. After the last extraction the middle emulsified layer was separated from upper aqueous layer. The emulsified layer was mixed with 200 mL of chloroform and celite and stirred at room temperature for 10 min, converting the emulsion to a suspension which was removed by filtration and washed with chloroform. The combined organic extracts were dried over solid anhydrous Na_2SO_4, filtered and evaporated to dryness *in vacuo*. The solid product was dried in a vacuum desiccator for 16 h at room temperatureyielding 2,4,6,8-tetrachloro-pyrimido[5,4-*d*]pyrimidine (**1**) (12.2 g, 37%y), as a yellow powder, mp: 254-256°C. Quality of the product may be verified by CHN elemental analysis.

Table 3: Representative Elemental Analysis of (**1**).

	C	H	N
Theoretical:	26.70	0.00	20.76
Found 1	26.67	0.06	20.85
Found 2	26.63	0.01	20.78

Stage 3: 2,6-Dichloro-N^4, N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (25)

A 0.5 L round bottom flask, equipped with a magnetic stir bar, temperature probe and a syringe pump, was charged with 2,4,6,8-tetrachloro-pyrimido[5,4-*d*] pyrimidine (**1**) (11.8 g, 43.9 mmol, 1 equiv) and anhydrous tetrahydrofuran (128 mL). The resulting suspension was cooled in an ice bath, then a 2M solution of $MeNH_2$ in tetrahydrofuran (98.6 mL, 197 mmol, 4.5 equiv) was added dropwise at 50 mL/h with a syringe pump. After the addition was complete, the reaction mixture was warmed to room temperature and stirred 0.5 h. LC-MS assay showed complete conversion. The tetrahydrofuran was stripped *in vacuo* and the orange semisolid residue was suspended in water (50 mL) and sonicated 30 min in an ultrasonic bath. The product was collected by filtration, washed with water (3 x 30 mL), and dried in air at 60°C yielding 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-*d*]pyrimidine-4,8-diamine (**25**) (10.9 g, 96%y), as an orange powder; mp: 257-258°C

Stage 4: N^2-N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (84)

An Ace glass pressure tube with a magnetic stir bar was charged with 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-*d*]pyrimidine-4,8-diamine (**25**) (10.9 g, 42.1 mmol, 1 equiv.), cyclopropylmethylamine (18 g, 21.6 mL, 252 mmol, 6 equiv.) and *n*BuOH (65 mL). The tube was sealed with a Teflon plug and heated 20 h at 135°C. At the end of the heating period the product had begun to precipitate. The mixture was cooled to room temperature and stirred 2 h, giving rise to additional solid product. Upon manipulating the solid product in the mother liquor with a spatula, additional solid product formed. The mixture was left for an additional 2 h at room temperature, then the solids were collected by filtration, washed with *n*BuOH (3 x 30 mL) and light petroleum ether (2 x 50 mL) and dried on the filter for 2 h at room temperature, affording 7.0 g of N^2-N^6-bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**), as a yellow crystalline solid.

The combined mother and wash liquors were evaporated to dryness; the resulting semisolid residue was suspended in diethyl ether (80 mL) and the mixture was sonicated for 1 h. The mixture was filtered to remove insolubles, and the filtrate was evaporated to dryness, affording a red oil consisting mainly of mono-chloro derivative ***iii***, an

intermediate of Stage 4. Crude *iii* can be treated under Stage 4 conditions with 3 molar equiv of cyclopropylmethylamine to produce additional N^2-N^6-bis-cyclopropylmethyl N^4, N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**).

Stage 5: Recrystallization of N^2-N^6-biscyclopropylmethyl N^4, N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (84)

N^2-N^6-biscyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**) (7.0 g) obtained in Stage 4 was dissolved in *n*-BuOH (200 mL) at reflux and the solution was filtered through a sintered glass filter while hot to remove insoluble particulates. The filter was washed with *n*-BuOH (3 x 20 mL) and the combined filtrates were concentrated by distillation under atmospheric pressure to a final volume of 110 mL. The solution was cooled to and maintained at room temperature and stirred for 16 h. The product was collected by filtration, washed with *n*-BuOH (3 x 15 mL) and light petroleum ether (3 x 40 mL), and dried on the filter at room temperature yielding N^2,N^6-bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**) (6.45 g, 47%y). mp: 264-268°C. XRPD as per Figure 13 with key signals as per Table 5.

Table 4: Elemental Analysis of (**84**).

	C	H	N
Theoretical:	58.52	7.37	34.12
Found 1	58.65	7.36	33.98
Found 2	58.68	7.42	33.97

Table 5: Key XRPD Signals for (**84**) as crystallized from *n*-butanol.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
8.1179	10.88256	24.14
9.5941	9.21115	100.00
12.6010	7.01914	67.39
15.0171	5.89481	7.68
16.3278	5.42445	1.84
17.3962	5.09364	2.86
18.9758	4.67302	10.75
20.6773	4.29217	4.83
21.7166	4.08905	12.39
22.2793	3.98703	50.27
23.9773	3.70839	4.78
25.2409	3.52554	4.60
26.7012	3.33594	5.35

Salt Screen Procedure

Free base N^2-N^6-bis-cyclopropylmethyl N^4, N^8-dimethyl-pyrimido[5,4-d]

pyrimidine-2,4,6,8-tetraamine (**84**) (900 mg) and one molar equivalent of the salt former were dissolved in 30 mL 1:1 (vol/vol) chloroform/acetonitrile or chloroform/ethanol. The mixture was heated at 50°C if necessary to form a clear solution and then the solution was concentrated to dryness *in vacuo*. The resulting solid residue was used as is, assuming that it is a 1:1 stoichiometric salt.

A 3 mL vial with a screw cap was charged with 50 mg of the solid salt and 1 mL of a solvent at room temperature. The mixture was heated if necessary to achieve a clear solution, in some examples producing a mixture comprising a clear portion and a melt or incompletely dissolved crystalline material. The hot mixture was cooled to room temperature. If crystallization did not occur or was incomplete at ambient temperature (small visible amount of crystals), the mixture was further cooled to about 0-5°C. Solid product was collected by filtration, dried at 45°C *in vacuo*, and characterized by melting point and elemental analysis. Solvents evaluated include acetonitrile, methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, water, heptane, methyl-*tert*-butyl ether, cyclohexane, toluene, methanol, ethanol, n-propanol, isopropanol, *n*-butanol, 2-butanol, isoamyl alcohol, and tetrahydrofuran. Salt formers evaluated include hydrochloric acid, sulphuric acid, phosphoric acid benzenesulphonic acid, methanesulphonic acid, p-toluenesulphonic acid, saccharin, malonic acid, L-aspartic acid, L-glutamic acid, maleic acid, L(+)-tartaric acid, fumaric acid, citric acid, malic acid, glycolic acid, mandelic acid, benzoic acid, succinic acid acetic acid, lactic acid, glycerophosphoric acid, D-glucuronic acid, and D-gluconic acid. Data for the salts isolated using various salt formers and solvents are provided in Tables 6A-6H.

Table 6A: Hydrogen chloride salt (**85a**)

Solvent	Solubility, r.t.	Solubility, Reflux	Final Isolation Temp.	Base/acid molar ratio	Elemental Analysis	MP (°C)
Ethanol	I	S	Ca. 0-5 °C	1 : 1.11	Theoretical C, 52.10, H, 6.86, N, 30.38 Found C, 52.17, H, 6.98, N, 30.20 C, 52.04, H, 6.88, N, 30.18	253-255
n-Propanol	I	S	Ca. 0-5 °C	1 : 1.15	Theoretical C, 51.89, H, 6.84, N, 30.26 Found	251-253

					C, 52.12, H, 6.85, N, 29.89 C, 52.13, H, 6.91, N, 30.01	
n-Butanol	I	S	Ca. 0-5°C	1 : 1.15	Theoretical C, 51.89, H, 6.84, N, 30.26 Found C, 52.00, H, 6.90, N, 30.08 C, 52.01, H, 6.93, N, 29.99	252-254

Table 6B: Sulfuric acid salt (**85b**)

Solvent	**Solubility r.t.**	**Solubility Reflux**	**Final Isolation Temp.**	**Base/acid molar ratio**	**Elemental Analysis**	**MP (°C)**
Methanol	I	S	Ca. 0-5°C.	1 : 1	Theoretical C, 45.06, H, 6.14, N, 26.27 Found C, 45.09, H, 6.39, N, 26.55 C, 45.14, H, 6.29, N, 26.54	228-230
Ethanol	I	PS	r.t.	1 : 1.04	Theoretical C, 44.73, H, 6.18, N, 25.76 7.66 Found C, 44.29, H, 6.07, N, 26.00, C, 44.38, H, 6.23, N, 26.06	226-228

I = Insoluble, S = Soluble, PS = partially soluble.

Table 6C: Benzesulfonic acid salt (**85c**)

Solvent	**Solubility r.t.**	**Solubility Reflux**	**Final Isolation Temp.**	**Base/acid molar ratio**	**Elemental Analysis**	**MP (°C)**
Methyl isobutyl-ketone	I	S	Ca. 0-5°C	1 : 1	Calculated C, 54.30, H, 6.21, N, 23.03, S, 6.59 Found C, 54.31, H, 6.22, N, 23.20, S, 6.53 C, 54.36, H, 6.24, N, 23.20, S, 6.57	149-150
Ethyl Acetate	I	S	Ca. 0-5°C	1 : 1	Calculated C, 54.30, H, 6.21, N, 23.03, S, 6.59 Found C, 54.07, H, 6.20, N, 23.07, S, 6.48 C, 54.21, H, 6.36, N, 23.14, S, 6.44	148-150

Isopropyl acetate	I	S	Ca. 0-5°C	1 : 1	Calculated C, 54.30, H, 6.21, N, 23.03, S, 6.59 Found C, 54.22, H, 6.20, N, 23.05, S, 6.43 C, 54.28, H, 6.34, N, 23.09, S, 6.53	146-148
Toluene	I	S	Ca. 0-5°C	1 : 1	Calculated C, 54.30, H, 6.21, N, 23.03, S, 6.59 Found C, 54.23, H, 6.32, N, 22.85, S, 6.18 C, 54.29, H, 6.20, N, 22.88, S, 6.23	147-149

Table 6D: Toluenesulfonic salt (**85d**)

Solvent	**Solubility r.t.**	**Solubility Reflux**	**Final Isolation Temp.**	**Base/acid molar ratio**	**Elemental Analysis**	**MP (°C)**
Isopropyl acetate	I	S	Ca. 0-5°C	1 :1.13	Theoretical C, 54.91, H, 6.37, N, 21.43, S, 6.93 Found C, 54.86, H, 6.40, N, 21.27, S, 6.65 C, 54.79, H, 6.39, N, 21.23, S, 6.68	142-144

Table 6E: Malonic acid salt (**85e**)

Solvent	**Solubility r.t.**	**Solubility Reflux**	**Final Isolation Temp.**	**Base/acid molar ratio**	**Elemental Analysis**	**MP (°C)**
Methanol	I	PS	r.t.	1 : 1.06	Theoretical C, 52.51, H, 6.49, N, 25.54 Found C, 52.47, H, 6.43, N, 25.56 C, 52.61, H, 6.39, N, 25.54	246-248
Tetrahydrofuran	I	PS	r.t.	1 : 1.3	Theoretical C, 51.55, H, 6.35, N, 24.17 Found C, 51.93, H, 6.49, N, 23.89 C, 52.20, H, 6.55, N, 24.03	247-249

5

Table 6F: Hydrogen tartrate salt (**85f**)

Solvent	**Solubility r.t.**	**Solubility Reflux**	**Final Isolation Temp.**	**Base/acid molar ratio**	**Elemental Analysis**	**MP (°C)**
Methanol	I	PS	r.t.	1 : 0.79	Theoretical	226-228

					C, 51.48, H, 6.48, N, 25.07 Found C, 51.24, H, 6.45, N, 25.28 C, 51.17, H, 6.45, N, 25.25	
n-Propanol	I	PS	r.t.	1 : 0.83	Theoretical C, 51.23, H, 6.45, N, 24.74 Found C, 51.25, H, 6.55, N, 24.66 C, 51.25, H, 6.56, N, 24.70	226-228
n-Butanol	I	PS	r.t.	1 : 0.83	Theoretical C, 51.23, H, 6.45, N, 24.74 Found C, 51.50, H, 6.62, N, 24.37 C, 51.71, H, 6.67, N, 24.48	224-228

Table 6G: Maleic acid salt (**85g**)

Solvent	**Solubility r.t.**	**Solubility Reflux**	**Final Isolation Temp.**	**Base/acid molar ratio**	**Elemental Analysis**	**MP (°C)**
Methanol	I	S	r.t.	1 : 1	Theoretical C, 54.04, H, 6.35, N, 25.21 Found C, 53.68, H, 6.30, N, 25.09 C, 53.95, H, 6.30, N, 25.24	175-177
n-Propanol	I	S	r.t.	1 : 1	Theoretical C, 54.04, H, 6.35, N, 25.21 Found C, 53.94, H, 6.36, N, 25.05 C, 53.89, H, 6.31, N, 25.02	174-176
n-Butanol	I	S	r.t.	1 : 1	Theoretical C, 54.04, H, 6.35, N, 25.21 Found C, 53.77, H, 6.31, N, 24.94 C, 54.01, H, 6.31, N, 25.07	174-176
Tetrahydro furan	I	S	r.t.	1 : 1	Theoretical C, 54.04, H, 6.35, N, 25.21 Found C, 54.10, H, 6.32, N, 25.20 C, 54.08, H, 6.33, N, 25.25	194-196

Table 6H: Methanesulfonic acid salt (**85h**)

Solvent	**Solubility, r.t.**	**Solubility, Reflux**	**Final Isolation Temp.**	**Base/acid molar ratio**	**Elemental Analysis**	**MP (°C)**
Ethyl Acetate	I	S	r.t.	1 :1.1	Theoretical C, 47.31, H, 6.59, N, 25.81 Found C, 47.16, H, 6.81, N, 25.41 C, 47.44, H, 6.81, N, 25.62	143-145

Example 40: N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-

tetraamine (86) and corresponding hydrochloride salt (87a) (Scheme 17)

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**86**):

A mixture of 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) (350 mg, 1.35 mmol) and isobutylamine (805 µL, 8.10 mmol) in *n*-butanol (5.0 mL) was heated in a closed vial at 120°C for 20 h. An additional portion of isobutylamine (805 µL, 8.10 mmol) was added and the heating was continued for 68 h. After cooling, a saturated $NaHCO_3$ solution (30 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with water (75 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (9:1) to give N^2,N^6-diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**86**) (180 mg, 40%y). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 7.00-6.90 (2H, m), 6.03 (2H, t, J=5.6 Hz), 3.16-3.09 (4H, m), 2.91 (6H, d, J=4.8 Hz), 1.91-1.76 (2H, m), 0.89 (12H, d, J=6.7 Hz). ESI-MS (m/z): 333 $[M+H]^+$.

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**87a**):

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**86**) (170 mg, 0.51 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane / EtOH (1/1) using procedure described for compound (**20a**) (170 mg, 90%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.96 (0.3H, s), 14.00 (1H, s), 9.60 (0.3H, s), 7.66 (0.7H, s), 7.41 (0.7H, s), 6.75 (1H, s), 4.93 (1H, s), 3.40-3.28 (2H, m), 3.28-3.13 (6H, m), 3.13-2.99 (2H, m), 2.00-1.81 (2H, m), 0.98 (12H, d, J=6.7 H). ESI-MS (m/z): 333 $[M+H]^+$; melting point: 208-210 °C.

Example 41: N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (88) and corresponding hydrochloride salt (89a) (Scheme 17)

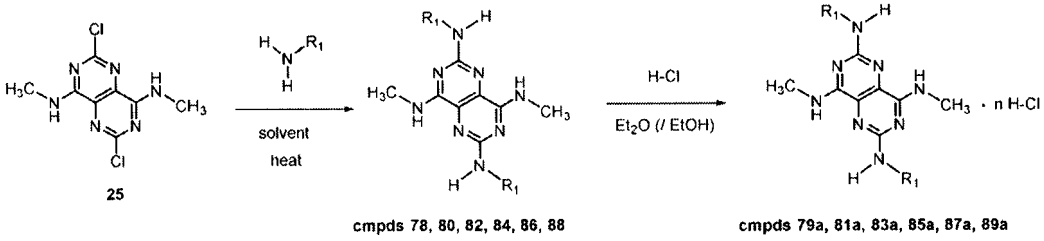
N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**88**):

A mixture of 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) (350 mg, 1.35 mmol) and allylamine (293 µL, 8.10 mmol) in *n*-butanol (5.0 mL) was heated in a closed vial at 120°C for 144 h. After cooling, a saturated $NaHCO_3$ solution (30 mL) was added and the resulting suspension was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (30 mL), and then with a brine solution (30 mL), and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was

removed; the residue was purified by flash column chromatography using gradient elution from $CHCl_3$ to $CHCl_3$/EtOAc (4:1) to give N^2,N^6-diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**88**) (151 mg, 37%). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.50-6.38 (2H, m), 6.00 (2H, ddt, J=17.1, 10.2, 5.7 Hz), 5.25 (2H, ddt, J=17.1, 1.6, 1.6 Hz), 5.11 (2H, ddt, J=10.2, 1.6, 1.6 Hz), 4.71 (2H, t, J=5.7 Hz), 4.05 (4H, ddt, J=5.7, 5.7, 1.6 Hz), 3.06 (6H, d, J=5.2 Hz). ESI-MS (m/z): 301 $[M+H]^+$.

N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**89a**):

N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**88**) (147 mg, 0.49 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (140 mg, 85%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 15.10 (1H, br s), 14.31-14.03 (0.4H, m), 9.90-9.60 (1H, m), 8.05-7.31 (1H, m), 6.73 (1.6H, s), 6.06-5.88 (2H, m), 5.36-5.12 (4H, m), 4.25-3.95 (4H, m), 3.32-2.95 (6H, m). ESI-MS (m/z): 301 $[M+H]^+$; melting point: 212-214 °C.



25 cmpds 78, 80, 82, 84, 86, 88 cmpds 79a, 81a, 83a, 85a, 87a, 89a

Scheme 17.

Example 42: 2-Chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-4,8-diamine (90), and 2,6-bis-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (91) (Scheme 18)

A mixture of 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**25**) (600 mg, 2.32 mmol), N,N'-dimethyl-hydrazine dihydrochloride (926 mg, 6.96 mmol) and N,N-diisopropylethylamine (2.6 mL, 15.08 mmol) in 1,4-dioxane (15.0 mL) was heated at 80°C for 20 h. Additional N,N'-dimethyl-hydrazine dihydrochloride (309 mg, 2.32 mmol) and N,N-diisopropylethylamine (0.87 mL, 5.03 mmol) was added, and heating was continued for 24 h. A saturated $NaHCO_3$ solution (30 mL) was added, and the suspension was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with water (75 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (97:3) to give 2-chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-

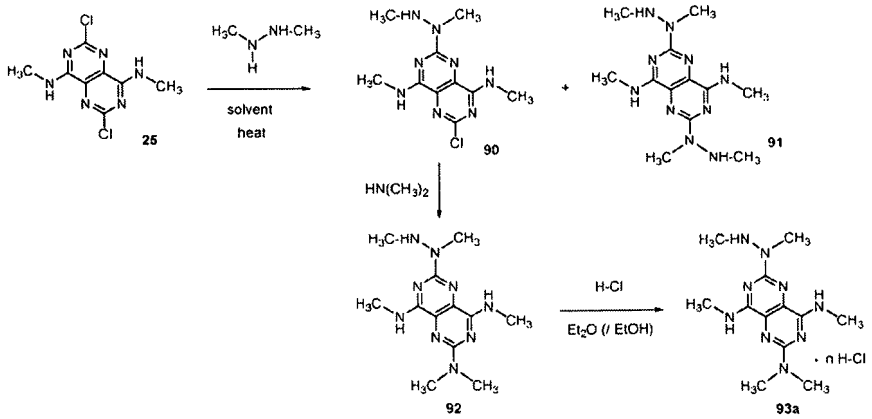
dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**90**) (310 mg, 47%y) and 2,6-bis-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**91**) (160 mg, 23%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.50-6.35 (2H, m), 5.35 (2H, s), 3.29 (6H, s), 3.11 (6H, d, J=5.0 Hz), 2.65 (6H, s). ESI-MS (m/z): 307 $[M+H]^+$; melting point: 219-221°C.

Compound (**90**): 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.67 (1H, s), 6.65 (1H, s), 5.36 (1H, s), 3.32 (3H, s), 3.16 (3H, d, J=5.2 Hz), 3.08 (3H, d, J=5.0 Hz), 2.66 (3H, s). ESI-MS (m/z): 283, 285 $[M+H]^+$.

Example 43: 6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (92) and corresponding hydrochloride salt (93a) (Scheme 18)

A mixture of 2-chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**90**) (260 mg, 0.92 mmol) and 2M dimethylamine / THF (4.6 mL, 9.20 mmol) in 1,4-dioxane (5.0 mL) was heated in a closed vial at 135°C for 20 h. The volatiles were removed, and the residue was partitioned between saturated $NaHCO_3$ solution (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water (30 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (95:5) to give 6-(N,N'-dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**92**) (180 mg, 67%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.50 (1H, s), 6.34 (1H, s), 5.38 (1H, br s), 3.28 (3H, s), 3.17 (6H, s), 3.11 (3H, d, J=5.1 Hz), 3.10 (3H, d, J=5.1 Hz), 2.65 (3H, s). ESI-MS (m/z): 292 $[M+H]^+$.

6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**92**) (170 mg, 0.58 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (155 mg, 81%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 11.0-8.0 (2H, br s), 9.08 (2H, s), 3.45 (3H, s), 3.29 (6H, s), 3.11 (3H, d, J=4.6 Hz), 3.05 (3H, d, J=4.6 Hz), 2.86 (3H, s). ESI-MS (m/z): 292 $[M+H]^+$; melting point: 273-275 °C.



25 90 91 92 93a

Scheme 18.

Example 44: N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (94) and corresponding hydrochloride salt (95a) (Scheme 19)

A NaH (60% suspension in mineral oil) (188 mg, 4.72 mmol) was added in portions to propanol (10 mL) at 0°C. The mixture was stirred for 10 min at 0°C, and then 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**54**) (250 mg, 0.89 mmol) was added. The mixture was heated at 110 °C for 16 h. The volatiles were removed and the residue was partitioned between a saturated NH_4Cl solution (30 mL) and CH_2Cl_2 (30 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration the solvent was removed and the residue was purified by flash column chromatography using PE/EtOAc (1:1) as an eluent to give N^4,N^8-dimethyl-N^2-*n*-propyl-6-propoxy-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**94**) (227 mg, 84%). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.64-6.57 (1H, m), 6.47-6.39 (1H, m), 4.82-4.75 (1H, m), 4.26 (2H, t, J=7.0 Hz), 3.40-3.34 (2H, m), 3.13 (3H, d, J=5.2 Hz), 3.07 (3H, d, J=5.2 Hz), 1.84 (2H, sextet, J=7.4 Hz), 1.63 (2H, sextet, J=7.4 Hz), 1.04 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 306 $[M+H]^+$.

N^4,N^8-Dimethyl-N^2-*n*-propyl- 6-propoxy-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**94**) (227 mg, 0.74 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (241 mg, 95%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.15-8.09 (1H, m), 7.77-7.47 (1H, m), 6.80-6.72 (1H, m), 4.29 (2H, t, J=6.9 Hz), 3.53-3.46 (2H, m), 3.21 (3H, d, J=5.2 Hz), 3.15 (3H, d, J=4.7 Hz), 1.84 (2H, sextet, J=7.4 Hz), 1.68 (2H, sextet, J=7.4 Hz), 1.04 (3H, t, J=7.4 Hz), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 306 $[M+H]^+$; melting point: 203-205 °C.

Example 45: N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (96) and corresponding hydrochloride salt (97a) (Scheme 19)

Propanethiol (89 µL, 0.98 mmol) was dissolved in DMF (4 mL) and NaHMDS in THF (1.0 M, 1.06 mL, 1.06 mmol) was added at ambient temperature. After stirring for 15 min the clear solution was added to a solution of 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**54**) (250 mg, 0.89 mmol) in DMF (6 mL). Stirring was continued for 3 h at ambient temperature, and then the reaction was heated at 60 °C for16 h. After this time, water (30 mL) was added, and the resulting suspension was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using PE/EtOAc (1:1) as an eluent to give N^4,N^8-dimethyl-N^2-*n*-propyl-N^4,N^8-dimethyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**96**) (263 mg, 92%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.55-6.47 (2H, m), 4.89-4.81 (1H, m), 3.41-3.34 (2H, m), 3.15-3.10 (5H, m), 3.07 (3H, d, J=5.2 Hz), 1.78 (2H, sextet, J=7.4 Hz), 1.63 (2H, sextet, J=7.4 Hz), 1.05 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 322 $[M+H]^+$.

N^4,N^8-Dimethyl-N^2-*n*-propyl- 6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**96**) (250 mg, 0.78 mmol) was treated with 2M HCl /diethyl ether in diethyl ether using procedure described for compound (**20a**) (262 mg, 94%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.09-8.02 (1H, m), 7.65-7.56 (1H, m), 6.87-6.81 (1H, m), 3.53-3.45 (2H, m), 3.21 (3H, d, J=5.1 Hz), 3.14 (3H, d, J=4.6 Hz), 3.14-3.08 (2H, m), 1.77 (2H, sextet, J=7.4 Hz), 1.68 (2H, sextet, J=7.4 Hz), 1.05 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 322 $[M+H]^+$; melting point: 218-220 °C.

Example 46: 6-Benzyloxy-N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (98) and corresponding hydrochloride salt (99a) (Scheme 19)

Benzyl alcohol (1.0 mL, 9.60 mmol) was added to a suspension of NaH (60% in mineral oil) (416 mg, 10.4 mmol) in 1,4-dioxane (10 mL) at 0°C. The mixture was stirred for 30 min. at 0°C, then 6-chloro- N^4,N^8-dimethyl-N^2-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**54**) (450 mg, 1.60 mmol) was added. The mixture was heated at 110 °C for 1 h. The volatiles were removed and the residue was partitioned between a saturated NH_4Cl solution (30 mL) and CH_2Cl_2 (30 mL). The aqueous phase was separated and extracted with

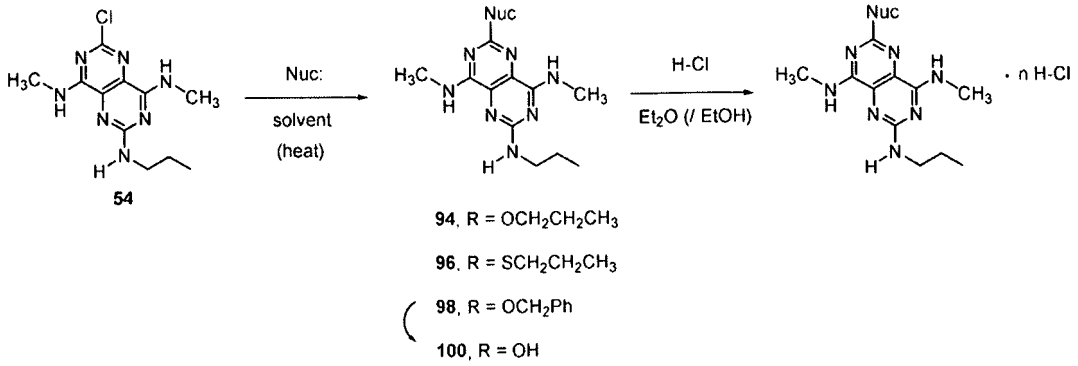
CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (9:1) to PE/EtOAc (1:9) to give N^4,N^8-dimethyl-N^2-*n*-propyl-N^4,N^8-dimethyl-6-benzyloxy-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**98**) (465 mg, 82%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.51-7.45 (2H, m), 7.38-7.32 (2H, m), 7.31-7.27 (1H, m), 6.68-6.58 (1H, m), 6.46-6.36 (1H, m), 5.39 (2H, s), 4.79 (1H, t, J=5.8 Hz), 3.37 (2H, td, J=7.3, 5.8 Hz), 3.13 (3H, d, J=5.2 Hz), 3.06 (3H, d, J=5.2 Hz), 1.7-1.58 (2H, m), 0.99 (3H, t, J=7.4 Hz). ESI-MS (m/z): 354 $[M+H]^+$.

N^4,N^8-Dimethyl-N^2-*n*-propyl- 6-benzyloxy-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**98**) (100 mg, 0.28 mmol) was treated with 2M HCl /diethyl ether in diethyl ether using procedure described for compound (**20a**) (104 mg, 95%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.27 (1H, br s), 7.76-7.59 (1H, m), 7.49-7.41 (2H, m), 7.40-7.29 (3H, m), 6.80-6.69 (1H, m), 5.41 (2H, s), 3.54-3.44 (2H, m), 3.20 (3H, d, J=5.2 Hz), 3.15 (3H, d, J=4.8 Hz), 1.74-1.62 (2H, m), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 354 $[M+H]^+$; melting point: 194-196 °C.

Example 47: 4,8-Bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ol (100) and corresponding hydrochloride salt (101a) (Scheme 19)

A mixture of N^4,N^8-dimethyl-N^2-n-propyl-6-benzyloxy-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**98**) (330 mg, 0.93 mmol) and 10% Pd/C (25 mg) in EtOAc (7 mL) was hydrogenated at atmospheric pressure for 4 h. The reaction mixture was filtered through Celite, and the Celite pad was washed with hot MeOH. The filtrate was evaporated. The residue were treated with EtOAc (80 mL) and the resultant precipitate were filtered and dried to give 4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ol (**100**) (160 mg, 65%y). 400 MHz ^{1}H NMR (CD_3OD, ppm): δ 3.36 (2H, t, J=7.0 Hz), 3.06 (3H, s), 3.01 (3H, s), 1.67-1.55 (2H, m), 0.98 (3H, t J=7.5 Hz). ESI-MS (m/z): 264 $[M+H]^+$.

4,8-Bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ol (**100**) (140 mg, 0.53 mmol) was treated with 2M HCl /EtOH in 1,4-dioxane / EtOH (1/1) using procedure described for compound (**20a**) (135 mg, 85%y). 400 MHz ^{1}H NMR (D_2O/acetic acid-d_4, ppm): δ 3.34 (2H, t, J=7.0 Hz), 3.14 (3H, s), 3.03 (3H, s), 1.63-1.50 (2H, m), 0.89 (3H, t, J=7.5 Hz). ESI-MS (m/z): 264 $[M+H]^+$; melting point: 238-240 °C.



Scheme 19.

Example 48: 4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile (102) and corresponding hydrochloride salt (103a) (Scheme 20)

To a solution of 6-chloro- N^4,N^8-dimethyl-N^2-*n*-propyl- pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (500 mg, 1.77 mmol) in DMSO (4 mL) was added KCN (243 mg, 3.73 mmol). The reaction mixture was heated at 140 °C for 40 h. The reaction mixture was poured into a saturated sodium chloride solution (100 mL). The resulting suspension was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (99:1) to PE/EtOAc (6:1) to give 4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile (**102**) (450 mg, 94%). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.74-6.55 (2H, m), 5.20-5.12 (1H, m), 3.46-3.38 (2H, m), 3.14 (3H, d, J=5.02 Hz), 3.07 (3H, d, J=4.8 Hz), 1.70-1.60 (2H, m), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 373 $[M+H]^+$.

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile (**102**) (140 mg, 0.51 mmol) was treated with 2M HCl / diethyl ether in methanol using procedure described for compound (**20a**) (125 mg, 79%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.86 (1H, s), 8.50 (1H, br s), 7.68 (1H, br s), 7.17-7.07 (1H, m), 3.57-3.50 (2H, m), 3.26 (3H, d, J=5.2 Hz), 3.17 (3H, d, J=4.8 Hz), 1.75-1.65 (2H, m), 1.01 (3H, t, J=7.4 Hz). ESI-MS (m/z): 373 $[M+H]^+$; melting point: 201-204 °C.

Example 49: N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (104) and corresponding hydrochloride salt (105a) (Scheme 20)

A mixture of 4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]

pyrimidine-2-carbonitrile (**102**) (200 mg, 0.73 mmol) and Re-Ni (50% slurry in H_2O, 75 mg) in EtOH (10 mL) was hydrogenated at 10 atm for 90 min. The reaction mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by flash column chromatography using gradient elution from CH_2Cl_2/MeOH (9/1) to (1:1) to give N^4,N^8-dimethyl-N^2-*n*-propyl-6-aminomethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**104**) (110 mg, 55%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.72-6.62 (1H, m), 6.56-6.47 (1H, m), 4.95-4.87 (1H, m), 3.87 (2H, s), 3.44-3.35 (2H, m), 3.13 (3H, d, J=5.1 Hz), 3.08 (3H, d, J=5.1 Hz), 1.83 (2H, s), 1.70-1.59 (2H, m), 1.00 (3H, t, J=7.4). MS (m/z): 277 $[M+H]^+$.

N^4,N^8-Dimethyl-N^2-*n*-propyl-N^4,N^8-dimethyl-6-aminomethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**104**) (110 mg, 0.40 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**29a**) in quantitative yield (125 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 12.76 (1H, br s), 9.08-8.62 (1H, m), 8.50 (1H, s), 7.80 (3H, br s), 4.60 (2H, s), 3.60-3.52 (2H, m), 3.29-3.17 (6H, m), 1.76-1.64 (2H, m), 0.99 (3H, t, J=7.3). ESI-MS (m/z): 277 $[M+H]^+$; melting point: 290 °C (dec.).

Example 50: 6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (106) and corresponding hydrochloride salt (107a) (Scheme 20)

A mixture of 4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d] pyrimidine-2-carbonitrile (**102**) (230 mg, 0.84 mmol) and 0.2 N NaOH (3 mL) in 1,4-dioxane (3 mL) was heated at 100 °C for 1 h. Water (15 mL) was added and the resulting suspension was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (50 mL), and then with a brine solution (50 mL), and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from $CHCl_3$/EtOAc (9:1) to $CHCl_3$/EtOAc/MeOH (4:2:1) to give 6-carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido [5,4-d]pyrimidine-2,4,8-triamine (**106**) (185 mg, 76%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.86 (1H, s), 7.06-6.88 (1H, m), 6.70-6.53 (1H, m), 6.00-5.83 (1H, m), 5.10 (1H, t, J=5.7 Hz), 3.46-3.36 (2H, m), 3.16 (3H, d, J=5.1 Hz), 3.05 (3H, d, J=5.1 Hz), 1.65 (2H, sextet, J=7.4 Hz), 1.00 (3H, t, J=7.4 Hz). MS (m/z): 291 $[M+H]^+$.

6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**106**) (150 mg, 0.52 mmol) was treated with 4M HCl /1,4-dioxane in 1,4-dioxane using procedure described for compound (**20a**) (140 mg, 82%y). 400 MHz ^{1}H NMR ($CDCl_3$/trifluoroacetic acid, ppm): δ 8.46-8.34 (1H, m), 8.23 (1H, s), 8.00-7.83 (2H, m), 7.21-

7.10 (1H, m), 3.62-3.54 (2H, m), 3.26 (3H, d, J=5.1 Hz), 3.21 (3H, s), 1.71 (2H, sextet, J=7.4 Hz), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 291 $[M+H]^+$; melting point: > 300 °C.

Example 51: 4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid (108) (Scheme 20)

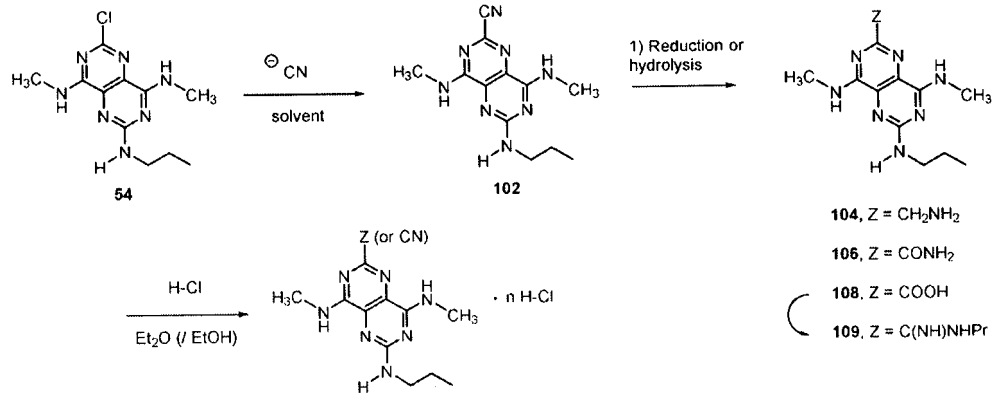
A mixture of 4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d] pyrimidine-2-carbonitrile (**102**) (300 mg, 1.10 mmol) and 2N NaOH (3 mL) in 1,4-dioxane (3 mL) was heated at 105 °C for 20 h. The reaction mixture was acidified (pH 4) with 5% $KHSO_4$ solution. A white precipitate formed upon addition of CH_2Cl_2 (10 mL), and it was filtered and then purified by reverse phase chromatography using gradient elution from 0.1% HCOOH to 95% MeCN in 0.1% HCOOH to give 4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid (**108**) (130 mg, 41%y). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 8.24 (1H, br s), 7.82 (1H, br s), 7.24 (1H, s), 3.02 (6H, d, J=4.8 Hz), 3.04-2.81 (2H, m), 1.64-1.48 (2H, m), 0.91 (3H, t, J=7.4 Hz). ESI-MS (m/z): 292 $[M+H]^+$; melting point: 218-220 °C.

Example 52: N-(*n*-Propyl)-[4,8-Bis-methylamino-6-n-propylamino-pyrimido[5,4-d] pyrimidin-2-yl]-amidine (109) and corresponding hydrochloride salt (110a) (Scheme 20)

A mixture of 4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d] pyrimidine-2-carbonitrile (**102**) (270 mg mg, 0.99 mmol), NaOAc (123 mg, 1.5 mmol) and *n*-propylamine (124 µL, 1.5 mmol) in MeOH (5 mL) was heated at 110 °C for 2 h. The volatiles were removed and the residue was partitioned between a saturated $NaHCO_3$ solution (15 mL) and $CHCl_3$ (15 mL). The aqueous phase was separated and extracted with $CHCl_3$ (2 x 15 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed, and the residue was purified reverse phase chromatography using gradient elution from 10% MeOH in water to 95% MeOH to give N-(*n*-propyl)-[4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-amidine (**109**) (160 mg, 49%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.3-7.8 (1H, br s), 6.75-6.65 (1H, m), 6.63-6.52 (2H, m), 5.01 (1H, t, J=5.6 Hz), 3.52-3.37 (4H, m), 3.18 (3H, d, J=5.2 Hz), 3.11 (3H, d, J=5.2 Hz), 1.78-1.69 (2H, m), 1.69-1.60 (2H, m), 1.03 (3H, t, J=7.5 Hz), 1.01 (3H, t, J=7.5 Hz). ESI-MS (m/z): 332 $[M+H]^+$.

N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl]-amidine (**109**) (150 mg, 0.45 mmol) was treated with 2M HCl / diethyl ether

in 1,4-dioxane using procedure described for compound (**20a**) (160 mg, 97%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 10.09 (1H, s), 9.87-9.46 (1H, m), 9.19-8.62 (2H, m), 6.71 (1H, s), 5.14 (1H, s), 3.93-3.80 (2H, m), 3.51-3.34 (2H, m), 3.21-3.03 (6H, m), 1.90-1.77 (2H, m), 1.71-1.60 (2H, m), 1.04 (3H, t, J=7.4 Hz), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 332 $[M+H]^+$; melting point: 172 °C (dec.).



Scheme 20.

Example 53: N^4,N^8-Dimethyl-N^2-*n*-Propyl-6-(4-fluorophenyl)-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (111) and corresponding hydrochloride salt (112a) (Scheme 21)

A mixture of 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (190 mg, 0.67 mmol), 4-fluorophenylboronic acid (141 mg, 1.01 mmol), 2M Na_2CO_3 solution (1.5 mL) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) in dimethoxyethane was heated at 105 °C for 4 h under argon atmosphere. The reaction mixture was cooled, water (15 mL) was added, and the resulting suspension was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (30 mL), and then with a brine solution (30 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (9:1) to PE/EtOAc (2:1) to give N^4,N^8-dimethyl-N^2-*n*-propyl-6-(4-fluoro-phenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**111**) (125 mg, 55%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.48-8.42 (2H, m), 7.15-7.07 (2H, m), 6.83-6.75 (1H, m), 6.56-6.48 (1H, m), 4.94 (1H, t, J=5.6 Hz), 3.46-3.39 (2H, m), 3.24 (3H, d, J=5.0 Hz), 3.13 (3H, d, J=5.0 Hz), 1.72-1.62 (2H, m), 1.02 (3H, t, J=7.4 Hz). ESI-MS (m/z): 342 $[M+H]^+$.

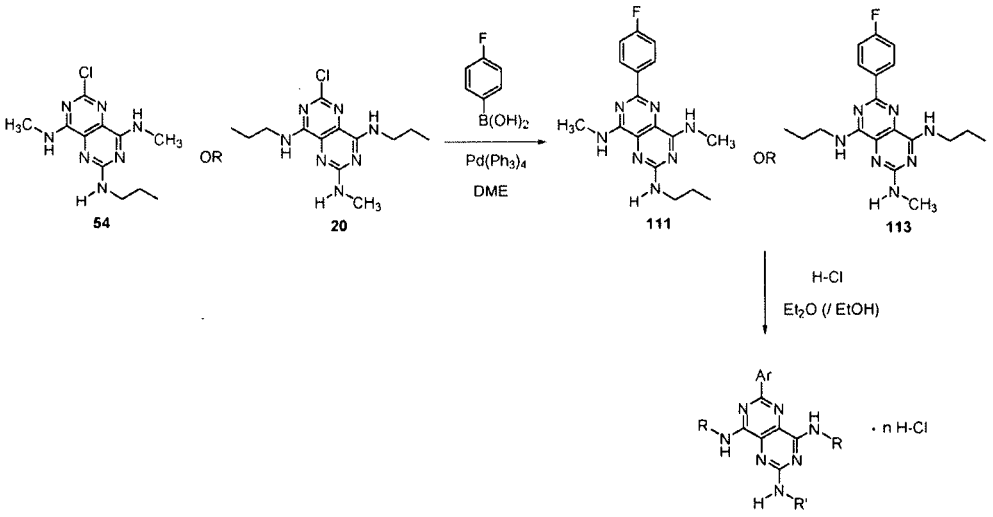
N^4,N^8-Dimethyl-N^2-*n*-propyl- 6-(4-fluoro-phenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**111**) (100 mg, 0.29 mmol) was treated with 2M HCl /diethyl ether in diethyl

ether /methanol (10/1) using procedure described for compound (**29a**) in quantitative yield (110 mg, ~100%y). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 13.2-12.7 (1H, br s), 9.60 (1H, br s), 8.66-8.59 (2H, m), 8.30 (1H, br s), 7.60 (1H, br s), 7.39-7.30 (2H, br s), 3.60-3.30 (2H, m, overlapped with water), 3.17-3.07 (6H, m), 1.70-1.60 (2H, m), 0.96 (3H, t, J=7.3 Hz). ESI-MS (m/z): 342 $[M+H]^+$; melting point: 270 °C (dec.).

Example 54: N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluoro-phenyl)-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (113) and corresponding hydrochloride salt (114a) (Scheme 21)

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) (250 mg, 0.81 mmol) and 4-fluorophenylboronic acid (166 mg, 1.2 mmol) were reacted using procedure described for compound (**111**) to produce N^2-methyl-N^4,N^8-di-*n*-propyl-6-(4-fluoro-phenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**113**) (200 mg, 67%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.46-8.40 (2H, m), 7.15-7.08 (2H, m), 6.83 (1H, t, J=5.7 Hz), 6.60 (1H, t, J=5.7 Hz), 4.91-4.82 (1H, m), 3.69-3.62 (2H, m), 3.56-3.49 (2H, m), 3.03 (3H, d, J=5.1 Hz), 1.84-1.69 (4H, m), 1.06 (3H, t, J=7.5 Hz), 1.04 (3H, t, J=7.5 Hz). ESI-MS (m/z): 370 $[M+H]^+$.

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**113**) (190 mg, 0.51 mmol) was treated with 2M HCl /diethyl ether in ethanol using procedure described for compound (**29a**) (207 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.42-8.35 (2H, m), 7.98-7.88 (1H, m), 7.88-7.79 (1H, m), 7.19-7.10 (2H, m), 6.99-6.88 (1H, m), 3.75-3.62 (4H, m), 3.11 (3H, d, J=4.8 Hz), 1.92-1.75 (4H, m), 1.08 (6H, t, J=7.4 Hz). ESI-MS (m/z): 370 $[M+H]^+$; melting point: 277-279 °C.



Scheme 21.

Example 55: N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (115) and corresponding hydrochloride salt (116a)

A mixture of 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (440 mg, 1.42 mmol), triethylamine (185 µL, 1.32 mmol) and 10% Pd/C (160 mg) in EtOH (10 mL) was hydrogenated at 10 atmospheres for 24 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The residue was dissolved in EtOAc (80 mL), washed with water (3 x 30 mL), and then with a brine solution (30 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed; the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (9:1) to PE/EtOAc (1:2) to give N^4,N^8-dimethyl-N^2-*n*-propyl- pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**115**) (185 mg, 84%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.26 (1H, s), 6.65 (1H, br s), 6.55 (1H, br s), 4.96 (1H, t, J=5.4 Hz), 3.44-3.37 (2H, m), 3.14 (3H, d, J=5.1 Hz), 3.07 (3H, d, J=5.0 Hz), 1.70-1.59 (2H, m), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 248 $[M+H]^+$.

N^4,N^8-Dimethyl-N^2-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**115**) (175 mg, 0.71 mmol) was treated with 2M HCl /diethyl ether in diethyl ether using procedure described for compound (**29a**) in quantitative yield (200 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.97-8.60 (2H, m), 8.43 (1H, s), 7.02-6.94 (1H, m), 3.52 (2H, td, J=6.8, 6.4 Hz), 3.24 (3H, d, J=5.1 Hz), 3.22 (3H, d, J=4.7 Hz), 1.75-1.64 (2H, m), 1.01 (3H, t, J=7.4 Hz). ESI-MS (m/z): 248 $[M+H]^+$; melting point: 180-182 °C.

Example 56: 6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (117) and corresponding hydrochloride salt (118a)

A mixture of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (400 mg, 1.29 mmol), butylboronic acid (223 mg, 2.19 mmol), K_2CO_3 (535 mg, 3.87 mmol), Ag_2O (748 mg, 3.23 mmol) and $Pd(dppf)Cl_2xCH_2Cl_2$ (114 mg, 0.14 mmol) in THF (1.0 mL) and 1,4-dioxane (7.0 mL) was heated at 115 °C for 20 h under argon atmosphere. Butylboronic acid (120 mg, 1.18 mmol) and $Pd(dppf)Cl_2xCH_2Cl_2$ (60 mg, 0.07 mmol) were added and heating was continued for 48 h. The reaction mixture was cooled and filtered through Celite. A saturated $NaHCO_3$ solution (20 mL) was added to the filtrate and the resulting suspension was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water (30 mL) and dried over solid anhydrous

Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (20:1) to PE/EtOAc (5:2) to give 6-*n*-butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**117**) (240 mg, 56%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.78-6.65 (1H, m), 6.52-6.42 (1H, m), 4.82-4.71 (1H, m), 3.57-3.50 (2H, m), 3.50-3.43 (2H, m), 2.99 (3H, d, J=5.1 Hz), 2.75-2.68 (2H, m), 1.83-1.65 (6H, m), 1.46-1.36 (2H, m), 1.01 (3H, t, J=7.3 Hz), 1.00 (3H, t, J=7.3Hz), 0.95 (3H, t, J=7.4 Hz). ESI-MS (m/z): 332 $[M+H]^+$.

6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**117** (230 mg, 0.69 mmol) was treated with 2M HCl /diethyl ether in diethyl ether using procedure described for compound (**29a**) (255 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.84-7.54 (2H, m), 6.88 (1H, br s), 3.71-3.51(4H, m), 3.08 (3H, d, J=4.5 Hz), 2.83-2.63 (2H, m), 1.85-1.70 (6H, m), 1.47-1.34 (2H, m), 1.09-0.99 (6H, m), 0.95 (3H, t, J=7.3). ESI-MS (m/z): 332 $[M+H]^+$; melting point: 125-127 °C.

Example 57: 6-Methoxy-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (119) and corresponding hydrochloride salt (120a)

A mixture of 6-chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d] pyrimidine-2,4,8-triamine (**20**) (300 mg, 0.97 mmol) and NaOMe (4M in MeOH; 620μL) in methanol (5 mL) was heated at 105 °C for 48 h. The volatiles were removed and the residue was partitioned between a saturated NH_4Cl solution (30 mL) and CH_2Cl_2 (30 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (50 mL) and and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (97:3) to give 6-methoxy-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**119**) (225 mg, 76%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.72-6.63 (1H, m), 6.51-6.43 (1H, m), 4.75-4.67 (1H, m), 3.95 (3H, s), 3.57-3.50 (2H, m), 3.50-3.44 (2H, m), 2.99 (3H, d, J=5.0 Hz), 1.77-1.64 (4H, m), 1.01 (3H, t, J=7.4 Hz), 1.00 (3H, t, J=7.4 Hz). ESI-MS (m/z): 306 $[M+H]^+$.

6-Methoxy-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**119**) (210 mg, 0.69 mmol) was treated with 2M HCl /diethyl ether in ethanol using procedure described for compound (**29a**) (235 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 8.38 (1H, s), 8.05 (1H, br s), 6.70 (1H, s), 4.00 (3H, m), 3.68-3.61 (4H, m), 3.08 (3H,

d, J=4.1 Hz), 1.87-1.70 (4H, m), 1.04 (3H, t, J=7.3 Hz), 1.03 (3H, t, J=7.3 Hz). ESI-MS (m/z): 306 $[M+H]^+$; melting point: 201-204 °C.

Example 58: 6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile (121) and corresponding hydrochloride salt (122a)

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine (**20**) (250 mg, 0.81 mmol) and KCN were reacted the using procedure described for compound (**102**) to produce 6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine-2-carbonitrile (**121**) (170 mg, 70%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.71 (1H, br s), 6.64 (1H, br s), 5.10-5.03 (1H, m), 3.57-3.51 (2H, m), 3.51-3.42 (2H, m), 3.02 (3H, d, J=5.0 Hz), 1.77-1.64 (4H, m), 1.02 (3H, t, J=7.4 Hz), 1.01 (3H, t, J=7.4 Hz). ESI-MS (m/z): 301 $[M+H]^+$.

6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile (**121**) (160 mg, 0.53 mmol) was treated with 2M HCl /diethyl ether in methanol using procedure described for compound (**20a**) (130 mg, 73%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.91 (0.8H, s), 14.64 (0.2H, s), 8.44 (0.8H, s), 8.34 (0.2H, s), 7.71-7.56 (1H, m), 7.07 (0.8H, s), 6.88 (0.2H, s), 3.69-3.63 (2H, m), 3.63-3.54 (2H, m), 3.16-3.07 (3H, m), 1.86-1.72 (4H, m), 1.06 (3H, t, J=7.4 Hz), 1.04 (3H, t, J=7.4 Hz). ESI-MS (m/z): 301 $[M+H]^+$; melting point: 204-206 °C.

Example 59: N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (124) and corresponding hydrochloride salt(125a)

2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**123**):

A 2M ethylamine/THF (6.69 mL, 13.38 mmol) solution was added to a solution of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine (**1**) (800 mg, 2.96 mmol) in THF (10 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 h. Water (30 mL) was added and the resultant precipitate was filtered, washed with water (10 mL) and dried over P_2O_5 to give 2,6-dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**123**) (745 mg, 88%). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.87 (2H, br s), 3.63 (4H, qd, J=7.3, 5.9 Hz), 1.32 (6H, t, J=7.3 Hz). ESI-MS (m/z): 287, 289, 291 $[M+H]^+$.

N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**124**):

A mixture of 2,6-dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**123**) and ethylamine (70% water solution, 2.00 mL) in *n*-butanol (3 mL) was heated

at 100°C for 44 h. The volatiles were removed by evaporation and the residue was partitioned between CH_2Cl_2 (20 mL) and a saturated $NaHCO_3$ solution (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (98:2) to give N^2,N^4,N^6,N^8-tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**124**) (233 mg, 91%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.42 (2H, s), 4.58 (2H, s), 3.57-3.48 (4H, m), 3.46-3.39 (4H, m), 1.28 (6H, t, J=7.3 Hz), 1.23 (6H, t, J=7.3 Hz). ESI-MS (m/z): 305 $[M+H]^+$.

N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**125a**):

N^2,N^4,N^6,N^8-tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**124**) (220 mg, 0.72 mmol) was treated with 4M HCl /1,4-dioxane in 1,4-dioxane/ EtOH (1/1) using procedure described for compound (**29a**) (245 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 9.63 (2H, s), 6.67 (2H, t, J=5.6 Hz), 3.74-3.66 (4H, m), 3.57-3.50 (4H, m), 1.41 (6H, t, J=7.3 Hz), 1.27 (6H, t, J=7.3 Hz). ESI-MS (m/z): 305 $[M+H]^+$; melting point: 247 °C (dec.).

Example 60: N^4,N^8-Diethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (126) and corresponding hydrochloride salt (127a)

A mixture of 2,6-dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**123**) (245 mg, 0.85 mmol) and *n*-propylamine (352 µL, 4.27 mmol) in n-butanol (5.0 mL) was heated at 130°C for 44 h. The volatiles were removed by evaporation, and the residue was partitioned between CH_2Cl_2 (20 mL) and a saturated $NaHCO_3$ solution (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOH (98:2) to give N^4,N^8-diethyl-N^2,N^6-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**126**) (220 mg, 78%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.48-6.37 (2H, m), 4.64 (2H, s), 3.57-3.48 (4H, m), 3.39-3.32 (4H, m), 1.67-1.57 (4H, m), 1.32-1.24 (6H, m), 1.02-0.96 (6H, m). ESI-MS (m/z): 333 $[M+H]^+$.

N^4,N^8-Diethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**126**) (220 mg, 0.66 mmol) was treated with 4M HCl /1,4-dioxane in 1,4-dioxane/

EtOH (1/1) using procedure described for compound (**29a**) (244 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 9.58 (2H, s), 6.75-6.68 (2H, m), 3.74-3.64 (4H, m), 3.49-3.41 (4H, m), 1.71-1.63 (4H, m), 1.41 (6H, t, J=7.2 Hz), 0.98 (6H, t, J=7.4 Hz). ESI-MS (m/z): 333 $[M+H]^+$; melting point: 248 °C (dec.).

Example 61: N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (128) and corresponding hydrochloride salt (129a)

A mixture of 2,6-dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**123**) (245 mg, 0.85 mmol) and cyclopropylmethylamine (370 µL, 4.27 mmol) in *n*-butanol (5.0 mL) was heated in a closed vial at 130°C for 44 h. The volatiles were removed by evaporation, and the residue was partitioned between CH_2Cl_2 (20 mL) and a saturated $NaHCO_3$ solution (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/MeOH (9:1) to give N^2,N^6-bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**128**) (135 mg, 45%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.03-6.98 (2H, m), 6.10-6.03 (2H, m), 3.48-3.40 (4H, m), 3.21-3.14 (4H, m), 1.20-1.13 (6H, m), 1.09-1.02 (2H, m), 0.44-0.36 (4H, m), 0.23-0.18 (4H, m). ESI-MS (m/z): 357 $[M+H]^+$.

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**128**) (135 mg, 0.66 mmol) was treated with 4M HCl /1,4-dioxane in 1,4-dioxane/ EtOH (1/1) using procedure described for compound (**29a**) (148 mg, ~100%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 9.66 (2H, s), 6.78 (2H, s), 3.76-3.64 (4H, m), 3.39-3.36 (4H, m), 1.45-1.38 (6H, m), 1.13-1.04 (2H, m), 0.63-0.56 (4H, m), 0.31-0.26 (4H, m). ESI-MS (m/z): 357 $[M+H]^+$; melting point: 243-245 °C.

Example 62: N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (131) and corresponding hydrochloride salt (132a)

2,6-Dichloro-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**130**):

Cyclopropylmethylamine (802 µL, 9.25 mmol) was added to a solution of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine (**1**) (500 mg, 1.85 mmol) in THF (8 mL) at 0°C. The reaction mixture was stirred at room temperature for 3 h. Water (30 mL) was then

added and the resulting suspension was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was triturated with diethyl ether. The resultant precipitate were filtered and dried to give 2,6-dichloro-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**130**) (480 mg, 76%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.96 (2H, t, J=5.7 Hz), 3.42 (4H, dd, J=7.3, 5.7 Hz), 1.16-1.05 (2H, m), 0.66-0.53 (4H, m), 0.38-0.25 (4H, m). ESI-MS (m/z): 339, 341, 343 $[M+H]^+$.

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**131**):

A mixture of 2,6-dichloro-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**130**) (220 mg, 0.65 mmol) and ethylamine (70% water solution, 1.00 mL) in 1,4-dioxane (5.0 mL) was heated at 130°C for 144 h. The volatiles were removed by evaporation, and the residue was partitioned between CH_2Cl_2 (20 mL) and a saturated $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (5:1) to PE/EtOAc (1:1) to give N^2,N^6-diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**131**) (190 mg, 82%). 400 MHz ^{1}H NMR (DMSO-d_6+TFA, ppm): δ 3.45-3.32 (8H, m), 1.17-1.08 (8H, m), 0.52-0.45 (4H, m), 0.31-0.25 (4H, m). ESI-MS (m/z): 357 $[M+H]^+$.

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**132a**):

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**131**) (170 mg, 0.45 mmol) was treated with 2M HCl / diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (140 mg, 74%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 14.90 (0.5H, s), 13.94 (1H, s), 9.70 (0.5H, s), 7.84 (0.5H, s), 7.53 (1H, s), 6.71 (1H, m), 4.80 (0.5H, s), 3.61-3.31 (8H, m), 1.33-1.08 (8H, m), 0.72-0.52 (4H, m), 0.44-0.28 (4H, m). ESI-MS (m/z): 357 $[M+H]^+$; melting point: 198-200 °C.

Example 63: N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (134) and corresponding hydrochloride salt (135a)

6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**133**):

A mixture of 2,6-dichloro-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**130**) (235 mg, 0.71 mmol) and ethylamine (70% water solution, 1.00 mL) in *n*-butanol (5.0 mL) was heated at 80°C for 18 h. The volatiles were removed by evaporation and the residue was partitioned between CH_2Cl_2 (20 mL) and a saturated $NaHCO_3$ solution (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed to give 6-chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**133**) (247 mg, 100%). ESI-MS (m/z): 348, 350 $[M+H]^+$.

N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**134**):

A mixture of 6-chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**133**) (243 mg, 0.70 mmol) and diethylamine (1.0 mL) in *n*-butanol (4.0 mL) was heated in a closed vial at 130°C for 110 h. The volatiles were removed by evaporation and the residue was partitioned between CH_2Cl_2 (35 mL) and a saturated $NaHCO_3$ solution (30 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (40 mL) and dried over solid anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (9:1) to PE/EtOAc (1:1) to give N^2,N^2,N^6-triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**134**) (210 mg, 78%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.74-6.29 (2H, m), 4.49 (1H, br s), 3.72-3.55 (4H, m), 3.51-3.26 (6H, m), 1.29-1.08 (11H, m), 0.62-0.48 (4H, m), 0.38-0.25 (4H, m). ESI-MS (m/z): 385 $[M+H]^+$.

N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**135a**):

N^2,N^2,N^6-triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**134**) (190 mg, 0.49 mmol) and 2M HCl / diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (170 mg, 82%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.91 (1H, s), 7.73 (1H, s), 7.56-7.47 (1H, m), 6.71-6.60 (1H, m), 3.60 (4H, q, J= 7.1 Hz), 3.55-3.45 (4H, m), 3.40 (2H, dd, J=7.0, 5.2 Hz), 1.27-1.11 (2H, m), 1.25 (3H, t, J=7.0 Hz), 1.19 (6H, t, J=7.2 Hz), 0.66-0.60 (2H, m), 0.60-0.54 (2H, m), 0.38-0.29 (4H, m). ESI-

MS (m/z): 385 $[M+H]^+$; melting point: 215-217 °C.

Example 64: N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (136) and corresponding hydrochloride salt (137a)

2,6-Dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-4,8-diamine (**2**) (250 mg, 0.79 mmol) and ethylamine (70% water solution) were reacted using procedure described for compound (**32**) to produce N^2,N^6-diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (**136**) (175 mg, 67%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.48 (2H, s), 4.55 (2H, s), 3.49-3.38 (8H, m), 1.69 (4H, sextet, J=7.4 Hz), 1.23 (6H, t, J=7.4 Hz), 1.00 (6H, t, J=7.4 Hz). ESI-MS (m/z): 333 $[M+H]^+$.

N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**136**) (160 mg, 0.48 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (155 mg, 87%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.92 (1H, s), 7.69 (1H, s), 7.47 (1H, s), 6.67 (1H, s), 4.80 (1H, s), 3.64-3.30 (8H, m), 1.82-1.68 (4H, m), 1.29-1.18 (6H, m), 1.02 (6H, t, J=7.4 Hz). ESI-MS (m/z): 333 $[M+H]^+$; melting point: 190-192 °C.

Example 65: N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (138)

A mixture of 2,6-dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-4,8-diamine (**2**) (300 mg, 0.95 mmol) and cyclopropylamine (396 µL, 5.71 mmol) in *n*-butanol (3.0 mL) was heated in a closed vial at 130°C for 72 h. An additional portion of cyclopropylamine (263 µL, 3.80 mmol) was added and heating was continued for 48 h at 130°C. The volatiles were removed by evaporation and the residue was partitioned between CH_2Cl_2 (35 mL) and a saturated $NaHCO_3$ solution (30 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (40 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2/EtOAc (1:1) to give N^2,N^6-dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**138**) (66 mg, 19%y). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 6.93-6.88 (2H, m), 6.36-6.33 (2H, m), 3.41-3.34 (4H, m), 2.85-2.77 (2H, m), 1.60 (4H, sextet, J=7.3 Hz), 0.90 (6H, t, J=7.3 Hz), 0.64-0.57 (4H, m), 0.46-0.41 (4H, m). ESI-MS (m/z): 357 $[M+H]^+$; melting point: 210-212 °C.

Example 66: N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-2,4,6,8-tetraamine (139) and corresponding hydrochloride salt (140a)

A mixture of 2,6-dichloro-N,N'-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**2**) (300 mg, 0.95 mmol) and cyclopropylmethylamine (1.0 mL, 11.53 mmol) in DMSO (1.0 mL) was heated in a closed vial at 145°C for 22 h. Water (10 mL) was added and the resultant precipitate were filtered and dried to give N^2,N^6-bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**139**) (320 mg, 88%y). 400 MHz ^{1}H NMR (DMSO-d6/trifluoroacetic acid, ppm): δ 9.0-7.0 (4H, br s), 3.50-3.40 (4H, m), 3.26 (4H, d, J=7.0 Hz), 1.69-1.58 (4H, m), 1.13-1.02 (2H, m), 0.93 (6H, t, J=7.4 Hz), 0.50-0.38 (4H, m), 0.31-0.19 (4H, m). ESI-MS (m/z): 385 $[M+H]^+$.

N^2,N^6-bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**139**) (280 mg, 0.73 mmol) was treated with 2M HCl /diethyl ether in ethanol using procedure described for compound (**29a**). The product was crystallized from ethanol to give N^2,N^6-bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (305 mg, 99%). 400 MHz ^{1}H NMR (DMSO-d_6, ppm): δ 9.3-6.7 (4H, m), 3.52-3.36 (4H, m), 3.28 (4H, d, J=6.8 Hz), 1.65 (4H, sextet, J=7.3 Hz), 1.15-1.04 (2H, m), 0.95 (6H, t, J=7.3 Hz), 0.54-0.40 (4H, m), 0.35-0.24 (4H, m). ESI-MS (m/z): 385 $[M+H]^+$; melting point: 221-224 °C.

Example 67: N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (141) and corresponding dihydrochloride (142a)

A mixture of 2,6-dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-4,8-diamine (**2**) (300 mg, 0.95 mmol) and 2M dimethylamine / THF (4.75 mL, 9.50 mmol) in *n*-butanol (5.0 mL) was heated in a closed vial at 110°C for 40 h. The volatiles were removed and the residue was partitioned between a saturated $NaHCO_3$ solution (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water (30 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (9:1) to PE/EtOAc (1:1) to give N^2,N^2,N^6,N^6-tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**141**) (280 mg, 89%y). ESI-MS (m/z): 333 $[M+H]^+$.

N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-

2,4,6,8-tetraamine (**141**) (270 mg, 0.81 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane/ethanol (3/1) using procedure described for compound (**3a**) (270 mg, 82%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 12.24 (2H, br s), 11.57 (2H, s), 3.67-3.56 (4H, m), 3.45 (12 H, s), 1.90-1.77 (4H, m), 1.01 (6H, t, J=7.3 Hz). ESI-MS (m/z): 333 $[M+H]^+$; melting point: 240-242 °C. Anal. Calcd for $C_{16}H_{30}Cl_2N_8$: C, 47.41; H, 7.46; N, 27.64. Found: C, 47.33; H, 7.46; N, 27.45.

Example 68: N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (144) and corresponding hydrochloride salt (145a)

N^4,N^8-Diallyl-2,6-dichloro-pyrimido[5,4-d]pyrimidine-4,8-diamine (**143**):

To a solution of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine (**1**) (700 mg, 2.59 mmol) in THF (20 mL), allylamine (815 µL, 10.89 mmol) in THF (5 mL) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 90 min and then at room temperature for 30 min. A saturated $NaHCO_3$ solution (30 mL) was added and the resulting suspension was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with water (50 mL), and then with a brine solution (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed to give N^4,N^8-diallyl-2,6-dichloro-pyrimido[5,4-d]pyrimidine-4,8-diamine (**143**) (730 mg, 91%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.00-6.91 (2H, m), 5.95 (2H, ddt, J=17.2, 10.2, 5.8 Hz), 5.32 (2H, ddt, J=17.2, 1.5, 1.5 Hz), 5.25 (2H, ddt, J=10.2, 1.5, 1.5 Hz), 4.23 (4H, ddt, J=5.8, 5.8, 1.5 Hz). ESI-MS (m/z): 311, 313, 315 $[M+H]^+$.

N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**144**):

A mixture of N^4,N^8-diallyl-2,6-dichloro-pyrimido[5,4-d]pyrimidine-4,8-diamine (**143**) (350 mg, 1.12 mmol) and methylamine (40% water solution, 1.0 mL) in *n*-butanol (1.0 mL) was heated in a closed vial at 130°C for 40 h. The reaction mixture was cooled, a saturated $NaHCO_3$ solution (30 mL) was added and the resulting suspension was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (30 mL), and then with a brine solution (30 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the product was purified by flash column chromatography using gradient elution from PE/EtOAc (20:1) to PE/EtOAc (1:2) to give N^4,N^8-diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**144**) (225 mg, 67%). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.57 (2H, s), 6.05-5.93 (2H, m), 5.32-5.23 (2H, m), 5.19-5.14 (2H, m), 4.61 (2H, s), 4.19-4.12 (4H, m), 2.96 (6H, d, J=5.1 Hz). ESI-MS (m/z): 301 $[M+H]^+$.

N^4,N^8-Diallyl-N^2,N^6-dimethyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine hydrochloride (**145a**):

N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**144**) (220 mg, 0.73 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane/ethanol (1/1) using procedure described for compound (**20a**) (130 mg, 89%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 15.22-15.01 (0.2H, m), 14.30-14.02 (0.8H, m), 9.90-9.62 (0.2H, m), 7.90-7.75 (0.8H, m), 7.66-7.49 (1H, m), 6.66 (1H, s), 6.06-5.88 (2H, m), 5.44-5.10 (4H, m), 4.86 (1H, m), 4.36-4.08 (4H, m), 3.13-2.88 (6H, m). ESI-MS (m/z): 301 $[M+H]^+$; melting point: 224-226 °C.

Example 69: N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (147) and corresponding dihydrochloride salt (148a) (Scheme 22)

6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**146**):

A mixture of 2,6-dichloro-N^4,N^8-diallyl-pyrimido[5,4-d]pyrimidine-4,8-diamine (**143**) (311 mg, 1.00 mmol) and allylamine (340 µL, 4.50 mmol) in *n*-butanol (1.0 mL) was heated in a closed vial at 70°C for 16 h. A saturated $NaHCO_3$ solution (20 mL) was added and resulting suspension was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (50 mL), and then with a brine solution (30 mL), and dried over solid anhydrous Na_2SO_4. After filtration, the product was purified by flash column chromatography using gradient elution from PE/EtOAc (20:1) to PE/EtOAc (1:2) to give 6-chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**146**) (230 mg, 69%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.76 (1H, t, J=5.8 Hz), 6.61 (1H, t, J=5.8 Hz), 6.04-5.89 (3H, m), 5.33-5.12 (6H, m), 5.01 (1H, t, J=5.7 Hz), 4.22 (2H, ddt, J=5.8, 5.8, 1.5 Hz), 4.14 (2H, ddt, J=5.8, 5.8, 1.5 Hz), 4.07 (2H, ddt, J=5.7, 5.7, 1.6 Hz). ESI-MS (m/z): 332, 334 $[M+H]^+$.

N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**147**):

A mixture of 6-chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**146**) (175 mg, 0.53 mmol) and 1-(4-fluorobenzyl)-piperazine (206 mg, 1.06 mmol) in *n*-butanol (5.0 mL) was heated in a closed vial at 70°C for 60 h. A saturated $NaHCO_3$ solution (20 mL) was added and resulting suspension was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with water (50 mL), and then with a brine

solution (30 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the product was purified by flash column chromatography using gradient elution from PE/EtOAc (20:1) to PE/EtOAc (2:1) to give N^2,N^4,N^8-triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**147**) (210 mg, 81%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.36-7.28 (2H, m), 7.05-6.96 (2H, m), 6.51 (2H, br s), 6.05-5.88 (3H, m), 5.32-5.20 (3H, m), 5.20-5.06 (3H, m), 4.69 (1H, br s), 4.20-4.10 (4H, m), 4.09-4.01 (2H, m), 3.82-3.70 (4H, m), 3.51 (2H, s), 2.53-2.42 (4H, m). ESI-MS (m/z): 490 $[M+H]^+$.

N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine dihydrochloride(**148a**):

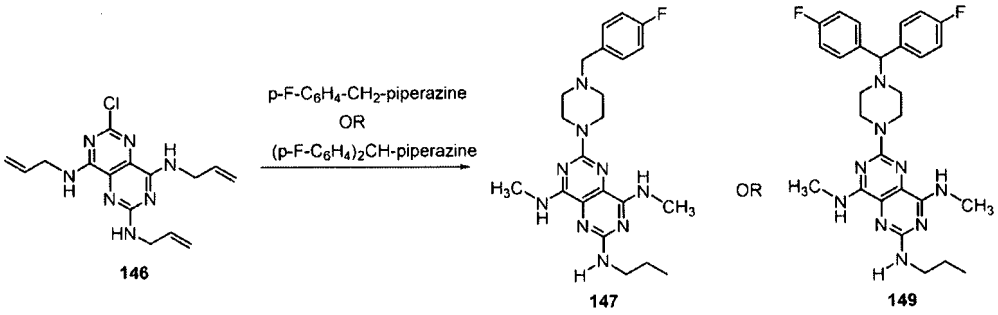
N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**147**) (200 mg, 0.41 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) (105 mg, 45%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 7.19-7.10 (2H, m), 6.91-6.79 (1H, m), 5.99-5.79 (3H, m), 5.35-5.24 (4H, m), 5.23-5.14 (2H, m), 4.79-4.68 (2H, m), 4.31-4.20 (2H, m), 4.20-4.05 (6H, m), 3.88-3.75 (2H, m), 3.51-3.37 (2H, m), 2.84-2.69 (2H, m). ESI-MS (m/z): 490 $[M+H]^+$; melting point: 239-241 °C.

Example 70: N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (149 and corresponding dihydrochloride salt (150a) (Scheme 22)

6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**146**) (230 mg, 0.69 mmol) and 1-[bis-(4-fluorophenyl)-methyl]-piperazine were reacted using procedure described for compound (**147**) to produce N^2,N^4,N^8-triallyl-6-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**149**) (260 mg, 64%y). 300 MHz ^{1}H-NMR ($CDCl_3$, ppm): δ 7.43-7.33 (4H, m), 7.04-6.93 (4H, m), 6.68-6.27 (2H, m), 6.07-5.86 (3H, m), 5.31-5.19 (3H, m), 5.19-5.06 (3H, m), 4.80-4.55 (1H, m), 4.24 (1H, m), 4.19-4.08 (4H, m), 4.08-3.99 (2H, m), 3.82-3.68 (4H, m), 2.49-2.35 (4H, m). ESI-MS (m/z): 584 $[M+H]^+$.

N^2,N^4,N^8-triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d]pyrimidine-2,4,8-triamine (**149**) (250 mg, 0.43 mmol) was treated with 2M HCl /diethyl ether in 1,4-dioxane using procedure described for compound (**20a**) in 85% yield (240 mg, 85%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.64 (1H, s), 8.11 (1H, s), 8.05-7.88 (4H, m), 7.47 (1H, s), 7.18-7.07 (4H, m), 6.81 (1H, t, J=5.7 Hz), 5.97-5.78 (3H, m),

5.33-5.26 (2H, m), 5.26-5.10 (4H, m), 4.91-4.80 (1H, m), 4.70-4.51 (2H, m), 4.26-4.19 (2H, m), 4.17-4.01 (6H, m), 3.58-3.43 (2H, m), 2.93-2.72 (2H, m). ESI-MS (m/z): 584 $[M+H]^+$; melting point: 240-242 °C.



146 147 149

Scheme 22.

Example 71: N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (151) and corresponding hydrochloride salt (152a)

A mixture of 2,6-dichloro-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d] pyrimidine-4,8-diamine (**2**) (215 mg, 0.68 mmol) and ethylamine (70% water solution, 1.00 mL) in *n*-butanol (2.0 mL) was heated at 80°C for 18 h. A saturated $NaHCO_3$ solution (15 mL) was added and resulting suspension was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (20 mL), and then with a brine solution (20 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed. The residue was dissolved in *n*-butanol (2.0 mL), and diethylamine (1.0 mL) was added. The mixture was heated in a closed vial at 130°C for 60 h. A saturated $NaHCO_3$ solution (15mL) was added and the resulting suspension was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (30 mL), and then with a brine solution (30 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (9:1) to PE/EtOAc (1:1) to give N^2,N^2,N^6-triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**151**) (222 mg, 91%). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.52 (1H, br s), 6.41 (1H, br s), 4.51 (1H, br s), 3.68-3.54 (4H, m), 3.52-3.34 (6H, m), 1.74-1.63 (4H, m), 1.22 (3H, t, J=7.2 Hz), 1.18 (6H, t, J=7.0 Hz), 0.99 (3H, t, J=7.4 Hz), 0.98 (3H, t, J=7.4 Hz). ESI-MS (m/z): 361 $[M+H]^+$.

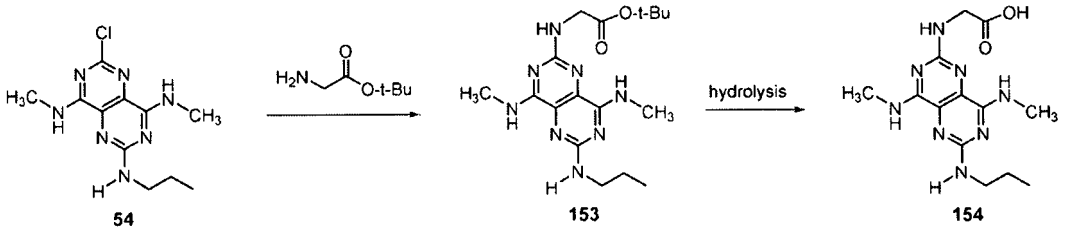
N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**151**) (207 mg, 0.57 mmol) was treated with 2M HCl /diethyl ether in diethyl ether/ ethanol (20/1) using procedure described for compound (**20a**) (220 mg, 97%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 13.91 (1H, br s), 7.9-7.2 (2H, m), 6.66-6.56 (1H, m), 3.75-

3.45 (10H, m), 1.82-1.69 (4H, m), 1.25 (3H, t, J=7.2 Hz), 1.20 (6H, t, J=6.9 Hz), 1.02 (3H, t, J=7.4 Hz), 1.01 (3H, t, J=7.4 Hz). ESI-MS (m/z): 361 $[M+H]^+$; melting point: 205-206 °C.

Example 72: (4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester (153) and (4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid (154) (Scheme 23)

A mixture of 6-chloro-N^2-*n*-propyl-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-2,4,8-triamine (**54**) (300 mg, 1.06 mmol), glycine ethyl ester hydrochloride (297 mg, 2.13 mmol) and N,N-diisopropylethylamine (732 µL, 4.24 mmol) in *n*-butanol (4.0 mL) was heated in a closed vial at 130°C for 90 h. A saturated $NaHCO_3$ solution (15 mL) was added and resulting suspension was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (9:1) to PE/EtOAc (1:3) to give (4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid *tert*-butyl ester (**153**) (150 mg, 38%y). ESI-MS (m/z): 377 $[M+H]^+$.

A 1N NaOH solution (2 mL) was added to a solution of (4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid *tert*-butyl ester (**153**) (150 mg, 0.40 mmol) in 1,4-dioxane (2 mL). The mixture was stirred at ambient temperature for 1 h, and then neutralized with 1N HCl (pH 6-7). The resultant precipitate was filtered, washed with water (5 mL) and dried to give (4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid (**154**) (60 mg, 47%y). 400 MHz 1H NMR (DMSO-d_6, ppm): δ 12.36 (1H, br s), 7.19 (2H, br s), 6.27 (1H, s), 6.17 (1H, br s), 4.06-3.96 (2H, m), 3.34-3.21 (2H, m, overlapped with water), 2.98-2.84 (6H, m), 1.60-1.46 (2H, m), 0.90 (3H, t, J=7.2 Hz). ESI-MS (m/z): 321 $[M+H]^+$; melting point: 210-212 °C.



Scheme 23.

Example 73: N-*n*-Propyl-[2-(4,8-Bis-methylamino-6-propylamino-pyrimido[5,4-d] pyrimidin-2-ylamino)]-acetamide (156) and corresponding hydrochloride salt (157a)

(6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester (**155**):

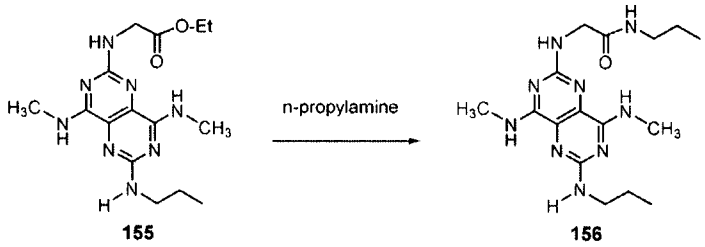
A mixture of 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-d] pyrimidine-4,8-diamine (**25**) (207 mg, 0.80 mmol), glycine ethyl ester hydrochloride (112 mg, 0.80 mmol) and N,N-diisopropylethylamine (276 µL, 1.60 mmol) in 1,4-dioxane (4.0 mL) was heated in a closed vial at 105°C for 64 h. An additional portion of glycine ethyl ester hydrochloride (112 mg, 0.80 mmol) and N,N-diisopropylethylamine (276 µL, 1.60 mmol) were added, and the mixture was heated for 80 h. After cooling, a saturated $NaHCO_3$ solution (15mL) was added and the resulting suspension was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with water (50 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from PE/EtOAc (9:1) to PE/EtOAc (1:9) to give (6-chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester (**155**). 400 MHz 1H NMR ($CDCl_3$, ppm): δ 6.72-6.64 (1H, m), 6.59-6.52 (1H, m), 5.43 (1H, t, J=5.6 Hz), 4.24 (2H, q, J=7.2 Hz), 4.18 (2H, d, J=5.6 Hz), 3.14 (3H, d, J=5.2 Hz), 3.05 (3H, d, J=5.2 Hz), 1.29 (3H, t, J=7.2 Hz). ESI-MS (m/z): 326, 328 $[M+H]^+$.

N-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide (**156**):

A mixture of (6-chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester (**155**) (204 mg, 0.63 mmol), *n*-propylamine (515 µL, 6.26 mmol) in *n*-butanol (4.0 mL) was heated in a closed vial at 125°C for 96 h. A saturated $NaHCO_3$ solution (15mL) was added and resulting suspension was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with water (40 mL) and dried over solid anhydrous Na_2SO_4. After filtration, the solvent was removed and the residue was purified by flash column chromatography using gradient elution from CH_2Cl_2/i-PrOH (97:3) to CH_2Cl_2/i-PrOH (97:3) (1:1) to give N-*n*-propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide (**156**) (125 mg, 55%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.66-6.60 (1H, m), 6.65 (1H, q, J=5.0 Hz), 6.37 (1H, q, J=5.0 Hz), 5.08-5.03 (1H, m), 4.76-4.71 (1H, m), 4.02 (2H, d, J=6.0 Hz), 3.38-3.32 (2H, m), 3.24-3.18 (2H, m), 3.06 (3H, d, J=5.1 Hz) 3.03 (3H, d, J=5.1 Hz) 1.62 (2H, sextet, J=7.3 Hz) 1.45 (2H, sextet, J=7.3 Hz) 0.98 (3H, t, J=7.3 Hz) 0.83 (3H, t, J=7.3 Hz). ESI-MS (m/z): 362 $[M+H]^+$.

N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide hydrochloride (**157a**):

N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d] pyrimidin-2-ylamino)]-acetamide (**156**) (113 mg, 0.31 mmol) was treated with 2M HCl /diethyl ether in diethyl ether/ ethanol (20/1) using procedure described for compound (**20a**) (105 mg, 85%y). 400 MHz ^{1}H NMR ($CDCl_3$, ppm): δ 6.67 (1H, s), 6.22 (2H, br s), 4.14-4.08 (2H, m), 3.51-3.44 (2H, m), 3.27-3.21 (2H, m), 3.21-3.18 (3H, m), 3.15-3.09 (3H, m), 1.67 (2H, sextet, J=7.3 Hz), 1.50 (2H, sextet, J=7.3 Hz), 0.99 (3H, t, J=7.3 Hz), 0.87 (3H, t, J=7.3 Hz). ESI-MS (m/z): 362 $[M+H]^+$; melting point: 262 °C (dec.).



Scheme 24.

Example 74: *In vitro* Metabolic Stability of Select Compounds in Rat Liver Microsomes (RLM) and Human Liver Microsomes (HLM)

Assay Description:

Liver microsomes were incubated with the test compound for a series of time points. Control compound (verapamil), with a known high clearance rate, was included in every experiment for comparison with the test compound. Analysis was conducted by evaluating the disappearance of parent compound over time. Microsomes from various animal species may be used to conduct a species comparison with human data.

Materials and Reagent Preparation:

A 0.5 M stock of potassium phosphate buffer was diluted in deionized water to make up 50 mM working buffer. A large scale solution that was sufficient for several experiments was prepared, filtered-sterilized through a 0.2-micron filter using vacuum and stored at room temperature. A 8 mM NADPH solution was prepared by dissolving 100 mg NADPH sodium salt powder in 15 mL potassium phosphate buffer as prepared above to yield a final concentration of 8 mM (aliquoted and stored at -20°C). Stock solution (5mM) of test compounds were prepared by dissolving the material in methanol or 50/50 methanol/water. Separately, RLM (male, pooled) and/or HLM (mix-gender, pooled) with stock concentration of 20 mg/mL was obtained.

Procedure:

A 10 mL (or 20 mL) of the previously prepared 0.05 M potassium phosphate

buffer was dispensed into a 50-mL conical tube and 1M $MgCl_2$ stock (20 µL or 40 µL) was added to a final concentration of 1.5 mM Mg^{2+}. The solution was then aliquoted into Falcon tubes (for each test compound). The 5 mM compound stock solutions (4 µL) were used to make up a final compound concentration of 5 µM. The final organic content in the assay was 0.1%. From this, 300 µL of the compounds-containing buffer solutions were divided into cluster tubes (duplicate reactions with microsomal incubations, and a singleton reaction for negative control). The 20 mg/mL microsomal stocks were diluted in potassium phosphate buffer to yield a concentration of 4 mg/mL. Then, 50 µL of the 4 mg/mL microsomal working solution were placed into the duplicate reaction wells. For the negative control wells, 50 µL of potassium phosphate buffer was used (without $MgCl_2$). The cluster tubes were pre-warmed for approximately 10 min in a 37°C 50-rpm shaking incubator. In the meantime, the appropriate volume (1.5 mL or 3 mL) of the 8 mM NADPH solution was warmed. The enzyme reaction was started by the addition of 50 µL pre-warmed NADPH solution to all cluster tubes using a multi-channel pipette. From this, 50 µL aliquots were removed at pre-determined time points (0, 5, 10, 15, 30, and 60 minutes) into a collection plate containing 150 µL acetonitrile containing propranolol as internal standard. After collecting the last time point, the plate(s) was/were centrifuged for 10 min at 2000*g* and the supernatant was transferred for LC-MS/MS analysis.

Data Interpretation:

The percent parent compound remaining was determined relative to 0-minute incubation samples for each replicate, from which the elimination half-life was calculated based on the natural log of % compound remaining vs. time plot. The following parameters were calculated to estimate the compounds *in vitro* metabolic stability:

C_{mp}= concentration of microsomal proteins (mg/mL)

$t_{1/2}$ = the half-life (min), where $t_{1/2}$ is equal to 0.693/slope

CL_{int} = the intrinsic hepatic clearance (uL/min/mg), where CL_{int} is equal to $0.693/(t_{1/2} \times C_{mp})$

The metabolic stability of a test compound was categorized as follows:

Low clearance: CL_{int} (µL/min/mg) < 10 (RLM) or 5 (HLM)

Moderate clearance: 10≤ CL_{int}(µL/min/mg)≤60 (RLM) or 5≤CL_{int}(µL/min/mg)≤35 (HLM)

High clearance: CL_{int} (µL/min/mg) > 60 (RLM) or 35 (HLM)

Example 75: Pharmacokinetic and Oral Bioavailability of Compound 4a in the Rat

In-Life Procedures:

Sprague-Dawley rats (200-300 g) were fed a standard laboratory rodent diet and housed in individual cages on a 12-hour light and 12-hour dark cycle with room temperature maintained at 22 ± 3^{0}C and relative humidity at 50 ± 20%. Rats were fasted overnight before dosing, with food returned after the 6 hour blood samples were obtained. Bedding was removed until after the 6 hour blood samples were obtained. Water was provided *ad libitum* throughout the study.

Oral Study:

Dosing solution of test compound was prepared in desired oral formulation for oral administration via gavage needle at 10-30 mg/kg (10 mL/kg) to three or four rats. All blood samples (250 µL per sample) were taken via jugular vein or femoral vein at 0 min (predose), 15 min, and 30 min and 1, 2, 4, 6, 8, and 24 h after oral dosing. Fluid replacement (1.5 mL of 0.9% sodium chloride injection, USP) were administered subcutaneously once after the 2 hr blood sampling. Blood samples were collected in BD Microtainer tubes coated with anticoagulant, placed on ice, and within 30 minutes, centrifuged at 15,000g for 3 min to obtain plasma samples. All plasma samples were stored at -70 °C until analysis by LC-MS/MS.

Intravenous Study:

Dosing solution of test compound was prepared in desired intravenous formulation for intravenous bolus injection via tail vein, jugular vein, or femoral vein at 2-5 mg/kg (2 mL/kg) to three or four rats. All blood samples (250 uL per sample) were taken via jugular vein or femoral vein at 0 (predose), 5, 15, and 30 min and 1, 2, 4, 6, 8, and 24 h following intravenous administration. Fluid replacement (1.5 mL of 0.9% sodium chloride injection, USP) was administered subcutaneously once after the 2 hr blood sampling. Blood samples were collected in BD Microtainer tubes coated with anticoagulant, placed on ice, and within 30 minutes, centrifuged at 15,000g for 3 minutes to obtain plasma samples. All plasma samples were stored at -70 °C until analysis by LC-MS/MS.

Bioanalytical Assay:

Plasma samples (incurred study samples, calibration standards, quality controls) were normally prepared as follows. Two volumes of acetonitrile containing an internal standard was added to one volume of plasma to precipitate plasma proteins. Samples were centrifuged (3,000 g for 5 min) and supernatant was removed for analysis by LC-MS-MS. Calibration standards were prepared by adding appropriate volumes of stock solution directly into blank plasma and treated identically to collected plasma samples. Calibration

standards were typically prepared in the range of 2 ng/ml to 10 μg/mL for quantitation. Quality control samples were prepared in parallel at high, medium and low concentrations in an identical manner and they were used to ensure the quality of the assay results. No more that 2 of the 6 QC standards were allowed to differ by more than 20% of their nominal value. LC-MS-MS analysis was performed utilizing multiple reaction monitoring for detection of characteristic ions for each test compound, additional related analytes and internal standard. All ion source and tandem MS instrument parameters for the analytes were optimized for high sensitivity and selectivity.

Pharmacokinetic Data Analysis:

All pharmacokinetic parameters were determined based on a non-compartmental approach using WinNonlin software (Pharsight, Version 5.1). The terminal elimination half-life ($t_{1/2}$) was calculated as ln2/λz using the slope (λz) from linear regression analysis of the terminal phase of the plasma concentration-time curve on a semi-log scale. The area under the plasma concentration-time curve (AUC_{inf}) was determined by non-compartmental analysis using the linear trapezoidal rule and extrapolated to infinity as C_{last}/λz using the last measurable concentration (C_{last}) and terminal slope (λz). The plasma concentration at time zero (C_0) following intravenous administration was estimated by linear extrapolation from the first two time points after dosing. The mean residence time (MRT) was obtained by dividing the area under the first moment curve ($AUMC_{inf}$) by AUC_{inf}. The systemic plasma clearance (CL_p) was calculated as intravenous dose divided by AUC_{inf}. The volume of distribution at steady state (V_{ss}) was determined as the product of CL_p and MRT. The time to reach maximum plasma concentration (T_{max}) was based on the time to reach observed maximum concentrations. The maximum plasma concentration (C_{max}) was the observed maximum concentration occurring at T_{max}. The absolute oral bioavailability (F) was calculated as the percentage ratio of mean dose-normalized oral AUC_{inf} to dose-normalized intravenous AUC_{inf}.

Statistical Analysis:

Summary statistics for bioanalytical data and calculated pharmacokinetic parameters such as means, standard deviations, and coefficients of variation were determined using WinNonlin or Microsoft Excel applications.

In this assay compound **4a** was found to have an oral bioavailability of 38%.

Example 76: Effect of Compounds of the Invention on Respiratory Rate (RR), Tidal

Volume (V_T), and the Product Minute Volume Using an Anesthetized Rat Spirometry Screening Assay

Anesthetized rats provide a quick method of screening compounds for respiratory and cardiovascular activity. In contrast to the conscious rat model, this model offers an experimental set up with less variation in the baseline cardiovascular and respiratory measures. Compounds screened in this assay may be examined in a conscious rat model.

Method outline:

Rats were initially anesthetized with 3% isoflurane (inhaled) and femoral artery and vein cannulas were surgically inserted. Once cannulated, the rats were transitioned to urethane anesthesia (1.5 g/kg; i.v.) and a tracheal cut-down was performed. After placing the tracheal cannula, it was connected to a pneumotachometer to record respiratory airflow from which respiratory rate (RR), tidal volume (V_T), and their product minute volume were derived. After the surgical preparation was complete, animals were allowed to stabilize for 30 minutes while respiratory rate, tidal volume, minute volume, blood pressure and heart rate were recorded continuously. Arterial blood gases (ABG) were obtained from arterial blood collected from the femoral artery. ABG measurements were taken before and 6 minutes after vehicle and each dose of compound administered. Compounds being screened were administered via bolus injections through the venous cannula followed by a saline flush (total time of administration is approximately 30 seconds), and the animal was monitored for at least 6 minutes for changes in cardiovascular efforts. Compounds were prepared in formulations identified to ensure optimal solubility. As such, vehicle controls were matched for the formulation of each compound tested. Dosing of the compound being screened was 0.1 and 0.3 mg/kg. The next dose was not administered until all cardiovascular and respiratory measures had returned to baseline levels. The positive control compounds used were N-[4,6-di-(*n*-propylamino)-[1,3,5]triazin-2-yl]-N,O-dimethyl-hydroxylamine or N-[2,6-di-(*n*-propylamino)-[1,3]pyrimidin-4-yl]-N,O-dimethyl-hydroxylamine (both administered at the end of each screening experiment (0.3 mg/kg dose) to validate the experiment and also to serve as a measure with which the compound being screened could be compared.

Data Analysis:

Data were analyzed by collecting cardiovascular and respiratory data in 30 second averages (BINs). Data were plotted 2 minutes before challenge and then 6 minutes after challenge.

Results:

Compound (**4a**) caused an immediate and short term (approximately 2 minutes

duration) increase in minute ventilation (Figure 1) above baseline values. This increase was due to stimulatory effects on respiratory rate primarily (Figure 2), rather than tidal volume (Figure 3). Compound (**4a**) produced negligible effects on pulse rate (Figure 5) and blood pressure (Figure 6). Compound (**4a**) produced a greater effect compared to a reference compound as measured by area-under-curve (Figure 4).

Compound (**27a**) caused an immediate and short term (approximately 2 minutes duration) increase in minute ventilation (Figure 7) above baseline values. This increase was due to stimulatory effects on respiratory rate (Figure 8), as well as tidal volume (Figure 9). Compound (**27a**) produced minimal effects on pulse rate (Figure 11) and blood pressure (Figure 12). Compound (**27a**) produces a greater effect compared to a reference compound as measured by area-under-curve (Figure 10).

Example 77: Microsomal Stability and Ventilatory Activity of Compounds of the Invention

Representative data are illustrated in Table 7, which summarizes the effects of individual compounds on peak minute ventilation (increase in V_E), overall increase in 2 minute area under the curve (AUC) which is a cumulative measure of effect, along with compound stability (half- life) in rat and human microsomes.

Table 7. Microsomal stability and ventilatory activity of compounds of the invention.

Cmpd #	V_E Peak (% Inc.)	AUC MV Inc (2 min) (ratio vs. std*)	RLM T½ (min)	HLM T½ (min)
4a	176	1.28	273	411
6a	60	0.54	416	>500
8a	44	0.14	331	>500
10a	11	0.07	162	462
13a	131	0.56	204	342
15a	6	0.00	34	91
17a	2	0.05	25	29
19a	4	0.00	106	110
22a	9	0.01	9	21
24a	123	0.43	162	119
27a	122	1.22	136	127
29a	135	0.95	44	94
31a	3	0.01	108	417
33a	88	0.29	106	115
35a	279	1.33	102	225

37a	128	1.23	76	135
39a	120	0.71	154	238
41a	57	0.36	100	187
43a	26	0.20	69	98
45a	87	0.41	>500	>500
47a	4	0.00	106	110
49a	19	0.11	84	190
51a	20	0.08	72	127
53a	15	0.06	94	79
54	30	0.09	40	82
56a	116	0.79	ND	ND
58a	32	0.18	ND	ND
60a	192, 172	0.46, 0.83	ND	ND
62a	85	0.55	ND	ND
64a	9	0.01	ND	ND
66a	12	0.14	ND	ND
68a	3	0.00	ND	ND
71a	36	0.13	ND	ND
73a	1	0.00	ND	ND
75a	2	0.02	ND	ND
77a	50	0.55	ND	ND
79a	3	0.00	388	>500
81a	0	0.00	274	198
83a	95	1.05	335	249
85a	104	0.51	386	389
87a	18	0.18	ND	ND
89a	169	0.92	ND	ND
91	9	0.08	24	102
93a	7	0.03	14	81
95a	115	0.36	ND	ND
97a	38	0.26	ND	ND
99a	24	0.19	ND	ND
101	3	0.00	ND	ND
103a	0	0.00	ND	ND
105a	7	0.00	ND	ND
107a	0	0.00	ND	ND
108	11	0.05	ND	ND
110a	0	0.00	ND	ND
112a	20	0.14	104	121
114a	6	0.05	249	305
116a	0	0.00	ND	ND
118a	5	0.05	34	72
120a	70	0.36	82	114
122a	6	0.00	ND	ND
125a	133	0.80	ND	ND
127a	125	0.86	ND	ND

129a	21	0.25	ND	ND
132a	76	0.98	ND	ND
135a	0	0.00	ND	ND
137a	197	0.88	97	227
138	77	0.53	331	>500
140a	3, 7	0.01, 0.05	50	71
142a	5	0.05	ND	ND
145a	146	0.88	ND	ND
148a	0	0.00	ND	ND
150a	0	0.00	ND	ND
152a	1	0.00	ND	ND
154	0	0.00	ND	ND
157a	5	0.04	ND	ND

* N-[2,6-*di*-(*n*-propylamino)-[1,3]pyrimidin-4-yl]-N,O-dimethyl-hydroxylamine used as comparator compound.

Example 78: Effects of Compounds of thes Invention on Apnea, Sleep Architecture and Ventilatory Response.

The objective of this study was to quantify the effects of selected compounds of this invention on apnea, ventilation and sleep structure in a rat model. The study consisted of two treatment conditions: (1) chronic morphine and test compound administered orally, and (2) chronic morphine and oral vehicle.

Adult male lean Zucker rats were anesthetized for electroencephalogram (EEG) and electromyogram (EMG) telemeter implantation. At least one week was permitted post-surgery before animals were used further. Morphine sulfate was added to the drinking water of singly housed rats beginning with 0.1 mg/ml morphine and increasing the concentration in increments, so that a final concentration of 0.6 mg/ml was achieved within 2 weeks. All respiratory measurements were made while animals were unrestrained in whole-body plethysmography chambers to permit animals to sleep and move freely. To avoid eliciting withdrawal, morphine water was continuously available during each plethysmography experiment. Minute volume and the number of central sleep apneas (CSA) were measured during all treatment conditions. A period of at least 1 to 1.5 h was permitted for animals to acclimate to the chamber before data collection began. The biopotential telemeters and their receivers were placed directly under the plethysmographic chambers and were used to continuously to capture EEG, EMG, and body temperature signals. Only data collected between the hours of 10 am to 4:30 pm were used in the final analysis to control for the effects of circadian rhythm on breathing.

Test compound in vehicle or an equivalent volume of vehicle was administered via an oral gavage tube at 12 pm. Data collected between 10 am and 12 pm represented baseline (pre-drug) conditions. Data collected between 12 pm and 4:30 pm represented post-drug conditions. Analyses of the EEG and EMG waveforms for the purpose of staging sleep-wake behavior in rats as awake, NREM sleep, and REM sleep were based on previous sleep studies involving rodents. Central apneas were defined as a respiratory cycle period that was more than or equal to twice the average cycle period during baseline recordings. Percent time in each sleep-wake state, minute volume, and central sleep apnea counts were compared between treatment groups using a two-way ANOVA (factors: drug treatment and time). Breathing data during wakefulness was not analyzed because movement prevents measurement of accurate volumes when using whole-body plethysmography. When differences were detected with ANOVA, Student-Neuman-Keuls post hoc tests were run for all main effects and interactions. Differences were considered significant when $p<0.05$. Values are expressed as means ± SE.

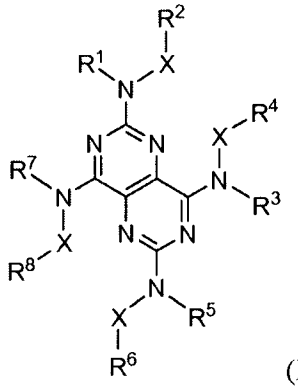
Compounds of this invention reduce apneas in rats, that were chronically administered opioid, at doses at which ventilatory stimulation (increase in minute volume) does not occur. As a non-limiting example, compounds (**27a**), (**85a**), (**137a**) and (**145a**) decreased apnea frequency (Figures 14, 19, 24 and 29), decreased the number of apneas per hr with respect to baseline (Figures 15, 20, 25 and 30), and decreased the number of apneas per hr with respect to vehicle (Figures 16, 21, 26 and 31). Furthermore, as a non-limiting example, compounds (**27a**), (**85a**), (**137a**) and (**145a**) do not cause increases in minute volume (Figures 17, 22, 27 and 32) and do not cause an increase in ventilation per unit time (Figures 18, 23, 28 and 33).

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

CLAIMS

What is claimed:

1. A compound or salt thereof selected from the group consisting of:



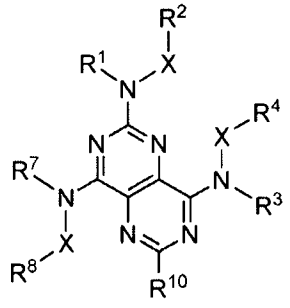
a compound of formula (I): (I), wherein in formula (I):

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; and,

each occurrence of X is independently alkyl or substituted alkyl;



a compound of formula (II): (II), wherein in formula (II):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted

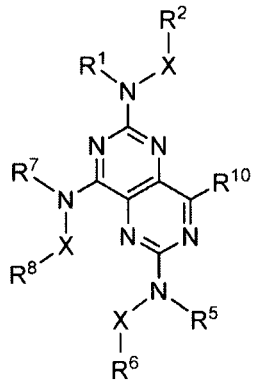
alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl, or substituted alkyl;

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy; and,

a compound of formula (III):  (III), wherein in formula (III):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl; and

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy;

and any combinations thereof.

2. The compound of claim 1, wherein the compound is selected from the group consisting of:

N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine;

N-(6-Chloro-4,8-*bis*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine;

N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-n-propylamino-pyrimido[5,4-d] pyrimidine hydrochloride;

N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl)-hydroxylamine;

N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-(4,8-Bis-*n*-propylamino-6-methylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol;

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine;

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol;

N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol;

N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-Chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Benzyloxy-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ol;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid;

N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-amidine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methoxy-N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

N^4,N^8-Diethyl-N^2,N^6-Di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d] pyrimidine-2,4,8-triamine;
N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester;
(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid;
N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide;
(6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester;
a salt or solvate thereof, and any combinations thereof.

3. The compound of claim 1, wherein the salt is selected from the group consisting of sulfate, hydrogen sulfate, hemisulfate, chloride, bromide, iodide, nitrate, carbonate, phosphate, hydrogen phosphate, dihydrogen phosphate, formate, acetate, propionate, succinate, glycolate, gluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, 4-hydroxybenzoate, phenylacetate, mandelate, pamoate, methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, trifluoromethanesulfonate, 2-hydroxyethanesulfonate, *p*-toluenesulfonate, sulfanilate, cyclohexylaminosulfonate, stearate, alginate, β-hydroxybutyrate, salicylate, galactarate, galacturonate, saccharin, saccharate, glycerophosphonate, and any combinations thereof.

4. A pharmaceutical composition comprising the compound of claim 1 and at least one pharmaceutically acceptable carrier.

5. The composition of claim 4, further comprising at least one agent selected from the group consisting of doxapram and enantiomers thereof, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients, benzodiazepine receptor

agonists, orexin antagonists, tricyclic antidepressants, serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids, orexins, melatonin agonists, ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics.

6. The composition of claim 5, wherein the compound and the agent are physically mixed in the composition.

7. The composition of claim 5, wherein the compound and the agent are physically separated in the composition.

8. The composition of claim 4, further comprising at least one agent known to cause changes in breathing control.

9. The composition in claim 8, wherein the at least one agent is selected from the group consisting of opioid narcotics, benzodiazepines, sedatives, sleeping aids, hypnotics, propofol, and any combinations thereof.

10. The composition of claim 8, wherein the compound and the agent are physically mixed in the composition.

11. The composition of claim 8, wherein the compound and the agent are physically separated in the composition.

12. The composition of claim 4, wherein the composition allows for modified delivery of the compound following oral administration to a subject.

13. The composition of claim 12, wherein the composition minimizes delivery of the compound to the stomach of the subject and maximizes delivery of the compound to the intestine of the subject.

14. The composition of claim 12, wherein the composition includes an enteric coating.

15. The composition of claim 12, wherein the compound is contained in a

pharmaceutically suitable capsule.

16. The composition of claim 15, wherein the capsule contains granules or powder of the compound, or an admixture of the compound with an excipient.

17. The composition of claim 16, wherein the excipient comprises a binder, disintegrant, diluent, buffer, lubricant, glidant, antioxidant, antimicrobial preservative, colorant, or flavorant.

18. The composition of claim 16, wherein the capsule is enterically coated but the granules or powders of the compound are not enterically coated.

19. The composition of claim 16, wherein the granules or powders of the compound are coated with an enteric coating before being placed into the capsule.

20. The composition of claim 19, wherein the granules or powders of the compound are coated with a multiplicity of enteric coatings, as to provide delivery of drug to different regions of the intestine of the subject.

21. The composition of claim 16, wherein at least a portion of the granules or powders of the compound are enterically coated.

22. The composition of claim 21, wherein the capsule is coated with an enteric coating that is different from the enteric coating that coats the granules or powders of the compound.

23. The composition of claim 12, wherein the compound is coated onto a base particle, whereby a core comprising the drug as a coating over the base particle is formed.

24. The composition of claim 23, wherein the base particle is not enterically coated and the composition is contained in a pharmaceutically acceptable capsule that is enterically coated.

25. The composition of claim 23, wherein the core is coated with an enteric coating, thereby forming an enterically coated bead.

26. The composition of claim 25, wherein the enterically coated bead is contained in a pharmaceutically acceptable capsule.

27. The composition of claim 26, wherein the capsule contains beads coated with a multiplicity of enteric coatings, so that the capsule provides delivery of the compound to different regions of the intestine of the subject.

28. The composition of claim 16, further wherein the contents of the capsule are dissolved or suspended in a pharmaceutically acceptable liquid as to provide a liquid-filled capsule.

29. The composition of claim 28, wherein the capsule is enterically coated but the liquid formulation contained within does not comprise an enteric coating.

30. The composition of claim 28, wherein the granules or powders of the compound are enterically coated.

31. The composition of claim 30, wherein the granules or powders of the compound are coated with a multiplicity of enteric coatings, as to provide delivery of drug to different regions of the intestine of the subject.

32. The composition of claim 30, wherein the enteric coating applied to the capsule differs from the enteric coating applied to any of the granules or powders of the compound.

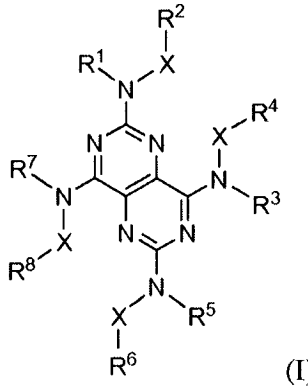
33. The composition of claim 15, wherein the compound is coated onto a base particle to form a core comprising the compound as a coating over the base particle, wherein the core is suspended in a pharmaceutically acceptable liquid, and wherein the suspended core is placed in a capsule.

34. The composition of claim 33, wherein the capsule is enterically coated

but the core is not enterically coated.

35. The composition of claim 33, wherein the capsule and the core are enterically coated.

36. A method of preventing or treating a breathing control disorder or disease in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and at least one compound or salt thereof selected from the group consisting of:



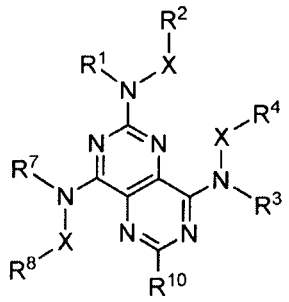
a compound of formula (I): (I), wherein in formula (I):

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; and,

each occurrence of X is independently alkyl or substituted alkyl;



a compound of formula (II): (II), wherein in formula (II):

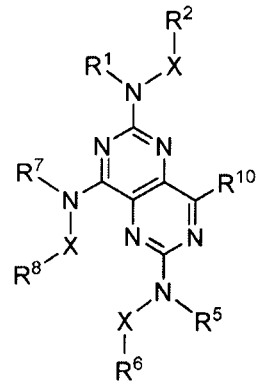
R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl;

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy; and,



a compound of formula (III): (III), wherein in formula (III):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted

heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl; and

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy.

37. The method of claim 36, wherein the breathing control disorder or disease is selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, altitude sickness, hypoxia, hypercapnia, chronic obstructive pulmonary disease (COPD), sudden infant death syndrome (SIDS), congenital central hypoventilation syndrome, Alzheimer's disease, Parkinson's disease, stroke, Duchenne muscular dystrophy, and brain and spinal cord traumatic injury.

38. The method of claim 37, wherein the respiratory depression is caused by an anesthetic, a sedative, a sleeping aid, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic.

39. The method of claim 36, wherein the subject is further administered at least one additional agent useful for treating the breathing disorder or disease.

40. The method of claim 39, wherein the at least one additional agent is selected from the group consisting of doxapram and enantiomers thereof, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients, benzodiazepine receptor agonists, orexin antagonists, tricyclic antidepressants, serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids, orexins, melatonin agonists, ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics.

41. The method of claim 39, wherein the compound and the agent are separately administered to the subject.

42. The method of claim 39, wherein the compound and the agent are co-administered to the subject, further wherein the compound and the agent are physically mixed or physically separated when administered to the subject.

43. The method of claim 36, wherein the subject is further administered at least one additional therapeutic agent known to change normal breathing control in the subject.

44. The method of claim 43, wherein at least one additional agent is selected from the group consisting of opioid narcotics, benzodiazepines, sedatives, sleeping aids, hypnotics, propofol, and any combinations thereof.

45. The method of claim 36, wherein the composition is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject.

46. The method of claim 36, wherein the subject is a mammal or bird.

47. The method of claim 46, wherein the mammal is a human.

48. The method of claim 36, wherein the composition is administered to the subject by a nasal, inhalational, topical, oral, buccal, rectal, pleural, peritoneal, vaginal, intramuscular, subcutaneous, transdermal, epidural, intratracheal, otic, intraocular, intrathecal or intravenous route.

49. The method of claim 48, wherein the composition is orally administered to the subject.

50. The method of claim 36, wherein the at least one compound is selected from the group consisting of:

N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine;

N-(6-Chloro-4,8-*bis*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine;

N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-n-propylamino-pyrimido[5,4-d] pyrimidine hydrochloride;

N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl)-hydroxylamine;

N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-(4,8-Bis-*n*-propylamino-6-methylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol;

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine;

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol;

N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol;

N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-Chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Benzyloxy-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ol;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid;

N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-amidine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methoxy-N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

N^4,N^8-Diethyl-N^2,N^6-Di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid;

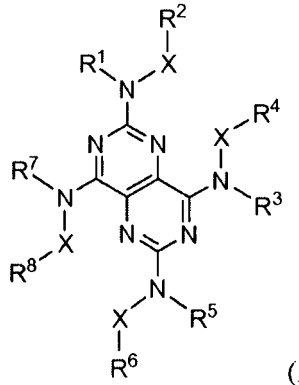
N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide;

(6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester;

a salt thereof, and any combinations thereof.

51. The method of claim 36, wherein the salt is selected from the group consisting of sulfate, hydrogen sulfate, chloride, bromide, iodide, nitrate, carbonate, phosphate, hydrogen phosphate, dihydrogen phosphate, formate, acetate, propionate, succinate, glycolate, gluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, 4-hydroxybenzoate, phenylacetate, mandelate, pamoate, methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, trifluoromethanesulfonate, 2-hydroxyethanesulfonate, *p*-toluenesulfonate, sulfanilate, cyclohexylaminosulfonate, stearate, alginate, β-hydroxybutyrate, salicylate, galactarate, galacturonate, saccharin, saccharate, and glycerophosphonate.

52. A method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and at least one compound or salt thereof selected from the group consisting of:



a compound of formula (I): (I), wherein in formula (I):

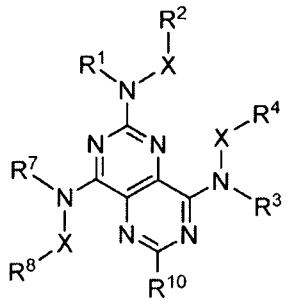
R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted

phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; and,

each occurrence of X is independently alkyl or substituted alkyl;

a compound of formula (II):  (II), wherein in formula (II):

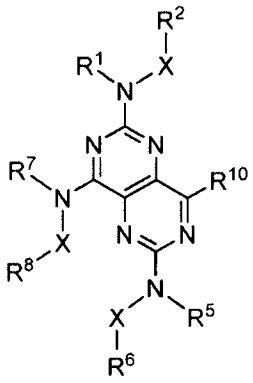
R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl;

R^{10} is H, halogen, cyano, alkyl, substituted alkyl, alkoxy or substituted alkoxy; and,



a compound of formula (III): (III), wherein in formula (III):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl; and

R^{10} is H, halogen, cyano, alkyl, substituted alkyl, alkoxy or substituted alkoxy.

53. The method of claim 52, wherein the destabilization is associated with a breathing control disorder or disease selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, altitude sickness, hypoxia, hypercapnia, chronic obstructive pulmonary disease (COPD), sudden infant death syndrome (SIDS), congenital central hypoventilation syndrome, Alzheimer's disease, Parkinson's disease, stroke, Duchenne muscular dystrophy, and brain and spinal cord traumatic injury.

54. The method of claim 53, wherein the respiratory depression is caused by an anesthetic, a sedative, a sleeping aid, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic.

55. The method of claim 52, wherein the subject is further administered at least one additional agent useful for treating the breathing disorder or disease.

56. The method of claim 55, wherein the at least one additional agent is selected from the group consisting of doxapram and enantiomers thereof, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients, benzodiazepine receptor agonists, orexin antagonists, tricyclic antidepressants, serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids, orexins, melatonin agonists, ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics.

57. The method of claim 55, wherein the compound and the agent are separately administered to the subject.

58. The method of claim 55, wherein the compound and the agent are co-administered to the subject, further wherein the compound and the agent are physically mixed or physically separated when administered to the subject.

59. The method of claim 52, wherein the subject is further administered at least one additional therapeutic agent known to change normal breathing control in the subject

60. The method of claim 59, wherein at least one additional agent is selected from the group consisting of opioid narcotics, benzodiazepines, sedatives, sleeping aids, hypnotics, propofol, and any combinations thereof.

61. The method of claim 52, wherein the composition is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject.

62. The method of claim 52, wherein the subject is a mammal or bird.

63. The method of claim 62, wherein the mammal is a human.

64. The method of claim 52, wherein the composition is administered to the subject by a nasal, inhalational, topical, oral, buccal, rectal, pleural, peritoneal, vaginal, intramuscular, subcutaneous, transdermal, epidural, intratracheal, otic, intraocular, intrathecal or intravenous route.

65. The method of claim 64, wherein the composition is orally administered to the subject.

66. The method of claim 52, wherein the at least one compound is selected from the group consisting of:

N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine;

N-(6-Chloro-4,8-*bis*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine;

N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-n-propylamino-pyrimido[5,4-d] pyrimidine hydrochloride;

N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl)-hydroxylamine;

N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-(4,8-Bis-*n*-propylamino-6-methylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol;

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine;

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol;

N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol;

N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-Chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Benzyloxy-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ol;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid;

N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-amidine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methoxy-N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

N^4,N^8-Diethyl-N^2,N^6-Di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d] pyrimidine-2,4,8-triamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid;

N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide;

(6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester; a salt thereof, and any combinations thereof.

67. The method of claim 52, wherein the salt is selected from the group consisting of sulfate, hydrogen sulfate, chloride, bromide, iodide, nitrate, carbonate, phosphate, hydrogen phosphate, dihydrogen phosphate, formate, acetate, propionate, succinate, glycolate, gluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, 4-hydroxybenzoate, phenylacetate, mandelate, pamoate, methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, trifluoromethanesulfonate, 2-hydroxyethanesulfonate, *p*-toluenesulfonate, sulfanilate, cyclohexylaminosulfonate, stearate, alginate, β-hydroxybutyrate, salicylate, galactarate, galacturonate, saccharin, saccharate, and glycerophosphonate.

68. The compound of claim 1, wherein the compound is N^2-N^6-bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine and wherein the X-ray powder diffraction spectrum of the compound comprises 2Θ values (in

degrees) of about 8.12, 9.59, 12.60, 15.02, 16.33, 17.40, 18.98, 20.68, 21.72, 22.28, 23.98, 25.24, and 26.70.

69. A method of preparing N^2-N^6-bis-cyclopropylmethyl N^4, N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**), comprising reacting 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-*d*]pyrimidine-4,8-diamine and cyclopropylmethylamine in a solvent.

70. The method of claim 69, wherein the reaction is run under heating and wherein (**84**) precipitates from the solvent once the reaction system is cooled to room temperature.

71. The method of claim 69, wherein the solvent comprises *n*-butanol.

72. The method of claim 70, wherein the precipitated (**84**) is recrystallized from *n*-butanol.

73. The method of claim 72, wherein the recrystallized (**84**) has a X-ray powder diffraction spectrum comprising 2Θ values (in degrees) of about 8.12, 9.59, 12.60, 15.02, 16.33, 17.40, 18.98, 20.68, 21.72, 22.28, 23.98, 25.24, and 26.70.

74. The method of claim 69, wherein the 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-*d*]pyrimidine-4,8-diamine is prepared by reacting 2,4,6,8-tetrachloro-pyrimido[5,4-*d*]pyrimidine and methylamine in a solvent.

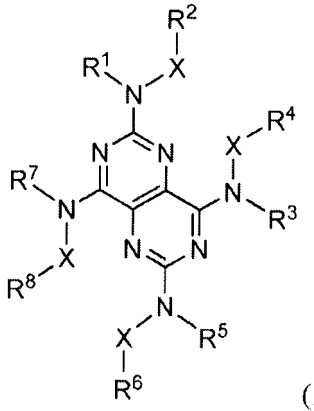
75. The method of claim 74, wherein the ratio of equivalents of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine to methylamine is about 1 : 4.5.

AMENDED CLAIMS
received by the International Bureau on 30 September 2014 (30.09.2014)

LISTING OF THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. A compound or salt thereof selected from the group consisting of:



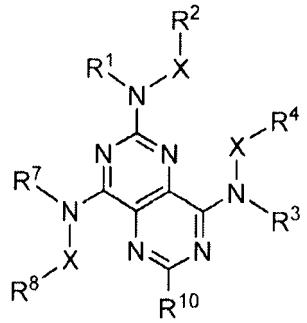
a compound of formula (I): (I), wherein in formula (I):

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; and,

each occurrence of R^9 is independently alkyl or substituted alkyl;



a compound of formula (II): (II), wherein in formula (II):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl,

AMENDED SHEET (ARTICLE 19)

substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

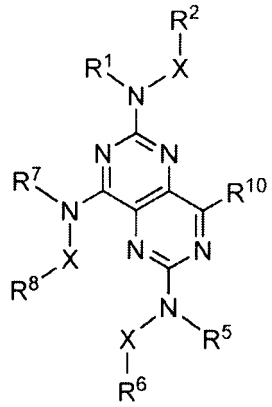
or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl, or substituted alkyl;

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy; and,

a compound of formula (III):



(III), wherein in formula (III):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond,

NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl; and

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy;

and any combinations thereof.

2. The compound of claim 1, wherein the compound is selected from the group consisting of:

N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine;

N-(6-Chloro-4,8-*bis*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine;

N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-n-propylamino-pyrimido[5,4-d] pyrimidine hydrochloride;

N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl)-hydroxylamine;

N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-(4,8-Bis-*n*-propylamino-6-methylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol;

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-

tetraamine

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine;

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol;

N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol;

N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-Chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Benzyloxy-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ol;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid;

N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-amidine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methoxy-N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

N^4,N^8-Diethyl-N^2,N^6-Di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;
N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;
(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester;
(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid;
N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide;
(6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester;
a salt or solvate thereof, and any combinations thereof.

3. The compound of claim 1, wherein the salt is selected from the group consisting of sulfate, hydrogen sulfate, hemisulfate, chloride, bromide, iodide, nitrate, carbonate, phosphate, hydrogen phosphate, dihydrogen phosphate, formate, acetate, propionate, succinate, glycolate, gluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, 4-hydroxybenzoate, phenylacetate, mandelate, pamoate, methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, trifluoromethanesulfonate, 2-hydroxyethanesulfonate, *p*-toluenesulfonate, sulfanilate, cyclohexylaminosulfonate, stearate, alginate, β-hydroxybutyrate, salicylate, galactarate, galacturonate, saccharin, saccharate, glycerophosphonate, and any combinations thereof.

4. A pharmaceutical composition comprising the compound of claim 1

and at least one pharmaceutically acceptable carrier.

5. The composition of claim 4, further comprising at least one agent selected from the group consisting of doxapram and enantiomers thereof, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients, benzodiazepine receptor agonists, orexin antagonists, tricyclic antidepressants, serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids, orexins, melatonin agonists, ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics.

6. The composition of claim 5, wherein the compound and the agent are physically mixed in the composition.

7. The composition of claim 5, wherein the compound and the agent are physically separated in the composition.

8. The composition of claim 4, further comprising at least one agent known to cause changes in breathing control.

9. The composition in claim 8, wherein the at least one agent is selected from the group consisting of opioid narcotics, benzodiazepines, sedatives, sleeping aids, hypnotics, propofol, and any combinations thereof.

10. The composition of claim 8, wherein the compound and the agent are physically mixed in the composition.

11. The composition of claim 8, wherein the compound and the agent are physically separated in the composition.

12. The composition of claim 4, wherein the composition allows for modified delivery of the compound following oral administration to a subject.

13. The composition of claim 12, wherein the composition minimizes

AMENDED SHEET (ARTICLE 19)

delivery of the compound to the stomach of the subject and maximizes delivery of the compound to the intestine of the subject.

14. The composition of claim 12, wherein the composition includes an enteric coating.

15. The composition of claim 12, wherein the compound is contained in a pharmaceutically suitable capsule.

16. The composition of claim 15, wherein the capsule contains granules or powder of the compound, or an admixture of the compound with an excipient.

17. The composition of claim 16, wherein the excipient comprises a binder, disintegrant, diluent, buffer, lubricant, glidant, antioxidant, antimicrobial preservative, colorant, or flavorant.

18. The composition of claim 16, wherein the capsule is enterically coated but the granules or powders of the compound are not enterically coated.

19. The composition of claim 16, wherein the granules or powders of the compound are coated with an enteric coating before being placed into the capsule.

20. The composition of claim 19, wherein the granules or powders of the compound are coated with a multiplicity of enteric coatings, as to provide delivery of drug to different regions of the intestine of the subject.

21. The composition of claim 16, wherein at least a portion of the granules or powders of the compound are enterically coated.

22. The composition of claim 21, wherein the capsule is coated with an enteric coating that is different from the enteric coating that coats the granules or powders of the compound.

23. The composition of claim 12, wherein the compound is coated onto a base particle, whereby a core comprising the drug as a coating over the base particle is formed.

24. The composition of claim 23, wherein the base particle is not enterically coated and the composition is contained in a pharmaceutically acceptable capsule that is enterically coated.

25. The composition of claim 23, wherein the core is coated with an enteric coating, thereby forming an enterically coated bead.

26. The composition of claim 25, wherein the enterically coated bead is contained in a pharmaceutically acceptable capsule.

27. The composition of claim 26, wherein the capsule contains beads coated with a multiplicity of enteric coatings, so that the capsule provides delivery of the compound to different regions of the intestine of the subject.

28. The composition of claim 16, further wherein the contents of the capsule are dissolved or suspended in a pharmaceutically acceptable liquid as to provide a liquid-filled capsule.

29. The composition of claim 28, wherein the capsule is enterically coated but the liquid formulation contained within does not comprise an enteric coating.

30. The composition of claim 28, wherein the granules or powders of the compound are enterically coated.

31. The composition of claim 30, wherein the granules or powders of the compound are coated with a multiplicity of enteric coatings, as to provide delivery of drug to different regions of the intestine of the subject.

32. The composition of claim 30, wherein the enteric coating applied to the

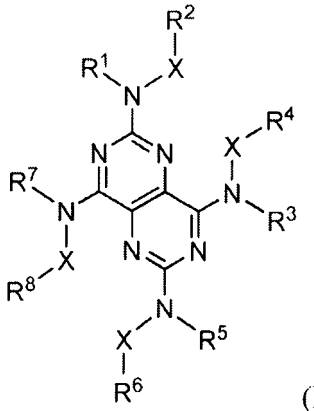
capsule differs from the enteric coating applied to any of the granules or powders of the compound.

33. The composition of claim 15, wherein the compound is coated onto a base particle to form a core comprising the compound as a coating over the base particle, wherein the core is suspended in a pharmaceutically acceptable liquid, and wherein the suspended core is placed in a capsule.

34. The composition of claim 33, wherein the capsule is enterically coated but the core is not enterically coated.

35. The composition of claim 33, wherein the capsule and the core are enterically coated.

36. A method of preventing or treating a breathing control disorder or disease in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and at least one compound or salt thereof selected from the group consisting of:



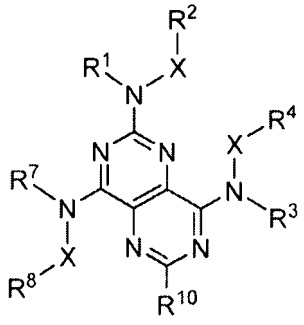
a compound of formula (I): (I), wherein in formula (I):

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; and,

each occurrence of R^9 is independently alkyl or substituted alkyl;

a compound of formula (II):  (II), wherein in formula (II):

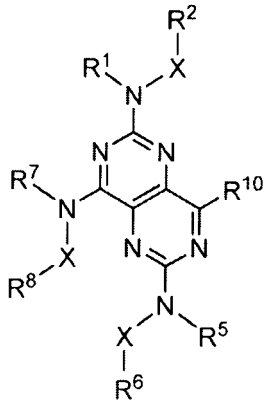
R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl;

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy; and,



a compound of formula (III): (III), wherein in formula (III):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl; and

R^{10} is H, halogen, CN, amidino, amido, carboxy, carboxamido, hydrazino, OH, alkyl or substituted alkyl, alkoxy or substituted alkoxy, or thioalkoxy or substituted thioalkoxy.

37. The method of claim 36, wherein the breathing control disorder or disease is selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, altitude sickness, hypoxia, hypercapnia, chronic obstructive pulmonary disease (COPD), sudden infant death syndrome (SIDS), congenital central hypoventilation syndrome, Alzheimer's disease, Parkinson's disease, stroke, Duchenne muscular dystrophy, and brain and spinal cord traumatic injury.

38. The method of claim 37, wherein the respiratory depression is caused by an anesthetic, a sedative, a sleeping aid, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic.

39. The method of claim 36, wherein the subject is further administered at least one additional agent useful for treating the breathing disorder or disease.

40. The method of claim 39, wherein the at least one additional agent is selected from the group consisting of doxapram and enantiomers thereof, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients, benzodiazepine receptor agonists, orexin antagonists, tricyclic antidepressants, serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids, orexins, melatonin agonists, ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics.

41. The method of claim 39, wherein the compound and the agent are separately administered to the subject.

42. The method of claim 39, wherein the compound and the agent are co-administered to the subject, further wherein the compound and the agent are physically mixed or physically separated when administered to the subject.

43. The method of claim 36, wherein the subject is further administered at least one additional therapeutic agent known to change normal breathing control in the subject.

44. The method of claim 43, wherein at least one additional agent is selected from the group consisting of opioid narcotics, benzodiazepines, sedatives, sleeping aids, hypnotics, propofol, and any combinations thereof.

45. The method of claim 36, wherein the composition is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject.

46. The method of claim 36, wherein the subject is a mammal or bird.

47. The method of claim 46, wherein the mammal is a human.

48. The method of claim 36, wherein the composition is administered to the subject by a nasal, inhalational, topical, oral, buccal, rectal, pleural, peritoneal, vaginal, intramuscular, subcutaneous, transdermal, epidural, intratracheal, otic, intraocular, intrathecal or intravenous route.

49. The method of claim 48, wherein the composition is orally administered to the subject.

50. The method of claim 36, wherein the at least one compound is selected from the group consisting of:

N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine;

N-(6-Chloro-4,8-*bis*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine;

N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-n-propylamino-pyrimido[5,4-d] pyrimidine hydrochloride;

N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl)-hydroxylamine;

N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-(4,8-Bis-*n*-propylamino-6-methylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol;

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine;

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol;

N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol;

N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-Chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Benzyloxy-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ol;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid;

N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-amidine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methoxy-N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

N^4,N^8-Diethyl-N^2,N^6-Di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid;

N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide;

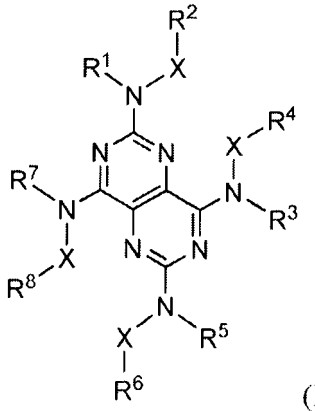
(6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester;

a salt thereof, and any combinations thereof.

51. The method of claim 36, wherein the salt is selected from the group consisting of sulfate, hydrogen sulfate, chloride, bromide, iodide, nitrate, carbonate, phosphate, hydrogen phosphate, dihydrogen phosphate, formate, acetate, propionate, succinate, glycolate, gluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, 4-hydroxybenzoate, phenylacetate, mandelate, pamoate, methanesulfonate, ethanesulfonate, benzenesulfonate,

pantothenate, trifluoromethanesulfonate, 2-hydroxyethanesulfonate, *p*-toluenesulfonate, sulfanilate, cyclohexylaminosulfonate, stearate, alginate, β-hydroxybutyrate, salicylate, galactarate, galacturonate, saccharin, saccharate, and glycerophosphonate.

52. A method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and at least one compound or salt thereof selected from the group consisting of:



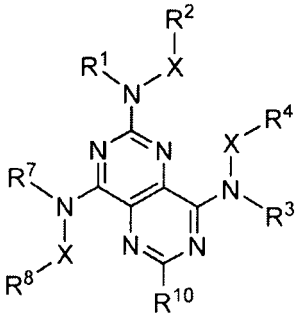
a compound of formula (I): (I), wherein in formula (I):

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O; and,

each occurrence of R^9 is independently alkyl or substituted alkyl;

a compound of formula (II):  (II), wherein in formula (II):

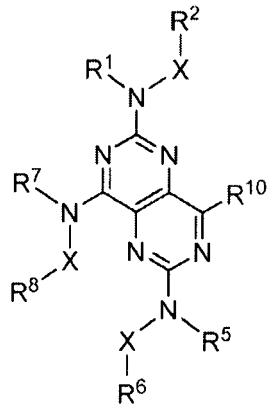
R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl;

R^{10} is H, halogen, cyano, alkyl, substituted alkyl, alkoxy or substituted alkoxy; and,

a compound of formula (III):  (III), wherein in formula (III):

R^1, R^2, R^3, R^4, R^7 and R^8 are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted

heteroarylalkyl, heteroaryl or substituted heteroaryl;

or R^1 and R^2, R^3 and R^4, R^5 and R^6, or R^7 and R^8 independently combine as to form a biradical selected from the group consisting of 3-hydroxy-pentane-1,5-diyl, 6-hydroxy-cycloheptane-1,4-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl;

each occurrence of X is independently selected from the group consisting of bond, NH, NR^9 and O;

each occurrence of R^9 is independently alkyl or substituted alkyl; and

R^{10} is H, halogen, cyano, alkyl, substituted alkyl, alkoxy or substituted alkoxy.

53. The method of claim 52, wherein the destabilization is associated with a breathing control disorder or disease selected from the group consisting of respiratory depression, sleep apnea, apnea of prematurity, obesity-hypoventilation syndrome, primary alveolar hypoventilation syndrome, dyspnea, altitude sickness, hypoxia, hypercapnia, chronic obstructive pulmonary disease (COPD), sudden infant death syndrome (SIDS), congenital central hypoventilation syndrome, Alzheimer's disease, Parkinson's disease, stroke, Duchenne muscular dystrophy, and brain and spinal cord traumatic injury.

54. The method of claim 53, wherein the respiratory depression is caused by an anesthetic, a sedative, a sleeping aid, an anxiolytic agent, a hypnotic agent, alcohol or a narcotic.

55. The method of claim 52, wherein the subject is further administered at least one additional agent useful for treating the breathing disorder or disease.

56. The method of claim 55, wherein the at least one additional agent is selected from the group consisting of doxapram and enantiomers thereof, acetazolamide, almitrine, theophylline, caffeine, methylprogesterone and related compounds, sedatives that increase arousal threshold in sleep disordered breathing patients, benzodiazepine receptor agonists, orexin antagonists, tricyclic antidepressants, serotonergic modulators, adenosine and adenosine receptor and nucleoside transporter modulators, cannabinoids, orexins, melatonin agonists, ampakines, sodium oxybate, modafinil, armodafinil, and inhaled therapeutics.

57. The method of claim 55, wherein the compound and the agent are separately administered to the subject.

58. The method of claim 55, wherein the compound and the agent are co-administered to the subject, further wherein the compound and the agent are physically mixed or physically separated when administered to the subject.

59. The method of claim 52, wherein the subject is further administered at least one additional therapeutic agent known to change normal breathing control in the subject

60. The method of claim 59, wherein at least one additional agent is selected from the group consisting of opioid narcotics, benzodiazepines, sedatives, sleeping aids, hypnotics, propofol, and any combinations thereof.

61. The method of claim 52, wherein the composition is administered in conjunction with the use of a mechanical ventilation device or positive airway pressure device on the subject.

62. The method of claim 52, wherein the subject is a mammal or bird.

63. The method of claim 62, wherein the mammal is a human.

64. The method of claim 52, wherein the composition is administered to the subject by a nasal, inhalational, topical, oral, buccal, rectal, pleural, peritoneal, vaginal, intramuscular, subcutaneous, transdermal, epidural, intratracheal, otic, intraocular, intrathecal or intravenous route.

65. The method of claim 64, wherein the composition is orally administered to the subject.

66. The method of claim 52, wherein the at least one compound is selected from the group consisting of:

N^2,N^6-Dimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^6,N^8-Tetra-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*i*-propyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dimethyl-N^4-*n*-propyl-N^8-prop-2-ynyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-(N-methoxy(N-methyl)amino)-N^4,N^8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidine;

N-(6-Chloro-4,8-*bis*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-O,N-dimethyl-hydroxylamine;

N^2,N^6-Bis-(N-Methoxy(N-methyl)amino)-N^4,N^8-bis-n-propylamino-pyrimido[5,4-d] pyrimidine hydrochloride;

N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

O,N-Dimethyl-N-(6-methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d] pyrimidin-2-yl)-hydroxylamine;

N^4,N^8-Dimethyl-N^2,N^6-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Trimethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-methyl-N^4,N^8-di-*n*-propylpyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2-Diethyl-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-(4,8-Bis-*n*-propylamino-6-methylamino-pyrimido[5,4-d]pyrimidin-2-yl-amino)-ethanol;

N^2-(2-Methoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl- pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(2-Isopropoxy-ethyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^8-Methyl-N^4,N^6-di-*n*-propyl-N^2-(3,3,3-trifluoropropyl)-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(morpholin-4-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-pyrrolidin-1-yl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-methoxy-piperidin-1-yl)-pyrimido[5,4,-d]pyrimidine-2,4,8-triamine;

N^2-(3-Chloro-2-methyl-benzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2-(3,4-Dichlorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-

tetraamine;

N^2-(4-Fluorobenzyl)-N^6-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^2,N^4,N^8-Tetramethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2-Diallyl-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-methyl-amino]-ethanol;

N^2-(2-Isopropoxy-ethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-[N-(2-Dimethylamino-ethyl)-N-methyl]amino-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-4,6,8-triamine;

2-[(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl)-(2-hydroxy-ethyl)-amino]-ethanol;

N^2,N^2-Bis-(2-methoxyethyl)-N^4,N^8-dimethyl-N^6-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-(4-Oxo-piperidin-1-yl)-N^4,N^8-dimethyl-N^2-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-(3-Trifluoromethyl-piperidin-1-yl)-N^4,N^8-dimethyl-6-*n*-propylamino-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-6-*n*-Propylamino-N^4,N^8-dimethyl-2-(1,1-dioxo-thiomorpholin-4-yl)-pyrimido-[5,4-d]pyrimidine-2,4,8-triamine;

N^2-*n*-Propyl-N^4,N^8-dimethyl-6-(4,4-difluoro-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^6,N^8-Tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Di-*n*-butyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diisobutyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diallyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

2-Chloro-6-(N,N'-dimethyl-hydrazino)-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

6-(N,N'-Dimethyl-hydrazino)-N^2,N^2,N^4,N^8-tetramethyl-pyrimido[5,4-d]pyrimidine-2,4,8-

triamine;

N^4,N^8-Dimethyl-6-propoxy-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-propylsulfanyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Benzyloxy-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ol;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(aminomethyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Carbamoyl-N^4,N^8-dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carboxylic acid;

N-(*n*-Propyl)-[4,8-bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-yl]-amidine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2-Methyl-N^4,N^8-di-*n*-propyl-6-(4-fluorophenyl)-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^4,N^8-Dimethyl-N^2-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-*n*-Butyl-N^2-methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methoxy-N^2-Methyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Methylamino-4,8-bis-*n*-propylamino-pyrimido[5,4-d]pyrimidine-2-carbonitrile;

N^2,N^4,N^6,N^8-Tetraethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine

2,6-Dichloro-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-4,8-diamine;

N^4,N^8-Diethyl-N^2,N^6-Di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-diethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Diethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

6-Chloro-N^2-ethyl-N^4,N^8-bis-cyclopropylmethyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^6-Diethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Dicyclopropyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^6-Bis-cyclopropylmethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^2,N^6,N^6-Tetramethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^4,N^8-Diallyl-N^2,N^6-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

N^2,N^4,N^8-Triallyl-6-[4-(4-fluorobenzyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

6-Chloro-N^2,N^4,N^8-triallyl-pyrimido[5,4-d]pyrimidine-2,4,8-triamine;

N^2,N^4,N^8-Triallyl-6-{4-[bis-(4-fluorophenyl)-methyl]-piperazin-1-yl}-pyrimido[5,4-d] pyrimidine-2,4,8-triamine;

N^2,N^2,N^6-Triethyl-N^4,N^8-di-*n*-propyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid tert-butyl ester;

(4,8-Bis-methylamino-6-*n*-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid;

N-*n*-Propyl-[2-(4,8-bis-methylamino-6-propylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)]-acetamide;

(6-Chloro-4,8-bis-methylamino-pyrimido[5,4-d]pyrimidin-2-ylamino)-acetic acid ethyl ester; a salt thereof, and any combinations thereof.

67. The method of claim 52, wherein the salt is selected from the group consisting of sulfate, hydrogen sulfate, chloride, bromide, iodide, nitrate, carbonate, phosphate, hydrogen phosphate, dihydrogen phosphate, formate, acetate, propionate, succinate, glycolate, gluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, 4-hydroxybenzoate, phenylacetate, mandelate, pamoate, methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, trifluoromethanesulfonate, 2-hydroxyethanesulfonate, *p*-toluenesulfonate, sulfanilate, cyclohexylaminosulfonate, stearate, alginate, β-hydroxybutyrate, salicylate, galactarate, galacturonate, saccharin, saccharate, and glycerophosphonate.

68. The compound of claim 1, wherein the compound is N^2-N^6-bis-cyclopropylmethyl-N^4,N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine and wherein the X-ray powder diffraction spectrum of the compound comprises 2Θ values (in degrees) of about 8.12, 9.59, 12.60, 15.02, 16.33, 17.40, 18.98, 20.68, 21.72, 22.28, 23.98, 25.24, and 26.70.

69. A method of preparing N^2-N^6-bis-cyclopropylmethyl N^4, N^8-dimethyl-pyrimido[5,4-d]pyrimidine-2,4,6,8-tetraamine (**84**), comprising reacting 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-*d*]pyrimidine-4,8-diamine and cyclopropylmethylamine in a solvent.

70. The method of claim 69, wherein the reaction is run under heating and wherein (**84**) precipitates from the solvent once the reaction system is cooled to room temperature.

71. The method of claim 69, wherein the solvent comprises *n*-butanol.

72. The method of claim 70, wherein the precipitated (**84**) is recrystallized from *n*-butanol.

73. The method of claim 72, wherein the recrystallized (**84**) has a X-ray powder diffraction spectrum comprising 2Θ values (in degrees) of about 8.12, 9.59, 12.60, 15.02, 16.33, 17.40, 18.98, 20.68, 21.72, 22.28, 23.98, 25.24, and 26.70.

74. The method of claim 69, wherein the 2,6-dichloro-N^4,N^8-dimethyl-pyrimido[5,4-*d*]pyrimidine-4,8-diamine is prepared by reacting 2,4,6,8-tetrachloro-pyrimido[5,4-*d*]pyrimidine and methylamine in a solvent.

75. The method of claim 74, wherein the ratio of equivalents of 2,4,6,8-tetrachloro-pyrimido[5,4-d]pyrimidine to methylamine is about 1 : 4.5.

AMENDED SHEET (ARTICLE 19)

STATEMENT UNDER RULE 46.4

Claims 1 through 75 are currently pending in the present application.

The present Amendment under Article 19 is being filed to correct typographical errors in original claims 1, 36 and 52, wherein the phrase "each occurrence of R^9 is independently alkyl or substituted alkyl" was incorrectly recited as "each occurrence of X is independently alkyl or substituted alkyl." This defect was acknowledged by the Authorized Officer in Box No. VII of the Written Opinion of the International Searching Authority. Support for the present amendments is found in the specification as filed (for example, page 40, lines 16-18) and the original figures.

Claims 1 through 75 remain unchanged aside from the amendments recited herein.

No new matter is introduced by way of these amendments to the claims.

Fig. 1

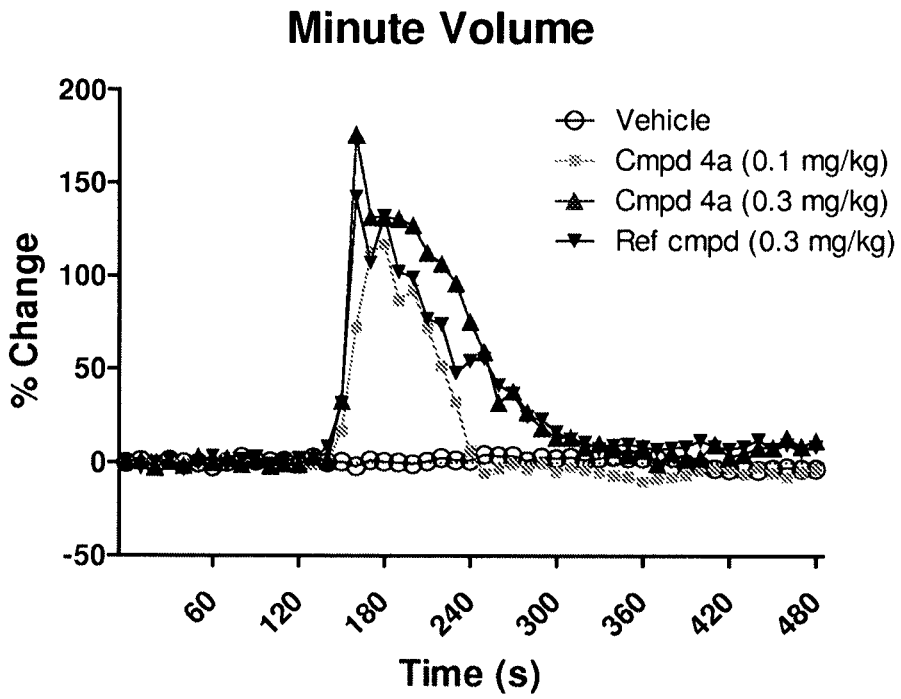

Minute Volume
200
150
100
50
0
-50
% Change
60
120
180
240
300
360
420
480
Time (s)
Vehicle
Cmpd 4a (0.1 mg/kg)
Cmpd 4a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)

Fig. 2

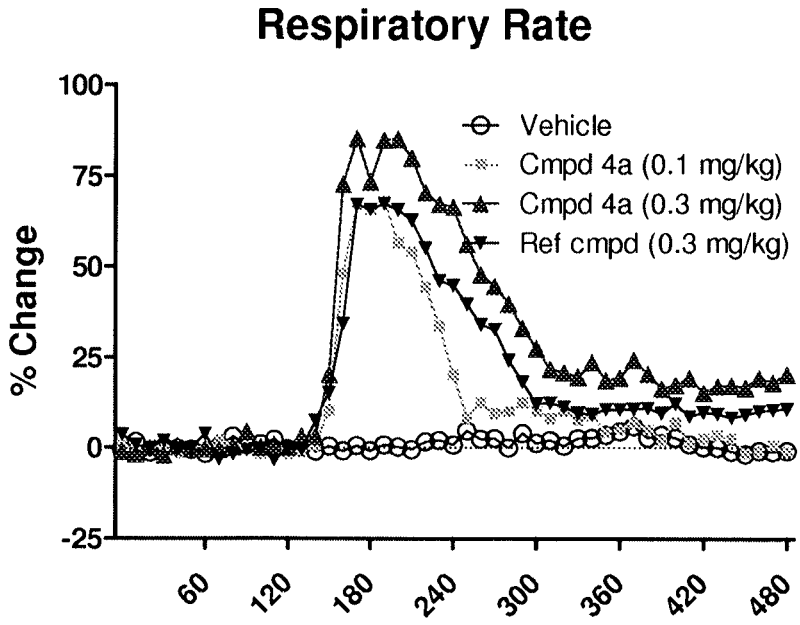

Respiratory Rate
100
75
50
25
0
-25
% Change
60
120
180
240
300
360
420
480
Vehicle
Cmpd 4a (0.1 mg/kg)
Cmpd 4a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)

Fig. 3

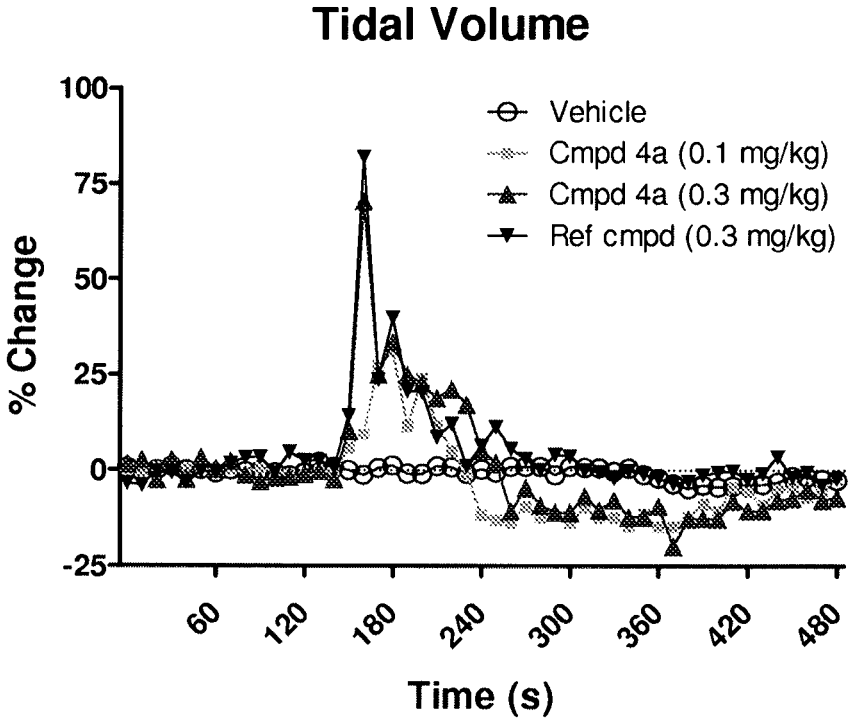

Tidal Volume
Vehicle
Cmpd 4a (0.1 mg/kg)
Cmpd 4a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)
% Change
100
75
50
25
0
-25
60
120
180
240
300
360
420
480
Time (s)

Fig. 4

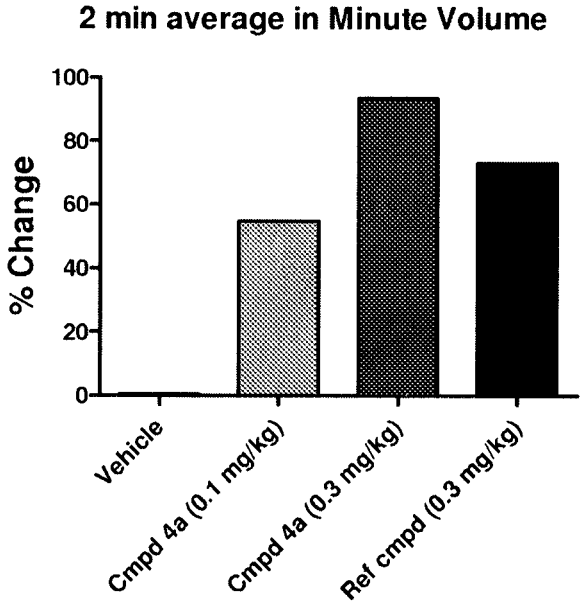

2 min average in Minute Volume
% Change
100
80
60
40
20
0
Vehicle
Cmpd 4a (0.1 mg/kg)
Cmpd 4a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)

Fig. 5

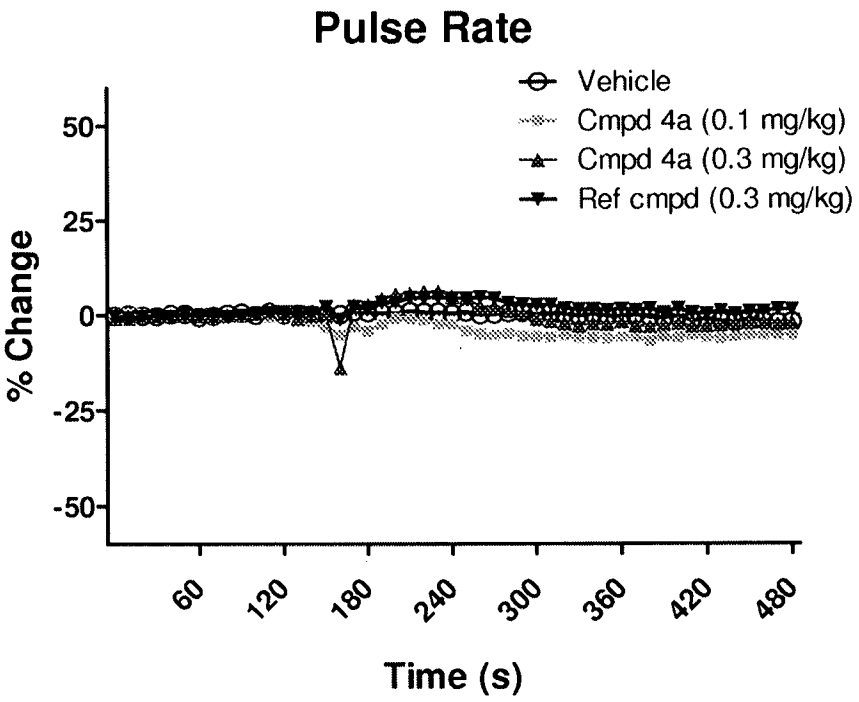

Pulse Rate
Vehicle
Cmpd 4a (0.1 mg/kg)
Cmpd 4a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)
% Change
50
25
0
-25
-50
60
120
180
240
300
360
420
480
Time (s)

Fig. 6

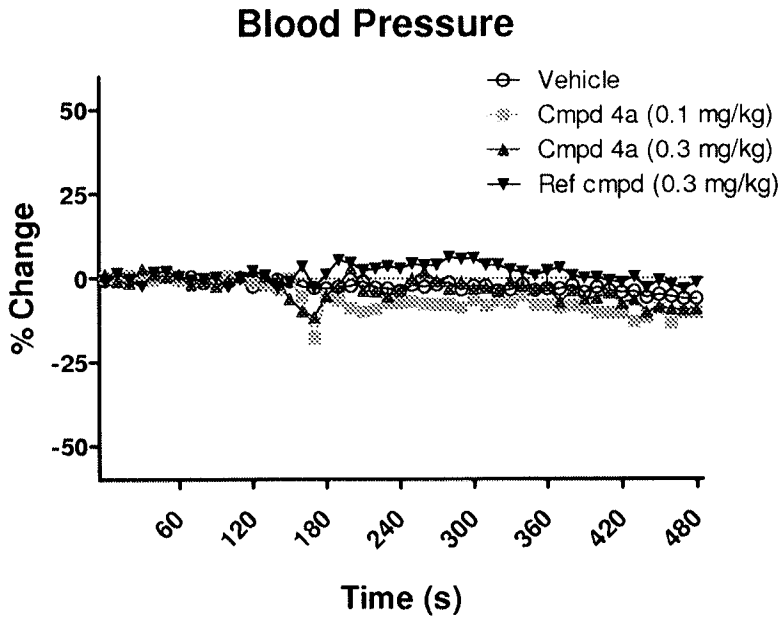

Blood Pressure
Vehicle
Cmpd 4a (0.1 mg/kg)
Cmpd 4a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)
% Change
50
25
0
-25
-50
60
120
180
240
300
360
420
480
Time (s)

Fig. 7

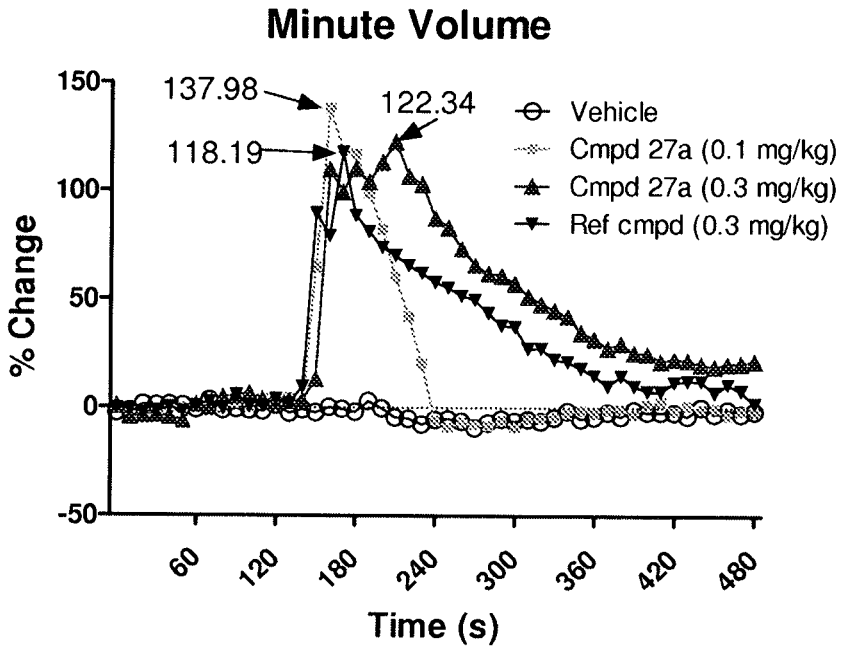

Minute Volume
137.98
122.34
118.19
Vehicle
Cmpd 27a (0.1 mg/kg)
Cmpd 27a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)
% Change
150
100
50
0
-50
60
120
180
240
300
360
420
480
Time (s)

Fig. 8

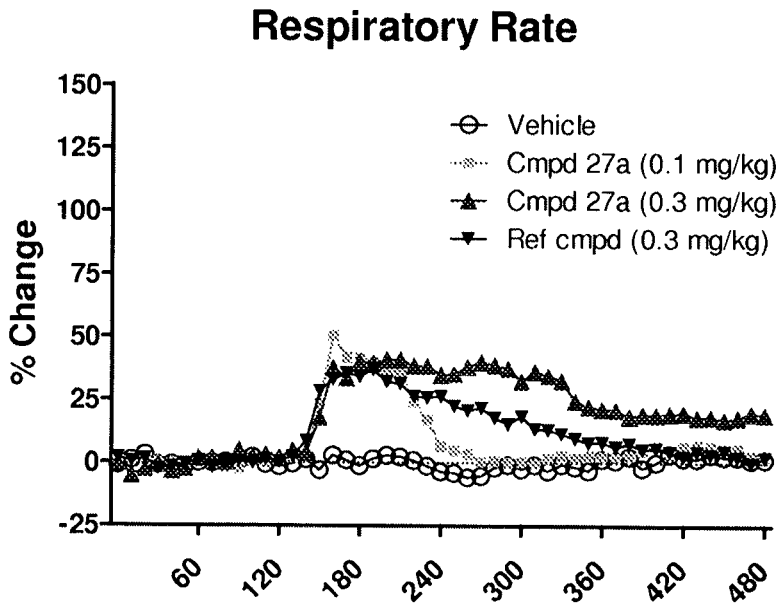

Respiratory Rate
Vehicle
Cmpd 27a (0.1 mg/kg)
Cmpd 27a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)
% Change
150
125
100
75
50
25
0
-25
60
120
180
240
300
360
420
480

Fig. 9

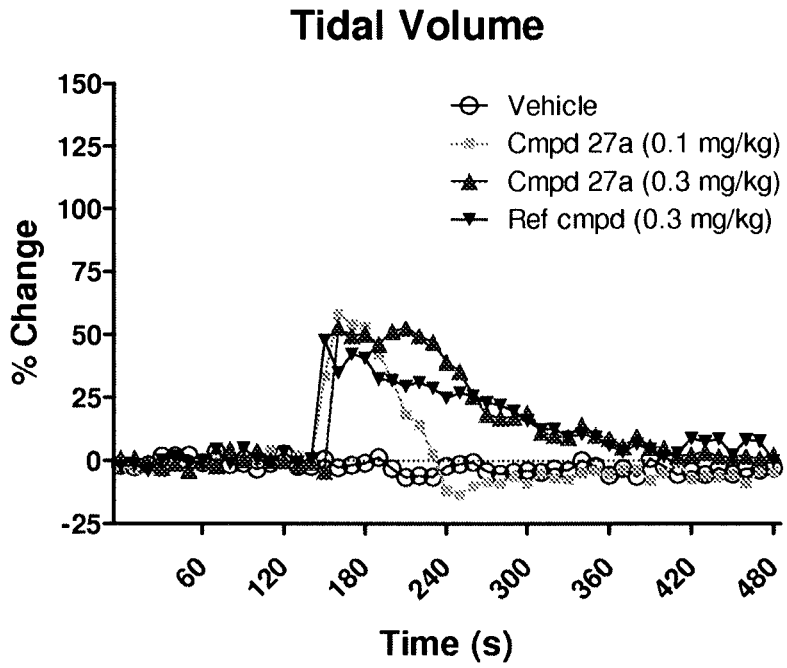

Tidal Volume
Vehicle
Cmpd 27a (0.1 mg/kg)
Cmpd 27a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)
% Change
150
125
100
75
50
25
0
-25
60
120
180
240
300
360
420
480
Time (s)

Fig. 10

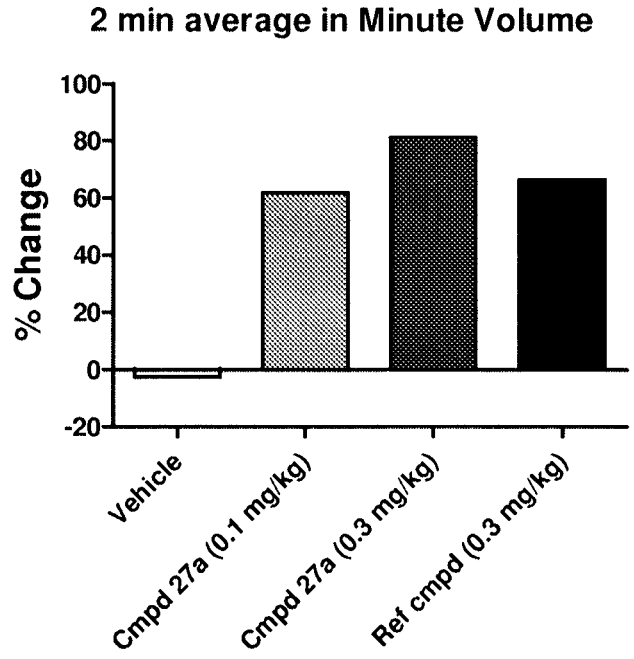

2 min average in Minute Volume
% Change
100
80
60
40
20
0
-20
Vehicle
Cmpd 27a (0.1 mg/kg)
Cmpd 27a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)

Fig. 11

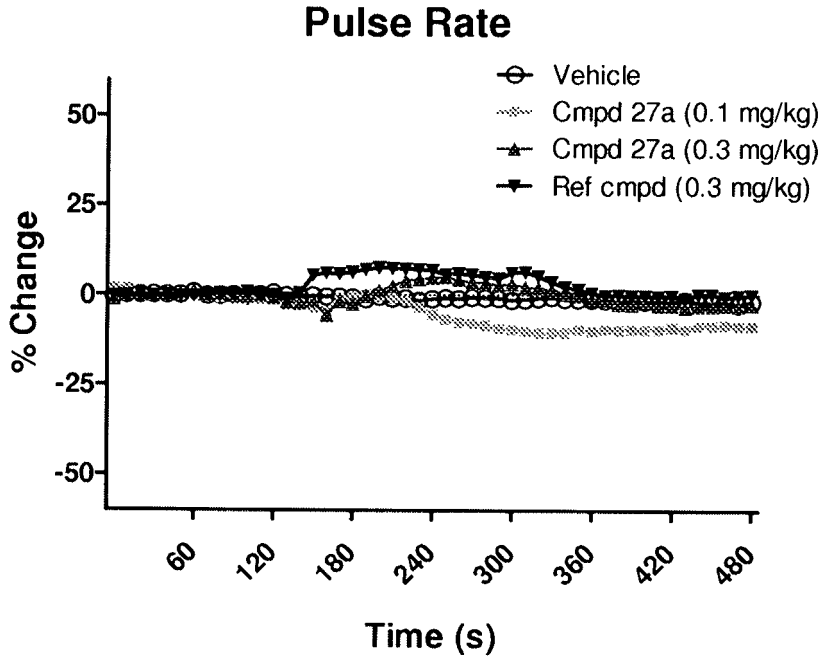

Pulse Rate
Vehicle
Cmpd 27a (0.1 mg/kg)
Cmpd 27a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)
% Change
50
25
0
-25
-50
60
120
180
240
300
360
420
480
Time (s)

Fig. 12

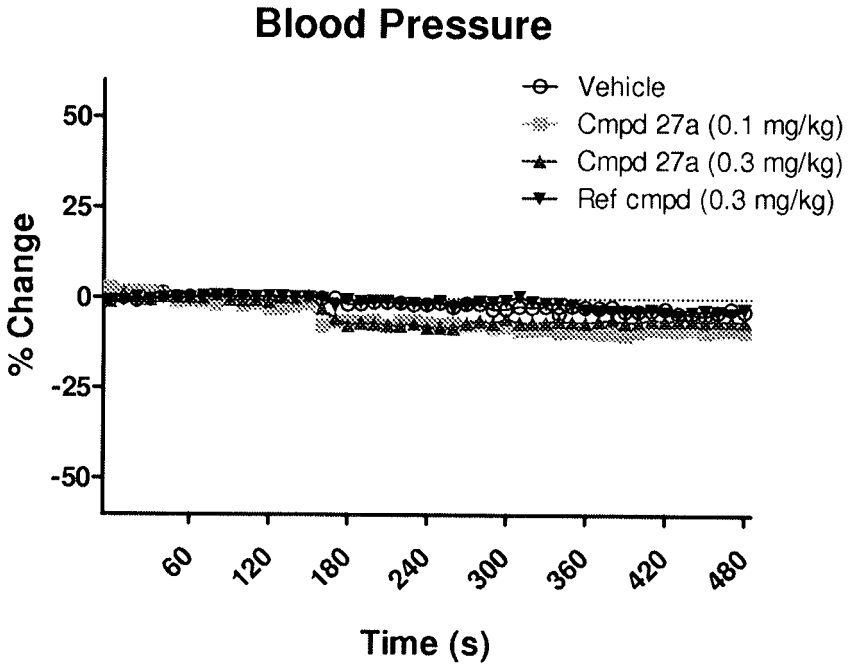

Blood Pressure
Vehicle
Cmpd 27a (0.1 mg/kg)
Cmpd 27a (0.3 mg/kg)
Ref cmpd (0.3 mg/kg)
% Change
50
25
0
-25
-50
60
120
180
240
300
360
420
480
Time (s)

Fig. 13

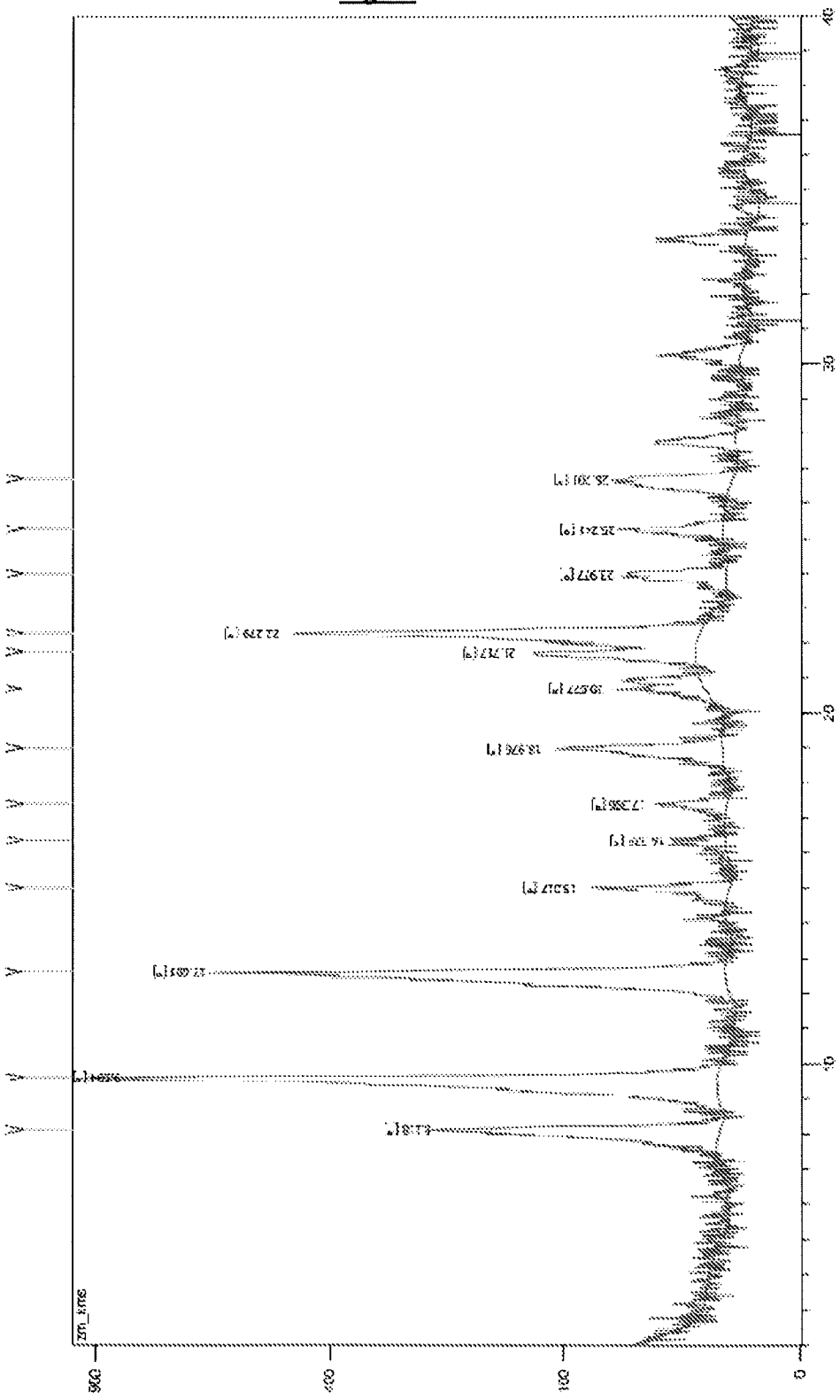


Fig. 14

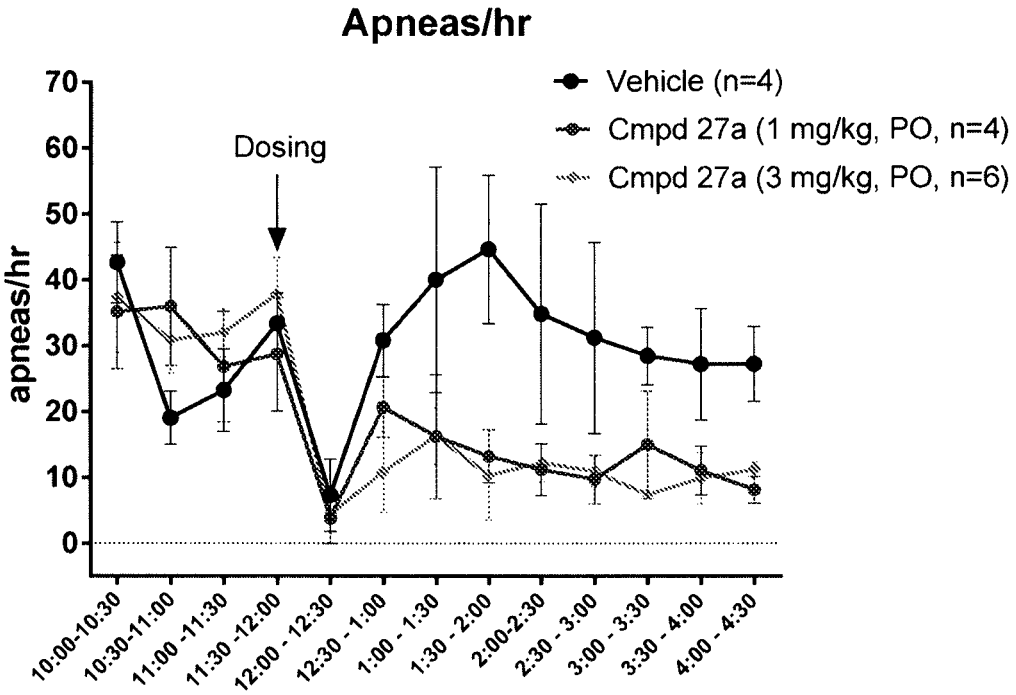

Apneas/hr
Vehicle (n=4)
Cmpd 27a (1 mg/kg, PO, n=4)
Cmpd 27a (3 mg/kg, PO, n=6)
Dosing
apneas/hr
70
60
50
40
30
20
10
0
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

Fig. 15

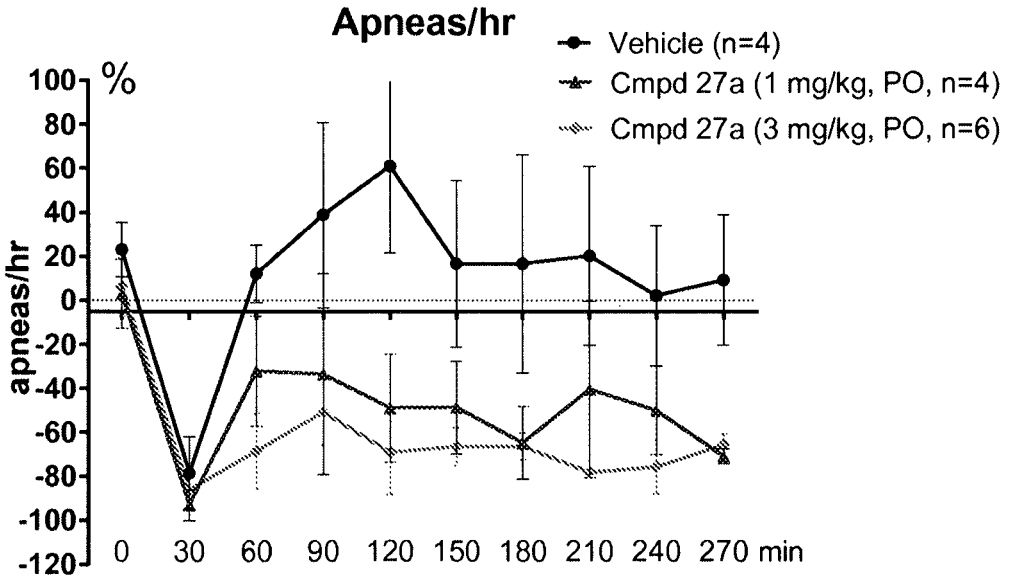

Apneas/hr
Vehicle (n=4)
Cmpd 27a (1 mg/kg, PO, n=4)
Cmpd 27a (3 mg/kg, PO, n=6)
%
apneas/hr
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
0
30
60
90
120
150
180
210
240
270 min

Fig. 16

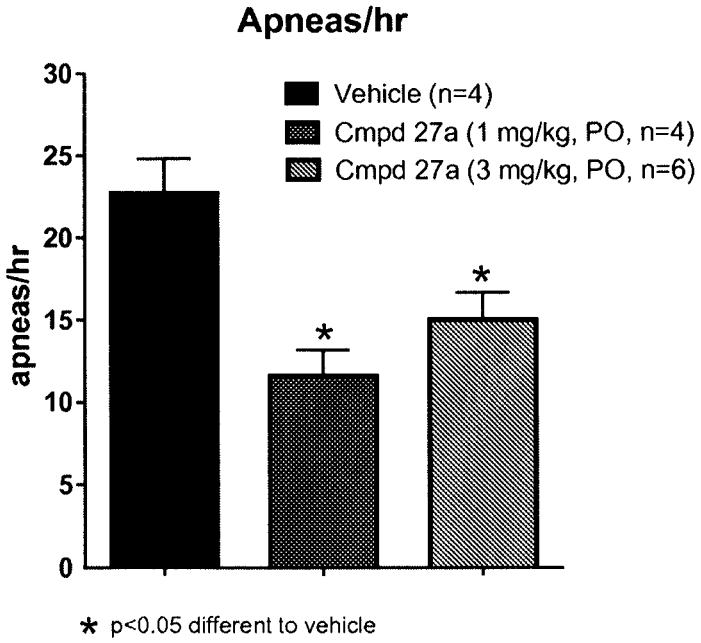

Apneas/hr
Vehicle (n=4)
Cmpd 27a (1 mg/kg, PO, n=4)
Cmpd 27a (3 mg/kg, PO, n=6)
apneas/hr
30
25
20
15
10
5
0
*
*
* p<0.05 different to vehicle

Fig. 17

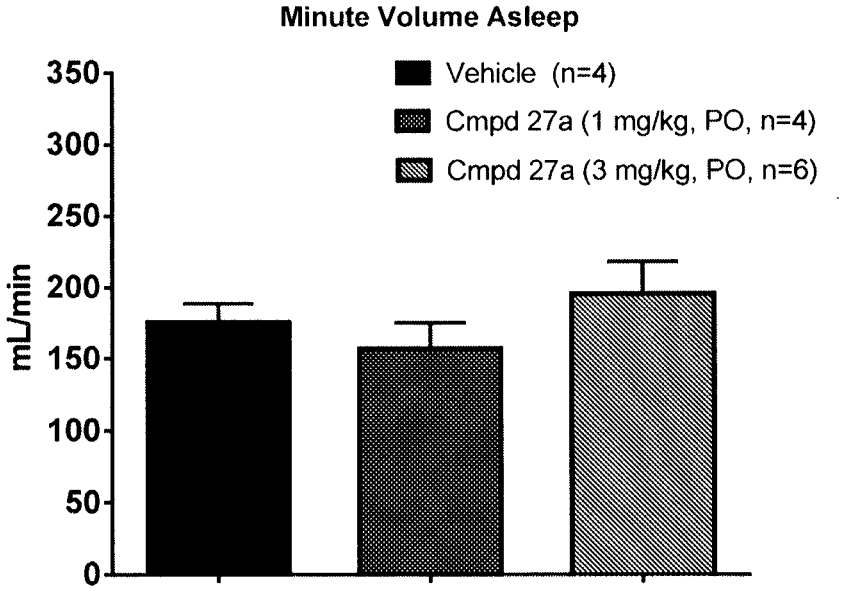

Minute Volume Asleep
Vehicle (n=4)
Cmpd 27a (1 mg/kg, PO, n=4)
Cmpd 27a (3 mg/kg, PO, n=6)
mL/min
350
300
250
200
150
100
50
0

Fig. 18

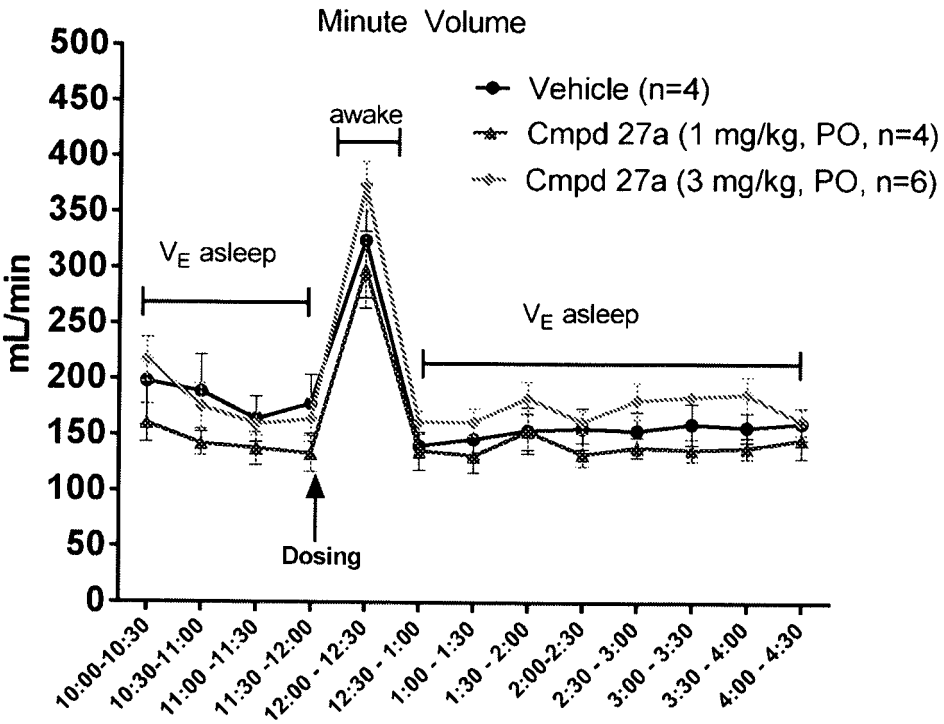

Minute Volume
Vehicle (n=4)
Cmpd 27a (1 mg/kg, PO, n=4)
Cmpd 27a (3 mg/kg, PO, n=6)
awake
V_E asleep
V_E asleep
Dosing
mL/min
500
450
400
350
300
250
200
150
100
50
0
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

Fig. 19

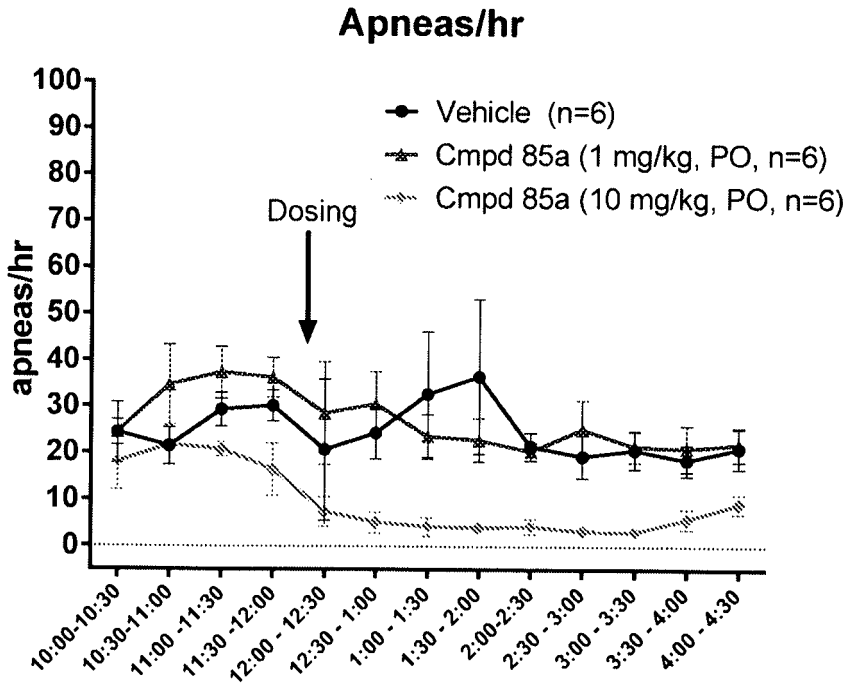

Apneas/hr
Vehicle (n=6)
Cmpd 85a (1 mg/kg, PO, n=6)
Cmpd 85a (10 mg/kg, PO, n=6)
Dosing
apneas/hr
100
90
80
70
60
50
40
30
20
10
0
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

Fig. 20

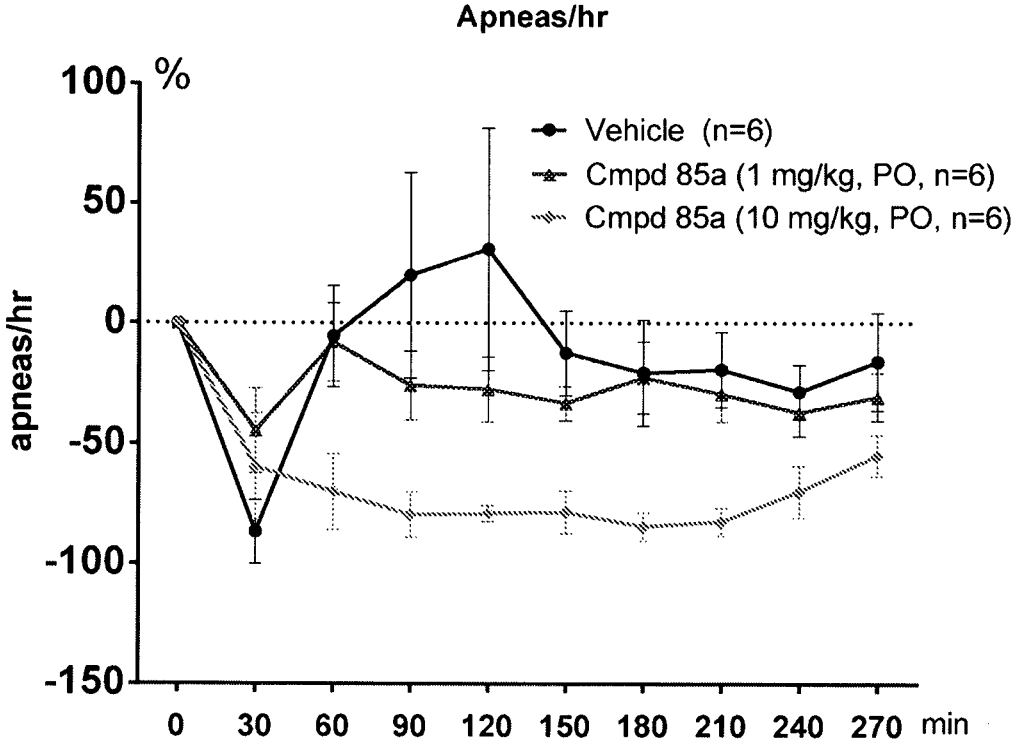

Apneas/hr
100
%
50
0
-50
-100
-150
apneas/hr
Vehicle (n=6)
Cmpd 85a (1 mg/kg, PO, n=6)
Cmpd 85a (10 mg/kg, PO, n=6)
0
30
60
90
120
150
180
210
240
270
min

Fig. 21

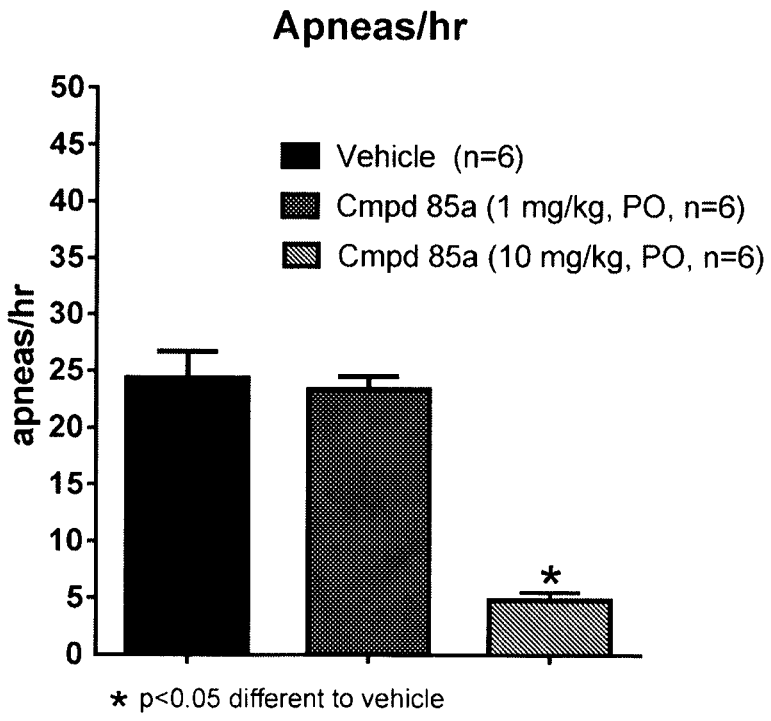

Apneas/hr
50
45
40
35
30
25
20
15
10
5
0
apneas/hr
Vehicle (n=6)
Cmpd 85a (1 mg/kg, PO, n=6)
Cmpd 85a (10 mg/kg, PO, n=6)
*
* p<0.05 different to vehicle

Fig. 22

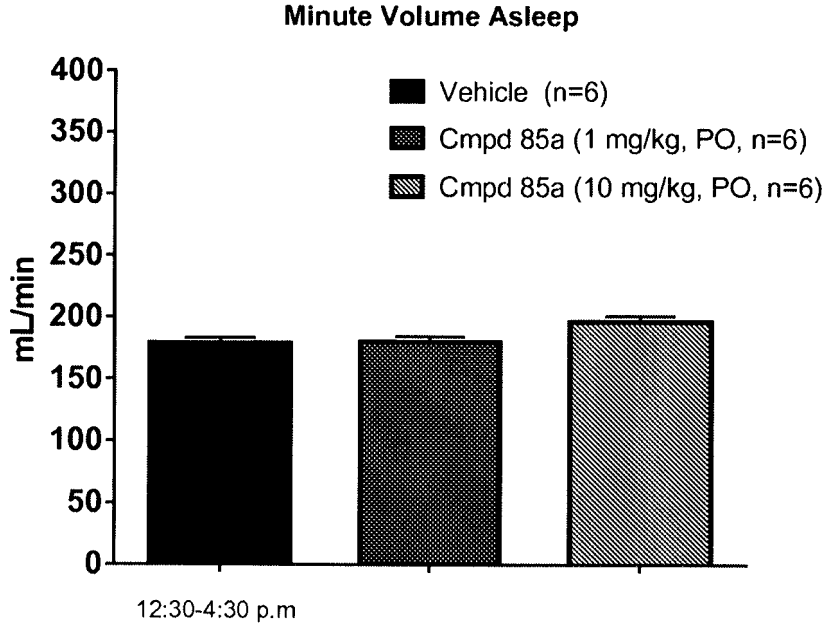

Minute Volume Asleep
Vehicle (n=6)
Cmpd 85a (1 mg/kg, PO, n=6)
Cmpd 85a (10 mg/kg, PO, n=6)
mL/min
400
350
300
250
200
150
100
50
0
12:30-4:30 p.m

Fig. 23

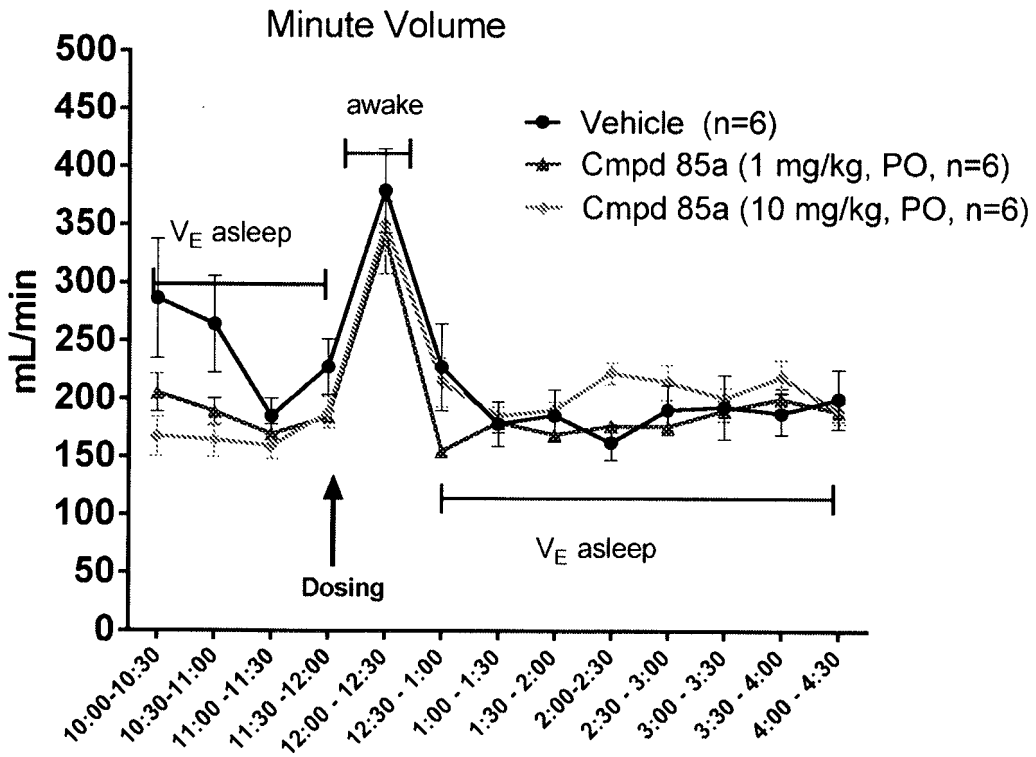

Minute Volume
awake
Vehicle (n=6)
Cmpd 85a (1 mg/kg, PO, n=6)
Cmpd 85a (10 mg/kg, PO, n=6)
mL/min
500
450
400
350
300
250
200
150
100
50
0
V_E asleep
Dosing
V_E asleep
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

Fig. 24

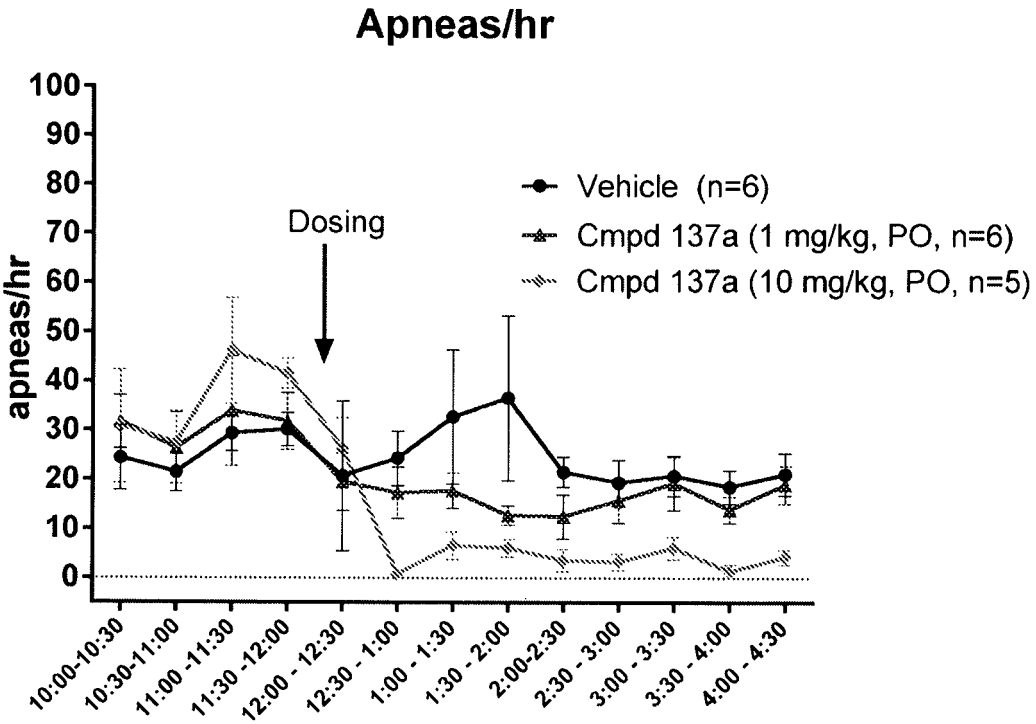

Apneas/hr
apneas/hr
100
90
80
70
60
50
40
30
20
10
0
Dosing
Vehicle (n=6)
Cmpd 137a (1 mg/kg, PO, n=6)
Cmpd 137a (10 mg/kg, PO, n=5)
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

Fig. 25

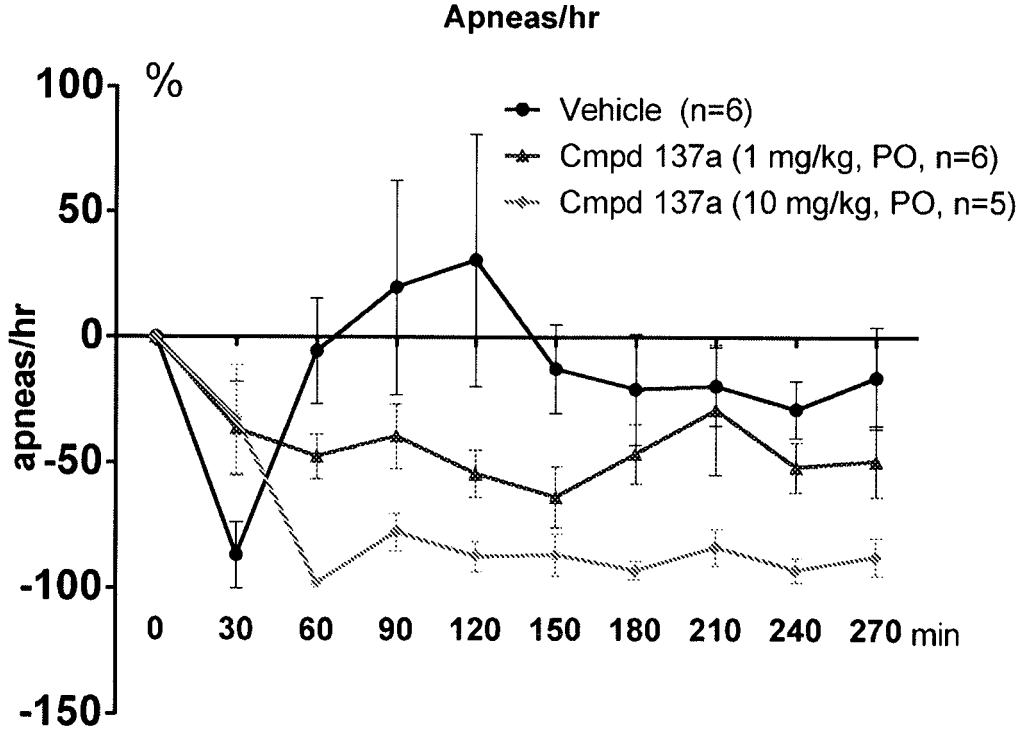

Apneas/hr
%
100
50
0
-50
-100
-150
apneas/hr
Vehicle (n=6)
Cmpd 137a (1 mg/kg, PO, n=6)
Cmpd 137a (10 mg/kg, PO, n=5)
0
30
60
90
120
150
180
210
240
270
min

Fig. 26

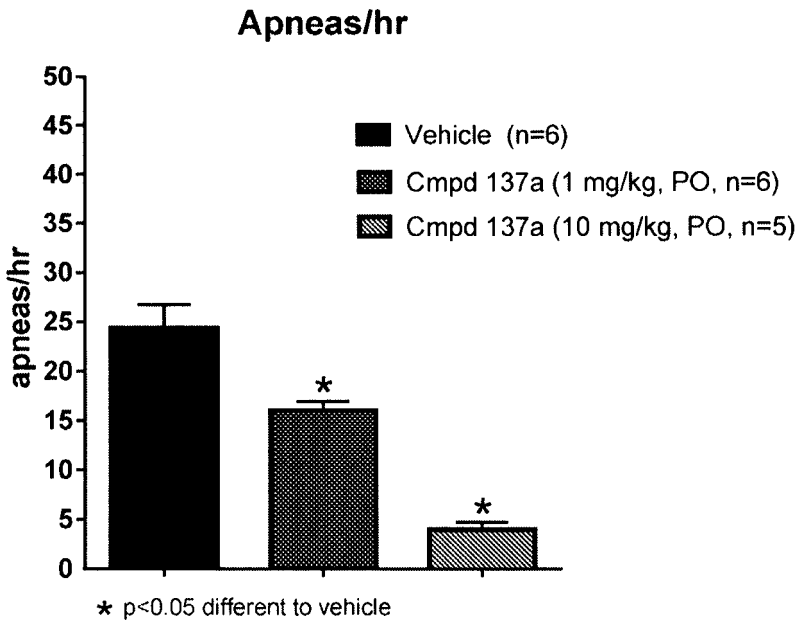

Apneas/hr
apneas/hr
50
45
40
35
30
25
20
15
10
5
0
Vehicle (n=6)
Cmpd 137a (1 mg/kg, PO, n=6)
Cmpd 137a (10 mg/kg, PO, n=5)
*
*
* p<0.05 different to vehicle

Fig. 27

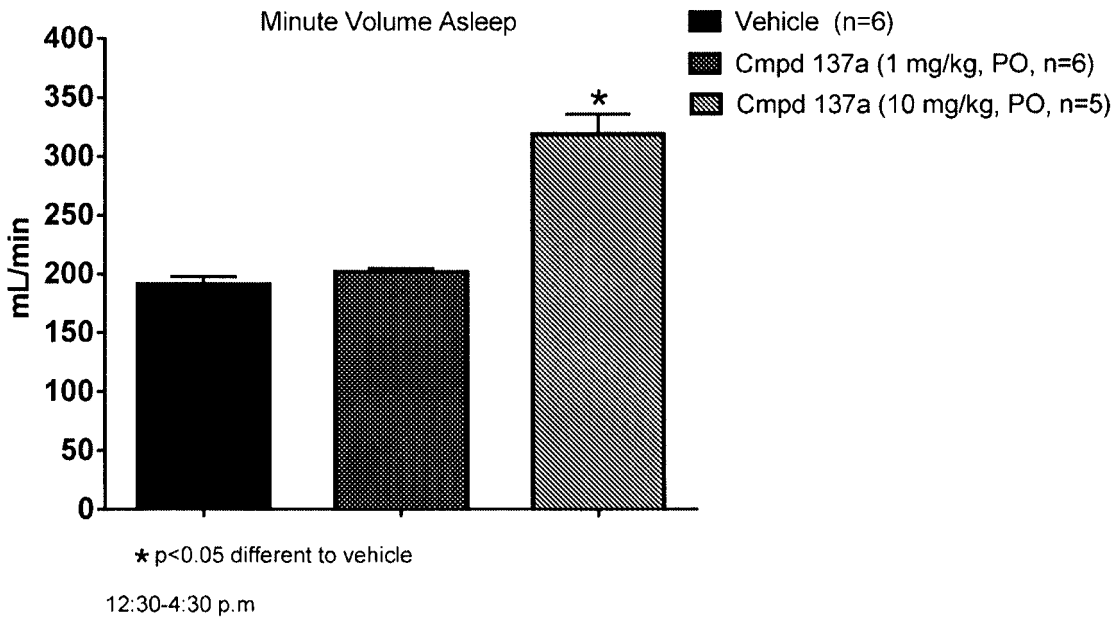

Minute Volume Asleep
mL/min
400
350
300
250
200
150
100
50
0
Vehicle (n=6)
Cmpd 137a (1 mg/kg, PO, n=6)
Cmpd 137a (10 mg/kg, PO, n=5)
*
* p<0.05 different to vehicle
12:30-4:30 p.m

Fig. 28

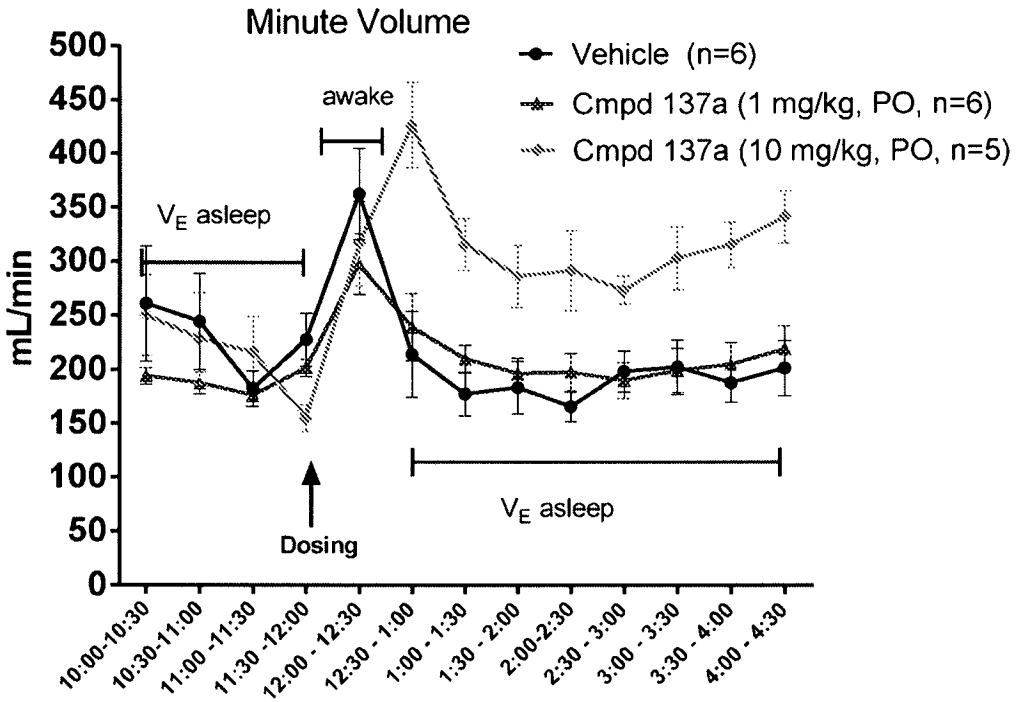

Minute Volume
Vehicle (n=6)
Cmpd 137a (1 mg/kg, PO, n=6)
Cmpd 137a (10 mg/kg, PO, n=5)
awake
V_E asleep
V_E asleep
Dosing
mL/min
500
450
400
350
300
250
200
150
100
50
0
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

Fig. 29

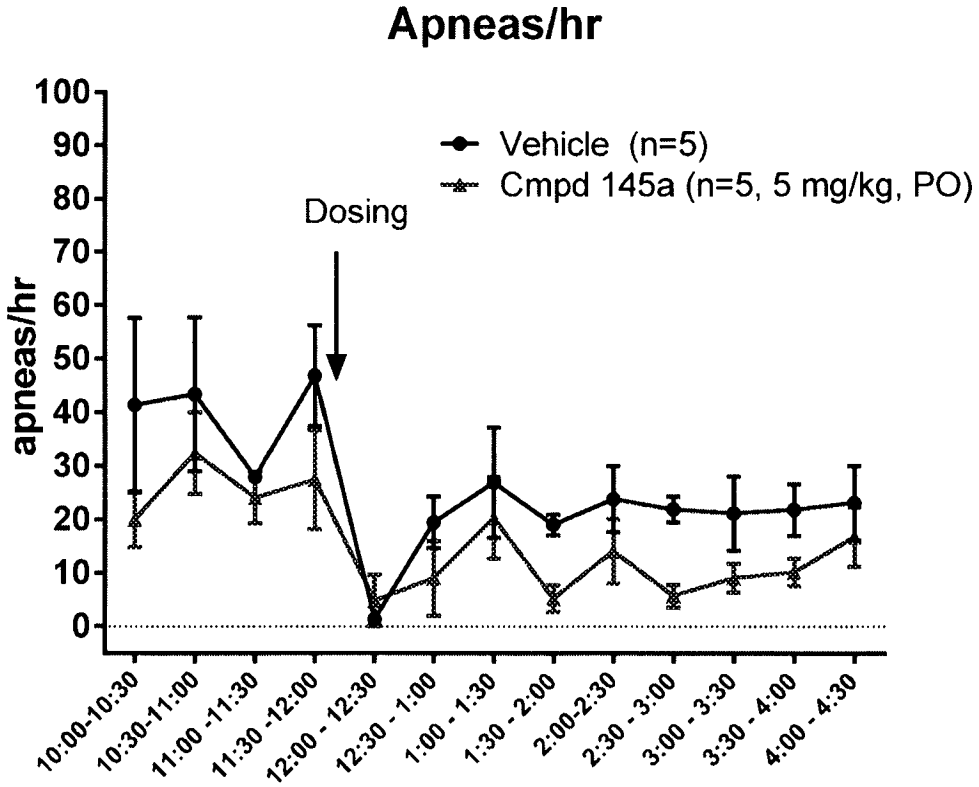

Apneas/hr
Vehicle (n=5)
Cmpd 145a (n=5, 5 mg/kg, PO)
Dosing
apneas/hr
100
90
80
70
60
50
40
30
20
10
0
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

Fig. 30

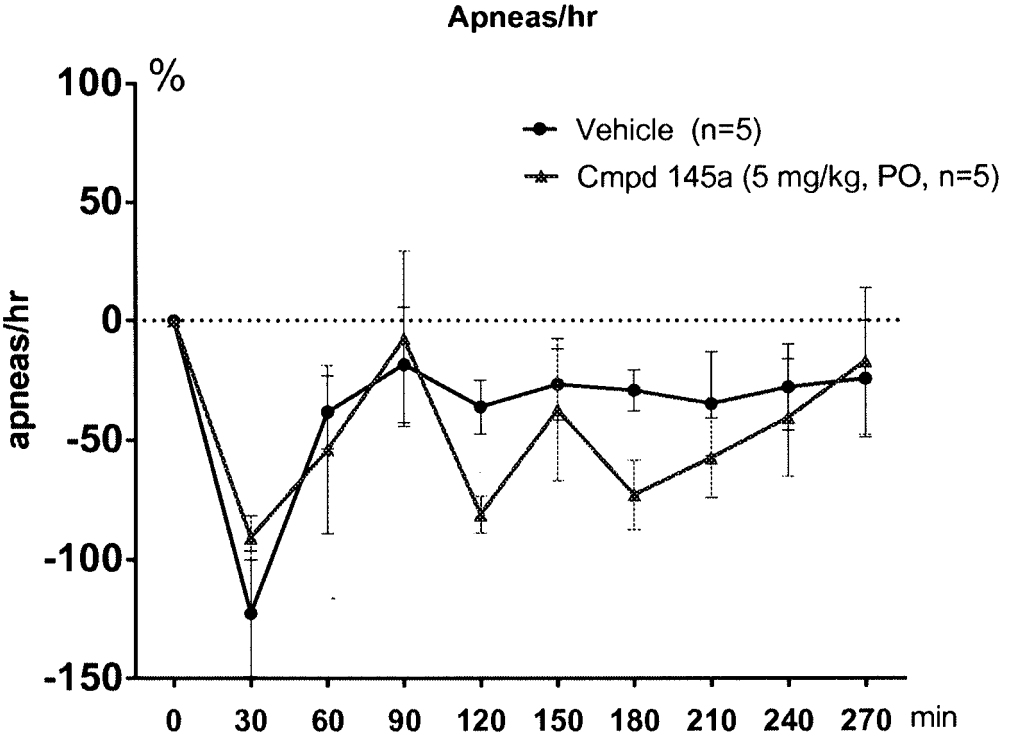

Apneas/hr
%
100
50
0
-50
-100
-150
apneas/hr
Vehicle (n=5)
Cmpd 145a (5 mg/kg, PO, n=5)
0
30
60
90
120
150
180
210
240
270
min

Fig. 31

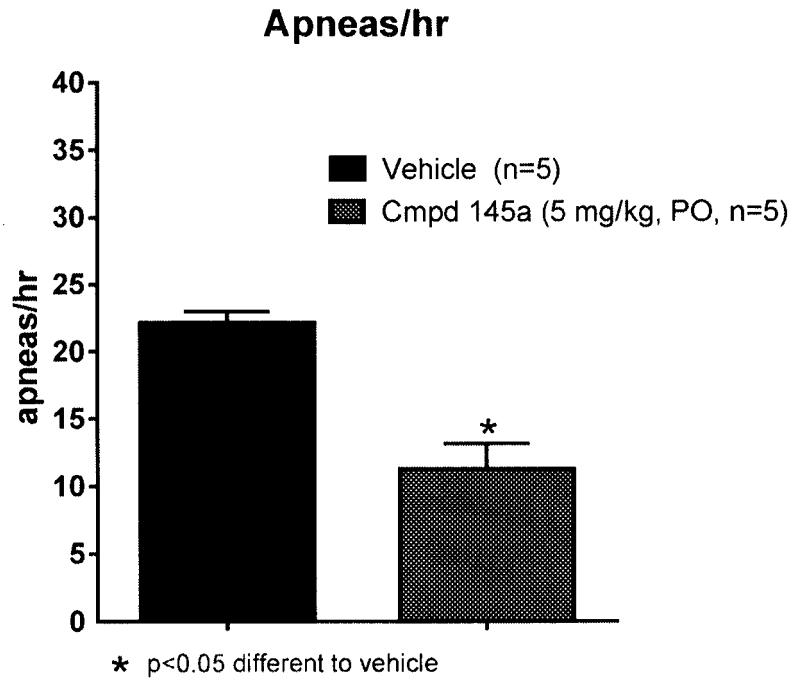

Apneas/hr
40
35
30
25
20
15
10
5
0
apneas/hr
Vehicle (n=5)
Cmpd 145a (5 mg/kg, PO, n=5)
*
* p<0.05 different to vehicle

Fig. 32

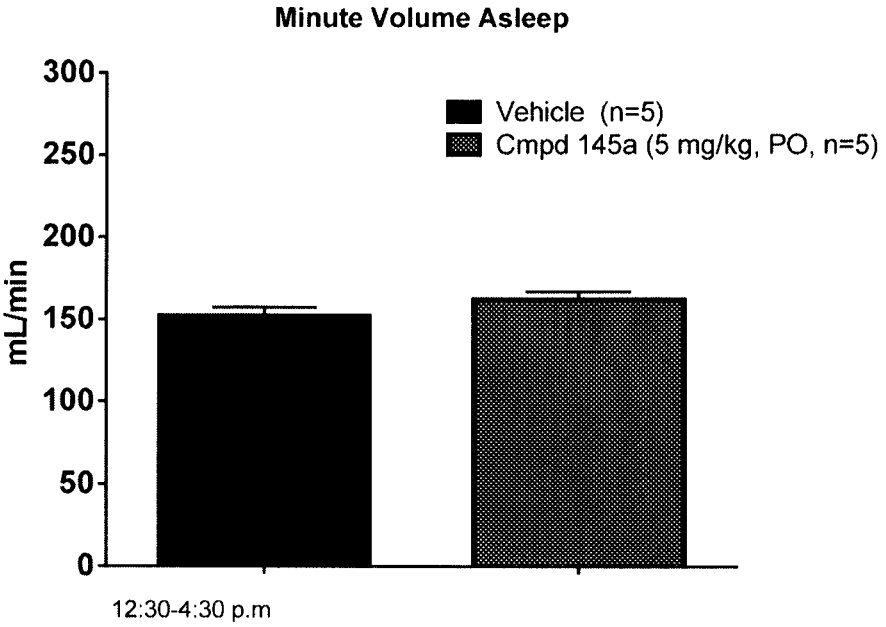
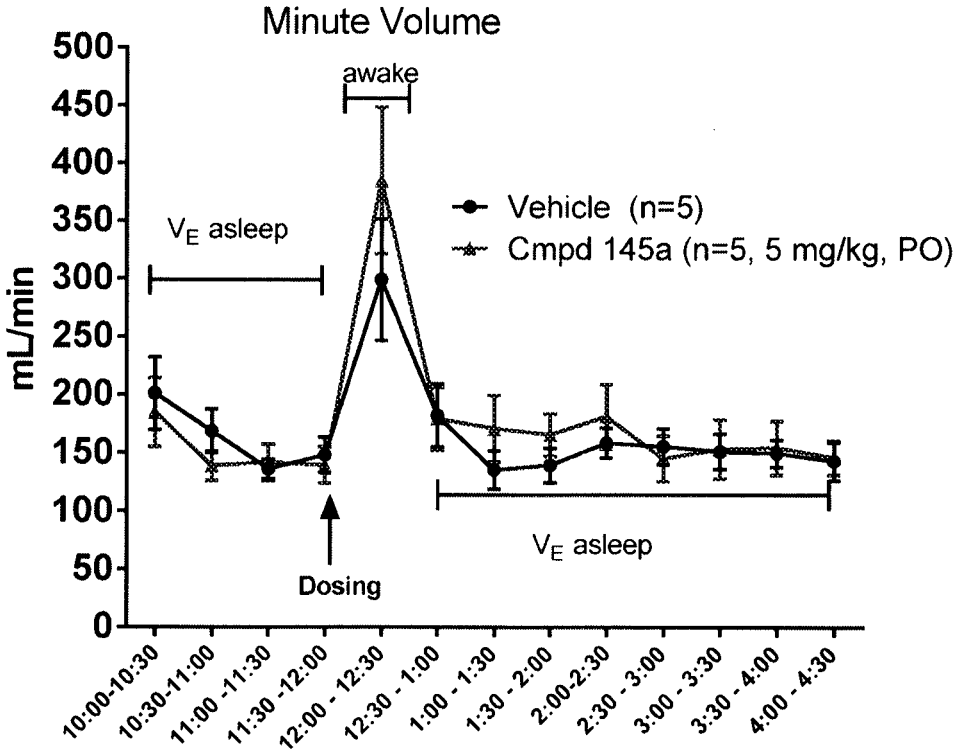

Minute Volume Asleep
300
250
200
150
100
50
0
mL/min
Vehicle (n=5)
Cmpd 145a (5 mg/kg, PO, n=5)
12:30-4:30 p.m

Fig. 33


Minute Volume
500
450
400
350
300
250
200
150
100
50
0
mL/min
awake
V_E asleep
Vehicle (n=5)
Cmpd 145a (n=5, 5 mg/kg, PO)
V_E asleep
Dosing
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/25792

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/505; A61P 11/00; C07D 257/12 (2014.01)
USPC - 514/258.1, 262.1
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(8): A61K 31/505; A61P 11/00; C07D 257/12 (2014.01)
USPC: 514/258.1, 262.1

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 practicable, search terms used)
MicroPatent (US Granted, US Applications, EP-A, EP-B, WO, JP, DE-G, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; Google Advanced Search; IP.com; KEYWORDS: pyrimidin*, treat*, breath* control*, COPD*, respira* depress*, accept* salt*, sulfate*, sulphate*, male*, stabili* breath* rhythm*, cyclopropylmethyl*, bis propylamin*, pyrimido pyrimidin*, breath*, respira* distress*, tetraamin*, dimethylamin*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	PUBCHEM SureCN7939019, CID 350861, pages 1-3, Create Date: 2005-03-26; page 1; [retrieved on 2014-06-18]. Retrieved from the Internet: <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=350861&loc=ec_rcs>	1 --- 2-75
X --- A	PUBCHEM SureCN7930960, CID 350874, pages 1-3, Create Date: 2005-03-26; page 1; [retrieved on 2014-06-18]. Retrieved from the Internet: <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=350874&loc=ec_rcs>	1 --- 2-75
A	US 6,232,312 B1 (PAMUKCU, R et al.) 15 May 2001; column 4, lines 37-67; column 5, lines 1-11, 33-37; column 6, lines 5-7	2-75
A	US 2005/0159414 A1 (NICKOLAUS, P et al.) 21 July 2005; paragraphs [0010]-[0020], [0082]-[0083], [0087]-[0088], [0102]	2-75
A	WO 2012/074999 A1 (DAX, SL et al.) 07 June 2012; page 34, lines 1-3, 25-27; page 37, lines 3-4; page 39, lines 25-32; page 149, Table 7	2-75

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2014 (30.06.2014)	30 JUL 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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(74) Agents: **SILVA, Domingos** et al.; Saul Ewing, LLP, Centre Square West, 1500 Market Street, Philadelphia, Pennsylvania 19102 (US).

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

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Published:

— *with international search report (Art. 21(3))*

— *with amended claims and statement (Art. 19(1))*

Date of publication of the amended claims and statement: 13 November 2014

(54) Title: NOVEL BREATHING CONTROL MODULATING COMPOUNDS, AND METHODS OF USING SAME

(57) Abstract: The present invention includes pyrimido[5,4-*d*]pyrimidines that are useful in the prevention and/or treatment of breathing control diseases or disorders in a subject in need thereof. The present invention also includes a method of preventing and/or treating a respiratory disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the invention. The present invention further includes a method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the invention.

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权利要求书17页 说明书106页 附图17页
按照条约第19条修改的权利要求书17页

(54)发明名称

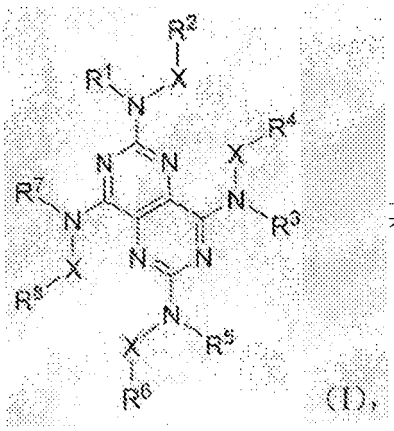
新型呼吸控制调节化合物及其使用方法

(57)摘要

本发明包括可用于在有需要的对象中预防和/或治疗呼吸控制疾病或障碍的嘧啶并[5,4-d]嘧啶。本发明还包括在有需要的对象中预防和/或治疗呼吸疾病或障碍的方法，包括给予对象治疗有效量的本发明化合物。本发明进一步包括在有需要的对象中预防呼吸节奏失稳或稳定呼吸节奏的方法，包括给予对象治疗有效量的本发明化合物。

CN 105209041 A

1. 化合物或其盐，选自：

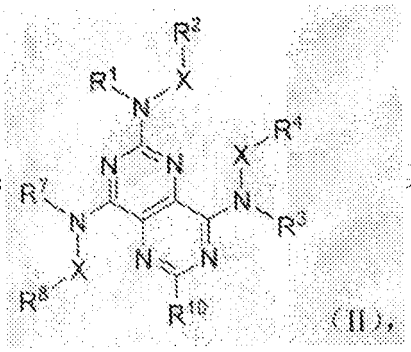
式（I）化合物：  （I），其中在式（I）中：

R^1、R^2、R^3、R^4、R^5、R^6、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；和

每次出现的 X 独立地是烷基或取代烷基；

式（II）化合物：  （II），其中在式（II）中：

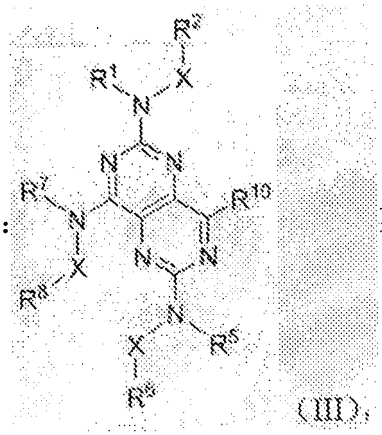
R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^1、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基、或取代烷基；

R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基；和

式（III）化合物：  （III），其中在式（III）中：

R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基或取代烷基；和

R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基；

以及其任意组合。

2. 根据权利要求 1 所述的化合物，其中所述化合物选自：

N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^4, N^6, N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 正丁基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 异丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二甲基 -N^4- 正丙基 -N^8- 丙 -2- 炔基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基）氨基）-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶；

N-(6- 氯 -4,8- 双 - 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基）-O,N- 二甲基 - 羟基胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基）氨基）-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶盐酸盐；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基）- 羟基胺；

N^4, N^8- 二甲基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6- 三甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2- 二乙基 -N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-(4,8- 双 - 正丙基氨基 -6- 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基 - 氨基）- 乙醇；

N^2-(2-甲氧基-乙基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2-(2-异丙氧基-乙基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^8-甲基-N^4,N^6-二-正丙基-N^2-(3,3,3-三氟丙基)-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2-甲基-N^4,N^8-二-正丙基-6-(吗啉-4-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2-甲基-N^4,N^8-二-正丙基-6-(哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2-甲基-N^4,N^8-二-正丙基-6-吡咯烷-1-基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2-甲基-N^4,N^8-二-正丙基-6-(4-甲氧基-哌啶-1-基)-嘧啶并[5,4,-d]嘧啶-2,4,8-三胺;

N^2-(3-氯-2-甲基-苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2-(3,4-二氯苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2-(4-氟苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

6-氯-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2,N^2,N^4,N^8-四甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2,N^2-二烯丙基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-甲基-氨基]-乙醇;

N^2-(2-异丙氧基-乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

2-[N-(2-二甲基氨基-乙基)-N-甲基]氨基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-4,6,8-三胺;

2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-(2-羟基-乙基)-氨基]-乙醇;

N^2,N^2-双-(2-甲氧基乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

6-(4-氧-哌啶-1-基)-N^4,N^8-二甲基-N^2-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺;

N^2-(3-三氟甲基-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺;

N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺;

N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2,N^6- 二 - 正丁基 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^6- 双 - 环丙基甲基 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^6- 二异丁基 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^6- 二烯丙基 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

2- 氯 -6-(N,N' - 二甲基 - 肼基)-N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 ;

6-(N,N' - 二甲基 - 肼基)-N^2,N^2,N^4,N^8- 四甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^4,N^8- 二甲基 -6- 丙氧基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^4,N^8- 二甲基 -N^2- 正丙基 -6- 丙基硫烷基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 苄氧基 -N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 醇 ;

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 ;

N^4,N^8- 二甲基 -N^2- 正丙基 -6-(氨基甲基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 氨甲酰基 -N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 羧酸 ;

N-(正丙基)-[4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基]- 脒 ;

N^4,N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^2- 甲基 -N^4,N^8- 二 - 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 正丁基 -N^2- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 甲氧基 -N^2- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 ;

N^2,N^4,N^6,N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺

2,6- 二氯 -N^4,N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 ;

N^4,N^8- 二乙基 -N^2,N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^6- 双 - 环丙基甲基 -N^4,N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^6- 二乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^2,N^6- 三乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

6- 氯 -N^2- 乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^2,N^6- 二乙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^6- 二环丙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^6- 双 - 环丙基甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^2,N^6,N^6- 四甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^4,N^8- 二烯丙基 -N^2,N^6- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2,N^4,N^8- 三烯丙基 -6-[4-(4- 氟苄基)- 哌嗪 -1- 基]- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 氯 -N^2,N^4,N^8- 三烯丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^2,N^4,N^8- 三烯丙基 -6-{4-[双 -(4- 氟苯基)- 甲基]- 哌嗪 -1- 基 }- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^2,N^2,N^6- 三乙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯；

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸；

N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺；

(6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯；

其盐或溶剂化物，和其任意组合。

3. 根据权利要求 1 所述的化合物，其中所述盐选自硫酸盐、硫酸氢盐、半硫酸盐、氯化物、溴化物、碘化物、硝酸盐、碳酸盐、磷酸盐、磷酸氢盐、磷酸二氢盐、甲酸盐、乙酸盐、丙酸盐、琥珀酸盐、乙醇酸盐、葡萄糖酸盐、乳酸盐、苹果酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐、葡萄糖醛酸盐、马来酸盐、富马酸盐、丙酮酸盐、天冬氨酸盐、谷氨酸盐、苯甲酸盐、邻氨基苯甲酸盐、4- 羟基苯甲酸盐、苯基乙酸盐、扁桃酸盐、扑酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、泛酸盐、三氟甲磺酸盐、2- 羟基乙磺酸盐、对甲苯磺酸盐、磺胺酸盐、环己基氨基磺酸盐、硬脂酸盐、海藻酸盐、β - 羟基丁酸盐、水杨酸盐、半乳糖酸盐、半乳糖醛酸盐、糖精、糖质酸盐、甘油膦酸盐、和其任意组合。

4. 药物组合物，包括根据权利要求 1 所述的化合物和至少一种药学上可接受的载体。

5. 根据权利要求 4 所述的组合物，进一步包括至少一种用剂，所述用剂选自多沙普仑及其对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂、苯二氮䓬受体激动剂、食欲肽拮抗剂、三环类抗抑郁剂、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素、食欲肽、褪黑激素激动剂、安帕金、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂。

6. 根据权利要求 5 所述的组合物，其中所述化合物和所述用剂在所述组合物中是物理混合的。

7. 根据权利要求 5 所述的组合物，其中所述化合物和所述用剂在所述组合物中是物理分开的。

8. 根据权利要求 4 所述的组合物，进一步包括已知导致呼吸控制变化的至少一种用剂。

9. 根据权利要求 8 所述的组合物，其中所述至少一种用剂选自阿片类麻醉剂、苯二氮䓬类、镇静剂、睡眠助剂、催眠剂、丙泊酚、和其任意组合。

10. 根据权利要求 8 所述的组合物，其中所述化合物和所述用剂在所述组合物中是物理混合的。

11. 根据权利要求 8 所述的组合物，其中所述化合物和所述用剂在组合物中是物理分开的。

12. 根据权利要求 4 所述的组合物，其中所述组合物允许改善所述化合物在口服给予对象后的递送。

13. 根据权利要求 12 所述的组合物，其中所述组合物最小化所述化合物至所述对象的胃的递送和最大化所述化合物至所述对象的肠的递送。

14. 根据权利要求 12 所述的组合物，其中所述组合物包括肠溶包衣。

15. 根据权利要求 12 所述的组合物，其中所述化合物被包含在药学上适合的胶囊中。

16. 根据权利要求 15 所述的组合物，其中所述胶囊包含所述化合物、或所述化合物与赋形剂的混合物的颗粒或粉末。

17. 根据权利要求 16 所述的组合物，其中所述赋形剂包括粘合剂、崩解剂、稀释剂、缓冲剂、润滑剂、助流剂、抗氧化剂、抗菌防腐剂、着色剂、或调味剂。

18. 根据权利要求 16 所述的组合物，其中所述胶囊有肠溶包衣，但所述化合物颗粒或粉末没有肠溶包衣。

19. 根据权利要求 16 所述的组合物，其中所述化合物颗粒或粉末在置入所述胶囊前包覆有肠溶包衣。

20. 根据权利要求 19 所述的组合物，其中所述化合物颗粒或粉末包覆有多种肠溶包衣，从而提供药物至所述对象的肠的不同区域的递送。

21. 根据权利要求 16 所述的组合物，其中至少部分所述化合物颗粒或粉末有肠溶包衣。

22. 根据权利要求 21 所述的组合物，其中所述胶囊包覆有与包覆所述化合物颗粒或粉末的肠溶包衣不同的肠溶包衣。

23. 根据权利要求 12 所述的组合物，其中所述化合物被包覆到基体颗粒上，从而形成内核，所述内核包括作为所述基体颗粒上的包衣的药物。

24. 根据权利要求 23 所述的组合物，其中所述基体颗粒没有肠溶包衣，并且所述组合物被包含在有肠溶包衣的药学上可接受的胶囊中。

25. 根据权利要求 23 所述的组合物，其中所述内核包覆有肠溶包衣，从而形成肠溶包衣小珠。

26. 根据权利要求 25 所述的组合物，其中所述肠溶包衣小珠被包含在药学上可接受的胶囊中。

27. 根据权利要求 26 所述的组合物，其中所述胶囊包含包覆有多种肠溶包衣的小珠，使得所述胶囊提供所述化合物至所述对象的肠的不同区域的递送。

28. 根据权利要求 16 所述的组合物，进一步其中所述胶囊的内含物溶解或悬浮于药学上可接受的液体中，以提供液体填充胶囊。

29. 根据权利要求 28 所述的组合物，其中所述胶囊有肠溶包衣，但其中包含的液体制剂不包括肠溶包衣。

30. 根据权利要求 28 所述的组合物，其中所述化合物颗粒或粉末有肠溶包衣。

31. 根据权利要求 30 所述的组合物，其中所述化合物颗粒或粉末包覆有多种肠溶包衣，以提供药物至所述对象的肠的不同区域的递送。

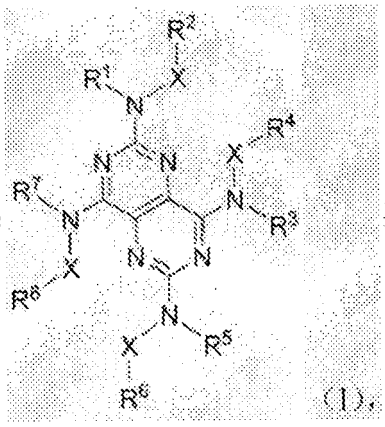
32. 根据权利要求 30 所述的组合物，其中施加于所述胶囊的肠溶包衣与施加于任何所述化合物颗粒或粉末的肠溶包衣不同。

33. 根据权利要求 15 所述的组合物，其中所述化合物被包覆在基体颗粒上，从而形成内核，所述内核包括作为所述基体颗粒上的包衣的所述化合物，其中所述内核悬浮于药学上可接受的液体中，并且其中悬浮的所述内核被置入胶囊。

34. 根据权利要求 33 所述的组合物，其中所述胶囊有肠溶包衣，但所述内核没有肠溶包衣。

35. 根据权利要求 33 所述的组合物，其中所述胶囊和所述内核有肠溶包衣。

36. 在有需要的对象中预防或治疗呼吸控制障碍或疾病的方法，所述方法包括给予所述对象有效量的药物组合物，所述药物组合物包括至少一种药学上可接受的载体和选自下列的至少一种化合物或其盐：

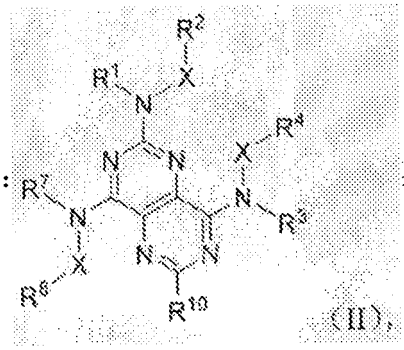
式（I）化合物：  （I），其中在式（I）中：

R^1、R^2、R^3、R^4、R^5、R^6、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；和

每次出现的 X 独立地是烷基或取代烷基；

式（II）化合物：  （II），其中在式（II）中：

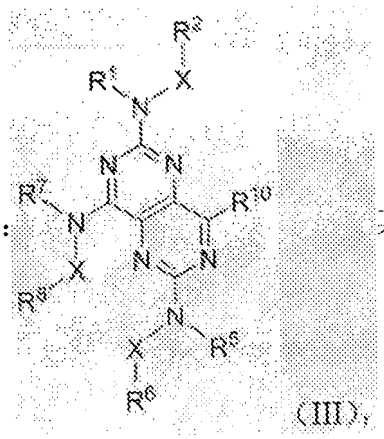
R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基或取代烷基；

R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基；和

式（III）化合物：  其中在式（III）中：

R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基或取代烷基；和

R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基。

37. 根据权利要求 36 所述的方法，其中所述呼吸控制障碍或疾病选自呼吸抑制、睡眠呼吸暂停、早产儿呼吸暂停、肥胖 - 通气不足综合征、原发性肺泡通气不足综合征、呼吸困难、高空病、氧不足、高碳酸血、慢性阻塞性肺部疾病（COPD）、婴儿猝死综合征（SIDS）、先天性中枢性通气不足综合征、阿尔茨海默氏症、帕金森病、中风、杜氏肌营养不良、和脑和脊髓创伤性损伤。

38. 根据权利要求 37 所述的方法，其中所述呼吸抑制由麻醉剂、镇静剂、睡眠助剂、抗焦虑剂、催眠剂、酒精或麻醉药引起。

39. 根据权利要求 36 所述的方法，其中所述对象被进一步给予可用于治疗呼吸障碍或疾病的至少一种另外的用剂。

40. 根据权利要求 39 所述的方法，其中所述至少一种另外的用剂选自多沙普仑及其对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂、苯二氮䓬受体激动剂、食欲肽拮抗剂、三环类抗抑郁剂、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素、食欲肽、褪黑激素激动剂、安帕金、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂。

41. 根据权利要求 39 所述的方法，其中所述化合物和所述用剂被分开给予所述对象。

42. 根据权利要求 39 所述的方法，其中所述化合物和所述用剂被共同给予所述对象，进一步其中所述化合物和所述用剂在被给予所述对象时是物理混合的或是物理分开的。

43. 根据权利要求 36 所述的方法，其中所述对象被进一步给予已知改变所述对象的正常呼吸控制的至少一种另外的治疗剂。

44. 根据权利要求 43 所述的方法，其中至少一种另外的治疗剂选自阿片类麻醉剂、苯

二氮䓬类、镇静剂、睡眠助剂、催眠剂、丙泊酚、和其任意组合。

45. 根据权利要求 36 所述的方法，其中所述组合物结合机械通气装置或气道正压装置对所述对象的应用被给予。

46. 根据权利要求 36 所述的方法，其中所述对象是哺乳动物或禽类。

47. 根据权利要求 46 所述的方法，其中所述哺乳动物是人。

48. 根据权利要求 36 所述的方法，其中所述组合物通过鼻部、吸入、局部、口服、颊部、直肠、胸膜、腹膜、阴道、肌内、皮下、透皮、硬膜外、气管内、耳部、眼内、鞘内或静脉内途径被给予所述对象。

49. 根据权利要求 48 所述的方法，其中所述组合物被口服给予所述对象。

50. 根据权利要求 36 所述的方法，其中所述至少一种化合物选自：

N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^4, N^6, N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 正丁基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 异丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二甲基 -N^4- 正丙基 -N^8- 丙 -2- 炔基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶；

N-(6- 氯 -4,8- 双 - 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-O,N- 二甲基 - 羟基胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶盐酸盐；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基) - 羟基胺；

N^4, N^8- 二甲基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6- 三甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2- 二乙基 -N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-(4,8- 双 - 正丙基氨基 -6- 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基 - 氨基) - 乙醇；

N^2-(2- 甲氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2-(2- 异丙氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^8- 甲基 -N^4, N^6- 二 - 正丙基 -N^2-(3,3,3- 三氟丙基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(吗啉 -4- 基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(哌啶 -1- 基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6- 吡咯烷 -1- 基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4,N^8- 二 - 正丙基 -6-(4- 甲氧基 - 哌啶 -1- 基) - 嘧啶并 [5,4,-d] 嘧啶 -2,4,8- 三胺；

N^2-(3-氯-2-甲基-苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2-(3,4-二氯苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2-(4-氟苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

6-氯-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

N^2,N^2,N^4,N^8-四甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^2-二烯丙基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-甲基-氨基]-乙醇；

N^2-(2-异丙氧基-乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

2-[N-(2-二甲基氨基-乙基)-N-甲基]氨基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-4,6,8-三胺；

2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-(2-羟基-乙基)-氨基]-乙醇；

N^2,N^2-双-(2-甲氧基乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

6-(4-氧-哌啶-1-基)-N^4,N^8-二甲基-N^2-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺；

N^2-(3-三氟甲基-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺；

N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺；

N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-二-正丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-双-环丙基甲基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-二异丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-二烯丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

2-氯-6-(N,N'-二甲基-肼基)-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺；

6-(N,N'-二甲基-肼基)-N^2,N^2,N^4,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

N^4,N^8-二甲基-6-丙氧基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

N^4,N^8-二甲基-N^2-正丙基-6-丙基硫烷基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

6-苄氧基-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-醇；

4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-腈；

N^4, N^8- 二甲基 -N^2- 正丙基 -6-(氨基甲基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 氨甲酰基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 羧酸 ;

N-(正丙基)-[4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基]- 脒 ;

N^4, N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 正丁基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 甲氧基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 ;

N^2, N^4, N^6, N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺

2,6- 二氯 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 ;

N^4, N^8- 二乙基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2, N^6- 二乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2, N^2, N^6- 三乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

6- 氯 -N^2- 乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^2, N^6- 二乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2, N^6- 二环丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2, N^2, N^6, N^6- 四甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^4, N^8- 二烯丙基 -N^2, N^6- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

N^2, N^4, N^8- 三烯丙基 -6-[4-(4- 氟苄基)- 哌嗪 -1- 基]- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

6- 氯 -N^2, N^4, N^8- 三烯丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^2,N^4,N^8- 三烯丙基 -6-{4-[双 -(4- 氟苯基)- 甲基]- 哌嗪 -1- 基 }- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

N^2, N^2, N^6- 三乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯 ;

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸 ;

N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺 ;

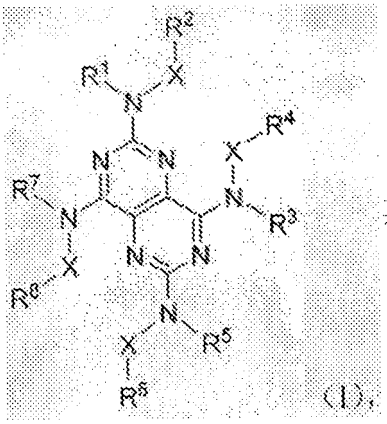
(6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯 ;

其盐、和其任意组合。

51. 根据权利要求 36 所述的方法,其中所述盐选自硫酸盐、硫酸氢盐、氯化物、溴化物、碘化物、硝酸盐、碳酸盐、磷酸盐、磷酸氢盐、磷酸二氢盐、甲酸盐、乙酸盐、丙酸盐、琥珀酸盐、乙醇酸盐、葡萄糖酸盐、乳酸盐、苹果酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐、葡萄糖醛酸盐、马来酸盐、富马酸盐、丙酮酸盐、天冬氨酸盐、谷氨酸盐、苯甲酸盐、邻氨基苯甲酸盐、

4- 羟基苯甲酸盐、苯基乙酸盐、扁桃酸盐、扑酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、泛酸盐、三氟甲磺酸盐、2- 羟基乙磺酸盐、对甲苯磺酸盐、磺胺酸盐、环己基氨基磺酸盐、硬脂酸盐、海藻酸盐、β - 羟基丁酸盐、水杨酸盐、半乳糖酸盐、半乳糖醛酸盐、糖精、糖质酸盐、和甘油膦酸盐。

52. 在有需要的对象中预防呼吸节奏失稳或稳定呼吸节奏的方法，所述方法包括给予所述对象有效量的药物组合物，所述药物组合物包括至少一种药学上可接受的载体和选自下列的至少一种化合物或其盐：

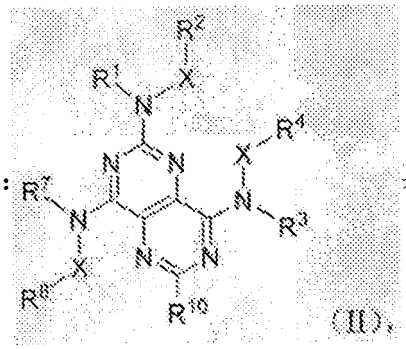
式 (I) 化合物：  其中在式 (I) 中：

R^1、R^2、R^3、R^4、R^5、R^6、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；和

每次出现的 X 独立地是烷基或取代烷基；

式 (II) 化合物：  其中在式 (II) 中：

R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

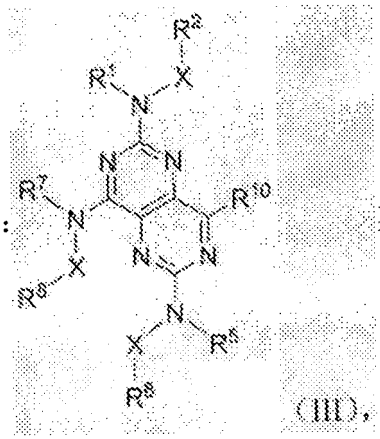
或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基或取代烷基；

R^{10}是 H、卤素、氰基、烷基、取代烷基、烷氧基或取代烷氧基；

和

式（III）化合物：  其中在式（III）中：

R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基或取代烷基；和

R^{10}是 H、卤素、氰基、烷基、取代烷基、烷氧基或取代烷氧基。

53. 根据权利要求 52 所述的方法，其中所述失稳与呼吸控制障碍或疾病有关，所述呼吸控制障碍或疾病选自呼吸抑制、睡眠呼吸暂停、早产儿呼吸暂停、肥胖 - 通气不足综合征、原发性肺泡通气不足综合征、呼吸困难、高空病、氧不足、高碳酸血、慢性阻塞性肺部疾病（COPD）、婴儿猝死综合征（SIDS）、先天性中枢性通气不足综合征、阿尔茨海默氏症、帕金森病、中风、杜氏肌营养不良、和脑和脊髓创伤性损伤。

54. 根据权利要求 53 所述的方法，其中所述呼吸抑制由麻醉剂、镇静剂、睡眠助剂、抗焦虑剂、催眠剂、酒精或麻醉药引起。

55. 根据权利要求 52 所述的方法，其中所述对象被进一步给予可用于治疗所述呼吸障碍或疾病的至少一种另外的用剂。

56. 根据权利要求 55 所述的方法，其中所述至少一种另外的用剂选自多沙普仑及其对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂、苯二氮䓬受体激动剂、食欲肽拮抗剂、三环类抗抑郁剂、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素、食欲肽、褪黑激素激动剂、安帕金、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂。

57. 根据权利要求 55 所述的方法，其中所述化合物和所述用剂被分开给予所述对象。

58. 根据权利要求 55 所述的方法，其中所述化合物和所述用剂被共同给予所述对象，进一步其中所述化合物和所述用剂在被给予所述对象时是物理混合的或是物理分开的。

59. 根据权利要求 52 所述的方法，其中所述对象被进一步给予已知改变所述对象的正

常呼吸控制的至少一种另外的治疗剂。

60. 根据权利要求 59 所述的方法，其中至少一种另外的治疗剂选自阿片类麻醉剂、苯二氮䓬类、镇静剂、睡眠助剂、催眠剂、丙泊酚、和其任意组合。

61. 根据权利要求 52 所述的方法，其中所述组合物联合机械通气装置或气道正压装置对所述对象的应用被给予。

62. 根据权利要求 52 所述的方法，其中所述对象是哺乳动物或禽类。

63. 根据权利要求 62 所述的方法，其中所述哺乳动物是人。

64. 根据权利要求 52 所述的方法，其中所述组合物通过鼻部、吸入、局部、口服、颊部、直肠、胸膜、腹膜、阴道、肌内、皮下、透皮、硬膜外、气管内、耳部、眼内、鞘内或静脉内途径被给予所述对象。

65. 根据权利要求 64 所述的方法，其中所述组合物被口服给予所述对象。

66. 根据权利要求 52 所述的方法，其中所述至少一种化合物选自：

N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^4, N^6, N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 正丁基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 异丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二甲基 -N^4- 正丙基 -N^8- 丙 -2- 炔基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶；

N-(6- 氯 -4,8- 双 - 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-O,N- 二甲基 - 羟基胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶盐酸盐；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)- 羟基胺；

N^4, N^8- 二甲基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6- 三甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2- 二乙基 -N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-(4,8- 双 - 正丙基氨基 -6- 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基 - 氨基)- 乙醇；

N^2-(2- 甲氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2-(2- 异丙氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^8- 甲基 -N^4, N^6- 二 - 正丙基 -N^2-(3,3,3- 三氟丙基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(吗啉 -4- 基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(哌啶 -1- 基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6- 吡咯烷 -1- 基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2-甲基-N^4,N^8-二-正丙基-6-(4-甲氧基-哌啶-1-基)-嘧啶并[5,4,-d]嘧啶-2,4,8-三胺；

N^2-(3-氯-2-甲基-苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2-(3,4-二氯苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2-(4-氟苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

6-氯-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

N^2,N^2,N^4,N^8-四甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^2-二烯丙基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-甲基-氨基]-乙醇；

N^2-(2-异丙氧基-乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

2-[N-(2-二甲基氨基-乙基)-N-甲基]氨基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-4,6,8-三胺；

2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-(2-羟基-乙基)-氨基]-乙醇；

N^2,N^2-双-(2-甲氧基乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

6-(4-氧-哌啶-1-基)-N^4,N^8-二甲基-N^2-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺；

N^2-(3-三氟甲基-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺；

N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺；

N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-二-正丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-双-环丙基甲基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-二异丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

N^2,N^6-二烯丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

2-氯-6-(N,N'-二甲基-肼基)-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺；

6-(N,N'-二甲基-肼基)-N^2,N^2,N^4,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

N^4,N^8-二甲基-6-丙氧基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

N^4,N^8-二甲基-N^2-正丙基-6-丙基硫烷基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

6-苄氧基-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 醇；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈；

N^4, N^8- 二甲基 -N^2- 正丙基 -6-(氨基甲基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 氨甲酰基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 羧酸；

N-(正丙基)-[4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基]- 脒；

N^4, N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 正丁基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 甲氧基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈；

N^2, N^4, N^6, N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺

2,6- 二氯 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺；

N^4, N^8- 二乙基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6- 三乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^6- 二乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二环丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6, N^6- 四甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^4, N^8- 二烯丙基 -N^2, N^6- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^4, N^8- 三烯丙基 -6-[4-(4- 氟苄基)- 哌嗪 -1- 基]- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 氯 -N^2, N^4, N^8- 三烯丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2,N^4,N^8- 三烯丙基 -6-{4-[双 -(4- 氟苯基)- 甲基]- 哌嗪 -1- 基 }- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2, N^6- 三乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯；

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸；

N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺；

(6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯；

其盐、和其任意组合。

67. 根据权利要求所述的方法 52，其中所述盐选自硫酸盐、硫酸氢盐、氯化物、溴化物、碘化物、硝酸盐、碳酸盐、磷酸盐、磷酸氢盐、磷酸二氢盐、甲酸盐、乙酸盐、丙酸盐、琥珀酸

盐、乙醇酸盐、葡萄糖酸盐、乳酸盐、苹果酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐、葡萄糖醛酸盐、马来酸盐、富马酸盐、丙酮酸盐、天冬氨酸盐、谷氨酸盐、苯甲酸盐、邻氨基苯甲酸盐、4- 羟基苯甲酸盐、苯基乙酸盐、扁桃酸盐、扑酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、泛酸盐、三氟甲磺酸盐、2- 羟基乙磺酸盐、对甲苯磺酸盐、磺胺酸盐、环己基氨基磺酸盐、硬脂酸盐、海藻酸盐、β - 羟基丁酸盐、水杨酸盐、半乳糖酸盐、半乳糖醛酸盐、糖精、糖质酸盐、和甘油膦酸盐。

68. 根据权利要求 1 所述的化合物，其中所述化合物是 N^2-N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺，并且其中所述化合物的 X 射线粉末衍射光谱包括约 8.12、9.59、12.60、15.02、16.33、17.40、18.98、20.68、21.72、22.28、23.98、25.24、和 26.70 的 2Θ 值（以度为单位）。

69. 制备 N^2-N^6- 双 - 环丙基甲基 N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84) 的方法，包括使 2,6- 二氯 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺和环丙基甲胺在溶剂中反应。

70. 根据权利要求 69 所述的方法，其中所述反应在加热下进行，并且其中在反应系统冷却至室温后，(84) 从所述溶剂析出。

71. 根据权利要求 69 所述的方法，其中所述溶剂包括正丁醇。

72. 根据权利要求 70 所述的方法，其中使析出的 (84) 从正丁醇重结晶。

73. 根据权利要求 72 所述的方法，其中重结晶的 (84) 的 X 射线粉末衍射光谱包括约 8.12、9.59、12.60、15.02、16.33、17.40、18.98、20.68、21.72、22.28、23.98、25.24、和 26.70 的 2Θ 值（以度为单位）。

74. 根据权利要求 69 所述的方法，其中通过使 2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶和甲胺在溶剂中反应来制备 2,6- 二氯 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺。

75. 根据权利要求 74 所述的方法，其中 2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶与甲胺的当量比为约 1 ： 4.5。

新型呼吸控制调节化合物及其使用方法

[0001] 相关申请的交叉参考

[0002] 本申请按照 35 U.S.C. § 119(e) 要求 2013 年 3 月 15 日提交的美国临时申请号 61/792,185 的优先权，其全部内容在此通过引用并入本文。

[0003] 发明背景

[0004] 正常的呼吸控制是一个复杂的过程，其部分涉及身体对化学刺激如血液、组织和脑的二氧化碳、pH和氧水平的诠释和响应。正常的呼吸控制还受其他因素影响，如觉醒状态（即，患者清醒或正在睡眠）、情绪、姿势和发声。脑髓质内有呼吸控制中枢，其通过向进行呼吸工作的肌肉发出命令来诠释影响呼吸的各种前馈和反馈信号。关键的肌肉群位于腹、膈、咽和胸部。于是位于中枢和外周的传感器向脑中枢呼吸控制区域提供输入，该脑中枢呼吸控制区域能够对变化的代谢需求做出响应。

[0005] 例如，满足身体代谢需求的充足通气主要通过身体对二氧化碳 (CO_2) 水平变化的快速响应来保持。增加的 CO_2水平（高碳酸血）向身体传导信号，以增加呼吸速率和深度，导致血氧水平较高和随后血液 CO_2水平较低。相反，低 CO_2水平（低碳酸血）可导致因呼吸刺激减少而造成的呼吸不足（呼吸减弱）时期，或者在极端情况下导致呼吸暂停（不呼吸）。

[0006] 有很多疾病，其中丧失正常呼吸控制是疾病的一级或二级特征。一级呼吸控制丧失的疾病实例是睡眠呼吸暂停（中枢性、混合性或阻塞性；其中呼吸反复停止 10 至 60 秒）和先天性中枢性通气不足综合征。二级呼吸控制丧失可源于慢性心肺疾病（例如，心脏衰竭、慢性支气管炎、气肿、和临近呼吸衰竭）、超重（例如，肥胖 - 通气不足综合征）、某些药物（例如，麻醉剂、镇静剂、睡眠助剂、抗焦虑剂、催眠剂、酒精、和麻醉性镇痛剂和 / 或影响神经系统的因素（例如，中风、肿瘤、创伤、辐射损伤、和 ALS）。在身体暴露于慢性高水平二氧化碳的慢性阻塞性肺疾病中，由于肾介导的碳酸氢盐滞留，身体容易呼吸性酸中毒 (pH 较低)，其结果是部分中和 CO_2/pH 呼吸刺激。因此，患者不能对代谢需求变化做出正常的通气响应。

[0007] 睡眠呼吸障碍是呼吸控制异常导致人类严重和常见疾病的一个实例。睡眠呼吸暂停的特征在于无呼吸或部分呼吸周期频繁。助长这些呼吸暂停的关键因素包括解剖结构因素（例如，肥胖）、高碳酸血和低氧通气响应减少（例如，分别对高二氧化碳和低氧水平的响应减少）和“觉醒”（即，睡眠期间对肺和 / 或咽扩张肌的呼吸动力）丧失。呼吸暂停事件导致氧不足（和相关的氧化应激），并最终导致严重的心血管后果（高血压、中风、心脏病发作）。

[0008] 遭受其中有呼吸控制受损的病况的美国个人的估测结果包括睡眠呼吸暂停 (1500-2000 万）；肥胖 - 通气不足综合征 (300-500 万）；慢性心脏疾病 (500 万）；慢性阻塞性肺部疾病 (COPD) / 慢性支气管炎 (1000 万）；药物致通气不足 (200-1000 万）；和机械性通气中断 (50 万）。

[0009] 药物最常通过生物转化和 / 或排泄到尿液、粪便或胆汁中而被排出。肝脏是异生物体生物转化的主要器官，因而在表征药物代谢稳定性、毒理、和药物 - 药物相互作用特性

中非常重要。药物代谢通过两个主要的位于肝脏的酶反应实现：I 期和 II 期反应。I 期酶包括细胞色素 P450(CYP450) 家族的酶，其位于光面内质网。I 期反应的基本过程是氧化、还原和 / 或水解，其中很多被 CYP450 系统催化并且需要 NADPH 作为辅因子。II 期酶位于细胞质和内质网，并且进行结合反应，包括葡萄糖醛酸、谷胱甘肽、硫酸盐（酯）、和谷氨酰胺结合。II 期反应大体上使药物失活——如果其在 I 期代谢后还未在治疗上失活，而且使药物更具水溶性，以有助于其排出。一些药物通过单独 I 期或 II 期酶来代谢，而其他则通过 I 期和 II 期酶两者来代谢 (Baranczewski et al.，2006，Pharmacol. Rep. 58 :453-472)。微粒体是亚细胞肝脏组织部分（光面内质网的膜囊泡），包含 I 期 CYP450 家族的酶。化合物在 NADPH 辅因子存在的情况下在肝脏微粒体中仅进行 I 期代谢。因此，在肝脏微粒体存在的情况下，显著的母体药物消失表示药物将被体内 CYP450 酶显著改变 (Rodrigues，1994，Biochem，Pharm. 48(12) :2147)。

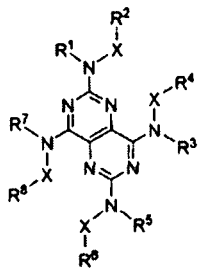
[0010] 药代动力学 (PK) 研究的目的是利用药物浓度 - 时间曲线和相关的药代动力学参数理解药物在给予动物后被如何加工、改变、分布和 / 或排出。在药物研发中，进行药代动力学研究，从而 (1) 指导动物效力和毒性研究的剂量方案设计，(2) 了解和诠释药理和毒理研究结果，和 (3) 选择对于目标疾病适应征具有期望的药代动力学特性的候选药物。动物研究的 PK 数据可经推断预测人的 PK 曲线，从而选择和优化在人临床试验中的候选药物剂量方案。

[0011] 本领域需要可用于响应 CO_2 和 / 或氧水平的变化恢复全部或部分身体正常呼吸控制系统并且具有最小副作用的新型化合物。进一步，本领域需要可用于恢复全部或部分身体正常呼吸控制系统、具有适当的代谢稳定性和适当的药代动力学特性如口服生物利用度的新型化合物。进一步，本领域需要可用于恢复全部或部分身体正常呼吸控制系统、可被口服给予并且以慢性方式使用，以及急性地通过包括静脉内给予的方法给予的新型化合物。本发明解决和满足了这些需求。

[0012] 发明概述

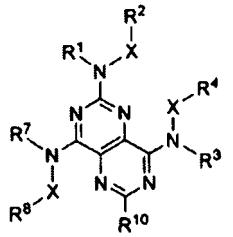
[0013] 本发明提供化合物或其盐。本发明进一步提供药物组合物，其包括本发明的化合物和至少一种药学上可接受的载体。本发明进一步提供在有需要的对象中预防或治疗呼吸控制障碍或疾病的方法，方法包括给予该对象有效量药物组合物，该药物组合物包括至少一种药学上可接受的载体和本发明至少一种化合物或其盐。本发明进一步提供在有需要的对象中预防呼吸节奏失稳或稳定呼吸节奏的方法，方法包括给予该对象有效量药物组合物，该药物组合物包括至少一种药学上可接受的载体和本发明至少一种化合物或其盐。本发明进一步提供制备 N^2-N^6- 双 - 环丙基甲基 N^4，N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84) 的方法。

[0014] 在某些实施方式中，化合物选自：

[0015] 式 (I) 化合物：  其中在式 (I) 中：

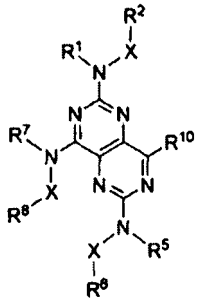
(I)，

[0016] R^1、R^2、R^3、R^4、R^5、R^6、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；或 R^1和 R^2、R^3和 R^4、R^5和 r^6、或 R^7和 R^8独立地组合形成双自由基，该双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；每次出现的 X 均独立地选自键、NH、NR^9和 O；以及，每次出现的 X 均独立地是烷基或取代烷基：

[0017] 式 (II) 化合物：  其中在式 (II) 中：

(II)，

[0018] R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，该双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；每次出现的 X 均独立地选自键、NH、NR^9和 O；每次出现的 R^9独立地是烷基、或取代烷基；R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基；和

[0019] 式 (III) 化合物：  其中在式 (III) 中：

(III)，

[0020] R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，该双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；每次出现的 X 均独立地选自键、NH、NR^9和 O；每次出现的 R^9独立地是烷基或取代烷基；和 R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基；和其任意组合。

[0021] 在某些实施方式中，化合物选自：N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；N^2, N^4, N^6, N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；N^2, N^6- 二 - 正丁基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；N^2, N^6- 二 - 异丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；N^2, N^6- 二甲基 -N^4- 正丙基 -N^8- 丙 -2- 炔基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；N^2,N^6- 双 -(N- 甲氧

基(N-甲基)氨基)-N^4,N^8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶;N-(6-氯-4,8-双-丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-0,N-二甲基-羟基胺;N^2,N^6-双-(N-甲氧基(N-甲基)氨基)-N^4,N^8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶;N^2-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;0,N-二甲基-N-(6-甲基氨基-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-羟基胺;N^4,N^8-二甲基-N^2,N^6-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2,N^2,N^6-三甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;6-氯-N^2-甲基-N^4,N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺;N^2,N^2-二乙基-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;2-(4,8-双-正丙基氨基-6-甲基氨基-嘧啶并[5,4-d]嘧啶-2-基-氨基)-乙醇;N^2-(2-甲氧基-乙基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2-(2-异丙氧基-乙基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^8-甲基-N^4,N^6-二-正丙基-N^2-(3,3,3-三氟丙基)-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2-甲基-N^4,N^8-二-正丙基-6-(吗啉-4-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;N^2-甲基-N^4,N^8-二-正丙基-6-(哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;N^2-甲基-N^4,N^8-二-正丙基-6-吡咯烷-1-基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;N^2-甲基-N^4,N^8-二-正丙基-6-(4-甲氧基-哌啶-1-基)-嘧啶并[5,4,-d]嘧啶-2,4,8-三胺;N^2-(3-氯-2-甲基-苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2-(3,4-二氯苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2-(4-氟苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;6-氯-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;N^2,N^2,N^4,N^8-四甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2,N^2-二烯丙基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-甲基-氨基]-乙醇;N^2-(2-异丙氧基-乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;2-[N-(2-二甲基氨基-乙基)-N-甲基]氨基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-4,6,8-三胺;2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-(2-羟基-乙基)-氨基]-乙醇;N^2,N^2-双-(2-甲氧基乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;6-(4-氧-哌啶-1-基)-N^4,N^8-二甲基-N^2-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺;N^2-(3-三氟甲基-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺;N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺;N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2,N^6-二-正丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2,N^6-双-环丙基甲基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2,N^6-二异丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;N^2,N^6-二烯丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;2-氯-6-(N,N'-二甲基-肼基)-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺;6-(N,N'-二甲基-肼基)-N^2,N^2,N^4,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;N^4,N^8-二甲基-6-丙氧基-N^2-正丙基-嘧啶并[5,4-d]

嘧啶 -2,4,8- 三胺 ;N^4, N^8- 二甲基 -N^2- 正丙基 -6- 丙基硫烷基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;6- 苄氧基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 醇 ;4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 ;N^4,N^8- 二甲基 -N^2- 正丙基 -6-(氨基甲基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;6- 氨甲酰基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 羧酸 ;N-(正丙基)-[4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基]- 脒 ;N^4, N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟苯基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 氟苯基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;6- 正丁基 -N^2- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;6- 甲氧基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 ;N^2, N^4,N^6,N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 2,6- 二氯 -N^4,N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 ;N^4,N^8- 二乙基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;N^2,N^6- 双 - 环丙基甲基 -N^4,N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;N^2,N^6- 二乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;N^2,N^2,N^6- 三乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;6- 氯 -N^2- 乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;N^2, N^6- 二乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;N^2, N^6- 二环丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;N^2,N^6- 双 - 环丙基甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;N^2, N^2, N^6, N^6- 四甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;N^4, N^8- 二烯丙基 -N^2, N^6- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;N^2, N^4, N^8- 三烯丙基 -6-[4-(4- 氟苄基) - 哌嗪 -1- 基]- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;6- 氯 -N^2,N^4,N^8- 三烯丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;N^2,N^4,N^8- 三烯丙基 -6-{4-[双 -(4- 氟苯基) - 甲基]- 哌嗪 -1- 基 }- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;N^2, N^2,N^6- 三乙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基) - 乙酸叔丁酯 ;(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基) - 乙酸 ;N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺 ;(6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基) - 乙酸乙基酯 ;其盐或溶剂化物,和其任意组合。

[0022] 在某些实施方式中,盐选自硫酸盐、硫酸氢盐、半硫酸盐、氯化物、溴化物、碘化物、硝酸盐、碳酸盐、磷酸盐、磷酸氢盐、磷酸二氢盐、甲酸盐、乙酸盐、丙酸盐、琥珀酸盐、乙醇酸盐、葡萄糖酸盐、乳酸盐、苹果酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐、葡萄糖醛酸盐、马来酸盐、富马酸盐、丙酮酸盐、天冬氨酸盐、谷氨酸盐、苯甲酸盐、邻氨基苯甲酸盐、4- 羟基苯甲酸盐、苯基乙酸盐、扁桃酸盐、扑酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、泛酸盐、三氟甲磺酸盐、2- 羟基乙磺酸盐、对甲苯磺酸盐、磺胺酸盐、环己基氨基磺酸盐、硬脂酸盐、海藻酸盐、β - 羟基丁酸盐、水杨酸盐、半乳糖酸盐、半乳糖醛酸盐、糖精、糖质酸盐、甘油膦酸盐、和其任意组合。

[0023] 在某些实施方式中,本发明的组合物进一步包括选自下列的至少一种用剂

(agent)：多沙普仑 (doxapram) 及其对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂、苯二氮䓬受体激动剂、食欲肽拮抗剂、三环类抗抑郁剂、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素、食欲肽、褪黑激素激动剂、安帕金 (ampakines)、羟丁酸钠、莫达非尼 (modafinil)、阿莫达非尼 (armodafinil)、和吸入式治疗剂。在其他实施方式中，化合物和该用剂在组合物中是物理混合的。在再其他实施方式中，化合物和该用剂在组合物中是物理分开的。

[0024] 在某些实施方式中，本发明的组合物进一步包括至少一种已知引起呼吸控制变化的用剂。在其他实施方式中，该至少一种用剂选自阿片类麻醉剂、苯二氮䓬类、镇静剂、睡眠助剂、催眠剂、丙泊酚、和其任意组合。在再其他实施方式中，化合物和该用剂在组合物中是物理混合的。在再其他实施方式中，化合物和该用剂在组合物中是物理分开的。

[0025] 在某些实施方式中，组合物能够改善化合物在口服给予对象后的递送。在其他实施方式中，组合物最小化化合物至对象的胃的递送，并且最大化化合物至对象的肠的递送。在再其他实施方式中，组合物包括肠溶包衣。在再其他实施方式中，化合物被包含在药学上适合的胶囊中。在再其他实施方式中，胶囊包含化合物或化合物与赋形剂的混合物的颗粒或粉末。在再其他实施方式中，赋形剂包括粘合剂、崩解剂、稀释剂、缓冲剂、润滑剂、助流剂、抗氧化剂、抗菌防腐剂、着色剂、或调味剂。在再其他实施方式中，胶囊有肠溶包衣，但化合物颗粒或粉末没有肠溶包衣。在再其他实施方式中，化合物颗粒或粉末在置于胶囊前被肠溶包衣包覆。在再其他实施方式中，化合物颗粒或粉末被多种肠溶包衣包覆，以提供药物至对象的肠的不同区域的递送。在再其他实施方式中，化合物颗粒或粉末至少部分有肠溶包衣。在再其他实施方式中，胶囊被与包覆化合物颗粒或粉末的肠溶包衣不同的肠溶包衣包覆。在再其他实施方式中，化合物被包覆在基体颗粒上，从而形成包括药物作为基体颗粒上的外衣的内核。在再其他实施方式中，基体颗粒没有肠溶包衣，并且组合物被包含在有肠溶包衣的药学上可接受的胶囊中。在再其他实施方式中，内核被肠溶包衣包覆，从而形成肠溶包衣小珠。在再其他实施方式中，肠溶包衣小珠被包含在药学上可接受的胶囊中。在再其他实施方式中，胶囊包含被多种肠溶包衣包覆的小珠，使得胶囊提供化合物至对象的肠的不同区域的递送。在再其他实施方式中，胶囊的内含物溶解或悬浮在药学上可接受的液体中，以提供液体填充胶囊。在再其他实施方式中，胶囊有肠溶包衣，但其中包含的液体制剂不包括肠溶包衣。在再其他实施方式中，化合物颗粒或粉末有肠溶包衣。在再其他实施方式中，化合物颗粒或粉末被多种肠溶包衣包覆，以提供药物至对象的肠的不同区域的递送。在再其他实施方式中，施用于胶囊的肠溶包衣不同于施用于化合物颗粒或粉末任一种的肠溶包衣。在再其他实施方式中，化合物被包覆到基体颗粒上，形成包括化合物作为基体颗粒上的包衣的内核，其中内核悬浮在药学上可接受的液体中，并且其中悬浮内核被置于胶囊中。在再其他实施方式中，胶囊有肠溶包衣，但内核没有肠溶包衣。在再其他实施方式中，胶囊和内核有肠溶包衣。

[0026] 在某些实施方式中，失稳与呼吸控制障碍或疾病有关。

[0027] 在某些实施方式中，呼吸控制障碍或疾病选自呼吸抑制、睡眠呼吸暂停、早产儿呼吸暂停、肥胖－通气不足综合征、原发性肺泡通气不足综合征、呼吸困难、高空病、氧不足、高碳酸血、慢性阻塞性肺部疾病 (COPD)、婴儿猝死综合征 (SIDS)、先天性中枢性通气不足

综合征、阿尔茨海默氏症、帕金森病、中风、杜氏肌营养不良、和脑和脊髓创伤性损伤。在其他实施方式中，呼吸抑制由麻醉剂 (anesthetic)、镇静剂、睡眠助剂、抗焦虑剂、催眠剂、酒精或麻醉药 (narcotic) 引起。

[0028] 在某些实施方式中，进一步给予对象可用于治疗呼吸障碍或疾病的至少一种额外用剂。在其他实施方式中，该至少一种额外用剂选自多沙普仑及其对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂、苯二氮䓬受体激动剂、食欲肽拮抗剂、三环类抗抑郁剂、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素、食欲肽、褪黑激素激动剂、安帕金、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂。在再其他实施方式中，化合物和该用剂被分开给予对象。在再其他实施方式中，化合物和该用剂被共同给予对象，进一步，其中化合物和该用剂在被给予对象时是物理混合的或是物理分开的。

[0029] 在某些实施方式中，进一步给予对象已知改变对象正常呼吸控制的至少一种额外治疗剂。在其他实施方式中，至少一种额外用剂选自阿片类麻醉剂、苯二氮䓬类、镇静剂、睡眠助剂、催眠剂、丙泊酚、和其任意组合。在再其他实施方式中，组合物联合对对象施用机械通气装置或气道正压装置被给予。

[0030] 在某些实施方式中，对象是哺乳动物或禽类。在其他实施方式中，哺乳动物是人。在再其他实施方式中，组合物通过鼻部、吸入、局部、口服、颊部、直肠、胸膜、腹膜、阴道、肌内、皮下、透皮、硬膜外、鞘内、气管内、耳部、眼内或静脉内途径被给予对象。在再其他实施方式中，组合物被口服给予对象。

[0031] 在某些实施方式中，化合物是 N^2-N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺，并且其中化合物的 X 射线粉末衍射光谱包括约 8.12、9.59、12.60、15.02、16.33、17.40、18.98、20.68、21.72、22.28、23.98、25.24、和 26.70 的 2Θ 值 (以度为单位)。

[0032] 在某些实施方式中，制备 (84) 的方法包括使 2,6- 二氯 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺和环丙基甲胺在溶剂中反应。在其他实施方式中，反应在加热下进行，并且在反应系统冷却至室温后 (84) 从溶剂析出。在再其他实施方式中，溶剂包括正丁醇。在再其他实施方式中，析出的 (84) 从正丁醇中重结晶。在再其他实施方式中，重结晶的 (84) 的 X 射线粉末衍射光谱包括约 8.12、9.59、12.60、15.02、16.33、17.40、18.98、20.68、21.72、22.28、23.98、25.24、和 26.70 的 2Θ 值 (以度为单位)。在再其他实施方式中，通过使 2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶和甲胺在溶剂中反应，制备 2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺。在再其他实施方式中，2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶与甲胺的当量比为约 1 ： 4.5。

[0033] 附图简述

[0034] 为示例本发明，在附图中显示了本发明的某些实施方式。然而，本发明不限于附图所示实施方式的确切安排和手段。

[0035] 图 1 是示例在麻醉大鼠肺量测定筛选试验中化合物 (4a) 对每分钟通气量的影响的图。

[0036] 图 2 是示例在麻醉大鼠肺量测定筛选试验中化合物 (4a) 对呼吸速率的影响的图。

[0037] 图 3 是示例在麻醉大鼠肺量测定筛选试验中化合物 (4a) 对潮气量的影响的图。

[0038] 图 4 是示例在麻醉大鼠肺量测定筛选试验中化合物 (4a) 对每分钟通气量 (基于两分钟平均值) 的剂量依赖性影响的柱形图。

[0039] 图 5 是示例在麻醉大鼠肺量测定筛选试验中化合物 (4a) 对脉率的影响的图。

[0040] 图 6 是示例在麻醉大鼠肺量测定筛选试验中化合物 (4a) 对血压的影响的图。

[0041] 图 7 是示例在麻醉大鼠肺量测定筛选试验中化合物 (27a) 对每分钟通气量的影响的图。

[0042] 图 8 是示例在麻醉大鼠肺量测定筛选试验中化合物 (27a) 对呼吸速率的影响的图。

[0043] 图 9 是示例在麻醉大鼠肺量测定筛选试验中化合物 (27a) 对潮气量的影响的图。

[0044] 图 10 是示例在麻醉大鼠肺量测定筛选试验中化合物 (27a) 对每分钟通气量 (基于两分钟平均值) 的剂量依赖性影响的柱形图。

[0045] 图 11 是示例在麻醉大鼠肺量测定筛选试验中化合物 (27a) 对脉率的影响的图。

[0046] 图 12 是示例在麻醉大鼠肺量测定筛选试验中化合物 (27a) 对血压的影响的图。

[0047] 图 13 是示例从正丁醇结晶的 N^2, N^6- 双 - 环丙基甲基 N^4, N^8- 二甲基 - 嘧啶并 [5, 4-d] 嘧啶 -2,4,6,8- 四胺 (84) 的 XRPD 的图。纵坐标相应于以任意单位表示的强度,横坐标相应于位置 (2Θ),铜 (Cu)。

[0048] 图 14 是示例如下发现的图 :相对于介质治疗,化合物 (27a) 降低以吗啡慢性治疗的大鼠的呼吸暂停频率。所有小组在 12 :00-12 :30PM 时间仓的呼吸暂停显著减少是由通过口服强饲法用药的明显刺激 (唤醒) 引起的。

[0049] 图 15 是示例如下发现的图 :相对于介质治疗,化合物 (27a) 使被慢性给予吗啡的大鼠的每小时呼吸暂停数量减少,以相对于基线 (药前) 的百分比变化表示。所有小组在治疗后 30min 时间呼吸暂停显著减少是由通过口服强饲法用药的明显刺激 (唤醒) 引起的。

[0050] 图 16 是示例如下发现的柱形图 :相对于介质治疗,化合物 (27a) 使被慢性给予吗啡的大鼠的每小时呼吸暂停数量减少。

[0051] 图 17 是示例如下发现的柱形图 :与介质治疗组相比,化合物 (27a) 不引起每分钟通气量增加。

[0052] 图 18 是示例如下发现的图 :与基线相比,化合物 (27a) 不引起每单位时间通气量增加,介质治疗也是。所有小组在治疗后 30min 时间 (12 :00-12 :30) 每分钟通气量显著增加是由通过口服强饲法用药的明显刺激引起的。

[0053] 图 19 是示例如下发现的图 :相对于介质治疗,化合物 (85a) 降低以吗啡慢性治疗的大鼠的呼吸暂停频率。所有小组在 12 :00-12 :30PM 时间仓呼吸暂停减少是由通过口服强饲法用药的明显刺激 (唤醒) 引起的。

[0054] 图 20 是示例如下发现的图 :相对于介质治疗,化合物 (85a) 使以吗啡慢性治疗的大鼠的每小时呼吸暂停数量减少,以相对于基线 (药前) 的百分比变化表示。所有小组在治疗后 30min 时间呼吸暂停显著减少是由通过口服强饲法用药的明显刺激 (唤醒) 引起的。

[0055] 图 21 是示例如下发现的柱形图 :相对于介质治疗,化合物 (85a) 使以吗啡慢性治疗的大鼠的每小时呼吸暂停数量减少。

[0056] 图 22 是示例如下发现的柱形图 :与介质治疗组相比,化合物 (85a) 不引起每分钟通气量增加。

[0057] 图 23 是示例如下发现的图 :与介质治疗相比,化合物 (85a) 不引起每单位时间通气量增加。所有小组在治疗后 30min 时间 (12 :00-12 :30) 每分钟通气量显著增加是由通过口服强饲法用药的明显刺激引起的。

[0058] 图 24 是示例如下发现的图 :相对于介质治疗,化合物 (137a) 降低以吗啡慢性治疗的大鼠的呼吸暂停频率。(注意 :所有小组在 12 :00-12 :30PM 时间仓呼吸暂停减少是由通过口服强饲法用药的明显刺激 (唤醒) 引起的)。

[0059] 图 25 是示例如下发现的图 :相对于介质治疗,化合物 (137a) 使以吗啡慢性治疗的大鼠的每小时呼吸暂停数量减少,以相对于基线 (药前) 的百分比变化表示。所有小组在治疗后 30min 时间呼吸暂停显著减少是由通过口服强饲法用药的明显刺激 (唤醒) 引起的。

[0060] 图 26 是示例如下发现的柱形图 :相对于介质治疗,化合物 (137a) 使以吗啡慢性治疗的大鼠的每小时呼吸暂停数量减少。

[0061] 图 27 是示例如下发现的柱形图 :与介质治疗组相比,低剂量的化合物 (137a) 不引起每分钟通气量增加。较高剂量的化合物 137a 引起每分钟通气量增加。

[0062] 图 28 是示例如下发现的图 :与介质治疗相比,化合物 (137a) 不引起每单位时间通气量增加。所有小组在治疗后 30min 时间 (12 :00-12 :30) 每分钟通气量显著增加是由通过口服强饲法用药的明显刺激引起的。

[0063] 图 29 是示例如下发现的图 :相对于介质治疗,化合物 (145a) 降低以吗啡慢性治疗的大鼠的呼吸暂停频率。所有小组在 12 :00-12 :30PM 时间仓呼吸暂停减少是由通过口服强饲法用药的明显刺激 (唤醒) 引起的。

[0064] 图 30 是示例如下发现的图 :相对于介质治疗,化合物 (145a) 使以吗啡慢性治疗的大鼠的每小时呼吸暂停数量减少,以相对于基线 (药前) 的百分比变化表示。所有小组在治疗后 30min 时间呼吸暂停显著减少是由通过口服强饲法用药的明显刺激 (唤醒) 引起的。

[0065] 图 31 是示例如下发现的柱形图 :相对于介质治疗,化合物 (145a) 使以吗啡慢性治疗的大鼠的每小时呼吸暂停数量减少。

[0066] 图 32 是示例如下发现的柱形图 :与介质治疗组相比,化合物 (145a) 不引起每分钟通气量增加。

[0067] 图 33 是示例如下发现的图 :与介质治疗相比,化合物 (145a) 不引起每单位时间通气量增加。所有小组在治疗后 30min 时间 (12 :00-12 :30) 每分钟通气量显著增加是由通过口服强饲法用药的明显刺激引起的。

[0068] 发明详述

[0069] 本发明涉及如下发现 :本发明的化合物是可口服生物利用的呼吸控制调节剂,并且可用于预防或治疗呼吸控制障碍或疾病。进一步,本发明的化合物是适于在呼吸控制障碍或疾病的预防或治疗中慢性施用的可口服生物利用的呼吸控制调节剂。进一步,本发明的化合物是呼吸控制调节剂,并且可通过口服给予用于预防或治疗呼吸控制障碍或疾病。

[0070] 一方面,本发明的化合物预防障碍和疾病导致的和响应 CO_2 和 / 或氧水平变化的身体正常呼吸控制系统变化,并且具有最小副作用。另一方面,本发明的化合物减少呼吸控制紊乱如睡眠呼吸暂停的发生和严重程度。再一方面,本发明的化合物减少呼吸暂停事件的发生和 / 或减少呼吸暂停事件的持续时间。再一方面,本发明的化合物具有良好的代谢稳定性和口服生物利用度。再一方面,本发明的化合物不干扰可引起呼吸控制变化的疗法

如阿片类镇痛的效用。这种改变呼吸控制的疗法得益于支持或恢复正常呼吸功能的用剂的给予。

[0071] 一方面，本发明的化合物是相对于以前报道的呼吸控制调节化合物如美国申请号13/306,349公开的化合物的改进。一方面，本发明的化合物相对于现有技术教导的化合物具有提高的微粒体稳定性和代谢稳定性。另一方面，本发明的化合物相对于现有技术教导的化合物具有提高的口服生物利用度。另一方面，本发明的化合物相对于现有技术教导的化合物具有提高的药理活性。再一方面，本发明的化合物显示可显色的(developable)细胞色素P450特征（代谢）和在心脏通道（如但不限于hERG)的低活性。

[0072] 在一个实施方式中，呼吸控制障碍或疾病选自呼吸抑制、睡眠呼吸暂停、早产儿呼吸暂停、肥胖-通气不足综合征、原发性肺泡通气不足综合征、呼吸困难、高空病、氧不足、高碳酸血、慢性阻塞性肺部疾病(COPD)和婴儿猝死综合征(SIDS)。在另一实施方式中，呼吸抑制由麻醉剂、镇静剂、睡眠助剂、抗焦虑剂、催眠剂、酒精或麻醉药引起。在再一实施方式中，呼吸抑制由遗传因素引起，如在先天性中枢性通气不足综合征中证实。在再一实施方式中，呼吸抑制由神经系统病况引起，如阿尔茨海默氏症、帕金森病、中风、杜氏肌营养不良、和脑或脊髓创伤性损伤。

[0073] 定义

[0074] 如本文所用，下文各术语的含义与本章节有关。除非另外限定，本文使用的所有技术和科学术语总体上与本发明所属领域技术人员的普遍理解具有相同的含义。总体而言，本文采用的命名和动物药理学、药物科学、分离科学和有机化学中的实验室程序是本领域公知且常用的。

[0075] 如本文所用，冠词“一个(a)”和“一个(an)”指代该冠词下的一个或多于一个（即至少一个）语法对象。作为实例，“一个要素(an element)”意为一个要素或多于一个要素。

[0076] 如本文所用，术语“约”被本领域技术人员理解，并且基于其应用的环境在一定程度上有所不同。如本文所用，在涉及可测值如含量、持续时间及类似值时，术语“约”意为包括指定值±20%或±10%的变动，更优选±5%，甚至更优选±1%，还更优选±0.1%，只要这种变动适于执行本公开的方法。

[0077] 如本文所用，“对象”可以是人或非人哺乳动物或禽类。非人哺乳动物包括，例如，家畜和宠物，如羊、牛、猪、犬、猫和鼠类哺乳动物。优选地，对象是人。

[0078] 在非限制性实施方式中，下文用于报告血气测量结果的术语是本领域技术人员公知的，可定义如下：每分钟通气量(MV)是每单位时间呼吸体积的度量，并且在本文中以mL/min给出；pCO_2是二氧化碳（气体）在（动脉）血液中的分压，以mm Hg（毫米Hg）为单位测量；pO_2是氧（气体）在（动脉）血液中的分压，以mmHg（毫米Hg）为单位测量；SaO_2是氧合血红蛋白饱和度（结合至血红蛋白的氧气）的百分比，其与血流中被氧占据的血红蛋白结合位点的百分比相关；潮气末CO_2是呼出的二氧化碳气的测量，利用量热法、二氧化碳检测法、或二氧化碳分析技术来检测。

[0079] 如本文所用，术语ED_{50}指代制剂在被给予该制剂的对象中产生最大效果的50%的有效剂量。

[0080] 如本文所用，术语“CYP450”或“P450”在用于酶时指代细胞色素P450（或P450）家族的酶。

[0081] 如本文所用，“疾病”是这样的对象健康状况：其中对象无法保持体内稳态，并且其中如果疾病未缓解，则对象的健康会继续恶化。

[0082] 如本文所用，“障碍”在对象中是这样的健康状况：其中对象能够保持体内稳态，但是对象的健康状况不如其在无障碍时好。若不进行治疗，障碍不一定会造成对象健康状况进一步下降。

[0083] 如本文所用，化合物的“有效量”、“治疗有效量”或“药学有效量”是足以向被给予化合物的对象提供有益效果的化合物量。

[0084] 术语“治疗”，如本文所用，意为通过给予对象药剂或化合物来降低对象所经受的疾病或病况的症状的频率或严重程度。

[0085] 术语“预防”，如本文所用，意为避免或延迟与疾病或病况有关的症状在药剂或化合物的给予开始时还未发生这种症状的对象中的发作。疾病、病况和障碍在本文中可互换使用。

[0086] 如本文所用，术语“药学上可接受的”指代这样的材料，如载体或稀释剂：不消除本发明中的有用化合物的生物活性或特性，并且相对无毒的，即，该材料可被给予对象，而不引起不期望的生物学效应或以不利方式与包含其的组合物的任何组分相互作用。

[0087] 如本文所用，术语“药学上可接受的盐”指代被给予的化合物的盐，由药学上可接受的无毒酸和碱制备，包括无机酸、无机碱、有机酸、无机碱、其溶剂化物、水合物、和包合物。

[0088] 如本文所用，术语“组合物”或“药物组合物”指代至少一种本发明中的有用化合物与药学上可接受的载体的混合物。药物组合物促进化合物至对象的给予。

[0089] 如本文所用，术语“药学上可接受的载体”意为在对象体内或向对象运载或输送本发明中的有用化合物以便其可执行其目标功能所涉及的药学上可接受的材料、组合物或载体，如液体或固体填充剂、稳定剂、分散剂、悬浮剂、稀释剂、赋形剂、增稠剂、溶剂或封装材料。一般，这种构建物从一个器官或身体部位被运载或输送至另一器官或身体部位。每种载体在下列意义上必须是“可接受的”：与制剂其他成分（包括本发明中的有用化合物）可相容，并且对对象无伤害。可充当药学上可接受的载体的材料的一些实例包括：糖，如乳糖、葡萄糖和蔗糖；淀粉，如玉米淀粉和马铃薯淀粉；纤维素及其衍生物，如羧甲基纤维素钠、乙基纤维素和乙酸纤维素；粉末状黄蓍胶；麦芽；明胶；滑石；赋形剂，如可可脂和栓剂蜡；油，如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油；二醇类，如丙二醇；多元醇类，如甘油、山梨醇、甘露醇和聚乙二醇；酯类，如油酸乙酯和月桂酸乙酯；琼脂；缓冲剂，如氢氧化镁和氢氧化铝；表面活性剂；海藻酸；无热原水；等渗盐水；林格氏溶液；乙醇；磷酸盐缓冲液；和药物制剂中使用的其他无毒可相容物质。如本文所用，“药学上可接受的载体”还包括与本发明中的有用化合物的活性可相容并且对象生理上可接受的任何和全部包衣、抗细菌和抗真菌剂、和吸收延迟剂、及类似物。补充型活性化合物也可被掺入组合物。“药学上可接受的载体”可进一步包括本发明中的有用化合物的药学上可接受的盐。可包括在本发明实践所用的药物组合物中的其他额外成分在本领域已知，并且被描述于例如 Remington's Pharmaceutical Sciences(Genaro, Ed., Mack Publishing Co., 1985, Easton, PA)，其通过引用并入本文。

[0090] 一方面，术语“共同给予的”和“共同给予”在涉及对象时指代给予对象本发明的

化合物或其盐以及也可治疗呼吸控制障碍的化合物和/或可用于治疗其他医学病况但其本身可改变呼吸控制的化合物。在一个实施方式中，共同给予的化合物被分开给予，或以任何类型的组合作为单一疗法的部分被给予。共同给予的化合物可以任何类型的组合被配制成基于各种固体、凝胶、和液体制剂的固体和液体混合物，和溶液。

[0091] 术语“特异性结合”或“特异性结合”，如本文所用，意为第一分子优先结合至第二分子（例如，特定受体或酶），但不一定仅结合至该第二分子。

[0092] 如本文所用，术语“烷基”本身或作为另一取代基的部分，除非另外说明，意为具有指定碳原子数的直链或支链烃（即，C_1-C_{10}意为1至10个碳原子），包括直链、支链或环状取代基。实例包括甲基、乙基、丙基、异丙基、丁基、异丁基、叔丁基、戊基、新戊基、己基、和环丙基甲基。最优选（C_1-C_6）烷基，如但不限于，乙基、甲基、异丙基、异丁基、正戊基、正己基和环丙基甲基。

[0093] 如本文所用，术语“环烷基”本身或作为另一取代基的部分，除非另外说明，意为具有指定碳原子数的环链烃（即，C_3-C_6意为包括由3至6个碳原子组成的环基团的环状基团），包括直链、支链或环状取代基。实例包括环丙基、环丁基、环戊基、环己基、环庚基和环辛基。最优选（C_3-C_6）环烷基，如但不限于，环丙基、环丁基、环戊基和环己基。

[0094] 如本文所用，单独或与其他术语组合使用的术语“烯基”，除非另外说明，意为具有指定碳原子数的稳定单不饱和或双不饱和直链或支链烃基团。实例包括乙烯基、丙烯基（或烯丙基）、丁烯基、异戊烯基、丁二烯基、1,3-戊二烯基、1,4-戊二烯基、和更高级同系物和异构体。表示烯烃的官能团由$-CH_2-CH=CH_2$示例。

[0095] 如本文所用，单独或与其他术语组合使用的术语“炔基”，除非另外说明，意为具有指定碳原子数的具有三重碳-碳键的稳定直链或支链烃基团。非限制性实例包括乙炔基和丙炔基、和更高级同系物和异构体。术语“炔丙基”指代由$-CH_2-C\equiv CH$示例的基团。术语“高炔丙基”(homopropargylic)指代由$-CH_2CH_2-C\equiv CH$示例的基团。术语“取代炔丙基”指代由$-CR_2-C\equiv CR$示例的基团，其中每次出现的R独立地是H、烷基、取代烷基、烯基或取代烯基，条件是至少一个R基团不是氢。术语“取代高炔丙基”指代由$-CR_2CR_2-C\equiv CR$示例的基团，其中每次出现的R独立地是H、烷基、取代烷基、烯基或取代烯基，条件是至少一个R基团不是氢。

[0096] 如本文所用，术语“取代烷基”、“取代环烷基”、“取代烯基”或“取代炔基”意为被1、2或3个取代基取代的如上文限定的烷基、环烷基、烯基或炔基，该取代基选自卤素、-OH、烷氧基、四氢-2-H-吡喃基、$-NH_2$、$-N(CH_3)_2$、(1-甲基-咪唑-2-基)、吡啶-2-基、吡啶-3-基、吡啶-4-基、$-C(=O)OH$、三氟甲基、$-C\equiv N$、$-C(=O)O(C_1$-$C_4)$烷基、$-C(=O)NH_2$、$-C(=O)NH(C_1$-$C_4)$烷基、$-C(=O)N((C_1$-$C_4)$烷基$)_2$、$-SO_2NH_2$、$-C(=NH)NH_2$、和$-NO_2$，优选包含一个或两个取代基，该取代基选自卤素、-OH、烷氧基、$-NH_2$、三氟甲基、$-N(CH_3)_2$、和$-C(=O)OH$，更优选选自卤素、烷氧基和-OH。取代烷基的实例包括但不限于，2,2-二氟丙基、2-羧基环戊基和3-氯丙基。

[0097] 如本文所用，单独或与其他术语组合使用的术语“烷氧基”，除非另外说明，意为通过氧原子连接至分子其余部分的上文限定的具有指定碳原子数的烷基，如，例如，甲氧基、乙氧基、1-丙氧基、2-丙氧基（异丙氧基）和更高级同系物和异构体。优选（C_1-C_3）烷氧基、如，但不限于，乙氧基和甲氧基。

[0098] 如本文所用，单独或作为另一取代基的部分使用的术语“卤”或“卤素”，除非另外说明，意为氟、氯、溴、或碘原子，优选氟、氯、或溴，更优选氟或氯。

[0099] 如本文所用，术语“杂烷基”本身或与另一术语组合，除非另外说明，意为由指定数量的碳原子和一个或两个选自 O、N、和 S 的杂原子组成的稳定直链或支链烷基，并且其中氮和硫原子可任选地被氧化，并且氮杂原子可任选地被季铵化。杂原子（一个或多个）可布置在杂烷基的任意位置，包括杂烷基其余部分和其所附接的片段之间，以及附接至杂烷基的最远碳原子。实例包括：$-O-CH_2-CH_2-CH_3$、$-CH_2-CH_2-CH_2-OH$、$-CH_2-CH_2-NH-CH_3$、$-CH_2-S-CH_2-CH_3$、和 $-CH_2CH_2-S(=O)-CH_3$。上至两个杂原子可以是连续的，如，例如、$-CH_2-NH-OCH_3$、或 $-CH_2-CH_2-S-S-CH_3$。

[0100] 如本文所用，术语“杂烯基”本身或与另一术语组合，除非另外说明，意为由指定数量的碳原子和一个或两个选自 O、N、和 S 的杂原子组成的稳定直链或支链单不饱和或双不饱和烃基团，并且其中氮和硫原子可任选地被氧化，并且氮杂原子可任选地被季铵化。上至两个杂原子可被连续布置。实例包括 $-CH=CH-O-CH_3$、$-CH=CH-CH_2-OH$、$-CH_2-CH=N-OCH_3$、$-CH=CH-N(CH_3)-CH_3$、和 $-CH_2-CH=CH-CH_2-SH$。

[0101] 如本文所用，术语“芳香族”指代这样的碳环或杂环：具有一个或多个多不饱和环，并且具有芳香族特征，即具有 (4n+2) 个离域（π）电子，其中 n 是整数。

[0102] 如本文所用，术语“芳基”单独或与其他术语组合使用的，除非另外说明，意为碳环芳香族系统，包含一个或多个环（一般 1、2 或 3 个环），其中该环可以悬垂方式附接在一起，如联苯基，或可稠和，如萘。实例包括苯基、蒽基、和萘基。优选苯基和萘基，最优选苯基。

[0103] 如本文所用，术语“芳基 $-(C_1-C_3)$ 烷基”意为这样的官能团：其中 1 至 3 个碳的亚烷基链附接至芳基，例如、$-CH_2CH_2-$ 苯基或 $-CH_2-$ 苯基（苄基）。优选芳基 $-CH_2-$ 和芳基 $-CH(CH_3)-$。术语“取代芳基 $-(C_1-C_3)$ 烷基”意为其中芳基被取代的芳基 $-(C_1-C_3)$ 烷基官能团。优选取代芳基 $(CH_2)-$。类似地，术语“杂芳基 $-(C_1-C_3)$ 烷基”意为这样的官能团：其中 1 至 3 个碳的亚烷基链附接至杂芳基，例如，$-CH_2CH_2-$ 吡啶基。优选杂芳基 $-(CH_2)-$。术语“取代杂芳基 $-(C_1-C_3)$ 烷基”意为其中杂芳基被取代的杂芳基 $-(C_1-C_3)$ 烷基官能团。优选取代杂芳基 $-(CH_2)-$。

[0104] 如本文所用，术语“杂环”或“杂环基”或“杂环状”本身或作为另一取代基的部分，除非另外说明，意为由碳原子和至少一个选自 N、O、和 S 的杂原子组成的未取代的或取代的、稳定的、单环或多环的杂环状环系统，并且其中氮和硫杂原子可任选地被氧化，并且氮原子可任选地被季铵化。除非另外说明，杂环状系统可附接在提供稳定结构的任何杂原子或碳原子处。杂环在性质上可以是芳香族或非芳香族的。在一个实施方式中，杂环是杂芳基。

[0105] 如本文所用，术语“杂芳基”或“杂芳香族”指代具有芳香族特征的杂环。多环杂芳基可包括一个或多个部分饱和的环。实例包括四氢喹啉和 2,3- 二氢苯并呋喃基。

[0106] 非芳香族杂环的实例包括单环基团，如氮丙啶、环氧乙烷、环硫乙烷、氮杂环丁烷、氧杂环丁烷、硫杂环丁烷、吡咯烷、吡咯啉、咪唑啉、吡唑烷、二氧戊烷、环丁砜、2,3- 二氢呋喃、2,5- 二氢呋喃、四氢呋喃、噻吩烷、哌啶、1,2,3,6- 四氢吡啶、1,4- 二氢吡啶、哌嗪、吗啉、硫代吗啉、吡喃、2,3- 二氢吡喃、四氢吡喃、1,4- 二**噁**烷、1,3- 二**噁**烷、高哌嗪、高哌啶、1,3- 二氧杂环庚烷、4,7- 二氢 -1,3- 二氧七环 (dioxepin) 和六亚甲基氧。

[0107] 杂芳基的实例包括吡啶基、吡嗪基、嘧啶基（如，但不限于，2- 和 4- 嘧啶基），哒嗪基、噻吩基、呋喃基、吡咯基、咪唑基、噻唑基、**噁**唑基、吡唑基、异噻唑基、1，2，3- 三唑基、1，2，4- 三唑基、1，3，4- 三唑基、四唑基、1，2，3- 噻二唑基、1，2，3- **噁**二唑基、1，3，4- 噻二唑基和 1，3，4- **噁**二唑基。

[0108] 多环杂环的实例包括吲哚基（如，但不限于，3-、4-、5-、6- 和 7- 吲哚基）、吲哚啉基、喹啉基、四氢喹啉基、异喹啉基（如，但不限于，1- 和 5- 异喹啉基）、1，2，3，4- 四氢异喹啉基、噌啉基、喹**噁**啉基（如，但不限于，2- 和 5- 喹**噁**啉基）、喹唑啉基、酞嗪基、1，8- 萘啶基、1，4- 苯并二**噁**烷基、香豆素、二氢香豆素、1，5- 萘啶基、苯并呋喃基（如，但不限于，3-、4-、5-、6- 和 7- 苯并呋喃基）、2，3- 二氢苯并呋喃基、1，2- 苯并异**噁**唑基、苯并噻吩基（如，但不限于，3-、4-、5-、6-、和 7- 苯并噻吩基）、苯并**噁**唑基、苯并噻唑基（如，但不限于，2- 苯并噻唑基和 5- 苯并噻唑基）、嘌呤基、苯并咪唑基、苯并三唑基、硫代黄嘌呤基（thioxanthinyl），咔唑基、咔啉基、吖啶基、吡咯里西啶基（pyrrolizidinyl）、和喹诺里西啶基（quinolizidinyl）。

[0109] 杂环基和杂芳基部分的上述列举意图作为代表，而非限制。

[0110] 如本文所用，术语“取代”意为原子或原子基团取代氢，作为附接至另一基团的取代基。

[0111] 关于芳基、芳基 -(C_1-C_3) 烷基和杂环基基团，术语“取代”在用于这些基团的环时，指代任何取代水平，即单 -、二 -、三 -、四 -、或五 - 取代——在允许这种取代的情况下。取代基被独立地选择，并且取代可在任何化学可及的的位置处。在一个实施方式中，取代基数量在 1 和 4 之间改变。在另一实施方式中，取代基数量在 1 和 3 之间改变。在再一实施方式中，取代基数量在 1 和 2 之间改变。在再一实施方式中，取代基独立地选自 $C_{1\ 6}$烷基、-OH、$C_{1\ 6}$烷氧基、卤素、氨基、乙酰氨基和硝基。如本文所用，在取代基是烷基或烷氧基的情况下，碳链可以是支链、直链或环状的，其中优选直链。

[0112] 本文使用下列缩写词：δ（德耳塔）：δ（ppm）；μL（μl）：微升；

[0113] ABG：动脉血气；AcOH：乙酸；

[0114] ASV：适应伺服通气；AUC：曲线下方面积；

[0115] BiPAP：双水平气道正压通气；nBuOH：正丁醇；

[0116] 2-BuOH：2- 丁醇；$CHCl_3$，氯仿；

[0117] $CDCl_3$：氯仿 -d；CH_2Cl_2：二氯甲烷或亚甲基氯；

[0118] CPAP：持续气道正压；DIPEA：N，N- 二异丙基乙胺；

[0119] DMAc：N，N- 二甲基乙酰胺；DMSO：二甲基亚砜；

[0120] EPAP：呼气气道正压；EtOAc：乙酸乙酯；

[0121] EtOH：乙醇；Et_2O：（二）乙醚；

[0122] f：（呼吸）频率；F（%）：生物利用度（百分比）

[0123] HCl：盐酸或盐酸盐；

[0124] hERG：人 Ether-a-go-go 相关基因（Kv11.1 离子通道）

[0125] H_2SO_4：硫酸；HLM：人肝脏微粒体；

[0126] HPLC：高压液相色谱；

[0127] ICU：重症监护室； IPA：异丙醇（或2-丙醇）；

[0128] IPAP：吸气气道正压；

[0129] LCMS：液相色谱-质谱；

[0130] MBP：平均血压； MeCN或CH_3CN：乙腈；

[0131] MEK：甲基乙基酮； MeOH或CH_3OH：甲醇；

[0132] MIBK：甲基异丁基酮； min：分钟

[0133] mL（或mL）：毫升； mpk：mg/kg；

[0134] MTBE：甲基-叔丁醚； MV：每分钟通气量；

[0135] MS：质谱； NaCl：氯化钠；

[0136] NaHMDS：六甲基二硅烷重氮钠； $NaHCO_3$：碳酸氢钠；

[0137] NaOH：氢氧化钠； Na_2SO_4：硫酸钠；

[0138] NAVA：神经调节辅助通气；

[0139] NIPPV：非侵入性正压通气；

[0140] NMR：核磁共振； PAV：比例辅助通气；

[0141] PE或pet醚：石油醚； ppm：每百万份的份数；

[0142] iPrOAc：乙酸异丙酯； nPrOH：正丙醇；

[0143] RLM：大鼠肝脏微粒体； RR：呼吸速率；

[0144] THF：四氢呋喃； TV：潮气量；

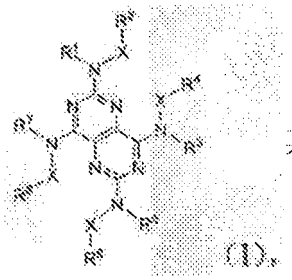
[0145] V_E：每分钟（呼气）量； XRPD：X射线粉末衍射（光谱）；

[0146] %y：产率百分比。

[0147] 术语“说明材料”在本文中使用时包括可用于传达试剂盒中的本发明组合物和/或化合物的效用的出版物、记录、图表或任何其他表述介质。试剂盒的说明材料可例如固定至包含本发明化合物和/或组合物的容器，或与包含化合物和/或组合物的容器一起装运。可选地，说明材料可与容器分开装运，目的是接受者配合使用说明材料和化合物。说明材料的递送可，例如，通过传达试剂盒效用的出版物或其他表述介质的物理递送进行，或可以可选地通过电子传输实现，例如通过计算机，如通过电子邮件、或从网站下载。

[0148] 本发明的化合物和组合物

[0149] 本发明包括式（I）化合物或其盐：

[0150]  其中：

[0151] R^1、R^2、R^3、R^4、R^5、R^6、R^7和R^8独立地是H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

[0152] 或R^1和R^2、R^3和R^4、R^5和R^6、或R^7和R^8独立地组合形成双自由基，该双自由基选自3-羟基-戊烷-1,5-二基、6-羟基-环庚烷-1,4-二基、丙烷-1,3-二基、丁烷-1,4-二基

和戊烷 -1,5- 二基；

[0153] 每次出现的 X 均独立地选自键、NH、NR^9和 O；和

[0154] 每次出现的 X 独立地是烷基或取代烷基。

[0155] 在一个实施方式中，R^1、R^3、R^5和 R^7是 H。

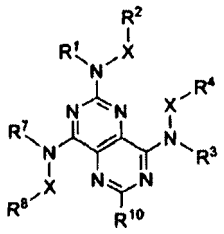
[0156] 在一个实施方式中，R^1、R^3、R^5和 R^7是 H；X 是 O；和 R^2、R^4、R^6和 R^8是烷基或取代烷基。在另一实施方式中，R^1、R^3、R^5和 R^7是 H；X 是 O；和 R^2、R^4、R^6和 R^8是 H。在再一实施方式中，R^1、R^3、R^5和 R^7是烷基或取代烷基；X 是 O；和 R^2、R^4、R^6和 R^8是 H。

[0157] 在一个实施方式中，R^1、R^3、R^5和 R^7是 H；X 是 NH；和 R^2、R^4、R^6和 R^8是烷基或取代烷基。在另一实施方式中，R^1、R^3、R^5和 R^7是 H；X 是 NH；和 R^2、R^4、R^6和 R^8是 H。

[0158] 在一个实施方式中，R^1、R^3、R^5和 R^7是 H；X 是 NR^9；和 R^2、R^4、R^6和 R^8是烷基或取代烷基。在另一实施方式中，R^1、R^3、R^5和 R^7是 H；X 是 NR^9；和 R^2、R^4、R^6和 R^8是 H。在再一实施方式中，R^1、R^3、R^5和 R^7是烷基或取代烷基；X 是 NR^9；和 R^2、R^4、R^6和 R^8是烷基或取代烷基。

[0159] 在一个实施方式中，R^1、R^3、R^5和 R^7是 H；X 是键；和 R^2、R^4、R^6和 R^8是烷基或取代烷基。

[0160] 本发明还包括式（II）化合物或其盐：

[0161]  其中：

（II），

[0162] R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

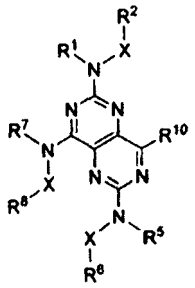
[0163] 或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，该双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

[0164] 每次出现的 X 均独立地选自键、NH、NR^9和 O；

[0165] 每次出现的 R^9独立地是烷基或取代烷基；

[0166] R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基。

[0167] 本发明还包括式（III）化合物或其盐：

[0168]  其中：

（III），

[0169] R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取

代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

[0170] 或 R^1 和 R^2、R^3 和 R^4、R^5 和 R^6、或 R^7 和 R^8 独立地组合形成双自由基，该双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

[0171] 每次出现的 X 均独立地选自键、NH、NR^9 和 O；

[0172] 每次出现的 R^9 独立地是烷基或取代烷基；

[0173] R^{10} 是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基。

[0174] 在一个实施方式中，本发明的化合物选自：

[0175] N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0176] N^2, N^4, N^6, N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0177] N^2, N^6- 二 - 正丁基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0178] N^2, N^6- 二 - 异丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0179] N^2, N^6- 二甲基 -N^4- 正丙基 -N^8- 丙 -2- 炔基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0180] N^2,N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4,N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶；

[0181] N-(6- 氯 -4,8- 双 - 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-O, N- 二甲基 - 羟基胺；

[0182] N^2,N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4,N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶；

[0183] N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

[0184] O, N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)- 羟基胺；

[0185] N^4, N^8- 二甲基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0186] N^2, N^2, N^6- 三甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0187] 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

[0188] N^2,N^2- 二乙基 -N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0189] 2-(4,8- 双 - 正丙基氨基 -6- 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基 - 氨基)- 乙醇；

[0190] N^2-(2- 甲氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0191] N^2-(2- 异丙氧基 - 乙基)-N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0192] N^8- 甲基 -N^4, N^6- 二 - 正丙基 -N^2-(3,3,3- 三氟丙基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0193] N^2- 甲基 -N^4,N^8- 二 - 正丙基 -6-(吗啉 -4- 基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三

胺；

[0194] N^2-甲基-N^4,N^8-二-正丙基-6-(哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0195] N^2-甲基-N^4,N^8-二-正丙基-6-吡咯烷-1-基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0196] N^2-甲基-N^4,N^8-二-正丙基-6-(4-甲氧基-哌啶-1-基)-嘧啶并[5,4,-d]嘧啶-2,4,8-三胺；

[0197] N^2-(3-氯-2-甲基-苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0198] N^2-(3,4-二氯苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0199] N^2-(4-氟苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0200] 6-氯-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0201] N^2,N^2,N^4,N^8-四甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0202] N^2,N^2-二烯丙基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0203] 2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-甲基-氨基]-乙醇；

[0204] N^2-(2-异丙氧基-乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0205] 2-[N-(2-二甲基氨基-乙基)-N-甲基]氨基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-4,6,8-三胺；

[0206] 2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-(2-羟基-乙基)-氨基]-乙醇；

[0207] N^2,N^2-双-(2-甲氧基乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0208] 6-(4-氧-哌啶-1-基)-N^4,N^8-二甲基-N^2-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺；

[0209] N^2-(3-三氟甲基-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺；

[0210] N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺；

[0211] N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0212] N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0213] N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0214] N^2,N^6-二-正丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0215] N^2,N^6-双-环丙基甲基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0216] N^2,N^6-二异丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0217] N^2,N^6-二烯丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0218] 2-氯-6-(N,N'-二甲基-肼基)-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺；

[0219] 6-(N,N'-二甲基-肼基)-N^2,N^2,N^4,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0220] N^4,N^8-二甲基-6-丙氧基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0221] N^4,N^8-二甲基-N^2-正丙基-6-丙基硫烷基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0222] 6-苄氧基-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0223] 4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-醇；

[0224] 4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-腈；

[0225] N^4,N^8-二甲基-N^2-正丙基-6-(氨基甲基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0226] 6-氨甲酰基-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0227] 4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-羧酸；

[0228] N-(正丙基)-[4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基]-脒；

[0229] N^4,N^8-二甲基-N^2-正丙基-6-(4-氟苯基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0230] N^2-甲基-N^4,N^8-二-正丙基-6-(4-氟苯基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0231] N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0232] 6-正丁基-N^2-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0233] 6-甲氧基-N^2-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0234] 6-甲基氨基-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-腈；

[0235] N^2,N^4,N^6,N^8-四乙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺

[0236] 2,6-二氯-N^4,N^8-二乙基-嘧啶并[5,4-d]嘧啶-4,8-二胺；

[0237] N^4,N^8-二乙基-N^2,N^6-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0238] N^2,N^6-双-环丙基甲基-N^4,N^8-二乙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0239] N^2,N^6-二乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0240] N^2,N^2,N^6-三乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0241] 6-氯-N^2-乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0242] N^2,N^6-二乙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0243] N^2,N^6-二环丙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0244] N^2,N^6-双-环丙基甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0245] N^2,N^2,N^6,N^6-四甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0246] N^4,N^8-二烯丙基-N^2,N^6-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0247] N^2,N^4,N^8-三烯丙基-6-[4-(4-氟苄基)-哌嗪-1-基]-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0248] 6- 氯 -N^2, N^4, N^8- 三烯丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

[0249] N^2,N^4,N^8- 三烯丙基 -6-{4-[双 -(4- 氟苯基)- 甲基]- 哌嗪 -1- 基 }- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

[0250] N^2, N^2, N^6- 三乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0251] (4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯；

[0252] (4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸；

[0253] N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺；

[0254] (6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯；

[0255] 其任何盐或溶剂化物，和其任意组合。

[0256] 在一个实施方式中，盐选自硫酸盐、硫酸氢盐、氯化物、溴化物、碘化物、硝酸盐、碳酸盐、磷酸盐、磷酸氢盐、磷酸二氢盐、甲酸盐、乙酸盐、丙酸盐、琥珀酸盐、乙醇酸盐、葡萄糖酸盐、乳酸盐、苹果酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐、葡萄糖醛酸盐、马来酸盐、富马酸盐、丙酮酸盐、天冬氨酸盐、谷氨酸盐、苯甲酸盐、邻氨基苯甲酸盐、4- 羟基苯甲酸盐、苯基乙酸盐、扁桃酸盐、扑酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、泛酸盐、三氟甲磺酸盐、2- 羟基乙磺酸盐、对甲苯磺酸盐、磺胺酸盐、环己基氨基磺酸盐、硬脂酸盐、海藻酸盐、β - 羟基丁酸盐、水杨酸盐、半乳糖酸盐、半乳糖醛酸盐、糖精、糖质酸盐、和甘油膦酸盐。在某些实施方式中，盐可包括关于本发明任何分子的一个或多个摩尔当量的盐前体。

[0257] 在一个实施方式中，本发明至少一种化合物是药物组合物的组分，该药物组合物进一步包括至少一种药学上可接受的载体。

[0258] 本发明的化合物可具有一个或多个立体中心，并且每个立体中心可独立地以 (R) 或 (S) 构型存在。在一个实施方式中，本文描述的化合物以光学活性或消旋形式存在。本文描述的化合物包括具有本文描述的治疗效用特性的消旋、光学活性、区域异构体和立体异构体形式、或其组合。光学活性形式的制备以任何适当的方式实现，作为非限制性实例包括，通过利用重结晶技术拆分消旋形式、由光学活性起始材料合成、手性合成、或利用手性固定相色谱分离。在一个实施方式中，一种或多种异构体的混合物用作本文描述的治疗化合物。在另一实施方式中，本文描述的化合物包含一个或多个手性中心。这些化合物被通过任意手段制备，包括立体选择性合成、对映选择性合成和 / 或对映体和 / 或非对映异构体混合物的分离。化合物和其异构体的拆分通过任何手段实现，作为非限制性实例包括，化学法、酶法、分级结晶、蒸馏、和色谱法。

[0259] 本文描述的方法和制剂包括使用具有本发明任何化合物结构的化合物的 N- 氧化物（若适当）、晶体形式（也被称为多晶型）、溶剂化物、无定形相、和 / 或药学上可接受的盐、以及这些化合物的具有相同活性类型的代谢产物和活性代谢产物。溶剂化物包括水、醚（例如，四氢呋喃、甲基叔丁醚）或酒精（例如，乙醇）溶剂化物、乙酸盐（酯）及类似物。在一个实施方式中，本文描述的化合物与药学上可接受的溶剂如水和乙醇一起以溶剂化形式存在。在另一实施方式中，本文描述的化合物以非溶剂化形式存在。在一个实施方式中，本发明的化合物作为互变异构体存在。所有互变异构体均被包括在本文描述的化合物范围内。

[0260] 在一个实施方式中，本文描述的化合物被制备成前体药物。“前体药物”是在体内转化成母体药物的药剂。在一个实施方式中，在体内给予后，前体药物化学转化成化合物的生物学、药学或治疗活性形式。在另一实施方式中，前体药物通过一个或多个步骤或过程酶促代谢成化合物的生物学、药学或治疗活性形式。

[0261] 在一个实施方式中，例如在本发明化合物芳香环部分上的位点容易发生各种代谢反应。适当取代基在芳香族环结构上的并入可减少、最小化或消除这种代谢途径。在一个实施方式中，适于减少或消除芳香环的代谢反应易感性的取代基是（仅作为实例）氘、卤素或烷基。

[0262] 本文描述的化合物还包括同位素标记的化合物，其中一个或多个原子被具有相同原子数，但原子质量或质量数与自然界通常发现的原子质量或质量数不同的原子代替。适于并入本文描述的化合物的同位素实例包括但不不限于 ^{2}H、^{3}H、^{11}C、^{13}C、^{14}C、^{36}Cl、^{18}F、^{123}I、^{125}I、^{13}N、^{15}N、^{15}O、^{17}O、^{18}O、^{32}P、和 ^{35}S。在一个实施方式中，同位素包括氘。在某些实施方式中，同位素标记的化合物可用于药物和/或底物组织分布研究。在另一实施方式中，用较重同位素如氘取代提供了较高的代谢稳定性（例如，体内半衰期增加或剂量需求减少）。在再一实施方式中，用正电子发射同位素如 ^{11}C、^{18}F、^{15}O 和 ^{13}N 取代可用于正电子发射断层扫描术(PET)研究，以检测底物受体占有率。同位素标记的化合物通过利用适当同位素标记型试剂代替否则使用的未标记试剂的任何适当的方法或过程来制备。同位素标记不应被解释为限于本发明的化合物，而适用于可与本发明化合物组合使用的化合物，如但不限于乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂、苯二氮䓬受体激动剂、食欲肽拮抗剂、三环类抗抑郁剂、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素、食欲肽、褪黑激素激动剂、安帕金、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂。在某些实施方式中，羟丁酸盐用一个或多个氘在 C-α 位进行同位素标记。

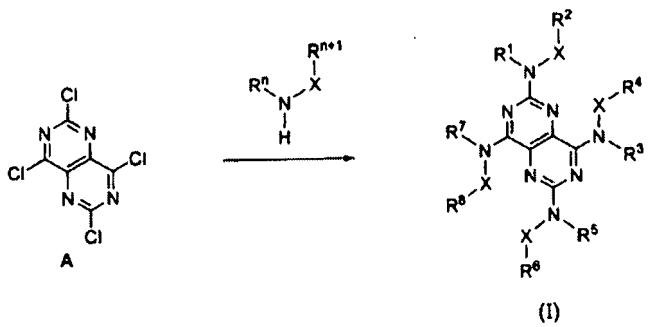
[0263] 在一个实施方式中，本文描述的化合物被其他手段标记，包括但不限于，使用发色团或荧光部分、生物发光标记、或化学发光标记。

[0264] 本发明化合物的制备

[0265] 本发明的化合物可按照下文所述合成方案示例的一般方法来制备。可改动本文描述的试剂和条件以提供本发明化合物的制备，并且这种改动是本领域技术人员已知的。本文包括的方案意图示例而非限制本领域技术人员可用来制备本发明化合物的化学和方法。

[0266] 在非限制性实例中，式(I)化合物可通过添加：(i)伯烷基胺或仲烷基胺或烯丙基胺或炔丙基胺、或(ii)N-烷氧基-N-烷基胺、或(iii)适当取代的肼，至适当氯化的中间体(A)来制备（方案1）。

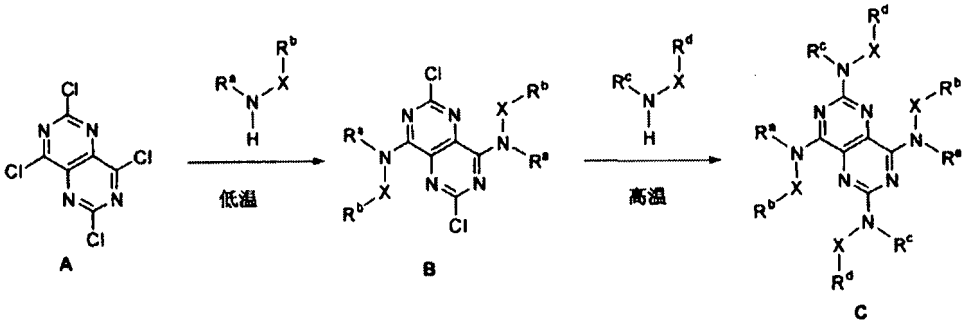
[0267]



方案 1（n = 1、3、5 和 7）

[0268] 在非限制性实例中，式 (I)-(III) 的化合物可通过相继添加 :(i) 伯烷基胺或仲烷基胺或烯丙基胺或炔丙基胺、和 (ii)N- 烷氧基 -N- 烷基胺或 (iii) 适当取代卟，至适当氯化的中间体 (A) 来制备 (方案 2)。反应温度可用来指导取代基在嘧啶并 [5,4-d] 嘧啶内核上的安置顺序。例如，低温，如 0℃至环境温度 (约 20℃)，使取代基选择性安置在环接点 (ring junction) 相邻的中心 (α 位)，生成化合物 (B)，而较高温度 (约 80-100℃) 将取代基添加至离环接点更远并且亲核置换活性较小的位置 (β 位)。因此，可获得不相似取代基四取代的嘧啶并 [5,4-d] 嘧啶化合物 (C)(方案 2)。淬灭反应可适当地提供三取代嘧啶并 [5,4-d] 嘧啶化合物。

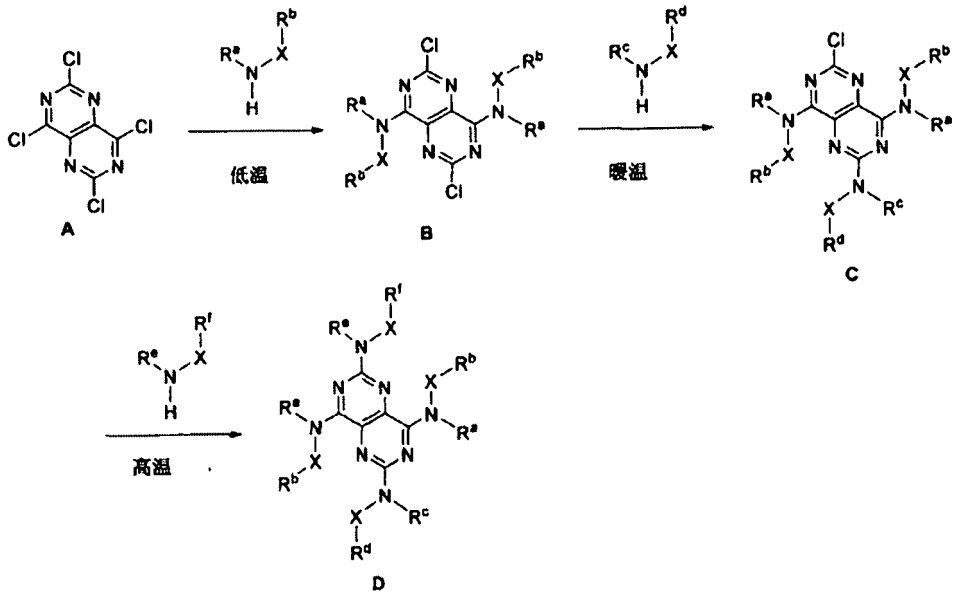
[0269]



方案 2

[0270] 在非限制性实例中，可通过如下获得具有不相似取代基的式 (I) 化合物 (D，方案 3) :在第一步附接两个相同烷基氨基取代基，然后在第二步附接与之前基团不相似的第三烷基氨基取代基，并最后附接与之前基团不相似的第四烷基氨基取代基。

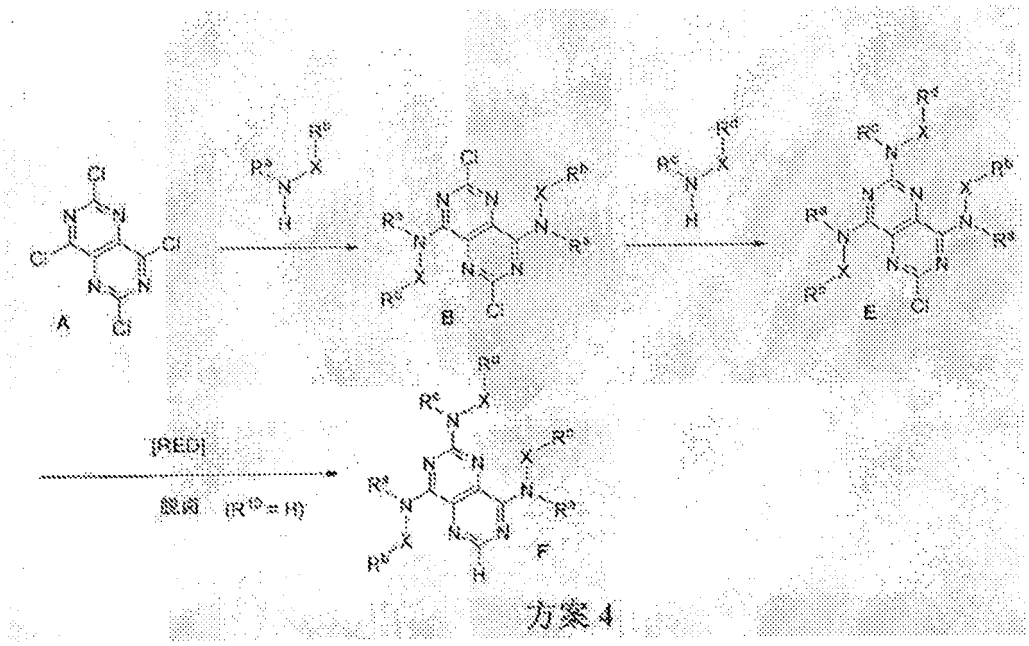
[0271]



方案 3

[0272] 在非限制性实例中，式 (II)-(III) 的化合物可通过如下制备——相继添加 :(i) 伯烷基胺或仲烷基胺或烯丙基胺或炔丙基胺、和 (ii)N- 烷氧基 -N- 烷基胺或 (iii) 适当取代肼至适当氯化的中间体 (A)，以提供单氯嘧啶并 [5,4-d] 嘧啶化合物 (E)，其可进一步脱卤 / 还原，生成式 (II) 的三取代嘧啶并 [5,4-d] 嘧啶化合物 (F)(方案 4)。

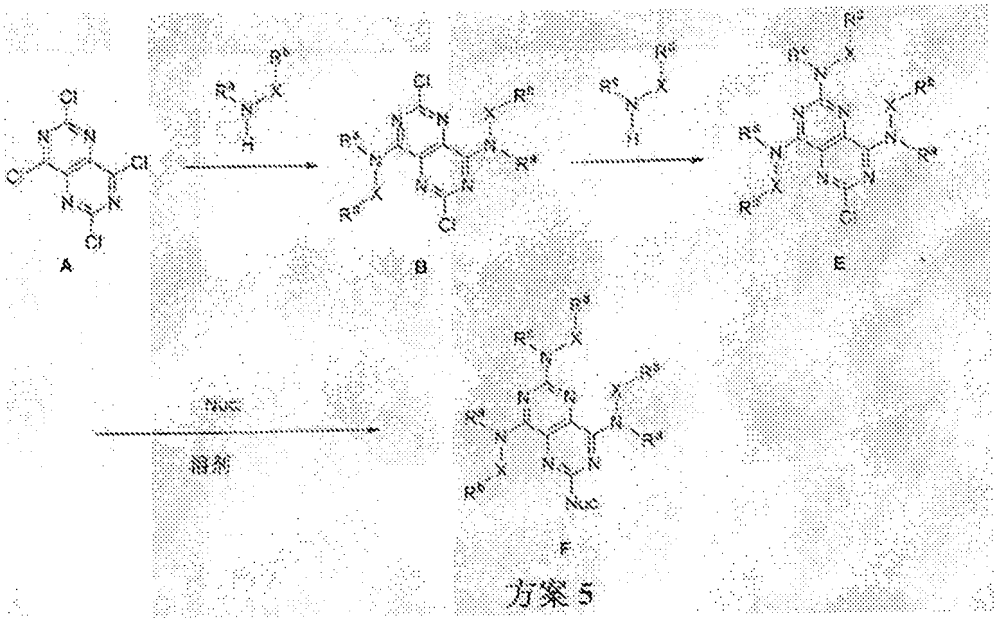
[0273]



方案 4

[0274] 在非限制性实例中，式 (I)-(III) 的化合物可通过如下获得 :用亲核试剂置换卤基团，生成包含卤素、氰基、脒基、酰氨基、肼基、羟基、烷基、取代烷基、烷氧基或取代烷氧基、羧酸、羧酰胺基、醚或硫醚取代基的嘧啶并 [5,4-d] 嘧啶化合物。

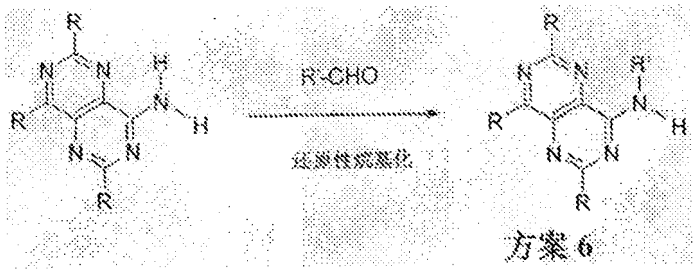
[0275]



方案 5

[0276] 在非限制性实例中，式 (I)-(III) 的化合物可通过氨基 - 取代嘧啶并 [5,4-d] 嘧啶化合物的还原性胺化来获得。

[0277]



方案 6

[0278] 盐

[0279] 本文描述的化合物可与酸形成盐，并且这种盐被包括在本发明中。在一个实施方式中，该盐是药学上可接受的盐。术语“盐”包括本发明方法中可用的游离酸加成盐。术语“药学上可接受的盐”指代具有在制药应用中提供效用的范围内的毒性特征的盐。但药学上不可接受的盐可具有在本发明实践中具有效用（如例如在本发明方法中可用的化合物的合成、纯化或配制过程中的效用）的特性，如高结晶度。

[0280] 适当的药学上可接受的酸加成盐可由无机酸或有机酸制备。无机酸的实例包括硫酸盐、硫酸氢盐、氢氯酸、氢溴酸、氢碘酸、硝酸、碳酸、硫酸、和磷酸（包括磷酸氢盐和磷酸二氢盐）。适当的有机酸可选自脂肪族、环脂族、芳香族、芳脂族、杂环、羧基和磺酸类有机酸，其实例包括甲酸、乙酸、丙酸、琥珀酸、乙醇酸、葡萄糖酸、乳酸、苹果酸、酒石酸、柠檬酸、抗坏血酸、葡萄糖醛酸、马来酸、富马酸、丙酮酸、天冬氨酸、谷氨酸、苯甲酸、邻氨基苯甲酸、4- 羟基苯甲酸、苯基乙酸、扁桃酸、双羟萘酸（扑酸）、甲磺酸、乙磺酸、苯磺酸、泛酸、三氟甲磺酸、2- 羟基乙磺酸、对甲苯磺酸、磺胺酸、环己基氨基磺酸、硬脂酸、海藻酸、β - 羟基丁酸、水杨酸、半乳糖酸、半乳糖醛酸酸、甘油膦酸和糖精（例如，糖精酸盐、糖质酸盐）。盐可包括相对于本发明的任何化合物小于一个、一个或多个摩尔当量的酸或碱。

[0281] 本发明化合物的适当药学上可接受碱加成盐包括，例如，金属盐，包括碱金属、碱土金属和过渡金属盐，如，例如，钙、镁、钾、钠和锌盐。药学上可接受的碱加成盐还包括由碱性胺制成的有机盐，如，例如，N,N'- 二苄基乙二胺、氯普鲁卡因、胆碱、二乙醇胺、乙二胺、葡

甲胺 (N- 甲基葡萄糖胺) 和普鲁卡因。这些盐都可由相应的化合物通过例如适当的酸或碱与化合物反应来制备。

[0282] 本发明的分子可作为晶体或无定形游离碱来分离。这种晶体或无定形游离碱可直接在处理步骤的过程中获得,其中最终胺在合成过程中附接;并且可另外或可选地通过分开溶解游离碱和从适当的溶剂或溶剂混合物结晶和/或析出游离碱而获得。适当的溶剂可包括但不限于,MeCN、MEK、MIBK、EtOAc、iPrOAc、水、庚烷、MTBE、环己烷、甲苯、MeOH、EtOH、n-PrOH、IPA、nBuOH、2-BuOH、异戊醇、和 THF。

[0283] 组合和同步治疗

[0284] 在一个实施方式中,本发明的化合物,在与至少一种另外的可用于预防和/或治疗呼吸控制障碍的化合物同步使用时,可用于本发明的方法。

[0285] 在一个实施方式中,本发明的化合物可与至少一种另外的可用于预防和/或治疗呼吸控制障碍的化合物组合用于本发明的方法。

[0286] 这些另外的化合物可包括本发明的化合物或其他化合物,如已知治疗、预防、或减轻呼吸障碍症状的市售化合物。在一个实施方式中,至少一种本发明的化合物或其盐与至少一种另外的可用于预防和/或治疗呼吸障碍的化合物的组合在呼吸障碍的预防和/或治疗和在睡眠相关呼吸障碍的预防和/或治疗中具有加成、互补或协同效果。

[0287] 在非限制性实例中,本发明的化合物或其盐可与下列一种或多种药物同步或组合使用:多沙普仑、多沙普仑对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂(如艾司佐匹克隆 (eszopiclone) 和唑吡坦 (zolpidem))、苯二氮䓬受体激动剂(例如,唑吡坦、扎来普隆 (zaleplon)、艾司唑仑 (estazolam)、氟西泮 (flurazepam)、夸西泮 (quazepam)、替马西泮 (temazepam)、三唑仑 (triazolam)) 食欲肽拮抗剂(例如苏沃雷生 (suvorexant))、三环类抗抑郁剂(例如,多塞平 (doxepin))、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素(如,但不限于,屈大麻酚 (dronabinol))、食欲肽、褪黑激素激动剂(如拉米替隆 (ramelteon))、被称为安帕金的化合物、羟丁酸钠、莫达非尼、和阿莫达非尼。

[0288] 在非限制性实例中,本发明的化合物或其盐可与用于治疗睡眠呼吸障碍的吸入式治疗剂如氧气和二氧化碳同步或组合应用。

[0289] 安帕金的非限制性实例是吡咯烷衍生物西坦型 (racetam) 药物,如吡拉西坦 (piracetam) 和茴拉西坦 (aniracetam);包括一系列苯甲酰哌啶和苯甲酰吡咯烷结构的"CX-"系列药物,如CX-516(6-(哌啶-1-基-羰基)喹噁啉)、CX-546(2,3-二氢-1,4-苯并二噁英-7-基-(1-哌啶基)-甲酮)、CX-614(2H,3H,6aH-吡咯烷并 (2,1-3',2')-1,3-噁嗪并-(6',5'-5,4) 苯并 (e)1,4-二噁烷-10-酮)、CX-691(2,1,3-苯并噁二唑-6-基-哌啶-1-基-甲酮)、CX-717、CX-701、CX-1739、CX-1763、和 CX-1837;苯并噻嗪衍生物,如环噻嗪和 IDRA-21(7-氯-3-甲基-3,4-二氢-2H-1,2,4-苯并噻二嗪 1,1-二氧);二芳基丙基磺酰胺类,如 LY-392,098、LY-404,187(N-[2-(4'-氰基联苯基-4-基)丙基]丙烷-2-磺酰胺)、LY-451,646 和 LY-503,430(4'-{(1S)-1-氟-2-[(异丙基磺酰基)氨基]-1-甲基乙基}-N-甲基联苯基-4-羧酰胺)。

[0290] 在一个实施方式中,本发明包括组合物,该组合物包括本发明的化合物和至少一

种选自下列的用剂：多沙普仑、多沙普仑对映体、多沙普仑对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂（如艾司佐匹克隆或唑吡坦）、苯二氮䓬受体激动剂（如唑吡坦、扎来普隆、艾司唑仑、氟西泮、夸西泮、替马西泮、或三唑仑）、食欲肽拮抗剂（例如苏沃雷生）、三环类抗抑郁剂（如多塞平）、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素（如但不限于屈大麻酚）、食欲肽、褪黑激素激动剂（如拉米替隆）、被称为安帕金的化合物、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂如氧气和二氧化碳气体。

[0291] 在另一非限制性实例中，本发明的化合物或其盐可与已知引起呼吸控制变化的下列药物和药物种类中的一种或多种同步或组合应用：阿片类麻醉剂（如吗啡、芬太尼（fentanyl）、可待因（codeine）、氢吗啡酮（hydromorphone）、氢可酮（hydrocodone）、羟吗啡酮（oxymorphone）、羟考酮（oxycodone）、哌替啶（meperidine）、布托啡诺（butorphanol）、卡芬太尼（carfentanil）、丁丙诺啡（buprenorphine）、美沙酮（methadone）、纳布啡（nalbuphine）、丙氧芬（propoxyphene）、喷他佐辛（pentazocine）、瑞芬太尼（remifentanil）、阿芬太尼（alfentanil）、舒芬太尼（sufentanil）和他喷他多（tapentadol））；苯二氮䓬类（如咪达唑仑（midazolam））；和镇静剂（如zolipidem和艾司佐匹克隆）；丙泊酚；羟丁酸钠、莫达非尼、和阿莫达非尼。在一个实施方式中，本发明包括组合物，其包括本发明的化合物和已知引起呼吸控制变化的至少一种用剂。在一个实施方式中，该至少一种用剂选自阿片类麻醉剂、苯二氮䓬类、镇静剂、睡眠助剂和丙泊酚。

[0292] 在另一非限制性实例中，本发明的化合物或其盐可与已知协助睡眠发生、维持睡眠和/或改变觉醒阈值的下列药物和药物种类中的一种或多种同步或组合应用：例如，zolipidem、扎来普隆、艾司佐匹克隆、拉米替隆、艾司唑仑、替马西泮、多塞平、苯巴比妥（phenobarbital）和其他巴比妥酸盐、苯海拉明、多西拉敏和相关化合物、羟丁酸钠、莫达非尼和阿莫达非尼。睡眠促进/稳定药物和本发明化合物的组合可加成或协同发挥作用，以改善睡眠呼吸障碍指数。在一个实施方式中，本发明的化合物稳定呼吸模式（即，减少呼吸基础的呼吸速率和呼吸潮气量改变）和呼吸动力（即，减少呼吸肌肉的神经控制的波动），从而减少中枢性和阻塞性呼吸暂停的发生，同时睡眠促进/稳定药物预防患者从睡眠觉醒——如果剩余呼吸暂停仍然存在。与剩余呼吸暂停有关的血气紊乱可引起化学受体刺激，进而引起广义的中枢神经系统唤醒。具有低睡眠觉醒阈值的患者很早和常常醒来（即，经历睡眠中断），并且这些患者经历由于过量化学受体刺激水平而突然觉醒导致的通气过度。睡眠促进/稳定药物延迟皮质唤醒，并允许对呼吸暂停引起的化学受体刺激做出更适当的通气响应。因为睡眠中断减少和通气过度导致的中枢性呼吸暂停少，患者由于睡眠觉醒延迟而获益。

[0293] 如本文所用，两种或更多种化合物的组合可指代组合物，其中各个化合物物理混合或其中各个化合物物理分开。组合治疗包括分开给予组分以产生期望的加成、互补或协同效果。

[0294] 在一个实施方式中，化合物和用剂在组合物中是物理混合的。在另一实施方式中，化合物和用剂在组合物中是物理分开的。

[0295] 在一个实施方式中，本发明的化合物与用于治疗另一障碍但导致呼吸控制丧失的

化合物被共同给予。在这方面，本发明的化合物阻碍或以其他方式减少共同给予的化合物引起的对正常呼吸控制的抑制效应。这种治疗另一障碍但抑制呼吸控制的化合物包括但不限于麻醉剂、镇静剂、睡眠助剂、抗焦虑剂、催眠剂、酒精、和麻醉性镇痛剂。共同给予的化合物可被单独给予，或者是组合的组合物——按照本领域技术人员已知的方法，组合成在固体、凝胶或液体制剂中的固体和 / 或液体混合物或组合成溶液。

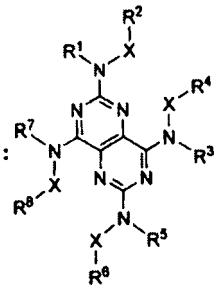
[0296] 在一个实施方式中，本发明的化合物可与至少一种另外的可用于治疗呼吸控制障碍的化合物和至少一种用于治疗其他障碍但引起呼吸控制丧失的化合物被共同给予。在这方面，本发明的化合物与共同给予的呼吸控制剂以加成、互补或协同方式一起工作，以阻碍或以其他方式减少其所组合的其他化合物引起的对正常呼吸控制的抑制效应。

[0297] 可计算协同效果——例如，利用适当的方法，如，例如，Sigmoid-E_{max}方程 (Holford&Scheiner,19981, Clin.Pharmacokinet.6 :429-453)、Loewe 相加性方程 (Loewe&Muischnek,1926, Arch.Exp.Pathol Pharmacol.114 :313-326)、中值效应方程 (Chou&Talalay,1984, Adv.Enzyme Regul.22 :27-55)、和通过采用等效线图 (Tallarida&Raffa,1996,Life Sci.58 :23-28)。上述各方程可用于实验数据，生成相应的图线，以协助评估药物组合的效果。与上述方程相关的相应图线分别是浓度 - 效果曲线、等效线图曲线和组合指数曲线。

[0298] 在一个实施方式中，本发明的化合物可与至少一种另外的可用于治疗呼吸控制障碍的化合物一起包装。在另一实施方式中，本发明的化合物可与已知引起呼吸控制变化的治疗剂一起包装，该治疗剂如但不限于，麻醉剂、镇静剂、抗焦虑剂、催眠剂、酒精、和麻醉性镇痛剂。共同包装可基于，但不限于，剂量单位。

[0299] 本发明的方法

[0300] 一方面，本发明包括在有需要的对象中预防或治疗呼吸控制障碍或疾病的方法。方法包括给予对象有效量药物制剂，其至少包括药学上可接受的载体和至少一种化合物或其盐，该化合物选自：

[0301] 式 (I) 化合物：  其中在式 (I) 中

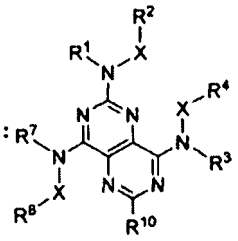
(I)，

[0302] R^1、R^2、R^3、R^4、R^5、R^6、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

[0303] 或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，该双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

[0304] 每次出现的 X 均独立地选自键、NH、NR^9和 O ；和

[0305] 每次出现的 R^9独立地是烷基或取代烷基；

[0306] 式（II）化合物：  其中在式（II）中：

（II），

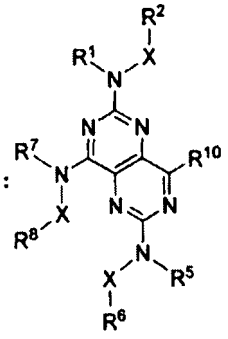
[0307] R^1、R^2、R^3、R^4、R^7和R^8独立地是H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

[0308] 或R^1和R^2、R^3和R^4、R^5和R^6、或R^7和R^8独立地组合形成双自由基，该双自由基选自3-羟基-戊烷-1,5-二基、6-羟基-环庚烷-1,4-二基、丙烷-1,3-二基、丁烷-1,4-二基和戊烷-1,5-二基；

[0309] 每次出现的X均独立地选自键、NH、NR^9和O；

[0310] 每次出现的R^9独立地是烷基或取代烷基；

[0311] R^{10}是H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基；和

[0312] 式（III）化合物：  其中在式（III）中：

（III），

[0313] R^1、R^2、R^3、R^4、R^7和R^8独立地是H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

[0314] 或R^1和R^2、R^3和R^4、R^5和R^6、或R^7和R^8独立地组合形成双自由基，该双自由基选自3-羟基-戊烷-1,5-二基、6-羟基-环庚烷-1,4-二基、丙烷-1,3-二基、丁烷-1,4-二基和戊烷-1,5-二基；

[0315] 每次出现的X均独立地选自键、NH、NR^9和O；

[0316] 每次出现的R^9独立地是烷基或取代烷基；

[0317] R^{10}是H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基。

[0318] 另一方面，本发明包括在有需要的对象内预防呼吸节奏失稳或稳定呼吸节奏的方法。方法包括给予对象有效量药物制剂，其至少包括药学上可接受的载体和本发明至少一种化合物或其盐。

[0319] 在一个实施方式中，给予本发明制剂使对象的呼吸节奏稳定。在另一实施方式中，给予本发明制剂使对象的每分钟通气量增加。

[0320] 在一个实施方式中，失稳与呼吸控制障碍或疾病有关。

[0321] 在一个实施方式中，呼吸障碍或疾病选自麻醉药引起的呼吸抑制、麻醉剂引起的呼吸抑制、镇静剂引起的呼吸抑制、睡眠助剂引起的呼吸抑制、抗焦虑剂引起的呼吸抑制、催眠剂引起的呼吸抑制、酒精引起的呼吸抑制、镇痛剂引起的呼吸抑制、睡眠呼吸暂停（包括但不限于混合中枢性、阻塞性、解剖结构性）、早产儿呼吸暂停、肥胖－通气不足综合征、原发性肺泡通气不足综合征、呼吸困难、高空病、氧不足、高碳酸血、慢性阻塞性肺部疾病(COPD)、婴儿猝死综合征 (SIDS)、阿尔茨海默氏症、帕金森病、中风、杜氏肌营养不良、和脑和脊髓创伤性损伤。在另一实施方式中，呼吸抑制由麻醉剂、镇静剂、抗焦虑剂、催眠剂、酒精或麻醉药引起。在再一实施方式中，本发明的化合物或其盐可与下列已知协助睡眠发生、维持睡眠和／或改变觉醒阈值的药物和药物种类中的一种或多种同步或组合应用：例如，zolipidem、扎来普隆、艾司佐匹克隆、拉米替隆、艾司唑仑、替马西泮、多塞平、苯巴比妥和其他巴比妥酸盐、苯海拉明、多西拉敏和相关化合物。

[0322] 在一个实施方式中，对象被进一步给予至少一种另外的可用于预防或治疗呼吸障碍或疾病的化合物。在另一实施方式中，该至少一种另外的化合物选自多沙普仑、多沙普仑对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、镇静剂如艾司佐匹克隆和唑吡坦、苯二氮䓬受体激动剂（例如，唑吡坦、扎来普隆、艾司唑仑、氟西泮、夸西泮、替马西泮、三唑仑）、食欲肽拮抗剂（例如，苏沃雷生）、三环类抗抑郁剂（例如，多塞平）、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素（如但不限于屈大麻酚）、食欲肽、褪黑激素激动剂（如拉米替隆）、被称为安帕金的化合物、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂。

[0323] 在再一实施方式中，制剂结合机械通气装置或气道正压装置的使用被给予对象。在一个实施方式中，制剂通过吸入、局部、口服、鼻部、颊部、直肠、胸膜、腹膜、阴道、肌内、皮下、透皮、硬膜外、鞘内、气管内、耳部、眼内或静脉内途径被给予对象。在另一实施方式中，对象是禽类或哺乳动物，包括但不限于小鼠、大鼠、雪貂、豚鼠、非人灵长类（如猴子）、狗、锚、马、牛、猪和其他农场动物。在一个实施方式中，对象是人。

[0324] 在一个实施方式中，本发明的化合物选自：

[0325] N^2,N^6-二甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0326] N^2,N^4,N^6,N^8-四-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0327] N^2,N^6-二-正丁基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0328] N^2,N^6-二-异丙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0329] N^2,N^6-二甲基-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺；

[0330] N^2,N^6-双-(N-甲氧基(N-甲基)氨基)-N^4,N^8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶；

[0331] N-(6-氯-4,8-双-丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-O,N-二甲基-羟基胺；

[0332] N^2,N^6-双-(N-甲氧基(N-甲基)氨基)-N^4,N^8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶；

[0333] N^2-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺；

[0334] O,N-二甲基-N-(6-甲基氨基-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧

啶 -2- 基)- 羟基胺 ;

[0335] N^4, N^8- 二甲基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0336] N^2, N^2, N^6- 三甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0337] 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0338] N^2, N^2- 二乙基 -N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0339] 2-(4,8- 双 - 正丙基氨基 -6- 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基 - 氨基)- 乙醇 ;

[0340] N^2-(2- 甲氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0341] N^2-(2- 异丙氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0342] N^8- 甲基 -N^4, N^6- 二 - 正丙基 -N^2-(3,3,3- 三氟丙基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0343] N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(吗啉 -4- 基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0344] N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(哌啶 -1- 基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0345] N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6- 吡咯烷 -1- 基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0346] N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 甲氧基 - 哌啶 -1- 基)- 嘧啶并 [5,4,-d] 嘧啶 -2,4,8- 三胺 ;

[0347] N^2-(3- 氯 -2- 甲基 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0348] N^2-(3,4- 二氯苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0349] N^2-(4- 氟苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0350] 6- 氯 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0351] N^2, N^2, N^4, N^8- 四甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0352] N^2, N^2- 二烯丙基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0353] 2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)- 甲基 - 氨基]- 乙醇 ;

[0354] N^2-(2- 异丙氧基 - 乙基)-N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0355] 2-[N-(2- 二甲基氨基 - 乙基)-N- 甲基] 氨基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,6,8- 三胺 ;

[0356] 2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-(2- 羟

基 - 乙基) - 氨基]- 乙醇 ;

[0357] N^2,N^2- 双 -(2- 甲氧基乙基)-N^4,N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0358] 6-(4- 氧 - 哌啶 -1- 基)-N^4, N^8- 二甲基 -N^2- 正丙基氨基 - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0359] N^2-(3- 三氟甲基 - 哌啶 -1- 基)-N^4,N^8- 二甲基 -6- 正丙基氨基 - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0360] N^2-6- 正丙基氨基 -N^4,N^8- 二甲基 -2-(1,1- 二氧 - 硫代吗啉 -4- 基) - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0361] N^2- 正丙基 -N^4,N^8- 二甲基 -6-(4,4- 二氟 - 哌啶 -1- 基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0362] N^2, N^4, N^6, N^8- 四甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0363] N^2, N^6- 二乙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0364] N^2, N^6- 二 - 正丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0365] N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0366] N^2, N^6- 二异丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0367] N^2, N^6- 二烯丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 ;

[0368] 2- 氯 -6-(N, N' - 二甲基 - 肼基)-N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 ;

[0369] 6-(N,N'- 二甲基 - 肼基)-N^2,N^2,N^4,N^8- 四甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0370] N^4, N^8- 二甲基 -6- 丙氧基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0371] N^4, N^8- 二甲基 -N^2- 正丙基 -6- 丙基硫烷基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0372] 6- 苄氧基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0373] 4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 醇 ;

[0374] 4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 ;

[0375] N^4, N^8- 二甲基 -N^2- 正丙基 -6-(氨基甲基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0376] 6- 氨甲酰基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0377] 4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 羧酸 ;

[0378] N-(正丙基)-[4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基]- 脒 ;

[0379] N^4, N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟苯基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0380] N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 氟苯基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0381] N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0382] 6- 正丁基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0383] 6- 甲氧基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 ;

[0384] 6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 ;

[0385] N^2, N^4, N^6, N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺

[0386] 2,6- 二氯 -N^4,N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺；

[0387] N^4,N^8- 二乙基 -N^2,N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0388] N^2,N^6- 双 - 环丙基甲基 -N^4,N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0389] N^2,N^6- 二乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0390] N^2,N^2,N^6- 三乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0391] 6- 氯 -N^2- 乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

[0392] N^2,N^6- 二乙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0393] N^2,N^6- 二环丙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0394] N^2,N^6- 双 - 环丙基甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0395] N^2,N^2,N^6,N^6- 四甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0396] N^4,N^8- 二烯丙基 -N^2,N^6- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0397] N^2,N^4,N^8- 三烯丙基 -6-[4-(4- 氟苄基)- 哌嗪 -1- 基]- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

[0398] 6- 氯 -N^2,N^4,N^8- 三烯丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

[0399] N^2,N^4,N^8- 三烯丙基 -6-{4-[双 -(4- 氟苯基)- 甲基]- 哌嗪 -1- 基 }- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

[0400] N^2,N^2,N^6- 三乙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

[0401] (4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯；

[0402] (4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸；

[0403] N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺；

[0404] (6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯；

[0405] 其任何盐、和其任意组合。

[0406] 药物组合物和制剂

[0407] 本发明还包括本发明至少一种化合物或其盐的药物组合物实践本发明方法的应用。

[0408] 这种药物组合物可由至少一种适于给予对象的形式的本发明化合物或其盐组成，或该药物组合物可包括本发明至少一种化合物或其盐、和一种或多种药学上可接受的载体、一种或多种额外成分、或这些的一定组合。本发明至少一种化合物可以生理可接受的盐形式存在于药物组合物中，如，如本领域公知，与生理可接受的阳离子或阴离子组合。

[0409] 在实施方式中，可用于实践本发明方法的药物组合物可被给予以递送 1ng/kg/ 日和 100mg/kg/ 日之间的剂量。在另一实施方式中，可用于实践本发明的药物组合物可被给予以递送 1ng/kg/ 日和 1,000mg/kg/ 日之间的剂量。

[0410] 本发明药物组合物中活性成分、药学上可接受的载体、和任何额外成分的相对量将改变——根据治疗对象的个性、大小和病况，和进一步根据组合物的给予途径。作为实例，组合物可包括 0.1% 和 100% (w/w) 之间的活性成分。

[0411] 可用于本发明方法的药物组合物可被适当地研发用于鼻部、吸入、口服、直肠、阴道、胸膜、腹膜、胃肠外、局部、透皮、肺部、鼻内、颊部、眼部、硬膜外、鞘内、气管内、耳部、眼内、静脉内或其他给予途径。本发明方法中可用的组合物可被直接给予脑、脑干、或哺乳动物或禽类中枢神经系统的任何其他部分。其他考虑制剂包括设计的纳米颗粒、微球、脂质体制剂、包衣颗粒、聚合物缀合物、包含活性成分的再密封红细胞、和免疫学基础制剂。另外，本发明方法中可用的组分和或工艺能使本发明至少一种化合物或其盐的药物组合物与其他物质组合或经其他物质处理，形成容易处理不溶性材料的药物基质，以提高本发明化合物或盐的生物利用度，生成受控和或持续释放产品的能力，和生成极其均质的化合物的能力。作为实例，实施热熔挤出、固体溶液、固体分散体、尺寸缩小技术、分子复合物（例如环糊精和其他）、微粒、颗粒和制剂包衣工艺。要理解在所有组分和或工艺中，技术人员可采用无定形或晶体相。给予途径（一个或多个）对于技术人员显而易见，并且取决于任何数量的因素，包括被治疗疾病的类型和严重程度、被治疗兽医患者或人患者的类型和年龄、及类似因素。

[0412] 本文描述的药物组合物的制剂可通过药理和制药领域已知或以后研发的任何方法来制备。总体而言，这种制备方法包括如下步骤：使活性成分与载体或一种或多种其他辅助成分结合，然后，若必要或需要，将产物塑形或包装成期望的单剂量或多剂量单位。

[0413] 如本文所用，“单位剂量”是药物组合物的离散量，包括预定量的活性成分。活性成分量大体上等于将被给予对象的活性成分剂量或这种剂量的便利部分如，例如，这种剂量的一半或三分之一。单位剂型可用于单个日剂量或多个日剂量中的一个（例如，每日约1至4或更多次）。当采用多个日剂量时，每个剂量的单位剂型可以相同或不同。

[0414] 虽然本文提供的药物组合物的描述主要针对适于凭处方给予人的药物组合物，但技术人员会理解这种组合物总体上适于给予所有种类的动物。对适于给予人的药物组合物进行改动以使该组合物适于给予至各种动物，是被充分理解的，并且兽医药理学普通技术人员仅通过普通实验（如有）就可设计和进行这种改动。考虑被给予本发明药物组合物的对象包括但不限于，人和其他灵长类，哺乳动物，包括商业相关哺乳动物，如牛、猪、马、羊、猫和狗。

[0415] 在一个实施方式中，本发明的组合物利用一种或多种药学上可接受的赋形剂或载体来配制。在一个实施方式中，本发明的药物组合物包括治疗有效量的本发明至少一种化合物和药学上可接受的载体。可用的药学上可接受的载体包括但不限于，甘油、水、盐水、乙醇、重组人白蛋白（例如**Recombumin®**）、增溶明胶（例如**Gelofusine®**）、和其他药学上可接受的盐溶液，如磷酸盐和有机酸盐。这些和其他药学上可接受的载体的实例被描述于Remington's Pharmaceutical Sciences(1991,Mack Publication Co.,New Jersey)。

[0416] 载体可以是溶剂或分散体介质，包括例如水、乙醇、多元醇（例如，甘油、丙二醇、和液体聚乙二醇、及类似物）、重组人白蛋白、增溶明胶、其适当混合物、和植物油。适当的流动性可被保持——例如，通过利用包衣如卵磷脂、在分散体情况下保持所需颗粒尺寸、和利用表面活性剂。微生物作用的预防可通过各种抗细菌和抗真菌剂实现，例如，对羟基苯甲酸酯类、氯丁醇、苯酚、抗坏血酸、硫柳汞、及类似物。在很多情况下，优选组合物中包括等渗剂，例如，糖、氯化钠、或多元醇如甘露醇和山梨醇。可注射组合物的吸收延长可通过在组合物中包括延迟吸收的用剂（例如，单硬脂酸铝或明胶）来实现。

[0417] 制剂可以与常规赋形剂的混合物的形式使用，该常规赋形剂即适于口服、胃肠外、鼻部、吸入、静脉内、皮下、透皮、肠内、或本领域已知的任何其他适当的给予方式的药学上可接受的有机或无机载体物质。药物制剂可被灭菌，和如需与助剂混合，该助剂例如润滑剂、防腐剂、稳定剂、润湿剂、乳化剂、影响渗透压的盐、缓冲剂、着色物、调味物、和/或香味赋予物、及类似物。其也可在需要的情况下与其他活性剂组合，该其他活性剂例如其他镇痛剂、抗焦虑剂或催眠剂。如本文所用，“额外成分”包括但不限于，可用作药物载体的一种或多种成分。

[0418] 本发明的组合物可包括组合物总重量约0.005%至2.0%的防腐剂。防腐剂用于在暴露于环境污染物的情况下预防腐败。根据本发明可用的防腐剂的实例包括但不限于选自下列的那些：苄醇、山梨酸、对羟基苯甲酸酯类、咪脲(imidurea)和其组合。特别优选的防腐剂是约0.5%至2.0%苄醇和0.05%至0.5%山梨酸的组合。

[0419] 组合物优选包括抗氧化剂和抑制化合物降解的螯合剂。一些化合物的优选抗氧化剂是BHT、BHA、α-生育酚和抗坏血酸，优选范围为组合物总重量的按重量计约0.01%至0.3%，更优选BHT的范围为0.03%至0.1%。优选地，螯合剂的存在量为组合物总重量的按重量计0.01%至0.5%。特别优选的螯合剂包括依地酸盐（例如依地酸二钠）和柠檬酸，其重量范围为组合物总重量的约0.01%至0.20%，更优选其范围为按重量计0.02%至0.10%。螯合剂可用于螯合组合物中可不利于制剂保质期的金属离子。虽然BHT和依地酸二钠分别是特别优选的抗氧化剂和螯合剂，但对于一些化合物而言，如本领域技术人员所知，其他适当和等效抗氧化剂和螯合剂可将其取代。

[0420] 液体悬浮液可利用实现活性成分在水性或油性介质中的悬浮液的常规方法来制备。水性介质包括，例如，水和等渗盐水。油性介质包括，例如，杏仁油、油性酯类、乙醇、植物油——如花生油、橄榄油、芝麻油、或椰子油、分馏植物油、和矿物油——如液体石蜡。液体悬浮液可进一步包括一种或多种额外成分，包括但不限于，悬浮剂、分散剂或润湿剂、乳化剂、缓和剂（润药，demulcents）、防腐剂、缓冲剂、盐、调味剂、着色剂、和甜味剂。油性悬浮液可进一步包括增稠剂。已知的悬浮剂包括但不限于，山梨醇糖浆、氢化食用脂肪、海藻酸钠、聚乙烯基吡咯烷酮、黄蓍胶、阿拉伯胶、和纤维素衍生物——如羧甲基纤维素钠、甲基纤维素、羟丙基甲基纤维素。已知的分散剂或润湿剂包括但不限于，天然存在的磷脂类——如卵磷脂、环氧烷与脂肪酸、与长链脂肪醇、与衍生自脂肪酸和己糖醇的部分酯、或与衍生自脂肪酸和己糖醇酐的部分酯的缩合产物（分别例如，聚氧乙烯硬脂酸酯、十七碳亚乙基氧基鲸蜡醇(heptadecaethyleneoxycetanol)、聚氧乙烯山梨醇单油酸酯、和聚氧乙烯山梨糖醇酐单油酸酯）。已知的乳化剂包括但不限于，卵磷脂、阿拉伯胶和其他离子型或非离子型表面活性剂。已知的防腐剂包括但不限于，对羟基苯甲酸甲酯、对羟基苯甲酸乙酯、或对羟基苯甲酸正丙酯、抗坏血酸、和山梨酸。

[0421] 活性成分在水性或油性溶剂中的液体溶液可以与液体悬浮液基本上相同的方式制备，主要区别是活性成分溶解而非悬浮在溶剂中。如本文所用，“油性”液体是包括含碳液体分子并且呈现比水更少极性特征的液体。本发明药物组合物的液体溶液可包括关于液体悬浮液描述的每一种组分，要理解悬浮剂不必有助活性成分在溶剂中的溶解。水性溶剂包括，例如，水和等渗盐水。油性溶剂包括，例如，杏仁油、油性酯类、乙醇、植物油——如花生油、橄榄油、芝麻油、或椰子油、分馏植物油、和矿物油——如液体石蜡。

[0422] 本发明药物制剂的粉末状和颗粒状制剂可利用已知方法制备。这种制剂可被直接给予对象，用于例如形成片剂、填充胶囊、或通过向其添加水性或油性介质而制备水性或油性悬浮液或溶液。这些制剂均可进一步包括下列中的一种或多种：分散剂或润湿剂、悬浮剂、离子型和非离子型表面活性剂、和防腐剂。另外的赋形剂，如填充剂和甜味剂、调味剂、或着色剂，也可被包括在这些制剂中。

[0423] 本发明的药物组合物也可以水包油乳液或油包水乳液的形式制备、包装、或销售。油相可以是植物油如橄榄油或花生油、矿物油如液体石蜡、或其组合。这种组合物可进一步包括一种或多种乳化剂，如天然存在的胶如阿拉伯胶或黄蓍胶、天然存在的磷脂类如大豆磷脂或卵磷脂、衍生自脂肪酸和己糖醇酐组合的酯类或部分酯类如山梨糖醇酐单油酸酯，和这种部分酯类与环氧乙烷的缩合产物如聚氧乙烯山梨糖醇酐单油酸酯。这些乳液还可包含额外成分，包括，例如，甜味剂或调味剂。

[0424] 用化学组合物浸渍或包覆材料的方法在本领域已知，包括但不限于将化学组合物沉积或结合到表面上的方法，在材料合成期间将化学组合物掺入材料结构（即，如与生理可降解的材料一起）的方法，和在有或无后续干燥的情况下将水性或油性溶液或悬浮液吸收到吸收材料中的方法。组分混合方法包括物理研磨、利用固体和悬浮液制剂中的丸剂、和混入透皮贴剂，如本领域技术人员已知。

[0425] 给药 / 用药

[0426] 给药方案可影响有效量构成。治疗制剂可在呼吸障碍事件发生之前或之后被给予患者。进一步，若干拆分剂量以及交错剂量可被每日或相继给予，或者剂量可被连续灌注，或可以是弹丸注射。进一步，治疗制剂的剂量可根据治疗或预防情况的紧急性的指示而成比例增加或减少。

[0427] 本发明组合物至患者——优选哺乳动物，更优选人——的给予可利用已知的程序以有效治疗患者呼吸控制障碍的剂量和时间来实施。实现治疗效果所需的治疗化合物的有效量可根据如下因素而改变：如所用具体化合物的活性；给药时间；化合物排泄速率；治疗持续时间；与该化合物组合应用的其他药物、化合物或材料；治疗患者的疾病或障碍状态、年龄、性别、体重、病况、总体健康和在前病史、和医学领域公知的类似因素。剂量方案可经调节提供最佳的治疗响应。例如，若干拆分剂量可被每日给予，或剂量可根据治疗情况紧急性指示而成比例减少。本发明的治疗化合物的有效剂量范围的非限制性实例为约 0.01mg/kg 至 100mg/kg 体重 / 每日。本领域技术人员能够研究相关因素并且在无过度实验的情况下做出关于治疗化合物有效量的决定。

[0428] 化合物可以一日几次的频率给予动物，或其可以更低频率给予，如一日一次、一周一次、每两周一次、一月一次、或甚至更低频率，如几个月一次、或甚至一年一次、或更少。要理解，每日施用的化合物量可在非限制性实例中被每日、隔日、每 2 日、每 3 日、每 4 日、或每 5 日给予。例如，在隔日给予时，5mg 每日剂量可始于星期一，并且第一个后续 5mg 每日剂量在星期三给予，第二个后续 5mg 每日剂量在星期五给予，等等。剂量频率对于技术人员显而易见，并且取决于任何数量的因素，如，但不限于，被治疗疾病的类型和严重程度、动物类型和年龄等。

[0429] 本发明药物组合物中活性成分的实际剂量水平可改变，从而获得对于具体患者、组合物、和给药方式而言有效实现期望治疗响应并且对患者无毒的活性成分量。

[0430] 掌握本领域普遍技术的医学专业人士，例如医生或兽医，可容易确定和指定所需的药物组合物有效量。例如，医生或兽医可使得用于药物组合物的本发明化合物的剂量始于低于实现期望治疗效果所需的水平，并逐渐增加剂量，直到实现期望的效果。

[0431] 在具体实施方式中，为给予方便和剂量均匀而将化合物配制成单位剂型是尤其有益的。单位剂型，如本文所用，指代适合作为待治疗患者的单位剂量的物理离散的单位；每个单位包含与所需的药物介质结合的经计算产生期望治疗效果的预定量的治疗化合物。本发明的单位剂型由下列控制并且直接取决于下列：(a) 治疗化合物的独特特征和待实现的具体治疗效果、和 (b) 合成 / 配制这种用于治疗患者呼吸障碍的治疗化合物的领域自身的限制。

[0432] 在一个实施方式中，本发明的组合物以每日 1 至 5 次或更多的范围内的剂量被给予患者。在另一实施方式中，本发明的组合物以如下剂量范围被给予患者：包括但不限于，每日一次、每两日一次、每 3 日一次至一周一次，和每两周一次。对于本领域技术人员显而易见的是，本发明的不同组合的组合物的给予频率将依对象而变，取决于很多因素，包括但不限于，年龄、待治疗疾病或障碍、性别、总体健康和其他因素。因此，本发明不应被解释为限于任何具体剂量方案，并且被给予任何患者的精确剂量和组合物将由主治医生通过将关于患者的所有其他因素纳入考虑来确定。

[0433] 给予的本发明化合物可在如下范围内：约 1 μg 至约 7,500mg、约 20 μg 至约 7,000mg、约 40 μg 至约 6,500mg、约 80 μg 至约 6,000mg、约 100 μg 至约 5,500mg、约 200 μg 至约 5,000mg、约 400 μg 至约 4,000mg、约 800 μg 至约 3,000mg、约 1mg 至约 2,500mg、约 2mg 至约 2,000mg、约 5mg 至约 1,000mg、约 10mg 至约 750mg、约 20mg 至约 600mg、约 30mg 至约 500mg、约 40mg 至约 400mg、约 50mg 至约 300mg、约 60mg 至约 250mg、约 70mg 至约 200mg、约 80mg 至约 150mg、和其间任何和所有完整或部分增量。

[0434] 在一些实施方式中，本发明化合物的剂量为约 0.5 μg 至约 5,000mg。在一些实施方式中，本文描述的组合物中所用的本发明化合物的剂量小于约 5,000mg、或小于约 4,000mg、或小于约 3,000mg、或小于约 2,000mg、或小于约 1,000mg、或小于约 800mg、或小于约 600mg、或小于约 500mg、或小于约 200mg、或小于约 50mg。类似地，在一些实施方式中，本文描述的第二化合物的剂量小于约 1,000mg、或小于约 800mg、或小于约 600mg、或小于约 500mg、或小于约 400mg、或小于约 300mg、或小于约 200mg、或小于约 100mg、或小于约 50mg、或小于约 40mg、或小于约 30mg、或小于约 25mg、或小于约 20mg、或小于约 15mg、或小于约 10mg、或小于约 5mg、或小于约 2mg、或小于约 1mg、或小于约 0.5mg、和其任何和所有完整或部分增量。

[0435] 在一个实施方式中，本发明涉及包装后的药物组合物，其包括容器，容纳治疗有效量的单独或与第二药剂组合的本发明化合物；和使用该化合物治疗、预防、或减轻患者呼吸障碍的一个或多个症状的说明书。

[0436] 术语“容器”包括容纳药物组合物或增加管控稳定性和或水摄入的保护的任何受器。例如，在一个实施方式中，容器是包含药物组合物如液体（溶液和悬浮液）、半固体、冻干固体、存在于双室中的溶液和粉末或冻干制剂的包装。在其他实施方式中，容器不是包含药物组合物的包装，即，容器是受器，如盒子或小瓶，包含包装后的药物组合物或未包装的药物组合物和药物组合物的使用说明书。此外，包装技术本领域公知。应理解，药物组合物

的使用说明书可被包含在包含药物组合物的包装上，由此说明书形成与被包装产品增加的功能关系。然而，应理解，说明书可包含关于化合物执行其目标功能（例如，治疗、预防、或减轻患者呼吸障碍）的能力的信息。

[0437] 给药途径

[0438] 给予本发明任何组合物的途径包括吸入、口服、鼻部、直肠、胃肠外、舌下、透皮、经粘膜（例如，舌下、舌、（经）颊部、（经）尿道、阴道（例如，经阴道和阴道周围）、鼻（内）、和（经）直肠）、膀胱内、肺内、十二指肠内、胃内、鞘内、硬膜外、胸膜内、腹膜内、气管内、耳部、眼内、皮下、肌内、皮内、动脉内、静脉内、支气管内、吸入、和局部给予。

[0439] 适当的组合物和剂型包括，例如，片剂、胶囊、囊片（caplets）、丸片、胶囊、锭剂、乳液、分散体、悬浮液、溶液、无菌注射液、糖浆、颗粒、小珠、透皮贴剂、凝胶、粉末、丸剂、浆、糖锭、乳膏、糊剂、石膏、洗剂、圆片（discs）、栓剂、鼻部或口服给予用液体喷雾剂、吸入用干燥粉末或雾化制剂、膀胱内给予用组合物和制剂、及类似物。应理解，可用于本发明的制剂和组合物不限于本文描述的具体制剂和组合物。

[0440] 口服给予

[0441] 在一个实施方式中，本发明的化合物可被配制以制备口服给予的药物组合物。在进一步实施方式中，口服给予的组合物可被设计以促进药物的改良释放，从而调节化合物在摄入时的暴露位置、程度和速率。影响药物暴露目标区域的因素可以是药物pH或酶稳定性、与其他药物（例如，某些抗生素）的反应性、作为盐或游离碱的溶解度、电离表现、和特定环境下的药效动力学和药代动力学表现。一些药物在十二指肠或其他肠位置被更好地吸收。

[0442] 延迟释放是改良释放的一种特别有用的模式，其将药物以其最浓形式递送至十二指肠或其他肠位置。在优选实施方式中，本发明的化合物被配制以促进至十二指肠和任选地其他肠位置的递送。延迟释放可利用包括肠溶包衣的组合物来实现。肠溶包衣在高度酸性环境中不溶，其中多元酸包衣在胃pH下保持不电离和完整。然而，在十二指肠或其他肠区域的弱酸性（＞pH 5.5）、中性或弱碱性条件（pH 6.5-7.6）下，包衣电离，溶胀和分解，使被包覆的实体暴露于环境。存在包衣选择，实现处于或接近特定pH（例如Eudragit L-110，电离阈值pH 6.0；Eudragit S-100，电离阈值pH 7.0）的电离。

[0443] 在进一步实施方式中，本发明化合物可与肠溶包衣一起配制，该肠溶包衣在包覆前通过将塑化剂加入聚合物而改性。可添加塑化剂以调节包衣碎裂或破裂抗性，同时还降低包衣的玻璃化转变温度，从而实现包衣在其施加过程中的光滑和均匀延展性。适当的塑化剂包括聚乙二醇8000（PEG 8000）、柠檬酸三乙酯（TEC）、和三醋汀，其可被掺入聚合物肠溶包衣用剂。

[0444] 本发明化合物可在多种剂型下被肠溶地配制，该剂型包括（但不限于）胶囊、活性药物颗粒本身、小珠、和片剂。在一个实施方式中，组合物可包括封装在肠溶包衣胶囊中的药物，从而在十二指肠或其他肠环境中释放药物。在本发明一方面，药学上可接受的胶囊包括硬胶囊，其可由植物衍生的多糖、淀粉、和纤维素、或明胶构成。在另一实施方式中，药学上可接受的胶囊包括软明胶胶囊。明胶胶囊可由动物衍生的胶原蛋白或羟丙甲纤维素——纤维素改性形式——构成，并且利用明胶、水和塑化剂如山梨醇或甘油的任选混合物生产。

[0445] 在一个实施方式中，本发明的分子可被封装在纯颗粒状或粉末状形式中，无载体、

赋形剂或其他药学上可接受的添加剂。在其他实施方式中，本发明的分子可与下列封装在一起：一种或多种药学上可接受的载体、赋形剂、抗氧化剂（例如，焦亚硫酸钠，丁基化羟基甲苯 [BHT]）、抗真菌剂（例如，苯甲酸和抗坏血酸及其盐，和酚类化合物如对羟基苯甲酸甲酯、对羟基苯甲酸乙酯、对羟基苯甲酸丙酯和对羟基苯甲酸丁酯（对羟基苯甲酸酯类））、抗菌防腐剂（例如，苯甲酸钠、山梨酸）、着色剂、和调味剂。赋形剂可有助于胶囊填充表现、稳定性、和在胶囊在体内崩解时的药物分布。在另一实施方式中，本发明化合物的颗粒和/或粉末在置于胶囊前被肠溶包衣。置于胶囊中的肠溶包衣颗粒和/或粉末可具有一种或几种类型的肠溶包衣，从而能够递送药物至肠不同区域。胶囊可没有肠溶包衣，或可包覆有与用于胶囊内部任何肠溶包衣材料的包衣匹配或完全不同的肠溶包衣。

[0446] 在进一步实施方式中，本发明的分子可被封装在液体中，其形式为在水或各种药学上可接受的油或其他分散体介质（例如，矿物油、芝麻油、红花油、椰子油）中的溶液或悬浮液，任选地与赋形剂一起，如共溶剂（例如，丙二醇、甘油）、溶解增强剂（例如，山梨醇、葡萄糖）、润湿剂（例如，聚山梨酯类 [吐温]、山梨糖醇酐酯类 [Span]、疏水性胶体 [纤维素衍生物]、增稠剂（例如，甲基纤维素、微晶纤维素）、缓冲剂（例如，磷酸氢二钠）、抗氧化剂（例如，丁基化羟基甲苯 [BHT]、柠檬酸、山梨酸钾）、抗真菌剂（例如，苯甲酸和抗坏血酸及其盐、和酚类化合物如对羟基苯甲酸甲酯、对羟基苯甲酸乙酯、对羟基苯甲酸丙酯和对羟基苯甲酸丁酯（对羟基苯甲酸酯类））、抗菌防腐剂（例如，苯甲酸钠、山梨酸）、着色剂和调味剂。在一些实施方式中，本发明化合物可被配制以纯药物形式作为液体中的颗粒和/或粉末用于液体填充胶囊。在相关实施方式中，包含在液体中的药物的胶囊可以有肠溶包衣。在另一实施方式中，本发明化合物的颗粒和/或粉末可被肠溶包衣，然后置于液体中和将该组合布置在胶囊中。肠溶包衣颗粒和/或粉末可具有一种或几种类型的肠溶包衣，从而能够递送药物至肠不同区域。胶囊可没有肠溶包衣，或可包覆有与用于胶囊内部任何肠溶包衣材料的包衣匹配或完全不同的肠溶包衣。

[0447] 在另一实施方式中，本发明的分子可被封装在胶囊中，所述胶囊由无需单独施加肠溶包衣（例如，Entericare 肠溶软凝胶）而提供胃后药物递送的材料组成。分子可被封装在这种胶囊中，作为有或无赋形剂的颗粒或粉末，和作为溶液或悬浮液，如上所述。

[0448] 在一些实施方式中，本发明化合物的固体颗粒，以多种颗粒尺寸和颗粒尺寸分布，可与赋形剂如微晶纤维素或乳糖混合，并形成小珠，该小珠包括施加了肠溶包衣的含药物内核。在一些实施方式中，本发明的分子可形成悬浮液或溶液——其包括，任选地，缓冲剂（例如，aq. 1N HCl 和三羟甲基氨基甲烷 [TRIS]）、和粘合剂（例如，Opadry 透明涂料粉末），和被包覆到基体颗粒上，例如糖珠（例如，糖球、NF 颗粒），形成小珠。在另一实施方式中，小珠可以有肠溶包衣。在再一实施方式中，本发明的分子可被配制成肠溶包衣小珠，如上所述，并且小珠进一步被通过封装配制。在进一步实施方式中，小珠与不同类型的肠溶包衣的组合可一起封装，从而在从胶囊释放后，本发明化合物在十二指肠至肠其他部分范围内的不同区域以受控方式可用。胶囊可没有肠溶包衣，或可包覆有与用于胶囊内部的任何肠溶包衣材料的包衣匹配或完全不同的肠溶包衣。

[0449] 在进一步实施方式中，本发明化合物可被配制成片剂或囊片，其单独或与其他制剂组分组合递送药物至十二指肠或其他肠区域。在一个实施方式中，本发明化合物被配制成片剂或囊片，该片剂或囊片有肠溶包衣并且构成给药剂型。在另一实施方式中，适当尺寸

和形状的片剂或囊片可被置于胶囊中。在一个这种实施方式中，胶囊可以有肠溶包衣，并且包含无肠溶包衣的片剂或囊片，该片剂或囊片在十二指肠或其他肠区域中从胶囊释放。在再一这种实施方式中，胶囊可被设计以在胃中崩解和释放肠溶包衣片剂或囊片，以随后递送至十二指肠或其他肠区域。在再一这种实施方式中，胶囊和其中包含的片剂或囊片可都有肠溶包衣，以提供对片剂或囊片从胶囊释放和药物从片剂或囊片的随后释放的进一步控制。在进一步相关实施方式中，具有多种肠溶包衣的片剂或囊片可被组合并置于胶囊，该胶囊本身可任选地也具有肠溶包衣。可用于片剂和囊片的肠溶包衣的材料包括但不限于上述用于胶囊的那些。

[0450] 肠溶包衣可允许在酸性介质中过早药物释放。在再进一步实施方式中，本发明的化合物可被配制使得亚包衣在施加肠溶包衣前被施加。亚包衣可包括可溶性亚包衣剂对肠溶底物的施加，亚包衣剂的实例是羟丙基甲基纤维素、聚维酮、羟丙基纤维素、聚乙二醇3350、4500、8000、甲基纤维素、假乙基纤维素和支链淀粉。肠溶底物上的亚包衣薄层阻止水渗透胶囊外壳上的肠溶包衣或渗入活性成分所在的内核，防止过早药物释放。亚包衣还可通过缓和内核和肠溶包衣之间界面的酸性微环境而促进药物在碱性环境中释放。在一些实施方式中，本发明化合物被配制具有包含有机酸的亚包衣，意图促进胶囊在包衣在 pH 5-6 的环境中降解时更快速的聚合物溶解，促进药物在碱性介质中的快速释放。

[0451] 关于口服应用，特别适合的是片剂、糖锭剂、液体、滴剂、胶囊、囊片和凝胶胶囊。适于口服给予的其他制剂包括但不限于，粉末状或颗粒状制剂、水性或油性悬浮液、水性或油性溶液、糊剂、凝胶、牙膏、漱口剂、包衣、口服冲洗剂、或乳液。意图口服使用的组合物可根据本领域已知的任何方法制备，并且这种组合物可包含一种或多种用剂，该用剂选自适于制备片剂的惰性、无毒、一般认为安全 (GRAS) 的药物赋形剂。这种赋形剂包括，例如惰性稀释剂，如乳糖；造粒剂和崩解剂，如玉米淀粉；粘合剂，如淀粉；和润滑剂。如硬脂酸镁。

[0452] 片剂可无包衣，或者其可利用已知方法包覆以实现在对象胃肠道中延迟崩解，从而提供活性成分持续释放和吸收。作为实例，材料如单硬脂酸甘油酯或二硬脂酸甘油酯可用于包覆片剂。进一步作为实例，片剂可利用美国专利号 4,256,108；4,160,452；和 4,265,874 描述的方法包覆，形成渗透受控的释放片剂。片剂可进一步包括甜味剂、调味剂用剂、着色剂、防腐剂、或这些的一定组合，以提供制药美观和可口的制剂。

[0453] 包括活性成分的硬胶囊可利用生理可降解的组合物如明胶制成。这种硬胶囊包括活性成分，并且可进一步包括额外成分，包括，例如，惰性固体稀释剂，如碳酸钙、磷酸钙、或高岭土。

[0454] 包括活性成分的软明胶胶囊可利用生理可降解的组合物如来自动物衍生的胶原蛋白或来自羟丙甲纤维素——纤维素改性形式——的明胶制成，并且利用明胶、水和塑化剂如山梨醇或甘油的任选混合物来制备。这种软胶囊包括活性成分，该性成分可与水或油介质如花生油、液体石蜡、或橄榄油混合。

[0455] 关于口服给予，本发明的化合物可以是通过常规方法与药学上可接受的赋形剂如粘合剂；填充剂；润滑剂；崩解；或润湿剂一起制备的片剂或胶囊形式。如需，片剂可利用适当的方法和包衣材料如可获自 Colorcon, West Point, Pa. 的 OPADRY™膜包衣系统（例如，OPADRY™ OY 型、OYC 型、有机肠溶 OY-P 型、水性肠溶 OY-A 型、OY-PM 型和 OPADRY™ White、32K18400）包覆。要理解，可使用其他公司的相似类型的膜包衣或聚合物产品。

[0456] 包括活性成分的片剂可以例如通过压缩或模塑活性成分和任选地一种或多种额外成分而制成。压缩片剂可通过在适当的装置中压缩自由流动形式的活性成分如粉末状或颗粒状制剂（任选地与粘合剂、润滑剂、赋形剂、表面活性剂、和分散剂中的一种或多种混合）来制备。模塑片剂可通过在适当的装置中模塑活性成分、药学上可接受的载体、和至少增湿混合物的充足液体的混合物来制备。片剂制备中使用的药学上可接受的赋形剂包括但不限于，惰性稀释剂、造粒剂和崩解剂、粘合剂、和润滑剂。已知的分散剂包括但不限于，马铃薯淀粉和淀粉乙醇酸钠。已知的表面活性剂包括但不限于，月桂基硫酸钠。已知的稀释剂包括但不限于，碳酸钙、碳酸钠、乳糖、微晶纤维素、磷酸钙、磷酸氢钙、和磷酸钠。已知的造粒剂和崩解剂包括但不限于，玉米淀粉和海藻酸。已知的粘合剂包括但不限于，明胶、阿拉伯胶、预胶化玉米淀粉、聚乙烯基吡咯烷酮、和羟丙基甲基纤维素。已知的润滑剂包括但不限于，硬脂酸镁、硬脂酸、二氧化硅、和滑石。

[0457] 造粒技术在制药领域公知用于改性活性成分的起始粉末或其他颗粒状材料。粉末一般与粘合剂材料混合形成较大永久性自由流动的团块或颗粒，被称为“造粒”。例如，使用溶剂的“湿”造粒法一般特征在于粉末与粘合剂材料组合并且在导致湿颗粒状物质形成的条件下被水或有机溶剂增湿，然后溶剂必须被蒸发。

[0458] 熔体造粒一般在于基本上在不添加水或其他液体溶剂的情况下使用在室温下是固体或半固体的材料（即，具有相对低的软化点或熔点范围）来促进粉末状或其他材料的造粒。低熔融固体在被加热至熔点范围内的温度时液化，充当粘合剂或造粒剂介质。液化的固体本身在其所接触的粉末状材料表面上蔓延，并且在冷却时形成固体颗粒状物质——其中初始材料结合在一起。然后所得熔体造粒可被提供至压片机或被封装，以制备口服剂型。熔体造粒通过形成固体分散液或固体溶液来提高活性物质（即，药物）的溶解速率和生物利用度。

[0459] 美国专利号 5,169,645 公开了可直接压缩的含蜡颗粒，其具有提高的流动性。在将熔融的蜡与某些促流动添加剂混合，然后将混合物冷却和造粒时，获得颗粒。在某些实施方式中，仅蜡自身在蜡（一种或多种）和添加剂（一种或多种）的熔体组合中熔融，而在其他情况下，蜡（一种或多种）和添加剂（一种或多种）都熔融。

[0460] 本发明还包括多层片剂，其包括提供本发明方法中可用的一种或多种化合物的延迟释放的层，和提供本发明方法中可用的一种或多种化合物的立即释放的进一步的层。利用蜡 /pH 敏感性聚合物混合物，可获得胃不溶性组合物，其中活性成分被包埋，确保其延迟释放。

[0461] 胃肠外给予

[0462] 如本文所用，药物组合物的“胃肠外给予”包括任何具有下列特征的给药途径：物理突破对象组织并通过组织的突破口给予药物组合物。因此胃肠外给予包括但不限于，通过注射组合物、通过外科切口施用组合物、通过组织穿透非手术创口施用组合物、及类似手段，来给予药物组合物。具体地，考虑胃肠外给予包括但不限于，皮下、静脉内、腹膜内、肌内、胸骨内注射、和肾透析灌注技术。

[0463] 适于胃肠外给予的药物组合物制剂包括与药学上可接受的载体如无菌水或无菌等渗盐水组合的活性成分。这种制剂可以适于弹丸给药或连续给药的形式制备、包装或销售。可注射制剂可以单位剂型制备、包装或销售，如在包含防腐剂的安瓿瓶中或多剂量容器

中。可注射制剂也可在诸如患者控制的镇痛（PCA）装置的装置中被制备、包装或销售。胃肠外给予的制剂包括但不限于，油性或水性介质中的悬浮液、溶液、乳液，糊剂，和可植入式持续释放制剂或可生物降解式制剂。这种制剂可进一步包括一种或多种额外成分，包括但不限于，悬浮剂、稳定化剂、或分散剂。在胃肠外给予的制剂的一个实施方式中，活性成分以干燥形式提供（即，粉末或颗粒状），用于被适当的介质（例如，无菌无热原水）复溶（重构，reconstitution），然后胃肠外给予复溶的组合物。

[0464] 药物组合物可以无菌可注射水性或油性悬浮液或溶液形式制备、包装或销售。这种悬浮液或溶液可按照现有技术配制，并且可除活性成分外还包括额外成分，如本文描述的分散剂、润湿剂、或悬浮剂。这种无菌可注射制剂可利用无毒胃肠外可接受的稀释剂或溶剂制备，如例如水或 1,3- 丁二醇。其他可接受的稀释剂和溶剂包括但不限于林格氏溶液、等渗氯化钠溶液、和混合油，如合成单甘油酯或二甘油酯。其他可胃肠外给予的可用制剂包括如下那些：包括活性成分——在重组人白蛋白中、在流化明胶中、或在微晶形式中、在脂质体制剂中、或作为可生物降解的聚合物系统的组分。用于持续释放或植入的组合物可包括药学上可接受的聚合物材料或疏水材料，如乳液、离子交换树脂、微溶性聚合物、或微溶性盐。

[0465] 局部给予

[0466] 药物局部给予的一个阻碍是表皮角质层。角质层是包括蛋白质、胆固醇、鞘脂、游离脂肪酸和各种其他脂质的高抗性层，并且包括角化细胞和活细胞。限制化合物穿过角质层的渗透速率（通量）的其中一个因素是可负载或施加于皮肤表面的活性物质量。施加于每单位皮肤面积的活性物质量越多，皮肤表面和皮肤下层之间的浓度梯度越大，进而活性物质穿过皮肤的扩散力越大。因此，包含较高活性物质浓度的制剂更可能导致活性物质渗透皮肤，和比具有较低浓度的制剂导致更多活性物质渗透皮肤，和以更一致的速率渗透皮肤，而其他方面相同。

[0467] 适于局部给予的制剂包括但不限于，液体或半液体制剂，如搽剂、洗剂、水包油或油包水乳液，如乳膏、油膏或糊剂，和溶液或悬浮液。可局部给予的制剂可例如包括约 1％至约 10％（w/w）的活性成分，虽然溶剂中活性成分的浓度可高达活性成分的溶解度限值。局部给予的制剂可进一步包括本文描述的额外成分中的一种或多种。

[0468] 可使用渗透增强剂。这些材料增加药物越过皮肤的渗透速率。本领域的一般增强剂包括乙醇、单月桂酸甘油酯、PGML（聚乙二醇单月桂酸酯）、二甲基亚砜、及类似物。其他增强剂包括油酸、油醇、乙氧基二甘醇、月桂氮䓬酮、烷烃羧酸、二甲基亚砜、极性脂质、或 N- 甲基 -2- 吡咯烷酮。

[0469] 用于本发明一些组合物的局部递送的一种可接受的介质可包含脂质体。脂质体组合物及其用途在本领域已知（例如，参见 Constanza，美国专利号 6,323,219）。

[0470] 在可选的实施方式中，局部活性药物组合物可任选地与其他成分组合，如佐剂、抗氧化剂、螯合剂、表面活性剂、起泡剂、润湿剂、乳化剂、增粘剂、缓冲剂、防腐剂、及类似物。在另一实施方式中，透过或渗透增强剂被包括在组合物中，并相对于无透过增强剂的组合物有效提高活性成分进入和穿过角质层的经皮渗透。各种透过增强剂，包括油酸、油醇、乙氧基二甘醇、月桂氮䓬酮、烷烃羧酸、二甲基亚砜、极性脂质、或 N- 甲基 -2- 吡咯烷酮，是本领域技术人员已知的。另一方面，组合物可进一步包括促水溶剂，其作用以增加角质层的结

构紊乱，因此允许穿过角质层的输送增加。各种促水溶剂如异丙醇、丙二醇、或二甲苯磺酸钠，是本领域技术人员已知的。

[0471] 局部活性药物组合物应以有效产生期望变化的量施用。如本文所用，“有效……的量”意为足以覆盖皮肤表面期望有变化的区域的量。活性化合物的存在量应为组合物的按重量体积计约0.0001%至约15%。更优选地，其存在量应为组合物的约0.0005%至约5%；最优选地，其存在量应为组合物的约0.001%至约1%。这种化合物可以是合成或天然来源的。

[0472] 颊部给予

[0473] 本发明的药物组合物可以适于颊部给予的制剂制备、包装或销售。这种制剂可例如是利用常规方法制成的片剂或糖锭形式，并且可包含例如0.1至20% (w/w)的活性成分，其余包括口服可溶解或可降解的组分，和任选地本文描述的额外成分中的一种或多种。可选地，适于颊部给予的制剂可包括包含活性成分的粉末或者气溶胶化或雾化溶液或悬浮液。这种粉末状、气溶胶化、或雾化制剂，在分散时，优选具有约0.1至约200纳米范围内的平均颗粒或液滴尺寸，并且可进一步包括本文描述的额外成分中的一种或多种。本文描述的制剂的实例不是详尽的，并且要理解，本发明包括对这些制剂和本文未描述但本领域技术人员已知的其他制剂的其他改动。

[0474] 直肠给予

[0475] 本发明的药物组合物可以适于直肠给予的制剂制备、包装或销售。这种组合物可以例如是栓剂、保留灌肠制剂、和直肠或结肠灌洗溶液形式。

[0476] 栓剂制剂可通过如下制备：组合活性成分与非刺激性的药学上可接受的赋形剂，该赋形剂在普通室温（即，约20℃）下是固体并且在对象的直肠温度下（即，健康人体内约37℃）是液体。适当的药学上可接受的赋形剂包括但不限于，可可脂、聚乙二醇类、和各种甘油酯。栓剂制剂可进一步包括各种额外成分，包括但不限于，抗氧化剂、和防腐剂。

[0477] 保留灌肠制剂或直肠或结肠灌洗溶液可通过组合活性成分与药学上可接受的液体载体来制备。本领域公知，灌肠制剂可利用适于对象直肠解剖结构的递送装置来给予，并且可被封装在其中。灌肠制剂可进一步包括各种额外成分，包括但不限于，抗氧化剂、和防腐剂。

[0478] 其他给予方式

[0479] 本发明的其他剂型包括美国专利号6,340,475、6,488,962、6,451,808、5,972,389、5,582,837和5,007,790描述的剂型。本发明的其他剂型还包括美国专利申请号20030147952、20030104062、20030104053、20030044466、20030039688、和20020051820描述的剂型。本发明的其他剂型还包括PCT申请号WO 03/35041、WO 03/35040、WO 03/35029、WO 03/35177、WO 03/35039、WO 02/96404、WO 02/32416、WO 01/97783、WO 01/56544、WO 01/32217、WO 98/55107、WO 98/11879、WO 97/47285、WO 93/18755、和WO 90/11757描述的剂型。

[0480] 受控释放制剂和药物递送系统

[0481] 在进一步实施方式中，组合物可被设计以促进药物的受控释放，以便调控化合物在被给予时的暴露位置、程度和速率。影响口服给予药物的目标暴露区域的因素可以是药物pH、酶稳定性、与其他药物（例如，某些抗生素）的反应性、作为盐或游离碱的溶解性、电

离表现、和特定环境下的药效动力学和药代动力学表现。

[0482] 本发明药物组合物的受控或持续释放制剂可利用常规技术制备。在一些情况下，待用剂型可利用例如羟丙基甲基纤维素、其他聚合物基质、凝胶、渗透膜、渗透系统、多层包衣、微粒、脂质体、或微球或其组合来提供以缓慢或受控释放其中一种或多种活性成分，从而提供不同比例的期望释放曲线。本领域技术人员已知的适当的受控释放制剂——包括本文描述的那些——可容易被选用于本发明的药物组合物。因此，适于受控释放的适于口服给予的单个单位剂型，如片剂、胶囊、凝胶胶囊、和囊片，被本发明包括在内。

[0483] 多数受控释放药物产品具有共同的目的，即相对于其非受控对应物所实现的程度提高药物治疗。理想地，最优设计的受控释放制剂在医疗中的应用的特征在于在最少时间量内使用最少药物物质治愈或控制病况。受控释放制剂的优点包括在口服给予后在胃肠道内靶向递送、延长药物活性、减少用药频率、和增加患者依从性。另外，受控释放制剂可用于影响作用发生时间或其他特征，如药物血液水平，因此可影响副作用的发生。

[0484] 多数受控释放制剂被设计以最初释放立即产生期望的治疗效果的药物量，并且逐渐和持续释放其他药物量以长期保持这种治疗效果水平。为保持体内这种恒定的药物水平，药物必须以替代被代谢和排出身体的药物量的速率从剂型释放。

[0485] 活性成分的受控释放可被多种诱因刺激，例如水、pH、温度、酶、细菌、或其他生理状况或化合物。本发明环境中的术语“受控释放组分”在本文中被限定为促进活性成分受控释放的一种或多种化合物，包括但不限于，聚合物、聚合物基质、凝胶、渗透膜、脂质体、或微球或其组合。

[0486] 在某些实施方式中，本发明的制剂可以是，但不限于，短期，快速补偿(rapid-offset)，以及受控，例如，持续释放、延迟释放和脉冲式释放制剂。活性药物物质也可被包覆在可植入医疗装置上，利用远程激活系统来洗脱或释放。

[0487] 术语持续释放以其常规含义使用，描述提供药物长期逐渐释放并且可以——虽非一定——造成长期基本恒定的药物血液水平的药物制剂。该时期可长达一个月或更久，并且将是比弹丸形式给予相同剂量更长久的释放。

[0488] 关于持续释放，化合物可与向化合物提供持续释放特性的适当的聚合物或疏水材料一起配制。如此，用于本发明方法的化合物可例如通过注射以微粒形式给予，或通过植入以晶片或圆片形式给予（药物嵌入聚合物基质）。

[0489] 在本发明的优选实施方式中，本发明的化合物单独或与另一药剂组合利用持续释放制剂被给予患者。

[0490] 术语延迟释放在本文中以其常规含义使用，描述在药物给予后一些延迟后提供药物最初释放并且可以——虽非一定——包括约 10 分钟上至约 24 小时延迟的药物制剂。

[0491] 术语脉冲式释放在本文中以其常规含义使用，描述以在药物给予后产生药物脉冲式血浆曲线的方式提供药物释放的药物制剂。

[0492] 术语立即释放在本文中以其常规含义使用，描述在药物给予后立即提供药物释放的药物制剂。

[0493] 如本文所用，短期指代在药物给予后上至并且包括约 24 小时、约 12 小时、约 8 小时、约 7 小时、约 6 小时、约 5 小时、约 4 小时、约 3 小时、约 2 小时、约 1 小时、约 40 分钟、约 20 分钟、或约 10 分钟的任何时间段，以及其任何或所有完整或部分增量。

[0494] 如本文所用，快速补偿指代在药物给予后上至并且包括约24小时、约12小时、约8小时、约7小时、约6小时、约5小时、约4小时、约3小时、约2小时、约1小时、约40分钟、约20分钟、或约10分钟的任何时间段，以及其任何和所有完整或部分增量。

[0495] 一些药物在十二指肠或其他肠位置被更好地吸附。受控释放的一种特别有用的模式是在递送最浓形式的药物至十二指肠或其他肠位置时最小化药物在胃中释放的模式。在优选实施方式中，本发明化合物被配制以促进至十二指肠和任选地其他肠位置的递送。递送药物至十二指肠或其他肠区域的受控释放可利用包括肠溶包衣的组合物来实现。肠溶包衣在高酸性环境中不溶，通常包括多元酸包衣，该多元酸包衣在胃pH下保持不电离和完整。然而，在十二指肠或其他肠区域的弱酸性（＞pH 5.5）、中性或弱碱性（pH 6.5-7.6）条件下，该包衣电离、溶胀和破裂，使被包覆实体暴露于环境。存在包衣选择，允许处于或接近具体pH时（例如，Eudragit L-110，电离阈值pH 6.0；Eudragit S-100，电离阈值pH 7.0）电离。要理解，可使用来自其他公司的相似类型或级别的膜包衣或聚合物产品。

[0496] 在进一步实施方式中，本发明化合物可与肠溶包衣一起配制，该肠溶包衣在包覆前已通过向聚合物添加塑化剂而改性。可添加塑化剂以调节包衣的碎裂或破裂抗性，同时还降低包衣的玻璃化转变温度，从而实现包衣在其施加过程中的光滑和均匀延展性。适当的塑化剂包括聚乙二醇8000(PEG 8000)、柠檬酸三乙基酯(TEC)和三醋汀，其可被掺入聚合物肠溶包衣剂。

[0497] 本发明化合物可在多种剂型下被肠溶地配制，包括（但不限于）胶囊、活性药物颗粒本身、小珠、微球、和片剂。在一个实施方式中，组合物可包括封装在肠溶包衣胶囊中的药物，从而在十二指肠或其他肠环境中释放药物。在本发明一方面，药学上可接受的胶囊包括硬胶囊。在另一实施方式中，药学上可接受的胶囊包括软明胶胶囊。

[0498] 在一个实施方式中，本发明的分子可以无载体、赋形剂或其他药学上可接受的添加剂的纯颗粒或粉末形式被封装。在其他实施方式中，本发明的分子可与一种或多种药学上可接受的载体、赋形剂、抗氧化剂、抗真菌剂（例如，苯甲酸和抗坏血酸及其盐、和酚类化合物如对羟基苯甲酸甲酯、乙酯、丙酯和丁酯（对羟基苯甲酸酯类））、抗菌防腐剂、着色剂、和调味剂一起封装。赋形剂可有助于胶囊填充表现、稳定性、和在胶囊在体内崩解时的药物分布。在另一实施方式中，本发明化合物的颗粒和/或粉末可在置于胶囊前被肠溶包衣。置于胶囊的肠溶包衣颗粒和/或粉末可具有一种或几种类型的肠溶包衣，以实现药物至肠不同区域的递送。胶囊可没有肠溶包衣，或可包覆有与用于胶囊内部任何肠溶包衣材料的包衣匹配或完全不同的肠溶包衣。

[0499] 在进一步实施方式中，本发明的分子可在液体中被封装，其形式为在水或各种药学上可接受的油或其他分散体介质中的溶液或悬浮液，任选地与赋形剂一起封装，该赋形剂如共溶剂（例如，PEG 300、PEG 400、丙二醇、甘油、吐温80、乙醇）、溶解增强剂（例如，山梨醇、葡萄糖）、润湿剂（增稠剂、缓冲剂（例如，磷酸氢二钠）、抗氧化剂、抗真菌剂、防腐剂、着色剂和调味剂。在一些实施方式中，本发明的化合物可以纯药物形式作为液体中的颗粒和/或粉末被配制用于液体填充胶囊。在相关实施方式中，包含在液体中的药物的胶囊可以有肠溶包衣。在另一实施方式中，本发明化合物的颗粒和/或粉末可被肠溶包衣，然后置于液体中和将该组合布置在胶囊中。肠溶包衣颗粒和/或粉末可具有一种或几种类型的肠溶包衣，以实现药物至肠不同区域的递送。胶囊可没有肠溶包衣，或可包覆有与用于胶囊

内部的任何肠溶包衣材料的包衣匹配或完全不同的肠溶包衣。

[0500] 在另一实施方式中，本发明的分子可被封装在由无需单独施加肠溶包衣而提供胃后药物递送的材料组成的胶囊（例如，Entericare 肠溶软凝胶）中。分子可作为有或无赋形剂的颗粒或粉末、和作为溶液或悬浮液被封装在这种胶囊，如上所述。

[0501] 在一些实施方式中，本发明化合物的固体颗粒，以多种颗粒尺寸和颗粒尺寸分布，可与赋形剂如微晶纤维素或乳糖混合并形成小珠，该小珠包括施加了肠溶包衣的含药物内核。在一些实施方式中，本发明的分子可形成包括任选地缓冲剂（例如，aq. 1N HCl 和三羟基甲基氨基甲烷 [TRIS]）和粘合剂（例如，OPADRY 透明涂料粉末）的悬浮液或溶液，并被包覆到基体颗粒例如糖珠（例如，糖球、NF 颗粒）上，形成小珠。在另一实施方式中，小珠可以有肠溶包衣。在再一实施方式中，本发明的分子可被配制成肠溶包衣小珠，如上所述，并且该小珠通过封装被进一步配制。在进一步实施方式中，小珠与不同类型肠溶包衣的组合可被封装，使得本发明化合物在从胶囊释放后以受控方式在十二指肠至肠其他部位范围内的不同区域可用。胶囊可没有肠溶包衣，或可包覆有与用于胶囊内部的任何肠溶包衣材料的包衣匹配或完全不同的肠溶包衣。

[0502] 在进一步实施方式中，本发明化合物可被配制成片剂或囊片，其单独或与其他制剂组分组合递送药物至十二指肠或其他肠区域。在一个实施方式中，本发明化合物被配制成片剂或囊片，该片剂或囊片有肠溶包衣并且构成给药剂型。在另一实施方式中，适当尺寸和形状的片剂或囊片可被置于胶囊中。在一个这种实施方式中，胶囊可以有肠溶包衣，并且包含无肠溶包衣的片剂或囊片，该片剂或囊片在十二指肠或其他肠区域中从胶囊释放。在再一这种实施方式中，胶囊可被设计以在胃中崩解并释放肠溶包衣片剂或囊片，以随后递送至十二指肠或其他肠区域。在再一这种实施方式中，胶囊和其中包含的片剂或囊片可都有肠溶包衣，以提供对片剂或囊片从胶囊释放和随后药物从片剂或囊片释放的进一步控制。在进一步相关实施方式中，具有多种肠溶包衣的片剂或囊片可被组合并置于胶囊中，胶囊本身也可任选地具有肠溶包衣。可用于片剂和囊片的肠溶包衣的材料包括但不限于上述用于胶囊的那些。

[0503] 肠溶包衣可允许在酸性介质中过早药物释放。在再进一步实施方式中，本发明的化合物可被配制使得亚包衣在施加肠溶包衣前被施加。亚包衣可包括可溶性亚包衣剂对肠溶底物的施加，亚包衣剂的实例是羟丙基甲基纤维素、聚维酮、羟丙基纤维素、聚乙二醇3350、4500、8000、甲基纤维素、假乙基纤维素和支链淀粉。要理解，可使用来自其他公司的相似类型的合成和半合成聚合物产品。肠溶底物上的亚包衣薄层阻止水渗透胶囊外壳上的肠溶包衣或渗入活性成分所在的内核，防止过早药物释放。亚包衣还可通过缓和内核和肠溶包衣之间界面的酸性微环境而促进药物在碱性环境中释放。在一些实施方式中，本发明化合物被配制具有包含有机酸的亚包衣，意图促进胶囊在包衣在 pH 5-6 的环境中降解时更快速的聚合物溶解，促进药物在碱性介质中的快速释放。

[0504] 机械装置

[0505] 在本发明一方面，治疗不具有正常通气和正常呼吸控制的患者的方法包括给予如本文所述可用于本发明的组合物，另外还利用援助呼吸的装置治疗患者。这种装置包括但不限于，通气装置、CPAP 和 BiPAP 装置。

[0506] 机械通气是机械协助或代替自主呼吸的方法。机械通气一般在侵入性插管——其

中将气管内管或气管造口管插入气道的程序——后应用。其常用于紧急情况，如在 ICU 中，在严重疾病期间短时间使用。其也可在家或在护理或康复机构应用，如果患者患有需要长期通气辅助的慢性疾病。机械通气的主要形式是正压通气，其通过增加患者气道压力并且因此迫使空气进入肺而作用。如今较不常见的是负压通气装置（例如，“铁肺”），其在患者胸部周围产生负压环境，因此将空气吸入肺。机械通气通常是一种救生干预，但附带很多可能的并发症，包括气胸、气道损伤、肺泡损伤、和通气装置相关的肺炎。因此，所用气体压力和体积被严格控制，并且尽可能快地中止。机械通气的类型有：常规正压通气、高频通气、非侵入性通气（非侵入性正压通气或 NIPPV）、比例辅助通气 (PAV)、适应伺服通气 (ASV) 和神经调节辅助通气 (NAVA)。

[0507] 非侵入性通气指代所有在不使用气管内管的情况下辅助通气的方式。非侵入性通气主要为了最小化患者不适和与侵入性通气有关的并发症，通常用于心脏疾病、慢性肺部疾病恶化、睡眠呼吸暂停、和神经肌肉疾病。非侵入性通气仅指患者界面，而非应用的通气模式；模式可包括自主或控制模式，并且可以是压力或体积循环模式。一些常用的 NIPPV 模式包括：

[0508] (a) 连续气道正压 (CPAP)：这种类型的机器过去主要被患者用于在家治疗睡眠呼吸暂停，但现在作为通气援助的一种形式被广泛用于重症监护室。CPAP 机器通过如下停止上气道阻碍：经由软管递送压缩气流至鼻枕、鼻罩或全面罩，用夹板使气道打开（在空气压力下保持其打开）使得不受阻的呼吸变得可能，减少和 / 或防止呼吸暂停和呼吸不足。当机器被打开时，但在护罩被置于头上前，空气流过护罩。在护罩被置于头上后，其被密封至面部，并且空气停止流动。此时，仅仅空气压力去实现期望的效果。这具有减少或消除有时伴随睡眠呼吸暂停的极响鼾声的额外助益。

[0509] (b) 双水平气道正压 (BIPAP)：压力在患者行动触发的吸气气道正压 (IPAP) 与较低呼气气道正压 (EPAP) 之间交替。在很多这种装置上，可设置后援 (backup) 速率，其在即使患者不能发动呼吸时依然递送 IPAP 压力。

[0510] (c) 间歇正压通气 (IPPV)，通过接嘴或护罩。

[0511] 本领域技术人员知道或能够利用不多于常规的实验确定本文描述的具体程序、实施方式、权利要求、和实例的多种等同形式。这种等同形式被认为在本发明的范围内并且被所附权利要求覆盖。例如，应理解，通过本领域公知的选择和利用不多于常规的试验进行的反应条件（包括但不限于反应时间、反应尺寸 / 体积、和实验试剂如溶剂、催化剂、压力、气氛条件例如氮气气氛、和还原剂 / 氧化剂）的改动在本申请的范围内。

[0512] 要理解，无论本文提供什么数值和范围，范围形式的描述只是为方便和简洁起见，不应被解释为本发明范围的僵硬限制。因此，这些数值和范围包括的所有数值和范围都意图被包括在本发明范围内。此外，落入这些范围的所有数值以及数值范围的上限或下限也被本申请包括。范围的描述应被认为具体公开了所有可能的子范围以及该范围内的单个数值，在适宜时，范围内数值的部分整数。例如，诸如 1 至 6 的范围描述应被认为具体公开了诸如 1 至 3、1 至 4、1 至 5、2 至 4、2 至 6、3 至 6 等的子范围，以及该范围内的单个数值，例如，1、2、2.7、3、4、5、5.3、和 6。这与范围宽度无关地适用。

[0513] 下列实施例进一步示例本发明的方面。然而，其绝不是本文描述的本发明教导或公开的限制。

实施例

[0514] 现参考下列实施例描述本发明。这些实施例的提供是仅为示例，本发明不限于这些实施例，而包括通过本文提供的教导而显而易见的所有改动。

[0515] 材料：

[0516] 除非另外明示，其余所有起始材料均获自商品供应商，并且不经纯化使用。除非另外明示，最终产品一般作为酸加成盐被分离。

[0517] 实施例 1:N^2,N^6- 二甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (3) 和相应的盐酸盐 (4a)(方案 7)

[0518] 2,6- 二氯 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (2)：

[0519] 向 2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶 (1)(2.20g,8.15mmol) 的 THF(55mL) 溶液，在 0℃下滴加 THF(15mL) 中的正丙胺 (2.68mL,32.60mmol)。将反应混合物在室温下搅拌 1h。在该时间后，加水 (50mL)，并将所得析出物过滤，用水 (30mL) 洗涤，和在 P_2O_5 上干燥，生成 2,6- 二氯 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (2)(2.49g,97% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) δ 6.92-6.85(2H, m),3.56(4H, td, J = 7.3,6.2Hz),1.73(4H, 六重峰, J = 7.3Hz),1.02(6H, t, J = 7.3Hz). ESI-MS(m/z) :315,317,319$[M+H]^+$。

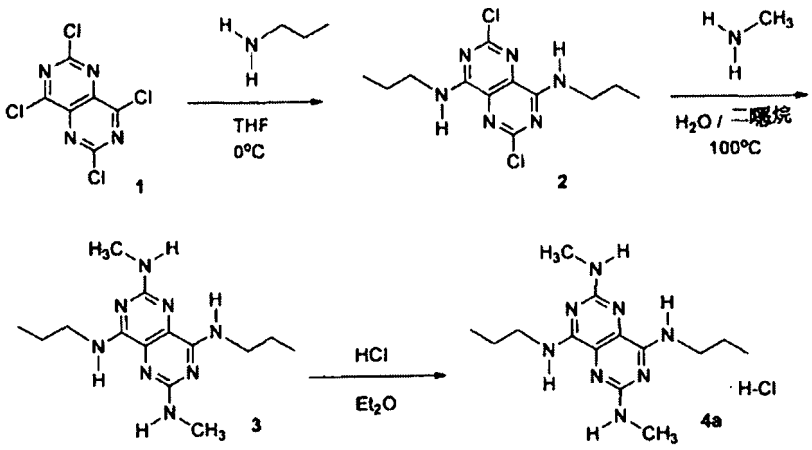
[0520] N^2,N^6- 二甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (3)：

[0521] 将 2,6- 二氯 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (2)(316mg, 1.00mmol) 和甲胺 (40% 水溶液)(2.00mL,718mg,23.15 毫摩尔) 在 1,4- 二噁烷 (3mL) 中的混合物在 100℃下加热 65h。在该时间后，通过蒸发去除挥发物，并将残余物在 CH_2Cl_2(40mL) 和水 (20mL) 之间分配。水相用 CH_2Cl_2(2x 30mL) 萃取。将组合的有机萃取物用水 (50mL) 洗涤，并在固体无水 Na_2SO_4 上干燥。过滤后，去除溶剂，并利用 CH_2Cl_2 至 CH_2Cl_2/EtOH(98 : 2) 的梯度洗脱通过快速柱层析纯化残留物，生成 N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (3)(220mg,72% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) δ 6.53(2H, br s),4.60(2H, br s),3.46(4H, q, J = 6.7Hz),2.97(6H, d, J = 4.5Hz),1.69(4H, 六重峰, J = 7.5Hz),1.00(6H, t, J = 7.5Hz). ESI-MS(m/z) :305$[M+H]^+$。

[0522] N^2,N^6- 二甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (4a)：

[0523] 将 2M HCl/ 二乙醚溶液 (0.35mL,0.70mmol) 加入 N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (3)(212mg,0.70mmol) 的甲醇 (15mL) 悬浮液。将混合物在 0℃下搅拌 0.5h，并将所得析出物过滤，用甲醇 (3mL) 洗涤，生成 N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (4a)(230mg,96% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) δ 9.70-9.41(1H, m),7.86-7.37(1H, m),6.63(1.3H, br s), 4.97-4.68(0.7H, m),3.77-3.38(4H, m),3.15-2.86(6H, m),1.93-1.68(4H, m),1.04(6H, t, J = 7.3Hz). ESI-MS(m/z) :305$[M+H]^+$;熔点 :229-232℃。

[0524]



方案 7

[0525] 实施例 2:N^2,N^4,N^6,N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (5) 和相应的盐酸盐 (6a) (方案 8)

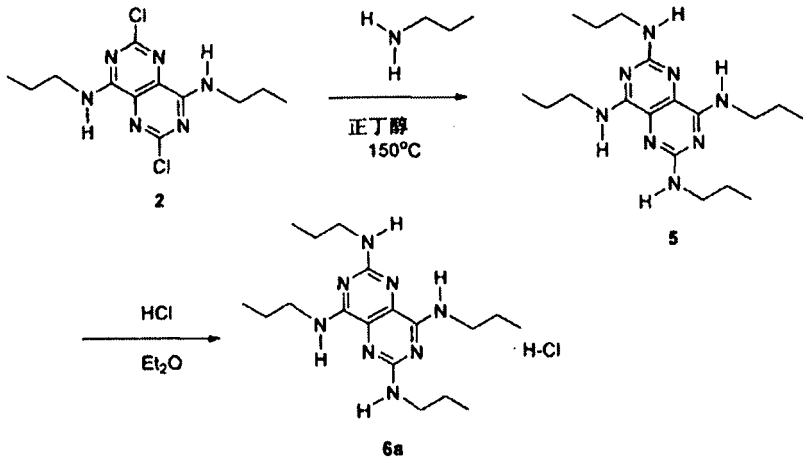
[0526] N^2,N^4,N^6,N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (5) :

[0527] 将 2,6- 二氯 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (2) (338mg, 1.07mmol)、K_2CO_3(296mg,2.14mmol) 和正丙胺 (2.20mL) 在正丁醇 (4mL) 中的混合物在 150℃下加热 45h。在该时间后,通过蒸发去除挥发物,并将残余物在 EtOAc(50mL) 和饱和 $NaHCO_3$溶液 (30mL) 之间分配。水相用 EtOAc(2x 40mL) 萃取。将组合的有机萃取物用水 (50mL),然后用盐水溶液 (50mL) 洗涤,最后在固体无水 Na_2SO_4上干燥。过滤后,去除溶剂,并利用 CH_2Cl_2至 CH_2Cl_2/EtOH(98 : 2) 的梯度洗脱通过快速柱层析纯化残留物,生成 N^2,N^4,N^6,N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (5) (235mg,61% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) δ 6.47(2H, br s),4.61(2H, br s),3.53-3.40, (4H, m),3.40-3.26(4H, m),1.76-1.54(8H, m),1.00(6H, t, J = 7.4Hz),0.99(6H, t, J = 7.4Hz). ESI-MS(m/z) : 361$[M+H]^+$。

[0528] N^2,N^4,N^6,N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (6a) :

[0529] 利用关于化合物 (4a) 描述的程序,使 N^2,N^4,N^6,N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (5) 和 2M HCl/ 二乙醚在 CH_2Cl_2/MeOH(15/1) 中反应,生成 N^2,N^4,N^6,N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (6a),定量产率。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 9.55(0.7H, br s),7.75-7-36(1.3H, m),6.71(1.3H, s),4.85(0.7H, br s),3.72-3.21(8H,m),1.90-1.52(8H,m),1.03(6H,t,J = 7.3Hz),0.98(6H,t,J = 7-3Hz). ESI-MS(m/z) :361$[M+H]^+$;熔点 :208-211℃。

[0530]



方案 8

[0531] 实施例 3:N^2,N^6- 二 - 正丁基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (7) 和相应的盐酸盐 (8a)

[0532] N^2,N^6- 二 - 正丁基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (7):

[0533] 利用关于化合物 (3) 描述的程序,使 2,6- 二氯 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (2) 和正丁胺反应,生成 N^2,N^6- 二 - 正丁基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (7),85% 产率。400MHz ^{1}H NMR($CDCl_3$,ppm) :δ 6.46(2H, br s),4.57(2H,br s),3.51-3.42(4H,m),3.42-3.32(4H,m),1.69(4H,六重峰,J = 7.4Hz),1.63-1.54(4H, m),1.48-1.37(4H, m),1.00(6H, t, J = 7.4Hz),0.96(6H, t, J = 7.4Hz). ESI-MS(m/z) :389$[M+H]^+$。

[0534] N^2,N^6- 二 - 正丁基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (8a):

[0535] 利用关于化合物 (4a) 描述的程序,使 N^2,N^6- 二 - 正丁基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (7) 和 2M HCl/ 二乙醚在 CH_2Cl_2/MeOH(15/1) 中反应,生成 N^2,N^6- 二 - 正丁基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (8a),定量产率。400MHz ^{1}H NMR($CDCl_3$,ppm) :δ 13.95(0.5H,s),9.54(0.5H,br s),7.67(1H, br s),7.45(1H,br s),6.69(1.2H,s),4.82(0.8H,br s),3.69-3.29(8H,m),1.85-1.67(4H, m),1.65-1.52(4H, m),1.41(4H,六重峰, J = 7.3Hz),1.02(6H, t, J = 7.3Hz),0.95(6H, t, J = 7.4Hz). ESI-MS(m/z) :389$[M+H]^+$;熔点 :205-208℃。

[0536] 实施例 4:N^2,N^6- 二 - 异丙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (9) 和相应的盐酸盐 (10a)

[0537] N^2,N^6- 二 - 异丙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (9):

[0538] 利用关于化合物 (3) 描述的程序,使 2,6- 二氯 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (2) 和异丙胺反应,生成 N^2,N^6- 二 - 异丙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (9),85% 产率。400MHz ^{1}H NMR($CDCl_3$, ppm) δ 6.45(2H, br s),4.44(2H,br s),4.20-4.05(2H,m),3.50-3.37(4H,m),1.68(4H,六重峰,J = 7.4Hz),1.23(12H, d, J = 6.5Hz),1.00(6H, t, J = 7.4Hz). ESI-MS(m/z) :361$[M+H]^+$。

[0539] N^2,N^6-二-异丙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(10a):

[0540] 利用关于化合物(4a)描述的程序,使N^2,N^6-二-正丙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(9)和2M HCl/二乙醚在CH_2Cl_2/MeOH(15/1)中反应,生成N^2,N^6-二-异丙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(10a),81%产率。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 13.90(0.6H,s),9.58(0.4H,s),7.71(1H,s),7.48-7.40(1H,m),6.50(1H,d,J = 7.4Hz),4.68(1H,d,J = 7.4Hz),4.29-4.02(2H,m),3.64-3.42(4H,m),1.80-1.68(4H,m),1.28(7.2H,d,J = 6.6Hz),1.23(4.8H,d,J = 6.6Hz),1.04-0.97(6H,m).ESI-MS(m/z):361[M+H]$^+$;熔点:158-161℃。

[0541] 实施例5:N^2,N^6-二甲基-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(12)和相应的盐酸盐(13a)(方案9)

[0542] 2,6-二氯-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-4,8-二胺(11):

[0543] 在-78℃下经30min将THF(15mL)中的正丙胺(283μL,3.45mmol)滴加至2,4,6,8-四氯-嘧啶并[5,4-d]嘧啶(1)(930mg,3.45mmol)和K_2CO_3(477mg,3.45mmol)在THF(20mL)中的混合物。使反应混合物达到环境温度,然后加入炔丙胺(442μL,6.90mmol)。将混合物搅拌1h。在该时间后,加水(50mL),并将所得悬浮液用EtOAc(3x 30mL)萃取。将组合的有机萃取物用水(50mL),然后用盐水溶液(50mL)洗涤,最后在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用从PE/EtOAc(99 : 1)至PE/EtOAc(9 : 1)的梯度洗脱通过快速柱层析纯化残留物,生成2,6-二氯-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-4,8-二胺(11)(740mg,70% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 7.01-6.95(1H,m),6.95-6.87(1H,m),4.39(2H,dd,J = 5.5,2.6Hz),3.56(2H,td,J = 7.3,6.1Hz),2.33(1H,t,J = 2.6Hz),1.73(2H,六重峰,J = 7.3Hz),1.04(3H,t,J = 7.3Hz).ESI-MS(m/z):311,313,315[M+H]$^+$。

[0544] N^2,N^6-二甲基-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(12):

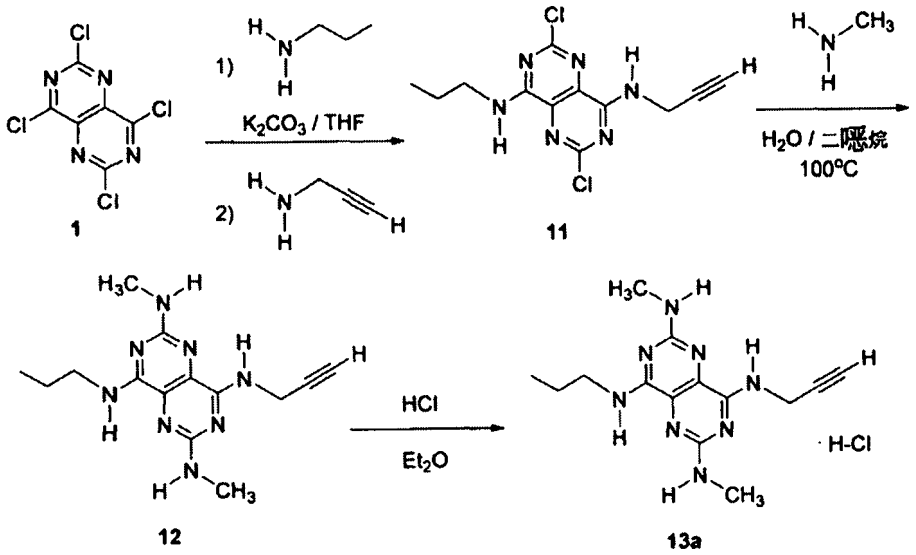
[0545] 将2,6-二氯-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-4,8-二胺(11)(312mg,1.00mmol)和甲胺(40%水溶液)(2.00mL)在1,4-二噁烷(3mL)中的混合物在100℃下加热30h。通过蒸发去除挥发物,将残余物在CH_2Cl_2(40mL)和水(20mL)之间分配。然后水相用CH_2Cl_2(2x 30mL)萃取。将组合的有机萃取物用水(50mL)洗涤,并在固体无水Na_2SO_4上干燥。在真空下去除溶剂,并利用CH_2Cl_2至CH_2Cl_2/EtOH(98 : 2)的梯度洗脱通过快速柱层析纯化残留物,生成N^2,N^6-二甲基-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(12)(150mg,50% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.68-6.44(2H,m),4.65(2H,br s),4.32(2H,dd,J = 5.7,2.6Hz),3.50-3.42(2H,m),2.98(3H,s),2.97(3H,s),2.24(1H,t,J = 2.6Hz),1.69(2H,六重峰,J = 7.4Hz),1.00(3H,t,J = 7.4Hz).ESI-MS(m/z):301[M+H]$^+$。

[0546] N^2,N^6-二甲基-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(13a):

[0547] 利用关于化合物(4a)描述的程序,使N^2,N^6-二甲基-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(12)和2M HCl/二乙醚在CH_2Cl_2/MeOH(15/1)中

反应，生成N^2,N^6-二甲基-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(13a)，定量产率。400MHz ^{1}H NMR($CDCl_3$, ppm)：δ 10.2-9.4(1H, m)，8.3-7.4(1H, m)，6.92-6.45(1.6H, m)，5.18-74.73(0.4H, m)，4.48-4.25(2H, m)，3.70-3.50(2H, m)，3.19-2.92(6H, m)，2.36-2.20(1H, m)，1.90-1.72(2H, m)，1.04(3H, t, J = 7.4Hz). ESI-MS(m/z)：301[M+H]$^+$；熔点：210-212℃。

[0548]



1 11 12 13a

方案9

[0549] 实施例6：N^2,N^6-双(N-甲氧基(N-甲基)氨基)-N^4-正丙基氨基-N^8-丙-2-炔基-氨基-嘧啶并[5,4-d]嘧啶(14)和相应的盐酸盐(15a)

[0550] N^2,N^6-双(甲氧基(甲基)氨基)-N^4-正丙基氨基-N^8-丙-2-炔基氨基-嘧啶并[5,4-d]嘧啶(14)：

[0551] 将2,6-二氯-N^4-正丙基-N^8-丙-2-炔基-嘧啶并[5,4-d]嘧啶-4,8-二胺(11)(350mg,1.12mmol)、N,O-二甲基羟基胺盐酸盐(3.28g,33.60mmol)和N,N-二异丙基乙胺(5.85mL,33.60mmol)在1,4-二噁烷(15mL)中的混合物在90℃下加热60h。然后冷却反应混合物，并添加饱和$NaHCO_3$溶液(30mL)。将所得析出物过滤，并溶解于CH_2Cl_2。将该溶液用水(2x 20mL)洗涤，并在固体无水Na_2SO_4上干燥。过滤后，在真空中去除溶剂，并利用CH_2Cl_2至CH_2Cl_2/EtOH(95：5)的梯度洗脱通过快速柱层析纯化残留物，生成N^2,N^6-双(N-甲氧基(N-甲基)氨基)-N^4-正丙基氨基-N^8-丙-2-炔基氨基-嘧啶并[5,4-d]嘧啶(14)(156mg,39% y)。400MHz ^{1}H NMR($CDCl_3$, ppm)：δ 6.84(1H, t, J = 5.6Hz)，6.80(1H, t, J = 6.0Hz)，4.52(2H, dd, J = 5.6,2.5Hz)，4.04(3H, s)，4.04(3H, s)，3.71-3.64(2H, m)，3.49(3H, s)，3.48(3H, s)，2.40(1H, t, J = 2.5Hz)，1.87(2H,六重峰, J = 7.4Hz)，1.16(3H, t, J = 7.4Hz). ESI-MS(m/z)：361[M+H]$^+$。

[0552] N^2,N^6-双(N-甲氧基(N-甲基)氨基)-N^4-正丙基氨基-N^8-丙-2-炔基氨基-嘧啶并[5,4-d]嘧啶盐酸盐(15a)：

[0553] 利用关于化合物(4a)描述的程序，使N^2,N^6-双(N-甲氧基(N-甲基)氨基)-N^4-正丙基氨基-N^8-丙-2-炔基氨基-嘧啶并[5,4-d]嘧啶(14)和2M HCl/二乙醚在MeOH中反应，生成N^2,N^6-双(N-甲氧基(N-甲基)氨基)-N^4-正丙基氨基-N^8-丙-2-炔基氨基-嘧啶

并[5,4-d]嘧啶盐酸盐(15a),90%产率。400MHz ^{1}H NMR(DMSO-d_6,ppm):δ 9.63(1H,br s),9.29(1H,br s),4.31(2H,dd,J=5.2,2.3Hz),3.82(3H,s),3.81(3H,s),3.53-3.47(2H,m),3.41(3H,s),3.38(3H,s),3.23(1H,t,J=2.3Hz),1.66(2H,六重峰,J=7.4Hz),0.92(3H,t,J=7.4Hz).ESI-MS(m/z):361[M+H]$^+$;熔点:176-177℃。

[0554] 实施例7:N-(6-氯-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-O,N-二甲基-羟基胺(16)和相应的盐酸盐(17a)(方案10)

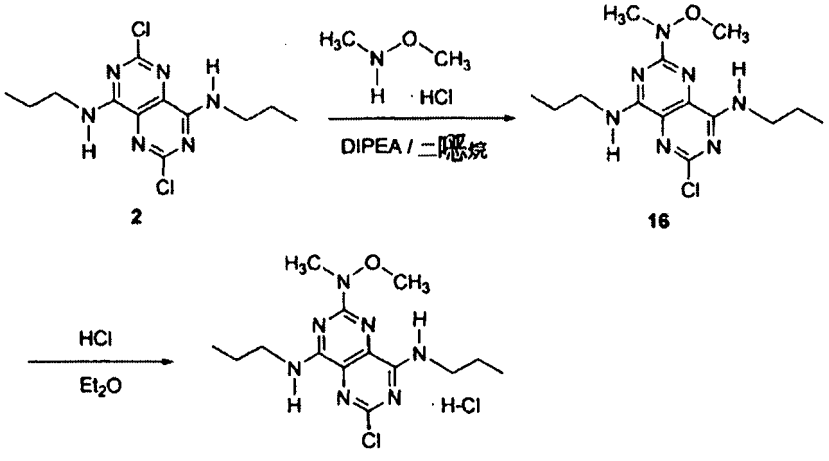
[0555] N-(6-氯-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-O,N-二甲基-羟基胺(16):

[0556] 将2,6-二氯-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-4,8-二胺(2)(316mg,1.00mmol)、N,O-二甲基羟基胺盐酸盐(975mg,10.00mmol)和N,N-二异丙基乙胺(1.74mL,10.00mmol)在1,4-二噁烷(10mL)中的混合物在90℃下加热5h。冷却反应混合物,并添加饱和$NaHCO_3$溶液(30mL)。将所得悬浮液用CH_2Cl_2(3x 20mL)萃取。将组合的有机萃取物用水(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用CH_2Cl_2至CH_2Cl_2/EtOH(98:2)的梯度洗脱通过快速柱层析纯化残留物,生成N-(6-氯-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-O,N-二甲基-羟基胺(16)(237mg,70% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.87-6.77(1H,m),6.68-6.64(1H,t,J=5.6Hz),3.86(3H,s),3.58-3.47(4H,m),3.36(3H,s),1.77-1.65(4H,m),1.02(3H,t,J=7.4Hz),1.00(3H,t,J=7.4Hz).ESI-MS(m/z):340,342[M+H]$^+$。

[0557] N-(6-氯-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-O,N-二甲基-羟基胺盐酸盐(17a):

[0558] 利用关于化合物(4a)描述的程序,使N-(6-氯-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-O,N-二甲基-羟基胺(16)和2M HCl/二乙醚在二乙醚中反应,生成N-(6-氯-4,8-双-丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-O,N-二甲基-羟基胺盐酸盐(17a),90%产率。400MHz ^{1}H NMR(DMSO-d6,ppm):δ 9.27-8.15(2H,m),3.81(3H,s),3.49-3.32(7H,m),1.70-1.54(4H,m),0.95-0.84(6H,m).ESI-MS(m/z):340,342[M+H]$^+$;熔点:142-145℃。

[0559]



方案10

[0560] 实施例8:N^2,N^6-双-(N-甲氧基(N-甲基)氨基)-N^4,N^8-双-正丙基氨基-嘧啶

并 [5,4-d] 嘧啶 (18) 和相应的盐酸盐 (19a) (方案 11)

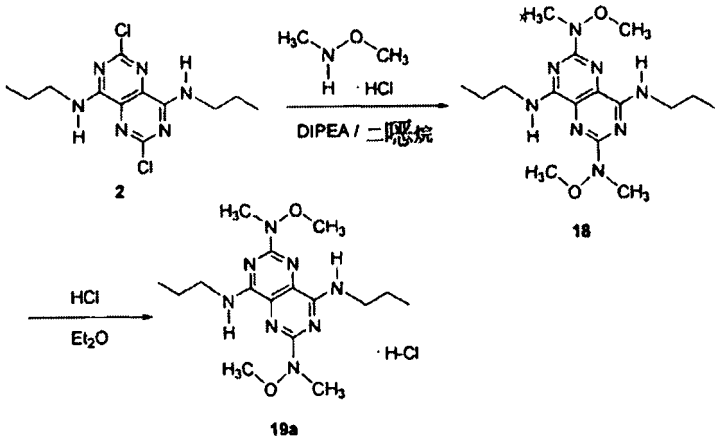
[0561] N^2,N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4,N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 (18) :

[0562] 利用关于化合物 (14) 描述的程序,使 2,6- 二氯 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (2) 和 N, O- 二甲基羟基胺盐酸盐反应,生成 N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 (18),94% 产率。400MHz ^{1}H NMR($CDCl_3$, ppm) :d 6.62(2H, t, J = 5.9Hz),3.88(6H, s),3.55-3.48(4H, m),3.32(6H, s),1.71(4H, 六重峰, J = 7.4Hz),1.00(6H, t, J = 7.4Hz). ESI-MS(m/z) :365[M+H]$^+$。

[0563] N^2,N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4,N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶盐酸盐 (19a) :

[0564] 利用关于化合物 (4a) 描述的程序,使 N^2,N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 (18) 和 2M HCl/ 二乙醚在 MeOH 中反应,生成 N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶盐酸盐 (19a),94% 产率。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 12.79(1H, br s),11.7-8.3(2H, m),3.94(6H, s),3.61-3.50(4H, m),3.42(6H, s),1.84-1.71(4H, m),1.04-0.94(6H, m). ESI-MS(m/z) :365[M+H]$^+$。

[0565]



方案 11

[0566] 实施例 9:N^2- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (21) 和相应的盐酸盐 (22a) (方案 12)

[0567] 6- 氯 -N^2- 甲基 -N^4,N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) :

[0568] 将 2,6- 二氯 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (2) (1.00g, 3.17mmol) 和 2M 甲胺 /THF(8mL) 的混合物在 60℃下加热 21h。通过蒸发去除挥发物,并将残余物在 EtOAc(30mL) 和饱和 $NaHCO_3$ 溶液 (30mL) 之间分配。水相用 EtOAc(2x 20mL) 萃取。将组合的有机萃取物用水 (50mL),然后用盐水溶液 (50mL) 洗涤,最后在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,生成 6- 氯 -N^2- 甲基 -N^4,N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) (975mg,99% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) δ 6.80-6.71(1H, m), 6.52(1H, t, J = 5.1Hz),4.93-4.85(1H, m),3.54(2H, td, J = 7.3,6.1Hz),3.49-3.42(2H, m),3.00(3H, d, J = 5.1Hz),1.77-1.63(4H, m),1.03(3H, t, J = 7.4Hz),1.01(3H, t, J = 7.4Hz). ESI-MS(m/z) :310,312[M+H]$^+$。

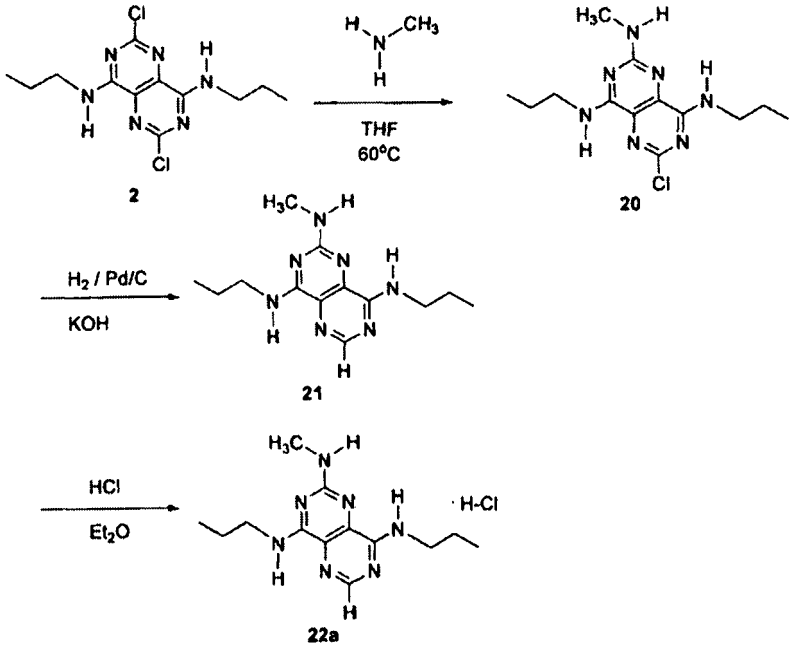
[0569] N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (21) :

[0570] 将 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) (440mg,1.42mmol)、KOH(319mg,5.68mmol) 和 10% Pd/C(310mg) 在 THF(20mL) 中的混合物在 30psi 下氢化 72h。将反应混合物过滤,并将滤液蒸发。将残留物溶解于 EtOAc(80mL),用水 (3x 30mL),然后用盐水溶液 (30mL) 洗涤,最后在固体无水 Na_2SO_4 上干燥。过滤后,在真空中去除溶剂,并利用 CH_2Cl_2 至 CH_2Cl_2/EtOH(98 : 2) 的梯度洗脱通过快速柱层析纯化残留物,生成 N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (21) (360mg, 92% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 8.25(1H, s),6.74-6.56(2H, m),4.92(1H, br s), 3.56-3.48(4H, m),3.00(3H, d, J = 5.1Hz),1.78-1.63(4H, m),1.02(3H, t, J = 7.3Hz), 1.00(3H, t, J = 7.3Hz). ESI-MS(m/z) :276$[M+H]^+$。

[0571] N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺盐酸盐 (22a) :

[0572] 利用关于化合物 (4a) 描述的程序,使 N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (21) 和 2M HCl/ 二乙醚在二乙醚中反应,生成 N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺盐酸盐 (22a),91% 产率。400MHz ^{1}H NMR(DMSO-d_6, ppm) : δ 13.8-13.0(1H,br s),9.78-8.83(1H,m),8.56(1H,br s),8.41(1H,s),7.33(1H,br s),3.55-3.35(4H,m,与水重叠),2.99(3H,s),1.71-1.60(4H,m),0.95(3H,t,J = 7.3Hz), 0.91(3H, t, J = 7.3Hz). ESI-MS(m/z) :276$[M+H]^+$;熔点 :139-142℃。

[0573]



方案 12

[0574] 实施例 10:O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)- 羟基胺 (23) 和相应的盐酸盐 (24a)

[0575] O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)- 羟基胺 (23) :

[0576] 将 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) (300mg,0.97mmol)、N, O- 二甲基羟基胺盐酸盐 (426mg,4.37mmol) 和 N, N- 二异丙基乙胺

(722 μL,4.37mmol) 在 1,4- 二噁烷 (10mL) 中的混合物在 90℃下加热 60h。冷却反应混合物,并添加饱和 $NaHCO_3$ 溶液 (30mL)。将所得悬浮液用 EtOAc(3x 20mL) 萃取。将组合的有机萃取物用水 (30mL),然后用盐水溶液 (20mL) 洗涤,最后在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 CH_2Cl_2 至 CH_2Cl_2/EtOH(95 : 5) 的梯度洗脱通过快速柱层析纯化残留物,生成 O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 丙基氨基 - 嘧啶并 [5,4-d] 噻啶 -2- 基)- 羟基胺 (23) (175mg,54% y)。400MHz ^{1}H NMR($CDCl_3$,ppm) :δ 6.57(2H,br s),4.67(1H,br s),3.88(3H, s),3.54-3.43(4H, m),3.30(3H, s),2.98(3H, d, J = 5.1Hz),1.76-1.64(4H, m),1.01(3H, t, J = 7.4Hz),0.99(3H, t, J = 7.4Hz). ESI-MS(m/z) :335[M+H]$^+$。

[0577] O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 噻啶 -2- 基)- 羟基胺盐酸盐 (24a) :

[0578] 利用关于化合物 (3a) 描述的程序,使 O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 噻啶 -2- 基)- 羟基胺 (23) 和 2M HCl/ 二乙醚在二乙醚中反应,生成 O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 噻啶 -2- 基)- 羟基胺盐酸盐 (24a),90% 产率。400MHz ^{1}H NMR($CDCl_3$,ppm) :13.24(0.2H,br s),8.26(1.8H, br s),6.71-6.63(1H, m),3.89(3H, s),3.66-3.60(2H, m),3.57-3.51(2H, m),3.37(3H, s),3.06(3H, d, J = 4.8Hz),1.85-1.74(4H, m),1.03(3H, t, J = 7.4Hz),1.02(3H, t, J = 7.4Hz). ESI-MS(m/z) :335[M+H]$^+$;熔点 :182-185℃。

[0579] 实施例 11:N^4,N^8- 二甲基 -N^2,N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 噻啶 -2,4,6,8- 四胺 (26) 和相应的盐酸盐 (27a)(方案 13)

[0580] 2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 噻啶 -4,8- 二胺 (25) :

[0581] 将 2M 甲胺 /THF(2.10mL,4.2mmol) 溶液在 0℃下加入 2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 噻啶 (1) (250mg,0.93mmol) 的 THF(5mL) 溶液。将反应混合物在室温下搅拌 1h。在该时间后,加水 (10mL),并过滤析出物,用水 (10mL) 洗涤,并在 P_2O_5 上干燥,生成 2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 噻啶 -4,8- 二胺 (25) (230mg,95% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 6.90(2H, br s),3.16(6H, d, J = 5.0Hz). ESI-MS(m/z) :259,261,263[M+H]$^+$。

[0582] N^4,N^8- 二甲基 -N^2,N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 噻啶 -2,4,6,8- 四胺 (26) :

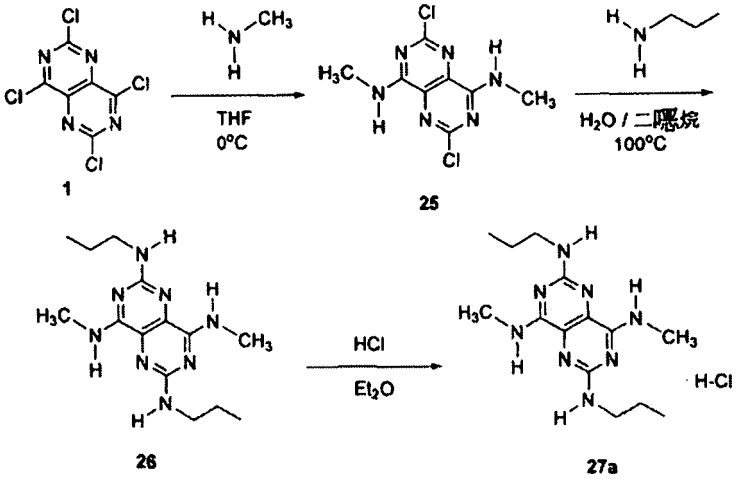
[0583] 利用关于化合物 3 描述的程序,使 2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 噻啶 -4,8- 二胺 (25) 和正丙胺反应,生成 N^2,N^6- 二 - 正丙基 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 噻啶 -2,4,6,8- 四胺 (26),90% 产率。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 6.49-6.38(2H, m),4.64(2H, t, J = 5.2Hz),3.38-3.33(4H, m),3.06(6H, d, J = 5.2Hz),1.63(4H, 六重峰, J = 7.3Hz),0.99(6H, t, J = 7.3Hz). ESI-MS(m/z) :305[M+H]$^+$. 。

[0584] N^4,N^8- 二甲基 -N^2,N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 噻啶 -2,4,6,8- 四胺盐酸盐 (27a) :

[0585] 利用关于化合物 (4a) 描述的程序,使 N^2, N^6- 二 - 正丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 噻啶 -2,4,6,8- 四胺 (26) 和 2M HCl/ 二乙醚在二乙醚 /1,4- 二噁烷 (5/1) 中反应,生成 N^2, N^6- 二 - 正丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 噻啶 -2,4,6,8- 四胺盐酸盐 (27a),88 % 产率。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 14.00(0.3H, s),9.65(0.7H, s),7.70(1H, s),7.44(1H, s),6.65(1.3H, s),4.89(0.7H, s),3.50-3.43(3H, m),3.39-3.30(1H, m),3.21-3.20(4H, m),3.08-3.03(2H, m),1.71-1.59(4H, m),0.99(6H, t, J = 7.5Hz).

ESI-MS(m/z) :305[M+H]$^+$;熔点 :237-240℃。

[0586]



1 25 26 27a

方案 13

[0587] 实施例 12:N^2,N^2,N^6-三甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(28)和相应的盐酸盐(29a)(方案 14)

[0588] 6-氯-N^2-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺盐酸盐(20a)

[0589] 将 2M HCl/二乙醚(260μL,0.52mmol)加入 6-氯-N^2-甲基-N^4,N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺(20)(160mg,0.52mmol)的二乙醚(10mL)溶液。将混合物在 0℃下搅拌 0.5h,并将所得析出物过滤,用二乙醚(3mL)洗涤并干燥,生成 6-氯-N^2-甲基-N^4,N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺盐酸盐(20a)(160mg,89 % y)。400MHz ^{1}H NMR(DMSO-d_6, ppm) :δ 9.44(1H, br s)8.96(1H, br s),7.37(1H, br s),3.78-3.12(4H, m,与水重叠),2.97(3H, s),1.71-1.56(4H, m),0.95(3H, t, J = 7.3Hz),0.89(3H, t, J = 7.3Hz). ESI-MS(m/z) :310,312[M+H]$^+$;熔点 :209-212℃。

[0590] N^2,N^2,N^6-三甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(28):

[0591] 将 6-氯-N^2-甲基-N^4,N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺(20)(310mg,1.00mmol)和二甲胺(40%水溶液,2.25mL)在 1,4-二噁烷(2.5mL)中的混合物在 105℃下在封闭瓶中加热 16h。通过蒸发去除挥发物,并将残余物在 CH_2Cl_2(35mL)和饱和 $NaHCO_3$溶液(30mL)之间分配。水相用 CH_2Cl_2(2x 35mL)萃取,并将组合的有机萃取物用水(40mL)洗涤,并在固体无水 Na_2SO_4上干燥。过滤后,去除溶剂,并利用从 PE/EtOAc(95 : 5)至 PE/EtOAc(85 : 15)的梯度洗脱通过快速柱层析纯化残留物,生成 N^2,N^2,N^6-三甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(28)(280mg,88 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 400MHz ^{1}H NMR($CDCl_3$, ppm) :6.61-6.40(2H, m),4.57(1H, br s),3.54-3.43(4H, m),3.15(6H, s),2.97(3H, d, J = 5.0Hz),1.76-1.65(4H, m),1.01(3H, t, J = 7.4Hz),1.00(3H, t, J = 7.4Hz). ESI-MS(m/z) :319[M+H]$^+$。

[0592] N^2,N^2,N^6-三甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(29a):

[0593] 将 2M HCl/二乙醚溶液(0.41mL,0.82mmol)加入 N^2,N^2,N^6-三甲基-N^4,N^8-二-正

丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(28)(264mg,0.83mmol)的甲醇(20mL)溶液。将混合物在0℃下搅拌0.5h,然后在减压下去除挥发物,生成N^2,N^2,N^6-三甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(29a)(292mg,~100% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 14.08(1H,br s),12.41(0.3H,s),8.4-7.2(1.7H,br s),6.59(1H,s),3.65-3.59(2H,m),3.56-3.48(2H,m),3.22(6H,s),3.04(2H,d,J = 4.8Hz),1.84-1.73(4H,m),1.03(3H,t,J = 7.4Hz),1.02(3H,t,J = 7.4Hz).ESI-MS(m/z):319[M+H]$^+$;熔点:241-243℃。

[0594] 实施例13:N^2,N^2-二乙基-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(30)和相应的盐酸盐(31a)(方案14)

[0595] N^2,N^2-二乙基-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(30):

[0596] 将6-氯-N^2-甲基-N^4,N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺(20)(300mg,0.97mmol)和二乙胺(500μL)在1,4-二**噁**烷(2.5mL)中的混合物在120℃下在封闭瓶中加热48h。添加另一部分二乙胺(500μL),并继续在120℃下加热48h。通过蒸发去除挥发物,并将残余物在CH_2Cl_2(35mL)和饱和$NaHCO_3$溶液(30mL)之间分配。水相用CH_2Cl_2(2x 30mL)萃取,并将组合的有机萃取物用水(40mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用CH_2Cl_2至CH_2Cl_2/EtOH(95 : 5)的梯度洗脱通过快速柱层析纯化残留物,得到N^2,N^2-二乙基-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(30)(130mg,39% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.52(1H,br s),6.45(1H,br s),4.53(1H,br s),3.67-3.57(4H,m),3.52-3.42(4H,m),2.97(3H,d,J = 4.4Hz),1.75-1.63(4H,m),1.19(6H,t,J = 7.0Hz),1.00(3H,t,J = 7.4Hz),0.99(3H,t,J = 7.4Hz).ESI-MS(m/z):347[M+H]$^+$。

[0597] N^2,N^2-二乙基-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(31a):

[0598] 利用关于化合物20a描述的程序,用2M HCl/二乙醚处理N^2,N^2-二乙基-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(30)(110mg,0.32mmol),生成N^2,N^2-二乙基-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(31a)(110mg,89% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 13.91(1H,s),7.56(1H,br s),7.51-7.43(1H,m),6.62-6.50(1H,m),3.65-3.54(6H,m),3.53-3.45(2H,m),3.04(3H,d,J = 4.8Hz),1.83-1.68(4H,m),1.18(6H,t,J = 7.0Hz),1.03(3H,t,J = 7.1Hz),1.01(3H,t,J = 7.1Hz).ESI-MS(m/z):347[M+H]$^+$;熔点:202-204℃。

[0599] 实施例14:2-(6-甲基氨基-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基-氨基)-乙醇(32)和相应的盐酸盐(33a)(方案14)

[0600] 利用关于化合物40描述的程序,使6-氯-N^2-甲基-N^4,N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺(20)(257mg,0.83mmol)和2-氨基乙醇反应,生成2-(6-甲基氨基-4,8-双-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基-氨基)-乙醇(32)(200mg,72% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.64(1H,br s),6.28(1H,br s),5.08(1H,t,J = 5.2Hz),4.86-4.37(2H,m),3.85-3.80(2H,m),3.60-3.53(2H,m),3.49-3.41(4H,m),2.96(3H,d,J = 5.2Hz),1.75-1.62(4H,m),1.01(3H,t,J = 7.4Hz),0.99(3H,t,J = 7.4Hz).ESI-MS(m/

z) :335[M+H]$^+$。

[0601] 利用关于化合物 (29a) 描述的程序，在甲醇中用 2M HCl/ 二乙醚处理 2-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基 - 氨基)- 乙醇 (32) (190mg, 0.57mmol) (210mg, ～ 100 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 15.1-13.7(1H, m), 8.00-7.31(1.5H, m), 6.95(0.5H, br s), 6.64(1H, br s), 5.5-4.7(1H, m), 3.86-3.81(2H, m), 3.70-3.45(6H, m), 3.04(3H, s), 3.0-2.5(1H, br s), 1.83-1.71(4H, m), 1.03(6H, t, J = 7.4Hz). ESI-MS(m/z) :335[M+H]$^+$;熔点 :194-196℃。

[0602] 实施例 15:N^2-(2- 甲氧基乙基)-N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (34) 和相应的盐酸盐 (35a) (方案 14)

[0603] 利用关于化合物 (9) 描述的程序，由 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) (300mg, 0.97mmol) 和 2- 甲氧基 - 乙胺在正丁醇中制备 N^2-(2- 甲氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (34) (215mg, 64% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 6.61-6.40(2H, m), 4.93(1H, s), 4.59(1H, br s), 3.63-3.53(4H, m), 3.50-3.41(4H, m), 3.39(3H, s), 2.97(3H, d, J = 5.2Hz), 1.74-1.63(4H, m), 1.00(3H, t, J = 7.4Hz), 0.99(3H, t, J = 7.4Hz). ESI-MS(m/z) : 349[M+H]$^+$。

[0604] 利用关于化合物 (29a) 描述的程序，在甲醇中用 2M HCl/ 二乙醚处理 N^2-(2- 甲氧基 - 乙基)-N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (34) (200mg, 0.57mmol) (178mg, 81 % y)。400MHz ^{1}H NMR(DMSO-d_6, ppm) : δ 9.3-8.0(1H, m), 6.94(2H, br s), 6.2-4.5(2H, br s), 3.60-3.54(2H, m), 3.51-3.41(6H, m), 3.27(3H, s), 2.92(3H, s), 1.70-1.59(4H, m), 0.93(6H, t, J = 7.4Hz). ESI-MS(m/z) :349[M+H]$^+$;熔点 :214-216℃。

[0605] 实施例 16:N^2-(2- 异丙氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (36) 和相应的盐酸盐 (37a) (方案 14)

[0606] 利用关于化合物 (40) 描述的程序，N^2-(2- 异丙氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (36) (249mg, 0.80mmol) 由 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) 和 2- 异丙基 - 乙胺制备 (165mg 55 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 6.55-6.42(2H, m), 4.97-4.89(1H, m), 4.60(1H, br s), 3.66-3.54(5H, m), 3.50-3.40(4H, m), 2.96(3H, d, J = 5.0Hz), 1.74-1.63(4H, m), 1.18(6H, d, J = 6.3Hz), 1.00(3H, t, J = 7.4Hz), 0.99(3H, t, J = 7.4Hz). ESI-MS(m/z) :377[M+H]$^+$。

[0607] 利用关于化合物 (29a) 描述的程序，在甲醇中用 2M HCl/ 二乙醚处理 N^2-(2- 异丙氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (36) (140mg, 0.37mmol) (152mg, ～ 100% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) :15.4-13.8(1H, m), 10.1-9.2(0.5H, m), 8.11-7.35(1.5H, m), 7.01-6.56(1H, m), 5.37-4.65(1H, m), 3.70-3.42(9H, m), 3.03(3H, s), 1.85-1.70(4H, m), 1.18(6H, d, J = 6.2Hz), 1.03(3H, t, J = 7.4Hz), 1.02(3H, t, J = 7.4Hz). ESI-MS(m/z) :377[M+H]$^+$;熔点 :154-156℃。

[0608] 实施例 17:N^8- 甲基 -N^4,N^6- 二 - 正丙基 -N^2-(3,3,3- 三氟丙基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (38) 和相应的盐酸盐 (39a) (方案 14)

[0609] N^8- 甲基 -N^4, N^6- 二 - 正丙基 -N^2-(3,3,3- 三氟丙基)- 嘧啶并 [5,4-d] 嘧啶 -2,

4,6,8-四胺(38):

[0610] 将6-氯-N^2-甲基-N^4,N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺(20)(300mg,0.97mmol)、3,3,3-三氟丙胺盐酸盐(435mg,2.91mmol)和N,N-二异丙基乙胺(503μL,2.91mmol)在正丁醇(1.5mL)中的混合物在140℃下在封闭瓶中加热24h。添加饱和$NaHCO_3$溶液(5mL),并将所得悬浮液用EtOAc(3x 10mL)萃取。将组合的有机萃取物用水(20mL),然后用盐水溶液(10mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用从PE/EtOAc(5 : 1)至PE/EtOAc(3 : 1)的梯度洗脱通过快速柱层析纯化残留物,得到N^8-甲基-N^4,N^6-二-正丙基-N^2-(3,3,3-三氟丙基)-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(38)(300mg,80% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.58(1H,br s),6.45(1H,br s),4.79(1H,s),4.63(1H,br s),3.66(2H,dt,J=7.4,6.4Hz),3.49-3.43(4H,m),2.98(3H,d,J=5.2Hz),2.55-2.43(2H,m),1.70(2H,六重峰,J=7.4Hz),1.69(2H,六重峰,J=7.4Hz),1.01(6H,t,J=7.4Hz).ESI-MS(m/z):387[M+H]$^+$。

[0611] N^8-甲基-N^4,N^6-二-正丙基-N^2-(3,3,3-三氟丙基)-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(39a):

[0612] 利用关于化合物(20a)描述的程序,在二乙醚/乙醇(15/1)中用2M HCl/二乙醚处理N^8-甲基-N^4,N^6-二-正丙基-N^2-(3,3,3-三氟丙基)-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(38)(290mg,0.75mmol),生成N^8-甲基-N^4,N^6-二-正丙基-N^2-(3,3,3-三氟丙基)-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(39a)(293mg,92% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 9.75(1H,br s),9.50(1H,br s),6.87(1H,br s),6.62(1H,s),3.79(2H,dt,J=7.4,6.7Hz),3.68-3.59(4H,m),3.08(3H,d,J=4.8Hz),2.54-2.41(2H,m),1.89-1.78(4H,m),1.06(3H,t,J=7.4Hz),1.05(3H,t,J=7.4Hz).ESI-MS(m/z):387[M+H]$^+$;熔点:259-260℃。

[0613] 实施例18:N^2-甲基-N^4,N^8-二-正丙基-6-(吗啉-4-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(40)和相应的盐酸盐(41a)(方案14)

[0614] N^2-甲基-N^4,N^8-二-正丙基-6-(吗啉-4-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(40):

[0615] 将6-氯-N^2-甲基-N^4,N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺(20)(250mg,0.81mmol)和吗啉(2.0mL)的混合物在105℃下在封闭瓶中加热16h。添加饱和$NaHCO_3$溶液(15mL),并将所得悬浮液用EtOAc(3x 25mL)萃取。将组合的有机萃取物用水(2x 15mL),然后用盐水溶液(20mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用CH_2Cl_2至CH_2Cl_2/EtOH(98 : 2)的梯度洗脱通过快速柱层析纯化残留物,得到N^2-甲基-N^4,N^8-二-正丙基-6-(吗啉-4-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(40)(265mg,91% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.65-6.37(2H,m),4.65(1H,br s),3.83-3.67(8H,m),3.54-3.40(4H,m),2.97(3H,s),1.76-1.63(4H,m),1.00(3H,t,J=7.4Hz),0.99(3H,t,J=7.4Hz).ESI-MS(m/z):361[M+H]$^+$。

[0616] N^2-甲基-N^4,N^8-二-正丙基-6-(吗啉-4-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(41a):

[0617] 利用关于化合物(20a)描述的程序,在甲醇中用2M HCl/二乙醚处理N^2-甲基-N^4,N^8-二-正丙基-6-(吗啉-4-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(40)(250mg,

0.69mmol)(226mg,82 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 14.07(1H, br s),7.72(1H, s),7.48-7.39(1H, m),6.66-6.54(1H, m),3.82-3.71(8H, m),3.61(2H, q, J = 7.8Hz),3.53-3.45(2H, m),3.05(3H, d, J = 4.8Hz),1.82-1.70(4H, m),1.03(3H, t, J = 7.4Hz),1.02(3H, t, J = 7.4Hz).ESI-MS(m/z):361[M+H]$^+$;熔点:240-242℃。

[0618] 实施例 19:N^2-甲基-N^4, N^8-二-正丙基-6-(哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(42)和相应的盐酸盐(43a)(方案 14)

[0619] 利用关于化合物(40)描述的程序,由 6-氯-N^2-甲基-N^4, N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺(20)(250mg,0.81mmol)和哌啶制备 N^2-甲基-N^4, N^8-二-正丙基-6-(哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(240mg,83% y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 6.49(2H, br s),4.59(1H, br s),3.83-3.65(4H, m),3.59-3.38(4H, m),2.96(3H, s),1.75-1.64(4H, m),1.64-1.54(6H, m),1.00(3H, t, J = 7.4Hz),0.99(3H, t, J = 7.4Hz).ESI-MS(m/z):359[M+H]$^+$。

[0620] 利用关于化合物(29a)描述的程序,在甲醇中用 2M HCl/二乙醚处理 N^2-甲基-N^4, N^8-二-正丙基-6-(哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(42)(220mg,0.61mmol)(242mg,~100% y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 14.8-13.8(1.2H, m),12.51(0.8H, br s),6.65-6.54(1H, m),4.06-3.72(4H, m),3.66-3.58(2H, m),3.57-3.48(2H, m),3.05(3H, d, J = 4.8Hz),1.80(4H,六重峰, J = 7.4Hz),1.73-1.62(6H, m),1.03(3H, t, J = 7.4Hz),1.02(3H, t, J = 7.4Hz).ESI-MS(m/z):359[M+H]$^+$;熔点:220-222℃。

[0621] 实施例 20:N^2-甲基-N^4, N^8-二-正丙基-6-吡咯烷-1-基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(44)和相应的二盐酸盐(45a)(方案 14)

[0622] 利用关于化合物(40)描述的程序,使 6-氯-N^2-甲基-N^4, N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺(20)(160mg,0.52mmol)和吡咯烷反应(135mg,76% y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 6.76-6.32(2H, m),4.58(1H, br s),3.74-3.34(8H, m),2.97(3H, s),1.98-1.90(4H, m),1.76-1.64(4H, m),1.00(6H, t, J = 7.4Hz).ESI-MS(m/z):345[M+H]$^+$。

[0623] 利用关于化合物(20a)描述的程序,在甲醇中用 2M HCl/二乙醚处理 N^2-甲基-N^4, N^8-二-正丙基-6-吡咯烷-1-基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(44)(125mg,0.36mmol)(76mg,50 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 14.66(1H, s),12.34(1H, s),11.72(1H, br s),9.39(1H, br s),6.69-6.58(1H, m),4.26-3.95(2H, m),3.83-3.51(6H, m),3.06(3H, d, J = 4.7Hz),2.21-1.92(4H, m),1.91-1.75(4H, m),1.07-0.99(6H, m).ESI-MS(m/z):345[M+H]$^+$;熔点:243-245℃。

[0624] 实施例 21:N^2-甲基-N^4, N^8-二-正丙基-6-(4-甲氧基-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(46)和相应的盐酸盐(47a)(方案 14)

[0625] 利用关于化合物 40 描述的程序,使 6-氯-N^2-甲基-N^4, N^8-二-正丙基嘧啶并[5,4-d]嘧啶-2,4,8-三胺(20)(260mg,0.84mmol)和 4-甲氧基哌啶反应,生成 N^2-甲基-N^4, N^8-二-正丙基-6-(4-甲氧基-哌啶-1-基)-嘧啶并[5,4, -d]嘧啶-2,4,8-三胺(46)(270mg,83 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 6.49(2H, s),4.62(1H, br s),4.42-4.30(2H, m),3.54-3.35(5H, m),3.39(3H, s),3.29-3.17(2H, m),2.98(3H, d, J = 4.4Hz),2.01-1.91(2H, m),1.76-1.63(4H, m),1.62-1.50(2H, m),1.00(3H, t, J = 7.4Hz),

0.99(3H, t, J = 7.4Hz). ESI-MS(m/z) :389[M+H]$^+$。

[0626] 利用关于化合物 (20a) 描述的程序,在甲醇中用 2M HCl/ 二乙醚处理 N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 甲氧基 - 哌啶 -1- 基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (46) (240mg,0.62mmol) (262mg,~ 100% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 13.99(1H, br s), 7.66(1H, br s), 7.47(1H, br s), 6.63-6.56(1H, m), 4.28-4.16(2H, m), 3.64-3.57(2H, m), 3.53-3.32(5H, m), 3.39(3H, s), 3.04(3H, d, J = 5.0Hz), 1.98-1.89(2H, m), 1.82-1.70(4H, m), 1.64-1.52(2H, m), 1.05-0.98(6H, m). ESI-MS(m/z) :389[M+H]$^+$;熔点 :221-223℃。

[0627] 实施例 22:N^2-(3- 氯 -2- 甲基 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (48) 和相应的盐酸盐 (49a)(方案 14)

[0628] N^2-(3- 氯 -2- 甲基 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (48) :

[0629] 将 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) (250mg,0.81mmol) 和 3- 氯 -2- 甲基 - 苄胺 (315mg,2.02mmol) 在正丁醇 (2.0mL) 中的混合物在 145℃下在封闭瓶中加热 23h。冷却反应混合物,并添加饱和 $NaHCO_3$ 溶液 (20mL)。将所得悬浮液用 CH_2Cl_2 (3x 15mL) 萃取。将组合的有机萃取物用水 (20mL) 洗涤,并在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 CH_2Cl_2 至 CH_2Cl_2/EtOH(98 : 2) 的梯度洗脱通过快速柱层析纯化残留物,得到 N^2-(3- 氯 -2- 甲基 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (48) (200mg,58%)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 7.33-7.24(2H, m), 7.07(1H, dd, J = 7.8,7.8Hz), 6.60-6.48(1H, m), 6.47-6.34(1H, m), 4.87-4.74(1H, m), 4.65-4.54(1H, m), 4.59(2H, d, J = 5.7Hz), 3.49-3.39(4H, m), 2.97(3H, d, J = 5.1Hz), 2.43(3H, s), 1.67(2H, 六重峰, J = 7.3Hz), 1.66(2H, 六重峰, J = 7.3Hz), 0.98(3H, t, J = 7.3Hz), 0.98(3H, t, J = 7.3Hz). ESI-MS(m/z) :429,431[M+H]$^+$。

[0630] N^2-(3- 氯 -2- 甲基 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (49a) :

[0631] 利用关于化合物 (29a) 描述的程序,用 2M HCl/ 二乙醚处理 N^2-(3- 氯 -2- 甲基 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (30) (140mg,0.33mmol),生成 N^2-(3- 氯 -2- 甲基 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (49a) (140mg,91% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 15.5-14.8(0.4H, m), 14.39-13.95(0.6H, m), 9.8-9.4(0.4H, m), 7.86-7.36(1H, m), 7.31(1H, d, J = 7.8Hz), 7.23-7.17(1H, m), 7.2-7.0(0.6H, m), 7.09(1H, dd, J = 7.8, 7.8Hz), 6.72-6.49(1H, m), 5.16-4.79(1H, m), 4.77-4.47(2H, m), 3.70-3.37(4H, m), 3.13-2.89(3H, m), 2.42(3H, s), 1.89-1.61(4H, m), 1.08-0.94(6H, m). ESI-MS(m/z) :429, 431[M+H]$^+$;熔点 :193-196℃。

[0632] 实施例 23:N^2-(3,4- 二氯苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (50) 和相应的盐酸盐 (51a)(方案 14)

[0633] 利用关于化合物 (48) 描述的程序,使 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) (250mg,0.81mmol) 和 3,4- 二氯苄胺在 DMSO 中反应,生成 N^2-(3,4- 二氯 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (50) (260mg,71% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 7.49(1H, d, J = 2.0Hz), 7.36(1H, d, J

= 8.2Hz), 7.21(1H, dd, J = 8.2, 2.0Hz), 6.58(1H, s), 6.38(1H, s), 5.08(1H, s), 4.67(1H, s), 4.54(2H, d, J = 6.0Hz), 3.46-3.40(4H, m), 2.96(3H, d, J = 5.1Hz), 1.71-1.61(4H, m), 0.98(3H, t, J = 7.4Hz), 0.97(3H, t, J = 7.4Hz). ESI-MS(m/z) :449, 451, 453[M+H]$^+$。

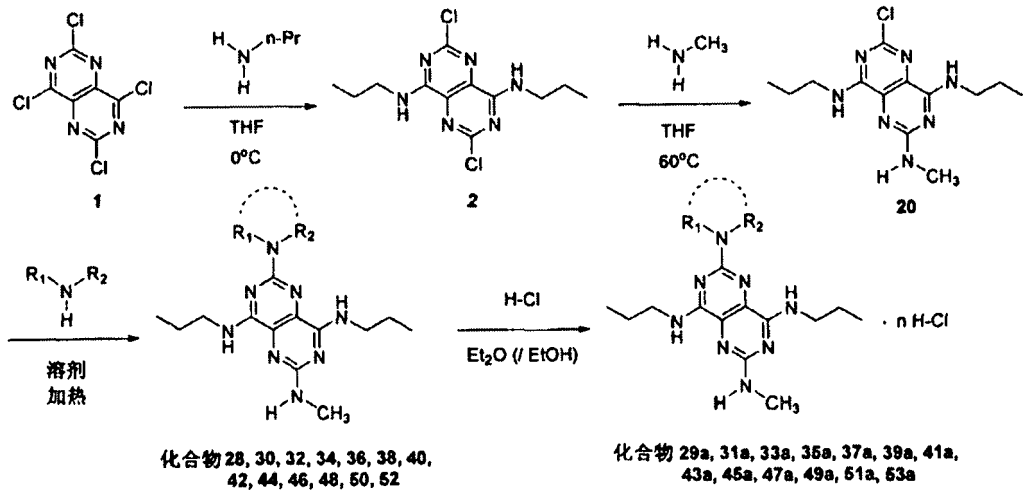
[0634] 利用关于化合物 (20a) 描述的程序，在二乙醚中用 2M HCl/ 二乙醚处理 N^2-(3, 4- 二氯 - 苄基)-N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (50) (240mg, 0.53mmol)。产物从乙醇结晶，得到 N^2-(3,4- 二氯 - 苄基)-N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (51a) (200mg, 78 % y)。400MHz ^{1}H NMR(DMSO-d_6, ppm) : δ 13.5-12.3(1H, m), 8.87(1H, br s), 8.5-7.9(1H, br s), 7.9-6.6(3H, m), 7.68(1H, s), 7.58(1H, d, J = 8.2Hz), 4.57(2H, s), 3.62-3.36(4H, m, 与水重叠), 2.96(3H, s), 1.75-1.41(4H, m), 1.00-0.75(6H, m). ESI-MS(m/z) :449, 451, 453[M+H]$^+$; 熔点 :176-179℃。

[0635] 实施例 24:N^2-(4- 氟苄基)-N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (52) 和相应的盐酸盐 (53a) (方案 14)

[0636] 利用关于化合物 (48) 描述的程序，使 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) (360mg, 1.16mmol) 和 4- 氟苄胺在正丁醇中反应，生成 N^2-(4- 氟 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (52) (169mg, 37% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) :7.39-7.30(2H, m), 7.06-6.93(2H, m), 6.56(1H, br s), 6.43(1H, br s), 4.95(1H, br s), 4.72-4.48(3H, m), 3.50-3.37(4H, m), 2.97(3H, d, J = 5.2Hz), 1.67(4H, 六重峰, J = 7.5Hz), 0.98(6H, t, J = 7.5Hz). ESI-MS(m/z) :399[M+H]$^+$。

[0637] 利用关于 (20a) 描述的程序，N^2-(4- 氟 - 苄基)-N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4,-d] 嘧啶 -2,4,8- 三胺 (52) (160mg, 0.40mmol) 和 2M HCl/ 二乙醚在甲醇中反应 (145mg, 83% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 15.32-14.86(1.5H, m), 9.79-9.43(1.5H, m), 7.35-7.21(2H, m), 7.13(1H, br s), 7.07-6.98(2H, m), 6.61(1H, s), 4.62(2H, s), 3.69-3.49(4H, m), 3.07(3H, s), 1.89-1.69(4H, m), 1.09-0.96(6H, m). ESI-MS(m/z) : 399[M+H]$^+$;熔点 :187-189℃。

[0638]



1 2 20

化合物 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52

化合物 29a, 31a, 33a, 35a, 37a, 39a, 41a, 43a, 45a, 47a, 49a, 51a, 53a

方案 14

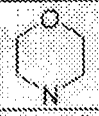
[0639] 表 1. 2- 取代 N^4, N^8- 二 - 正丙基 -N^6- 甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四

胺和相应的盐酸盐

[0640]

化合物#	R_1-N-R_2 / H-Cl
28 / 29a	CH_3-N-CH_3
30 / 31a	CH_3-CH_2-N-CH_2-CH_3
32 / 33a	H-N-CH_2-CH_3-OH
34 / 35a	H-N-CH_2-CH_3-O-CH_3
36 / 37a	H-N-CH_2-CH_3-O-$CH(CH_3)_2$
38 / 39a	H-N-CH_2-CH_2-CF_3

[0641]

40 / 41a	
42 / 43 a	
44 / 45a	
46 / 47a	
48 / 49a	
50 / 51a	
52 / 53a	

[0642] 实施例 25:N^2,N^2,N^4,N^8- 四甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (55) 和盐酸盐 (56a) (方案 15)

[0643] 2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25) :

[0644] 将 2M 甲胺 /THF(2.10mL,4.2mmol) 在 0℃下加入 2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶 (1) (250mg,0.93mmol) 的 THF(5mL) 溶液。将反应混合物在室温下搅拌 1h。然后加水 (10mL),并将所得析出物过滤,用水 (10mL) 洗涤,最后在 P_2O_5 上干燥,得到 2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25) (230mg,95% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 6.90(2H, br s),3.16(6H, d, J = 5.0Hz). ESI-MS(m/z) :259,261,263$[M+H]^+$。

[0645] 6- 氯 -N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54) :

[0646] 将 2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25) (325mg, 3.17mmol) 和正丙胺 (206μL,2.5mmol) 在正丁醇 (5mL) 中的混合物在 90℃下在封闭瓶中加热 8h。通过蒸发去除挥发物,并将残余物在 EtOAc(20mL) 和饱和 $NaHCO_3$ 溶液 (20mL) 之间分配。分离水相,然后用 EtOAc(2x 15mL) 萃取。将组合的有机萃取物用水 (30mL),然后用盐水溶液 (30mL) 洗涤,最后在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 PE/

EtOAc(5 ： 1) 作为洗脱剂通过二氧化硅凝胶垫过滤残留物，得到 6- 氯 -N^2- 正丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54) (320mg,91％ y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 6.72(1H, br s),6.49(1H, br s),4.97(1H, t, J = 5.4Hz),3.42-3.35(2H, m), 3.14(3H, d, J = 5.2Hz),3.04(3H, d, J = 5.0Hz),1.69-1.59(2H, m),0.99(3H, t, J = 7.4Hz). ESI-MS(m/z) ：282,284$[M+H]^+$。

[0647] N^2, N^2, N^4, N^8- 四甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (55) ：

[0648] 将 6- 氯 -N^2- 正丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54) (300mg,1.06mmol) 和二甲胺 (40％水溶液,5.0mL) 在正丁醇 (5.0mL) 中的混合物在 135℃下在封闭瓶中加热 36h。通过蒸发去除挥发物，并将残余物在 CH_2Cl_2(35mL) 和饱和 $NaHCO_3$ 溶液 (30mL) 之间分配。分离水相并用 CH_2Cl_2(2x 35mL) 萃取。将组合的有机萃取物用水 (40mL) 洗涤，并在固体无水 Na_2SO_4 上干燥。过滤后，去除溶剂，并利用 PE/EtOAc(99 ： 1) 至 PE/EtOAc(1 ： 99) 的梯度洗脱通过快速柱层析纯化残留物，得到 N^2, N^2, N^4, N^8- 四甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (55) (245mg,80％ y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 6.48(1H,s),6.40(1H,s),4.64(1H,s),3.39-3.32(2H,m),3.16(6H,s),3.08(3H,d, J＝5.3Hz),3.06(3H,d,J＝5.3Hz),1.63(2H,六重峰,J＝7.4Hz),0.99(3H,t,J＝7.4Hz). ESI-MS(m/z) ：291$[M+H]^+$。

[0649] N^2, N^2, N^4, N^8- 四甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (56a) ：

[0650] 利用关于化合物 (20a) 描述的程序，在二乙醚 / 乙醇 (1/2) 中用 2M HCl/ 二乙醚处理 N^2, N^2, N^4, N^8- 四甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (55) (240mg,0.83mmol) (216mg,80％ y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 13.87(1H,s),7.62(1H, s),7.46(1H, s),6.64(1H, s),3.49-3.42(2H, m),3.20(3H, d, J = 5.2Hz),3.15(6H, s), 3.08(3H,d, J = 4.6Hz),1.66(2H,六重峰, J = 7.2Hz),0.98(3H,t, J = 7.2Hz). ESI-MS(m/z) ：291$[M+H]^+$；熔点 ：285℃ (dec.)。

[0651] 实施例 26：N^2, N^2- 二烯丙基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (57) 和盐酸盐 (58a)(方案 15)

[0652] 将 6- 氯 -N^2- 正丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54) (225mg,0.80mmol) 和二烯丙胺 (2.0mL) 的混合物在 120℃下在封闭瓶中加热 144h。添加饱和 $NaHCO_3$ 溶液 (15mL)，并将所得悬浮液用 EtOAc(3x 25mL) 萃取。将组合的有机萃取物用水 (2x 15mL)，然后用盐水溶液 (20mL) 洗涤，并在固体无水 Na_2SO_4 上干燥。过滤后，去除溶剂，并利用 PE/EtOAc(10 ： 1) 至 PE/EtOAc(1 ： 1) 的梯度洗脱通过快速柱层析纯化残留物，得到 N^2, N^2- 二烯丙基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (57) (170mg,62％ y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 6.50-6.30(2H,m),5.90(2H,ddt,J＝17.2, 10.2,5.8Hz),5.16(2H, ddt, J = 17.2,1.6,1.6Hz),5.11(2H, ddt, J = 10.2,1.6,1.6Hz), 4.62(1H,br s),4.26-4.22(4H,m),3.39-3.32(2H,m),3.07(3H,d,J = 5.0Hz),3.06(3H,d, J = 5.0Hz),1.68-1.57(2H,m)0.99(3H, t, J = 7.4Hz). ESI-MS(m/z) ：343$[M+H]^+$。

[0653] 利用关于化合物 (20a) 描述的程序，在 1,4- 二噁烷中用 2M HCl/ 二乙醚处理 N^2, N^2- 二烯丙基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (57) (150mg 0.44mmol) (130mg,78 ％ y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 13.91(1H, s),7.68(1H, s),

7.39(1H,s),6.65(1H,t,J = 5.3Hz),5.92-5.78(2H,m),5.18-5.14(2H,m),5.14-5.11(2H,m),4.20(4H,d,J = 5.6Hz),3.47(2H,q,J = 6.7Hz),3.19(3H,d,J = 5.3Hz),3.07(3H,d,J = 4.6Hz),1.71-1.60(2H,m),0.98(3H,t,J = 7.4Hz).ESI-MS(m/z) :343[M+H]$^+$;熔点:199-201℃。

[0654] 实施例27:2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-甲基-氨基]-乙醇(59)和相应的盐酸盐(60a)(方案15)

[0655] 将6-氯-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(54)(300mg,1.06mmol)和(2-羟基乙基)-甲胺(510μL,6.36mmol)在正丁醇(5.0mL)中的混合物在115℃下在封闭瓶中加热48h。冷却反应混合物,并添加饱和$NaHCO_3$溶液(20mL)。将所得悬浮液用CH_2Cl_2(3x 15mL)萃取。将组合的有机萃取物用水(20mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用PE/EtOAc(5 : 1)至PE/EtOAc(1 : 1)的梯度洗脱通过快速柱层析纯化残留物,得到2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-甲基-氨基]-乙醇(59)(300mg,88% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ6.52(1H,br s),6.30(1H,br s),5.15-4.82(1H,br s),4.66(1H,s),3.95-3.84(2H,m),3.81-3.70(2H,m),3.44-3.30(2H,m),3.21(3H,s),3.08(6H,s),1.69-1.57(2H,m),0.99(3H,t,J = 7.4Hz).ESI-MS(m/z) :321[M+H]$^+$。

[0656] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中用2M HCl/二乙醚处理2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-甲基-氨基]-乙醇(59)(300mg,0.94mmol)(270mg,81 % y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ13.83(1H,s),7.83(1H,s),7.44(1H,s),6.72-6.60(1H,m),3.92-3.85(2H,m),3.84-3.77(2H,m),3.50-3.40(2H,m),3.26(1H,s),3.22-3.17(6H,m),3.06(3H,d,J = 4.7Hz),1.71-1.60(2H,m),0.98(3H,t,J = 7.4Hz).ESI-MS(m/z) :321[M+H]$^+$;熔点:246-248℃。

[0657] 实施例28:N^2-(2-异丙氧基-乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(61)和相应的盐酸盐(62a)(方案15)

[0658] 根据关于化合物(59)描述的程序,将6-氯-N^2-正丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(54)(300mg,1.06mmol)和2-异丙氧基-乙胺加热144h,生成N^2-(2-异丙氧基-乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(61)(210mg,57% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ6.43(2H,br s),5.01-4.91(1H,m),4.64(1H,s),3.67-3.54(5H,m),3.39-3.32(2H,m),3.07(3H,d,J = 4.5Hz),3.05(3H,d,J = 4.5Hz),1.68-1.58(2H,m),1.18(6H,d,J = 6.1Hz),0.99(3H,t,J = 7.4Hz).ESI-MS(m/z) :349[M+H]$^+$。

[0659] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中用2M HCl/二乙醚处理N2-(2-异丙氧基-乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(61)(190mg,0.55mmol)(190mg,89 % y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ8.5-7.2(2H,m),7.0-6.3(2H,m),5.23(1H,br s),3.61-3.56(4H,m),3.62(1H,septet,J = 6.1Hz),3.50-3.37(2H,m),3.25-3.04(6H,m),1.72-1.60(2H,m),1.19(6H,d,J = 6.1Hz),0.99(3H,t,J = 7.4Hz).ESI-MS(m/z) :349[M+H]$^+$;熔点:150-152℃。

[0660] 实施例29:2-[N-(2-二甲基氨基-乙基)-N-甲基]氨基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-4,6,8-三胺(63)和相应的盐酸盐(64a)(方案15)

[0661] 根据关于化合物 (60) 描述的程序，使 6- 氯 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54) (300mg,1.06mmol) 与 N,N,N'- 三甲基 - 乙 -1,2- 二胺通过加热 78h 反应，生成 2-[N-(2- 二甲基氨基 - 乙基)-N- 甲基] 氨基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,6,8- 三胺 (63) (310mg,84% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 6.60(1H, s),6.45(1H, s),4.76(1H, s),3.82-3.76(2H, m),3.39-3.32(2H, m),3.16(3H, s),3.07(3H, d, J = 5.0Hz),3.06(3H, d, J = 5.0Hz),2.56-2.54(2H, m),2.34(6H, s),1.68-1.58(2H, m),0.99(3H, t, J = 7.4Hz). ESI-MS(m/z) :348$[M+H]^+$。

[0662] 利用关于化合物 (29a) 描述的程序，在二乙醚 / 乙醇 (1/1) 中用 2M HCl/ 二乙醚处理 2-[N-(2- 二甲基氨基 - 乙基)-N- 甲基] 氨基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,6,8- 三胺 (63) (292mg,0.84mmol) (322mg, ~ 100% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 8.3-7.6(1H, br s),7.17(1H, s),5.75(1H, s),4.06-3.97(2H, m),3.45-3.38(2H, m),3.17(3H, s),3.14(3H, d, J = 4.9Hz),3.07(3H, d, J = 4.9Hz),2.95-2.86(2H, m),2.60(6H, s),1.69-1.59(2H, m),0.98(3H, t, J = 7.4Hz). ESI-MS(m/z) :348$[M+H]^+$。

[0663] 实施例 30 :2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-(2- 羟基 - 乙基)- 氨基]- 乙醇 (65) 和相应的盐酸盐 (66a) (方案 15)

[0664] 2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-(2- 羟基 - 乙基)- 氨基]- 乙醇 (65) :

[0665] 将 6- 氯 -N^2- 正丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54) (275mg,0.98mmol) 和 2-(2- 羟基乙基氨基)- 乙醇 (385 μL,3.88mmol) 在正丁醇 (5.0mL) 中的混合物在 135℃下在封闭瓶中加热 100h。通过蒸发去除挥发物，并将残余物在 CH_2Cl_2(35mL) 和饱和 $NaHCO_3$ 溶液 (30mL) 之间分配。分离水相，并用 CH_2Cl_2(2x 30mL) 萃取。将组合的有机萃取物用水 (20mL) 洗涤，并在固体无水 Na_2SO_4 上干燥。过滤后，去除溶剂，并利用 PE/EtOAc(99 : 1) 至 PE/EtOAc(1 : 99) 的梯度洗脱通过快速柱层析纯化残留物，得到 2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-(2- 羟基 - 乙基)- 氨基]- 乙醇 (65) (217mg,63% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 6.71-6.64(1H,m),6.12-6.06(1H,m),5.03-4.86(2H,m),4.75-4.66(1H,m),3.92-3.87(4H,m),3.82-3.76(4H,m),3.38-3.31(2H,m),3.07(3H, d, J = 5.2Hz),3.05(3H, d, J = 5.1Hz),1.62(2H, 六重峰, J = 7.4Hz),0.98(3H, t, J = 7.4Hz). ESI-MS(m/z) :351$[M+H]^+$。

[0666] 2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-(2- 羟基 - 乙基)- 氨基]- 乙醇盐酸盐 (66a) :

[0667] 利用关于化合物 (20a) 描述的程序，在二乙醚 / 乙醇 (1/1) 中用 2M HCl/ 二乙醚处理 2-[(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-(2- 羟基 - 乙基)- 氨基]- 乙醇 (65) (206mg,0.59mmol) (215mg,95 % y)。400MHz ^{1}H NMR(D_2O, ppm) : δ 3.85-3.79(4H, m),3.76-3.71(4H, m),3.41-3.35(2H, m),3.08(3H, s),2.99(3H, s),1.65(2H, 六重峰, J = 7.4Hz),0.97(3H, t, J = 7.4Hz). ESI-MS(m/z) :351$[M+H]^+$; 熔点 : 220-222℃。

[0668] 实施例 31:N^2, N^2- 双 -(2- 甲氧基乙基)-N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (67) 和相应的盐酸盐 (68a) (方案 15)

[0669] 根据关于化合物 (60) 描述的程序，使 6- 氯 -N^2- 正丙基 -N^4, N^8- 二甲基 - 嘧啶并

[5,4-d] 嘧啶 -2,4,8- 三胺 (54) (275mg,0.97mmol) 与双 -(2- 甲氧基乙基)- 胺通过加热 78h 反应,生成 N^2,N^2- 双 -(2- 甲氧基乙基)-N^4,N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (67) (220mg,60% y)。400MHz ^{1}H NMR($CDCl_3$,ppm) :δ 6.46-6.31(2H,m),4.69-4.57(1H,m),3.86-3.80(4H,m),3.62(4H,t,J = 6.3Hz),3.39-3.32(2H,m),3.38(6H,s),3.09-3.03(6H,m),1.63(2H,六重峰,J = 7.4Hz),0.99(3H,t,J = 7.4Hz). ESI-MS(m/z) :379$[M+H]^+$。

[0670] 利用关于化合物 (20a) 描述的程序,在二乙醚中用 2M HCl/ 二乙醚处理 N^2,N^2- 双 -(2- 甲氧基乙基)-N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (67) (205mg,0.65mmol) (210mg,94% y)。400MHz ^{1}H NMR($CDCl_3$,ppm) :δ 6.66-6.60(1H,m),3.91-3.82(4H,m),3.59(4H,t,J = 6.0Hz),3.49-3.43(2H,m),3.35(6H,s),3.19(3H,d,J = 5.2Hz),3.07(3H,d,J = 4.7Hz),1.66(2H,六重峰,J = 7.4Hz),0.98(3H,t,J = 7.4). ESI-MS(m/z) :379$[M+H]^+$;熔点 :196-198℃。

[0671] 实施例 32:6-(4- 氧 - 哌啶 -1- 基)-N^4,N^8- 二甲基 -N^2- 正丙基氨基 - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺 (70) 和相应的盐酸盐 (71a)(方案 15)

[0672] 6-(1,4- 二氧杂 -8- 氮杂 - 螺 [4.5] 癸 -8- 基)-N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d]嘧啶 -2,4,8- 三胺 (69) :

[0673] 将正丁醇 (5.0mL) 中的 6- 氯 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54) (230mg,0.82mmol) 和 4- 哌啶酮亚乙基缩酮 (314 μL,2.45mmol) 在 120℃下在封闭瓶中加热 24h。冷却反应混合物,并添加饱和 $NaHCO_3$溶液 (20mL)。将所得悬浮液用 EtOAc(3x 15mL) 萃取。将组合的有机萃取物用水 (40mL),然后用盐水溶液 (30mL) 洗涤,并在固体无水 Na_2SO_4上干燥。过滤后,去除溶剂,并利用 CH_2Cl_2至 CH_2Cl_2/EtOAc(3 : 2) 的梯度洗脱通过快速柱层析纯化残留物,得到 6-(1,4- 二氧杂 -8- 氮杂 - 螺 [4.5] 癸 -8- 基)-N^4,N^8- 二甲基 -N^2- 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (69) (309mg,97% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 6.50-6.35(2H, m),4.66(1H, br s),4.00(4H, s),3.93-3.89(4H, m),3.36(2H, td, J = 7.2,6.1Hz),3.07(3H, d, J = 5.1Hz),3.06(3H, d, J = 5.3Hz),1.77-1.72(4H, m),1.67-1.57(2H, m),0.99(3H, t, J = 7.4Hz). ESI-MS(m/z) :389$[M+H]^+$。

[0674] 6-(4- 氧 - 哌啶 -1- 基)-N^4, N^8- 二甲基 -N^2- 正丙基氨基 - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺 (70) :

[0675] 将 6-(1,4- 二氧杂 -8- 氮杂 - 螺 [4.5] 癸 -8- 基)-N^4,N^8- 二甲基 -N^2- 丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (69) (300mg,0.77mmol) 和 4N HCl(6mL) 在 THF(5mL) 中的混合物在室温下搅拌 20h。通过添加饱和 $NaHCO_3$溶液,将溶液的 pH 调节至 9。将所得悬浮液用 EtOAc(3x 15mL) 萃取。将组合的有机萃取物用水 (40mL),然后用盐水溶液 (30mL) 洗涤,并在固体无水 Na_2SO_4上干燥。过滤后,去除溶剂,并利用 $CHCl_3$至 $CHCl_3$/EtOAc(9 : 1) 的梯度洗脱通过快速柱层析纯化残留物,得到 6-(4- 氧 - 哌啶 -1- 基)-N^4,N^8- 二甲基 -N^2- 正丙基氨基 - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺 (70) (213mg,80% y)。400MHz ^{1}H NMR($CDCl_3$,ppm) :δ 6.49(1H,s),6.41(1H,s),4.70(1H,s),4.15-4.08(4H,m),3.41-3.33(2H,m),3.10(3H,d,J = 5.1Hz),3.08(3H,d,J = 5.2Hz),2.49(4H,t,J = 6.1Hz),1.64(2H,六重峰,J = 7.4Hz),1.00(3H, t, J = 7.4Hz). ESI-MS(m/z) :345$[M+H]^+$。

[0676] 6-(4-氧-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺盐酸盐(71a):

[0677] 利用关于化合物(20a)描述的程序,在二乙醚中用2M HCl/二乙醚处理6-(4-氧-哌啶-1-基)-N^4,N^8-二甲基-N^2-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺(70)(213mg,0.62mmol)(210mg,89%y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 14.08(1H,s),7.87(1H,s),7.41(1H,s),6.75-6.62(1H,m),4.15-4.07(4H,m),3.53-3.42(2H,m),3.22(3H,d,J=5.1Hz),3.09(3H,d,J=4.5Hz),2.51(4H,t,J=6.1Hz),1.67(2H,六重峰,J=7.4Hz),0.99(3H,t,J=7.4Hz).ESI-MS(m/z):345$[M+H]^+$;熔点:267℃(dec.)。

[0678] 实施例33:N^2-(3-三氟甲基-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(72)和相应的盐酸盐(73a)(方案15)

[0679] 根据关于化合物(69)描述的程序,使6-氯-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(54)(221mg,0.78mmol)与3-三氟甲基-哌啶(311μL,2.34mmol)反应,生成N^2-(3-三氟甲基-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(72)(285mg,91%y)。400MHz ^{1}H NMR($CDCl_3$,ppm):6.52-6.32(2H,m),5.02-4.94(1H,m),4.82-4.74(1H,m),4.67(1H,br s),3.41-3.31(2H,m),3.08(3H,d,J=5.0Hz),3.07(3H,d,J=5.1Hz),2.84-2.71(2H,m),2.39-2.24(1H,m),2.13-2.01(1H,m),1.85-1.74(1H,m),1.70-1.47(4H,m),0.99(3H,t,J=7.4Hz).ESI-MS(m/z):399$[M+H]^+$。

[0680] 利用关于化合物(20a)描述的程序,在二乙醚中用2M HCl/二乙醚处理N^2-(3-三氟甲基-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(72)(283mg,0.71mmol)(215mg,70%y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 14.21(1H,s),13.2-12.6(0.5H,br s),8.6-8.0(1.5H,br s),6.73-6.55(1H,m),4.91-4.83(1H,m),4.83-4.71(1H,m),3.52-3.42(2H,m),3.20(3H,d,J=5.1Hz),3.11(3H,d,J=4.6Hz),3.08-2.92(2H,m),2.38-2.22(1H,m),2.15-2.04(1H,m),1.94-1.83(1H,m),1.73-1.47(4H,m),0.99(3H,t,J=7.4Hz).ESI-MS(m/z):399$[M+H]^+$;熔点:270℃(dec.)。

[0681] 实施例34:N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺(74)和相应的盐酸盐(75a)(方案15)

[0682] N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺(74):

[0683] 将6-氯-N^2-正丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(54)(282mg,1.00mmol)和1,1-二氧化硫代吗啉(406mg,3.00mmol)在正丁醇(5.0mL)中的混合物在130℃下在封闭瓶中加热48h。冷却反应混合物,并添加饱和$NaHCO_3$溶液(20mL)。将所得悬浮液用EtOAc(3x 15mL)萃取。将组合的有机萃取物用水(30mL),然后用盐水溶液(30mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用$CHCl_3$作为洗脱剂通过快速柱层析纯化残留物,得到N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺(74)(378mg,99%)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.55(1H,s),6.31(1H,s),4.80-4.67(1H,m),4.43-4.24(4H,m),3.41-3.32(2H,m),3.07(6H,d,J=5.1Hz),3.10-3.02(4H,m),1.69-1.55(2H,m),0.99(3H,t,J=7.4Hz).ESI-MS(m/z):381$[M+H]^+$。

[0684] N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺盐酸盐(75a):

[0685] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中用2M HCl/二乙醚处理N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺(375mg,0.97mmol)(198mg,48% y)。400MHz ^{1}H NMR($CDCl_3$/TFA,ppm):δ 9.79(1H,s),9.30-8.90(1H,m),7.65-7.14(1H,m),4.57-4.43(4H,m),3.51(2H,t,J = 7.4Hz),3.39-3.29(4H,m),3.23(3H,s),3.21(3H,d,J = 4.5Hz),1.68(2H,六重峰,J = 7.4Hz),0.98(3H,t,J = 7.4Hz).ESI-MS(m/z):381$[M+H]^+$;熔点>300℃。

[0686] 实施例35:N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(76)和相应的盐酸盐(77a)(方案15)

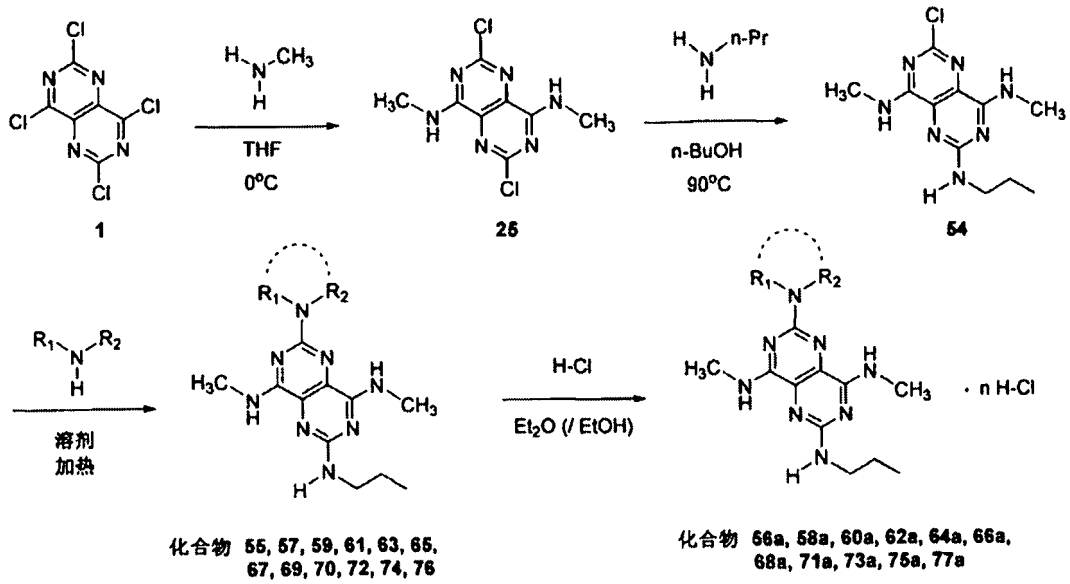
[0687] N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(76):

[0688] 将6-氯-N^2-正丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(54)(282mg,1.00mmol)、4,4-二氟-哌啶盐酸盐(158mg,2.91mmol)和N,N-二异丙基乙胺(345μL,2.00mmol)在1,4-二噁烷(4mL)中的混合物在120℃下在封闭瓶中加热48h。添加额外部分的4,4-二氟-哌啶盐酸盐(158mg,2.91mmol)和N,N-二异丙基乙胺(345μL,2.00mmol),并继续加热18h。冷却后,添加饱和$NaHCO_3$溶液(5mL),并将所得悬浮液用CH_2Cl_2(3x 10mL)萃取。将组合的有机萃取物用水(20mL),然后用盐水溶液(10mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用PE/EtOAc(7 : 1)至PE/EtOAc(1 : 1)的梯度洗脱通过快速柱层析纯化残留物,得到N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(76)(303mg,83% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.52-6.34(2H,m),4.69(1H,br s),3.96-3.91(4H,m),3.39-3.33(2H,m),3.08(3H,d,J = 5.1Hz),3.07(3H,d,J = 5.1Hz),2.04-1.94(4H,m),1.63(2H,六重峰,J = 7.3Hz),0.99(3H,t,J = 7.3Hz).ESI-MS(m/z):367$[M+H]^+$。

[0689] N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺盐酸盐(77):

[0690] 利用关于(20a)描述的程序,在二乙醚中用2M HCl/二乙醚处理N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(76)(303mg,0.83mmol)(319mg,96 % y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 8.20-7.40(3H,m),6.82-6.57(1H,m),3.97-3.90(4H,m),3.48-3.42(2H,m),3.19(3H,d,J = 5.1Hz),3.06(3H,d,J = 5.1Hz),2.05-1.93(4H,m),1.65(2H,六重峰,J = 7.3Hz),0.97(3H,t,J = 7.3Hz).ESI-MS(m/z):367$[M+H]^+$;熔点:290℃(dec.)。

[0691]



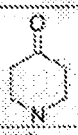
方案 15

[0692] 表 2. 2- 取代 N^1, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺和相应的盐酸盐

[0693]

化合物#	R_1-N-R_2 / H-Cl

[0694]

55 / 56a	CH_3-N-CH_3
57 / 58a	CH_2=CH-CH_2-N-CH_2-CH=CH_2
59 / 60a	CH_3-N-CH_2-CH_2-OH
61 / 62a	H-N-CH_2-CH_2-O-$CH(CH_3)_2$
63 / 64a	CH_3-N-CH_2-CH_2-$N(CH_3)_2$
65 / 66a	H-N-(CH_2-CH_2-$OH)_2$
67 / 68a	H-N-(CH_2-CH_2-$OCH_3)_2$
69	
70 / 71a	
72/ 73a	
74 / 75a	
1. 76 / 77a	 2.

[0695] 实施例 36 :N^2, N^4, N^6, N^8- 四甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (78) 和相应的盐酸盐 (79a) (方案 16)

[0696] N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(78):

[0697] 将2,6-二氯-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺(25)(310mg,1.35mmol)和甲胺(40%水溶液,1.0mL)在正丁醇(1.0mL)中的混合物在125℃下在封闭瓶中加热20h。冷却反应混合物,并加水(10mL)。将所得析出物过滤,用水(10mL)洗涤,并干燥。利用CH_2Cl_2至CH_2Cl_2/MeOH(97:3)的梯度洗脱通过快速柱层析纯化产物,得到N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(78)(230mg,69% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.48(2H,br s),4.62(2H,br s),3.07(6H,d,J = 5.1Hz),2.97(6H,d,J = 5.1Hz).ESI-MS(m/z):249[M+H]$^+$。

[0698] N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(79a):

[0699] 利用关于化合物(20a)描述的程序,在1,4-二㗁烷中用2M HCl/二乙醚处理N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(78)(220mg,0.89mmol)(200mg,80% y)。400MHz ^{1}H NMR(DMSO-d_6,ppm):δ 9.2-7.9(3H,m),7.5-6.3(2H,br s),2.99(6H,s),2.92(6H,s).ESI-MS(m/z):249[M+H]$^+$;熔点>300℃。

[0700] 实施例37:N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(80)和相应的盐酸盐(81a)(方案16)

[0701] N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(80):

[0702] 将2,6-二氯-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺(25)和乙胺(70%水溶液,1.0mL)在正丁醇(1.0mL)中的混合物在140℃下在封闭瓶中加热24h。冷却后,添加饱和$NaHCO_3$溶液(20mL),并将所得悬浮液用CH_2Cl_2(3x 20mL)萃取。将组合的有机萃取物用水(20mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用CH_2Cl_2至CH_2Cl_2/MeOH(98:2)的梯度洗脱通过快速柱层析纯化残留物,得到N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(80)(130mg,41% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.45(2H,br s),4.59(2H,br s),3.48-3.36(4H,m),3.06(6H,d,J = 5.0Hz),1.23(6H,t,J = 7.2).ESI-MS(m/z):277[M+H]$^+$。

[0703] N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(81a):

[0704] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中用2M HCl/二乙醚处理N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(80)(120mg,0.43mmol)(90mg,67 % y)。400MHz ^{1}H NMR(DMSO-d_6,ppm):δ 9.2-8.2(3H,m),7.6-6.5(2H,m),3.49-3.37(4H,m),3.06-2.90(6H,m),1.14(6H,t,J = 7.2Hz).ESI-MS(m/z):277[M+H]$^+$;熔点:256-258℃。

[0705] 实施例38:N^2,N^6-二-正丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(82)和相应的盐酸盐(83a)(方案16)

[0706] N^2,N^6-二-正丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(82):

[0707] 根据关于化合物(80)描述的程序,使2,6-二氯-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺(25)(250mg,0.96mmol)和正丁胺(6eq.)在正丁醇中反应。从EtOAc/石油醚重结晶后,获得N^2,N^6-二-正丁基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(82)(110mg,34% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.43(2H,br s),4.61(2H,br s),3.43-3.53(4H,m),3.06(6H,d,J = 5.0Hz),1.64-1.54(4H,m),1.49-1.37(4H,m),0.96(6H,t,J = 7.4Hz).ESI-MS(m/z):333[M+H]$^+$。

[0708] N^2, N^6- 二 - 正丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (83a) :

[0709] 利用关于化合物 (29a) 描述的程序，在 1,4- 二噁烷中用 2M HCl/ 二乙醚处理 N^2, N^6- 二 - 正丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (82) (100mg, 0.30mmol) (110mg, ～ 100 % y)。400MHz ^{1}H NMR(DMSO-d_6, ppm) : δ 9.2-7.8(3H, m), 7.4-6.5(2H, m), 3.48-3.32(4H, m), 2.99(6H, s), 1.59-1.46(4H, m), 1.42-1.27(4H, m), 0.90(6H, t, J = 7.3Hz). ESI-MS(m/z) :333[M+H]$^+$;熔点 :199-201℃。

[0710] 实施例 39:N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84) 和相应的盐酸盐 (85a) (方案 16)

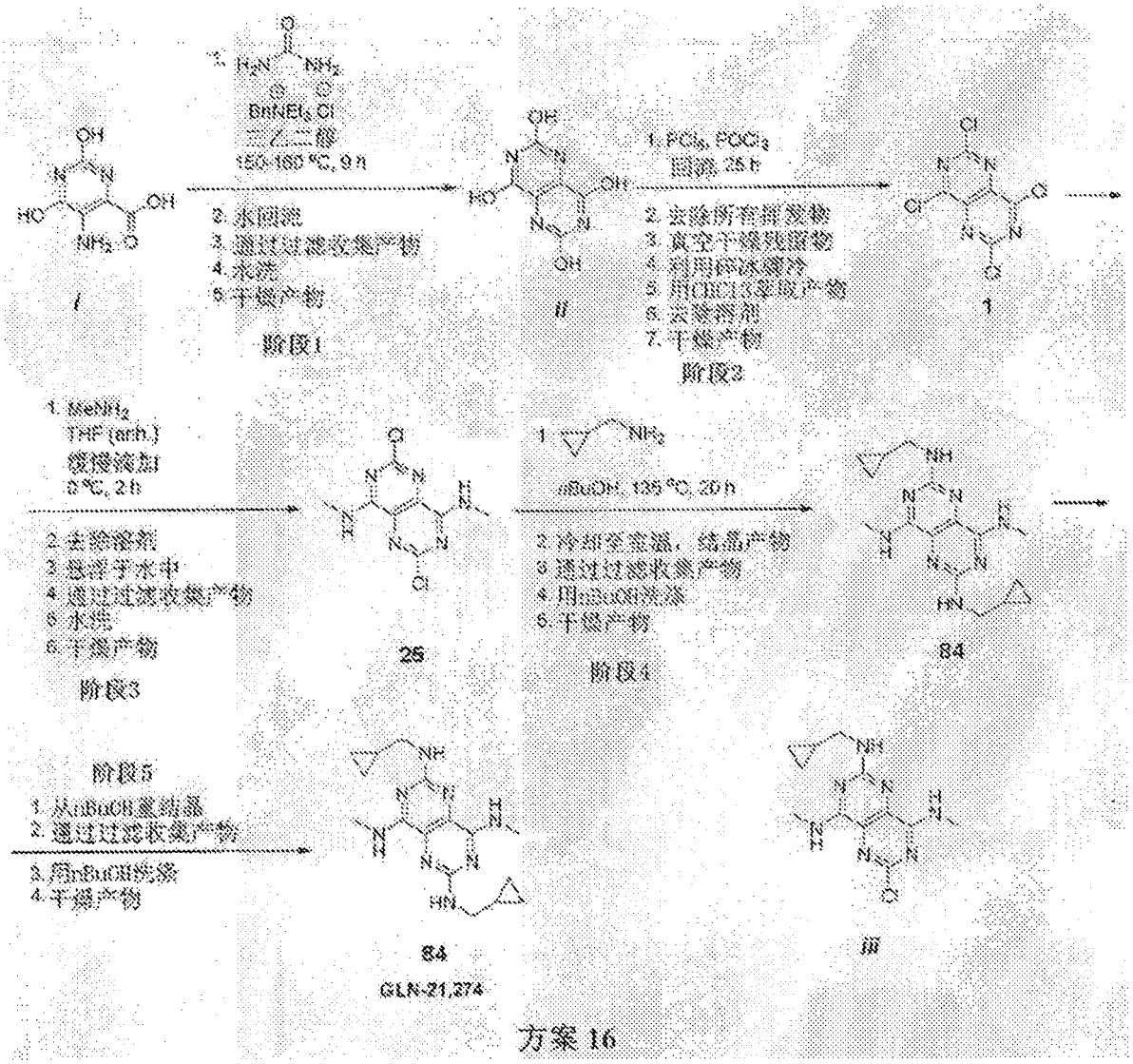
[0711] N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84) :

[0712] 将 2,6- 二氯 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25) (2.0g, 7.72mmol) 和环丙基甲胺 (4.0mL, 46.31mmol) 在正丁醇 (15.0mL) 中的混合物在 130℃下在封闭瓶中加热 34h。冷却后，添加饱和 $NaHCO_3$ 溶液 (100mL) 和水 (100mL)，并将所得悬浮液用 $CHCl_3$ (3x 200mL) 萃取。将组合的有机萃取物用水 (150mL) 洗涤，并在固体无水 Na_2SO_4 上干燥。过滤后，去除溶剂，并利用 CH_2Cl_2 至 CH_2Cl_2/MeOH(96 : 4) 的梯度洗脱通过快速柱层析纯化残留物，得到 N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84) (1.35g, 53% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 6.43(2H, br s), 4.78(2H, br s), 3.25(4H, dd, J = 6.8, 5.6Hz), 3.07(6H, d, J = 5.2Hz), 1.15-1.04(2H, m), 0.54-0.49(4H, m), 0.27-0.22(4H, m). ESI-MS(m/z) :329[M+H]$^+$。

[0713] N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (85a) :

[0714] 将 2.5M HCl/EtOH 溶液 (3.2mL, 8.0mmol) 加入 N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84) (2.63g, 8.01mmol) 的 CH_2Cl_2/EtOH(100mL/100mL) 悬浮液。将混合物在室温下搅拌 0.5h，然后在减压下去除挥发物。用二乙醚 (30mL) 处理残留物。将所得析出物过滤，用二乙醚 (15mL)，然后用石油醚 (15mL) 洗涤，并干燥，得到 N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (85a) (2.75g, 94% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 13.1-12.7(1H, br s), 8.85(1H, s), 8.04(1H, br s), 7.42-6.62(2H, m), 3.30-3.18(4H, m), 3.07-2.88(6H, m), 1.15-1.03(2H, m), 0.50-0.37(4H, m), 0.33-0.17(4H, m). ESI-MS(m/z) :329[M+H]$^+$; 熔点 : 264-265℃。

[0715]



[0716] 实施例 39A:制备 N^2-N^6- 双环丙基甲基 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84)(方案 16)

[0717] 阶段 1. 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四醇 (ii)

[0718] 将带有磁力搅拌棒、温度探针和空气冷凝器的 250mL 三颈圆底烧瓶装载 5- 氨基乳清酸 (i)(15g,87.6mmol,1 当量)、尿素 (42g,701mmol,8 当量)、苄基三乙基氯化铵 (0.3g,1.3mmol,0.015 当量) 和三乙二醇 (13mL)。将该悬浮液加热并搅拌,并保持 150-160℃ (反应混合物温度)9h。最初粘性不均质混合物在加热 10 分钟后变得更均质并且容易搅拌。加热 3-4h 后,反应混合物形成浓稠的团块状糊,并且在加热期即将结束时变得不可搅拌。加热期间发生尿素升华。反应过程通过用润湿的 pH 试纸检测气态 NH_3 排放来监测。

[0719] 反应结束后 (NH_3 不再放出),将混合物冷却至 90℃,并加水 (120mL)。将混合物在回流下搅拌 1h,期间最初糊状物质转化成稀薄悬浮液。将混合物冷却至室温,过滤,并用水 (3x 50mL) 洗涤褐色固体产物。将产物在空气中在 60℃下干燥 16h,生成嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四醇 (ii)(16.8g,98% y),为褐色粉末。产物按原样用于下个步骤。

[0720] 阶段 2 :2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶 (1)

[0721] 将带有磁力搅拌棒、回流冷凝器和 $CaCl_2$ 干燥管的 1L 圆底烧瓶装载嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四醇 (ii)(23.9g,122mmol,1 当量)、PCl_5(152g,732mmol,6 当量) 和

$POCl_3$(387.3mL,4150mmol,34 当量)。将所得悬浮液在 145℃下回流 25h。在回流期结束时,反应混合物变得完全均质。冷却至室温后发生固体析出。将回流冷凝器换成蒸馏釜顶盖,所有挥发物在大气压和 145℃下蒸出。在蒸馏终止时,将蒸馏烧瓶冷却至室温,并施加吸水器真空以部分干燥产物。将还留在蒸馏烧瓶中的粘性产物在真空下 145℃下进一步干燥 30min。将还留在蒸馏烧瓶中的产物冷却至室温,并引入碎冰 (350mL),导致生热和变成水的冰的沸腾。将所得浆液冷却至室温,与 400mL 氯仿混合,并将乳化的混合物通过玻璃料过滤。滤液包括下层透明有机层、中层乳化层和上层水层。将有机层分离并保存,将其他两层组合并用另外四份 200mL 氯仿萃取。在最后一次萃取后,将中层乳化层与上层水层分离。将乳化层与 200mL 氯仿和 C 盐 (celite) 混合,并在室温下搅拌 10min,使乳液变成悬浮液,其通过过滤去除,并用氯仿洗涤。将组合的有机萃取物在固体无水 Na_2SO_4上干燥,过滤,和在真空中蒸发至干燥。将固体产物在室温下在真空干燥器中干燥 16h,生成 2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶 (1)(12.2g,37% y),为黄色粉末,mp :254-256℃。产物的性质可通过 CHN 元素分析来验证。

[0722] 表 3 :(1) 的代表性元素分析

[0723]

	C	H	N
理论值 :	26.70	0.00	20.76
实际值 1	26.67	0.06	20.85
实际值 2	26.63	0.01	20.78

[0724] 阶段 3 :2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25)

[0725] 将配备有磁力搅拌棒、温度探针和注射泵的 0.5L 圆底烧瓶装载 2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶 (1)(11.8g,43.9mmol,1 当量) 和无水四氢呋喃 (128mL)。将所得悬浮液在冰浴中冷却,然后用注射泵以 50mL/h 滴加 2M $MeNH_2$的四氢呋喃 (98.6mL,197mmol,4.5 当量) 溶液。在添加完成后,将反应混合物升温至室温并搅拌 0.5h。LC-MS 测定显示转化完成。将四氢呋喃在真空下去除,并将橙色半固体残留物悬浮于水 (50mL) 中,在超声波浴中超声处理 30min。产物通过过滤收集,用水 (3x 30mL) 洗涤,并在 60℃下在空气中干燥,生成 2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25)(10.9g,96% y),为橙色粉末 ;mp :257-258℃

[0726] 阶段 4 :N^2-N^6- 双 - 环丙基甲基 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84)

[0727] 将带有磁力搅拌棒的 Ace 玻璃压力管装载 2,6- 二氯 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25)(10.9g,42.1mmol,1 当量)、环丙基甲胺 (18g,21.6mL,252mmol,6 当量) 和 nBuOH(65mL)。将管用特氟隆塞密封,并在 135℃下加热 20h。在加热期结束时,产物已开始析出。将混合物冷却至室温并搅拌 2h,生成额外的固体产物。在用刮铲处理母液中的固体产物后,形成额外的固体产物。将混合物在室温下再留置 2h,然后通过过滤收集固体,用 nBuOH(3x 30mL) 和轻石油醚 (2x 50mL) 洗涤,并在室温下在过滤器上干燥 2h,提供 7.0g N^2-N^6- 双 - 环丙基甲基 -N^4,N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84),

为黄色晶体固体。

[0728] 将组合的母液和洗液蒸发至干燥；将所得半固体残留物悬浮于二乙醚（80mL）中，并将混合物超声处理 1h。将混合物过滤以去除不溶物，并将滤液蒸发至干燥，提供红色油，其主要由单－氯衍生物 iii——阶段 4 中间体——组成。可在阶段 4 条件下用 3 摩尔当量的环丙基甲胺处理粗制 iii，生成额外的 N^2-N^6-双－环丙基甲基 N^4,N^8-二甲基－嘧啶并［5,4-d］嘧啶 -2,4,6,8-四胺（84）。

[0729] 阶段 5：重结晶 N^2-N^6-双环丙基甲基 N^4, N^8-二甲基－嘧啶并［5,4-d］嘧啶 -2,4,6,8-四胺（84）

[0730] 将阶段 4 获得的 N^2-N^6-双环丙基甲基 -N^4, N^8-二甲基－嘧啶并［5,4-d］嘧啶 -2,4,6,8-四胺（84）（7.0g）在回流下溶解于 n-BuOH（200mL），并将溶液趁热通过热烧结玻璃过滤器过滤，去除不溶性颗粒。用 n-BuOH（3x 20mL）洗涤过滤器，并通过在大气压下蒸馏将组合的滤液浓缩至最终体积 110mL。将溶液冷却至室温，并且保持室温并搅拌 16h。产物通过过滤收集，用 n-BuOH（3x 15mL）和轻石油醚（3x 40mL）洗涤，并在室温下在过滤器上干燥，生成 N^2, N^6-双－环丙基甲基 -N^4, N^8-二甲基－嘧啶并［5,4-d］嘧啶 -2,4,6,8-四胺（84）（6.45g,47% y）。mp：264-268℃。XRPD 如图 13，并且关键信号如表 5。

[0731] 表 4：(84) 的元素分析

[0732]

	C	H	N
理论值：	58.52	7.37	34.12
实际值 1	58.65	7.36	33.98
实际值 2	58.68	7.42	33.97

[0733] 表 5：从正丁醇结晶的 (84) 的关键 XRPD 信号

[0734]

位置[°2Θ]	d-间距[Å]	相对强度[%]
8.1179	10.88256	24.14
9.5941	9.21115	100.00
12.6010	7.01914	67.39
15.0171	5.89481	7.68

[0735]

16.3278	5.42445	1.84
17.3962	5.09364	2.86
18.9738	4.67302	10.75
20.6773	4.29217	4.83
21.7166	4.08905	12.39
22.2793	3.98703	50.27
23.9773	3.70839	4.78
25.2409	3.52554	4.60
26.7012	3.33594	5.35

[0736] 盐筛选程序

[0737] 将游离碱 N^2-N^6- 双 - 环丙基甲基 N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (84) (900mg) 和 1 摩尔当量的成盐剂 (salt former) 溶解于 30mL 1 ： 1(vol/vol) 氯仿 / 乙腈或氯仿 / 乙醇中。如需，将混合物在 50℃下加热，形成透明溶液，然后在真空中将溶液浓缩至干燥。所得固体残留物原样使用，假设其是 1 ： 1 化学计量盐。

[0738] 将带有螺旋盖的 3mL 小瓶在室温下装载 50mg 固体盐和 1mL 溶剂。如需，加热混合物，以得到透明溶液，在一些实施例中生成包括透明部分和熔体或不完全溶解的晶体材料的混合物。将热混合物冷却至室温。如果结晶在环境温度下不发生或不充分（很少可见的晶体量），则将混合物进一步冷却至约 0-5℃。固体产物通过过滤收集，在 45℃下真空干燥，并通过熔点和元素分析表征。评价的溶剂包括乙腈、甲基乙基酮、甲基异丁基酮、乙酸乙酯、乙酸异丙酯、水、庚烷、甲基 - 叔丁醚、环己烷、甲苯、甲醇、乙醇、正丙醇、异丙醇、正丁醇、2- 丁醇、异戊醇、和四氢呋喃。评价的成盐剂包括盐酸、硫酸、磷酸、苯磺酸、甲磺酸、对甲苯磺酸、糖精、丙二酸、L- 天冬氨酸、L- 谷氨酸、马来酸、L(+)- 酒石酸、富马酸、柠檬酸、苹果酸、乙醇酸、扁桃酸、苯甲酸、琥珀酸乙酸、乳酸、甘油磷酸、D- 葡萄糖醛酸、和 D- 葡萄糖酸。利用不同成盐剂和溶剂分离的盐的数据被提供在表 6A-6H 中。

[0739] 表 6A ：盐酸盐 (85a)

[0740]

溶剂	溶解度 室温	溶解度 回流	最终 分离 温度	碱/酸 摩尔比	元素分析	MP (℃)
乙醇	I	S	Ca. 0-5 ℃	1 ： 1.11	理论值 C，52.10，H，6.86，N，30.38 实际值 C，52.17，H，6.98，N，30.20 C，52.04，H，6.88，N，30.18	253-255
正丙醇	I	S	Ca. 0-5 ℃	1 ： 1.15	理论值 C，51.89，H，6.84，N，30.26	251-253

[0741]

					实际值 C，52.12，H，6.85，N，29.89 C，52.13，H，6.91，N，30.01	
正丁醇	I	S	Ca. 0-5℃	1 ： 1.15	理论值 C，51.89，H，6.84，N，30.26 实际值 C，52.00，H，6.90，N，30.08 C，52.01，H，6.93，N，29.99	252-254

[0742] 表 6B :硫酸盐 (85b)

[0743]

溶剂	溶解度室温	溶解度回流	最终分离温度	碱/酸摩尔比	元素分析	MP (℃)
甲醇	I	S	Ca. 0-5℃.	1 : 1	理论值 C，45.06，H，6.14，N，26.27 实际值 C，45.09，H，6.39，N，26.55 C，45.14，H，6.29，N，26.54	228-230
乙醇	I	PS	室温	1 : 1.04	理论值 C，44.73，H，6.18，N，25.76 7.66 实际值 C，44.29，H，6.07，N，26.00, C，44.38，H，6.23，N，26.06	226-228

[0744] I =不溶，S =可溶，PS =部分可溶。

[0745] 表 6C :苯磺酸盐 (85c)

[0746]

溶剂	溶解度室温	溶解度回流	最终分离温度	碱/酸摩尔比	元素分析	MP (℃)
甲基异丁基酮	I	S	Ca. 0-5 ℃	1 : 1	计算值 C，54.30，H，6.21，N，23.03，S，6.59 实际值 C，54.31，H，6.22，N，23.20，S，6.53 C，54.36，H，6.24，N，23.20，S，6.57	149-150

[0747]

乙酸乙酯	I	S	Ca. 0-5 ℃	1 : 1	计算值 C，54.30，H，6.21，N，23.03，S，6.59 实际值 C，54.07，H，6.20，N，23.07，S，6.48 C，54.21，H，6.36，N，23.14，S，6.44	148-150
乙酸异丙酯	I	S	Ca. 0-5 ℃	1 : 1	计算值 C，54.30，H，6.21，N，23.03，S，6.59 实际值 C，54.22，H，6.20，N，23.05，S，6.43 C，54.28，H，6.34，N，23.09，S，6.53	146-148
甲苯	I	S	Ca. 0-5 ℃	1 : 1	计算值 C，54.30，H，6.21，N，23.03，S，6.59 实际值 C，54.23，H，6.32，N，22.85，S，6.18 C，54.29，H，6.20，N，22.88，S，6.23	147-149

[0748] 表 6D :甲苯磺酸盐 (85d)

[0749]

溶剂	溶解度 室温	溶解度 回流	最终 分离 温度	碱/酸 摩尔 比	元素分析	MP (℃)
乙酸异丙酯	I	S	Ca. 0-5 ℃	1 : 1.13	理论值 C，54.91，H，6.37，N，21.43，S，6.93 实际值 C，54.86，H，6.40，N，21.27，S，6.65 C，54.79，H，6.39，N，21.23，S，6.68	142-144

[0750] 表 6E :丙二酸盐 (85e)

[0751]

溶剂	溶解度室温	溶解度回流	最终分离温度	碱/酸摩尔比	元素分析	MP（℃）
甲醇	I	PS	r.t。	1 ： 1.06	理论值 C、52.51、H、6.49，N、25.54 实际值 C、52.47，H、6.43、N、25.56	246-248

[0752]

					C、52.61、H、6.39，N、25.54	
四氢呋喃	I	PS	r.t。	1 ： 1.3	理论值 C、51.55、H、6.35、N、24.17 实际值 C、51.93、H、6.49，N、23.89 C、52.20，H、6.55、N、24.03	247-249

[0753] 表 6F ：酒石酸氢盐 (85f)

[0754]

溶剂	溶解度室温	溶解度回流	最终分离温度	碱/酸摩尔比	元素分析	MP（℃）
甲醇	I	PS	室温	1 ： 0.79	理论值 C，51.48，H，6.48，N，25.07 实际值 C，51.24，H，6.45，N，25.28 C，51.17，H，6.45，N，25.25	226-228
正丙醇	I	PS	室温	1 ： 0.83	理论值 C，51.23，H，6.45，N，24.74 实际值 C，51.25，H，6.55，N，24.66 C，51.25，H，6.56，N，24.70	226-228
正丁醇	I	PS	室温	1 ： 0.83	理论值 C，51.23，H，6.45，N，24.74 实际值 C，51.50，H，6.62，N，24.37 C，51.71，H，6.67，N，24.48	224-228

[0755] 表 6G：马来酸盐（85g）

[0756]

溶剂	溶解度室温	溶解度回流	最终分离温度	碱/酸摩尔比	元素分析	MP（℃）
甲醇	I	S	室温	1：1	理论值 C，54.04，H，6.35，N，25.21 实际值 C，53.68，H，6.30，N，	175-177

[0757]

					25.09 C，53.95，H，6.30，N，25.24	
正丙醇	I	S	室温	1：1	理论值 C，54.04，H，6.35，N，25.21 实际值 C，53.94，H，6.36，N，25.05 C，53.89，H，6.31，N，25.02	174-176
正丁醇	I	S	室温	1：1	理论值 C，54.04，H，6.35，N，25.21 实际值 C，53.77，H，6.31，N，24.94 C，54.01，H，6.31，N，25.07	174-176
四氢呋喃	I	S	室温	1：1	理论值 C，54.04，H，6.35，N，25.21 实际值 C，54.10，H，6.32，N，25.20 C，54.08，H，6.33，N，25.25	194-196

[0758] 表 6H：甲磺酸盐（85h）

[0759]

溶剂	溶解度，室温	溶解度，回流	最终分离温度	碱/酸摩尔比	元素分析	MP（℃）
乙酸乙酯	I	S	室温	1：1.1	理论值 C，47.31，H，6.59，N，25.81 实际值 C，47.16，H，6.81，N，25.41 C，47.44，H，6.81，N，25.62	143-145

[0760] 实施例 40:N^2, N^6- 二异丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (86) 和相应的盐酸盐 (87a)(方案 17)

[0761] N^2, N^6- 二异丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (86) :

[0762] 将 2,6- 二氯 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25)(350mg, 1.35mmol) 和异丁胺 (805μL,8.10mmol) 在正丁醇 (5.0mL) 中的混合物在 120℃下在封闭瓶中加热 20h。添加另一份异丁胺 (805μL,8.10mmol), 并继续加热 68h。冷却后, 添加饱和 $NaHCO_3$ 溶液 (30mL), 并将所得悬浮液用 CH_2Cl_2(3x 30mL) 萃取。将组合的有机萃取物用水 (75mL) 洗涤, 并在固体无水 Na_2SO_4 上干燥。过滤后, 去除溶剂, 并利用 CH_2Cl_2 至 CH_2Cl_2/MeOH(9 : 1) 的梯度洗脱通过快速柱层析纯化残留物, 得到 N^2, N^6- 二异丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (86)(180mg,40 % y)。400MHz ^{1}H NMR(DMSO-d_6, ppm) : δ 7.00-6.90(2H, m), 6.03(2H, t, J = 5.6Hz), 3.16-3.09(4H, m), 2.91(6H, d, J = 4.8Hz), 1.91-1.76(2H, m), 0.89(12H, d, J = 6.7Hz). ESI-MS(m/z) : 333$[M+H]^+$. 。

[0763] N^2, N^6- 二异丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (87a) :

[0764] 利用关于化合物 (20a) 描述的程序, 在 1,4- 二噁烷 /EtOH(1/1) 中用 2M HCl/ 二乙醚处理 N^2, N^6- 二异丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (86)(170mg,0.51mmol)(170mg,90% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 14.96(0.3H, s), 14.00(1H, s), 9.60(0.3H, s), 7.66(0.7H, s), 7.41(0.7H, s), 6.75(1H, s), 4.93(1H, s), 3.40-3.28(2H, m), 3.28-3.13(6H, m), 3.13-2.99(2H, m), 2.00-1.81(2H, m), 0.98(12H, d, J = 6.7H). ESI-MS(m/z) :333$[M+H]^+$; 熔点 :208-210℃。

[0765] 实施例 41:N^2, N^6- 二烯丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (88) 和相应的盐酸盐 (89a)(方案 17)

[0766] N^2, N^6- 二烯丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (88) :

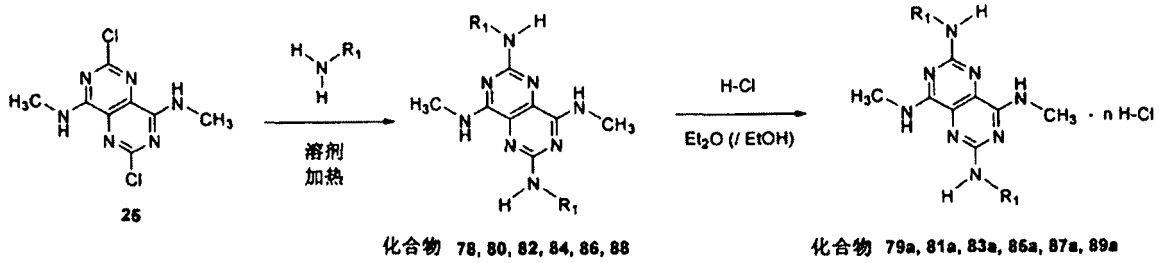
[0767] 将 2,6- 二氯 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25)(350mg, 1.35mmol) 和烯丙胺 (293μL,8.10mmol) 在正丁醇 (5.0mL) 中的混合物在 120℃下在封闭瓶中加热 144h。冷却后, 添加饱和 $NaHCO_3$ 溶液 (30mL), 并将所得悬浮液用 EtOAc(3x 10mL) 萃取。将组合的有机萃取物用水 (30mL), 然后用盐水溶液 (30mL) 洗涤, 并在固体无水 Na_2SO_4 上干燥。过滤后, 去除溶剂 ; 利用 $CHCl_3$ 至 $CHCl_3$/EtOAc(4 : 1) 的梯度洗脱通过快速柱层析纯化残留物, 得到 N^2, N^6- 二烯丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (88)(151mg,37 %)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 6.50-6.38(2H, m), 6.00(2H, ddt, J = 17.1,10.2,5.7Hz), 5.25(2H, ddt, J = 17.1,1.6,1.6Hz), 5.11(2H, ddt, J = 10.2, 1.6,1.6Hz), 4.71(2H, t, J = 5.7Hz), 4.05(4H, ddt, J = 5.7,5.7,1.6Hz), 3.06(6H, d, J = 5.2Hz). ESI-MS(m/z) :301$[M+H]^+$。

[0768] N^2, N^6- 二烯丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (89a) :

[0769] 利用关于化合物 (20a) 描述的程序, 在 1,4- 二噁烷中用 2M HCl/ 二乙醚处理 N^2, N^6- 二烯丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (88)(147mg,0.49mmol) (140mg,85% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 15.10(1H, br s), 14.31-14.03(0.4H, m),

9.90-9.60(1H,m),8.05-7.31(1H,m),6.73(1.6H,s),6.06-5.88(2H,m),5.36-5.12(4H,m),4.25-3.95(4H,m),3.32-2.95(6H,m).ESI-MS(m/z):301[M+H]$^+$;熔点:212-214℃。

[0770]



25

化合物 78, 80, 82, 84, 86, 88

化合物 79a, 81a, 83a, 85a, 87a, 89a

方案 17

[0771] 实施例 42:2-氯-6-(N,N'-二甲基-肼基)-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺(90),和 2,6-双-(N,N'-二甲基-肼基)-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺(91)(方案 18)

[0772] 将 2,6-二氯-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺(25)(600mg,2.32mmol)、N,N'-二甲基-肼二盐酸盐(926mg,6.96mmol)和 N,N-二异丙基乙胺(2.6mL,15.08mmol)在 1,4-二噁烷(15.0mL)中的混合物在 80℃下加热 20h。再添加 N,N'-二甲基-肼二盐酸盐(309mg,2.32mmol)和 N,N-二异丙基乙胺(0.87mL,5.03mmol),并继续加热 24h。添加饱和 $NaHCO_3$ 溶液(30mL),并用 CH_2Cl_2(3x 30mL)萃取悬浮液。将组合的有机萃取物用水(75mL)洗涤,并在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 CH_2Cl_2 至 CH_2Cl_2/MeOH(97 : 3)的梯度洗脱通过快速柱层析纯化残留物,得到 2-氯-6-(N,N'-二甲基-肼基)-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺(90)(310mg,47% y)和 2,6-双-(N,N'-二甲基-肼基)-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺(91)(160mg,23% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.50-6.35(2H,m),5.35(2H,s),3.29(6H,s),3.11(6H,d,J = 5.0Hz),2.65(6H,s).ESI-MS(m/z):307[M+H]$^+$;熔点:219-221℃。

[0773] 化合物(90):400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.67(1H,s),6.65(1H,s),5.36(1H,s),3.32(3H,s),3.16(3H,d,J = 5.2Hz),3.08(3H,d,J = 5.0Hz),2.66(3H,s).ESI-MS(m/z):283,285[M+H]$^+$。

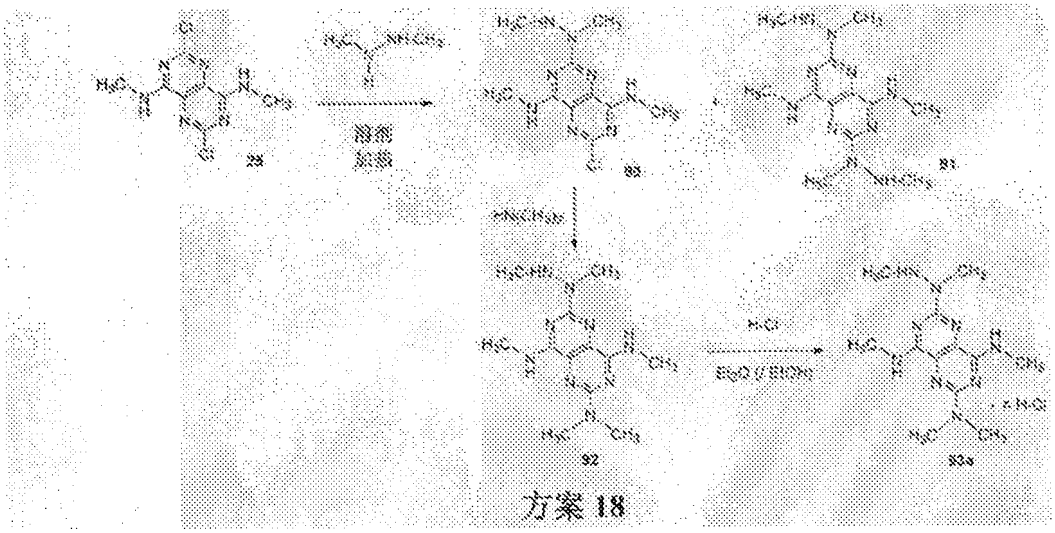
[0774] 实施例 43:6-(N,N'-二甲基-肼基)-N^2,N^2,N^4,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(92)和相应的盐酸盐(93a)(方案 18)

[0775] 将 2-氯-6-(N,N'-二甲基-肼基)-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺(90)(260mg,0.92mmol)和 2M 二甲胺/THF(4.6mL,9.20mmol)在 1,4-二噁烷(5.0mL)中的混合物在 135℃下在封闭瓶中加热 20h。去除挥发物,并将残余物在饱和 $NaHCO_3$ 溶液(20mL)和 CH_2Cl_2(20mL)之间分配。分离水相,并用 CH_2Cl_2(2x 20mL)萃取。将组合的有机萃取物用水(30mL)洗涤,并在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 CH_2Cl_2 至 CH_2Cl_2/MeOH(95 : 5)的梯度洗脱通过快速柱层析纯化残留物,得到 6-(N,N'-二甲基-肼基)-N^2,N^2,N^4,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(92)(180mg,67% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.50(1H,s),6.34(1H,s),5.38(1H,br s),3.28(3H,s),3.17(6H,s),3.11(3H,d,J = 5.1Hz),3.10(3H,d,J = 5.1Hz),2.65(3H,s).ESI-MS(m/z):292[M+H]$^+$。

[0776] 利用关于化合物(20a)描述的程序,在 1,4-二噁烷中用 2M HCl/二乙醚处理

6-(N,N'-二甲基-肼基)-N^2,N^2,N^4,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(92)(170mg,0.58mmol)(155mg,81% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 11.0-8.0(2H,br s),9.08(2H,s),3.45(3H,s),3.29(6H,s),3.11(3H,d,J = 4.6Hz),3.05(3H,d,J = 4.6Hz),2.86(3H,s).ESI-MS(m/z):292$[M+H]^+$;熔点:273-275℃。

[0777]



方案18

[0778] 实施例44:N^4,N^8-二甲基-6-丙氧基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(94)和相应的盐酸盐(95a)(方案19)

[0779] 将NaH(60%矿物油悬浮液)(188mg,4.72mmol)在0℃下逐部分加入丙醇(10mL)。混合物在0℃下搅拌10min,然后添加6-氯-N^2-正丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(54)(250mg,0.89mmol)。将混合物在110℃下加热16h。去除挥发物,并将残余物在饱和NH_4Cl溶液(30mL)和CH_2Cl_2(30mL)之间分配。分离水相,并用CH_2Cl_2(2x 30mL)萃取。将组合的有机萃取物用水(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用PE/EtOAc(1 : 1)作为洗脱剂通过快速柱层析纯化残留物,得到N^4,N^8-二甲基-N^2-正丙基-6-丙氧基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(94)(227mg,84%)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.64-6.57(1H,m),6.47-6.39(1H,m),4.82-4.75(1H,m),4.26(2H,t,J = 7.0Hz),3.40-3.34(2H,m),3.13(3H,d,J = 5.2Hz),3.07(3H,d,J = 5.2Hz),1.84(2H,六重峰,J = 7.4Hz),1.63(2H,六重峰,J = 7.4Hz),1.04(3H,t,J = 7.4Hz),0.99(3H,t,J = 7.4Hz).ESI-MS(m/z):306$[M+H]^+$。

[0780] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中用2M HCl/二乙醚处理N^4,N^8-二甲基-N^2-正丙基-6-丙氧基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(94)(227mg,0.74mmol)(241mg,95 % y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 8.15-8.09(1H,m),7.77-7.47(1H,m),6.80-6.72(1H,m),4.29(2H,t,J = 6.9Hz),3.53-3.46(2H,m),3.21(3H,d,J = 5.2Hz),3.15(3H,d,J = 4.7Hz),1.84(2H,六重峰,J = 7.4Hz),1.68(2H,六重峰,J = 7.4Hz),1.04(3H,t,J = 7.4Hz),1.00(3H,t,J = 7.4Hz).ESI-MS(m/z):306$[M+H]^+$;熔点:203-205℃。

[0781] 实施例45:N^4,N^8-二甲基-N^2-正丙基-6-丙基硫烷基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(96)和相应的盐酸盐(97a)(方案19)

[0782] 将丙三醇(89 μL,0.98mmol)溶解于DMF(4mL),并在环境温度下添加THF中的

NaHMDS(1.0M,1.06mL,1.06mmol)。搅拌15min后,将该透明溶液加入6-氯-N^2-正丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(54)(250mg,0.89mmol)的DMF(6mL)溶液。在环境温度下继续搅拌3h,然后将反应在60℃下加热16h。在该时间后,加水(30mL),并将所得悬浮液用EtOAc(3x 30mL)萃取。将组合的有机萃取物用水(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用PE/EtOAc(1 ∶ 1)作为洗脱剂通过快速柱层析纯化残留物,得到N^4,N^8-二甲基-N^2-正丙基-N^4,N^8-二甲基-6-丙基硫烷基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(96)(263mg,92% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.55-6.47(2H,m),4.89-4.81(1H,m),3.41-3.34(2H,m),3.15-3.10(5H,m),3.07(3H,d,J = 5.2Hz),1.78(2H,六重峰,J = 7.4Hz),1.63(2H,六重峰,J = 7.4Hz),1.05(3H,t,J = 7.4Hz),0.99(3H,t,J = 7.4Hz).ESI-MS(m/z):322$[M+H]^+$。

[0783] 利用关于化合物(20a)描述的程序,在二乙醚中用2M HCl/二乙醚处理N^4,N^8-二甲基-N^2-正丙基-6-丙基硫烷基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(96)(250mg,0.78mmol)(262mg,94 % y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 8.09-8.02(1H,m),7.65-7.56(1H,m),6.87-6.81(1H,m),3.53-3.45(2H,m),3.21(3H,d,J = 5.1Hz),3.14(3H,d,J = 4.6Hz),3.14-3.08(2H,m),1.77(2H,六重峰,J = 7.4Hz),1.68(2H,六重峰,J = 7.4Hz),1.05(3H,t,J = 7.4Hz),0.99(3H,t,J = 7.4Hz).ESI-MS(m/z):322$[M+H]^+$;熔点:218-220℃。

[0784] 实施例46:6-苄氧基-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(98)和相应的盐酸盐(99a)(方案19)

[0785] 将苄醇(1.0mL,9.60mmol)在0℃下加入NaH(60%,在矿物油中)(416mg,10.4mmol)的1,4-二噁烷(10mL)悬浮液。将混合物在0℃下搅拌30min,然后添加6-氯-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(54)(450mg,1.60mmol)。将混合物在110℃下加热1h。去除挥发物,并将残余物在饱和NH_4Cl溶液(30mL)和CH_2Cl_2(30mL)之间分配。分离水相,并用CH_2Cl_2(2x 30mL)萃取。将组合的有机萃取物用水(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用PE/EtOAc(9 ∶ 1)至PE/EtOAc(1 ∶ 9)的梯度洗脱通过快速柱层析纯化残留物,得到N^4,N^8-二甲基-N^2-正丙基-N^4,N^8-二甲基-6-苄氧基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(98)(465mg,82% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 7.51-7.45(2H,m),7.38-7.32(2H,m),7.31-7.27(1H,m),6.68-6.58(1H,m),6.46-6.36(1H,m),5.39(2H,s),4.79(1H,t,J = 5.8Hz),3.37(2H,td,J = 7.3,5.8Hz),3.13(3H,d,J = 5.2Hz),3.06(3H,d,J = 5.2Hz),1.7-1.58(2H,m),0.99(3H,t,J = 7.4Hz).ESI-MS(m/z):354$[M+H]^+$。

[0786] 利用关于化合物(20a)描述的程序,在二乙醚中用2M HCl/二乙醚处理N^4,N^8-二甲基-N^2-正丙基-6-苄氧基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(98)(100mg,0.28mmol)(104mg,95 % y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 8.27(1H,br s),7.76-7.59(1H,m),7.49-7.41(2H,m),7.40-7.29(3H,m),6.80-6.69(1H,m),5.41(2H,s),3.54-3.44(2H,m),3.20(3H,d,J = 5.2Hz),3.15(3H,d,J = 4.8Hz),1.74-1.62(2H,m),1.00(3H,t,J = 7.4Hz).ESI-MS(m/z):354$[M+H]^+$;熔点:194-196℃。

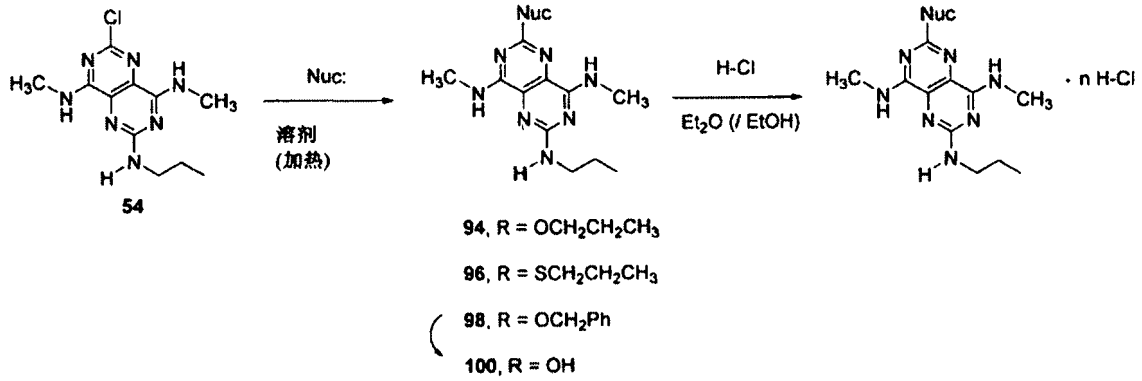
[0787] 实施例47:4,8-双-甲基氨基-6-丙基氨基-嘧啶并[5,4-d]嘧啶-2-醇(100)和相应的盐酸盐(101a)(方案19)

[0788] 将N^4,N^8-二甲基-N^2-正丙基-6-苄氧基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(98)

(330mg,0.93mmol) 和 10% Pd/C(25mg) 在 EtOAc(7mL) 中的混合物在大气压下氢化 4h。将反应混合物通过 C 盐过滤,并用热 MeOH 洗涤 C 盐垫。蒸发滤液。将残留物用 EtOAc(80mL) 处理,并将所得析出物过滤并干燥,得到 4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 醇 (100)(160mg,65% y)。400MHz ^{1}H NMR(CD_3OD, ppm) :δ 3.36(2H, t, J = 7.0Hz),3.06(3H,s),3.01(3H,s),1.67-1.55(2H,m),0.98(3H,t J = 7.5Hz). ESI-MS(m/z) :264[M+H]$^+$。

[0789] 利用关于化合物 (20a) 描述的程序,在 1,4- 二噁烷 /EtOH(1/1) 中用 2M HCl/EtOH 处理 4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 醇 (100)(140mg,0.53mmol)(135mg,85% y)。400MHz ^{1}H NMR(D_2O/ 乙酸 -d_4, ppm) :δ 3.34(2H, t, J = 7.0Hz),3.14(3H, s),3.03(3H, s),1.63-1.50(2H, m),0.89(3H, t, J = 7.5Hz). ESI-MS(m/z) :264[M+H]$^+$;熔点 :238-240℃。

[0790]



方案 19

[0791] 实施例 48:4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 (102) 和相应的盐酸盐 (103a)(方案 20)

[0792] 向 6- 氯 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54)(500mg,1.77mmol) 的 DMSO(4mL) 溶液添加 KCN(243mg,3.73mmol)。将反应混合物在 140℃下加热 40h。将反应混合物倒入饱和氯化钠溶液 (100mL)。将所得悬浮液用 EtOAc(3x 50mL) 萃取。将组合的有机萃取物用水 (50mL) 洗涤,并在固体无水 Na_2SO_4 上干燥。去除溶剂,并利用 PE/EtOAc(99 : 1) 至 PE/EtOAc(6 : 1) 的梯度洗脱通过快速柱层析纯化残留物,得到 4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 (102)(450mg,94%)。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 6.74-6.55(2H,m),5.20-5.12(1H,m),3.46-3.38(2H, m),3.14(3H, d, J = 5.02Hz),3.07(3H, d, J = 4.8Hz),1.70-1.60(2H, m),1.00(3H, t, J = 7.4Hz). ESI-MS(m/z) :373[M+H]$^+$。

[0793] 利用关于化合物 (20a) 描述的程序,在甲醇中用 2M HCl/ 二乙醚处理 4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 (102)(140mg,0.51mmol)(125mg,79 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 14.86(1H, s),8.50(1H, br s),7.68(1H, br s),7.17-7.07(1H, m),3.57-3.50(2H, m),3.26(3H, d, J = 5.2Hz),3.17(3H, d, J = 4.8Hz),1.75-1.65(2H, m),1.01(3H, t, J = 7.4Hz). ESI-MS(m/z) :373[M+H]$^+$;熔点 :201-204℃。

[0794] 实施例 49:N^4, N^8- 二甲基 -N^2- 正丙基 -6-(氨基甲基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (104) 和相应的盐酸盐 (105a)(方案 20)

[0795] 将4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-腈(102)(200mg,0.73mmol)和Re-Ni(50%H_2O中浆液,75mg)在EtOH(10mL)中的混合物在10atm下氢化90min。将反应混合物通过C盐过滤,并将滤液蒸发。利用CH_2Cl_2/MeOH(9/1)至(1:1)的梯度洗脱通过快速柱层析纯化残留物,得到N^4,N^8-二甲基-N^2-正丙基-6-氨基甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(104)(110mg,55%y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ6.72-6.62(1H,m),6.56-6.47(1H,m),4.95-4.87(1H,m),3.87(2H,s),3.44-3.35(2H,m),3.13(3H,d,J=5.1Hz),3.08(3H,d,J=5.1Hz),1.83(2H,s),1.70-1.59(2H,m),1.00(3H,t,J=7.4).MS(m/z):277$[M+H]^+$。

[0796] 利用关于化合物(29a)描述的程序,在1,4-二噁烷中用2M HCl/二乙醚处理N^4,N^8-二甲基-N^2-正丙基-N^4,N^8-二甲基-6-氨基甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(104)(110mg,0.40mmol),定量产率(125mg,~100%y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ12.76(1H,br s),9.08-8.62(1H,m),8.50(1H,s),7.80(3H,br s),4.60(2H,s),3.60-3.52(2H,m),3.29-3.17(6H,m),1.76-1.64(2H,m),0.99(3H,t,J=7.3).ESI-MS(m/z):277$[M+H]^+$;熔点:290℃(dec.)。

[0797] 实施例50:6-氨甲酰基-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(106)和相应的盐酸盐(107a)(方案20)

[0798] 将4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-腈(102)(230mg,0.84mmol)和0.2N NaOH(3mL)在1,4-二噁烷(3mL)中的混合物在100℃下加热1h。加水(15mL)并将所得悬浮液用EtOAc(3x 20mL)萃取。将组合的有机萃取物用水(50mL),然后用盐水溶液(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用$CHCl_3$/EtOAc(9:1)至$CHCl_3$/EtOAc/MeOH(4:2:1)的梯度洗脱通过快速柱层析纯化残留物,得到6-氨甲酰基-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(106)(185mg,76%y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ7.86(1H,s),7.06-6.88(1H,m),6.70-6.53(1H,m),6.00-5.83(1H,m),5.10(1H,t,J=5.7Hz),3.46-3.36(2H,m),3.16(3H,d,J=5.1Hz),3.05(3H,d,J=5.1Hz),1.65(2H,六重峰,J=7.4Hz),1.00(3H,t,J=7.4Hz).MS(m/z):291$[M+H]^+$。

[0799] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中用4M HCl/1,4-二噁烷处理6-氨甲酰基-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(106)(150mg,0.52mmol)(140mg,82%y)。400MHz ^{1}H NMR($CDCl_3$/trifluoroacetic acid,ppm):δ8.46-8.34(1H,m),8.23(1H,s),8.00-7.83(2H,m),7.21-7.10(1H,m),3.62-3.54(2H,m),3.26(3H,d,J=5.1Hz),3.21(3H,s),1.71(2H,六重峰,J=7.4Hz),1.00(3H,t,J=7.4Hz).ESI-MS(m/z):291$[M+H]^+$;熔点:>300℃。

[0800] 实施例51:4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-羧酸(108)(方案20)

[0801] 将4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-腈(102)(300mg,1.10mmol)和2N NaOH(3mL)在1,4-二噁烷(3mL)中的混合物在105℃下加热20h。将反应混合物用5%$KHSO_4$溶液酸化(pH 4)。在添加CH_2Cl_2(10mL)后形成白色析出物,并将其过滤,然后利用0.1%HCOOH至0.1%HCOOH中95%MeCN的梯度洗脱通过反相色谱法纯化,得到4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-羧酸(108)(130mg,41%y)。

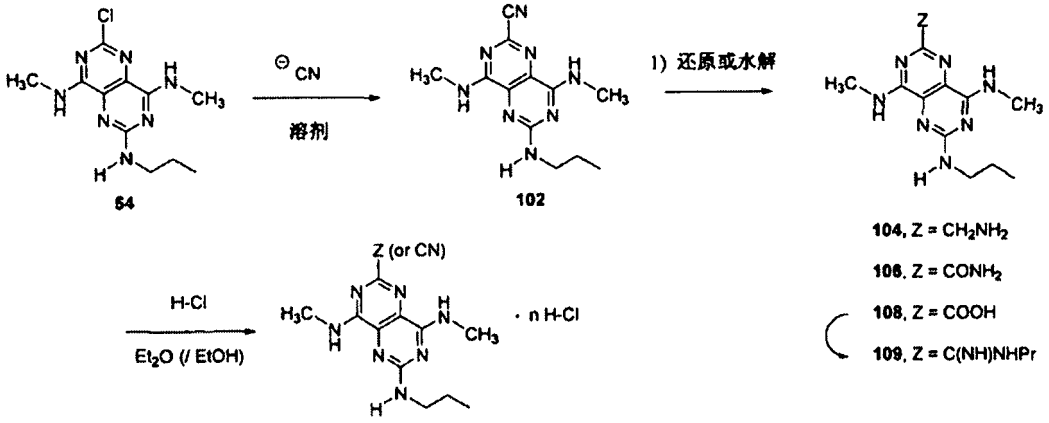
400MHz ^{1}H NMR(DMSO-d_6, ppm) :δ 8.24(1H, br s),7.82(1H, br s),7.24(1H, s),3.02(6H, d, J = 4.8Hz),3.04-2.81(2H, m),1.64-1.48(2H, m),0.91(3H, t, J = 7.4Hz). ESI-MS(m/z) :292[M+H]$^+$;熔点 :218-220℃。

[0802] 实施例 52:N-(正丙基)-[4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基]-脒(109)和相应的盐酸盐(110a)(方案 20)

[0803] 将 4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-腈(102)(270mg mg,0.99mmol)、NaOAc(123mg,1.5mmol)和正丙胺(124μL,1.5mmol)在MeOH(5mL)中的混合物在 110℃下加热 2h。去除挥发物,并将残余物在饱和 $NaHCO_3$溶液(15mL)和 $CHCl_3$(15mL)之间分配。分离水相,并用 $CHCl_3$(2x 15mL)萃取。将组合的有机萃取物用水(50mL)洗涤,并在固体无水 Na_2SO_4上干燥。过滤后,去除溶剂,并利用水中 10% MeOH 至 95% MeOH 的梯度洗脱通过反相色谱法纯化残留物,得到 N-(正丙基)-[4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基]-脒(109)(160mg,49% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 8.3-7.8(1H,br s),6.75-6.65(1H,m),6.63-6.52(2H,m),5.01(1H,t,J = 5.6Hz),3.52-3.37(4H, m),3.18(3H, d, J = 5.2Hz),3.11(3H, d, J = 5.2Hz),1.78-1.69(2H, m),1.69-1.60(2H, m),1.03(3H, t, J = 7.5Hz),1.01(3H, t, J = 7.5Hz). ESI-MS(m/z) :332[M+H]$^+$。

[0804] 利用关于化合物(20a)描述的程序,在 1,4-二噁烷中用 2M HCl/二乙醚处理 N-(正丙基)-[4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基]-脒(109)(150mg,0.45mmol)(160mg,97 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm) :δ 10.09(1H, s),9.87-9.46(1H, m),9.19-8.62(2H, m),6.71(1H, s),5.14(1H, s),3.93-3.80(2H, m),3.51-3.34(2H, m),3.21-3.03(6H, m),1.90-1.77(2H, m),1.71-1.60(2H, m),1.04(3H, t, J = 7.4Hz),1.00(3H, t, J = 7.4Hz). ESI-MS(m/z) :332[M+H]$^+$;熔点 :172℃ (dec.)。

[0805]



方案 20

[0806] 实施例 53:N^4,N^8-二甲基-N^2-正丙基-6-(4-氟苯基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(111)和相应的盐酸盐(112a)(方案 21)

[0807] 将 6-氯-N^2-正丙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(54)(190mg,0.67mmol)、4-氟苯硼酸(141mg,1.01mmol)、2M Na_2CO_3溶液(1.5mL)和 $Pd(PPh_3)_4$(35mg,0.03mmol)在二甲氧基乙烷中的混合物在 105℃下在氩气气氛下加热 4h。冷却反应混合物,加水(15mL),并将所得悬浮液用 EtOAc(3x 15mL)萃取。将组合的有机萃

取物用水 (30mL)，然后用盐水溶液 (30mL) 洗涤，并在固体无水 Na_2SO_4 上干燥。过滤后，去除溶剂，并利用 PE/EtOAc(9 ： 1) 至 PE/EtOAc(2 ： 1) 的梯度洗脱通过快速柱层析纯化残留物，得到 N^4,N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟 - 苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (111) (125mg,55% y)。400MHz ^{1}H NMR($CDCl_3$,ppm) ：δ 8.48-8.42(2H,m),7.15-7.07(2H,m),6.83-6.75(1H,m),6.56-6.48(1H,m),4.94(1H,t,J = 5.6Hz),3.46-3.39(2H,m),3.24(3H,d,J = 5.0Hz),3.13(3H,d,J = 5.0Hz),1.72-1.62(2H,m),1.02(3H,t,J = 7.4Hz). ESI-MS(m/z) :342[M+H]$^+$。

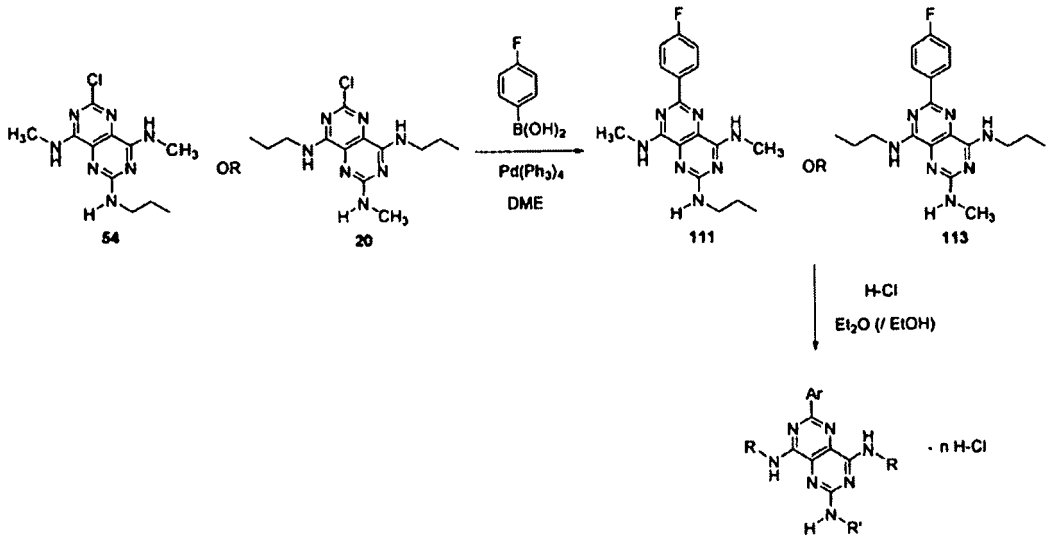
[0808] 利用关于化合物 (29a) 描述的程序，在二乙醚 / 甲醇 (10/1) 中用 2M HCl/ 二乙醚处理 N^4, N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟 - 苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (111) (100mg,0.29mmol)，定量产率 (110mg，～ 100% y)。400MHz ^{1}H NMR(DMSO-d_6, ppm) ：δ 13.2-12.7(1H, br s),9.60(1H, br s),8.66-8.59(2H, m),8.30(1H, br s),7.60(1H, br s),7.39-7.30(2H, br s),3.60-3.30(2H, m,与水重叠),3.17-3.07(6H, m),1.70-1.60(2H, m),0.96(3H, t, J = 7.3Hz). ESI-MS(m/z) :342[M+H]$^+$;熔点 :270℃ (dec.)。

[0809] 实施例 54:N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 氟 - 苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (113) 和相应的盐酸盐 (114a)(方案 21)

[0810] 利用关于化合物 (111) 描述的程序，使 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) (250mg,0.81mmol) 和 4- 氟苯硼酸 (166mg,1.2mmol) 反应，生成 N^2- 甲基 -N^4,N^8- 二 - 正丙基 -6-(4- 氟 - 苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (113) (200mg,67% y)。400MHz ^{1}H NMR($CDCl_3$,ppm) ：δ 8.46-8.40(2H,m),7.15-7.08(2H,m),6.83(1H,t,J = 5.7Hz),6.60(1H,t,J = 5.7Hz),4.91-4.82(1H,m),3.69-3.62(2H,m),3.56-3.49(2H, m),3.03(3H, d, J = 5.1Hz),1.84-1.69(4H, m),1.06(3H, t, J = 7.5Hz),1.04(3H, t, J = 7.5Hz). ESI-MS(m/z) :370[M+H]$^+$。

[0811] 利用关于化合物 (29a) 描述的程序，在乙醇中用 2M HCl/ 二乙醚处理 N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (113) (190mg,0.51mmol) (207mg，～ 100% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 8.42-8.35(2H, m),7.98-7.88(1H,m),7.88-7.79(1H,m),7.19-7.10(2H,m),6.99-6.88(1H,m),3.75-3.62(4H,m),3.11(3H, d, J = 4.8Hz),1.92-1.75(4H, m),1.08(6H, t, J = 7.4Hz). ESI-MS(m/z) :370[M+H]$^+$;熔点 :277-279℃。

[0812]



54 20 111 113

方案 21

[0813] 实施例 55:N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (115) 和相应的盐酸盐 (116a)

[0814] 将 6- 氯 -N^2- 正丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54) (440mg,1.42mmol)、三乙胺 (185 μL,1.32mmol) 和 10% Pd/C(160mg) 在 EtOH(10mL) 中的混合物在 10 个大气压下氢化 24h。将反应混合物通过 C 盐过滤,并将滤液蒸发。将残留物溶解于 EtOAc(80mL),用水 (3x30mL),然后用盐水溶液 (30mL) 洗涤,并在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂;利用 PE/EtOAc(9 : 1) 至 PE/EtOAc(1 : 2) 的梯度洗脱通过快速柱层析纯化残留物,得到 N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (115) (185mg,84% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 8.26(1H, s),6.65(1H, br s),6.55(1H, br s),4.96(1H, t, J = 5.4Hz),3.44-3.37(2H, m),3.14(3H, d, J = 5.1Hz),3.07(3H, d, J = 5.0Hz),1.70-1.59(2H, m),1.00(3H, t, J = 7.4Hz). ESI-MS(m/z) :248$[M+H]^+$。

[0815] 利用关于化合物 (29a) 描述的程序,在二乙醚中用 2M HCl/ 二乙醚处理 N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (115)(175mg,0.71mmol),定量产率 (200mg, ~ 100% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 8.97-8.60(2H, m),8.43(1H, s),7.02-6.94(1H, m),3.52(2H, td, J = 6.8,6.4Hz),3.24(3H, d, J = 5.1Hz),3.22(3H, d, J = 4.7Hz),1.75-1.64(2H, m),1.01(3H, t, J = 7.4Hz). ESI-MS(m/z) :248$[M+H]^+$;熔点 : 180-182℃。

[0816] 实施例 56:6- 正丁基 -N^2- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (117) 和相应的盐酸盐 (118a)

[0817] 将 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20) (400mg,1.29mmol)、丁基硼酸 (223mg,2.19mmol)、K_2CO_3(535mg,3.87mmol)、Ag_2O(748mg,3.23mmol) 和 Pd(dppf)Cl_2xCH_2Cl_2(114mg,0.14mmol) 在 THF(1.0mL) 和 1,4- 二[illegible]烷 (7.0mL) 中的混合物在 115℃下在氩气气氛下加热 20h。添加丁基硼酸 (120mg,1.18mmol) 和 Pd(dppf)Cl_2xCH_2Cl_2(60mg,0.07mmol),并继续加热 48h。冷却反应混合物,并通过 C 盐过滤。将饱和 $NaHCO_3$ 溶液 (20mL) 加入滤液,并将所得悬浮液用 CH_2Cl_2(2x 20mL) 萃取。将组合的有机萃取物用水 (30mL) 洗涤,并在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 PE/

EtOAc(20 ： 1) 至 PE/EtOAc(5 ： 2) 的梯度洗脱通过快速柱层析纯化残留物，得到 6- 正丁基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (117)(240mg,56% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 6.78-6.65(1H, m),6.52-6.42(1H, m),4.82-4.71(1H, m),3.57-3.50(2H, m),3.50-3.43(2H, m),2.99(3H, d, J = 5.1Hz),2.75-2.68(2H, m),1.83-1.65(6H, m),1.46-1.36(2H, m),1.01(3H, t, J = 7.3Hz),1.00(3H, t, J = 7.3Hz),0.95(3H, t, J = 7.4Hz). ESI-MS(m/z) :332$[M+H]^+$。

[0818] 利用关于化合物 (29a) 描述的程序，在二乙醚中用 2M HCl/ 二乙醚处理 6- 正丁基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (117(230mg, 0.69mmol)(255mg, ～ 100% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 7.84-7.54(2H, m),6.88(1H, br s),3.71-3.51(4H, m),3.08(3H, d, J = 4.5Hz),2.83-2.63(2H, m),1.85-1.70(6H, m),1.47-1.34(2H, m),1.09-0.99(6H, m),0.95(3H, t, J = 7.3). ESI-MS(m/z) :332$[M+H]^+$；熔点 :125-127℃。

[0819] 实施例 57:6- 甲氧基 -N^2- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (119) 和相应的盐酸盐 (120a)

[0820] 将 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20)(300mg,0.97mmol) 和 NaOMe(4M, 在 MeOH 中 ;620 μL) 在甲醇 (5mL) 中的混合物在 105℃下加热 48h。去除挥发物，并将残余物在饱和 NH_4Cl 溶液 (30mL) 和 CH_2Cl_2(30mL) 之间分配。分离水相，并用 CH_2Cl_2(2x30mL) 萃取。将组合的有机萃取物用水 (50mL) 洗涤，并在固体无水 Na_2SO_4上干燥。过滤后，去除溶剂，并利用 CH_2Cl_2至 CH_2Cl_2/MeOH(97 ： 3) 的梯度洗脱通过快速柱层析纯化残留物，得到 6- 甲氧基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (119)(225mg,76% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 6.72-6.63(1H, m),6.51-6.43(1H, m),4.75-4.67(1H, m),3.95(3H, s),3.57-3.50(2H, m),3.50-3.44(2H, m),2.99(3H, d, J = 5.0Hz),1.77-1.64(4H, m),1.01(3H, t, J = 7.4Hz),1.00(3H, t, J = 7.4Hz). ESI-MS(m/z) :306$[M+H]^+$。

[0821] 利用关于化合物 (29a) 描述的程序，在乙醇中用 2M HCl/ 二乙醚处理 6- 甲氧基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (119)(210mg, 0.69mmol)(235mg, ～ 100% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 8.38(1H, s),8.05(1H, br s),6.70(1H, s),4.00(3H, m),3.68-3.61(4H, m),3.08(3H, d, J = 4.1Hz),1.87-1.70(4H, m),1.04(3H, t, J = 7.3Hz),1.03(3H, t, J = 7.3Hz). ESI-MS(m/z) :306$[M+H]^+$；熔点 : 201-204℃。

[0822] 实施例 58:6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 (121) 和相应的盐酸盐 (122a)

[0823] 利用关于化合物 (102) 描述的程序，使 6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (20)(250mg,0.81mmol) 和 KCN 反应，生成 6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 (121)(170mg,70% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) ：δ 6.71(1H, br s),6.64(1H, br s),5.10-5.03(1H, m),3.57-3.51(2H, m),3.51-3.42(2H, m),3.02(3H, d, J = 5.0Hz),1.77-1.64(4H, m),1.02(3H, t, J = 7.4Hz),1.01(3H, t, J = 7.4Hz). ESI-MS(m/z) :301$[M+H]^+$。

[0824] 利用关于化合物 (20a) 描述的程序，在甲醇中用 2M HCl/ 二乙醚处理 6- 甲基氨

基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈 (121) (160mg,0.53mmol) (130mg, 73 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 14.91(0.8H, s),14.64(0.2H, s),8.44(0.8H, s),8.34(0.2H, s),7.71-7.56(1H, m),7.07(0.8H, s),6.88(0.2H, s),3.69-3.63(2H, m), 3.63-3.54(2H,m),3.16-3.07(3H,m),1.86-1.72(4H,m),1.06(3H, t, J = 7.4Hz),1.04(3H, t, J = 7.4Hz). ESI-MS(m/z) :301[M+H]$^+$;熔点 :204-206℃。

[0825] 实施例 59:N^2N^4,N^6,N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (124) 和相应的盐酸盐 (125a)

[0826] 2,6- 二氯 -N^4N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (123) :

[0827] 将 2M 乙胺 /THF(6.69mL,13.38mmol) 溶液在 0℃下加入 2,4,6,8- 四氯 - 嘧啶并 [5,4-d] 嘧啶 (1) (800mg,2.96mmol) 的 THF(10mL) 溶液。将反应混合物在室温下搅拌 1h。加水 (30mL),并将所得析出物过滤,用水 (10mL) 洗涤,并在 P_2O_5 上干燥,得到 2,6- 二氯 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (123) (745mg,88%)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 6.87(2H,br s),3.63(4H,qd, J = 7.3,5.9Hz),1.32(6H, t, J = 7.3Hz). ESI-MS(m/z) :287,289,291[M+H]$^+$。

[0828] N^2, N^4, N^6, N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (124) :

[0829] 将 2,6- 二氯 -N^4,N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (123) 和乙胺 (70% 水溶液,2.00mL) 在正丁醇 (3mL) 中的混合物在 100℃下加热 44h。通过蒸发去除挥发物,并将残余物在 CH_2Cl_2(20mL) 和饱和 $NaHCO_3$ 溶液 (20mL) 之间分配。分离水相,并用 CH_2Cl_2(2x 20mL) 萃取。将组合的有机萃取物用水 (50mL) 洗涤,并在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 CH_2Cl_2 至 CH_2Cl_2/EtOH(98 : 2) 的梯度洗脱通过快速柱层析纯化残留物,得到 N^2, N^4, N^6, N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (124) (233mg,91% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 6.42(2H, s),4.58(2H, s),3.57-3.48(4H, m),3.46-3.39(4H, m),1.28(6H, t, J = 7.3Hz),1.23(6H, t, J = 7.3Hz). ESI-MS(m/z) :305[M+H]$^+$。

[0830] N^2, N^4, N^6N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺盐酸盐 (125a) :

[0831] 利用关于化合物 (29a) 描述的程序,在 1,4- 二▒烷 /EtOH(1/1) 中用 4M HCl/1,4- 二▒烷处理 N^2, N^4, N^6, N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (124) (220mg, 0.72mmol) (245mg, ~ 100% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 9.63(2H, s),6.67(2H, t, J = 5.6Hz),3.74-3.66(4H, m),3.57-3.50(4H, m),1.41(6H, t, J = 7.3Hz),1.27(6H, t, J = 7.3Hz). ESI-MS(m/z) :305[M+H]$^+$;熔点 :247℃ (dec.)。

[0832] 实施例 60:N^4,N^8- 二乙基 -N^2,N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (126) 和相应的盐酸盐 (127a)

[0833] 将 2,6- 二氯 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (123) (245mg, 0.85mmol) 和正丙胺 (352 μL,4.27mmol) 在正丁醇 (5.0mL) 中的混合物在 130℃下加热 44h。通过蒸发去除挥发物,并将残余物在 CH_2Cl_2(20mL) 和饱和 $NaHCO_3$ 溶液 (20mL) 之间分配。分离水相,并用 CH_2Cl_2(2x 20mL) 萃取。将组合的有机萃取物用水 (50mL) 洗涤,并在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 CH_2Cl_2 至 CH_2Cl_2/EtOH(98 : 2) 的梯度洗脱通过快速柱层析纯化残留物,得到 N^4,N^8- 二乙基 -N^2,N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (126) (220mg,78% y)。400MHz ^{1}H NMR($CDCl_3$, ppm) : δ 6.48-6.37(2H, m),4.64(2H, s),3.57-3.48(4H, m),3.39-3.32(4H, m),1.67-1.57(4H, m),1.32-1.24(6H,

m),1.02-0.96(6H,m).ESI-MS(m/z):333[M+H]$^+$。

[0834] 利用关于化合物(29a)描述的程序,在1,4-二㗁烷/EtOH(1/1)中用4M HCl/1,4-二噁烷处理N^4,N^8-二乙基-N^2,N^6-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(126)(220mg,0.66mmol)(244mg,~100% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ9.58(2H,s),6.75-6.68(2H,m),3.74-3.64(4H,m),3.49-3.41(4H,m),1.71-1.63(4H,m),1.41(6H,t,J=7.2Hz),0.98(6H,t,J=7.4Hz).ESI-MS(m/z):333[M+H]$^+$;熔点:248℃(dec.)。

[0835] 实施例61:N^2,N^6-双-环丙基甲基-N^4,N^8-二乙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(128)和相应的盐酸盐(129a)

[0836] 将2,6-二氯-N^4,N^8-二乙基-嘧啶并[5,4-d]嘧啶-4,8-二胺(123)(245mg,0.85mmol)和环丙基甲胺(370μL,4.27mmol)在正丁醇(5.0mL)中的混合物在130℃下在封闭瓶中加热44h。通过蒸发去除挥发物,并将残余物在CH_2Cl_2(20mL)和饱和$NaHCO_3$溶液(20mL)之间分配。分离水相,并用CH_2Cl_2(2x 20mL)萃取。将组合的有机萃取物用水(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用CH_2Cl_2至CH_2Cl_2/MeOH(9∶1)的梯度洗脱通过快速柱层析纯化残留物,得到N^2,N^6-双-环丙基甲基-N^4,N^8-二乙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(128)(135mg,45% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ7.03-6.98(2H,m),6.10-6.03(2H,m),3.48-3.40(4H,m),3.21-3.14(4H,m),1.20-1.13(6H,m),1.09-1.02(2H,m),0.44-0.36(4H,m),0.23-0.18(4H,m).ESI-MS(m/z):357[M+H]$^+$。

[0837] 利用关于化合物(29a)描述的程序,在1,4-二噁烷/EtOH(1/1)中用4M HCl/1,4-二噁烷处理N^2,N^6-双-环丙基甲基-N^4,N^8-二乙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(128)(135mg,0.66mmol)(148mg,~100% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ9.66(2H,s),6.78(2H,s),3.76-3.64(4H,m),3.39-3.36(4H,m),1.45-1.38(6H,m),1.13-1.04(2H,m),0.63-0.56(4H,m),0.31-0.26(4H,m).ESI-MS(m/z):357[M+H]$^+$;熔点:243-245℃。

[0838] 实施例62:N^2,N^6-二乙基-N^4N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(131)和相应的盐酸盐(132a)

[0839] 2,6-二氯-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(130):

[0840] 将环丙基甲胺(802μL,9.25mmol)在0℃下加入2,4,6,8-四氯-嘧啶并[5,4-d]嘧啶(1)(500mg,1.85mmol)的THF(8mL)溶液。将反应混合物在室温下搅拌3h。然后加水(30mL),并将所得悬浮液用CH_2Cl_2(3x 20mL)萃取。将组合的有机萃取物用水(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并将残留物用二乙醚捣碎。将所得析出物过滤并干燥,得到2,6-二氯-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(130)(480mg,76% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ6.96(2H,t,J=5.7Hz),3.42(4H,dd,J=7.3,5.7Hz),1.16-1.05(2H,m),0.66-0.53(4H,m),0.38-0.25(4H,m).ESI-MS(m/z):339,341,343[M+H]$^+$。

[0841] N^2N^6-二乙基-N^4N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(131):

[0842] 将2,6-二氯-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(130)(220mg,0.65mmol)和乙胺(70%水溶液,1.00mL)在1,4-二㗁烷(5.0mL)中的混合物在130℃下加热144h。通过蒸发去除挥发物,并将残余物在CH_2Cl_2(20mL)和饱和$NaHCO_3$溶液

(20mL)之间分配。用CH_2Cl_2(2x 30mL)萃取水相。将组合的有机萃取物用水(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用PE/EtOAc(5 : 1)至PE/EtOAc(1 : 1)的梯度洗脱通过快速柱层析纯化残留物,得到N^2,N^6-二乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(131)(190mg,82%)。400MHz ^1H NMR(DMSO-d_6+TFA,ppm):δ 3.45-3.32(8H,m),1.17-1.08(8H,m),0.52-0.45(4H,m),0.31-0.25(4H,m).ESI-MS(m/z):357$[M+H]^+$。

[0843] N^2,N^6-二乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(132a):

[0844] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中用2M HCl/二乙醚处理N^2,N^6-二乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(131)(170mg,0.45mmol)(140mg,74% y)。400MHz ^1H NMR($CDCl_3$,ppm):δ 14.90(0.5H,s),13.94(1H,s),9.70(0.5H,s),7.84(0.5H,s),7.53(1H,s),6.71(1H,m),4.80(0.5H,s),3.61-3.31(8H,m),1.33-1.08(8H,m),0.72-0.52(4H,m),0.44-0.28(4H,m).ESI-MS(m/z):357$[M+H]^+$;熔点:198-200℃。

[0845] 实施例63:N^2,N^2,N^6-三乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(134)和相应的盐酸盐(135a)

[0846] 6-氯-N^2-乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(133):

[0847] 将2,6-二氯-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(130)(235mg,0.71mmol)和乙胺(70%水溶液,1.00mL)在正丁醇(5.0mL)中的混合物在80℃下加热18h。通过蒸发去除挥发物,并将残余物在CH_2Cl_2(20mL)和饱和$NaHCO_3$溶液(20mL)之间分配。分离水相,并用CH_2Cl_2(2x 30mL)萃取。将组合的有机萃取物用水(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,得到6-氯-N^2-乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(133)(247mg,100%)。ESI-MS(m/z):348,350$[M+H]^+$。

[0848] N^2,N^2,N^6-三乙基-$N^4$$N^8$-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(134):

[0849] 将6-氯-N^2-乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(133)(243mg,0.70mmol)和二乙胺(1.0mL)在正丁醇(4.0mL)中的混合物在130℃下在封闭瓶中加热110h。通过蒸发去除挥发物,并将残余物在CH_2Cl_2(35mL)和饱和$NaHCO_3$溶液(30mL)之间分配。分离水相,并用CH_2Cl_2(2x 30mL)萃取。将组合的有机萃取物用水(40mL)洗涤,并在固体无水Na_2SO_4上干燥。去除溶剂,并利用PE/EtOAc(9 : 1)至PE/EtOAc(1 : 1)的梯度洗脱通过快速柱层析纯化残留物,得到N^2,N^2,N^6-三乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(134)(210mg,78% y)。400MHz ^1H NMR($CDCl_3$,ppm):δ 6.74-6.29(2H,m),4.49(1H,br s),3.72-3.55(4H,m),3.51-3.26(6H,m),1.29-1.08(11H,m),0.62-0.48(4H,m),0.38-0.25(4H,m).ESI-MS(m/z):385$[M+H]^+$。

[0850] N^2,N^2,N^6-三乙基-N^4,N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(135a):

[0851] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中处理N^2,N^2,N^6-三乙基-N^4,

N^8-双-环丙基甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(134)(190mg,0.49mmol)和2M HCl/二乙醚(170mg,82% y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 13.91(1H, s),7.73(1H, s),7.56-7.47(1H,m),6.71-6.60(1H,m),3.60(4H,q,J = 7.1Hz),3.55-3.45(4H,m),3.40(2H,dd,J = 7.0,5.2Hz),1.27-1.11(2H,m),1.25(3H,t,J = 7.0Hz),1.19(6H,t,J = 7.2Hz),0.66-0.60(2H,m),0.60-0.54(2H,m),0.38-0.29(4H,m).ESI-MS(m/z):385$[M+H]^+$;熔点:215-217℃。

[0852] 实施例64:N^2,N^6-二乙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(136)和相应的盐酸盐(137a)

[0853] 利用关于化合物(32)描述的程序,使2,6-二氯-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-4,8-二胺(2)(250mg,0.79mmol)和乙胺(70%水溶液)反应,生成N^2,N^6-二乙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(136)(175mg,67% y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 6.48(2H, s),4.55(2H, s),3.49-3.38(8H, m),1.69(4H,六重峰,J = 7.4Hz),1.23(6H, t, J = 7.4Hz),1.00(6H, t, J = 7.4Hz).ESI-MS(m/z):333$[M+H]^+$。

[0854] 利用关于化合物(20a)描述的程序,在1,4-二**噁**烷中用2M HCl/二乙醚处理N^2,N^6-二乙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(136)(160mg,0.48mmol)(155mg,87 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 13.92(1H, s),7.69(1H, s),7.47(1H, s),6.67(1H, s),4.80(1H, s),3.64-3.30(8H, m),1.82-1.68(4H, m),1.29-1.18(6H, m),1.02(6H, t, J = 7.4Hz).ESI-MS(m/z):333$[M+H]^+$;熔点:190-192℃。

[0855] 实施例65:N^2,N^6-二环丙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(138)

[0856] 将2,6-二氯-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-4,8-二胺(2)(300mg,0.95mmol)和环丙胺(396 μL,5.71mmol)在正丁醇(3.0mL)中的混合物在130℃下在封闭瓶中加热72h。添加另一份环丙胺(263 μL,3.80mmol),并在130℃下继续加热48h。通过蒸发去除挥发物,并将残余物在CH_2Cl_2(35mL)和饱和$NaHCO_3$溶液(30mL)之间分配。分离水相,并用CH_2Cl_2(2x 30mL)萃取。将组合的有机萃取物用水(40mL)洗涤,并在上干燥固体无水Na_2SO_4。过滤后,去除溶剂,并利用CH_2Cl_2至CH_2Cl_2/EtOAc(1 : 1)的梯度洗脱通过快速柱层析纯化残留物,得到N^2,N^6-二环丙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(138)(66mg,19% y)。400MHz ^{1}H NMR(DMSO-d_6, ppm):δ 6.93-6.88(2H,m),6.36-6.33(2H,m),3.41-3.34(4H,m),2.85-2.77(2H,m),1.60(4H,六重峰,J = 7.3Hz),0.90(6H,t,J = 7.3Hz),0.64-0.57(4H,m),0.46-0.41(4H,m).ESI-MS(m/z):357$[M+H]^+$;熔点:210-212℃。

[0857] 实施例66:$N^2$$N^6$-双-环丙基甲基-$N^4$,$N^8$-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(139)和相应的盐酸盐(140a)

[0858] 将2,6-二氯-N,N'-二-正丙基-嘧啶并[5,4-d]嘧啶-4,8-二胺(2)(300mg,0.95mmol)和环丙基甲胺(1.0mL,11.53mmol)在DMSO(1.0mL)中的混合物在145℃下在封闭瓶中加热22h。加水(10mL),并将所得析出物过滤并干燥,得到N^2,N^6-双-环丙基甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(139)(320mg,88% y)。400MHz ^{1}H NMR(DMSO-d6/三氟乙酸, ppm):δ 9.0-7.0(4H, br s),3.50-3.40(4H, m),3.26(4H, d, J = 7.0Hz),1.69-1.58(4H, m),1.13-1.02(2H, m),0.93(6H, t, J = 7.4Hz),0.50-0.38(4H,

m),0.31-0.19(4H,m).ESI-MS(m/z):385[M+H]$^+$。

[0859] 利用关于化合物(29a)描述的程序,在乙醇中用2M HCl/二乙醚处理N^2,N^6-双-环丙基甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(139)(280mg,0.73mmol)。将产物从乙醇结晶,得到N^2,N^6-双-环丙基甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(305mg,99%)。400MHz ^{1}H NMR(DMSO-d_6,ppm):δ9.3-6.7(4H,m),3.52-3.36(4H,m),3.28(4H,d,J = 6.8Hz),1.65(4H,六重峰,J = 7.3Hz),1.15-1.04(2H,m),0.95(6H,t,J = 7.3Hz),0.54-0.40(4H,m),0.35-0.24(4H,m).ESI-MS(m/z):385[M+H]$^+$;熔点:221-224℃。

[0860] 实施例67:N^2,N^2,N^6,N^6-四甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(141)和相应二盐酸盐(142a)

[0861] 将2,6-二氯-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-4,8-二胺(2)(300mg,0.95mmol)和2M二甲胺/THF(4.75mL,9.50mmol)在正丁醇(5.0mL)中的混合物在110℃下在封闭瓶中加热40h。去除挥发物,并将残余物在饱和$NaHCO_3$溶液(20mL)和CH_2Cl_2(20mL)之间分配。分离水相,并用CH_2Cl_2(2x 20mL)萃取。将组合的有机萃取物用水(30mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,并利用PE/EtOAc(9∶1)至PE/EtOAc(1∶1)的梯度洗脱通过快速柱层析纯化残留物,得到N^2,N^2,N^6,N^6-四甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(141)(280mg,89% y)。ESI-MS(m/z):333[M+H]$^+$。

[0862] 利用关于化合物(3a)描述的程序,在1,4-二**噁**烷/乙醇(3/1)中用2M HCl/二乙醚处理N^2,N^2,N^6,N^6-四甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(141)(270mg,0.81mmol)(270mg,82% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ12.24(2H,br s),11.57(2H,s),3.67-3.56(4H,m),3.45(12H,s),1.90-1.77(4H,m),1.01(6H,t,J = 7.3Hz).ESI-MS(m/z):333[M+H]$^+$;熔点:240-242℃。$C_{16}H_{30}Cl_2N_8$分析计算值:C,47.41;H,7.46;N,27.64。实际值:C,47.33;H,7.46;N,27.45。

[0863] 实施例68:N^4,N^8-二烯丙基-N^2,N^6-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(144)和相应的盐酸盐(145a)

[0864] N^4,N^8-二烯丙基-2,6-二氯-嘧啶并[5,4-d]嘧啶-4,8-二胺(143):

[0865] 在0℃下向2,4,6,8-四氯-嘧啶并[5,4-d]嘧啶(1)(700mg,2.59mmol)的THF(20mL)溶液滴加THF(5mL)中的烯丙胺(815μL,10.89mmol)。将反应混合物在0℃下搅拌90min,然后在室温下搅拌30min。添加饱和$NaHCO_3$溶液(30mL),并将所得悬浮液用EtOAc(3x 30mL)萃取。将组合的有机萃取物用水(50mL),然后用盐水溶液(50mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除溶剂,得到N^4,N^8-二烯丙基-2,6-二氯-嘧啶并[5,4-d]嘧啶-4,8-二胺(143)(730mg,91% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ7.00-6.91(2H,m),5.95(2H,ddt,J = 17.2,10.2,5.8Hz),5.32(2H,ddt,J = 17.2,1.5,1.5Hz),5.25(2H,ddt,J = 10.2,1.5,1.5Hz),4.23(4H,ddt,J = 5.8,5.8,1.5Hz).ESI-MS(m/z):311,313,315[M+H]$^+$。

[0866] N^4,N^8-二烯丙基-N^2,N^6-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(144):

[0867] 将N^4,N^8-二烯丙基-2,6-二氯-嘧啶并[5,4-d]嘧啶-4,8-二胺(143)(350mg,1-12mmol)和甲胺(40%水溶液,1.0mL)在正丁醇(1.0mL)中的混合物在130℃下在封闭瓶中加热40h。冷却反应混合物,添加饱和$NaHCO_3$溶液(30mL),并将所得悬浮液用

EtOAc(3x15mL)萃取。将组合的有机萃取物用水(30mL),然后用盐水溶液(30mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,利用PE/EtOAc(20 ∶ 1)至PE/EtOAc(1 ∶ 2)的梯度洗脱通过快速柱层析纯化产物,得到N^4,N^8-二烯丙基-N^2,N^6-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(144)(225mg,67%)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.57(2H,s),6.05-5.93(2H,m),5.32-5.23(2H,m),5.19-5.14(2H,m),4.61(2H,s),4.19-4.12(4H,m),2.96(6H,d,J = 5.1Hz).ESI-MS(m/z):301[M+H]$^+$。

[0868] N^4,N^8-二烯丙基-N^2,N^6-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺盐酸盐(145a):

[0869] 利用关于化合物(20a)描述的程序,在1,4-二噁烷/乙醇(1/1)中用2M HCl/二乙醚处理N^4,N^8-二烯丙基-N^2,N^6-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(144)(220mg,0.73mmol)(130mg,89 % y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 15.22-15.01(0.2H,m),14.30-14.02(0.8H,m),9.90-9.62(0.2H,m),7.90-7.75(0.8H,m),7.66-7.49(1H,m),6.66(1H,s),6.06-5.88(2H,m),5.44-5.10(4H,m),4.86(1H,m),4.36-4.08(4H,m),3.13-2.88(6H,m).ESI-MS(m/z):301[M+H]$^+$;熔点:224-226℃。

[0870] 实施例69:N^2,N^4,N^8-三烯丙基-6-[4-(4-氟苄基)-哌嗪-1-基]-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(147)和相应的二盐酸盐(148a)(方案22)

[0871] 6-氯-N^2,N^4,N^8-三烯丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(146):

[0872] 将2,6-二氯-N^4,N^8-二烯丙基-嘧啶并[5,4-d]嘧啶-4,8-二胺(143)(311mg,1.00mmol)和烯丙胺(340μL,4.50mmol)在正丁醇(1.0mL)中的混合物在70℃下在封闭瓶中加热16h。添加饱和$NaHCO_3$溶液(20mL),并用EtOAc(3x 15mL)萃取所得悬浮液。将组合的有机萃取物用水(50mL),然后用盐水溶液(30mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,利用PE/EtOAc(20 ∶ 1)至PE/EtOAc(1 ∶ 2)的梯度洗脱通过快速柱层析纯化产物,得到6-氯-N^2,N^4,N^8-三烯丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(146)(230mg,69% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 6.76(1H,t,J = 5.8Hz),6.61(1H,t,J = 5.8Hz),6.04-5.89(3H,m),5.33-5.12(6H,m),5.01(1H,t,J = 5.7Hz),4.22(2H,ddt,J = 5.8,5.8,1.5Hz),4.14(2H,ddt,J = 5.8,5.8,1.5Hz),4.07(2H,ddt,J = 5.7,5.7,1.6Hz).ESI-MS(m/z):332,334[M+H]$^+$。

[0873] N^2,N^4,N^8-三烯丙基-6-[4-(4-氟苄基)-哌嗪-1-基]-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(147):

[0874] 将6-氯-N^2,N^4,N^8-三烯丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(146)(175mg,0.53mmol)和1-(4-氟苄基)-哌嗪(206mg,1.06mmol)在正丁醇(5.0mL)中的混合物在70℃下在封闭瓶中加热60h。添加饱和$NaHCO_3$溶液(20mL),并用EtOAc(3x 25mL)萃取所得悬浮液。将组合的有机萃取物用水(50mL),然后用盐水溶液(30mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,利用PE/EtOAc(20 ∶ 1)至PE/EtOAc(2 ∶ 1)的梯度洗脱通过快速柱层析纯化产物,得到N^2,N^4,N^8-三烯丙基-6-[4-(4-氟苄基)-哌嗪-1-基]-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(147)(210mg,81% y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ 7.36-7.28(2H,m),7.05-6.96(2H,m),6.51(2H,br s),6.05-5.88(3H,m),5.32-5.20(3H,m),5.20-5.06(3H,m),4.69(1H,br s),4.20-4.10(4H,m),4.09-4.01(2H,m),3.82-3.70(4H,m),3.51(2H,s),2.53-2.42(4H,m).ESI-MS(m/z):490[M+H]$^+$。

[0875] N^2,N^4,N^8-三烯丙基-6-[4-(4-氟苄基)-哌嗪-1-基]-嘧啶并[5,4-d]嘧啶-2,4,8-三胺二氢氯化物(148a):

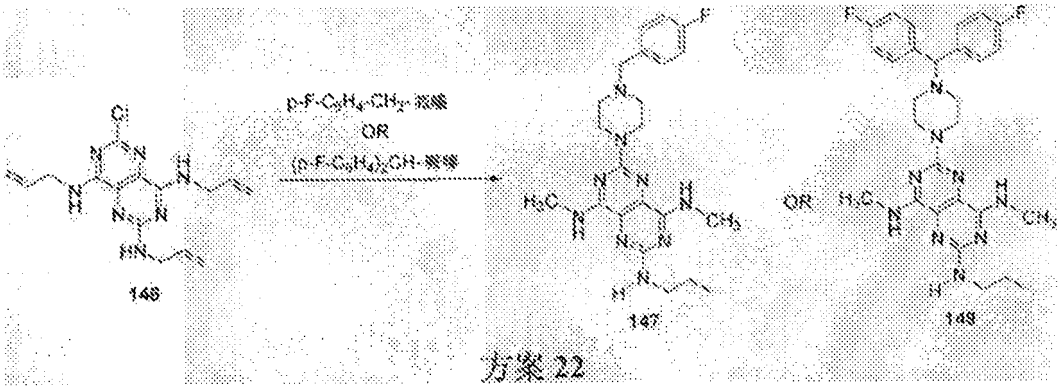
[0876] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中用2M HCl/二乙醚处理N^2,N^4,N^8-三烯丙基-6-[4-(4-氟苄基)-哌嗪-1-基]-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(147)(200mg,0.41mmol)(105mg,45%y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ7.19-7.10(2H,m),6.91-6.79(1H,m),5.99-5.79(3H,m),5.35-5.24(4H,m),5.23-5.14(2H,m),4.79-4.68(2H,m),4.31-4.20(2H,m),4.20-4.05(6H,m),3.88-3.75(2H,m),3.51-3.37(2H,m),2.84-2.69(2H,m).ESI-MS(m/z):490$[M+H]^+$;熔点:239-241℃。

[0877] 实施例70:N^2,N^4,N^8-三烯丙基-6-{4-[双-(4-氟苯基)-甲基]-哌嗪-1-基}-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(149和相应的二盐酸盐(150a)(方案22)

[0878] 利用关于化合物(147)描述的程序,使6-氯-N^2,N^4,N^8-三烯丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(146)(230mg,0.69mmol)和1-[双-(4-氟苯基)-甲基]-哌嗪反应,生成N^2,N^4,N^8-三烯丙基-6-{4-[双-(4-氟-苯基)-甲基]-哌嗪-1-基}-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(149)(260mg,64%y)。300MHz ^{1}H-NMR($CDCl_3$,ppm):δ7.43-7.33(4H,m),7.04-6.93(4H,m),6.68-6.27(2H,m),6.07-5.86(3H,m),5.31-5.19(3H,m),5.19-5.06(3H,m),4.80-4.55(1H,m),4.24(1H,m),4.19-4.08(4H,m),4.08-3.99(2H,m),3.82-3.68(4H,m),2.49-2.35(4H,m).ESI-MS(m/z):584$[M+H]^+$。

[0879] 利用关于化合物(20a)描述的程序,在1,4-二噁烷中用2M HCl/二乙醚处理N^2,N^4,N^8-三烯丙基-6-{4-[双-(4-氟苯基)-甲基]-哌嗪-1-基}-嘧啶并[5,4-d]嘧啶-2,4,8-三胺(149)(250mg,0.43mmol),85%产率(240mg,85%y)。400MHz ^{1}H NMR($CDCl_3$,ppm):δ13.64(1H,s),8.11(1H,s),8.05-7.88(4H,m),7.47(1H,s),7.18-7.07(4H,m),6.81(1H,t,J=5.7Hz),5.97-5.78(3H,m),5.33-5.26(2H,m),5.26-5.10(4H,m),4.91-4.80(1H,m),4.70-4.51(2H,m),4.26-4.19(2H,m),4.17-4.01(6H,m),3.58-3.43(2H,m),2.93-2.72(2H,m).ESI-MS(m/z):584$[M+H]^+$;熔点:240-242℃。

[0880]



方案22

[0881] 实施例71:N^2,N^2,N^6-三乙基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(151)和相应的盐酸盐(152a)

[0882] 将2,6-二氯-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-4,8-二胺(2)(215mg,0.68mmol)和乙胺(70%水溶液,1.00mL)在正丁醇(2.0mL)中的混合物在80℃下加热18h。添加饱和$NaHCO_3$溶液(15mL),并用EtOAc(3x 15mL)萃取所得悬浮液。将组合的有机萃取物用水(20mL),然后用盐水溶液(20mL)洗涤,并在固体无水Na_2SO_4上干燥。过滤后,去除

溶剂。将残留物溶解于正丁醇 (2.0mL)，并添加二乙胺 (1.0mL)。将混合物在 130℃下在封闭瓶中加热 60h。添加饱和 $NaHCO_3$ 溶液 (15mL)，并将所得悬浮液用 EtOAc(3x 20mL) 萃取。将组合的有机萃取物用水 (30mL)，然后用盐水溶液 (30mL) 洗涤，并在固体无水 Na_2SO_4 上干燥。过滤后，去除溶剂，并利用 PE/EtOAc(9 ： 1) 至 PE/EtOAc(1 ： 1) 的梯度洗脱通过快速柱层析纯化残留物，得到 N^2,N^2,N^6- 三乙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (151)(222mg,91％)。400MHz ^1H NMR($CDCl_3$, ppm) ：δ 6.52(1H, br s),6.41(1H, br s),4.51(1H, br s),3.68-3.54(4H, m),3.52-3.34(6H, m),1.74-1.63(4H, m),1.22(3H, t, J = 7.2Hz),1.18(6H, t, J = 7.0Hz),0.99(3H, t, J = 7.4Hz),0.98(3H, t, J = 7.4Hz). ESI-MS(m/z) :361$[M+H]^+$。

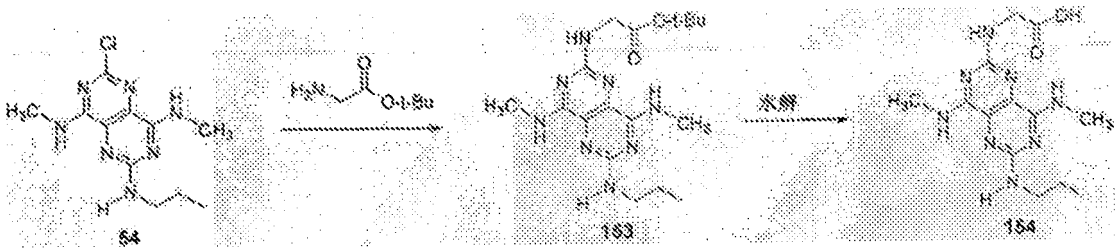
[0883] 利用关于化合物 (20a) 描述的程序，在二乙醚 / 乙醇 (20/1) 中用 2M HCl/ 二乙醚处理 N^2, N^2, N^6- 三乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺 (151)(207mg,0.57mmol)(220mg,97 % y)。400MHz ^1H NMR($CDCl_3$, ppm) ：δ 13.91(1H, br s), 7.9-7.2(2H, m),6.66-6.56(1H, m),3.75-3.45(10H, m),1.82-1.69(4H, m),1.25(3H, t, J = 7.2Hz),1.20(6H, t, J = 6.9Hz),1.02(3H, t, J = 7.4Hz),1.01(3H, t, J = 7.4Hz). ESI-MS(m/z) :361$[M+H]^+$;熔点 :205-206℃。

[0884] 实施例 72:(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯 (153) 和 (4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸 (154)(方案 23)

[0885] 将 6- 氯 -N^2- 正丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺 (54)(300mg,1.06mmol)、甘氨酸乙酯盐酸盐 (297mg,2.13mmol) 和 N,N- 二异丙基乙胺 (732μL, 4.24mmol) 在正丁醇 (4.0mL) 中的混合物在 130℃下在封闭瓶中加热 90h。添加饱和 $NaHCO_3$ 溶液 (15mL)，并用 CH_2Cl_2(3x30mL) 萃取所得悬浮液。将组合的有机萃取物用水 (50mL) 洗涤，并在固体无水 Na_2SO_4 上干燥。过滤后，去除溶剂，并利用 PE/EtOAc(9 ： 1) 至 PE/EtOAc(1 ： 3) 的梯度洗脱通过快速柱层析纯化残留物，得到 (4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯 (153)(150mg,38％ y)。ESI-MS(m/z) :377$[M+H]^+$。

[0886] 将 1N NaOH 溶液 (2mL) 加入 (4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯 (153)(150mg,0.40mmol) 的 1,4- 二[illegible]烷 (2mL) 溶液。将混合物在环境温度下搅拌 1h，然后用 1N HCl(pH 6-7) 中和。将所得析出物过滤，用水 (5mL) 洗涤，并干燥，得到 (4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸 (154)(60mg,47％ y)。400MHz 1H NMR(DMSO-d_6, ppm) ：δ 12.36(1H, br s),7.19(2H, br s),6.27(1H, s),6.17(1H, br s),4.06-3.96(2H, m),3.34-3.21(2H, m, 与水重叠),2.98-2.84(6H, m),1.60-1.46(2H, m),0.90(3H, t, J = 7.2Hz). ESI-MS(m/z) : 321$[M+H]^+$;熔点 :210-212℃。

[0887]



[0888]

方案 23

[0889] 实施例 73:N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺 (156) 和相应的盐酸盐 (157a)

[0890] (6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯 (155):

[0891] 将 2,6- 二氯 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺 (25)(207mg, 0.80mmol)、甘氨酸乙酯盐酸盐 (112mg,0.80mmol) 和 N, N- 二异丙基乙胺 (276μL, 1.60mmol) 在 1,4- 二噁烷 (4.0mL) 中的混合物在 105℃下在封闭瓶中加热 64h。添加另一份甘氨酸乙酯盐酸盐 (112mg,0.80mmol) 和 N, N- 二异丙基乙胺 (276μL,1.60mmol),并将混合物加热 80h。冷却后,添加饱和 $NaHCO_3$ 溶液 (15mL),并将所得悬浮液用 CH_2Cl_2(3x20mL) 萃取。将组合的有机萃取物用水 (50mL) 洗涤,并在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 PE/EtOAc(9 ： 1) 至 PE/EtOAc(1 ： 9) 的梯度洗脱通过快速柱层析纯化残留物,得到 (6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯 (155)。400MHz 1H NMR($CDCl_3$, ppm) : δ 6.72-6.64(1H, m),6.59-6.52(1H, m),5.43(1H, t, J = 5.6Hz),4.24(2H, q, J = 7.2Hz),4.18(2H, d, J = 5.6Hz),3.14(3H, d, J = 5.2Hz), 3.05(3H, d, J = 5.2Hz),1.29(3H, t, J = 7.2Hz). ESI-MS(m/z) :326,328$[M+H]^+$。

[0892] N- 丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺 (156):

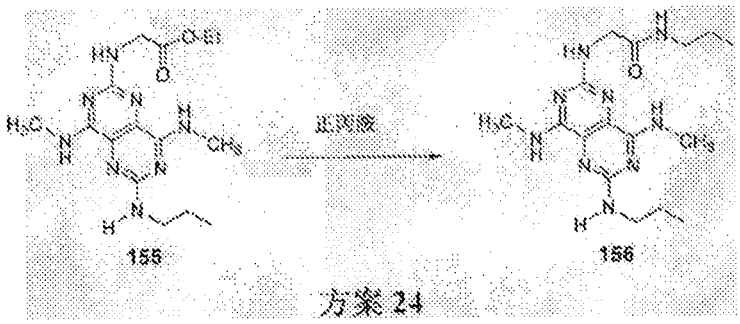
[0893] 将 (6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯 (155)(204mg,0.63mmol)、正丙胺 (515μL,6.26mmol) 在正丁醇 (4.0mL) 中的混合物在 125℃下在封闭瓶中加热 96h。添加饱和 $NaHCO_3$ 溶液 (15mL),并将所得悬浮液用 CH_2Cl_2(3x 20mL) 萃取。将组合的有机萃取物用水 (40mL) 洗涤,并在固体无水 Na_2SO_4 上干燥。过滤后,去除溶剂,并利用 CH_2Cl_2/i-PrOH(97 ： 3) 至 CH_2Cl_2/i-PrOH(97 ： 3)(1 ： 1) 的梯度洗脱通过快速柱层析纯化残留物,得到 N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺 (156)(125mg,55% y)。400MHz ^1H NMR($CDCl_3$, ppm) : δ 6.66-6.60(1H, m),6.65(1H, q, J = 5.0Hz),6.37(1H, q, J = 5.0Hz),5.08-5.03(1H, m), 4.76-4.71(1H, m),4.02(2H, d, J = 6.0Hz),3.38-3.32(2H, m),3.24-3.18(2H, m),3.06(3H, d, J = 5.1Hz)3.03(3H, d, J = 5.1Hz)1.62(2H, 六重峰, J = 7.3Hz)1.45(2H, 六重峰, J = 7.3Hz)0.98(3H, t, J = 7.3Hz)0.83(3H, t, J = 7.3Hz). ESI-MS(m/z) :362$[M+H]^+$。

[0894] N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺盐酸盐 (157a):

[0895] 利用关于化合物 (20a) 描述的程序,在二乙醚 / 乙醇 (20/1) 中用 2M HCl/ 二乙醚处理 N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基

氨基)]- 乙酰胺 (156)(113mg,0.31mmol)(105mg,85 % y)。400MHz ^{1}H NMR($CDCl_3$, ppm):δ 6.67(1H, s),6.22(2H, br s),4.14-4.08(2H, m),3.51-3.44(2H, m),3.27-3.21(2H, m),3.21-3.18(3H,m),3.15-3.09(3H,m),1.67(2H,六重峰,J = 7.3Hz),1.50(2H,六重峰,J = 7.3Hz),0.99(3H, t, J = 7.3Hz),0.87(3H, t, J = 7.3Hz). ESI-MS(m/z) :362[M+H]$^+$;熔点:262℃ (dec.)。

[0896]



方案 24

[0897] 实施例 74:选择化合物在大鼠肝脏微粒体 (RLM) 和人肝脏微粒体 (HLM) 中的体外代谢稳定性

[0898] 测定描述:

[0899] 利用测试化合物培育肝脏微粒体一系列时间点。每个实验包括具有已知高清除率的对照化合物(维拉帕米),以与测试化合物进行比较。分析通过评价母体化合物随时间流逝的消失来进行。可利用不同动物物种的微粒体与人数据进行物种比较。

[0900] 材料和试剂制备:

[0901] 将 0.5M 磷酸钾缓冲剂原液在去离子水中稀释,以构成 50mM 工作缓冲剂。制备足以进行数次实验的大规模溶液,利用真空通过 0.2 微米过滤器过滤除菌,并在室温下储存。如下制备 8mM NADPH 溶液:在 15mL 如上制备的磷酸钾缓冲剂中溶解 100mg NADPH 钠盐粉末,生成最终浓度 8mM(等分并储存在 -20℃下)。测试化合物原液 (5mM) 通过在甲醇中或 50/50 甲醇 / 水中溶解材料来制备。分别地,获得 20mg/mL 原液浓度的 RLM(男性,合并)和 / 或 HLM(混合性别,合并)。

[0902] 程序:

[0903] 将 10mL(或 20mL)之前制备的 0.05M 磷酸钾缓冲剂分配于 50-mL 锥形管中,并添加 1M $MgCl_2$ 原液 (20 μL 或 40 μL) 至最终浓度 1.5mM Mg^{2+}。将溶液等分到 Falcon 管中(用于各测试化合物)。利用 5mM 化合物原液 (4 μL) 构成最终化合物浓度 5 μM。测定中的最终有机物含量为 0.1%。然后,将 300 μL 包含化合物的缓冲液分到成束管 (cluster tubes) 中(微粒体培育物反应两次,阴性对照反应一次)。将 20mg/mL 微粒体原液在磷酸钾缓冲剂中稀释,生成 4mg/mL 浓度。然后,将 50 μL 的 4mg/mL 微粒体工作液置于双反应孔中。对于阴性对照孔,使用 50 μL 磷酸钾缓冲剂(无 $MgCl_2$)。将成束管在 37℃的 50-rpm 振荡培育箱中预升温约 10min。同时,使适当体积 (1.5mL 或 3mL) 的 8mM NADPH 溶液升温。通过利用多通道移液器向所有成束管添加 50 μL 预升温的 NADPH 溶液开始酶反应。然后,在预定时间点 (0、5、10、15、30、和 60 分钟) 将 50 μL 等份移入包含 150 μL 乙腈的收集板,其中包含普萘洛尔作为内标。收集最后一个时间点后,将该板(一个或多个)在 2000g 下离心 10min,并将上清液转移进行 LC-MS/MS 分析。

[0904] 数据解释：

[0905] 确定每次重复的相对于第 0 分钟培育样品的残留母体化合物百分比，由此基于残留化合物%的自然 log vs 时间作图计算消除半衰期。计算下列参数，以估测化合物的体外代谢稳定性：

[0906] C_{mp}＝微粒体蛋白质浓度 (mg/mL)

[0907] $t_{1/2}$＝半衰期 (min)，其中 $t_{1/2}$等于 0.693/ 斜率

[0908] CL_{int}＝固有肝清除率 (uL/min/mg)，其中 CL_{int}等于 $0.693/(t_{1/2}\times C_{mp})$ 测试化合物的代谢稳定性归类如下：

[0909] 低清除率：CL_{int}(μL/min/mg) ＜ 10(RLM) 或 5(HLM)

[0910] 中 清 除 率：$10 \leqslant CL_{int}$(μL/min/mg) $\leqslant$ 60(RLM) 或 $5 \leqslant CL_{int}$(μL/min/mg) $\leqslant$ 35(HLM)

[0911] 高清除率：CL_{int}(μL/min/mg) ＞ 60(RLM) 或 35(HLM)

[0912] 实施例 75：化合物 4a 在大鼠内的药代动力学和口服生物利用度

[0913] 世间程序：

[0914] Sprague-Dawley 大鼠 (200-300g) 被喂以标准实验室啮齿动物饮食并被以 12 小时亮和 12 小时暗周期养于单独笼子，保持室温在 22±3℃并且相对湿度在 50±20%。大鼠在用药前被禁食过夜，并在获得 6 小时血液样品后恢复供食。铺垫在获得 6 小时血液样品后被取出。水在研究过程始终被随意提供。

[0915] 口服研究：

[0916] 测试化合物的用药溶液以期望的口服制剂制备，用于通过强饲针以 10-30mg/kg(10mL/kg) 口服给予 3 或 4 只大鼠。所有血液样品（每个样品 250 μL）在 0min（药前）、口服用药后 15min、和 30min 和 1、2、4、6、8 和 24h 经由颈静脉或股静脉采集。补液 (1.5mL 0.9%氯化钠注射液，USP) 在 2hr 血液取样后被皮下给予一次。血液样品被收集在覆有抗凝血剂的 BD 微量管中，置于冰上，并且在 30 分钟内，15,000g 离心 3min，以获得血浆样品。所有血浆样品储存在 -70℃下，直到通过 LC-MS/MS 进行分析。

[0917] 静脉内研究：

[0918] 测试化合物的用药溶液以期望的静脉内制剂制备，用于经由尾静脉、颈静脉、或股静脉以 2-5mg/kg(2mL/kg) 静脉内弹丸注射给 3 或 4 只大鼠。所有血液样品（每个样品 250uL）在 0（药前）、静脉内给予后 5、15、和 30min 和 1、2、4、6、8、和 24h 经由颈静脉或股静脉采集。补液 (1.5mL0.9%氯化钠注射液，USP) 在 2hr 血液采样后被皮下给予一次。血液样品被收集在覆有抗凝血剂的 BD 微量管中，置于冰上，并在 30 分钟内，15,000g 离心 3 分钟，以获得血浆样品。所有血浆样品储存在 -70℃下，直到通过 LC-MS/MS 进行分析。

[0919] 生物分析测定：

[0920] 血浆样品（产生的研究样品、校准标准品、质量控制品）被如下常规制备。将 2 体积的包含内标的乙腈加入 1 体积的血浆，以析出血浆蛋白质。将样品离心 (3,000g,5min)，并将上清液取出进行 LC-MS-MS 分析。校准标准品通过将适当体积原液直接加入空白血浆来制备，并与收集的血浆样品经相同处理。校准标准品一般制成 2ng/ml 至 10 μg/mL 的范围，以进行定量。质量控制样品以相同的方式以高、中和低浓度平行制备，其用于确保测定结果的质量。允许 6 个 QC 标准品中不超过 2 个与其标称值差异大于 20%。利用多个反应

监测进行 LC-MS-MS 分析，以检测各测试化合物、其他相关分析物和内标的特征离子。分析物的所有离子来源和串联 MS 设备参数被优化具有高灵敏度和选择性。

[0921] 药代动力学数据分析：

[0922] 所有药代动力学参数利用 WinNonlin 软件 (Pharsight，5.1 版）基于非房室法来确定。末期消除半衰期 ($t_{1/2}$) 以 ln2/λz 计算——利用基于半 log 标度的血浆浓度-时间曲线末期的线性回归分析的斜率（λz）。血浆浓度-时间曲线下方面积 (AUC_{inf}) 利用线性梯形法则通过非房室分析确定，并利用最后一次可测量的浓度 ($C_{最后}$) 和末期斜率（λz）向无穷大外推为 $C_{最后\,t}/\lambda z$。通过根据用药后前两个时间点的线性外推，估测静脉内给予后时间 0 的血浆浓度 (C_0)。通过一阶矩曲线下面积 (the Area under the first moment curve) ($AUMC_{inf}$) 除以 AUC_{inf}，获得平均停留时间 (MRT)。以静脉内剂量除以 AUC_{inf} 计算全身血浆清除率 (CL_p)。通过 CL_p 和 MRT 的乘积，确定稳态分布体积 (V_{ss})。达到最大血浆浓度的时间 (T_{max}) 基于达到观察到的最大浓度的时间。最大血浆浓度 (C_{max}) 是在 T_{max} 观察到的存在的最大浓度。以平均剂量标准化口服 AUC_{inf} 与剂量标准化静脉内 AUC_{inf} 的百分比比例计算绝对口服生物利用度 (F)。

[0923] 统计学分析：

[0924] 生物分析数据和计算药代动力学参数的汇总统计如平均值、标准偏差和变异系数利用 WinNonlin 或 Microsoft Excel 应用来确定。

[0925] 在此测定中，发现化合物 4a 具有 38％的口服生物利用度。

[0926] 实施例 76：利用麻醉大鼠肺量测定筛选试验的本发明化合物对呼吸速率 (RR)、潮气量 (V_T)、和乘积 (Product) 每分钟通气量的影响

[0927] 麻醉后的大鼠提供针对呼吸和心血管活性筛选化合物的快速方法。与清醒大鼠模型相比，这种模型提供了基线心血管和呼吸测量变动较少的实验设置。在此试验中筛选的化合物可在清醒大鼠模型中进行考察。

[0928] 方法概述：

[0929] 首先将大鼠用 3％异氟醚（吸入）麻醉，并手术插入股动脉和静脉插管。在插管后，将大鼠转变为尿烷麻醉 (1.5g/kg；i.v.)，并进行气管截切。在布置气管插管后，将其连接至呼吸速度描记器，以记录呼吸气流，由此得到呼吸速率 (RR)、潮气量 (V_T)、及其乘积每分钟通气量。在手术制备完成后，使动物稳定 30 分钟，同时连续记录呼吸速率、潮气量、每分钟通气量、血压和心率。从股动脉收集的动脉血液获得动脉血气 (ABG)。在介质和各剂量化合物给予之前和给予后 6 分钟进行 ABG 测量。通过静脉插管经由弹丸注射给予筛选的化合物，然后盐水冲洗（总给予时间为约 30 秒），并监测动物的心血管工作变化至少 6 分钟。化合物以确定确保最佳溶解度的制剂来制备。由此，介质对照匹配各测试化合物的制剂。筛选的化合物的用药为 0.1 和 0.3mg/kg。直到所有心血管和呼吸测量已恢复基线水平才给予下一剂量。所用阳性对照化合物是 N-[4,6-二-(正丙基氨基)-[1,3,5] 三嗪-2-基]-N,O-二甲基-羟基胺或 N-[2,6-二-(正丙基氨基)-[1,3] 嘧啶-4-基]-N,O-二甲基-羟基胺（均在各筛选实验结束时被给予 (0.3mg/kg 剂量)，以验证实验并且充当可与筛选化合物比较的度量。

[0930] 数据分析：

[0931] 通过收集平均 30 秒 (BIN) 的心血管和呼吸数据，来分析数据。将挑战前 2 分钟然

后挑战后 6 分钟的数据作图。

[0932] 结果：

[0933] 化合物 (4a) 导致每分钟通气量在基线值以上立即并且短期（约 2 分钟持续时间）增加（图 1）。这种增加主要源于对呼吸速率的刺激效果（图 2），而非潮气量（图 3）。化合物 (4a) 对脉率（图 5）和血压（图 6）产生可忽略不计的效果。根据曲线下方面积的测量，化合物 (4a) 与参考化合物相比产生较大效果（图 4）。

[0934] 化合物 (27a) 导致每分钟通气量在基线值以上立即并且短期（约 2 分钟持续时间）增加（图 7）。这种增加源于对呼吸速率（图 8）以及潮气量（图 9）的刺激效果。化合物 (27a) 对脉率（图 11）和血压（图 12）产生最小效果。根据曲线下方面积的测量，化合物 (27a) 与参考化合物相比产生较大效果（图 10）。

[0935] 实施例 77：本发明化合物的微粒体稳定性和通气活性

[0936] 代表性数据示例在表 7 中，总结了在大鼠和人微粒体中各个化合物对每分钟通气量峰值 (V_E增加量）、2 分钟曲线下方面积 (AUC) 整体增加量——效果累积度量、以及化合物稳定性（半衰期）的影响。

[0937] 表 7. 本发明化合物的微粒体稳定性和通气活性

[0938]

化合物#	V_E 峰值（增加%）	AUC MV 增加量（2 min）（与标准*之比）	RLM T ½（min）	HLM T ½（min）
4a	176	1.28	273	411
6a	60	0.54	416	>500
8a	44	0.14	331	>500
10a	11	0.07	162	462
13a	131	0.56	204	342
15a	6	0.00	34	91
17a	2	0.05	25	29
19a	4	0.00	106	110
22a	9	0.01	9	21
24a	123	0.43	162	119
27a	122	1.22	136	127
29a	135	0.95	44	94
31a	3	0.01	108	417
33a	88	0.29	106	115
35a	279	1.33	102	225
37a	128	1.23	76	135
39a	120	0.71	154	238
41a	57	0.36	100	187
43a	26	0.20	69	98
45a	87	0.41	>500	>500
47a	4	0.00	106	110
49a	19	0.11	84	190
51a	20	0.08	72	127
53a	15	0.06	94	79
54	30	0.09	40	82
56a	116	0.79	ND	ND
58a	32	0.18	ND	ND
60a	192，172	0.46，0.83	ND	ND
62a	85	0.55	ND	ND
64a	9	0.01	ND	ND
66a	12	0.14	ND	ND
68a	3	0.00	ND	ND
71a	36	0.13	ND	ND
73a	1	0.00	ND	ND
75a	2	0.02	ND	ND
77a	50	0.55	ND	ND
79a	3	0.00	388	>500
81a	0	0.00	274	198
83a	95	1.05	335	249
85a	104	0.51	386	389
87a	18	0.18	ND	ND
89a	169	0.92	ND	ND
91	9	0.08	24	102
93a	7	0.03	14	81
95a	115	0.36	ND	ND
97a	38	0.26	ND	ND
99a	24	0.19	ND	ND
101	3	0.00	ND	ND
103a	0	0.00	ND	ND
105a	7	0.00	ND	ND

[0939]

107a	0	0.00	ND	ND
108	11	0.05	ND	ND
110a	0	0.00	ND	ND
112a	20	0.14	104	121
114a	6	0.05	249	305
116a	0	0.00	ND	ND
118a	5	0.05	34	72
120a	70	0.36	82	114
122a	6	0.00	ND	ND
125a	133	0.80	ND	ND
127a	125	0.86	ND	ND
129a	21	0.25	ND	ND
132a	78	0.98	ND	ND
135a	0	0.00	ND	ND
137a	197	0.88	97	227
138	77	0.53	331	>500
140a	3、7	0.01、0.05	50	71
142a	5	0.05	ND	ND
145a	146	0.88	ND	ND
148a	6	0.00	ND	ND
150a	0	0.00	ND	ND
152a	1	0.00	ND	ND
154	0	0.00	ND	ND
157a	5	0.04	ND	ND

[0940] *N-[2,6-二-(正丙基氨基)-[1,3]嘧啶-4-基]-N,O-二甲基-羟基胺,用作比较化合物。

[0941] 实施例78:本发明化合物对呼吸暂停、睡眠结构和通气响应的影响。

[0942] 此研究的目的是在大鼠模型中定量选择的本发明化合物对呼吸暂停、通气和睡眠结构的影响。研究由两种治疗条件组成:(1)慢性吗啡和测试化合物,被口服给予,和(2)慢性吗啡和口服介质。

[0943] 麻醉成年雄性瘦Zucker大鼠,进行脑电图(EEG)和肌电图(EMG)遥测计植入。允许在术后至少一周后再将动物进一步投入使用。将硫酸吗啡加入单独安置的大鼠的饮用水,以0.1mg/ml吗啡开始,并且逐渐增加浓度,从而在2周内达到最终浓度0.6mg/ml。所有呼吸测量都在动物在全身体积描记室中不受约束、允许动物睡眠和自由活动时进行。为避免引起退出,各体积描记实验期间吗啡水持续可用。在所有治疗条件期间测量每分钟通气量和中枢性睡眠呼吸暂停(CSA)数量。允许动物对该室适应至少1至1.5h的时间,然后开始数据采集。生物电位遥测计及其接收器被布置在体积描记室正下方,用于连续捕获EEG、EMG、和体温信号。只有在10am至4:30pm数小时之间采集的数据用于最终分析,以控制昼夜节律对呼吸的影响。

[0944] 在12pm经口服强饲管给予介质中的测试化合物或等体积的介质。在10am和12pm之间采集的数据表示基线(药前)条件。在12pm和4:30pm之间采集的数据表示药后条件。对EEG和EMG波形的分析——目的是将大鼠睡眠-觉醒表现分级为觉醒、NREM睡眠、和REM睡眠——基于此前的涉及啮齿动物的睡眠研究。中枢性呼吸暂停被限定为大于或等于基线记录期间平均周期的2倍的呼吸周期。利用双向ANOVA(因素:药物治疗和时间)在治疗组之间比较各睡眠-觉醒状态的时间百分比、每分钟通气量、和中枢性睡眠呼吸暂停计数。不分析觉醒期间的呼吸数据,因为在应用全身体积描记术时运动会阻碍准确体积的测量。当

通过 ANOVA 检测到差异时，对所有主要影响和相互作用进行 Student-Neuman-Keuls post hoc 检验。当 $p < 0.05$ 时，认为差异显著。数值表示为平均值 ±SE。

[0945] 在不发生通气刺激（每分钟通气量增加）的剂量下，本发明化合物减少被慢性给予阿片类的大鼠的呼吸暂停。作为非限制性实例，化合物 (27a)、(85a)、(137a) 和 (145a) 降低呼吸暂停频率（图 14、19、24 和 29），相对于基线减少每小时呼吸暂停数量（图 15、20、25 和 30），并且相对于介质减少每小时呼吸暂停数量（图 16、21、26 和 31）。此外，作为非限制性实例，化合物 (27a)、(85a)、(137a) 和 (145a) 不导致每分钟通气量增加（图 17、22、27 和 32），并且不导致每单位时间通气量增加（图 18、23、28 和 33）。

[0946] 本文引述的所有专利、专利申请和出版物的公开全部内容通过引用并入本文。虽然参考具体实施方式对本发明进行了公开，但要理解本领域技术人员可想到本发明的其他实施方式和改动，而没有脱离本发明的实际精神和范围。所附权利要求意图被解释为包括全部这种实施方式和等效改动。

每分钟通气量

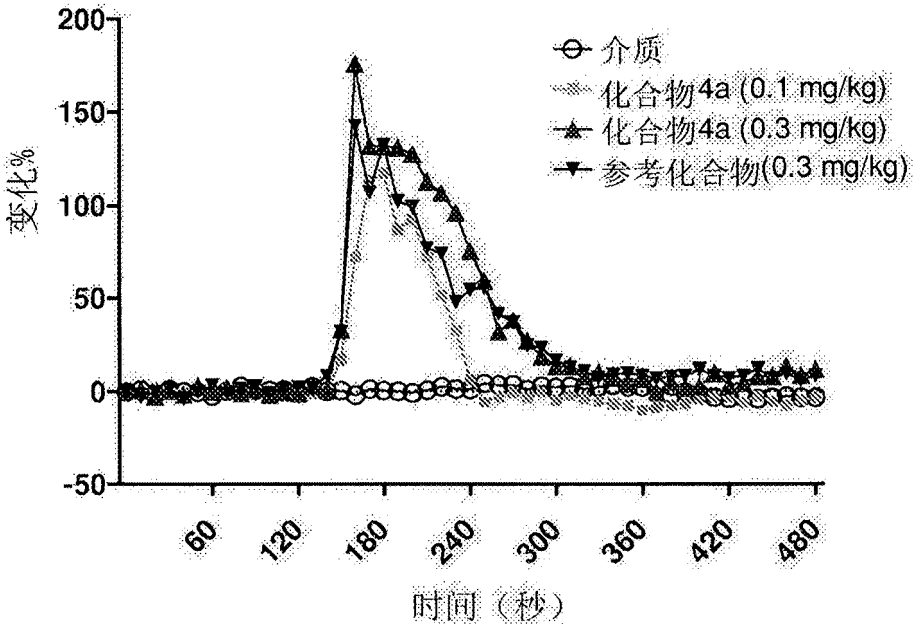


图 1

呼吸速率

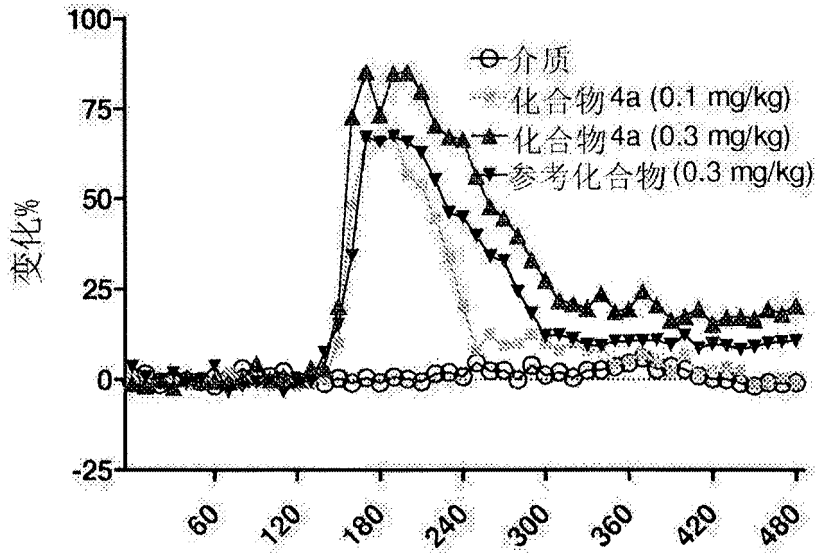


图 2

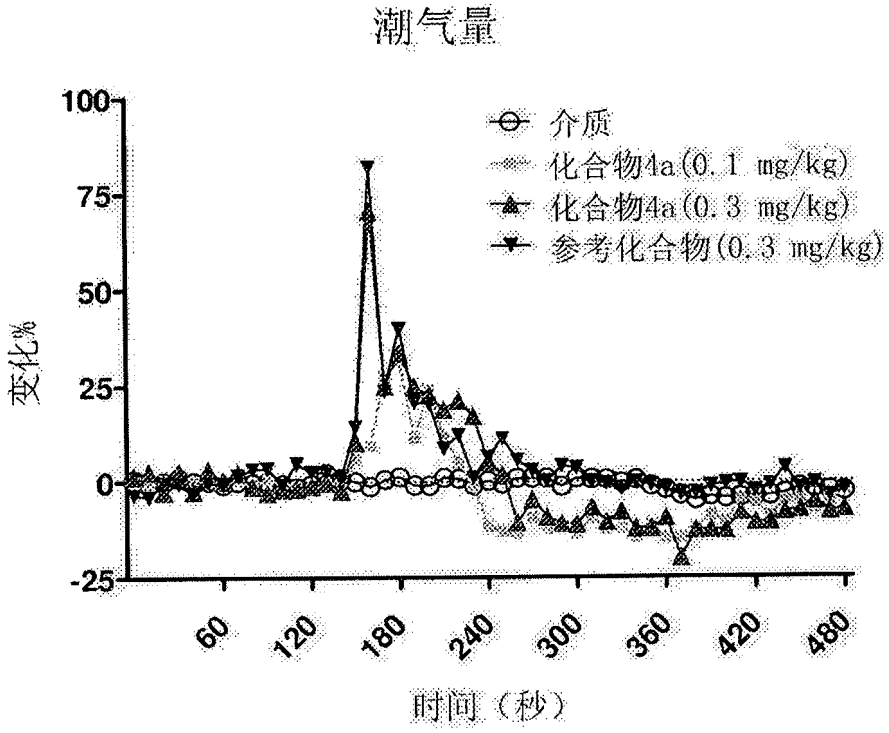

潮气量
介质
化合物4a(0.1 mg/kg)
化合物4a(0.3 mg/kg)
参考化合物(0.3 mg/kg)
变化%
100
75
50
25
0
-25
60
120
180
240
300
360
420
480
时间（秒）

图 3

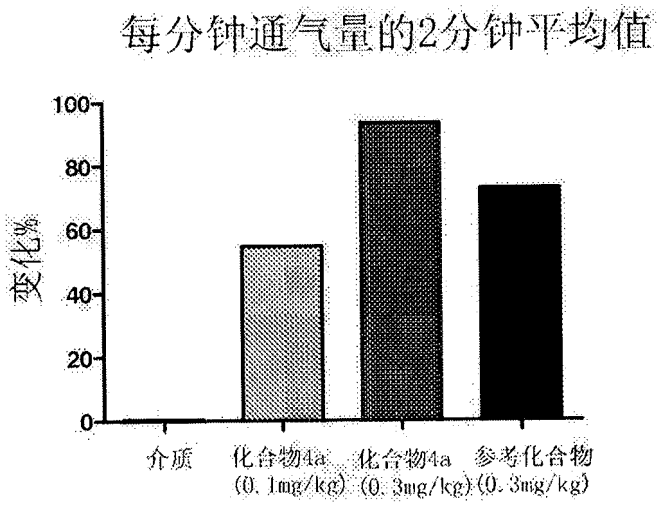

每分钟通气量的2分钟平均值
变化%
100
80
60
40
20
0
介质
化合物4a (0.1mg/kg)
化合物4a (0.3mg/kg)
参考化合物 (0.3mg/kg)

图 4

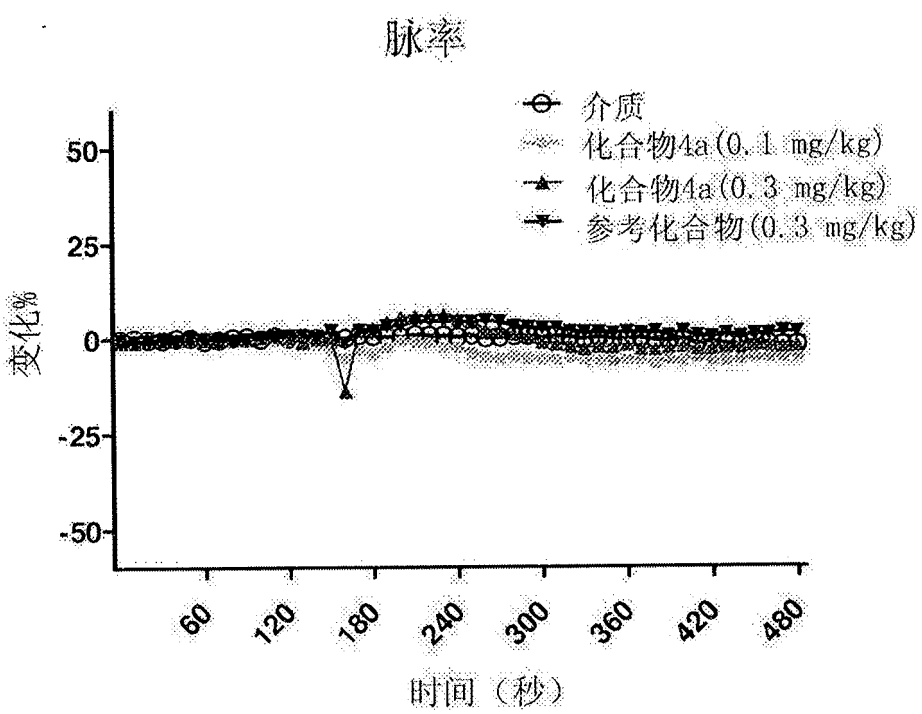

脉率
介质
化合物4a(0.1 mg/kg)
化合物4a(0.3 mg/kg)
参考化合物(0.3 mg/kg)
50
25
0
-25
-50
变化%
60
120
180
240
300
360
420
480
时间（秒）

图 5

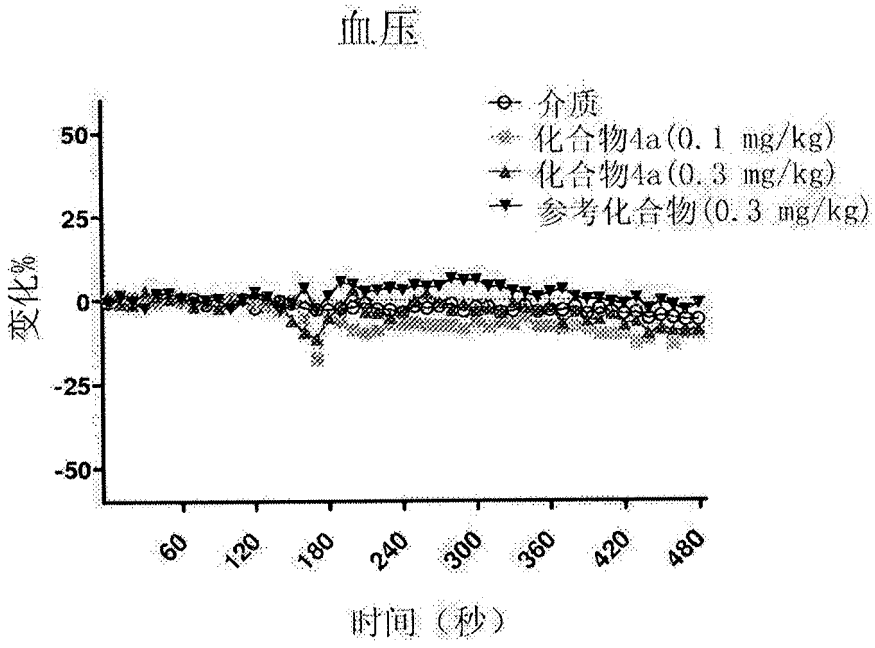

血压
介质
化合物4a(0.1 mg/kg)
化合物4a(0.3 mg/kg)
参考化合物(0.3 mg/kg)
50
25
0
-25
-50
变化%
60
120
180
240
300
360
420
480
时间（秒）

图 6

每分钟通气量

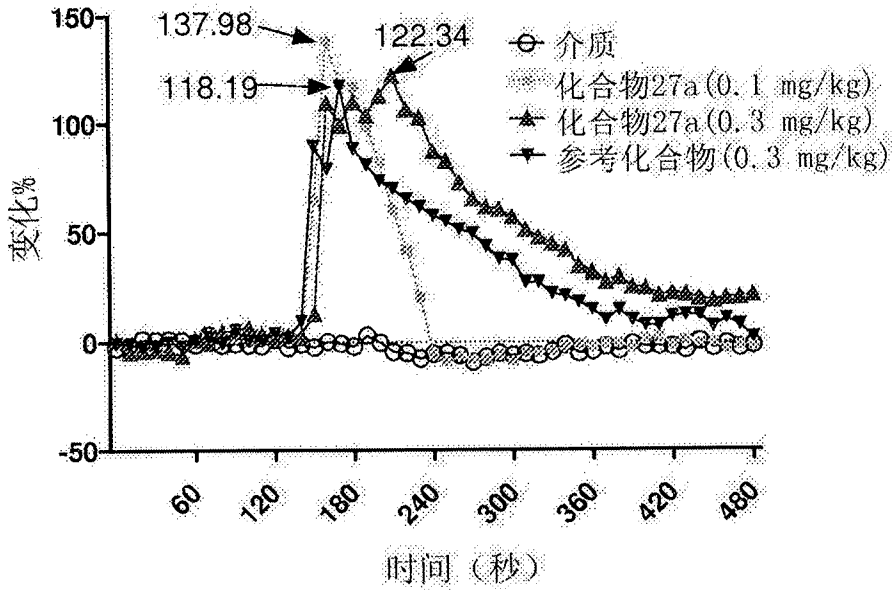


图 7

呼吸速率

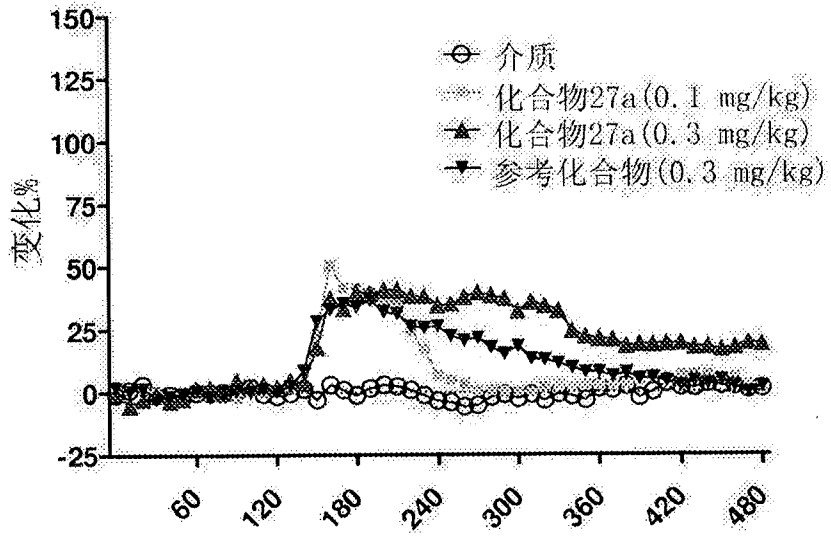


图 8

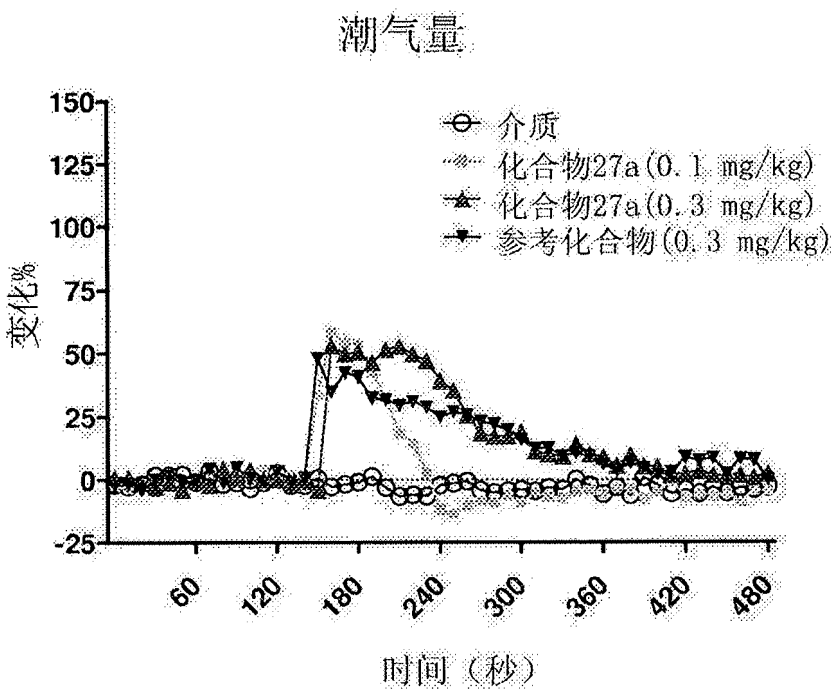

潮气量
介质
化合物27a(0.1 mg/kg)
化合物27a(0.3 mg/kg)
参考化合物(0.3 mg/kg)
变化%
150
125
100
75
50
25
0
-25
60
120
180
240
300
360
420
480
时间（秒）

图 9

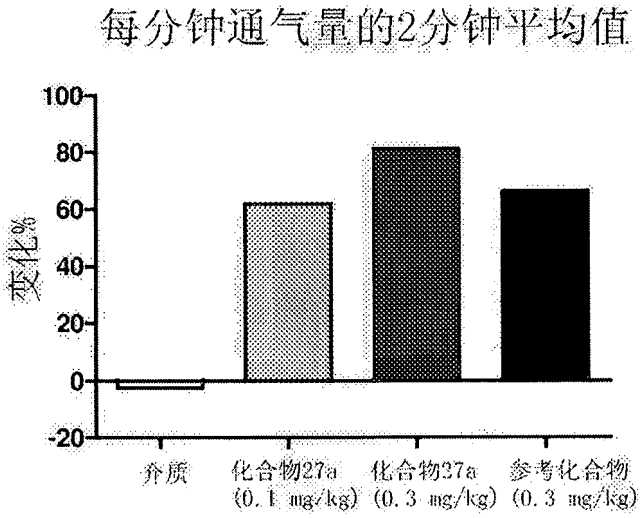

每分钟通气量的2分钟平均值
变化%
100
80
60
40
20
0
-20
介质
化合物27a (0.1 mg/kg)
化合物27a (0.3 mg/kg)
参考化合物 (0.3 mg/kg)

图 10

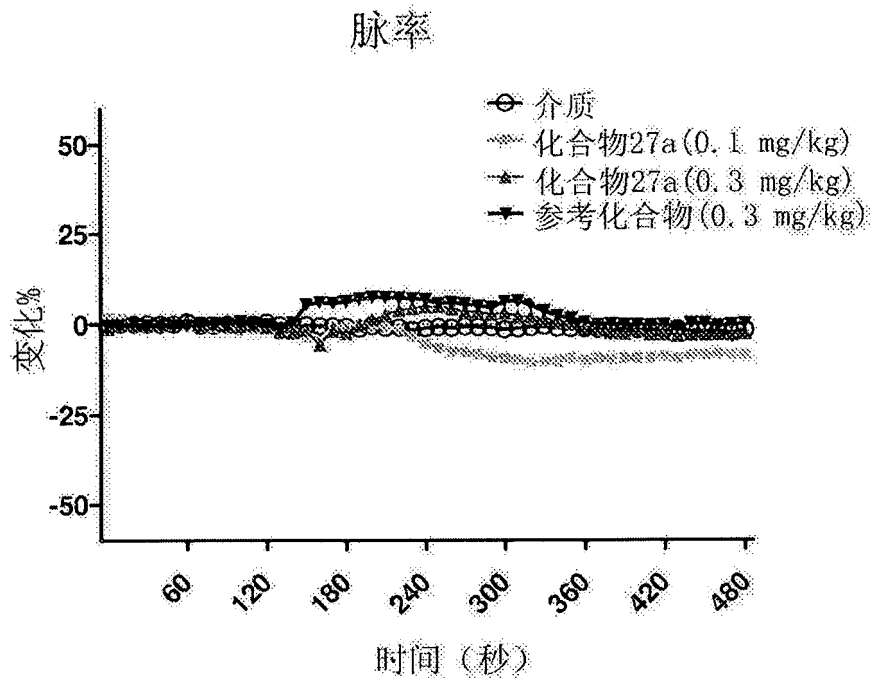

脉率
介质
化合物27a(0.1 mg/kg)
化合物27a(0.3 mg/kg)
参考化合物(0.3 mg/kg)
50
25
0
-25
-50
变化%
60
120
180
240
300
360
420
480
时间（秒）

图 11

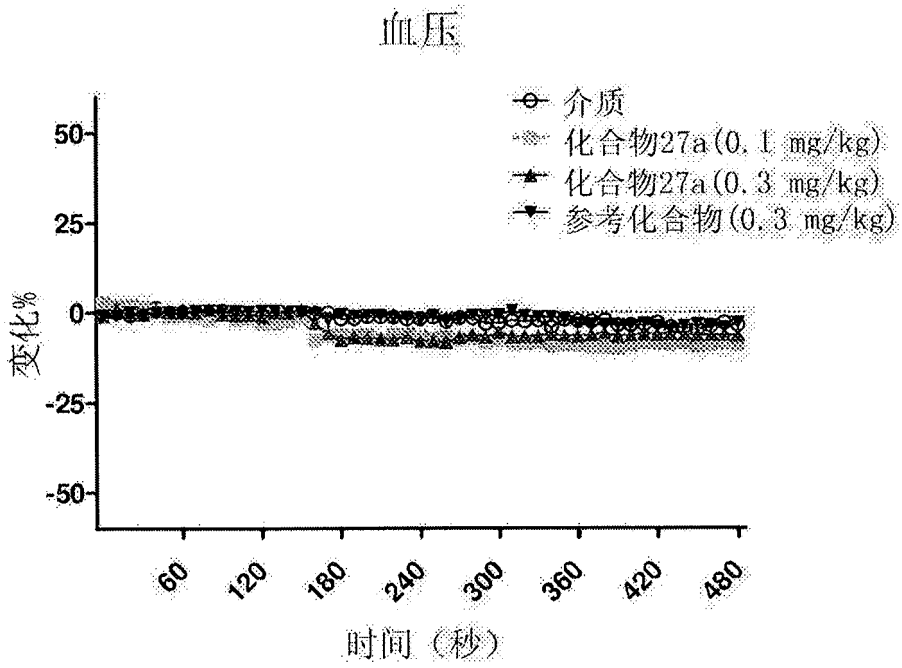

血压
介质
化合物27a(0.1 mg/kg)
化合物27a(0.3 mg/kg)
参考化合物(0.3 mg/kg)
50
25
0
-25
-50
变化%
60
120
180
240
300
360
420
480
时间（秒）

图 12

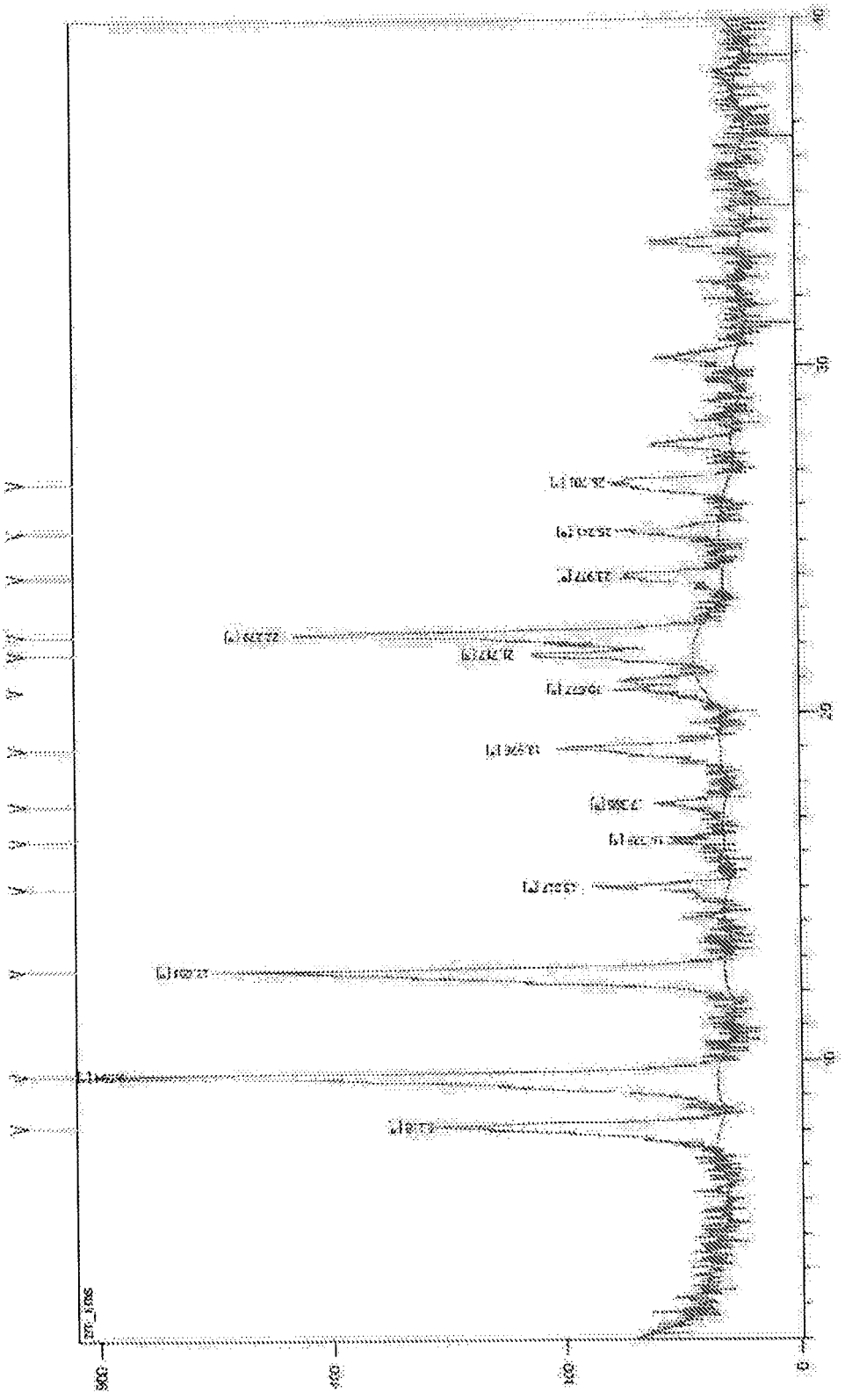


图 13

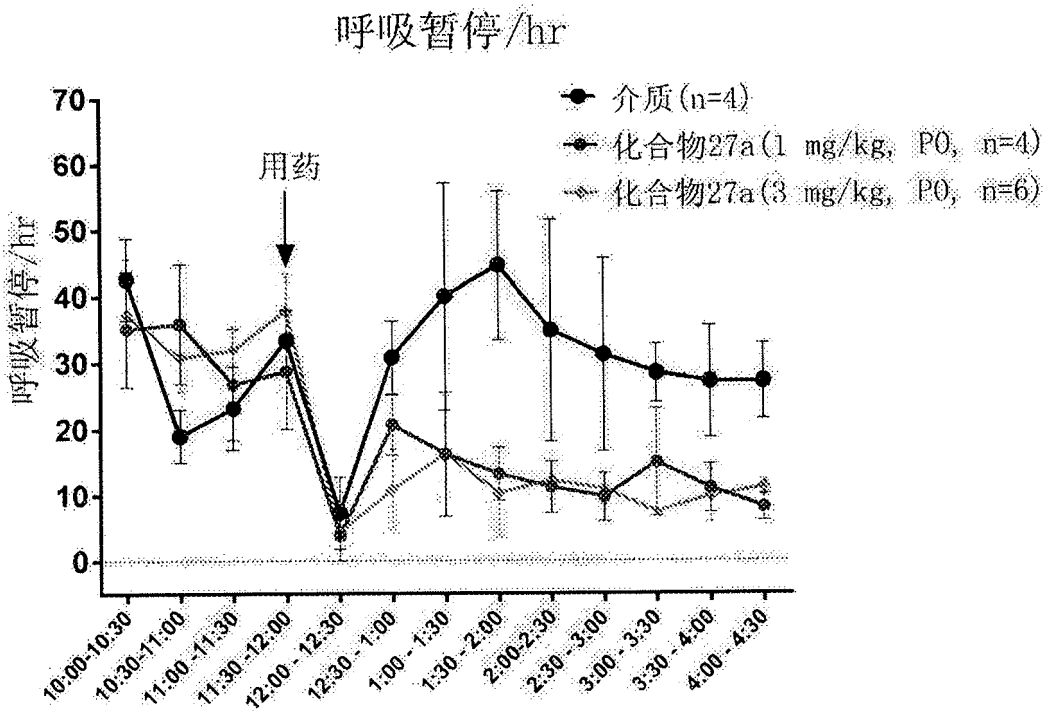

呼吸暂停/hr
介质(n=4)
化合物27a(1 mg/kg, PO, n=4)
化合物27a(3 mg/kg, PO, n=6)
用药
呼吸暂停/hr
70
60
50
40
30
20
10
0
10:00-10:30
10:30-11:00
11:00-11:30
11:30-12:00
12:00-12:30
12:30-1:00
1:00-1:30
1:30-2:00
2:00-2:30
2:30-3:00
3:00-3:30
3:30-4:00
4:00-4:30

图 14

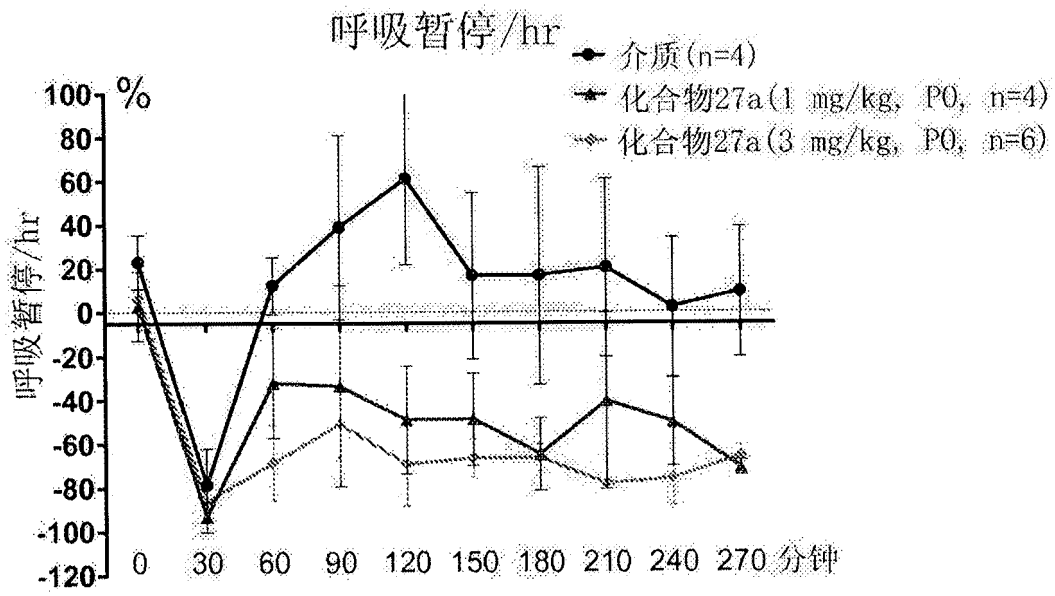

呼吸暂停/hr
介质(n=4)
化合物27a(1 mg/kg, PO, n=4)
化合物27a(3 mg/kg, PO, n=6)
%
呼吸暂停/hr
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
0 30 60 90 120 150 180 210 240 270 分钟

图 15

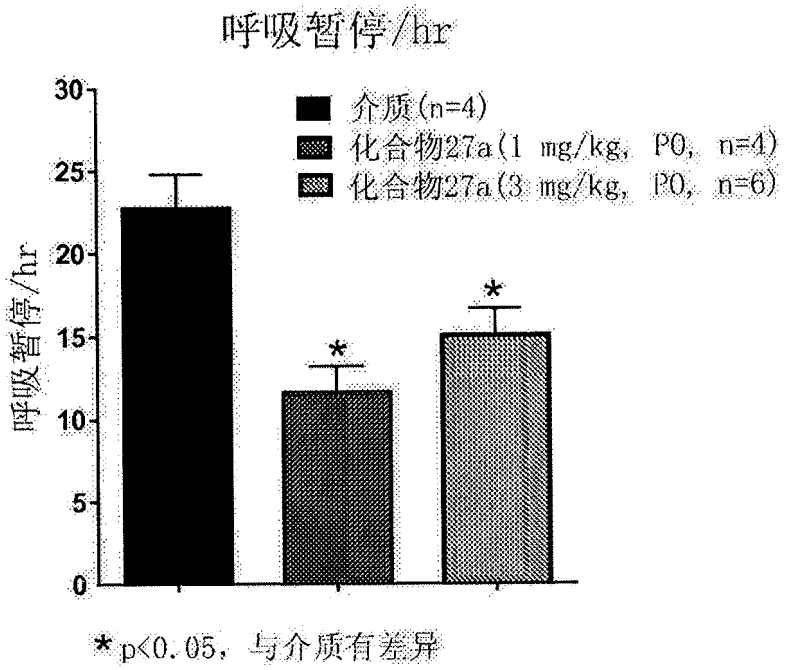

呼吸暂停/hr
介质(n=4)
化合物27a(1 mg/kg, PO, n=4)
化合物27a(3 mg/kg, PO, n=6)
呼吸暂停/hr
30
25
20
15
10
5
0
*
*
*p<0.05，与介质有差异

图 16

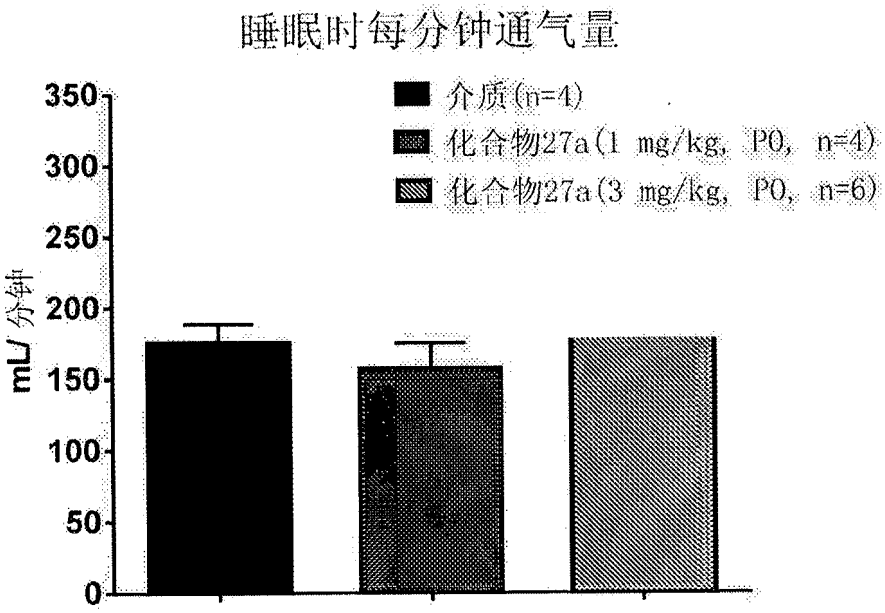

睡眠时每分钟通气量
介质(n=4)
化合物27a(1 mg/kg, PO, n=4)
化合物27a(3 mg/kg, PO, n=6)
mL/分钟
350
300
250
200
150
100
50
0

图 17

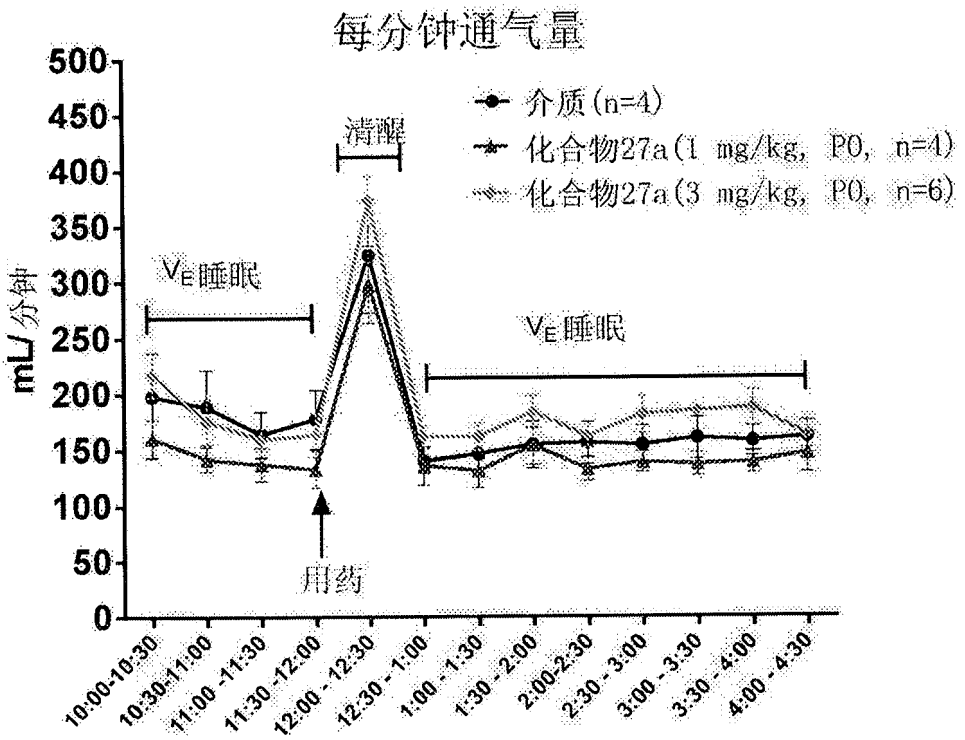

每分钟通气量
介质(n=4)
化合物27a(1 mg/kg, PO, n=4)
化合物27a(3 mg/kg, PO, n=6)
清醒
VE睡眠
VE睡眠
用药
mL/分钟
500
450
400
350
300
250
200
150
100
50
0
10:00-10:30
10:30-11:00
11:00-11:30
11:30-12:00
12:00-12:30
12:30-1:00
1:00-1:30
1:30-2:00
2:00-2:30
2:30-3:00
3:00-3:30
3:30-4:00
4:00-4:30

图 18

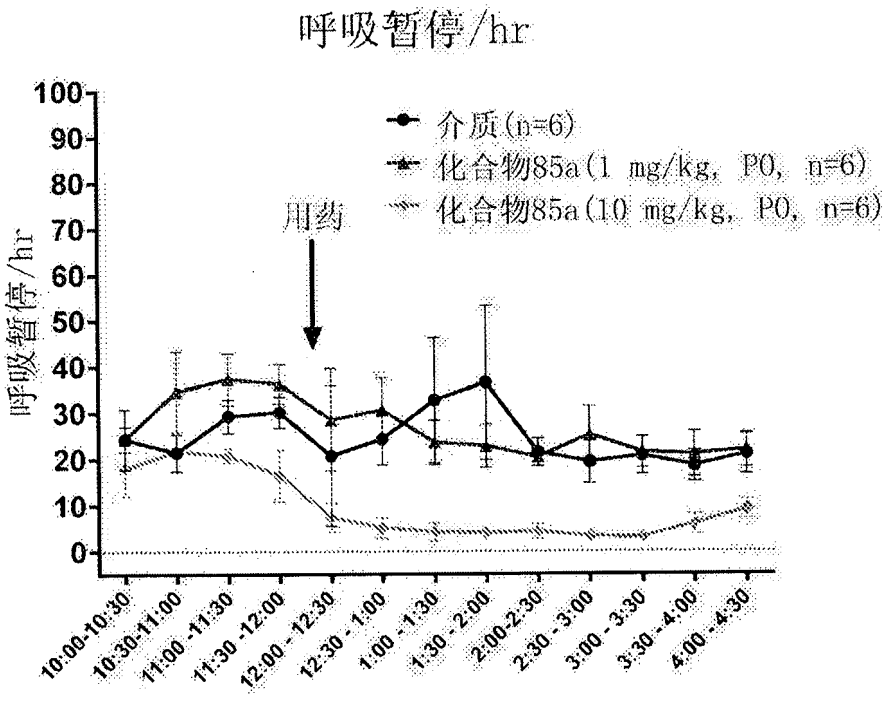

呼吸暂停/hr
介质(n=6)
化合物85a(1 mg/kg, PO, n=6)
化合物85a(10 mg/kg, PO, n=6)
用药
呼吸暂停/hr
100
90
80
70
60
50
40
30
20
10
0
10:00-10:30
10:30-11:00
11:00-11:30
11:30-12:00
12:00-12:30
12:30-1:00
1:00-1:30
1:30-2:00
2:00-2:30
2:30-3:00
3:00-3:30
3:30-4:00
4:00-4:30

图 19

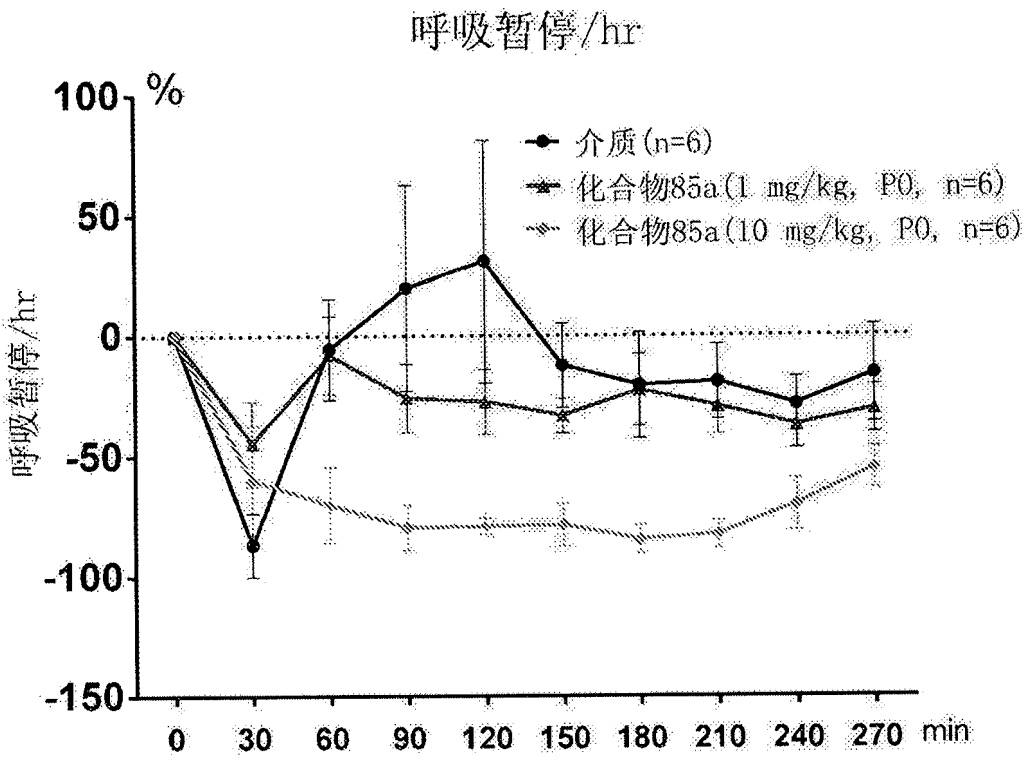

呼吸暂停/hr
100
%
50
0
-50
-100
-150
呼吸暂停/hr
介质(n=6)
化合物85a(1 mg/kg, PO, n=6)
化合物85a(10 mg/kg, PO, n=6)
0
30
60
90
120
150
180
210
240
270
min

图 20

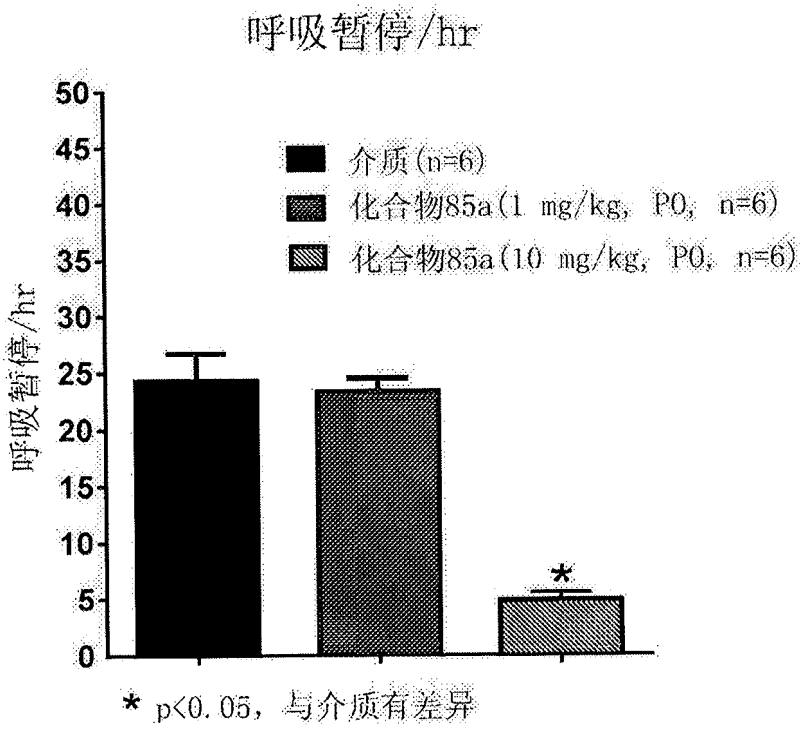

呼吸暂停/hr
50
45
40
35
30
25
20
15
10
5
0
呼吸暂停/hr
介质(n=6)
化合物85a(1 mg/kg, PO, n=6)
化合物85a(10 mg/kg, PO, n=6)
*
* p<0.05，与介质有差异

图 21

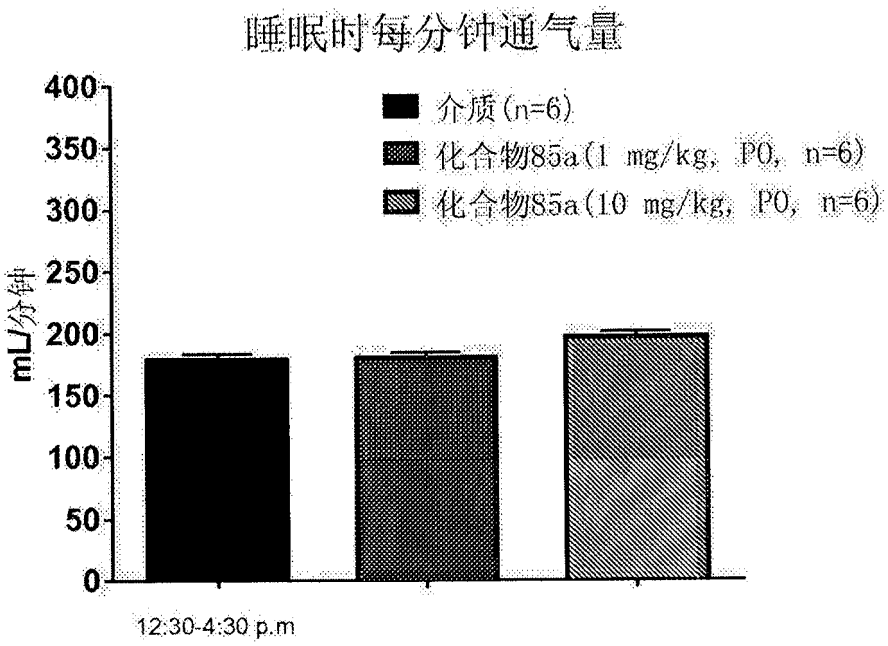

睡眠时每分钟通气量
介质(n=6)
化合物85a(1 mg/kg, PO, n=6)
化合物85a(10 mg/kg, PO, n=6)
mL/分钟
400
350
300
250
200
150
100
50
0
12:30-4:30 p.m

图 22

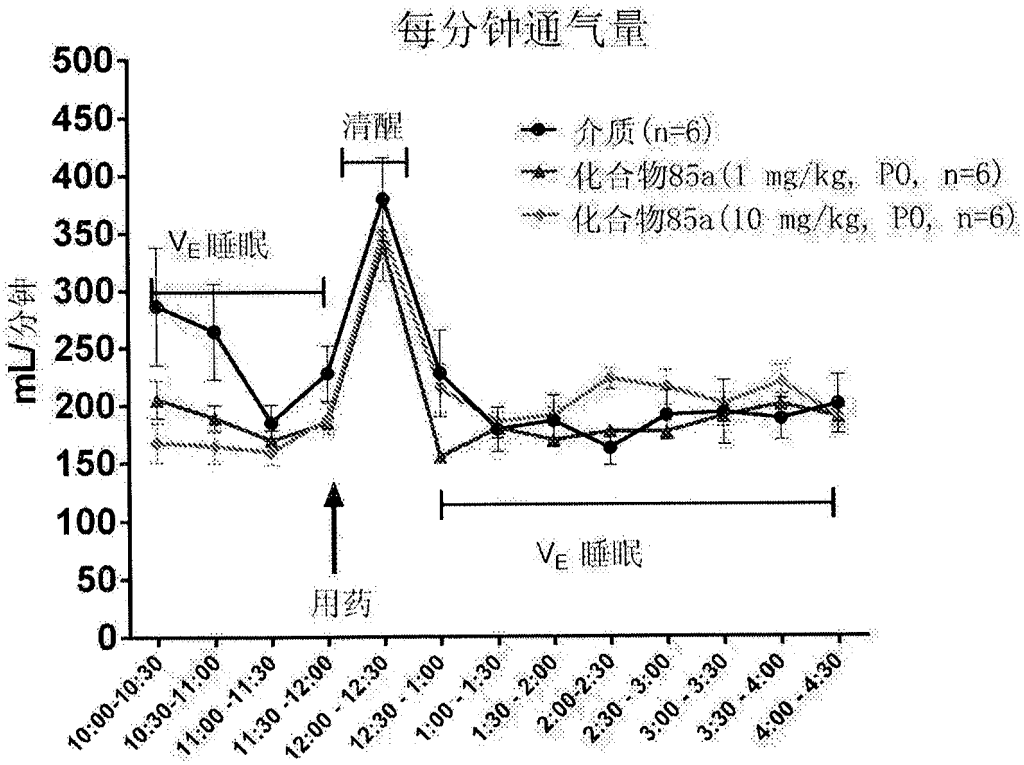

每分钟通气量
介质(n=6)
化合物85a(1 mg/kg, PO, n=6)
化合物85a(10 mg/kg, PO, n=6)
mL/分钟
500
450
400
350
300
250
200
150
100
50
0
清醒
VE 睡眠
用药
VE 睡眠
10:00-10:30
10:30-11:00
11:00-11:30
11:30-12:00
12:00-12:30
12:30-1:00
1:00-1:30
1:30-2:00
2:00-2:30
2:30-3:00
3:00-3:30
3:30-4:00
4:00-4:30

图 23

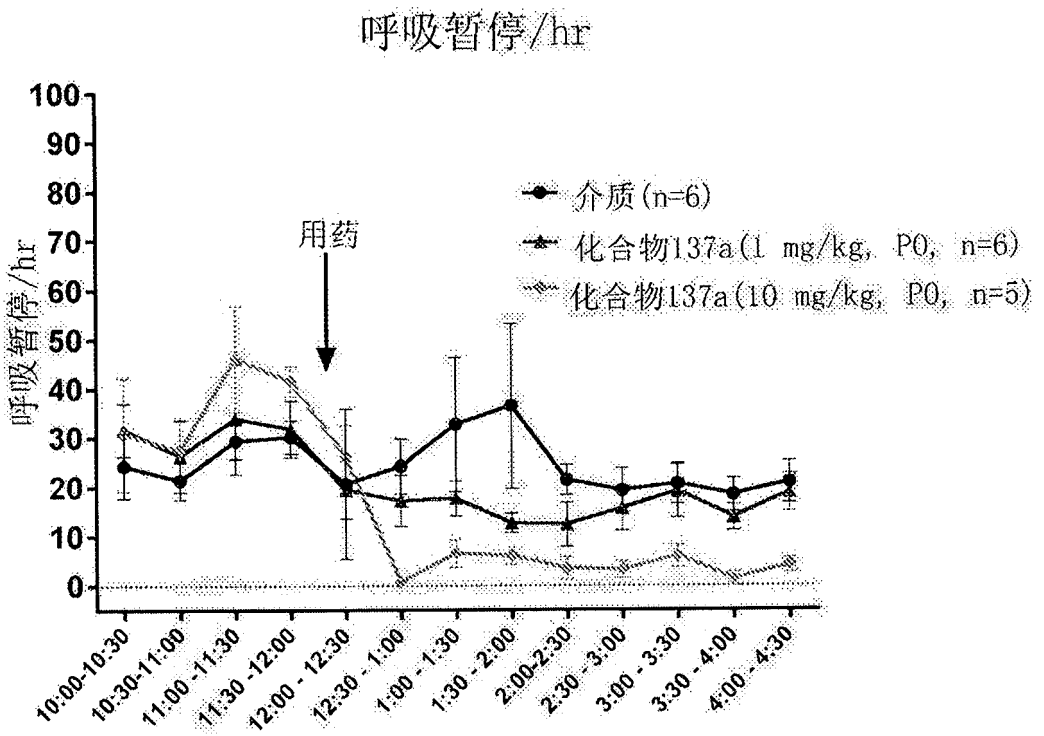

呼吸暂停/hr
呼吸暂停/hr
100
90
80
70
60
50
40
30
20
10
0
用药
介质(n=6)
化合物137a(1 mg/kg, PO, n=6)
化合物137a(10 mg/kg, PO, n=5)
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

图 24

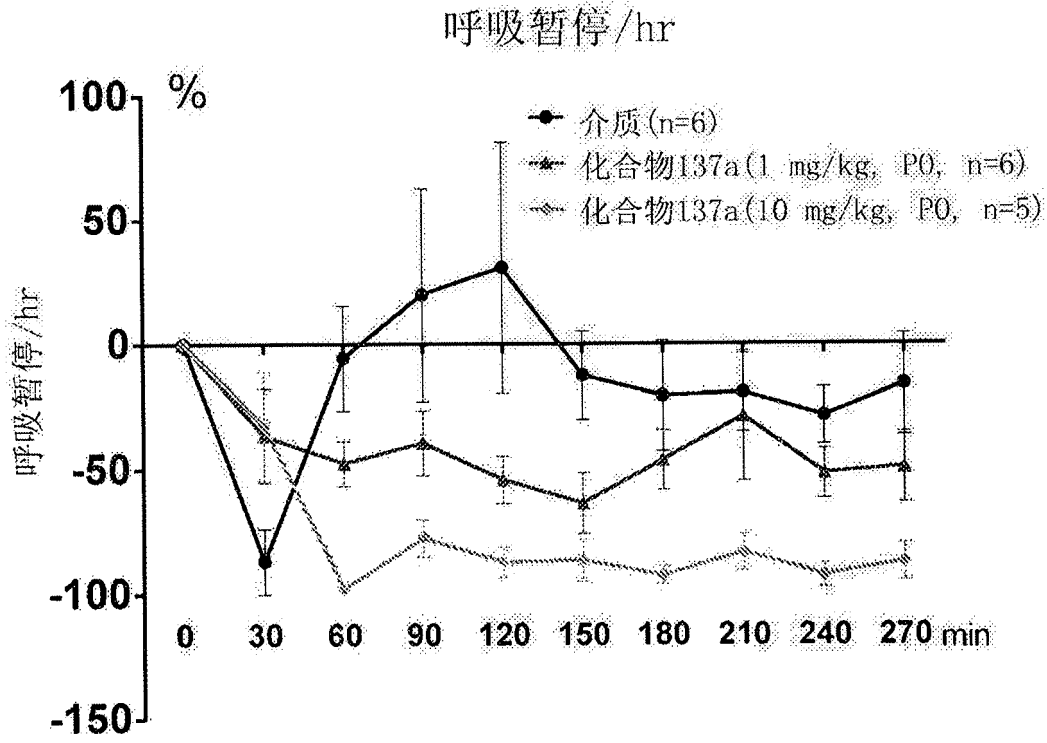

呼吸暂停/hr
%
100
50
0
-50
-100
-150
呼吸暂停/hr
介质(n=6)
化合物137a(1 mg/kg, PO, n=6)
化合物137a(10 mg/kg, PO, n=5)
0
30
60
90
120
150
180
210
240
270
min

图 25

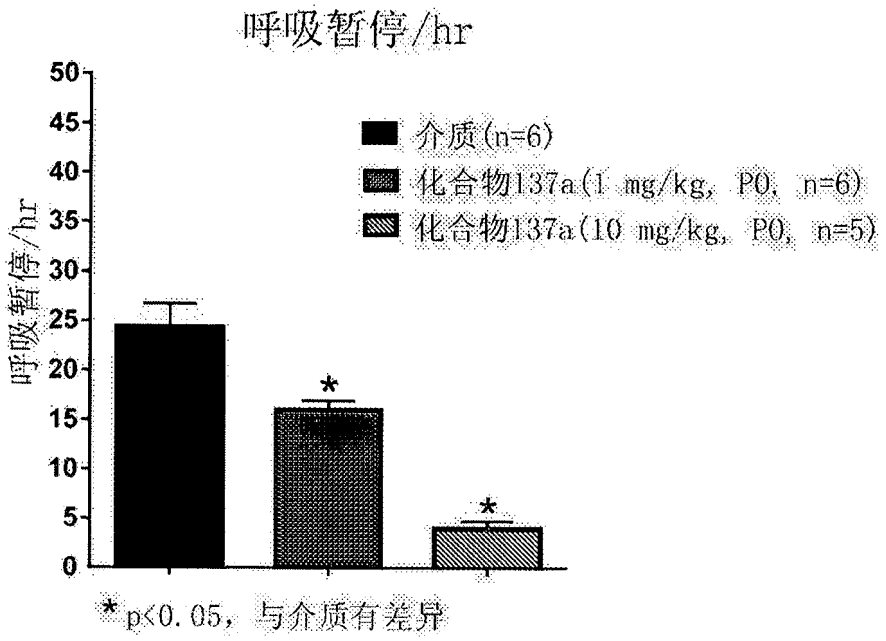

呼吸暂停/hr
呼吸暂停/hr
50
45
40
35
30
25
20
15
10
5
0
介质(n=6)
化合物137a(1 mg/kg, PO, n=6)
化合物137a(10 mg/kg, PO, n=5)
*
*
* p<0.05，与介质有差异

图 26

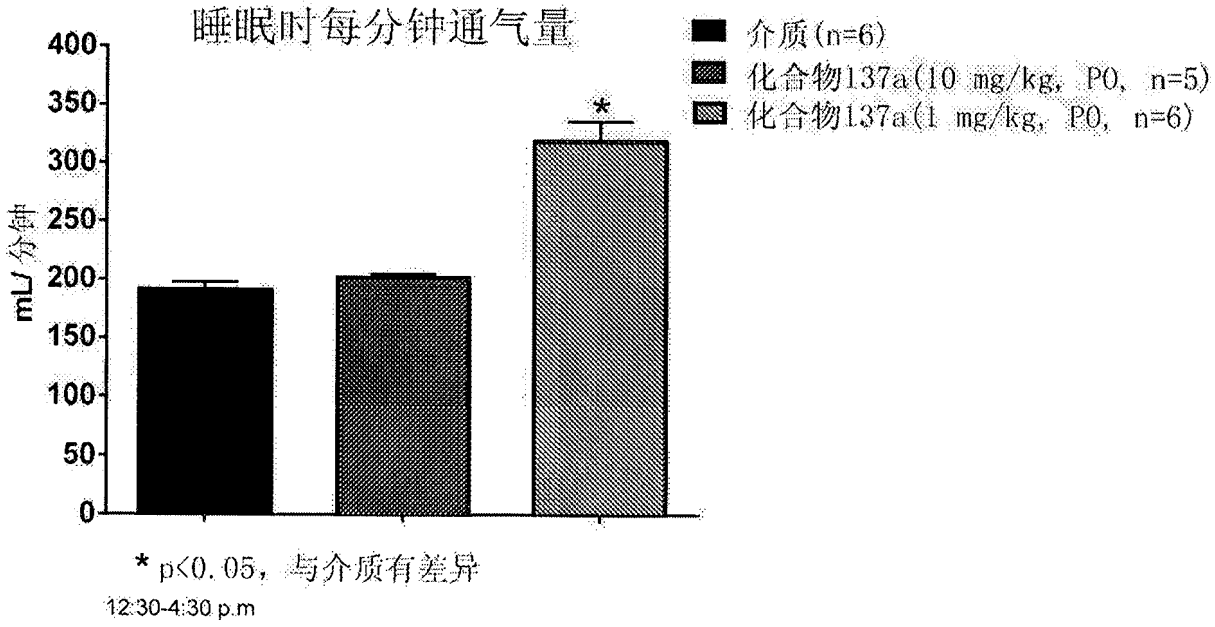

睡眠时每分钟通气量
mL/分钟
400
350
300
250
200
150
100
50
0
介质(n=6)
化合物137a(10 mg/kg, PO, n=5)
化合物137a(1 mg/kg, PO, n=6)
*
* p<0.05，与介质有差异
12:30-4:30 p.m

图 27

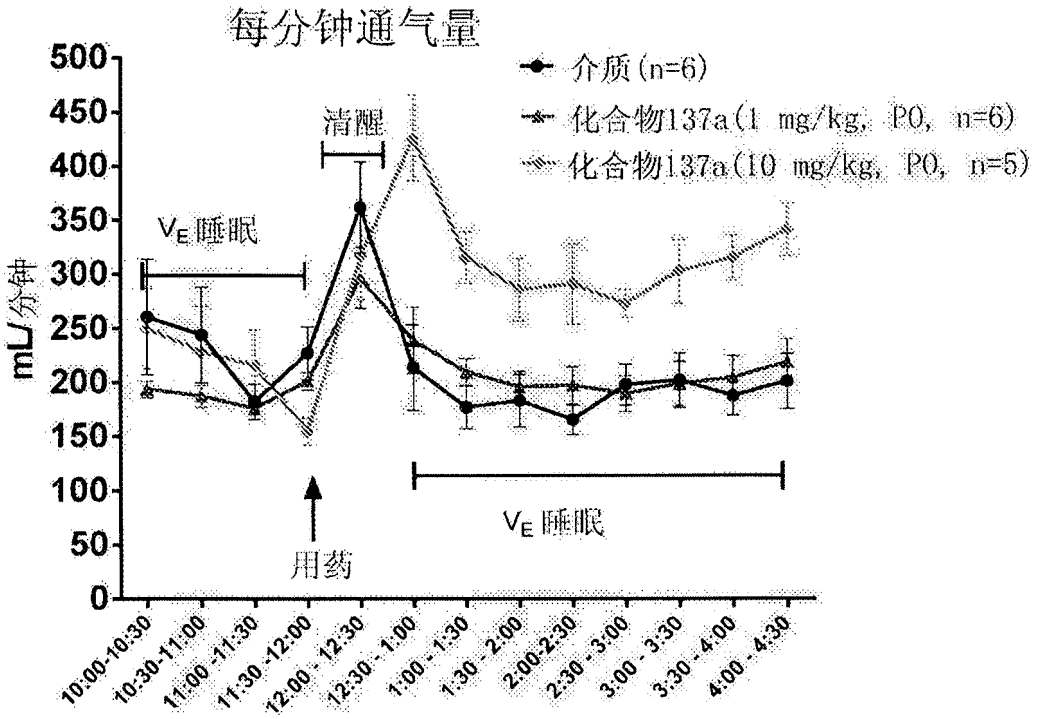

每分钟通气量
介质(n=6)
化合物137a(1 mg/kg, PO, n=6)
化合物137a(10 mg/kg, PO, n=5)
清醒
VE 睡眠
VE 睡眠
用药
mL/分钟
500
450
400
350
300
250
200
150
100
50
0
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

图 28

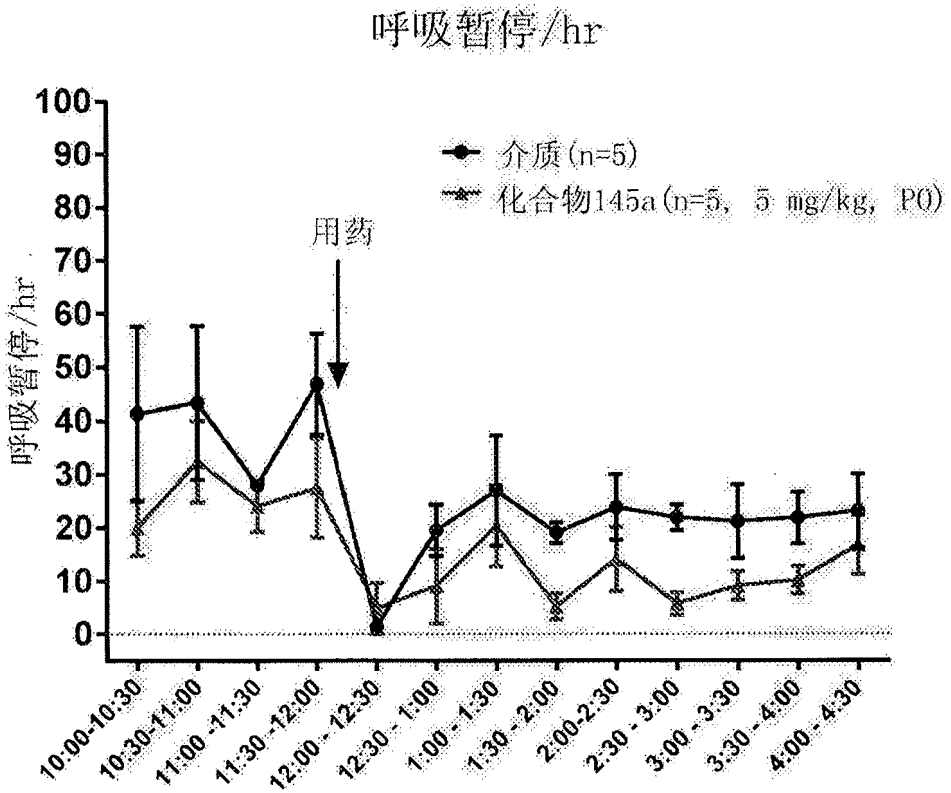

呼吸暂停/hr
介质(n=5)
化合物145a(n=5, 5 mg/kg, PO)
用药
呼吸暂停/hr
100
90
80
70
60
50
40
30
20
10
0
10:00-10:30
10:30-11:00
11:00 -11:30
11:30 -12:00
12:00 - 12:30
12:30 - 1:00
1:00 - 1:30
1:30 - 2:00
2:00-2:30
2:30 - 3:00
3:00 - 3:30
3:30 - 4:00
4:00 - 4:30

图 29

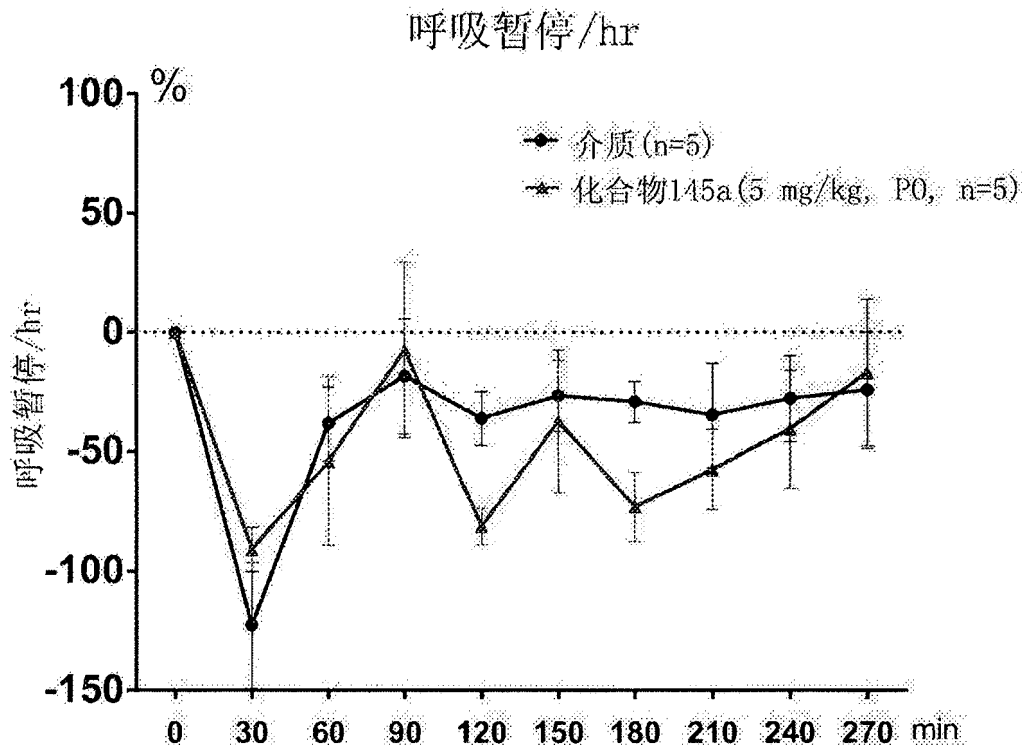

呼吸暂停/hr
100
%
50
0
-50
-100
-150
呼吸暂停/hr
介质(n=5)
化合物145a(5 mg/kg, PO, n=5)
0
30
60
90
120
150
180
210
240
270
min

图 30

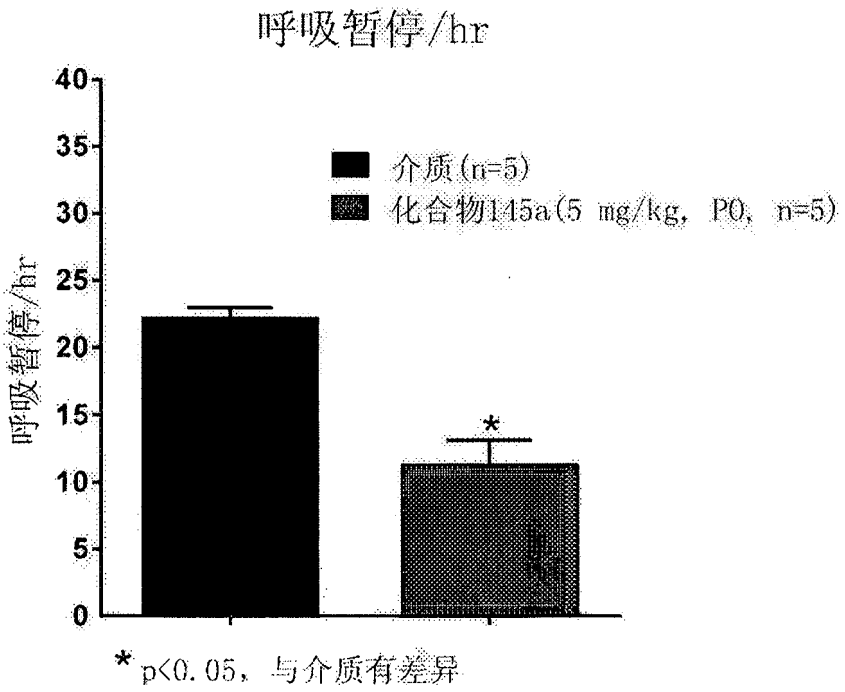

呼吸暂停/hr
40
35
30
25
20
15
10
5
0
呼吸暂停/hr
介质(n=5)
化合物145a(5 mg/kg, PO, n=5)
*
* p<0.05，与介质有差异

图 31

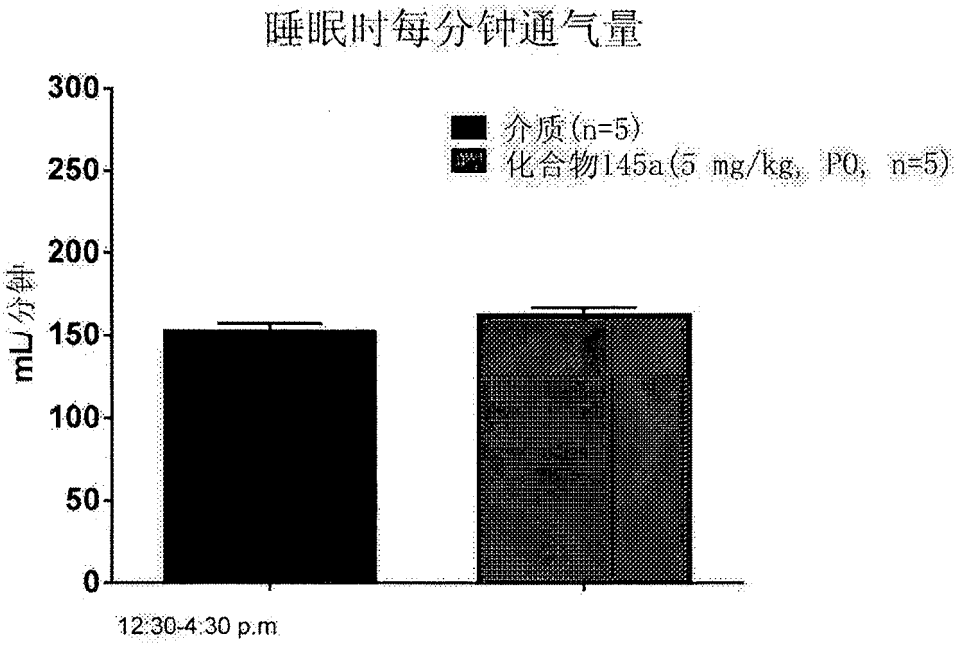

睡眠时每分钟通气量
介质(n=5)
化合物145a(5 mg/kg, PO, n=5)
mL/分钟
300
250
200
150
100
50
0
12:30-4:30 p.m

图 32

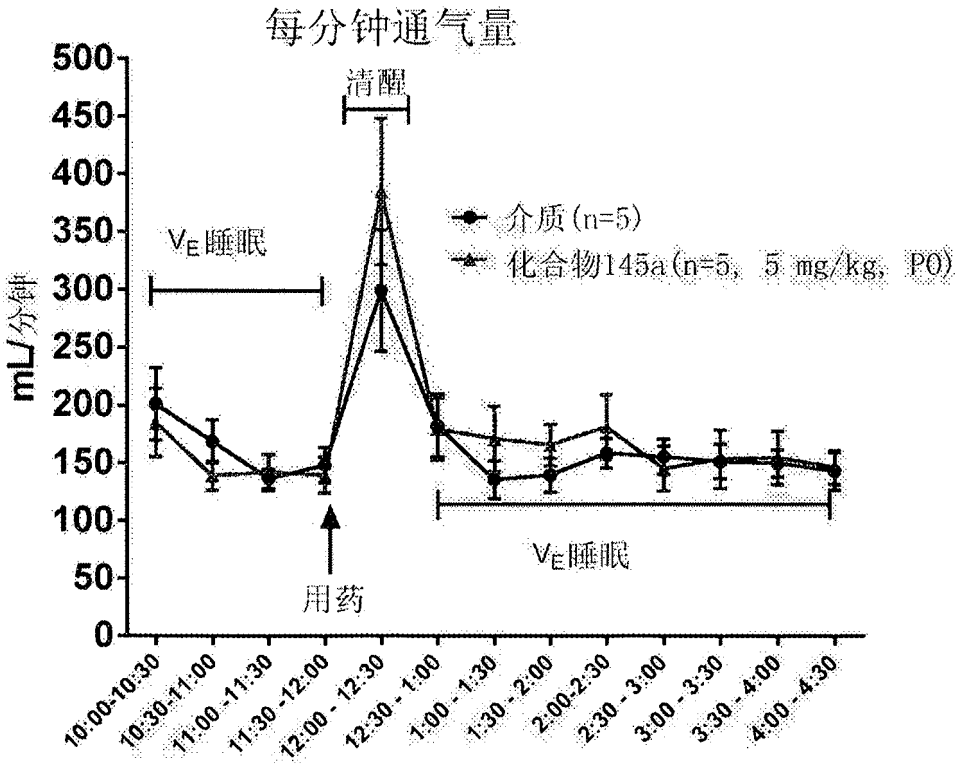
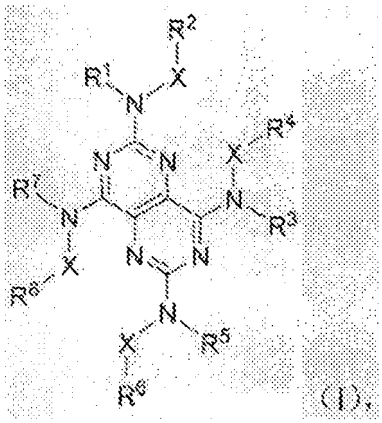

每分钟通气量
清醒
介质(n=5)
化合物145a(n=5, 5 mg/kg, PO)
VE睡眠
VE睡眠
用药
mL/分钟
500
450
400
350
300
250
200
150
100
50
0
10:00-10:30
10:30-11:00
11:00-11:30
11:30-12:00
12:00-12:30
12:30-1:00
1:00-1:30
1:30-2:00
2:00-2:30
2:30-3:00
3:00-3:30
3:30-4:00
4:00-4:30

图 33

1. 化合物或其盐，选自：

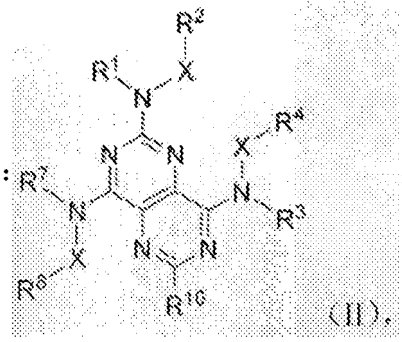
式（I）化合物：  （I），其中在式（I）中：

R^1、R^2、R^3、R^4、R^5、R^6、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；和

每次出现的 R^9独立地是烷基或取代烷基；

式（II）化合物：  （II），其中在式（II）中：

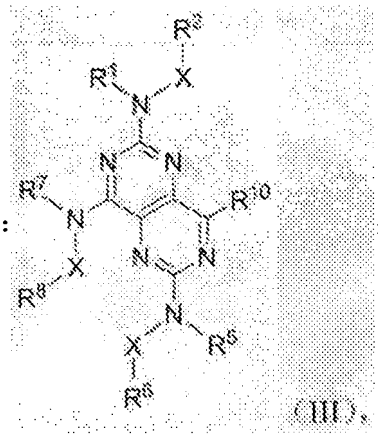
R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基、或取代烷基；

R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基；和

式（III）化合物：  其中在式（III）中：

R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基或取代烷基；和

R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基；

以及其任意组合。

2. 根据权利要求 1 所述的化合物，其中所述化合物选自：

N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^4, N^6, N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 正丁基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 异丙基 -N^4, N^8-2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二甲基 -N^4- 正丙基 -N^8- 丙 -2- 炔基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基）氨基）-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶；

N-(6- 氯 -4,8- 双 - 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基）-O,N- 二甲基 - 羟基胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基）氨基）-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶盐酸盐；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基）- 羟基胺；

N^4, N^8- 二甲基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6- 三甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2- 二乙基 -N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-(4,8- 双 - 正丙基氨基 -6- 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基 - 氨基）- 乙醇；

N^2-(2-甲氧基-乙基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2-(2-异丙氧基-乙基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^8-甲基-N^4,N^6-二-正丙基-N^2-(3,3,3-三氟丙基)-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2-甲基-N^4,N^8-二-正丙基-6-(吗啉-4-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2-甲基-N^4,N^8-二-正丙基-6-(哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2-甲基-N^4,N^8-二-正丙基-6-吡咯烷-1-基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2-甲基-N^4,N^8-二-正丙基-6-(4-甲氧基-哌啶-1-基)-嘧啶并[5,4,-d]嘧啶-2,4,8-三胺;

N^2-(3-氯-2-甲基-苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2-(3,4-二氯苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2-(4-氟苄基)-N^6-甲基-N^4,N^8-二-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

6-氯-N^4,N^8-二甲基-N^2-正丙基-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2,N^2,N^4,N^8-四甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2,N^2-二烯丙基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-甲基-氨基]-乙醇;

N^2-(2-异丙氧基-乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

2-[N-(2-二甲基氨基-乙基)-N-甲基]氨基-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-4,6,8-三胺;

2-[(4,8-双-甲基氨基-6-正丙基氨基-嘧啶并[5,4-d]嘧啶-2-基)-(2-羟基-乙基)-氨基]-乙醇;

N^2,N^2-双-(2-甲氧基乙基)-N^4,N^8-二甲基-N^6-正丙基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

6-(4-氧-哌啶-1-基)-N^4,N^8-二甲基-N^2-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺;

N^2-(3-三氟甲基-哌啶-1-基)-N^4,N^8-二甲基-6-正丙基氨基-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺;

N^2-6-正丙基氨基-N^4,N^8-二甲基-2-(1,1-二氧-硫代吗啉-4-基)-嘧啶并-[5,4-d]嘧啶-2,4,8-三胺;

N^2-正丙基-N^4,N^8-二甲基-6-(4,4-二氟-哌啶-1-基)-嘧啶并[5,4-d]嘧啶-2,4,8-三胺;

N^2,N^4,N^6,N^8-四甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2,N^6-二乙基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺;

N^2, N^6- 二 - 正丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二异丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二烯丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2- 氯 -6-(N, N' - 二甲基 - 肼基)-N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺；

6-(N,N' - 二甲基 - 肼基)-N^2, N^2, N^4, N^8- 四甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4, N^8- 二甲基 -6- 丙氧基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4, N^8- 二甲基 -N^2- 正丙基 -6- 丙基硫烷基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 苄氧基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 醇；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈；

N^4, N^8- 二甲基 -N^2- 正丙基 -6-(氨基甲基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 氨甲酰基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 羧酸；

N-(正丙基)-[4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基]- 脒；

N^4, N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 正丁基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 甲氧基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈；

N^2, N^4, N^6, N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺

2,6- 二氯 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺；

N^4, N^8- 二乙基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6- 三乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^6- 二乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二环丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6, N^6- 四甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^4, N^8- 二烯丙基 -N^2, N^6- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^4, N^8- 三烯丙基 -6-[4-(4- 氟苄基)- 哌嗪 -1- 基]- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 氯 -N^2, N^4, N^8- 三烯丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2,N^4,N^8- 三烯丙基 -6-{4-[双 -(4- 氟苯基)- 甲基]- 哌嗪 -1- 基 }- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2, N^6- 三乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯 ;

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸 ;

N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺 ;

(6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯 ;

其盐或溶剂化物,和其任意组合。

3. 根据权利要求 1 所述的化合物,其中所述盐选自硫酸盐、硫酸氢盐、半硫酸盐、氯化物、溴化物、碘化物、硝酸盐、碳酸盐、磷酸盐、磷酸氢盐、磷酸二氢盐、甲酸盐、乙酸盐、丙酸盐、琥珀酸盐、乙醇酸盐、葡萄糖酸盐、乳酸盐、苹果酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐、葡萄糖醛酸盐、马来酸盐、富马酸盐、丙酮酸盐、天冬氨酸盐、谷氨酸盐、苯甲酸盐、邻氨基苯甲酸盐、4- 羟基苯甲酸盐、苯基乙酸盐、扁桃酸盐、扑酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、泛酸盐、三氟甲磺酸盐、2- 羟基乙磺酸盐、对甲苯磺酸盐、磺胺酸盐、环己基氨基磺酸盐、硬脂酸盐、海藻酸盐、β - 羟基丁酸盐、水杨酸盐、半乳糖酸盐、半乳糖醛酸盐、糖精、糖质酸盐、甘油膦酸盐、和其任意组合。

4. 药物组合物,包括根据权利要求 1 所述的化合物和至少一种药学上可接受的载体。

5. 根据权利要求 4 所述的组合物,进一步包括至少一种用剂,所述用剂选自多沙普仑及其对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂、苯二氮䓬受体激动剂、食欲肽拮抗剂、三环类抗抑郁剂、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素、食欲肽、褪黑激素激动剂、安帕金、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂。

6. 根据权利要求 5 所述的组合物,其中所述化合物和所述用剂在所述组合物中是物理混合的。

7. 根据权利要求 5 所述的组合物,其中所述化合物和所述用剂在所述组合物中是物理分开的。

8. 根据权利要求 4 所述的组合物,进一步包括已知导致呼吸控制变化的至少一种用剂。

9. 根据权利要求 8 所述的组合物,其中所述至少一种用剂选自阿片类麻醉剂、苯二氮䓬类、镇静剂、睡眠助剂、催眠剂、丙泊酚、和其任意组合。

10. 根据权利要求 8 所述的组合物,其中所述化合物和所述用剂在所述组合物中是物理混合的。

11. 根据权利要求 8 所述的组合物,其中所述化合物和所述用剂在组合物中是物理分开的。

12. 根据权利要求 4 所述的组合物,其中所述组合物允许改善所述化合物在口服给予对象后的递送。

13. 根据权利要求 12 所述的组合物,其中所述组合物最小化所述化合物至所述对象的胃的递送和最大化所述化合物至所述对象的肠的递送。

14. 根据权利要求 12 所述的组合物,其中所述组合物包括肠溶包衣。

15. 根据权利要求 12 所述的组合物，其中所述化合物被包含在药学上适合的胶囊中。

16. 根据权利要求 15 所述的组合物，其中所述胶囊包含所述化合物、或所述化合物与赋形剂的混合物的颗粒或粉末。

17. 根据权利要求 16 所述的组合物，其中所述赋形剂包括粘合剂、崩解剂、稀释剂、缓冲剂、润滑剂、助流剂、抗氧化剂、抗菌防腐剂、着色剂、或调味剂。

18. 根据权利要求 16 所述的组合物，其中所述胶囊有肠溶包衣，但所述化合物颗粒或粉末没有肠溶包衣。

19. 根据权利要求 16 所述的组合物，其中所述化合物颗粒或粉末在置入所述胶囊前包覆有肠溶包衣。

20. 根据权利要求 19 所述的组合物，其中所述化合物颗粒或粉末包覆有多种肠溶包衣，从而提供药物至所述对象的肠的不同区域的递送。

21. 根据权利要求 16 所述的组合物，其中至少部分所述化合物颗粒或粉末有肠溶包衣。

22. 根据权利要求 21 所述的组合物，其中所述胶囊包覆有与包覆所述化合物颗粒或粉末的肠溶包衣不同的肠溶包衣。

23. 根据权利要求 12 所述的组合物，其中所述化合物被包覆到基体颗粒上，从而形成内核，所述内核包括作为所述基体颗粒上的包衣的药物。

24. 根据权利要求 23 所述的组合物，其中所述基体颗粒没有肠溶包衣，并且所述组合物被包含在有肠溶包衣的药学上可接受的胶囊中。

25. 根据权利要求 23 所述的组合物，其中所述内核包覆有肠溶包衣，从而形成肠溶包衣小珠。

26. 根据权利要求 25 所述的组合物，其中所述肠溶包衣小珠被包含在药学上可接受的胶囊中。

27. 根据权利要求 26 所述的组合物，其中所述胶囊包含包覆有多种肠溶包衣的小珠，使得所述胶囊提供所述化合物至所述对象的肠的不同区域的递送。

28. 根据权利要求 16 所述的组合物，进一步其中所述胶囊的内含物溶解或悬浮于药学上可接受的液体中，以提供液体填充胶囊。

29. 根据权利要求 28 所述的组合物，其中所述胶囊有肠溶包衣，但其中包含的液体制剂不包括肠溶包衣。

30. 根据权利要求 28 所述的组合物，其中所述化合物颗粒或粉末有肠溶包衣。

31. 根据权利要求 30 所述的组合物，其中所述化合物颗粒或粉末包覆有多种肠溶包衣，以提供药物至所述对象的肠的不同区域的递送。

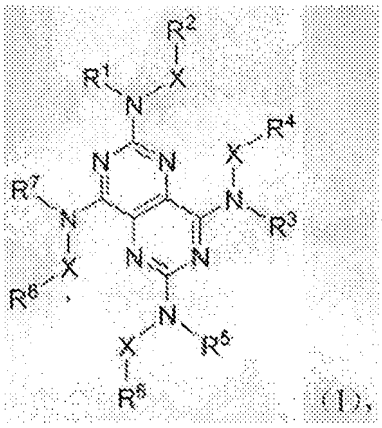
32. 根据权利要求 30 所述的组合物，其中施加于所述胶囊的肠溶包衣与施加于任何所述化合物颗粒或粉末的肠溶包衣不同。

33. 根据权利要求 15 所述的组合物，其中所述化合物被包覆在基体颗粒上，从而形成内核，所述内核包括作为所述基体颗粒上的包衣的所述化合物，其中所述内核悬浮于药学上可接受的液体中，并且其中悬浮的所述内核被置入胶囊。

34. 根据权利要求 33 所述的组合物，其中所述胶囊有肠溶包衣，但所述内核没有肠溶包衣。

35. 根据权利要求 33 所述的组合物，其中所述胶囊和所述内核有肠溶包衣。

36. 在有需要的对象中预防或治疗呼吸控制障碍或疾病的方法，所述方法包括给予所述对象有效量的药物组合物，所述药物组合物包括至少一种药学上可接受的载体和选自下列的至少一种化合物或其盐：

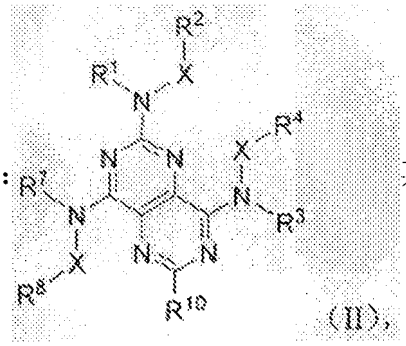
式（I）化合物：  （I），其中在式（I）中：

R^1、R^2、R^3、R^4、R^5、R^6、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；和

每次出现的 R^9独立地是烷基或取代烷基；

式（II）化合物：  （II），其中在式（II）中：

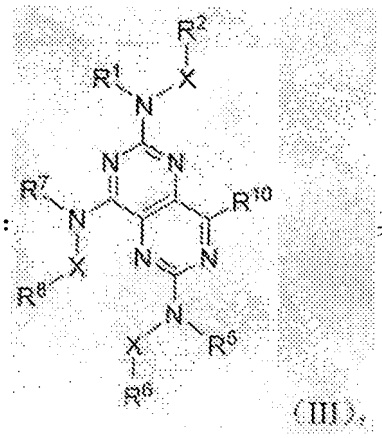
R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基或取代烷基；

R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基；和

式（III）化合物：  其中在式（III）中：

R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9独立地是烷基或取代烷基；和

R^{10}是 H、卤素、CN、脒基、酰氨基、羧基、羧酰胺基、肼基、OH、烷基或取代烷基、烷氧基或取代烷氧基、或硫代烷氧基或取代硫代烷氧基。

37. 根据权利要求 36 所述的方法，其中所述呼吸控制障碍或疾病选自呼吸抑制、睡眠呼吸暂停、早产儿呼吸暂停、肥胖 - 通气不足综合征、原发性肺泡通气不足综合征、呼吸困难、高空病、氧不足、高碳酸血、慢性阻塞性肺部疾病（COPD）、婴儿猝死综合征（SIDS）、先天性中枢性通气不足综合征、阿尔茨海默氏症、帕金森病、中风、杜氏肌营养不良、和脑和脊髓创伤性损伤。

38. 根据权利要求 37 所述的方法，其中所述呼吸抑制由麻醉剂、镇静剂、睡眠助剂、抗焦虑剂、催眠剂、酒精或麻醉药引起。

39. 根据权利要求 36 所述的方法，其中所述对象被进一步给予可用于治疗呼吸障碍或疾病的至少一种另外的用剂。

40. 根据权利要求 39 所述的方法，其中所述至少一种另外的用剂选自多沙普仑及其对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂、苯二氮䓬受体激动剂、食欲肽拮抗剂、三环类抗抑郁剂、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素、食欲肽、褪黑激素激动剂、安帕金、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂。

41. 根据权利要求 39 所述的方法，其中所述化合物和所述用剂被分开给予所述对象。

42. 根据权利要求 39 所述的方法，其中所述化合物和所述用剂被共同给予所述对象，进一步其中所述化合物和所述用剂在被给予所述对象时是物理混合的或是物理分开的。

43. 根据权利要求 36 所述的方法，其中所述对象被进一步给予已知改变所述对象的正常呼吸控制的至少一种另外的治疗剂。

44. 根据权利要求 43 所述的方法，其中至少一种另外的治疗剂选自阿片类麻醉剂、苯二氮䓬类、镇静剂、睡眠助剂、催眠剂、丙泊酚、和其任意组合。

45. 根据权利要求 36 所述的方法，其中所述组合物结合机械通气装置或气道正压装置对所述对象的应用被给予。

46. 根据权利要求 36 所述的方法，其中所述对象是哺乳动物或禽类。

47. 根据权利要求 46 所述的方法，其中所述哺乳动物是人。

48. 根据权利要求 36 所述的方法，其中所述组合物通过鼻部、吸入、局部、口服、颊部、直肠、胸膜、腹膜、阴道、肌内、皮下、透皮、硬膜外、气管内、耳部、眼内、鞘内或静脉内途径被给予所述对象。

49. 根据权利要求 48 所述的方法，其中所述组合物被口服给予所述对象。

50. 根据权利要求 36 所述的方法，其中所述至少一种化合物选自：

N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^4, N^6, N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 正丁基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 异丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二甲基 -N^4- 正丙基 -N^8- 丙 -2- 炔基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶；

N-(6- 氯 -4,8- 双 - 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-O,N- 二甲基 - 羟基胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶盐酸盐；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基) - 羟基胺；

N^4, N^8- 二甲基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6- 三甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2- 二乙基 -N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-(4,8- 双 - 正丙基氨基 -6- 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基 - 氨基) - 乙醇；

N^2-(2- 甲氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2-(2- 异丙氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^8- 甲基 -N^4, N^6- 二 - 正丙基 -N^2-(3,3,3- 三氟丙基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(吗啉 -4- 基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(哌啶 -1- 基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6- 吡咯烷 -1- 基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 甲氧基 - 哌啶 -1- 基) - 嘧啶并 [5,4,-d] 嘧啶 -2,

4,8- 三胺；

N^2-(3- 氯 -2- 甲基 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2-(3,4- 二氯苄基)-N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2-(4- 氟苄基)-N^6- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2, N^4, N^8- 四甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2- 二烯丙基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)- 甲基 - 氨基]- 乙醇；

N^2-(2- 异丙氧基 - 乙基)-N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-[N-(2- 二甲基氨基 - 乙基)-N- 甲基] 氨基 -N^4,N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,6,8- 三胺；

2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-(2- 羟基 - 乙基)- 氨基]- 乙醇；

N^2, N^2- 双 -(2- 甲氧基乙基)-N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6-(4- 氧 - 哌啶 -1- 基)-N^4, N^8- 二甲基 -N^2- 正丙基氨基 - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺；

N^2-(3- 三氟甲基 - 哌啶 -1- 基)-N^4, N^8- 二甲基 -6- 正丙基氨基 - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺；

N^2-6- 正丙基氨基 -N^4,N^8- 二甲基 -2-(1,1- 二氧 - 硫代吗啉 -4- 基)- 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 正丙基 -N^4,N^8- 二甲基 -6-(4,4- 二氟 - 哌啶 -1- 基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^4, N^6, N^8- 四甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二乙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 正丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二异丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二烯丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2- 氯 -6-(N,N' - 二甲基 - 肼基)-N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺；

6-(N,N' - 二甲基 - 肼基)-N^2,N^2,N^4,N^8- 四甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4, N^8- 二甲基 -6- 丙氧基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4, N^8- 二甲基 -N^2- 正丙基 -6- 丙基硫烷基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 苄氧基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 醇；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈；

N^4,N^8- 二甲基 -N^2- 正丙基 -6-(氨基甲基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 氨甲酰基 -N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 羧酸；

N-(正丙基)-[4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基]- 脒；

N^4,N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4,N^8- 二 - 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4,N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 正丁基 -N^2- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 甲氧基 -N^2- 甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈；

N^2,N^4,N^6,N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺

2,6- 二氯 -N^4,N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺；

N^4,N^8- 二乙基 -N^2,N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2,N^6- 双 - 环丙基甲基 -N^4,N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2,N^6- 二乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2,N^2,N^6- 三乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 乙基 -N^4,N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2,N^6- 二乙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2,N^6- 二环丙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2,N^6- 双 - 环丙基甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2,N^2,N^6,N^6- 四甲基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^4,N^8- 二烯丙基 -N^2,N^6- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2,N^4,N^8- 三烯丙基 -6-[4-(4- 氟苄基)- 哌嗪 -1- 基]- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 氯 -N^2,N^4,N^8- 三烯丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2,N^4,N^8- 三烯丙基 -6-{4-[双 -(4- 氟苯基)- 甲基]- 哌嗪 -1- 基 }- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2,N^2,N^6- 三乙基 -N^4,N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯；

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸；

N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺；

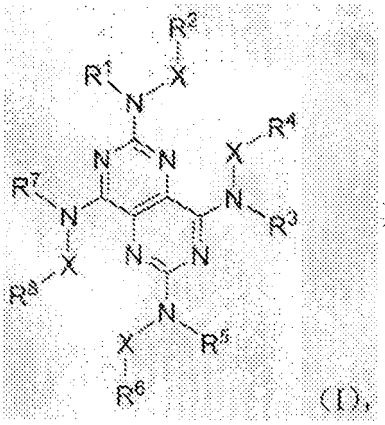
(6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯；

其盐、和其任意组合。

51. 根据权利要求 36 所述的方法，其中所述盐选自硫酸盐、硫酸氢盐、氯化物、溴化物、碘化物、硝酸盐、碳酸盐、磷酸盐、磷酸氢盐、磷酸二氢盐、甲酸盐、乙酸盐、丙酸盐、琥珀酸盐、乙醇酸盐、葡萄糖酸盐、乳酸盐、苹果酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐、葡萄糖醛

酸盐、马来酸盐、富马酸盐、丙酮酸盐、天冬氨酸盐、谷氨酸盐、苯甲酸盐、邻氨基苯甲酸盐、4-羟基苯甲酸盐、苯基乙酸盐、扁桃酸盐、扑酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、泛酸盐、三氟甲磺酸盐、2-羟基乙磺酸盐、对甲苯磺酸盐、磺胺酸盐、环己基氨基磺酸盐、硬脂酸盐、海藻酸盐、β-羟基丁酸盐、水杨酸盐、半乳糖酸盐、半乳糖醛酸盐、糖精、糖质酸盐、和甘油膦酸盐。

52. 在有需要的对象中预防呼吸节奏失稳或稳定呼吸节奏的方法，所述方法包括给予所述对象有效量的药物组合物，所述药物组合物包括至少一种药学上可接受的载体和选自下列的至少一种化合物或其盐：

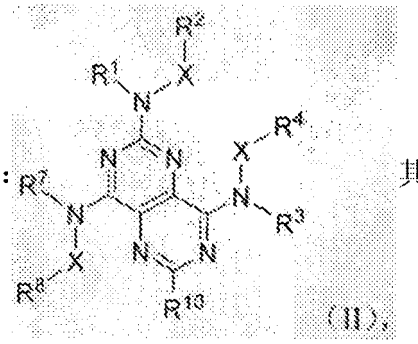
式（I）化合物：  其中在式（I）中：

R^1、R^2、R^3、R^4、R^5、R^6、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自3-羟基-戊烷-1,5-二基、6-羟基-环庚烷-1,4-二基、丙烷-1,3-二基、丁烷-1,4-二基和戊烷-1,5-二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；和

每次出现的 R^9独立地是烷基或取代烷基；

式（II）化合物：  其中在式（II）中：

R^1、R^2、R^3、R^4、R^7和 R^8独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

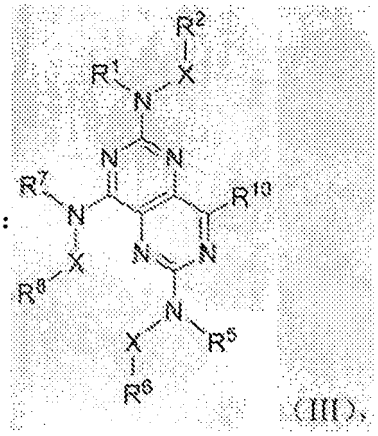
或 R^1和 R^2、R^3和 R^4、R^5和 R^6、或 R^7和 R^8独立地组合形成双自由基，所述双自由基选自3-羟基-戊烷-1,5-二基、6-羟基-环庚烷-1,4-二基、丙烷-1,3-二基、丁烷-1,4-二基和戊烷-1,5-二基；

每次出现的 X 均独立地选自键、NH、NR^9和 O；

每次出现的 R^9 独立地是烷基或取代烷基；

R^{10} 是 H、卤素、氰基、烷基、取代烷基、烷氧基或取代烷氧基；

和

式（III）化合物：  其中在式（III）中：

R^1、R^2、R^3、R^4、R^7 和 R^8 独立地是 H、烷基、取代烷基、环烷基、取代环烷基、烯基、取代烯基、炔基、取代炔基、苯基、取代苯基、苯基烷基、取代苯基烷基、芳基、取代芳基、芳基烷基、取代芳基烷基、杂芳基烷基、取代杂芳基烷基、杂芳基或取代杂芳基；

或 R^1 和 R^2、R^3 和 R^4、R^5 和 R^6、或 R^7 和 R^8 独立地组合形成双自由基，所述双自由基选自 3- 羟基 - 戊烷 -1,5- 二基、6- 羟基 - 环庚烷 -1,4- 二基、丙烷 -1,3- 二基、丁烷 -1,4- 二基和戊烷 -1,5- 二基；

每次出现的 X 均独立地选自键、NH、NR^9 和 O；

每次出现的 R^9 独立地是烷基或取代烷基；和

R^{10} 是 H、卤素、氰基、烷基、取代烷基、烷氧基或取代烷氧基。

53. 根据权利要求 52 所述的方法，其中所述失稳与呼吸控制障碍或疾病有关，所述呼吸控制障碍或疾病选自呼吸抑制、睡眠呼吸暂停、早产儿呼吸暂停、肥胖 - 通气不足综合征、原发性肺泡通气不足综合征、呼吸困难、高空病、氧不足、高碳酸血、慢性阻塞性肺部疾病（COPD）、婴儿猝死综合征（SIDS）、先天性中枢性通气不足综合征、阿尔茨海默氏症、帕金森病、中风、杜氏肌营养不良、和脑和脊髓创伤性损伤。

54. 根据权利要求 53 所述的方法，其中所述呼吸抑制由麻醉剂、镇静剂、睡眠助剂、抗焦虑剂、催眠剂、酒精或麻醉药引起。

55. 根据权利要求 52 所述的方法，其中所述对象被进一步给予可用于治疗所述呼吸障碍或疾病的至少一种另外的用剂。

56. 根据权利要求 55 所述的方法，其中所述至少一种另外的用剂选自多沙普仑及其对映体、乙酰唑胺、阿米三嗪、茶碱、咖啡碱、甲基甲孕酮和相关化合物、增加睡眠呼吸障碍患者的觉醒阈值的镇静剂、苯二氮䓬受体激动剂、食欲肽拮抗剂、三环类抗抑郁剂、血清素调节剂、腺苷和腺苷受体和核苷转运体调节剂、大麻素、食欲肽、褪黑激素激动剂、安帕金、羟丁酸钠、莫达非尼、阿莫达非尼、和吸入式治疗剂。

57. 根据权利要求 55 所述的方法，其中所述化合物和所述用剂被分开给予所述对象。

58. 根据权利要求 55 所述的方法，其中所述化合物和所述用剂被共同给予所述对象，进一步其中所述化合物和所述用剂在被给予所述对象时是物理混合的或是物理分开的。

59. 根据权利要求 52 所述的方法，其中所述对象被进一步给予已知改变所述对象的正常呼吸控制的至少一种另外的治疗剂。

60. 根据权利要求 59 所述的方法，其中至少一种另外的治疗剂选自阿片类麻醉剂、苯二氮䓬类、镇静剂、睡眠助剂、催眠剂、丙泊酚、和其任意组合。

61. 根据权利要求 52 所述的方法，其中所述组合物联合机械通气装置或气道正压装置对所述对象的应用被给予。

62. 根据权利要求 52 所述的方法，其中所述对象是哺乳动物或禽类。

63. 根据权利要求 62 所述的方法，其中所述哺乳动物是人。

64. 根据权利要求 52 所述的方法，其中所述组合物通过鼻部、吸入、局部、口服、颊部、直肠、胸膜、腹膜、阴道、肌内、皮下、透皮、硬膜外、气管内、耳部、眼内、鞘内或静脉内途径被给予所述对象。

65. 根据权利要求 64 所述的方法，其中所述组合物被口服给予所述对象。

66. 根据权利要求 52 所述的方法，其中所述至少一种化合物选自：

N^2, N^6- 二甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^4, N^6, N^8- 四 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 正丁基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 异丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二甲基 -N^4- 正丙基 -N^8- 丙 -2- 炔基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶；

N-(6- 氯 -4,8- 双 - 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-O,N- 二甲基 - 羟基胺；

N^2, N^6- 双 -(N- 甲氧基 (N- 甲基) 氨基)-N^4, N^8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶盐酸盐；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

O,N- 二甲基 -N-(6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基) - 羟基胺；

N^4, N^8- 二甲基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6- 三甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 甲基 -N^4, N^8- 二 - 正丙基嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2- 二乙基 -N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-(4,8- 双 - 正丙基氨基 -6- 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基 - 氨基) - 乙醇；

N^2-(2- 甲氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2-(2- 异丙氧基 - 乙基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^8- 甲基 -N^4, N^6- 二 - 正丙基 -N^2-(3,3,3- 三氟丙基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(吗啉 -4- 基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(哌啶 -1- 基) - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6- 吡咯烷 -1- 基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 甲氧基 - 哌啶 -1- 基)- 嘧啶并 [5,4,-d] 嘧啶 -2,4,8- 三胺；

N^2-(3- 氯 -2- 甲基 - 苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2-(3,4- 二氯苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2-(4- 氟苄基)-N^6- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2, N^4, N^8- 四甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2- 二烯丙基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)- 甲基 - 氨基]- 乙醇；

N^2-(2- 异丙氧基 - 乙基)-N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2-[N-(2- 二甲基氨基 - 乙基)-N- 甲基] 氨基 -N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -4,6,8- 三胺；

2-[(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基)-(2- 羟基 - 乙基)- 氨基]- 乙醇；

N^2, N^2- 双 -(2- 甲氧基乙基)-N^4, N^8- 二甲基 -N^6- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6-(4- 氧 - 哌啶 -1- 基)-N^4, N^8- 二甲基 -N^2- 正丙基氨基 - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺；

N^2-(3- 三氟甲基 - 哌啶 -1- 基)-N^4, N^8- 二甲基 -6- 正丙基氨基 - 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺；

N^2-6- 正丙基氨基 -N^4, N^8- 二甲基 -2-(1,1- 二氧 - 硫代吗啉 -4- 基)- 嘧啶并 -[5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 正丙基 -N^4, N^8- 二甲基 -6-(4,4- 二氟 - 哌啶 -1- 基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^4, N^6, N^8- 四甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二乙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二 - 正丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二异丁基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二烯丙基 -N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

2- 氯 -6-(N,N' - 二甲基 - 肼基)-N^4, N^8- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺；

6-(N,N' - 二甲基 - 肼基)-N^2, N^2, N^4, N^8- 四甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4, N^8- 二甲基 -6- 丙氧基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4, N^8- 二甲基 -N^2- 正丙基 -6- 丙基硫烷基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 苄氧基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 醇；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈；

N^4, N^8- 二甲基 -N^2- 正丙基 -6-(氨基甲基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 氨甲酰基 -N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 羧酸；

N-(正丙基)-[4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基]- 脒；

N^4, N^8- 二甲基 -N^2- 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2- 甲基 -N^4, N^8- 二 - 正丙基 -6-(4- 氟苯基)- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^4, N^8- 二甲基 -N^2- 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 正丁基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 甲氧基 -N^2- 甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 甲基氨基 -4,8- 双 - 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 腈；

N^2, N^4, N^6, N^8- 四乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺

2,6- 二氯 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -4,8- 二胺；

N^4, N^8- 二乙基 -N^2, N^6- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二乙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6- 三乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

6- 氯 -N^2- 乙基 -N^4, N^8- 双 - 环丙基甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^6- 二乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 二环丙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^6- 双 - 环丙基甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^2, N^6, N^6- 四甲基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^4, N^8- 二烯丙基 -N^2, N^6- 二甲基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

N^2, N^4, N^8- 三烯丙基 -6-[4-(4- 氟苄基)- 哌嗪 -1- 基]- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

6- 氯 -N^2, N^4, N^8- 三烯丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^4, N^8- 三烯丙基 -6-{4-[双 -(4- 氟苯基)- 甲基]- 哌嗪 -1- 基 }- 嘧啶并 [5,4-d] 嘧啶 -2,4,8- 三胺；

N^2, N^2, N^6- 三乙基 -N^4, N^8- 二 - 正丙基 - 嘧啶并 [5,4-d] 嘧啶 -2,4,6,8- 四胺；

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸叔丁酯；

(4,8- 双 - 甲基氨基 -6- 正丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸；

N- 正丙基 -[2-(4,8- 双 - 甲基氨基 -6- 丙基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)]- 乙酰胺；

(6- 氯 -4,8- 双 - 甲基氨基 - 嘧啶并 [5,4-d] 嘧啶 -2- 基氨基)- 乙酸乙基酯；

其盐、和其任意组合。

67. 根据权利要求所述的方法 52，其中所述盐选自硫酸盐、硫酸氢盐、氯化物、溴化物、

碘化物、硝酸盐、碳酸盐、磷酸盐、磷酸氢盐、磷酸二氢盐、甲酸盐、乙酸盐、丙酸盐、琥珀酸盐、乙醇酸盐、葡萄糖酸盐、乳酸盐、苹果酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐、葡萄糖醛酸盐、马来酸盐、富马酸盐、丙酮酸盐、天冬氨酸盐、谷氨酸盐、苯甲酸盐、邻氨基苯甲酸盐、4-羟基苯甲酸盐、苯基乙酸盐、扁桃酸盐、扑酸盐、甲磺酸盐、乙磺酸盐、苯磺酸盐、泛酸盐、三氟甲磺酸盐、2-羟基乙磺酸盐、对甲苯磺酸盐、磺胺酸盐、环己基氨基磺酸盐、硬脂酸盐、海藻酸盐、β-羟基丁酸盐、水杨酸盐、半乳糖酸盐、半乳糖醛酸盐、糖精、糖质酸盐、和甘油膦酸盐。

68. 根据权利要求 1 所述的化合物，其中所述化合物是 N^2-N^6-双-环丙基甲基-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺，并且其中所述化合物的 X 射线粉末衍射光谱包括约 8.12、9.59、12.60、15.02、16.33、17.40、18.98、20.68、21.72、22.28、23.98、25.24、和 26.70 的 2Θ 值（以度为单位）。

69. 制备 N^2-N^6-双-环丙基甲基 N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-2,4,6,8-四胺(84)的方法，包括使 2,6-二氯-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺和环丙基甲胺在溶剂中反应。

70. 根据权利要求 69 所述的方法，其中所述反应在加热下进行，并且其中在反应系统冷却至室温后，(84)从所述溶剂析出。

71. 根据权利要求 69 所述的方法，其中所述溶剂包括正丁醇。

72. 根据权利要求 70 所述的方法，其中使析出的(84)从正丁醇重结晶。

73. 根据权利要求 72 所述的方法，其中重结晶的(84)的 X 射线粉末衍射光谱包括约 8.12、9.59、12.60、15.02、16.33、17.40、18.98、20.68、21.72、22.28、23.98、25.24、和 26.70 的 2Θ 值（以度为单位）。

74. 根据权利要求 69 所述的方法，其中通过使 2,4,6,8-四氯-嘧啶并[5,4-d]嘧啶和甲胺在溶剂中反应来制备 2,6-二氯-N^4,N^8-二甲基-嘧啶并[5,4-d]嘧啶-4,8-二胺。

75. 根据权利要求 74 所述的方法，其中 2,4,6,8-四氯-嘧啶并[5,4-d]嘧啶与甲胺的当量比为约 1 ： 4.5。

NOVEL BREATHING CONTROL MODULATING COMPOUNDS, AND METHODS OF USING SAME

Abstract

The present invention includes pyrimido[5,4-d]pyrimidines that are useful in the prevention and/or treatment of breathing control diseases or disorders in a subject in need thereof. The present invention also includes a method of preventing and/or treating a respiratory disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the invention. The present invention further includes a method of preventing destabilization or stabilizing breathing rhythm in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the invention.

新型呼吸控制调节化合物及其使用方法

摘　要

本发明包括可用于在有需要的对象中预防和/或治疗呼吸控制疾病或障碍的嘧啶并[5，4-d]嘧啶。本发明还包括在有需要的对象中预防和/或治疗呼吸疾病或障碍的方法，包括给予对象治疗有效量的本发明化合物。本发明进一步包括在有需要的对象中预防呼吸节奏失稳或稳定呼吸节奏的方法，包括给予对象治疗有效量的本发明化合物。